Investigator Studies Program
Clinical Protocol

Section #1 - Protocol Identification

Study Title:	The effect of omega 3 supplementation on postoperative delirium in elderly patients undergoing major cardiac surgery: a prospective, randomized, controlled trial.
Date:	v1: October 26, 2023, v2: April 25, 2024, v3: July 18, 2024, v4: June 3, 2025
Institution Name	The Curators of the University of Missouri School of Medicine Department of Anesthesiology and Perioperative Medicine
Institutional Review Board	University of Missouri Institutional Review Board 310 Jesse Hall Columbia, MO 65211
Research Facilities	University of Missouri Hospital 1 Hospital Dr. Columbia, MO 65212
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Section #2- Core Protocol	
2.1 Objectives & Hypotheses	2.1.1 Objectives The primary objective is to determine whether the supplementation of omega-3 fatty acids prior to and after cardiac bypass surgeries decreases the incidence of postoperative delirium in elderly patients. The secondary objectives between patients who received a high dose or low dose of omega-3 fatty acids or standard of care are: 1) To compare postoperative delirium symptoms using standardized tests. 2) To compare length of stay. 3) To compare the type of anesthesia used. 4) To compare types and amounts of pain management used. 2.1.2 Clinical Hypothesis Our hypothesis is that supplementation with omega-3 fatty acids will decrease the incidence of postoperative delirium compared to standard of care after cardiac bypass surgery.
2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	2.2.1 Background Postoperative delirium (POD) is a growing issue in surgeries involving older patients ages 65 years and older. In cardiac surgeries, POD occurs in up to 52% of patients, and can increase negative outcomes from surgery, including death, and increases length of stay in the hospital (2). Many risk factors for POD have been identified, including age, diabetes, preexisting cognitive impairments, and metabolic syndromes. However, no definitive biomarkers have been identified, and there is currently no approved prevention method for POD.

Polyunsaturated fatty acids (PUFAs) such as omega-3 and omega-6 fatty acids present in fish oil supplements, exhibit anti-inflammatory and antioxidant properties (4). POD is often cited as being caused by oxidative stress and inflammation, and patients with POD have been found to have deficiencies in omega-3 and omega-6 fatty acids (5, 6).

Therefore, we hypothesized that supplementation of omega-3 fatty acids prior to surgery would decrease the incidence of POD in older patients undergoing cardiac bypass surgeries. Cardiac surgeries have the highest incidence rate compared to other surgeries, and cardiac bypass surgeries are common in older patients. Patients undergoing cardiac surgeries are also kept for at least 3 days postoperatively, making it easier to contact patients to screen them for POD.

We will use prescription omega-3 ethyl esters (Generic). Omega-3 ethyl esters are a 1 g soft-gel capsule containing approximately 465 mg of eicosapentaenoic acid (EPA) and 375 mg of docosahexaenoic acid (DHA) (8). The capsules are taken orally.

Bleeding risk
No evidence was found that omega-3 supplements increase bleeding risk (1, 7-8).

Diabetes
Omega-3 ethyl esters are not contraindicated for patients with diabetes. However, because patients may already have high triglyceride levels as a result of diabetes, it is recommended that patients talk to their doctor before taking Omega-3 ethyl esters (Prescribing Information). Patients will be screened by a medical doctor prior to consent to ensure they are eligible for the study and to ensure they 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, patients undergo blood draws as standard of care. If a

patient's triglyceride level is found to be at a significantly high level, they will be removed from the study and the medication will be stopped immediately.

2.2.2 Medications Used

- Omega-3 ethyl esters, Epic Pharma LLC, NDC: 42806-0552-12
    - Dose:
        - Group 1: 4 grams
        - Group 2: 2 grams
    - Route: Oral
    - Regimen: One dose prior to surgery followed by one dose daily for 3 days postoperatively.

