Trial to Assess Chelation Therapy- 2 (TACT2)

NCT02733185

Informed Consent Form

Version Date: 05.01.2019

PARTICIPANT INFORMED CONSENT FORM AND AUTHORIZATION TO USE AND DISCLOSE MEDICAL INFORMATION

STUDY TITLE: A randomized, double blind controlled factorial clinical trial of edetate disodium-based chelation and high-dose oral vitamins and minerals to prevent recurrent cardiac events in diabetic patients with a prior myocardial infarction.

PROTOCOL NO: TACT2

STUDY DOCTOR: «First_Name» «Middle_Name» «Last_Name», «Suffix»

STUDY SITE: «Company_Name»
«Address»
«City_State_ZIP»

TELEPHONE: «Telephone»
«Telephone_2_if_applicable»

SPONSOR: National Institutes of Health

INTRODUCTION

You are being asked to take part in TACT2, a research study funded by the National Institutes of Health (NIH), because you have diabetes and had a heart attack. Mount Sinai Medical Center and Duke Clinical Research Institute (DCRI) are the research centers that received funding from NIH. As the Data Coordinating Center, DCRI is responsible for data collection, analysis of results, and monitoring the participating sites. The clinical coordinating center, Mount Sinai, is responsible for the clinical and medical management of the study activities with the study doctor and staff.

Your participation in this research study is strictly voluntary, meaning that you may or may not choose to take part. To decide whether or not you want to be part of this research, the risks and possible benefits of the study are described in this form so that you can make an informed decision. This process is known as informed consent. This consent form describes the purpose, procedures, possible benefits and risks of the study. This form explains how your medical information will be used and who may see it. You may have a copy of this form to review at your leisure or to ask advice from others.

The study doctor or study staff will answer any questions you may have about this form or about the study. Please read this document carefully and do not hesitate to ask anything about this information. This form may contain words that you do not understand. Please ask the study doctor or study staff to explain the words or information that you do not understand. After reading the consent form, if you would like to participate, you will be asked to sign this form. You will be given a signed copy of your consent form to take home and keep for your records. You

will also be asked to complete and sign a medical release form and a form authorizing the study staff to receive your study vitamins and minerals.

PURPOSE OF THE STUDY

The purpose of this study is to find out if chelation therapy (a chemical process in which a synthetic solution is infused into the bloodstream to remove heavy metals and/or minerals from the body) and oral vitamins and minerals help decrease the risk of new heart events (including another heart attack, death, chest pains, or heart surgery to open blood vessels) in research participants with diabetes who have already survived a heart attack. This study is being carried out because a prior study suggested benefit with chelation therapy when given to research participants with diabetes who had had a heart attack. The study drug, chelation, is a drug given by vein that that sticks to heavy metals in the blood, like lead and cadmium. These metals can then come out of the body in the urine. Lead and cadmium may lead to heart disease.

We will also collect and store blood and urine samples to determine:

- whether other metals or blood changes account for the effect of chelation
- whether we can predict cardiac events like heart attacks based on your body metal levels
- for future analyses that we have not thought of yet

- You will be 1 of about 1,200 people in this study
- There are about 120 research sites in North America
- You will be in this study for up to 5 years
- The study requires:
  - 40 weekly IV's (through a vein in your arm) and taking vitamins and minerals or inactive placebo (identical in appearance to vitamins and minerals but contain no active ingredient) twice a day by mouth
  - up to 48 months of follow-up and taking pills twice a day by mouth

BACKGROUND

The study drug, chelation therapy, consists of a drug in a solution of dissolved materials that bind to heavy metals, including lead and cadmium, and allow them to come out in the urine. These metals may lead to heart disease.

The drug in the solution used in this study is edetate disodium (also called disodium EDTA or EDTA). The United States Food and Drug Administration (FDA) has not approved EDTA for treating heart disease in heart attack survivors, making its use in this study investigational. The drug under use in this study is not the same drug approved by the FDA for use in cases of lead poisoning (calcium EDTA or edetate calcium disodium). The FDA is aware of this study and receives regular reports.

This infusion is given over 3–4 hours, through a needle placed into your arm by medical staff.

This study is funded by the US government (NIH), and receives no support from pharmaceutical or other commercial drug companies.

PROCEDURES

You will be asked to have a study screening visit, which will take about 1 hour. At the visit, we will:

- Review and ask you to sign this Participant Informed Consent Form and Authorization To Use and Disclose Medical Information and a Pharmacy Designation Form after all of your questions are answered.
- Review the study inclusion and exclusion criteria
- Ask you to provide contact information for follow-up
- Ask you to complete medical history forms
- Ask you questions about your health, activities, and how you are feeling emotionally
- Perform a brief physical exam. The physical exam will not include a breast, pelvic, or rectal exam
- Get a blood sample (3 tablespoons) to check your blood cell counts and kidney and liver function.

