Written Consent to Participate in a Research Study

Project Title: The effect of omega-3 supplementation on postoperative delirium in elderly patients undergoing major cardiac surgery: a prospective, randomized, controlled trial.
Principal Investigator Name: Quinn Johnson, MD
Sponsor: Department of Anesthesiology and Perioperative Medicine
IRB Assigned Project Number: 2099184
Consent Version: 4

Key Information About the Study

You are being asked to participate in a clinical trial. The purpose of the clinical trial is to determine whether supplementation of omega-3 fatty acids via the prescription drug, omega-3 ethyl esters, prior to cardiac bypass surgeries decreases the incidence of postoperative delirium in elderly patients. omega-3 ethyl esters is a prescription medication currently used to lower triglyceride levels, a type of fat in the blood. Postoperative delirium is defined as a short-term change in mental state after surgery caused by anesthesia.

You are being asked to participate by: (1) taking a supplement prior to your scheduled surgery and throughout the study and (2) being asked questions daily regarding your mental state after surgery.

There are no known direct benefits to this study.

Some possible risks may include increased bleeding during surgery, although research shows that taking omega-3 ethyl esters before surgery is unlikely to cause bleeding problems. There is also a limited risk for the loss or misuse of your protected health information. Despite this, medical staff are trained in the protection of this information and preventative steps are in place for to monitor the access and storage of your information as part of this study.

Please read this form carefully and take your time. You are encouraged to discuss this study with your family, friends, or doctor if you want. Let us know if you have any questions before participating. The research team can explain words or information that you do not understand. Research is voluntary and you can choose not to participate. If you do not want to participate or choose to start then stop later, there will be no penalty or loss of benefits to which you are otherwise entitled.

There may be reasons why you are not allowed to take part in this study. The study doctor or staff will discuss these reasons and review with you why you may not be allowed to enter the study or why you may be removed from the study at a later date.

Purpose of the Research

You are being asked to participate in this study because you are 65 years of age or older and undergoing an on-pump open heart surgery. There are additional requirements to participate in this study which the study staff will discuss with you.

The purpose of the study is to determine if omega-3 ethyl esters will decrease the incidence of postoperative delirium in adults undergoing cardiac bypass surgeries and whether there are any side effects. The use of omega-3 ethyl esters in this project is considered off-label, meaning omega-3 ethyl esters has not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of postoperative delirium. Omega-3 ethyl esters is approved by the FDA for a different use.

Postoperative delirium typically occurs in older patients 65 years and older who undergo anesthesia. It is characterized by a change in mental state following surgery. Postoperative delirium typically presents within 3 days after surgery. Delirium is often short term, usually only lasting for a few hours or days, but may continue for months in rare cases. There is no known prevention method or cure for postoperative delirium. Some potential causes have been identified, including inflammation and stress caused by surgery and anesthesia.

Omega-3 ethyl esters are the purified form of omega-3 fatty acids. Omega-3 fatty acids are known to be both antioxidants and anti-inflammatory. Many people are familiar with omega-3 fatty acids, as they are present in over-the-counter fish oil supplements. Omega-3 ethyl esters are similar in composition and appearance to a fish oil pill, but it is purer than an over-the-counter supplement and it is regulated by the FDA, unlike dietary supplements. Some literature has found that patients with postoperative delirium have decreased levels of omega-3 fatty acids prior to and during their delirium. Therefore, we are researching the effect of omega-3 ethyl esters, which contains omega-3 acids, on patients who are at high risk of developing postoperative delirium.

In this study, we want to find out if prescription omega-3 ethyl esters (also called the study drug in this form) works better than routine care for the treatment of postoperative delirium. Omega-3 ethyl esters are a purified form of omega-3 fatty acids. To do this, there will be 3 study groups:

- One group will take 4 capsules of omega-3 ethyl esters
- One group will take 2 capsules of omega-3 ethyl esters
- One group will not receive any drug

A regular dose of omega-3 ethyl esters is 4 capsules for the treatment of high triglycerides.

We will compare the study drug against routine care in people at high risk of postoperative delirium and see which one is more effective at reducing the incidence of postoperative delirium.

We will check the symptoms of everyone in the groups for at least 3 days after your surgery and will review your medical chart 1 month following your surgery and compare the results.

Omega-3 ethyl esters may work better or have different side effects than routine care, but we won't know until we do more research studies.

What will happen during the study?

There will be about 90 participants in this study.