2.2.3 Rationale:

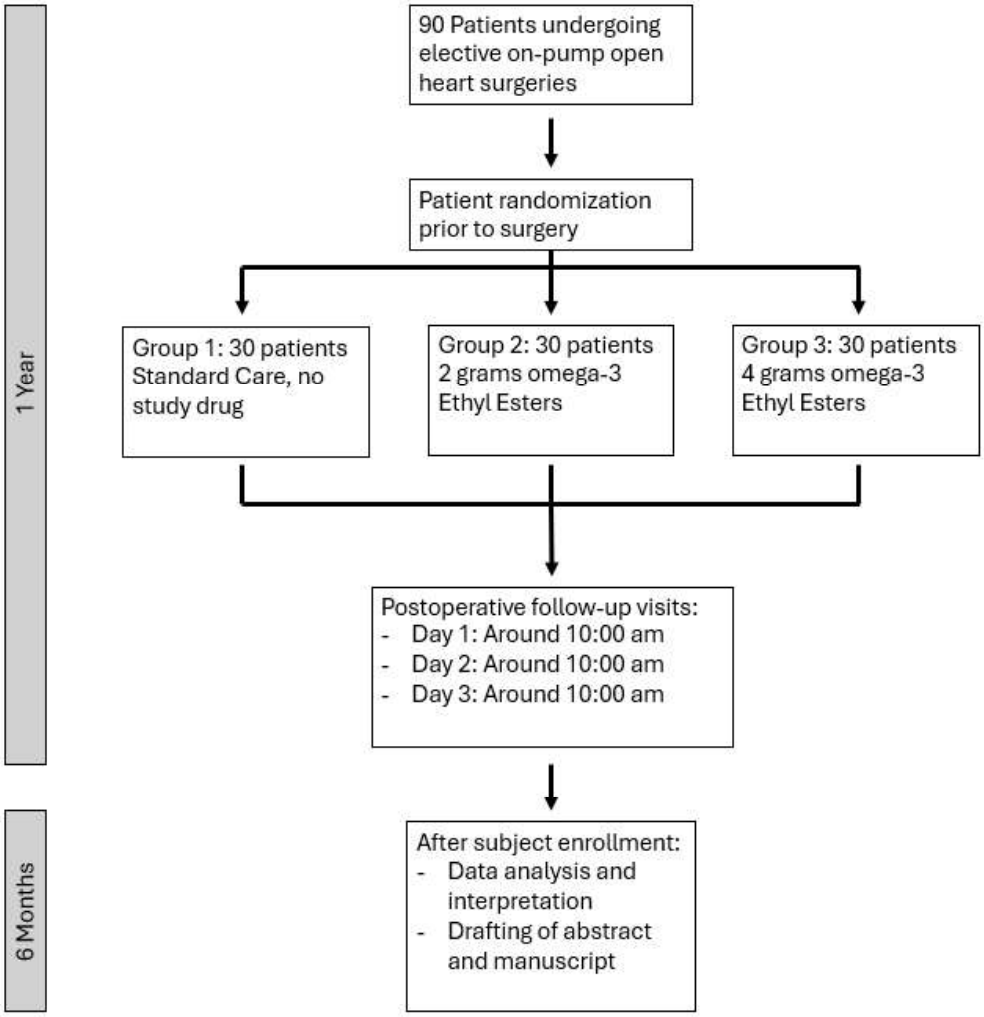
Omega-3 ethyl esters were chosen because they are a prescription version of omega-3 fatty acids. It is FDA regulated and all components are known and purified as opposed to over-the-counter fish oil supplements. The dose of 4 grams daily is recommended for labeled use and has been established to be a safe dose in this population. The dose of 2 grams daily is more similar to that of an over-the-counter fish oil supplement and has also been established to be safe in this population.

2.2.4 Standard Reference Therapy Justification

The standard reference therapy against which omega-3 ethyl esters will be compared is standard of care. There is currently no defined treatment or therapy to reduce or prevent postoperative delirium. After discussing with the IDS pharmacy, it was concluded that a viable placebo could not be made due to manufacturing limitations and inability to replicate the taste, size, and physical description of omega-3 ethyl esters.

2.3 Study Design	2.3 Study Design This is a prospective, open label, randomized, parallel group, single center study. The study expects to enroll 90 patients from clinic to participate. Patients will be randomized into one of three groups according to dosage, with 30 patients in each group. The randomization will be conducted using block randomization with blocks of 10. Note that this ensures that for each group of 30 participants, the sequence or permuted block, the treatments are approximately evenly distributed. As the "block" here is **not** a *statistical* block, there is no need to include block effects in the analysis plan. Sequence generation will be done using SPSS and at least one extra block will be included to account for patient drop-out, screen failures, or other unintended enrollment issues. Sequence generation will be provided using an Excel file or other preference of the investigational pharmacist, in full, so that the compounds can be created and numbered accordingly. Patients will be approached in clinic and asked if they would like to participate in the study. After written consent is received, supplements will be given prior to surgery. Surgery will be performed as usual, and anesthesiologists will follow American Society of Anesthesiologists (ASA) standardized protocol during surgery. Patients will continue to receive drug for 3 days postoperatively. 2.3.1 Study Population All adult patients undergoing elective on-pump open heart procedures at the Missouri University Hospital (University of Missouri Health Care, Columbia, Missouri, USA). 2.3.2 Inclusion Criteria - Age ≥ 65 years - ASA Physical Status I-IV 2.3.3 Exclusion Criteria

