Pilot Study of Zinc Supplementation and Cardiovascular risk in HIV

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UNIVERSITY HOSPITALS CLEVELAND MEDICAL CENTER
CONSENT FOR INVESTIGATIONAL STUDIES
(v. 12.2018)

Project Title: Pilot Study of Zinc Supplementation and Cardiovascular Risk in HIV

Principal Investigator: Grace McComsey, M.D.

Key Information: The following is a short summary to help you decide whether or not to be a part of this study. More detailed information is listed later on in this form.

Why am I being invited to take part in a research study?
We invite you to take part in a research study because you have HIV and you are receiving HIV medications.

Things I should know about a research study
- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Introduction/Purpose
You are being asked to take part in this research study because you are infected with Human Immunodeficiency Virus (HIV) and you are receiving HIV medications. People living with HIV have early signs of damage to their blood vessels. In this trial, the investigators are observing early indicators of vascular (blood vessel) damage that leads to heart disease seen in people with HIV. One such early indicator is zinc deficiency, which is thought to play a role in this damage. Ninety-five (95) subjects will be given zinc supplements on this study; 63 subjects will receive two 45 mg (or 90mg) capsules and 32 subjects will receive two matching capsules of placebo drug. The purpose of this study is to determine if zinc can reduce risks of heart disease. To qualify for this study, you must have a viral load of 400 copies/mL or less for the last 4 months and be taking your HIV medications for at least 12 weeks (and have taken HIV medications for a total of 6 months or more).

Before you decide whether or not to take part in this study, the study team would like to explain the purpose of the study, how it may help you, any risks to you, and what is expected of you.

Key Study Procedures
- We expect that you will be in this research study for 24 weeks (a total of 7 study visits).
- You will be asked to
  1. Complete 7 study visits over 24 weeks
  2. Have blood tests
  3. Have height, weight, waist, and hip measurements taken
  4. Have a brief physical examination
  5. Have an EndoPat procedure
  6. Have an AGE (advanced glycation end product) test
  7. Have a REE (Resting Energy Expenditure) test
  8. Answer questions about your health and your smoking habits

9. Measurements of your waist and hip
10. Complete a 10 - 30 minute computer questionnaire that measures your brain's ability to think, understand, and remember Take daily zinc supplements that we provide
11. Take your HIV medication while in the study (unless your doctor does not think you should)

More information about the study procedures can be found under "Detailed Study Procedures".

Key Risks

- Drawing blood: pain, bleeding, and bruising at the site of the blood draw; other rare risks: lightheadedness and/or fainting or infection.
- Fasting: feeling anxious, irritable, or hungry
- Measurements: minimal discomfort in exposing your waist and hips
- Pregnancy: ***Zinc is not safe for unborn babies***.
- Zinc Supplementation: nausea, vomiting, abdominal pain
- **More information about the risks of this study can be found under "Detailed Risks."**

Benefits

There may be no direct benefit to patients from participating in this study. Your participation in the study will allow collection of valuable information about the effect of HIV infection on cardiovascular disease. This information may be useful to you and other people with HIV disease.

Alternatives to Study Participation

Alternatives to your participation in this study are not to participate and to receive the standard of care from your primary care doctor.

Detailed Information: The following is more detailed information about this study in addition to the information listed above.

Detailed Study Procedures

Screening I/II

Before you enter, you will be asked to visit the clinic at least once to be screened and ensure that you meet the requirements for entry into the study. Screening may take place on the same day as a normally scheduled clinic appointment. Before any tests can be obtained as part of this study, you would have to decide whether or not you would like to participate in this study. If you choose to enroll, this informed consent form will be signed. A zinc level will be obtained via a blood draw. Once the results are available, if your level is 75 or below you would be asked to return to clinic for Screening II evaluations. At this evaluation a targeted physical examination will be performed and the HIV-1 RNA, and HIV testing to confirm HIV status will be obtained from the clinical chart as these are a part of routine care. For woman of reproductive potential, a urine sample will be taken for pregnancy test. Some of the plasma and serum will be stored for potential future testing such

as additional tests for inflammation, cardiovascular markers, endothelial function markers, oxidative markers. These blood samples will be batched and the tests will be done at the end of the study and are part of this study.

