Washington University in St. Louis

Title: Omega-3 for Depression and Other Cardiac Risk Factors
Principal Investigator: Robert M. Carney, Ph.D.

Co investigators: Kenneth E. Freedland, Ph.D., Eugene H. Rubin, M.D., Ph.D., Michael W. Rich, M.D., Phyllis K. Stein, Ph.D.
Study team members: Patricia Herzing, R.N., Carol Sparks, L.P.N., Brian Steinmeyer, M.S.

OVERVIEW

Background information: Depression increases the risk for cardiac morbidity and mortality 2-4 fold in patients with stable coronary heart disease or with two or more major cardiac risk factors (smoking, diabetes, hypertension, hyperlipidemia, family history of heart disease, elevated body mass index (kg/m^2). Recent clinical trials for comorbid depression in patients with heart disease have tested the efficacy of a variety of treatments including fluoxetine, sertraline, citalopram, and mirtazapine, as well as cognitive behavior therapy, interpersonal psychotherapy, and exercise. Several trials have also evaluated the effects of these treatments on cardiac morbidity and mortality. These trials have produced only small differences in depression outcome between the intervention and control group. Consequently, they have provided only weak tests of the hypothesis that effective treatment of depression can improve cardiac outcomes.

Rationale: There is preliminary evidence that co-administration of the omega-3 fatty acid (FA) eicosapentaenoic acid (EPA) can improve the efficacy of antidepressants. There is also evidence that administration of omega-3 FAs improves cardiac risk factors, and may even reduce the risk of sudden cardiac death and other major adverse cardiac events in patients with heart disease. However, our study of omega-3 augmentation of sertraline, published in JAMA in 2009, is the only trial to date that has evaluated whether omega-3 FAs improve depression and reduce other cardiovascular risk markers in patients with heart disease and depression. We found that a combination of 930 mg/day EPA and 750 mg/day DHA (a 1.2:1 ratio of EPA:DHA) had cardiovascular benefits, but that it was not efficacious for depression. More recently, several small psychiatric trials have suggested that coadministration of a standard antidepressant with an O-3 FA formulation containing 2 grams of EPA may greatly improve the efficacy of standard antidepressants. Smaller dosages of EPA and combinations with a low ratio of EPA to DHA seem to have no effect on depression.

Research Objectives: The proposed study is a 3.5 year randomized, placebo-controlled, double-blind clinical trial to determine whether antidepressant augmentation with two grams of EPA per day is superior to antidepressant therapy alone for major depression in patients with heart disease or cardiac risk factors, and to investigate its effects on other cardiac risk markers in these patients.

Potential Contribution: The results of this study will provide important information about the efficacy of omega-3 augmentation of standard pharmacologic treatment for depression in patients with or at risk for heart disease. This should contribute to the improvement of standard clinical care of such patients, and may result in improved medical outcomes.

METHODS

With their cardiologist's permission patients with documented coronary heart disease or two or more cardiac risk factors who are scheduled for an outpatient visit, laboratory test or diagnostic procedure at the Washington University Center for Advanced Medicine (CAM) and BJC Healthcare will be evaluated for study recruitment.

Exclusions

Patients will be excluded if they: 1) have moderate-severe cognitive impairment; 2) have a major Axis I psychiatric disorder other than unipolar depression, a high risk of suicide, or current substance abuse other than tobacco; 3) are not expected to survive one year or are physically unable to tolerate the study protocol; 4) have a known sensitivity to sertraline or omega-3, or an allergy to fish oil or shellfish; 5) (at time of randomization) are taking an antidepressant, lithium, or omega-3 supplements; or 6) are exempted by their cardiologist or primary care physician, refuse to sign an informed consent, or are participating in a competing protocol or trial. These exclusions may be determined during the phone call, after a review of medical records, or at any time during screening and eligibility evaluation.

Screening & Eligibility Evaluation

Recruitment: The nurse recruiters will identify potential participants with documented coronary heart disease or cardiac risk factors from the cardiac diagnostic laboratory and the cardiology outpatient visit lists. They will obtain permission from the potential participant's physician to send a letter explaining our study and inviting the person to call if interested. If there is no response to the letter within two weeks, the nurse recruiter will follow up with a phone call to personally invite the potential candidate and/or answer questions regarding the study. If interested, the potential candidate may be sent a copy of the informed consent and be scheduled for an office visit.

At the time of the office visit, the nurse who recruited the potential participant will begin the visit by having the participant read the Consent and Notice of Privacy Practices. She will answer any questions the participant may have regarding the study and the protection of his/her health information. It is clearly stated that the person's participation is entirely voluntary and there is no pressure placed on the potential candidate to sign the consent. The participant then signs and dates the consent if they desire. A copy of the consent is given to the participant for his/her records. The following assessments will then be conducted. The screening and all baseline assessments can take place during the same office visit, or a second can be scheduled if preferred by the patient.