	- Inability to obtain written informed consent. - Inability to take study drug due to intubation or other reason. - Delirium present at screening. - Known hypersensitivity (e.g. anaphylactic reaction) to omega-3 ethyl esters or any of its components - Allergy to fish or shellfish. - Currently taking omega-3, omega-6, vitamin E, or fish oil supplements. - Significant renal disease with a serum creatinine ≥ 2 mg/dL. - Significant liver disease with ALT levels 1.5 times the normal range of 6-45 units/liter and AST levels 1.5 times the normal range of 10-42 units/liter. - History or diagnosis of neurodegenerative disease such as Parkinson's, Alzheimer's, or dementia. - History or diagnosis of bleeding disorder. - History or diagnosis of metabolic syndrome or disorder. - History or diagnosis of thyroid problems such as hyperthyroidism or hypothyroidism.
2.4 Diversity & Inclusion	All patients eligible for study enrollment will be approached to participate in the study regardless of age, race, ethnicity, and sex, pursuant to available randomization slots.

2.5 Study Flowchart	
2.6 Study Procedures	2.6.1 Experimental Design - A prospective, open label, randomized, controlled, parallel design, single center study. - Patients undergoing elective on-pump open heart procedures. - Patients will be randomized into one of three groups to receive either: high dose (4 capsules) of omega-3 ethyl esters, low dose (2 capsules) of omega-3 ethyl esters, or standard of care. - Each group will have 30 patients. 2.6.2 Study Periods

1. Study preparation: Protocol budget, departmental and hospital meetings, institutional review board (IRB) preparation, registration to clinicaltrials.gov, coordinator and co-investigator training, permuted block randomization sequence generation, source document development, drug storage and documentation by MU IDS Pharmacy.
2. Ongoing study maintenance: Departmental and hospital meetings, coordinator and co-investigator training, IRB maintenance, clinicaltrials.gov maintenance.
3. During clinic visit before surgery: Patient screening, obtaining of informed written consent, administration of cognitive assessments, and patient randomization.
4. Day before surgery: Notification of study physicians, coordinators, and pharmacy of potential patients, and drug preparation by MU IDS Pharmacy.
5. Day of surgery: Confirmation of inclusion and exclusion criteria, go through informed written consent for possible questions and confirm that patient still wants to participate, patient education with provision of examples for study measures and symptom grading criteria used in study questionnaires, administration of cognitive assessments, drug delivery to patient room before surgery, document medications, times, and adverse events.
6. Patient visit at approximately 10 AM ± 1 hour on Post-Op Day 1-3 or until delirium resolves: Record cognitive assessments, perioperative times, adverse events.
7. Electronic chart review one week after discharge: Record all adverse events, medications, hospital discharge information, and readmission/emergency room visits.

2.6.3 Postoperative Pain Management

Postoperative pain management will be per clinical team and hospital standard care. Opioid requirements during hospitalization will be

	calculated in milligram morphine equivalents (MME) for research purposes. Postoperative nausea and vomiting treatment will be managed by the clinical team. 2.6.4 Postoperative Follow-Up 1. Visits at approximately 10 AM ± 1 hour on post-op Days 1, 2, and 3, or until delirium resolves: a. Conduct delirium assessments, recording of adverse events. b. Patient re-education of remaining study measures and provision of answers to any follow-up questions. 2. Electronic chart review one week after discharge: a. Record all adverse events, medications, hospital discharge time, and need for any readmission/emergency room visits.
2.7 Study Duration	The patients will be identified and approached regarding participation in preoperative clinic, where informed consent will be obtained. Eligibility screening will be confirmed the day before the surgery. The total study duration is 30 days. Our institution has two cardiothoracic surgeons each performing about 3-4 cardiopulmonary bypass, cardiac bypass and cardiac bypass with grafting surgeries per week. We expect to complete the study within 1 year.
2.8 Statistical Analysis and Sample Size Justification	2.8.2 Data Storage and Analysis The study data will be electronically coded in a database. Analyses will be performed by the investigator team. SPSS statistical software will be used for all analyses. Data will be summarized overall and by treatment. All data will be tested for normality. Normally distributed data will undergo Analysis of Variance and non-normally distributed data will be analyzed with Kruskal-Wallis test. Post hoc analyses will be applied as appropriate. Correlations will be determined with Pearson Product Moment or Spearman's Rank Order tests as appropriate. For the primary outcome, a logistic regression analysis will be