If you have been hospitalized with fluid in your lungs due to a weak heart within the last 6 months, you will not be permitted to participate in the study.

Your blood test results and medical history will confirm if you are eligible to participate in the study.

You will be assigned by chance (like a coin toss) to a study group. You will be assigned to one of the following 4 study groups:

- Chelation solution + oral multivitamins and multiminerals
- Chelation placebo solution + oral multivitamins and multiminerals
- Chelation solution + placebo oral multivitamins and multiminerals
- Chelation placebo solution + placebo oral multivitamins and multiminerals

Placebo is identical in appearance to the active solution or multivitamins and multiminerals but contains no active ingredients.

All participants will also take an additional low-dose vitamin and mineral pill each day while they are receiving infusions, to replace essential vitamins and minerals (in addition to the ones mentioned above).

You have an equal chance of being assigned to any of the 4 study groups. Neither you, nor the study doctor and study staff will know to which study group you have been assigned. Your assigned study group will be available to your study doctor in the event of a medical emergency.

Your first infusion visit will be scheduled.

Infusion Visits (40 visits over 52 weeks, about 4 hours for each visit)

At each infusion visit:

- We will check your blood pressure, pulse, weight, and listen to your heart and lungs
- You will have your blood collected at screening and infusions 5, 10, 20, 30, and 40 (or at 1 year, whichever is first), to check for kidney function, control of your diabetes, calcium, and blood counts
- Additional blood and urine samples are collected at Visits 1, 5, 20, and 40 (or at 1 year) to see if long-term EDTA chelation infusions can reduce lead and cadmium levels. These are harmful metals that when removed or decreased may be related to lowering the risk for heart disease These specimens will be shipped to the central metals laboratory for processing and the results will be in the study database at DCRI
- Each sample will require about 3 tablespoons of blood, and 2 ounces of urine
- Trained medical staff will use a needle to insert a catheter into a vein in your arm
- The chelation infusion will be given slowly, over at least 3 hours
- We will ask you how you are feeling and whether you have any new health problems, new heart problems, or hospital visits

Follow-up Contacts (beginning 6 and 12 months after randomization, and every 4 months until the study ends, for about 15–20 minutes)

- You will be contacted by phone by trained research staff from the Economics and Patient Reported Outcomes Center at Duke Clinical Research Institute (the DCRI Call Center).
- If the research staff cannot reach you, they will call the people you have listed as your contacts and ask how to get in touch with you. If you have chosen a person who is allowed to answer questions for you in your absence, the interview team may call this person and ask questions about how you are doing.
- These interviews will take place every 4 months for up to 5 years.
- You will continue taking your assigned multivitamins and multiminerals or oral placebo.
- You will be asked about changes in how you feel, in your ability to perform your daily activities, if you have had any hospital visits, medications, vitamin use, questions related to your diabetes and your working status.

If you had a hospital visit during the follow-up period, you will be asked to sign a medical release. This will give the study access to any medical records related to that hospital visit.

The DCRI Call Center will also receive a copy of your signed Participant Informed Consent Form and Authorization to Use and Disclose Medical Information. This will be used to obtain copies of your medical records, tests, and bills during the study. This information will help determine the details of any hospitalizations related to your heart disease and the cost effects of the study chelation infusion. At the conclusion of the study, your contact information will be destroyed.

YOUR RESPONSIBILITIES

Taking part in this research study is voluntary. If you choose to take part in this study, your major responsibilities will include:

- Telling the study staff of any changes in your health.
- Telling the study staff if there is any change in your contact information.
- Telling study staff if you need to reschedule an infusion visit.
- Allowing at least 5 hours for each infusion visit.
- On the day of your infusion visit, taking your vitamins after the infusion
- Allowing the study pharmacy to send your multivitamins and multiminerals or oral placebo, to your home through the mail.
- Taking all other medications for your heart disease, diabetes, and other conditions as prescribed by your physician.
- Completing the interviews over the phone.

RISKS AND SIDE EFFECTS

Of the 1,708 people who were in the prior chelation study, there were no more serious study drug complications, including death, in the group that received chelation study drugs when compared to those who received the inactive, or placebo, study drug.

The side effects that other doctors have reported are listed below. In addition, there may be other side effects.