Table 1: Assessment Schedule				
	Assessment Phase			
Measure	Screening	Baseline	TX Contacts	Post-TX
Current medical status & medical history	X			X
OMCT dementia screening (Short Blessed)	X			
PHQ-9 depression screening	X		X	
Depression interview (DISH)	X			X
Beck Depression Inventory-II	X		X	X
Beck Anxiety Inventory		X		X
Generalized Anxiety Disorder (GAD-7)		X	X	X
Nonstudy depression treatments		X	X	X
Diet and medications/change		X	X	X
Side effects and adverse events		X	X	X
Somatic Symptom Scale-8		X	X	X
International Physical Activity Questionnaire		X		X
24h ambulatory monitoring (HRV, HR)		X		X
Coagulant and inflammatory markers		X		X
RBC levels of omega-3 and omega 6 FAs		X		X
Antidepressant/omega-3 pill counts			X	X

Cardiovascular History: Medical records will be reviewed to obtain data on the cardiac risk factors,etiology, history, and sequelae of CHD, including prior ACS, sleep apnea, arrhythmias, other ECG abnormalities, and other chronic illnesses. The latest left ventricular ejection fraction (LVEF), history of coronary revascularization, and current medications will be recorded. Risk factor data will be collected, including history of smoking, diabetes, hypertension, hyperlipidemia, family history of heart disease , body mass index (kg/m^2), and daily physical activity level.

Dementia Screening: The six-item Short Blessed Orientation Memory Concentration Test (OMCT) will be used to screen for moderate to severe cognitive impairment. Patients who score $\geq$ 20 will be excluded.

Patient Health Questionnaire (PHQ-9): The PHQ-9 is a multi-instrument for screening, diagnosing, monitoring and measuring the severity of depression.

Beck Depression Inventory II (BDI-II): The BDI-II is a 21 item questionnaire that will be administered to assess severity of depression symptoms.

Interview: The Depression Interview and Structured Hamilton (DISH) will then be administered and used to diagnose major depression according to the DSM-V criteria and to measure the severity of depression on an embedded 17-item version of the HAM-D. The DISH can also be used to diagnose anxiety disorders and to rule out bipolar disorder and other major psychiatric disorders. The interviews will be conducted by experienced research nurses who have been trained in the administration of the DISH. The results will

be reviewed with the patient by the study psychiatrist who will determine whether there are any psychiatric or medical reasons the patient should not participate in the study.

Patients, who meet the DSM-V criteria for major unipolar depression, are approved by the study psychiatrist, and score ≥17 on the BDI-2 will continue with baseline evaluation.

Other Assessments (see Table 1)

Beck Anxiety Inventory (BAI): The BAI is a 21 item questionnaire that will be used to measure the severity of anxiety symptoms.

Generalized Anxiety Disorder Scale (GAD-7): The GAD-7 is a self-administered patient questionnaire used as a screening tool and severity measure for generalized anxiety disorder.

Somatic Symptom Scale-8 (SSS-8): The SSS-8 will be administered to determine the number and severity of common somatic symptoms.

International Physical Activity Questionnaire (IPAQ): The IPAQ is a brief measure of physical activity that has been used in previous research on heart disease which assesses the frequency, duration and effort of physical activity performed.

Cardiovascular Assessments: Nearly all patients will be taking β-blockers, aspirin, statins, and other drugs that are likely to affect the risk markers to be assessed in this study. They will not be asked to discontinue these medications for the laboratory visits. However, participants will be asked to refrain from antioxidants and nonsteroidal anti-inflammatory medications for 24 hours. This should not pose a problem as most of these drugs are taken in the morning. Participants will be asked to bring these medications to the laboratory and take them immediately after the blood draw. They will also be instructed to eat a light, low-fat dinner, and then fast and refrain from food, alcohol, and tobacco for 12 hours prior to the examination. All nonstudy medications will be recorded and their associations with study outcomes will be evaluated. The examination will begin in the morning to control for circadian variability. Blood pressure will be taken on two occasions, 2 minutes apart.

Blood Specimens and Assays: Oral body temperature will be measured as a second screen for infectious diseases and other disorders that could cause a systemic increase in inflammatory markers. The patient will rest supine on the examination table for ten minutes. Three 4 ml, two 7.5 ml, and one 10 ml tube of blood will be drawn and centrifuged within 30 minutes. After centrifugation, the serum will be divided into aliquots and frozen at -80^{o} c. Samples will be identified by a code to insure that the technician is blinded to group and assessment period. At the end of the study, the samples will be assayed in a single batch. The inflammatory and coagulant markers were selected on the basis of evidence of association with cardiac risk, depression, and improvement with omega-3 supplementation. The following will be measured at baseline and post-treatment:

1. Lipid profile (triglycerides, total cholesterol, and lipid fractions)
2. Basic metabolic panel (creatinine, BUN, fasting blood glucose, electrolytes, etc.)
3. Complete blood count (CBC) with differential
4. Proinflammatory markers: high-sensitivity C-reactive protein (hsCRP), interluekin-6 (Il-6), and tumor necrosis factor alpha (TNF-α).
5. Coagulation factors: Platelet factor 4 (PF4), fibrinogen.

6. Omega-3: RBC levels of EPA, DHA, and other omega-3 and omega-6 fatty acids.
7. Thyroid panel.

Ambulatory ECG (Holter) Monitoring and ECG Analysis: Patients will rest supine for ten minutes and blood pressure will be measured twice, 2 minutes apart, with a random zero sphygmomanometer. The patient will then be fitted with a DMS300a Holter recorder (DMS Holter, Stateside, NV). The standard electrode configuration for HRV and ST-segment depression analysis will be utilized. The patient will be instructed in the use of the monitor and asked to wear it for 24 hours while maintaining normal activities.
Dietary Evaluation: The research nurse will estimate each patient's dietary intake of omega-3 FAs before randomization and after each treatment contact via a brief structured dietary recall interview that was validated in a depressed patient sample and shown to have a high level of agreement with RBC omega-3 levels.

