

# Pilot, Randomized, Double-blind Trial To Study The Effect Of Parenteral Supplementation With Fish Oil Emulsion In The Nutritional Support Of Esophagectomized Patients

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**Study protocol**

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# Abstract

Background Esophagectomy is a major surgical procedure with a high degree of catabolic and postsurgical inflammatory response that conditions a high morbidity and a significant mortality. Enteral administration of  $\omega$ -3 fatty acids has been seen to be effective although its use is limited due to tolerance. There are few clinical trials with  $\omega$ -3 fatty acids parenterally in these patients, so we propose to investigate the effect of combining a lipid emulsion rich in fish oil with the standard enteral nutrition support. Methods Prospective, single-center, randomized, double-blind study in patients diagnosed with esophageal cancer and after esophagectomy treated with a lipid emulsion rich in  $\omega$ -3 fatty acid emulsion or a mixture of  $\omega$ -6 long chain triglycerides (LCT) / short chain triglycerides (MCT) 50%. After surgery, these emulsions will be added to the standard nutritional support in continuous infusion until complete 5 days of treatment. Patients will be randomized 1:1:1 in Group A 0,4g/kg/day of lipid emulsion rich in fish oil; Group B 0,8g/kg/day of lipid emulsion rich in fish oil and Group C 0,8g/kg/day of LCT/MCT emulsion. The main objective is to determine whether the administration for 5 days of intravenous lipid emulsions rich in  $\omega$ -3 fatty acids in patients after esophagectomy is effective in normalizing the interleukin-6 (IL6) compared with LCT/MCT emulsions, and if 0,8 g/kg/day dose is more effective than 0,4g/kg/day. Secondary outcomes include other inflammatory markers as C reactive protein (CRP), tumor necrosis factor alpha (TNF-a) and interleukin-10 (IL-10), and parameters of morbidity, safety, nutrition and mortality. Samples will be collected at the moment of surgery indication and on days 0, 1, 3, 5 and 21 to determine inflammatory, nutritional, hepatic and security parameters. In addition, clinical follow-up throughout the hospital stay and up to one year after surgery. Discussion There are few studies of fatty acids  $\omega$ -3 administered via parenteral in oesophagectomized patients. This study proposes to investigate the effect of combining fish-oil lipid emulsions administered via parenteral with enteral nutrition support, implying benefits such as: fast incorporation of lipids to the cellular membranes and to the inflammatory cascade, and the use of only one pharmaconutrient.

## Background

Esophageal cancer incidence increases with age, is more prevalent in men and is associated with risk factors such as smoking habit, obesity and alcoholism [1].

This cancer is frequently associated with protein-energy malnutrition [2] and usually has a poor prognosis due to late presentation and diagnosis, as well as patients not meeting criteria for curative treatment at the time of diagnosis. About one in five patients needs surgical resection.

Esophagectomy (EPG) is a major surgical intervention which involves total or partial esophageal resection and restoration of gastrointestinal continuity [1]. Despite improvements in perioperative care, EPG continues to be associated with high rates of morbidity and mortality [1, 2]. In fact, postoperative complications are common, including both primary surgical events, such as anastomosis dehiscence or chylothorax, and adverse medical events, principally pneumonia [1, 2].

Nutritional support therapy is important in these patients due to the malnutrition associated with this pathology. Additionally, some enterally administered pharmaconutrients have been shown to be effective in the reduction of postoperative complications [2]. Recent studies show that early enteral nutrition (EN) has other benefits: it increases immunocompetence, reduces infection rates and maintains intestinal functionality and structure. EN is cheaper and safer than parenteral nutrition (PN), however postoperative EN is associated with tolerance problems such as: diarrhea, abdominal distension, and paralytic ileus or nausea, and only 50% of patients achieve their nutritional objective [3]. Sometimes, symptoms become worse when caloric intake is increased, and EN discontinuation may be necessary [4].