Study Entry/On-study evaluations

For the first study visit (the entry visit into the study), you will be asked to "fast." That is, you will be asked ***not to eat or drink anything*** except your HIV medications and the usual amounts of plain water for at least 8-hours before you come in for this visit. If you must take medication with food, you will be asked to bring your medicines with you to the study visit so that you can take them with food after your blood has been drawn and tests has been completed. This visit must be within 30 days of your screening visit. The following procedures will be done at the first visit.

- At this visit you will have a medical history and a targeted physical exam done. You will also be provided with questionnaires to assess your diet, level of physical activity, alcohol smoking intake and substance use.
- You will then have approximately 8 tablespoons of blood taken from a vein in your arm for laboratory tests. These tests include: tests to measure the amount of blood vessel damage that is present, tests to measure the amount of inflammation in your body, tests to check your blood sugar and insulin levels (insulin is the hormone that controls blood sugar levels in the body), a test for lipids like cholesterol, a complete blood count to check the number of white and red blood cells as well as platelets (the cells that help blood clot), a test to check your electrolytes (salts in your body) and tests for your kidney and liver function. A HIV viral load and CD4 count will be obtained from your clinical chart as these will be done as part of routine care.
- EndoPAT will be performed at this visit. This is a painless test that involves a finger probe to measure blood flow. A blood pressure cuff will be applied to your upper arm and inflated for approximately 5 minutes. After release of the cuff, the machine will measure the return of normal blood flow. This test will take about 30 minutes to do. Results will not be available until the end of study.
- A noninvasive test called the AGE Reader (at visits Entry, week 12, and week 24). This test involves placing your forearm over a window that uses ultraviolet light to detect advanced glycation end products (AGE).
- You will have a test to measure Resting Energy Expenditure (REE). You will be required to rest for about 20 min and then a nose clip will be placed over your nose for about 10 minutes. You will have to breathe normally by mouth into a device during this time. The nose clip can be slightly uncomfortable for some people. Each session will take about 20-30 minutes.
- You will be given a zinc supplement capsule to be taken every day while on study. You will be randomly given a dose of 90 mg (two capsule), or 90 mg (two 45 mg capsules) of matching placebo, which you will take once per day with food. If you lose or misplace the capsules at any time, please call us to receive replacements at **216-844-2739**.
- You will be asked to give urine and stool specimens which will be stored for possible future testing for substances that could indicate organ damage. Some of your blood will be stored for future testing such as additional tests for blood vessel damage, tests that indicate risk of heart disease, additional tests for bone

metabolism, inflammation, and additional testing of oxidative markers (markers of levels of free radicals in your blood). Free radicals are waste substances produced by our body that can damage tissues, like the heart vessels. These blood samples will be batched and the tests will be done at the end of the study. In addition, some of this stored blood may be used for measurements of antiretroviral concentrations. Results will not be available until the end of study.

- Cognivue: At each visit you will be asked to answer a series of questions to measure your brain's ability to think, make decisions, detect differences between things, movement skills, remembering things and other skills using a computer monitor with a small wheel that you turn to indicate your answers. This test takes about 10 - 30 minutes to complete. Changes in how your brain works can be due to many things; some of these are being looked at in this study. The results of this test will not be provided to you because the test is not a routine clinical test and no change in your treatment will result

- Your total duration of the study visit will be approximately 1 hour.

The follow-up study visits at the clinic visits will be at 6, 12, 18 and 24 weeks (end of study). You will need to ***come fasting*** for all visits. ***No food or drinks for 8-hours*** before these visits. At each of these visits, patients will be asked about symptoms or any change in health status. A short targeted physical exam will be done.

- You will bring your zinc capsules to all visits. We will count them and return them or order more capsules as needed.
- At all visits, a HIV viral load and CD4 count will be obtained from your clinical chart as these will be done as part of routine care.
- Approximately 8 tablespoons of blood will be collected at all visits.
- At Entry, week 12 and week 24 additional testing will be done to check for inflammation markers, oxidative markers, glucose and insulin. Lipids, HIV-1 RNA, and CD4 count will be obtained from the clinical chart. Also a urine pregnancy test will be done if applicable. At all visits some of the blood will be stored for potential future testing such as additional tests for inflammation, oxidative stress, immunology, and cardiovascular and metabolic markers. Patients will also be asked about diet and level of physical activity.
- At week 24 only you will complete the cognivue assessment

Premature study discontinuation

If you withdraw from the study before week 24, you will be asked to come back for final study evaluations. The evaluations to be performed at this premature study visit will be the same as the evaluations outlined for week 24.