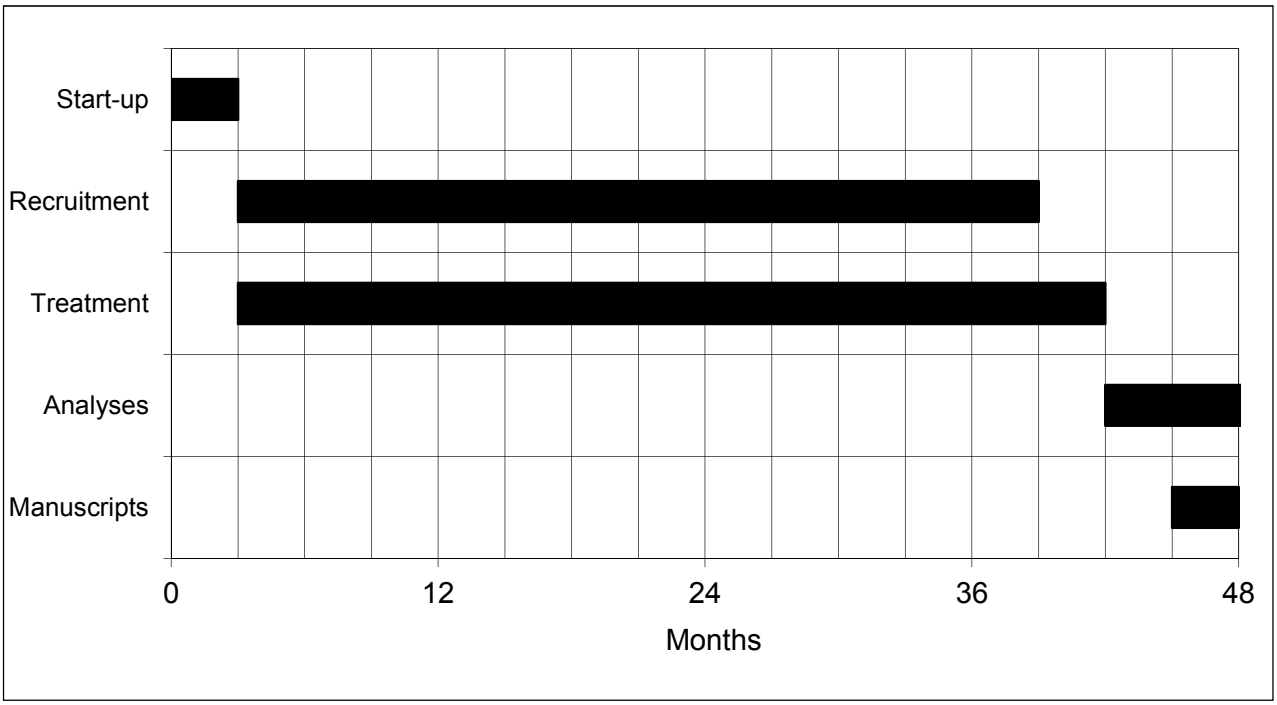
Randomization and Treatment
Randomization: Participants will be randomly assigned to receive 50 mg/day of sertraline plus omega-3 capsules or 50 mg/day of sertraline plus placebo (corn oil) capsules, following a permuted block random assignment sequence. The assignments will be coded and concealed to ensure that the double-blind is maintained. Patients will then be given a 5 week supply of the assigned medications. They will be given a 5 week supply at the end of week 4 for a total of 10 weeks of medications.
Agents and Dosages: Sertraline has the most empirical support of any antidepressant for its safety in cardiac patients. The study psychiatrist will initiate sertraline at 50 mg/day. Fifty mg/day is well tolerated by most patients. Although dosage escalation for nonresponders is common in clinical practice, this could produce an imbalance in dosages between the groups in this study, making it difficult to interpret the results. Furthermore, previous studies found little incremental improvement in response rates with higher doses of sertraline (100-200 mg/day), despite significant increases in side effects.
The psychiatrist, blinded to treatment assignment, will also initiate a regimen consisting of either four capsules per day of omega-3 totaling 2 g/day of EPA, or four capsules of an identical comparator placebo (corn oil). The duration of treatment will be 10 weeks, consistent with most trials of antidepressants.
Clinical Management and Monitoring: The psychiatrist or psychiatric nurse will see the patients for clinical management on 2 occasions or more depending on need during the 10 weeks of treatment, as per standard clinical practice. The sessions will last approximately 20 minutes and will entail a review of the patient's adherence to the protocol, progress, new symptoms, and medication side-effects. The psychiatric nurse will conduct assessments via telephone during the weeks between these visits. Any significant worsening of the patient's psychiatric or cardiac status will be addressed as needed. Patients' returned pills will be counted and recorded after each week.
Nonstudy Treatment: Patients will be asked to refrain from nonstudy depression care during the 10 weeks of the study intervention. A nonstudy treatment form will be completed at each psychiatric visit to document whether the patient is receiving any nonstudy treatment for depression or any other psychiatric condition, including psychiatric