Because we don't know which of the study drugs is best, we will "randomize" you into one of the 3 study groups. "Randomize" means putting you into a group by chance. It is like flipping a

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coin or pulling a number from a hat. You will have a one in three chance of being placed in any group. A computer program chooses which group you go in. You and the study doctor cannot choose which group you go into.

If you take part in this study, you will have the following tests and procedures:

Before Surgery:

- The study doctor or staff will explain the study to you and obtain your informed consent.
- Review your medical history.
- Review your prior and current medications.
- Review the inclusion and exclusion criteria to see if you can be in the study.
- Explain and review the forms with you that will be used to ask you study questions.
- Complete the study questions (research only procedure).
- Take the study drug before your procedure (research only procedure).

After Surgery:

- You will take the study drug for 3 days after your surgery (research only procedure).
- You will be asked simple questions once a day about your mental state (research only procedure) for at least 3 days.
    - If you have delirium symptoms and they continue past your third day post-surgery, we will continue to follow up with you until your symptoms stop.

Your surgery will be performed as usual.

Will you share with me any results or health problems/issues that you learn about me while in the study?

This study will not reveal any incidental findings.

How long will I be in the study?

Your participation is expected to last one month. Your active participation will last for at least 3 days following your surgery and will continue until your delirium symptoms stop, if you experience postoperative delirium at all. You will be considered finished with the study one week after you are discharged from the hospital.

Are there benefits to taking part in the study?

We don't know if this study will help you. Your condition may get better, but it could stay the same or even get worse. We hope that this study will help us to learn more about omega-3 ethyl esters and to develop new treatments for postoperative delirium in the future.

Information learned from the study may help other people in the future.

What are the possible risks of participating in this study?

There are risks expected when taking part in this study. There are some that we know about and some we may not know about yet. Some risks include:

The most common side effects of omega-3 ethyl esters are:

- Unpleasant or "fishy" taste
- Bad breath
- Belching
- Heartburn
- Indigestion

Other side effects include:

- Headache
- Nausea
- Constipation
- Diarrhea
- Rash
- Itching
- Vomiting
- Infection
- Flu symptoms
- Back pain
- Decreased blood pressure
- Changes to ALT and LDL-C blood tests
- Increased risk of heart rhythm problems
- Excessive bleeding during surgery

Research has shown that omega-3 ethyl esters and omega-3 fatty acids do not increase bleeding during cardiac surgery or significantly decrease blood pressure, but it is still possible.

To help lower these possible risks, we will monitor you closely as is standard for our institution. If you have any history or diagnosis of bleeding, you will not be able to participate in this study. If you do have excessive blood loss during surgery, your surgical team may choose to transfuse blood following standard procedure. Your healthcare team will monitor you closely during and after your surgery to ensure your wellbeing. Your study staff will review your electronic medical records to evaluate your wellbeing while you are a part of this study.

Patients that have diabetes mellitus may already have high triglyceride levels as a result of their diabetes. It is recommended that patients talk to their doctor before taking Omega-3 ethyl esters. A medical doctor will review your electronic medical record prior to consent to ensure you are eligible for the study and to ensure you can safely participate. All patients, regardless of diabetes diagnosis, will be monitored closely during their hospital stay as is standard of care for the facility. Additionally, you will undergo blood draws as standard of care while you are in the

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hospital. If a your triglyceride level is too high during the study, you may be removed from the study and the medication will be stopped immediately.

We will tell you about any new important information we learn that may affect your decision to continue to participate in this study.

You will be put into a group by chance. The medication you receive may turn out to be less effective or have more side effects than that in the other groups.

What other choices do I have if I don't want to be in this study?

You are not required to be in this study. You can simply choose not to participate.

Will I receive compensation for taking part in this study?

You will not be compensated for taking part in this study.

Are there any costs for participating in this study?

The study will pay for all research tests and procedures. You and/or your health plan/insurance will not be billed for tests and procedures that are done for research only. The following will be considered research only procedures:

- Cognitive assessments
- Taking the study drug

You and/or your health plan/insurance will be billed for everything that is considered standard of care. This includes tests and procedures you would receive without being in this study. Some health plans/insurance companies will not pay for these costs for people who are in research studies. Check with your plan/company to find out what they will pay for.

Other costs to you from being in this study may include testing or treatment for existing or new health conditions, insurance co-payments for doctor visits, transportation, parking, childcare, and/or time off work.

A social worker and financial counselor are available to discuss concerns with you. Please let the research staff know if you would like to visit with them and an appointment will be made.