Omega-3 fatty acids, the principal components of which are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are one of the pharmaconutrients with beneficial effects in postoperative morbidity. They are essential polyunsaturated fatty acids (PUFAs) and fish oil derivatives. Their administration can reduce proinflammatory cytokine production and regulate eicosanoid synthesis [5-7]. Immunomodulation with  $\omega$ -3 fatty acid based nutritional therapy has demonstrated benefits in reducing infectious postoperative complications and length of stay in elective gastrointestinal surgery patients, particularly in those who present with preoperative malnutrition [8, 9]. The enteral administration of  $\omega$ -3 fatty acids in esophagectomized patients has been assessed in different studies [3, 10-12]. These assays verify the variability in the assimilation of  $\omega$ -3 fatty acids when they are administered enterally, and show different results in relation to postoperative morbidity. However, two meta analyses [13, 14] conclude that enteral immunonutrition improves patient's morbidity without modifying their mortality.

The physiological role of  $\omega$ -3 fatty acids is extensively reported, not only in maintaining nutritional homeostasis but also in the resolution of inflammatory mechanisms [15] and in the course of inflammatory pathologies such as atherosclerosis or cancer. The effects of  $\omega$ -3 fatty acid administration in the metabolic response are still being explored and discovered. Due to their protective effect in inflammatory processes such as colitis, ischemia-reperfusion syndrome, pain, sepsis or acute pulmonary pathology, the role of  $\omega$ -3 fatty acids is relevant in artificial nutrition support.

PUFAs are precursors of proinflammatory as well as anti-inflammatory secondary messengers, and the physiological response produced depends on the balance of the lipid composition of the membrane. The eicosanoids derived from these PUFAs present receptors in different kinds of cells executing different physiological functions. The study of these secondary messengers in the esophagectomized patient, may establish their correlation with the patient's clinical pathway depending on the capacity of the  $\omega$ -3 fatty acids to modulate these secondary messengers.

Due to their iso-osmolarity, intravenous administration of lipid emulsions (LE) does not require a central line thereby avoiding any extra invasive treatment for the patient. In fact, LE may have protective properties for the vascular wall. Moreover, in patients considered for the study, the LE could be administered simultaneously with EN, so that gastrointestinal tract stimulation will not be interrupted, and the caloric goal achieved.

Studies of  $\omega$ -3 fatty acids administered parenterally in esophagectomized patients are poorly reported in the literature. This study proposes to investigate the effect of combining fish-oil LE administered parenterally with EN support in the framework of a randomized clinical trial. The difference between this approach and previous published studies is two-fold:

- Parenteral administration facilitates fast incorporation of lipids to the cellular membranes, and consequently to the inflammatory cascade [16].
- Use of only one parenteral pharmaconutrient ( $\omega$ -3 fatty acids) facilitates the caloric goal and enables the study of the immunomodulatory effect of one nutrient without interference from other nutrients. When immunonutrition is administered enterally, the commercialized products available are combinations of different immunonutrients. LE comprising combined long-chain  $\omega$ -6 fatty acids (LCT) and medium-chain fatty acids (MCT) is proposed as a control lipid to compare the effects on immunomodulation. These emulsions have the same physical appearance as  $\omega$ -3 LE. Although LCT emulsions have an active role in the reticuloendothelial system and on the inflammatory response, MCT emulsions are not sensitive to peroxidation and do not participate in the eicosanoid synthesis, so in consequence reduce the impact of the immunomodulatory effect derived from LCT[17].

## Methods

This trial is a prospective, single-center, randomized, double-blind study in patients diagnosed with esophageal cancer who post EPG are treated with a LE of  $\omega$ -3 fatty acid or a mixture of LCT/MCT 50%.

### 2.1 STUDY OBJECTIVES

The main objective of this study is:

- To establish if the endovenous administration of  $\omega$ -3 fatty-acid fish-oil LE for 5 days in esophagectomized patients is effective in reducing inflammation – measured as seric concentration of Interleukin-6 (IL6) – compared to the administration of LE of LCT/MCT. Additionally, to determine if doses of 0.8 g/kg/d are more effective than doses of 0.4 g/kg/d in the normalization of IL-6.