IV Chelation Side Effects

Low Blood Calcium

The IV chelation can cause calcium in the blood to be too low. This can cause tingling, muscle cramps, lightheadedness, severe muscular spasms, low blood pressure, and even heart rhythm problems that could cause death. These symptoms may be seen when the IV chelation is given too quickly. They are hardly ever seen when the IV is given correctly.

Low Blood Pressure

Giving the IV chelation too quickly may cause your blood pressure to drop. Your blood pressure will be checked before and after the IV.

Heart Problems

If your heart is weak, you may be at risk of building water in your lungs, in your ankles, or having rapid weight gain. These symptoms may happen because your heart cannot tolerate the amount of water in the IV.

We will check your weight to make sure you are not retaining fluid. Chelation infusions may be stopped for a short time if your study doctor determines that your weight gain is related to the infusions. Your study doctor may decide to give you a diuretic (water pill) to help prevent any further fluid in your lungs that may lead to shortness of breath.

Low Kidney Function

If your kidneys get worse during the infusions, then the dose will be reduced, or the IV will be stopped.

Flu-like Symptoms

You may develop flu-like symptoms, such as low-grade fevers, sneezing, muscle and joint aches, headaches and watery eyes. These symptoms may occur 4 to 8 hours after receiving the IV.

Death

Death is a very rare complication of IV chelation.

Diabetes

The IV chelation may cause low blood sugar. You should eat a snack before your study visits, and we will watch for symptoms of low blood sugar.

Some participants using continuous glucose monitors (CGMs) may have incorrect readings. This could result in either not giving insulin when it is needed or giving too much insulin. To avoid insulin dosing errors as a result of an incorrect CGM reading you should do the following:

- Do not depend on the results of CGM for insulin dosing while you are receiving an infusion and for 12 hours from the beginning of the infusion.
- If you have a closed loop insulin pump system, you should put your pump into manual mode for 24 hours starting at the time of the infusion.
- If, during the above time periods, you note a low or high reading on your CGM, you should perform a fingerstick measurement to determine if you need insulin.

IV site problems

You might have some discomfort at the needle puncture site. There is also a risk of bruising, swelling, and redness developing at the needle puncture site. Infection at the needle site is a rare risk.

You may also experience these discomforts when having your blood drawn.

During the IV you may experience a “burning-like” sensation at the site of the infusion, or through the vein.

Certain vitamins and minerals that are needed by your body may be excreted (come out in the urine) after chelation. This can cause symptoms such as feeling tired, dry skin, tingling in your hands and feet, a skin rash, diarrhea, and constipation. You will be provided with oral multivitamins and multiminerals to replace these elements.

The effectiveness of some of the medications you are taking may decrease during chelation. You must tell your study doctor about any medications, including prescription, over-the-counter, and herbal supplements, that you are taking while in this study.

Vitamins B_1, B_6, pantothenic acid, and vitamin C also are included in the IV. These vitamins have no significant side effects. However, vitamin C is being used at a higher dose than usual, and at this dose may be associated with kidney stones.

Procaine is a numbing medicine that will help with discomfort at the needle puncture site. The main side effect of procaine is the possibility of allergy.

Any component in the chelation solution could possibly cause allergies. Please tell your doctor if you have any allergies. Symptoms of any allergic reaction can include a rash, hives, itching, and/or difficulty breathing, closing of the throat, or swelling of the lips, tongue, or face. Rarely it can cause death. You will be monitored carefully after administration of the IV solution for signs of an allergic reaction. There are trained medical staff and emergency equipment and medicines available at the study site to treat you in the event of an allergic reaction. **If you think you are having a severe allergic reaction after you leave the study site, dial 9-1-1 and seek medical attention immediately.**

There could be additional side effects from the chelation solution that we cannot predict at this time.

Side Effects of Vitamins and Mineral Pills

Vitamin A, in doses much higher than those used in this study, may cause dizziness, nausea, vomiting, headache, skin damage, mental disturbances, and, in women, infrequent periods.

Vitamin D, in doses much higher than those used in this study, may cause increased blood calcium levels, muscle weakness, anorexia, vomiting, diarrhea, and mental changes.

Vitamin E, in doses much higher than those used in this study, may cause bleeding problems, mostly in people taking anti-clotting medications.

Vitamin K, in doses much higher than those used in this study, may cause allergic-type responses, including rash and itching. If you are taking Coumadin (warfarin), a blood thinner, you should not take Vitamin K without checking with your physician.

Beta-carotene has been related with cancer in participants who smoke. Do not start smoking while you are in this study.