hospitalizations, ECT, TMS, medications, psychotherapy or counseling, support groups, self-help books, and complementary/alternative medicine remedies. Participants will also be asked to refrain from taking omega-3 dietary supplements and from increasing their consumption of fish during the study intervention. OTC fish oil supplements usually contain <0.3 g of EPA/DHA omega-3. Nevertheless, patients will be asked to refrain from supplements, both for their safety and for the integrity of the study. None of the participants in our first trial received any relevant nonstudy treatments during the 10 weeks of the trial.
Tolerability, Safety, and Medication Adherence: Omega-3 is recommended by the American Heart Association to improve risk factors in cardiac patients, and the FDA considers the dosage to be used in this study to be safe. Sertraline has also been shown in recent trials to be safe for patients following an acute MI and was recommended by an NHLBI expert panel for the treatment of depression in these patients. It is unlikely that sertraline and omega-3 will interact to produce problems that are not encountered with either agent alone. Nevertheless, care will be taken to document the possibility of any adverse event that might be attributable to the treatment regimen. The safety and tolerability of the combination of sertraline and omega-3 will be assessed by comparing patients receiving sertraline plus omega-3 to patients receiving sertraline plus placebo on 1) adverse events, 2) protocol deviations (including nonadherence), 3) worsening of depression, and 4) suicidal features. In our previous clinical trial, there were no differences in side effects or adverse outcomes between omega-3 and placebo. Participants will be carefully monitored via a series of systematic screening questions by the psychiatrist and nurse. Adverse events will be recorded on the Washington University IRB Adverse Event Report form by type, severity, and duration.

Participants will be compensated $100.00 for completing the trial.

Follow-up: After the study, the participants are instructed to contact their own physician for continuing treatment. If the participant decides to discontinue taking the antidepressant at the end of their participation, a 2 week supply of a tapering dose will be given to them by the study team to avoid abrupt discontinuation of this medication.

Study Timeline:



INFORMED CONSENT

At the time of the Screening office visit, the nurse who recruited the potential participant will begin the visit by having the participant read the Consent and Notice of Privacy Practices. She will answer any questions the participant might have regarding the study and the protection of their health information. It is clearly stated that the person's participation is entirely voluntary and there is no pressure placed on the potential candidate to sign the consent. The participant then signs and dates the consent if they desire. A copy of the consent is given to the participant for their records.

PROCEDURES FOR MAINTAINING CONFIDENTIALITY

Permission will be obtained from treating physicians before any contact is made with a physician's patients. It has been requested that HRPO approve granting trained research nurses access to only the information needed to identify those qualified to participate in the study. If a patient is found to be ineligible for the study, all of that patient's information is destroyed. All interviews take place in private rooms. Notes and questionnaires are kept private on a secured server and only accessible to study staff and the PI. Participants are asked to sign a release of information so their treating physicians may receive copies of lab work or Holter monitoring results if desired or if the results require physician attention. The participant is not billed for any study related tests and no information is sent to their insurance provider. The information in a participant's study file is labeled with a code number instead of a name and all written information is kept secure in locked file cabinets.

Paper/hard copy records (hard copy surveys, questionnaires, case report forms, etc.) are also kept in locked file cabinets, in locked offices, in a locked suite. A participant's paper chart is identified only by the study ID number. A listing that links study ID numbers with participant's names are kept locked in a separate file cabinet in the study coordinator's office.

Electronic records (computer files, electronic databases, etc.) are listed under the participant's study ID number only and stored on the secured server of the Department of Psychiatry, behind the university firewall. Only study personnel have password protected access to study files.

Biologic samples (blood specimens) are identified with participant ID numbers only and transported by couriers employed by Quest Diagnostics. Those samples that are frozen for future transport are also identified with participant ID numbers only. The freezer is located in a locked lab in our locked suite.

ASSESSMENT OF RISKS AND BENEFITS

Risks

Some participants may experience emotional distress during evaluations for depression and anxiety. ECG monitoring poses negligible risks. Slight discomfort may result from the placement, use, or removal of electrodes. Blood draws may cause minor bruising, and very rarely, infection at the site of the needle stick. Side effects of sertraline and omega-3 are usually mild. Serious side effects are rare, especially at the dosages used in this study. Omega-3 side effects include indigestion, burping, bloating, diarrhea, slight increase in fasting blood glucose levels in those with type II diabetes, and prolonged bleeding time. Sertraline side effects may include dry mouth, tremors/shakiness, upset stomach, decreased appetite, increased sweating, sleepiness, sexual dysfunction, insomnia, prolonged bleeding time, headache, and dizziness. Serious adverse events due to sertraline or omega-3, while very unlikely, cannot be ruled out. Depressed patients in any study may become more depressed or experience suicidal thoughts during the course of the study. Finally, confidentiality would be compromised if unauthorized individuals were to discover a participant's identity.

Plan to minimize the risks:

Participants will remain under the care of their own physician(s) throughout the study. The physician will be notified that their patient meets the criteria for major depression. All participants will receive a standard antidepressant (50 mg/day of sertraline). Patients' psychiatric and cardiac status will be reviewed weekly by the PI, the psychiatric nurse, the study psychiatrist, and the study cardiologist. Emergency care will be provided as needed.

Medical Tests/Procedures: The blood draws and placement and removal of the Holter monitor will be performed by an experienced cardiac nurse.

Medication Side Effects: Potential side effects of sertraline and omega-3 will be closely

monitored. A previous RCT of sertraline with over 150 post-ACS patients produced no treatment-related adverse events; there was a trend toward a lower risk for cardiovascular adverse events in the sertraline than the placebo arm. Only nausea and diarrhea were more common in the sertraline arm, and these effects were mild and transitory. Similarly, studies of omega-3 supplements of 1-2 g/day have reported minor GI side effects in a small proportion of patients. In our study of sertraline and omega-3, no symptoms or side effects occurred more often in the omega-3 than in the placebo group. Nevertheless, possible adverse events and potential medication side effects will be monitored weekly by either the study psychiatrist or the research nurse, and will be reviewed by the study cardiologist. All SAEs judged to be study-related will be reported immediately to the Data and Safety Monitoring Committee (DSMC), and within 7 days to the IRB. Treatment will be terminated for any patients deemed to be at risk by the psychiatrist or cardiologist, and appropriate steps will be taken to assure the patient's continued safety.