Detailed Risks
The risks for taking part in this study are:

Blood Draw Risks associated with drawing blood include: pain, bleeding, and bruising at the site of the blood draw. Other rare risks include: lightheadedness and/or fainting or infection at the site.

Zinc Supplementation At the dose used, uncommon side effects include nausea, vomiting, abdominal pain (gastritis). At higher doses and when used for a long periods (years), copper deficiency and related anemia may happen. This is an extremely unlikely since we are only giving 90 mg, daily and for up to 24 weeks. Such doses have been shown to be safe even when given for 12 months to elderly frail subjects. In addition, in diseases such as Wilson's disease, zinc is given at a dose of 50 mg three times daily for prolonged durations. We will closely monitor your blood draws for chemistries, hematology and liver enzymes every 6 weeks, and as needed between study visits.

Fasting Some individuals find fasting to be bothersome. It may make some individuals feel anxious, irritable, or hungry. Patients who are required to take their morning medications with food should wait until after the visit has been completed to take their medications. In addition, there may be other risks or side effects that cannot be anticipated at the present time. You will be carefully monitored during the entire study.

Pregnancy Zinc may not be safe for unborn babies. Women must have a pregnancy test before they enter this study. The pregnancy test must be negative. In addition, **if you think you may be pregnant** at any time during the study, you are to tell the study staff right away. In the event that you become pregnant while on study, you will be taken off study, and no further evaluations or tests will be performed as part of the study. If you are of reproductive potential, you must agree to use at least 2 forms of birth control until 6 weeks after the study ends.

EndoPAT This is a painless imaging tests and have no short or long-term risks. The EndoPAT test may be mildly to moderately uncomfortable because of the blood pressure cuff that is applied tightly to your arm.

AGE Reader Skin Measurement Some individuals are known to have, or are at risk for, photosensitivity reactions (e.g., sensitive to ultraviolet light, or taking medication known to cause photosensitivity). We will exclude from the study those potential participants who report having these risk factors. However, there is a negligible risk that these participants might not be known until they develop a reaction.

If you have a lot of hair on the underside of your forearm, as determined by the investigator, a small area (2" x 3") will be shaved with a safety razor and shaving cream before being tested with the research instrument. Only investigators will operate the device and perform the scan.

Resting Energy Expenditure (REE): There are no risks associated with REE.

Cognivue: There are no physical risks associated with completing this computerized questionnaire. The test will take about 10 - 30 minutes to complete during each visit.

Other risks You should tell your study doctor or study nurse about all other drugs you are currently taking including non-prescription medications, alcohol, recreational drugs, and herbal products. These substances, if taken with the study medication, can result in dangerous interactions. If you have questions about the drug that will be used in this study and the potential for interaction with other substances that you take, you are instructed to ask your study doctor to provide additional information.

There is a risk of breach of confidentiality which means that someone who is not listed in this

form might view your data either by accident or from malicious actions they take to hack the data. We are protecting against this by only storing information that can be directly linked to you on UH computers, in password-protected files which are behind firewalls.
In addition to the risks and discomforts listed here, there may be others that are currently not known.

Consequences of Withdrawing or Being Discontinued from the Research
If you withdraw from the study before week 24, you will be asked to come back for final study evaluations. The evaluations to be performed at this premature study visit will be the same as the evaluations outlined for week 24.

Financial Information
There is no cost to participants for the study related clinic visits, examinations or laboratory test required by this study.

- To receive payment you must agree to complete a W-9 form which requires you to provide an address and social security number to the accounting department. This payment to you may be considered taxable income by the IRS. You will be issued a 1099-Misc form only if payment exceeds $600 from all studies in which you are participating, in a fiscal year.

Medical costs of other treatment or examinations outside of the study will be the responsibility of the patient or their insurance company. If during the study, subjects suffer from symptoms requiring any of the tests done within the study evaluations (but outside of the study window period), they will have these tests ordered by their primary care provided and charged to the subject insurance.