The secondary objectives aim to determine if the intravenous administration of  $\omega$ -3 fatty-acid fish-oil LE for 5 days in esophagectomized patients shows differences compared with the administration of LCT/MCT LE with regard to:

- Seric concentration of other inflammatory parameters: C-reactive protein (CRP), tumoral necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-10 (IL-10), interleukin-8 (IL-8) and soluble interleukin-2 receptor (sIL-2R / CD25s). In addition, whether these markers, alone or in combination, show equal or greater efficacy in the measure of the inflammatory response compared to IL-6.
- Postoperative complications: suture dehiscence, chylothorax, pneumonia and other infections.
- Safety, measured as hepatic impairment and alterations in coagulation parameters.

- Nutritional parameters: albumin, prealbumin and lymphocytes.
- Mortality: evaluated at hospital admission and at one year post-surgical intervention.

## 2.2. STUDY DESIGN

Prospective, unicentric, randomized, double-blinded study in patients with esophageal cancer and esophagectomized by the Ivor-Lewis or McEwan techniques. The study will be carried out in accordance with the good clinical practice in our hospital.

All participants will receive a LE by continuous infusion in addition to EN support for 5 days post-surgery. The standard EN support will be initiated with Impact Neutre® 500ml (a normocaloric, hyperproteic and immunomodulatory diet composed of 3.9g of lipids in each 100ml, 1.8g of MCT/100ml, 0.61 g of  $\omega$ -6 fatty acids/100 ml and 0.6g of  $\omega$ -3 fatty acids/100 ml, with a caloric input of 144kcal/100ml daily); it will be initiated at 21 ml/h and titrated to 1500ml daily.

When the body mass index (BMI) is greater than 25, the ideal adjusted body weight will be applied following the formula: "Ideal adjusted body weight = ideal body weight + (actual body weight - ideal body weight) \* 0.25 (if BMI 26-30) or \*0.5 (if BMI>30)". Group A will receive a LE mixture of 0.4 g/kg/d of fish-oil and 0.4g/kg/d of LCT/MCT, Group B will receive 0.8 g/kg/d of fish-oil LE and Group C will receive a LE mixture of 0.8 g/kg/d of LCT/MCT 50%.

### 2.2.1 Study population

Patients diagnosed with esophageal cancer and candidates for EPG by the Ivor-Lewis or MacEwan techniques, and who meet the following **inclusion criteria**:

1. 18 years old or older, any gender and any race.
2. Willing and able to give their written informed consent (IC) for the study. If a subject is unable to give written IC, his legal representative may do so in his/her place.
3. Having access to the digestive tract.

Patients who meet the following **exclusion criteria** will not be chosen:

1. Hypersensitivity type 1 or idiosyncratic reactions to any of the LE components.
2. Pregnant or breastfeeding women.
3. Plasmatic triglycerides concentration >3 mmol/L.
4. In receipt of chronic treatment with corticosteroids or immunosuppressants in the last month.
5. HIV diagnosis.
- 6.

7. Hepatic impairment classified as Child-Pugh grade B (significant functional compromise) or grade C (decompensated disease).

#### Subject and/or treatment withdrawal criteria:

Patients can voluntarily refuse to continue in the study at any time. In addition, presentation of any adverse effect related to the treatment will lead to a treatment withdrawal and to exclusion from the study.

All patients who present with surgical complications classifiable as grade IV of the Dindo-Clavien classification [18] will be excluded from the study.

### **2.2.2 Patients recruitment, randomization and allocation**

All patients allocated for EPG following medical criteria, and those who meet the inclusion criteria will be candidates to participate in the trial.

The surgical team will be responsible for communicating the possibility of participating in this trial when informed consent is obtained for the surgical intervention. Informed consent for participation in this trial will be collected before randomization.