Completion of Diagnostic Interview and Self-Report Inventories: Any patient who reports any emotional discomfort while completing the psychological tests or interviews will be reminded that the evaluation will be discontinued if he or she wishes, and that doing so will not affect his or her medical care. Experienced, licensed psychologist- and psychiatrist-investigators will be on call in case a patient has an adverse reaction to a screening or outcome evaluation. We have administered these tests and interviews to over 2,500 patients without a single subject reporting more than mild, transient emotional distress.

Suicidality: The principal investigator and other qualified members of the study team will monitor suicidal ideation and behavior, via the standardized questionnaires and interviews described in the study protocol, and via in-person and/or telephone contacts between the participant and the study staff. Whenever suicidal ideation or behavior is identified, the study staff will follow an established protocol for evaluating suicide risk. The protocol was originally developed for the ENRICHD clinical trial and has been extended and tailored for use in other depression studies at our center. The protocol uses a standard set of risk indicators to assign patients to low, intermediate, or high risk categories. Patients considered to be at intermediate risk are monitored by study staff, evaluated by a study psychiatrist or psychologist, and are provided with suicide prevention recommendations. Patients who are classified as being at high risk are regarded as experiencing a psychiatric emergency, in which case the study team works to arrange emergency services and other protective actions as appropriate. We have followed these procedures for over 15 years in numerous studies and clinical trials of depressed CHD patients without a single suicide attempt.

Worsening depression: Patients who experience significantly worsening depression during the intervention phase of the trial, as defined as either >8 points increase on the BDI-II or as observed by the psychiatric nurse during phone or in person contacts, will be evaluated by the study psychiatrist or psychologist to determine whether the patient should remain in the study. Based on all findings, patients may either be allowed to continue in the study under

careful observation and more frequent contacts, or be referred to their own physician or nonstudy psychiatrist who will be asked to consider initiating or referring for nonstudy antidepressant therapy. The DSMC will also review all cases in which study participants are or should be referred to their own physician for evaluation of a medical or psychiatric problem as needed.

Cardiac events: The study team will consult with the cardiologist co-investigator if there are questions about the medical safety of any study procedures or any concerns about the patient's cardiac status. The DSMC will monitor cardiac hospitalizations and other SAEs, evaluate whether the SAE is study related, and take appropriate actions including informing the IRB.

Nonstudy treatment: For their safety and for the integrity of the study, patients will be advised that if they initiate nonstudy depression treatment, including antidepressants, psychotherapy, ECT, or any recognized or novel therapy during the intervention phase of the trial, they may be withdrawn from the trial if the additional treatment is viewed as potentially unsafe in combination with the trial regimen. Based on our experience in previous trials, we expect few patients to seek or receive nonstudy treatment during the 10 weeks of the trial.

Confidentiality: All study data forms will be kept in a locked file cabinet in a locked office and identified only by an ID number. The master list of subject IDs and names will be kept in a separate locked file cabinet in a separate locked office by the P.I. Computerized research data will be identified only by subject ID, and confidential data files will be password protected. Written records of treatment sessions will be kept in a locked cabinet and will be destroyed within one year of the termination of the project. Only authorized individuals will be permitted to review these records. We have followed these procedures in the past without any breeches of confidentiality, and we feel certain that we will be able to maintain the same level of security for this project.

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Benefits: The trial participants will receive a therapeutic dose of a widely used antidepressant. Therefore, the potential benefits for participants randomized to either arm include remission of depression, improved psychosocial adjustment, and improvement in cardiac risk markers that may be affected by depression.

The results of this study will provide important information about the efficacy of omega-3 augmentation of standard pharmacologic treatment for depression in patients with or at risk for heart disease. This should contribute to the improvement of standard clinical care of such patients, and may result in improved medical outcomes.

Statistical Analysis Plan

Chi-square tests and analysis-of-variance (ANOVA) will be used to compare the groups on demographic, psychiatric, and medical characteristics as well as other treatment process variables such as compliance and severe adverse events. The primary analysis will determine whether the course of depression differed between groups, where the weekly BDI-II scores will be regressed on treatment group, time and the interaction between treatment group and time in a series of linear, mixed regression models that account for both inter-subject and intra-subject variation. Analysis of covariance (ANCOVA) models will be fitted to secondary outcomes, where the scores at 10 weeks will be regressed on treatment group and the pre-measurement scores at baseline.

Additional secondary analyses will compare the groups' remission (HAM-D score < 8) and response (≥50% reduction from the baseline HAM-D score) rates at 10 weeks. These dichotomous outcomes will be regressed on treatment group in a series of logistic regression models. All model fitting will follow the intent-to-treat (ITT) principle, where data plausibly missing at random will be imputed by standard, multiple imputation methods. All hypothesis tests will be 2-tailed, with $p<.05$ denoting statistical significance and all statistical analyses will be performed with SAS version 9.4 statistical software.

Washington University in St. Louis

INFORMED CONSENT DOCUMENT

Project Title: Omega-3 for Depression and Other Cardiac Risk Factors

Principal Investigator: Robert Carney, Ph.D.