Any component of the oral multivitamins and multiminerals could possibly cause allergies. Please tell your doctor if you have any allergies.

There could be additional side effects from the oral vitamins that we cannot predict at this time.

There also may be other side effects or discomforts, especially to a fetus or embryo. Because the drug in this study is not approved for use in pregnancy, you should not become pregnant while on this study. Your study doctor will discuss this with you. You should not breast-feed a baby while on this study.

There is a possible risk to your privacy. Every effort will be made to maintain your privacy, however this cannot be guaranteed

Your treatment and medical care will not change because you are taking part in this study. Your doctor will continue to make all decisions regarding your proper care.

If you have any questions about the risks or discomforts, contact Dr. «Last_Name» at «Telephone».

NEW FINDINGS

An independent group of medical experts will review the information from this research often throughout this study. You will be told in a timely manner if new information becomes available that may change your mind about participating in this study.

BENEFITS

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

ALTERNATIVE TREATMENTS

If you choose not to take part in this study, it will not affect your other heart treatments as directed and recommended by your doctor. You should continue to use proven standard medicines for diabetes and heart attack patients whether or not you participate in this research study. You may be able to receive chelation therapy and oral multivitamins and multiminerals outside of the study. Ask your study doctor about the risks and benefits of alternative treatments before you take part in this study.

COSTS TO YOU

You or your insurance company will not be charged for the study chelation infusions or for tests required by the study. All the study drugs are provided at no charge to you.

COMPENSATION TO YOU

If you complete all study visits you will receive up to a total of «Total_Comp». If you withdraw from the study before it is completed, you will receive «Per_Visit» for each completed visit. A completed visit means all scheduled study procedures have been carried out.

COMPENSATION FOR RESEARCH-RELATED INJURY

In case of medical illness or injury related directly or indirectly to your participation in this study, you will receive all appropriate treatments. You or your insurance company will be billed for any research-related injury in the ordinary manner; however, you do not waive any of your legal rights or release anyone from liability for negligence by signing this document.

In case of injury, contact Dr. «Last_Name» at telephone number «Telephone».

RIGHT TO WITHDRAW

Your decision to participate is entirely voluntary. You may elect to receive alternative treatment. You may refuse to participate without penalty or loss of benefits to which you are otherwise entitled. Your ongoing medical care will not be affected by your decision to be in this study or to withdraw from the study.

If you decide to participate in this study, you can withdraw at any time. You have the right to change your mind to not have any of your information collected. You have the option to choose to withdraw from all or parts of the study. We ask that you contact Dr. «Last_Name» in writing and let him/her know which specific part of the study that you are withdrawing:

- chelation infusions
- oral multivitamins and multiminerals
- follow-up phone calls

Your study doctor will ask to schedule one last visit with you.

INVOLUNTARY WITHDRAWAL

Your study doctor may ask you to leave this study if he/she decides it is appropriate or necessary. Your study doctor will notify you if this should occur. This in no way will affect your continued medical care and treatment by your physician.

CONFIDENTIALITY

Your study records will be kept private as required by law. Information that could identify you by name will not be used if the results of this study are published. You will be assigned a unique code number at the time of study entry, and your name will be available on a highly restricted basis to your clinical enrolling site, to the Central Pharmacy so you can get your study medicines to the DCRI Call Center, so they can reach you after the infusions are over and find out how you are doing, and to the Mount Sinai Clinical Coordinating Center. At each site, all your data will be kept in secure computers available by password only, and behind secure firewalls (high-security computer networks). Your personal health information (PHI) will be protected.

Government agencies, such as the Food and Drug Administration, may inspect the study records. This includes the information about you, collected for study purposes.

AUTHORIZATION TO COLLECT, USE AND DISCLOSE MEDICAL INFORMATION

If you sign this consent form, you are giving your permission for Dr. «Last_Name» and his/her study team to report your study-related test results and medical information to the following people or groups for research:

- National Institutes of Health (NIH)
- Department of Health and Human Services (DHHS)
- United States Food and Drug Administration (FDA)
- Other government agencies in other countries
- Sterling Institutional Review Board (IRB)
- Duke Clinical Research Institute (DCRI)
- Mount Sinai Clinical Coordinating Center
- The TACT2 Central Pharmacy
- The TACT2 Central Laboratory
- The TACT2 Central Metal Laboratory
- The TACT2 Biorepository Laboratory

Your study information may be released to the groups listed above. If your study information is reviewed by these people, they may need to see your entire medical record; it is possible that your Social Security number may be included in the records reviewed. Because of this, it cannot be assured that your confidentiality will always be protected. It is possible that your information will be shared (re-disclosed) in a way that it would no longer be protected. However, this access to your records will be granted without violating your confidentiality to the extent permitted by applicable laws and regulations. By signing this form, you are authorizing this access to your records.