Subjects will be randomized to three groups (1:1:1) by a pharmaceutical researcher after recruitment by the surgical team:

- Group A will receive 0.4 g/kg/d of fish-oil LE and 0.4g/kg/d of a LE mixture LCT/MCT receiving a total dose of 0.8g/kg/d of LE over 5 days post-surgery,
- Group B will receive 0.8 g/kg/d of fish-oil LE,
- And Group C will receive 0.8 g/kg/d of a LE mixture of LCT/MCT 50%.

This allocation will be blind for all patients and health personnel. The allocation sequence (computer-generated random numbers) will be generated by the pharmaceutical researcher and it will be performed by randomized blocks permuted with the block size defined at random. In the first step, blocks of size 3 with possible sequences ABC, ACB, CAB and CBA, and size 6 will be defined. In a second step the clusters will be randomized, and in a third step the sequences will be randomized within the blocks. This method ensures that the groups are balanced throughout the study, and that the researcher cannot predict the sequence. The pharmaceutical researcher will be responsible for patient assignment to the corresponding intervention group, and will also assign a numbered patient identification code for each patient in the trial. The composition of the emulsion administered to each patient will only be known by: the pharmaceutical researcher responsible for clinical trials, the pharmaceutical researcher who will validate its conduct, and the personnel who will conduct it.

### **2.2.3 Number of participants subjects and trial duration:**

Recruitment will last a total of 24 months from the approval date. Each subject will participate in the trial for a year post-surgical intervention.

On the basis of the results obtained and as referenced by Furukawa et al [19] (a study of the values of IL6 in esophagectomized patients who received PN with  $\omega$ -6 fatty acids or without lipids), and considering that the effect of administration of fish-oil emulsion (with  $\omega$ -3 fatty acids) will be similar to the non-administration of  $\omega$ -6 fatty acids, a sample size of 33 patients is estimated for 80% of potency and 5% of  $\alpha$  error with 10% of anticipated losses.

## **2.3 STUDY VARIABLES**

The main variable of this study is the variation of seric concentration levels of IL6 at randomization and on Days 1, 3, 5, 21 post surgery in esophagectomized patients receiving fish-oil LE parenterally for 5 days compared with those receiving LCT/MCT LE.

The secondary variables will examine whether intravenous administration of fish-oil LE instead of LCT/MCT for 5 days leads to differences from randomization and on Days 1, 3, 5 and 21 post-randomization regarding to:

- Seric concentrations of inflammatory markers: CRP, TNF- $\alpha$ , IL-10, IL-8 and sIL-2R / CD25s.
- Morbidity measured as postoperative complications: suture dehiscence, chylothorax, pneumonia and other infections.
- Safety measured as hepatic impairment (total bilirubin, alanin-aminotransferase, aspartate-aminotransferase, gammaglutamil transferase, alkaline phosphatase) and alteration in coagulation parameters (International Normalized Ratio, prothrombin time, platelet count).
- Nutritional parameters: albumin, prealbumin and lymphocytes.
- Mortality measured for a year after surgical intervention.

## **2.4 TREATMENTS USED IN THE TRIAL**

### **Research Drugs**

The fish-oil emulsion employed in the study is commercialized as Omegaven®, and the mixture emulsion of LCT/MCT is commercialized as Lipofundina®

Lipids emulsions will be prepared at the Pharmacy Department with the same aseptic conditions used for PN (in a laminar flow cabinet). They will be delivered ready for administration in a multilayer bag, and will be stored and conserved in accordance with the normal procedures of the department of Pharmacy. The double blind will be facilitated by the identical galenic presentation of the LE.

Emulsions will be dispensed when the trial recipe used in the University Hospital of Bellvitge is finalized.

### **Others concomitant treatments**

During this trial both the patient's usual medication and any support medication needed during admission will be maintained as usual.

## 2.5 DATA COLLECTION

### **Demographic, pharmacological, clinical and analytical data**

Demographics, clinical and analytical data generated following normal clinical practice will be collected and recorded in the Data Collection Logbook (DCL).

Demographic data: age, gender, body weight, height and BMI will be recorded.

Pharmacological data: any adjuvant chemotherapy received by a patient after trial treatment will be recorded specifying the treatment scheme.