You should discuss any questions about costs with the researchers before agreeing to participate.

Will information about me be kept private?

The research team is committed to respecting your privacy and keeping your personal information confidential, including health information. We will make every effort to protect your information to the extent allowed by law. Your records will be given a code number and will not contain your name or other information that could identify you. The code number that connects your name to your information will be kept in a separate, secure location.

The FDA may inspect these records since the study is FDA regulated.

When the results of this research are shared, we will remove all identifying information so it will not be known who provided the information. Your information will be kept as secure as possible to prevent your identity from being disclosed.

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We will scan a copy of this consent form into your medical record. We may also record your research information, including the results of tests and procedures, in your medical record if the information could be useful for future treatment.

We may share what we collected from you as part of this research, after removing your identifiers, for future research without additional informed consent from you.

Permission to Use your Protected Health Information:

State and federal privacy laws (HIPAA) protect the use and release of your health information. If you decide to take part in this study, you also give us your permission to use your private health information, including the health information in your medical records and information that can identify you.

You have the right to refuse to give us your permission for us to use your health information. However, doing so would mean that you could not take part in this study.

Some identifiers about you will be obtained from your health records and are necessary for this research. The identifiers will include your name, dates related to you, phone numbers, email addresses, medical record number, account numbers, health plan beneficiary number, photos, and other characteristics that could identify you.

We may share any of this information with the following:

- Authorized members and staff of the University of Missouri Institutional Review Board (IRB).
- Laboratories and other individuals and organizations that may need to see your health information in connection with this study.
- Study monitors and auditors who make sure that the study is being done properly.
- Government agencies and public health authorities, such as the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS), and the Office for Human Research Protections (OHRP)

Any research information shared with outside entities will not contain your name, address, telephone or social security number, or any other personal identifier unless it is necessary for review or required by law.

The people who get your health information may not be required by Federal privacy laws (such as the HIPAA Privacy Rule) to protect it. Some of those people may be able to share your information with others without your separate permission.

Your permission for us to use and/or release your information will not expire unless you cancel your permission in writing.

<u>You can cancel your permission at any time by writing to:</u>

Investigator's Name: Quinn Johnson, MD

Institution: University of Missouri School of Medicine

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Department: Anesthesiology & Perioperative Medicine

Address: 1 Hospital Dr., DC005.00, Columbia, Missouri, 65212

The information we have already collected may still be used for this clinical trial, but we will not collect anymore information after we receive your letter.

You have the right to access your protected health information that is obtained or created during your clinical care.

You will not be allowed to access your protected health information that is obtained or created for research-only purposes during this research project until the end of the study.

If you have not already received a copy of the University of Missouri Health Care Privacy Notice, you may request one. If you have any questions or concerns about your privacy rights, you may contact the Privacy Officer at 573-882-9054.

What if I am injured during the study?

It is not the policy of the University of Missouri to compensate human subjects in the event the research results in injury.

The University of Missouri, in fulfilling its public responsibility, has provided medical, professional, and general liability insurance coverage for any injury in the event such injury is caused by the negligence of the University of Missouri, its faculty and staff. The University of Missouri also will provide, within the limitations of the laws of the State of Missouri, facilities and medical attention to subjects who suffer injuries while participating in the research projects of the University of Missouri.

In the event you have suffered injury as the result of participation in this research program, you are to contact the Risk Management Officer, telephone number (573) 882-1181, at the Health Sciences Center, who can review the matter and provide further information. This statement is not to be construed as an admission of liability.

Where can I get more information about this clinical trial?

A description of this clinical trial will be available on 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.

Who do I contact if I have questions or concerns?

If you have questions about this study or experience a research-related injury, you can contact the University of Missouri researcher at 573-884-3740 or aburger@health.missouri.edu.

If you have questions about your rights as a research participant, or have problems or complaints, please contact the University of Missouri Institutional Review Board (IRB) at 573-882-3181 or muresearchirb@missouri.edu. The IRB is a group of people who review research studies to make sure the rights and welfare of participants are protected.

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If you want to talk privately about any concerns or issues related to your participation, you may contact the Research Participant Advocacy at 888-280-5002 (a free call) or email muresearchrpa@missouri.edu.

Do I get a copy of this consent?

You will receive a copy of this consent for your records.

We appreciate your consideration to participate in this study.

Consent to Participate - Signatures

Subject's Signature	**Date**

Investigator Authorized to Obtain Consent	**Date**