Research Team Contact: Patricia Herzing, RN (314) 286-1360

This consent form describes the research study and helps you decide if you want to participate. It provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research participant. By signing this form you are agreeing to participate in this study.

- If you have any questions about anything in this form, you should ask the research team for more information.
- You may also wish to talk to your family or friends about your participation in this study.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We invite you to participate in this research study because you have been diagnosed with heart disease or cardiac risk factors (smoking, diabetes, hypertension, hyperlipidemia, family history of heart disease, elevated body mass index) and may or may not be depressed.

Many people with or at risk for heart disease also have depression. In addition to reducing the quality of their lives, depression may increase their risk for additional heart-related problems. There are many treatments available for depression, but none of them are as effective as patients or their doctors would like. There is some evidence that antidepressant medications can be made more effective by adding another type of drug, or even a food supplement, to their regimen. Omega-3 free fatty acid is one such food supplement. omega-3 fatty acid is a substance that the body needs to function, and it is found only in certain foods, such as fish. Consuming fish high in omega-3 is part of a heart-healthy diet, as recommended by the American Heart Association. There is also some evidence that omega-3 may improve the effectiveness of antidepressant drugs. This study is being done to see if taking a form of omega-3 free fatty acid together with an approved antidepressant, Zoloft (generic name: sertraline) will treat depression more effectively in patients with or at risk for heart disease.

Because it has not yet been proven that taking omega-3 will improve the effectiveness of an antidepressant, this use of omega-3 is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration for this purpose. Every patient who qualifies for study treatment will receive the antidepressant, Zoloft, which is recognized and approved for the treatment of depression. In addition, a patient will receive either daily supplements of omega-3, or placebo pills that look like the omega-3 capsule but contain corn oil.

WHAT WILL HAPPEN DURING THIS STUDY?

Before being enrolled in the study, a research nurse will call you to schedule a study visit on a day of your choosing. This visit is expected to take 3-4 hours to complete. You will be allowed to rest as needed.

Prior to this visit, you will be asked to stop taking any non-steroidal anti-inflammatory drugs (aspirin, ibuprofen, naproxen, Motrin, Aleve, etc.) for 24 hours. **You will NOT be asked to stop taking any other medications.** You will be asked to avoid excess caffeine (you may have one cup of black coffee or tea), alcohol and all food and liquids except for water after 12:00 midnight the night before the visit (8 hour fast). If you are a smoker, you will be allowed one cigarette 30 minutes before the scheduled visit. You may smoke again after the blood drawing is completed. You will be sent an instruction sheet to remind you of these restrictions.

After you arrive for the first visit you will be asked questions about depression symptoms, including how your mood, appetite, and sleep have been for the last two weeks or more. This portion of the interview takes from 40-60 minutes, depending on how much you feel like talking. With your permission your medical records will be reviewed for information about the history of your heart problems and other major health problems. You will also be asked whether you have been having heart symptoms, the medications you are taking, and your diet. Your answers to these questions will be kept private except in the case of information that suggests a life-threatening situation exists. The medical interview should take about 15 minutes to complete.

If you are found to have 5 or more symptoms of depression, you will then meet with the doctor who will review your information and determine whether you might benefit from taking the antidepressant medication, Zoloft. If the doctor believes that it is safe and potentially beneficial for you to participate in the study, the sertraline and omega-3/placebo will be dispensed.

You will then go to the exam room and we will take your blood pressure, temperature, and height/weight measurements. You will be asked to rest for 10 minutes on the exam table and have about 2 tablespoons of blood drawn for laboratory testing. If you wish, you may take a break and have a snack after your blood is drawn. Because these tests are repeated at the end of 10 weeks, you will have a total of about 5 tablespoons of blood drawn over the course of this study.

You will then be fitted with a 24-hour heart monitor that continuously records your electrocardiogram (ECG or EKG). This takes about 10 minutes to complete. The monitoring device is a 2¼" X 2½" X ¾" 3-ounce digital recorder about the size of a small cell phone. To do the recording, you will wear 7 small adhesive discs and the wires will be connected to the box. Most people wear the monitor on a belt, around their neck, or in a pocket. Except for showering, taking a tub bath, or swimming, your activities will not be restricted during the 24-hour recording period. You will be given a postage paid envelope to mail the heart monitor back to us the following day. You may place it in any mailbox for mailing.

You will be asked to complete some questionnaires about symptoms of depression and anxiety, usual activity, physical symptoms, and sleep. Typically take about 15 minutes to complete.

You will be then assigned to one of two groups. One group will be given 50mg. of Zoloft, an approved antidepressant to take once daily, plus four omega-3 capsules to take daily with meals (two in the morning and two in the evening). The other group will be given 50mg. of Zoloft plus four capsules containing corn oil. You will have a fifty-fifty chance of being in either group. Both groups will receive Zoloft, a recognized and approved antidepressant, but only one group will also receive the omega-3 supplement. The groups are assigned by computer using a process that is like flipping a coin. The research staff will not know which group you are in.

Once you are assigned to treatment, you will be asked to take the Zoloft and the study capsules (omega-3 or placebo) every day for 10 weeks.