	used, with known covariate age and suspected covariate sex. Additional covariates may be considered, if warranted (e.g., length of stay). 2.8.3 Variables/Time Points of Interest 1. Demographics: Sex, age, weight, height, BMI, ASA PS classification, comorbidities especially ones listed in exclusion criteria (autoimmune disease, neurodegenerative disorder, cancer, liver, or kidney disease). 2. Intraoperative: Medications, reversal agents, fluids, blood loss/transfusion, duration of surgery and anesthesia. 3. Post-Op Day 1-3 or until delirium resolves: Delirium assessment scores, narcotics/pain medications, time supplement was given. 4. One Week After Discharge: Any adverse events or complications, time of discharge from hospital (hospital length of stay). 2.8.4 Statistical Power and statistical analyses Power and sample size were calculated with the method described by Day and Graham (1989) specifically for comparing multiple groups in clinical trials. Power was set at 0.8 with an alpha of 0.05, yielding a sample size of 30 patients per group to account for dropouts.
2.9 Specific Drug Supply Requirements	2.9.1 Drug Supply Omega-3 ethyl esters will be purchased locally by the MU IDS Pharmacy as marketed product. 2.9.2 Drug List - Omega-3 ethyl esters, Epic Pharma LLC., NCD: 42806-0552-12, 120 capsules per bottle 2.9.2 Drug Preparation

	The MU IDS Pharmacy will prepare all medications according to patient randomization. Medications will be placed in envelopes and delivered to the patient by study staff.
2.10 Adverse Experience Reporting	2.10.1 Adverse Event Reporting All patient adverse events will be recorded and reported according to the study visit schedule. Postoperative complications including the need for postoperative mechanical ventilation, re-intubation, residual paralysis, pneumonia, infections, other adverse events during the hospital stay, and readmissions/emergency room visits during first week post discharge. Adverse events, protocol deviations, and other unanticipated problems will be reported by either the principal investigator or the co-investigators to the IRB within 5 business days. Unanticipated deaths will be reported to the IRB within 1 working day. 2.10.2 Data Safety Monitoring Plan All study-related electronic data will be kept in an access-controlled folder on the University of Missouri's OneDrive. Only individuals registered on this study with the IRB will have access to these data. Paper records will be kept in a fire-safe, access-controlled cabinet. Data will be de-identified after the study's conclusion to ensure patient confidentiality.
2.11 Itemized Study Budget	Itemized budget will be uploaded to eCompliance upon completion.
2.12 Compensation	Subjects will not receive compensation for their participation in this study.
2.13 References	2.12.1 References 1. Akintoye, E., Sethi, P., Harris, W. S., Thompson, P. A., Marchioli, R., Tavazzi, L., Latini, R., Pretorius, M., Brown, N. J., Libby, P., & Mozaffarian, D. (2018). Fish Oil and Perioperative Bleeding. Circulation. Cardiovascular Quality and Outcomes, 11(11), e004584. https://doi.org/10.1161/CIRCOUTCOMES.118.004584

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7. Kepler, C. K., Huang, R. C., Meredith, D., Kim, J.-H., & Sharma, A. K. (2012). Omega-3 and Fish Oil Supplements Do Not Cause Increased Bleeding During Spinal Decompression Surgery. www.jspinaldisorders.com

8. Omega-3 Ethyl Esters. Prescribing information. Epic Pharma LLC; 2020.

2.14 Publication Plan	After the completed data analysis (~3 months after completion of the study) we will submit an abstract(s) to the annual meeting for the American Society of Anesthesiologists (ASA) and in the same year submit a manuscript for peer reviewed publication according to the rules of the ASA conference embargo period (requirement of ASA scientific presentations) in a peer-reviewed anesthesiology or spine care journal.
2.15 Curriculum Vitaes	Updated curriculum vitaes are uploaded into the study's OneDrive folder.