Analytical data:

- Inflammatory parameters: values of IL-6, CRP, TNF- $\alpha$ , IL-10, IL-8 y CD25 on Days 0, 1, 3, 5 and 21 post surgery will be recorded. These values have been selected according to what is reported in the literature in similar studies [19-25]. Also, these same values will be recorded pre-operatively at the time surgical intervention is indicated to show the patient's baseline inflammatory status.
- Nutritional parameters: albumin, prealbumin and lymphocytes at the time surgical intervention is indicated and on Days 0, 1, 3, 5 and 21.
- Hepatic parameters: total bilirubin, alanin-aminotransferase, aspartat aminotransferase, gammaglutamil transpherase and alkaline phosphatase at the time surgical intervention is indicated and on Days 0, 1, 3, 5 and 21.
- Safety: INR, prothrombin time and platelet count at the time surgical intervention is indicated and on Days 0, 1, 3, 5 and 21.

The total number of blood extractions per patient will be 6.

Clinical data: the following data will be recorded:

- Post-surgery complications such as chylothorax, dehiscence, pneumonia and other infections.
- Mortality: from the day of surgery to one year following surgery.
- Nutritional support: the amount of EN received by each patient will be recorded to determinate total calories administered.

Quantification of cytokines:

- Sample collection: Samples will be centrifugated at 700xg an hour post-extraction. Samples will be aliquoted and stored frozen at -80°C until analysis (1 year). Cytokine values will be determined by

Enzyme-Linked ImmunoSorbent Assay (ELISA).

## **2.6 RESPONSE ASSESSMENT**

### **2.6.1 Statistical analysis:**

Descriptive statistics will be employed for all collected variables data, such as baseline values for inflammatory, nutritional, hepatic and safety parameters, in frequency tables. For continuous variables, statistical descriptions will be used (n, average, standard deviation, value range and median), meanwhile grouped percentages will be used for categorical variables.

The main objective is to establish the difference between basal values of inflammatory parameters and values at Day 5 post randomization, and to assess differences between Days 1, 3 and 21. The secondary objectives are to establish the difference between basal values of morbidity, safety and nutritional parameters and those values at Day 5 post randomization.

Significance will be calculated using Student t-test for matching data or Wilcoxon-test (non-parametric test) depending on whether normality can be assumed or not. To establish the differences among the 3 groups for the same period of time, Student's t-test (parametric test) or Mann Whitney U test (non-parametric test) will be used, depending on whether normality can be assumed or not. For categorical variables, the chi-square test or the Fisher test will be used when necessary.

The significance level will be established with a 95% confidence interval (CI). Data will be processed with SPSS v 19.

## **2.7. ADVERSE EVENTS NOTIFICATION**

All serious adverse events, regardless of their causal relation, will be reported to the study monitor immediately, sending a fax to +34932607884, in a maximum of 1 working day. According to articles 43 and 44 of the RD1090/2015, which regulates clinical trials in Spain, and in accordance also with sections 25 to 27 from the regulatory document concerning implementation of normal clinical trials (6th version, May 2008), the monitor will be responsible for communicating every serious and unexpected adverse event to the competent Health Authorities.

<http://www.aemps.es/actividad/invClinica/ensayosClinicos.html>

## **2.8. MONITORING**

Monitoring tasks will be carried out by a monitoring company hired for this purpose. The person responsible for monitoring this study will have access to any clinical data required for the conduct of the trial and to all interim results. There will be four monitor-auditing visits that will take place at the beginning of the study prior to the first patient recruitment, two during recruitment of patients, and when the follow-up of the last patient is finished, which means the end of the study. The monitor will be responsible for communicating any adverse events to the health authorities.

## Discussion

These days,  $\omega$ -3 fatty acids are playing an increasingly emergent role in artificial nutrition, due to the discovery of their protective and immunomodulatory effects in inflammatory processes [20-26].

It is known that the PUFAs of cellular membranes are precursors of secondary messengers that can act as pro-inflammatory or as anti-inflammatory agents, and physiological response depends on the balance of the lipid composition of membranes [12, 15, 16].