During the same 10 weeks, you will be monitored closely by the study staff. You will be asked questions concerning how well you are taking the medications, what if any side effects you may have experienced, and any dietary or medication changes. You will be asked to fill out weekly anxiety and depression questionnaires, and these will be reviewed by the study nurse every week, either by phone or during an office visit. This will help us to determine when the medication starts to help you feel better, or if you are not improving. It is very important that the nurse be able to reach you, so we will ask for all your phone numbers and any alternate contacts you are willing to provide. To insure your safety, patients will be required to come to the office at least 2 times during the treatment period, and others may be asked to come in more frequently for closer monitoring. This will be determined by the study nurse and the doctor. Telephone contact will be made at every week for which there is no office visit. If, at any time during your study participation, you feel that you need to speak with someone about your participation, please call the study nurse. The nurse will arrange for phone contact or an extra visit with the doctor if this is clinically indicated. At the end of 10 weeks, there will be a final visit to evaluate your depression, which should take about an hour and a half and includes the final blood draw and heart monitor.

Throughout the ten weeks, you will be required to refrain from using any non-study treatment for depression (pills, counseling, or other therapies) and refrain from taking non-study omega-3 supplements. If you prefer to get other treatment for depression, please do not take part in this trial.

If your treatment was successful and you no longer feel depressed, or if you are still depressed, you will be referred to your own doctor to discuss treatment options. If you decide to discontinue taking Zoloft at the end of your participation in the study, a 2-week supply of a tapering dose will be given to you by the study to avoid abrupt discontinuation of this medication.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 170 people will take part in this study conducted by investigators at Washington University.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will last for 10 weeks, including the evaluation and treatment periods. There will also be a 2-week period after the treatment phase of the study for medication tapering. There will be 2 post-study phone calls to check on you and see how you are doing. One will be 1 week after your last visit, and one will be 30 days after your last visit.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Blood draw

Likely / Common

- You may have some brief discomfort when the needle is inserted to draw blood.

Less Likely / Less Common

- You may have bleeding or bruising at the site of needle insertion for the drawing of blood.

Rare

- Some individuals feel faint when their blood is drawn and there is a rare risk of infection.

Heart Monitoring device

- Although the 24-hour heart rate recording device is small and lightweight, you may find it bothersome. There is also a risk of minor, temporary, skin discomfort caused by application of the electrode discs, and some people are not comfortable with waiting for 24 hours before taking a full bath or shower.

Questionnaires

- Some of the questions on the interview and on the questionnaires may be uncomfortable for you to answer. If a particular question makes you uncomfortable, you may discuss it with the interviewer. You may choose not to answer any question that makes you feel uncomfortable. Although this interview is for research purposes, the same types of questions are asked of patients who might be depressed, as part of standard care.

Zoloft

Less Likely / Less Common

- You may experience certain side effects from the antidepressant medication (Zoloft). The most common of these side effects include insomnia (trouble sleeping), sedation (feeling sleepy during the day), and sexual dysfunction and/or decreased sexual arousal in men and women. These problems are usually only temporary and occur in fewer than 15% of those patients given the medication.

Omega-3
Less Likely / Less Common

- Indigestion or stomach upset

Rare

- Patients with diabetes have a low risk of increased blood sugar, and patients with very high triglycerides have a slight risk of an increase in LDL-cholesterol.
- An increased risk of bleeding has been reported with doses of omega-3 at more than twice the amount used in this study.

Treatments in this study may disqualify you for other research studies using omega-3.

One risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure, and we think the risk of accidental disclosure is very small. Please see the section in this consent form titled *"How will you keep my information confidential?"* for more information.

WHAT ARE THE BENEFITS OF THIS STUDY?

You may or may not benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because if omega-3 does improve the effectiveness of medical treatment for depression, there could be improved quality of life and improved functioning for heart patients with depression, and decreased costs associated with lost work-time due to depression. It is also possible that the extra health problems associated with having both heart disease and depression may be less if depression is more successfully treated.

WHAT OTHER TREATMENT OPTIONS ARE THERE?

Taking part in this research study is voluntary. You may choose not to take part in this research study or you may withdraw your consent at any time. Your choice will not at any time affect the commitment of your health care providers to administer care. There will be no penalty or loss of benefits to which you are otherwise entitled. Other than not taking part in the research, you may talk to your doctor about other treatment options, or get treatment from a counselor, psychologist, or psychiatrist on your own.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

You will not have any costs for being in this research study. All study procedures, including lab tests, study interviews, doctor visits, medications, and supplements are free to you and your insurance company.

You and/or your medical/hospital insurance provider will remain responsible for your regular medical care expenses.

WILL I BE PAID FOR PARTICIPATING?

You will be paid for being in this research study. To be paid, you will need to provide your social security number (SSN) and mailing address. You may choose to participate without being paid if you do not wish to provide your social security number (SSN) for this purpose. You will receive compensation for your time in this study, based on the number of assessments you complete. There will be three times throughout the study when you will receive $33.00. One payment after the first visit, one payment after treatment week five, and one payment after the final visit. You should receive a check within two weeks after completing each of these points. Please call the study personnel if you do not receive your check within two weeks. If your social security number is obtained for payment purposes only, it will not be retained for research purposes.

WHO IS FUNDING THIS STUDY?

The National Institutes of Health (NIH) is funding this research study. This means that Washington University is receiving payments from NIH to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from NIH for conducting this study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator at (314) 286-1313 or 1-(877)-717-0757 and/or the Human Research Protection Office at 1-(800)-438-0445.