The health information about you that the people or groups listed above may give to the researchers to use in this research study includes**:**

- Medical History and current medications
- Blood pressure
- Heart rate
- Height and weight
- Hospitalizations, clinic visits, emergency department visits
- New and existing medical records
- Laboratory results
- Types, dates and results of various tests and procedures

Research information collected about you might be put in your medical record. It's possible that you may not be able to see the research study information that has become part of your medical record until the entire research study is over.

A public data set that is not identifiable with your personal information will become available when the study has been completed. Other scientists may use the information to perform additional research that has not been thought of yet.

This permission (also called an authorization) will have no end date.

You may also take away (or withdraw) your permission for the use of your protected health information at any time. If you choose to withdraw your permission, you must write your study doctor a letter.

The study doctor's mailing address is «Company_Name», «Address», «City_State_ZIP». The study doctor will still be able to use the health information collected about you before you withdrew your permission. Information that has already been sent to the sponsor of the study cannot be taken back.

If you withdraw your permission after you have entered the study, you cannot continue participating in the study. If you refuse to give permission or withdraw your permission, your medical care and your relationship with the health care providers at the study center will not be affected.

QUESTIONS

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If you have questions, concerns or complaints about the research study or you experience a research-related injury, please contact Dr. «Last_Name» or the study staff at «Telephone» or «Telephone_2_if_applicable».

If you have questions regarding your rights as a research participant, or if you have questions, concerns, complaints about the research, would like information, or would like to offer input, you may contact the Sterling Institutional Review Board Regulatory Department, 6300 Powers Ferry Road, Suite 600-351, Atlanta, Georgia 30339 (mailing address) at telephone number 1-888-636-1062 (toll free).

STATEMENT OF CONSENT

The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have received answers to any questions. I have been told whom to contact if I have additional questions.

I voluntarily consent to participate in this research study and I understand that I may withdraw my consent at any time without penalty or prejudice to my subsequent care. I give my permission to the study doctor to use and disclose my protected health information as described in this consent form.

I will receive a signed copy of this form, which has 15 pages.

I have not waived any of my legal rights by signing this document.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____
Printed Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Witness (if applicable)

_____ _____
Signature of Witness (if applicable) Date

*A witness is not required unless the participant is unable to read (such as blind or illiterate). If a witness is present, however, the witness must observe the entire informed consent process, including participant signature.

INFORMED CONSENT FORM FOR BLOOD AND URINE BIOREPOSITORY

The National Institutes of Health (NIH) would like to keep in storage some of the blood and urine specimens that are taken during the study. If you agree, the blood and urine will be kept and may be used in future research to learn more about heart attacks and other diseases. These specimens will be stored at the study central metal and biorepository laboratory and will be used for research studies in the future. You have the right to not have your samples placed in the biorepository and/or removed from the biorepository.

Any research study using your blood and urine must be approved by an Institutional Review Board (IRB) that provides oversight for human subject rights in research studies. The research that may be done with your blood and urine is not designed to help you specifically. It might help people who have heart attacks and other diseases in the future. Reports about research done with your blood and urine will not be given to you or your doctor. These reports will not have any information that could identify you by name and will not be put in your health records. The research using your blood and urine will not affect your care.

The choice to let the NIH keep the blood and urine for future research is up to you. No matter what you decide to do, it will not affect your care in this study. If you decide now that your blood and urine can be kept for research, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want NIH to use your samples and they will no longer be used for research. Otherwise, the blood and urine may be kept until it is used up, or until NIH decides to destroy it.

In the future, people who do research may need to know more about your health. While NIH may give them reports about your health, they will not give them your name, address, phone number, or any other information that will let the researchers know who you are. Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, the results will not be told to you. You are not consenting to have these results put in your health records. Your blood and urine will be used only for research and will not be sold. The research done with your blood and urine may help to develop new products in the future, but you will not get paid.

The possible benefits of research from your blood and urine include learning more about what causes heart attacks and other diseases, how to prevent them, and how to treat them. The greatest risk to you is the release of information from your health records. NIH will protect your records so that your name, address, and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any blood and urine collected and stored by NIH.

Please read the following sentence and think about your choice. After reading the sentence, indicate "yes" or "no." If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and use of your blood and urine, you may still take part in this study.

I agree to the use of my blood and urine for other research studies: _____Yes _____No

_____ _____
Participant's Signature Date