The study of these secondary messengers in esophagectomized patients, may establish their correlation with the patient's clinical progress, depending on the capacity of the  $\omega$ -3 fatty acids to modulate these secondary messengers.

This study combines high-risk patients with considerable inflammatory response with intravenous administration of significant quantities of  $\omega$ -3 fatty-acids, and may lead to the discovery of a new pharmacological strategy that is simple, safe and cost-effective. It will also provide useful data through the study of a new mediator.

## Trial Status

Protocol version 2 of 06/08/2017

Patient recruitment began: 11/05/2018

Approximate date of completed patient recruitment: 01/05/2020

## Abbreviations

Body Mass Index (BMI)

C-Reactive Protein (CRP)

Confidence Interval (CI)

Data Collection Logbook (DCL)

Docosahexaenoic Acid (DHA)

Eicosapentaenoic Acid (EPA)

Enteral Nutrition (EN)

Enzyme-Linked ImmunoSorbent Assay (ELISA)

Esophagectomy (EPG)

Informed Consent (IC)

Interleukin-6 (IL6)

Interleukin-10 (IL-10)

Interleukin-8 (IL-8)

Lipid Emulsions (LE)

Ω-6 long-chain fatty acids (LCT)

Medium-chain fatty acids (MCT)

Parenteral Nutrition (PN)

Polyunsaturated Fatty Acids (PUFAs)

Soluble interleukin-2 receptor (sIL 2R / CD25s)

Tumoral Necrosis Factor-α (TNF-α)

## Declarations

### **Ethical aspects and confidentiality:**

Data will be collected in a database where patients will be codified with an assigned consecutive number, avoiding the use of any clinical history number or initials, and thereby ensuring data protection.

All participating patients will have signed an informed consent form following the recommendations of RD 223/04. Clinical treatment will be in accordance with good clinical practice.

Confidentiality will be guaranteed following the Organic Law of Personal Data Protection 15/99. This trial has been approved by the Ethics Committee of Clinical Investigation of our Hospital and by the Spanish Agency of Drugs and Sanitary Products.

### **Availability of data and material**

The datasets used and/or analyzed during the current study will be available from the corresponding author on reasonable request.

### **Consent for publication**

Not Applicable

#### **1. Competing interests**

ASL, MFA, MMM, GCC, JBM, EPC, SNV have no competing interests to declare. MBT has received payment for development of educational presentations including service on speakers' bureaus from Baxter and Fresenius Kabi in the context of educational sessions (approximately 4 hours every year). MBT has also received payment for Congress subscriptions and accommodation (one European congress every 2 or 3 years) from Fresenius Kabi. JLT has received payment for development of educational presentations including service on speakers' bureaus from Baxter and Fresenius Kabi in the context of educational sessions (approximately 4 hours every year). JLT has also received payment for Congress subscriptions and accommodation (ESPEN European Congress 2015 and 2018) from Fresenius Kabi. NVC has received payment for development of educational presentations including service on speakers' bureaus from Shire. NVC also has received payment for Congress subscriptions and accommodation from Nutricia and Nestlé. MBT, JLT, ELB, JLT and NVC received a grant from the Ministry of Economy, Industry and Competitiveness, which is part of the State Research Agency, through the project AES-FIS PI14/00706 (15FIS026), and also received a grant from the Spanish Society of Hospital Pharmacists through the project AISEFH PR030/14 (14PSJ009). Both projects take place in the Hospital University of Bellvitge.

## 2. Funding

This study will be funded by the research foundation of our hospital by donations from pharmaceutical laboratories not related to the products used in this study or involved in the conduct of the study.

## 3. Author's contributions

MBT, JLT, ELB, and ASG conceived the work. ASG, MBT, ELB and JLT contributed equally to the writing of this study protocol. MFA, LFT, MMM, NVC, GCC, JBM, EPC, SNV contributed equally to the final review of this study protocol.