Decisions about payment for medical treatment for injuries relating to your participation in research will be made by Washington University. If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

HOW WILL YOU KEEP MY INFORMATION CONFIDENTIAL?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- Government representatives, (including the Office for Human Research Protections) to complete federal or state responsibilities
- The U.S. Food and Drug Administration
- National Institutes of Health
- Your primary care physician if a medical condition that needs urgent attention is discovered
- Hospital or University representatives, to complete Hospital or University responsibilities

- Information about your participation in this study may be documented in your health care records and be available to your health care providers who are not part of the research team.
- Washington University's Institutional Review Board (a committee that oversees the conduct of research involving human participants.) The Institutional Review Board has reviewed and approved this study.

We will do everything we can to protect your privacy. As part of the screening phase of this study, you will be asked about any recent or current use of illegal substances and about severe mental illness. You will not be eligible for study participation if you have any of these. No identifying information is kept on those who are not eligible for the study, so reasons for ineligibility cannot be disclosed.

In addition to health information that may be created by the study, the research team may access your medical chart and laboratory test results from your most recent heart-related hospitalizations, procedures, tests, or outpatient visits to your physician, and information about any mental health problems. This information will be reviewed to assure that you meet all eligibility requirements for this study and to obtain information about any other major medical problems you may have that could have an effect on your ability to benefit from this study. We will ask you to sign a Release of Information form so that we can obtain information about your health from your physician and notify your physician that you are in a trial that will involve the taking of medication.

Your research records will be stored separately from your medical charts in locked files, in a locked office in a locked suite in a building with a security system. The information in your file is labeled with a code number instead of your name. All electronic records are listed under your code number only and stored on a secured server, behind the university firewall. Only the research team will have password protected access to your files. Blood samples are identified with your code number only.

If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

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.

Are there additional protections for my health information?

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. The research team will follow state and federal laws and may share your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?"

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form or as permitted or required by law. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

Although you will not be allowed to see the study information, you may be given access to your health care records by contacting your health care provider.

If you decide not to sign this form, it will not affect:

- your treatment or the care given by your health provider.
- your insurance payment or enrollment in any health plans.
- any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
- This authorization does not expire.
- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).
    - To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ or you may request that the Investigator send you a copy of the letter.
        - If you revoke your authorization:
            - The research team may only use and share information already collected for the study.
            - Your information may still be used and shared as necessary to maintain the integrity of the research, for example, to account for a participant's withdrawal from the research study or for safety reasons.
            - You will not be allowed to continue to participate in the study.

Can we contact you by email?

We would like to contact you by email for the purposes listed below. Some of these emails may contain health information that identifies you.

- Schedule and confirm study appointments.
- Send general participant information and education materials.
- Weekly contact with the study nurse to verify pill counts, discuss any side effects from study medications, and any medication or treatment changes prescribed by your own doctor.

Only the research team will have access to your email communications. We will only communicate by email to send you the information listed above. If you have any questions or need to contact us for an urgent or emergent situation, please contact our office at (314) 286-1313 or 1-(877)-717-0757.

You should be aware that there are risks associated with sending your health information via email.

- There is always a risk that the message could be intercepted or sent to the wrong email address. To avoid sending messages to the wrong email address, the first email we send you will be a test message to ensure we have the correct email address.
- When using any computer you should be careful to protect your username and password. Make sure you log-out before getting up from the computer.
- If you share a home computer with other family members, and do not want them to know you are participating in this study make sure you provide an email address that only you can access.
- Your employer will have access to any email communications sent or received on any electronic devices used for work or through a work server.

Do you agree to allow us to send your protected health information via email?

_____ Yes **_____ No**
Initials **Initials**

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I decide to withdraw from the study?

You may withdraw by telling the study team you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ under Withdrawing from a Research Study.

If you do decide to leave the study early, we ask that you contact the study team as soon as possible, so we can order you a 2-week supply of a tapering dose of study medications to avoid abrupt discontinuation of these medications.

Will I receive new information about the study while participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can someone else end my participation in this study?

Under certain circumstances, the researchers might decide to end your participation in this research study earlier than planned. This might happen because your depression is worsening and the study treatment does not seem to be helping you. For safety, it may be in your best interest to allow follow-up outside the study. This decision would be made in consultation with the research team.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Patricia Herzing at (314) 286-1360 or 1-(877)-717-0757. If you experience a research-related injury, please contact: Robert M. Carney, Ph.D. at (314) 286-1313 or 1-(877)-717-0757.

If you have questions, concerns, or complaints about your rights as a research participant, please contact the Human Research Protection Office, 660 South Euclid Avenue, Campus Box 8089, St. Louis, MO 63110, 1-(800)-438-0445, or email hrpo@wustl.edu. General information about being a research participant can be found on the Human Research Protection Office web site, http://hrpo.wustl.edu. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Research Protection Office at the number above.

This consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study. As a participant you have rights and responsibilities as described in this document and including:

- To be given enough time before signing below to weigh the risks and potential benefits and decide if you want to participate without any pressure from the research team or others.
- To understand all of the information included in the document, have your questions answered, and receive an explanation of anything you do not understand.
- To follow the procedures described in this document and the instructions of the research team to the best of your ability unless you choose to stop your participation in the research study.
- To give the research team accurate and complete information.
- To tell the research team promptly about any problems you have related to your participation, or if you are unable to continue and wish to stop participating in the research study.

Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a signed and dated copy of this form.

Do not sign this form if today's date is after EXPIRATION DATE: 05/21/19.

_____ _____
(Signature of Participant) (Date)

_____
(Participant's name – printed)

Statement of Person Who Obtained Consent

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that they understand the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)

_____
(Name of Person who Obtained Consent - printed)