Compensation

For completed study visits screening II, week 6 and week 18, patients will receive $25.00 that day. Entry, week 12 and week 24, patients will receive $50.00 that day (total of $225 for completing the entire study). The screening I visit a food voucher and either RTA pass or parking pass will be provided. This payment will help cover the expense of childcare, transportation and time off work that patients may incur as a result of being in this study. To help with the cost of gas, for participants traveling 20-40 miles one way for their appointments, they will also be given a $15.00 gas card to cover the cost of the transportation. Participants traveling > 40 miles one way for their appointments will also be given a $30.00 gas card to cover the cost of transportation. Subjects will be asked to fast (nothing to eat or drink for 8 hours prior to visit) at entry, week 6, week 12, week 18 and

week 24, therefore a $5.00 meal voucher will be provided for subjects to use in the University Hospitals cafeteria. In addition either one all day RTA pass will be provided or a parking voucher to use in designated University Hospitals parking garages will be provided to cover the cost of transportation.

Research-Related Injury
If injury occurs as a result of your involvement in this research, medical treatment is available from University Hospitals or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

Clinically Relevant Research Results
Most tests done on samples in research studies are only for research and have no clear meaning for health care. If the research with your identifiable information or samples gives results that do have meaning for your health, the researchers will provide your physician with a copy of your results.

Contact for Future Research
Our study team may have additional research studies in the future. We would like your permission to contact you in the future if we think you could be a potential participant in one of our studies. Please check one of the boxes below that indicates your choice to be contacted for future research.

- ☐ Please contact me by _____ for future research opportunities.

- ☐ Please do not contact me for future research opportunities.

Clinical Trial Information
U.S. NATIONAL INSTITUTES OF HEALTH (NIH) CLINICAL TRIAL DATABASE: A description of this clinical trial will be available on http:///www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time to find out information about the trial and basic results.

Student/Employee Rights
Choosing not to participate or withdrawing from this study will not affect your employment or class standing, nor will the results be shared with your supervisor.

Termination of Participation
Your participation in this study may be discontinued by the sponsor or investigator without your consent if:

- The study is cancelled by the site's institutional review board (IRB; a committee that watches over the safety and rights of research participant), the sponsor, or the Food and Drug Administration (FDA).
- You have a bad effect from the study medication and/or procedures.
- Your doctor decides it is in your best interest.
- You become pregnant.
- You become incarcerated.
- You do not come to 2 visits in a row.

Confidentiality

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally. All laboratory specimens, evaluation forms, reports, and other study materials will be identified by a coded number to maintain participant confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done with coded numbers only.

If identifiers are removed from your identifiable private information or identifiable samples that are collected during this research, that information or those samples could be used for future research studies or distributed to another investigator for future research studies without your additional informed consent.

In this study, you will be asked about illegal activities (illicit drug use). The researchers will keep information about you as confidential as possible, but complete confidentiality cannot be guaranteed. On rare occasion, courts have subpoenaed research records.

- The results of your examinations will be collected in a centralized computer or data registry at University Hospitals Cleveland Medical Center.
- If identifiers are removed from your identifiable private information or identifiable samples that are collected during this research, that information or those samples could be used for future research studies or distributed to another investigator for future research studies without your additional informed consent.

Privacy of Protected Health Information (HIPAA)

The Health Insurance Portability & Accountability Act (HIPAA) is a Federal law that helps to protect the privacy of your health information and to whom this information may be shared within and outside of University Hospitals. This authorization form is specifically for a research study entitled "Pilot Study of Zinc Supplementation and Cardiovascular Risk in HIV" and will tell you what health information (called Protected Health Information or PHI) will be collected for this research study, who will see your PHI, and in what ways they can use the information. In order for the Principal Investigator, Grace McComsey, and the research study staff to collect and use your PHI, you must sign this authorization form. You will receive a copy of this signed Authorization for your records. If you do not sign this form, you may not join this study. Your decision to

allow the use and disclosure of your PHI is voluntary and will have no impact on your treatment at University Hospitals. By signing this form, you are allowing the researchers for this study to use and disclose your PHI in the manner described below.