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## Figures

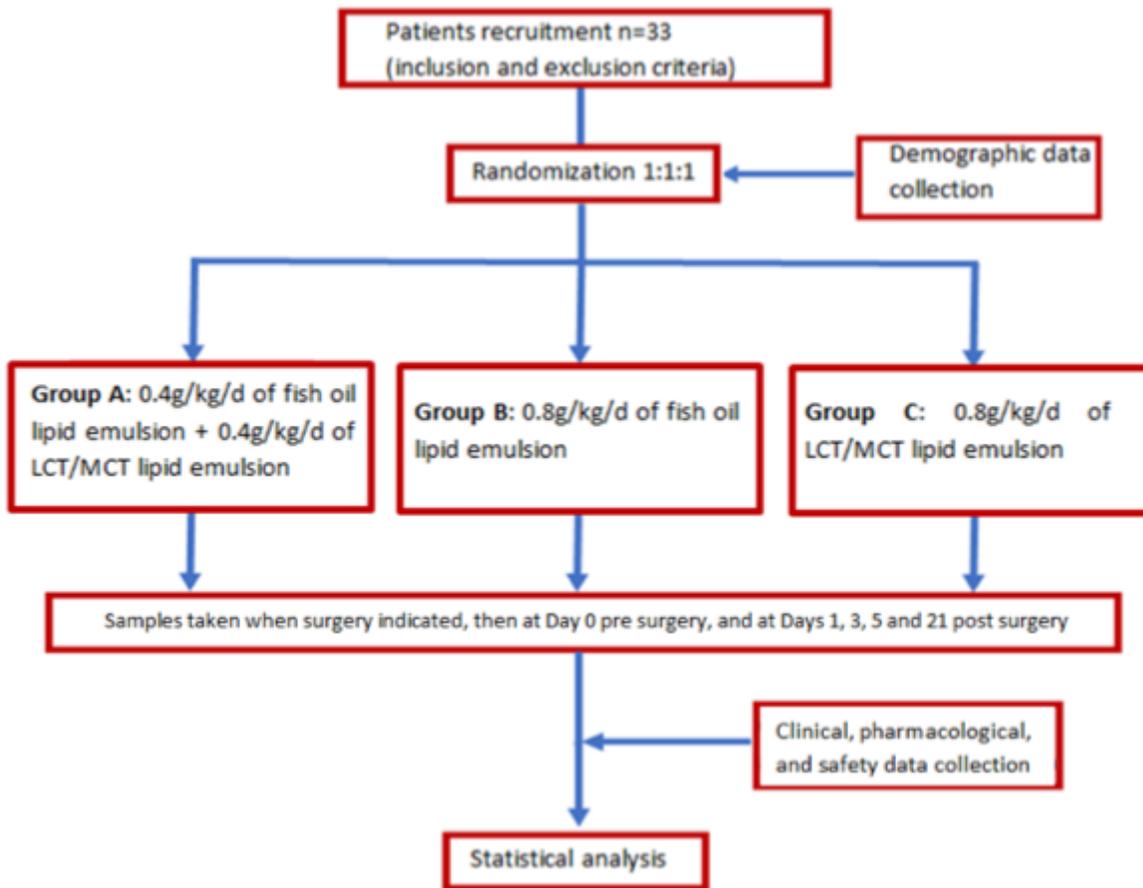


Figure 1

Study design flow chart.

TIMEPOINT**	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
	-t <sub>1</sub>	0	t <sub>1</sub>	t <sub>2</sub>	t <sub>3</sub>	t <sub>4</sub>	etc.	t <sub>c</sub>
<b>ENROLMENT:</b>								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
<b>INTERVENTIONS:</b>								
[Intervention A]			X					
[Intervention B]			X					
[Intervention C]			X					
<b>ASSESSMENTS:</b>								
[List baseline variables]	X	X						
[List outcome variables]				X	X	X	etc.	X
[List other clinical data variables]			X	X	X	X	etc.	X

Figure 2

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SPIRITFillablechecklist15Aug2013ANA.doc](#)