Generally, the Principal Investigator and study staff at University Hospitals and Case Western Reserve University who are working on this research project will know that you are in a research study and will see and use your PHI. The researchers working on this study will collect the following PHI about you: your demographic information, such as your age, ethnicity and body mass index (BMI); your medical history, including information about medical conditions that may affect your treatment, conditions related to mental and behavioral health, psychiatric disorders, alcohol and drug dependence or abuse, specific information about your antiretroviral therapy and any other medications you are taking just before and during the research study; and numbers or codes that identify you, such as your social security number, medical record number, and research study case number. This PHI will be used to evaluate the safety of semaglutide, as well as lipids, blood sugar and the body's sensitivity to insulin. Your access to your PHI may be limited during the study to protect the study results.

Your PHI may also be shared with the following groups/persons associated with this research study or involved in the review of research: study nurses and coordinators; staff involved in evaluations and testing described in this protocol; other staff from the Principal Investigator's medical practice group; University Hospitals, including the Center for Clinical Research and the Law Department; Government representatives or Federal agencies, when required by law.

Your permission to use and disclose your PHI does not expire. However, you have the right to change your mind at any time and revoke your authorization. If you revoke your authorization, the researchers will continue to use the information that they previously collected, but they will not collect any additional information. Also, if you revoke your authorization, you may no longer be able to participate in the research study. To revoke your permission, you must do so in writing by sending a letter to Grace McComsey, M.D. at 11100 Euclid Ave, Lakeside 1400, Cleveland, OH, 44106. If you have a complaint or concern about the privacy of your health information, you may also write to the UH Privacy Officer, Management Service Center, 3605 Warrensville Center, MSC 9105, Shaker Heights, OH 44122 or to the Federal Department of Health and Human Services (DHHS) at DHHS Regional Manager, Office of Civil Rights, US Department of Health and Human Services Government Center, JF Kennedy Federal Building, Room 1875, Boston, MA 02203. Complaints should be sent within 180 days of finding out about the problem.

The researchers and staff agree to protect your health information by using and disclosing it only as permitted by you in this authorization and as directed by state and Federal law. University Hospitals is committed to protecting your confidentiality. Please understand that once your PHI has been disclosed to anyone outside of University Hospitals, there is a risk that your PHI may no longer be protected; however, other Federal and State laws may provide continued protection of your information.

UNIVERSITY HOSPITALS CLEVELAND MEDICAL CENTER
CONSENT FOR INVESTIGATIONAL STUDIES
(v. 12.2018)

Project Title: Pilot Study of Zinc Supplementation and Cardiovascular Risk in HIV

Principal Investigator: Grace McComsey, M.D.

Summary of Your Rights as a Participant in a Research Study Your participation in this research study is voluntary. Refusing to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed. In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating. If you experience physical injury or illness as a result of participating in this research study, medical care is available at University Hospitals Cleveland Medical Center (UHCMC) or elsewhere; however, UHCMC has no plans to provide free care or compensation for lost wages.

Disclosure of Your Study Records
Efforts will be made to keep the personal information in your research record private and confidential, but absolute confidentiality cannot be guaranteed. The University Hospitals Cleveland Medical Center Institutional Review Board may review your study records. If this study is regulated by the Food and Drug Administration (FDA), there is a possibility that the FDA might inspect your records. In addition, for treatment studies, the study sponsor and possibly foreign regulatory agencies may also review your records. If your records are reviewed, your identity could become known.

Contact Information
_____ has described to you what is going to be done, the risks, hazards, and benefits involved. The Principal Investigator, Grace McComsey, MD, can also be contacted at 216-844-5936. If you have any questions, concerns or complaints about the study in the future, you may also contact the researchers later.

If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: concerns regarding the study, research participant's rights, research-related injury, or other human subject issues, please call the University Hospitals Cleveland Medical Center's Research Subject Rights phone line at (216) 983-4979 or write to: President, University Hospitals Cleveland Medical Center, The Center for Clinical Research, University Hospitals Cleveland Medical Center, 11100 Euclid Avenue, Lakeside 1400, Cleveland, Ohio, 44106-7061.

Signature
Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate, that you have asked any questions about the study that you may have, and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

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Principal Investigator: Grace McComsey, M.D.

x	
Signature of Participant	Date/Time
x	
Printed Name of Participant	

x	
Signature of person obtaining informed consent	Date/Time
x	
Printed name of person obtaining informed consent	

x	
Signature of Witness	Date/Time
x	
Printed Name of Witness	