Version date 1/12/2018

Title of project:
Use of an intravenous fish oil emulsion in infants with cholestasis

Sponsored by:
N/A

Pharmaceutical Support Provided by: [if applicable]
N/A

IND # or non-IND Protocol *[Select one]*
N/A – IND# to be obtained from FDA if a patient qualifies for study

Protocol Chair/Principal Investigator:	**Arthur J. de Lorimier**
Protocol Co-Chair(s)/PIs:	**N/A**
Protocol Vice Chair(s): [if applicable]	**N/A**
Clinical Trials Specialist: [if applicable]	**N/A**

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03/11/11

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SITES PARTICIPATING IN THE STUDY

Sites Participating in the Study [remove Main if no substudy]

UC-Davis

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PROTOCOL TEAM ROSTER

Chair Arthur J. de Lorimier

Co-Chairs No

Vice Chair(s) No

Clinical Representative No

Clinical Trials Specialist No

Statistician(s) No

Scientific Committee Representative (if assigned) No

Data Manager No

Pharmacist No

Field Representative No

Laboratory Technologist No

Laboratory Data Coordinator No

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STUDY MANAGEMENT

SCHEMA

Use of an intravenous fish oil emulsion in infants with cholestasis

DESIGN Observational, compassionate use, single cohort study

DURATION Open

SAMPLE SIZE 25

POPULATION Infants less than 12m of age at time of recruitment

STRATIFICATION *(as required)* N/A

REGIMEN OR INTERVENTION *(as required)* N/A

SUBSTUDIES *(as required)* N/A

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1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

Use of omegaven in infants with cholestasis will be temporally related to resolution of cholestasis.

1.2 Primary Objective(s)

The aims of the study are to assess the effect of intravenous fish oil emulsion (omegaven™) in place of the currently used intravenous soybean oil lipid emulsion (Intralipid™) in subjects with short bowel syndrome and cholestasis or with PNALD (parenteral nutrition associated liver disease).

2.0 INTRODUCTION

2.1 Background

Functional short gut (or short bowel syndrome, SBS) is defined as the inability to tolerate all nutritional requirements via the enteral route, and a continuing dependence of partial or complete parenteral nutrition.

Development of SBS (short bowel syndrome) is more common in newborn infants than at any other age group, and may result from gastroschisis, gastrointestinal atresia, intestinal volvulus, or necrotizing enterocolitis. Treatment is aimed at:

1. Nutritional support, through the use of parenteral nutrition.
2. Gut rehabilitation and adaptation through gradual introduction and advancement of enteral feeds.
3. Prevention of secondary problems (e.g. bile acid deficiency or bacterial overgrowth).
4. Prevention of complications (e.g. cholestasis).

Concerted, coordinated management, including parenteral nutrition, has greatly improved the survival and quality of life of subjects with SBS. However, prolonged use of parenteral nutrition is not without risk. Parenteral nutrition associated cholestasis (PNAC); also know as parenteral nutrition associated liver disease (PNALD) or intestinal failure associated liver disease (IFALD); is one of the leading causes of death in SBS.

The causes of PNALD are unclear, but may include:

1. Absence of enteral feeds.
2. “Toxic” components in parenteral nutrition (e.g. aluminium, phytosterols, methionine, tryptophan).
3. Lack of certain beneficial nutrients in parenteral nutrition (e.g. serine, choline).

In recent years, much attention has been paid to the effect of parenteral lipid on PNAC. In the US, parenteral lipids are vegetable-based. Most widely used is Intralipid™ with is

a mixture of soybean oil and egg phospholipids. Although it has a generally excellent short- and long-term safety record, there are concerns about its long term use. As it is vegetable based is contains relatively high amounts of phytosterols (cholesterol-like lipids derived from plants). In adults and children with SBS and PNAC, serum levels of phytosterols correlate with the degree of hepatic and biliary dysfunction.

Omegaven is a fish-oil derived intravenous lipid emulsion that is not licensed in the US, but is widely used in Europe. It differs in composition from intralipid in many ways, for example it is much higher in omega-3 fats, lower in omega-6 fats, and contains no phytosterols.

Composition of Different iv lipid emulsions (from Puder 2009)

TABLE 1. Comparison and Characteristics of Parenteral Lipid Emulsions (100 g fat/L)

Product	Intralipid	Liposyn II	Omegaven
Manufacturer	Fresenius Kabi	Hospira	Fresenius Kabi
Oil source (g)			
Soybean	100	50	0
Safflower	0	50	0
MCT	0	0	0
Olive oil	0	0	0
Fish	0	0	100
Fat composition (%)*			
Linoleic	50	65	0.4
α-Linolenic	9	4	<0.2
EPA	0	0	2.1
DHA	0	0	2.3
Oleic	26	17.7	1.0
Palmitic	10	8.8	0.6
Stearic	3.5	3.4	0.1
Arachidonic	0	0	0.3

There are an increasing number of case-control studies suggesting significant clinical benefits to the use of omegaven in established PNALD in infants (Gura 2006, Gura 2008, Diamond 2009, Puder 2009).

The largest of these published cohorts is that of Puder, from Boston Children's Hospital (see attached file). In that study 42 infants who developed PNALD on standard intravenous lipid emulsions were given omegaven, and compared to 49 historical controls. Subjects were eligible for omegaven if they had cholestasis (direct bilirubin ≥ 2 mg/dL), were likely to be on parenteral nutrition at least 30d, and had acquired or congenital GI disease. Subjects with cystic fibrosis, metabolic disorders or hepatitis C were excluded. They were compared to historical controls who had two consecutive direct bilirubin measurements ≥ 2 mg/dL. Omegaven was given at a dose of 1 g/kg/d, and intalipid at 1-4 g/kg/d (depending on attending preference and lipid tolerance). The fish oil group were generally more sick at study entry than the historical controls, they had been on parenteral nutrition longer (63d *vs.* 40d, p=0.008) and their direct bilirubin was higher (5.5 *vs.* 3.3, p=0.0003). Despite these baseline differences, the fish oil group had a steady and sustained fall in direct bilirubin and ALT, while these measures continued to increase in the historical controls.

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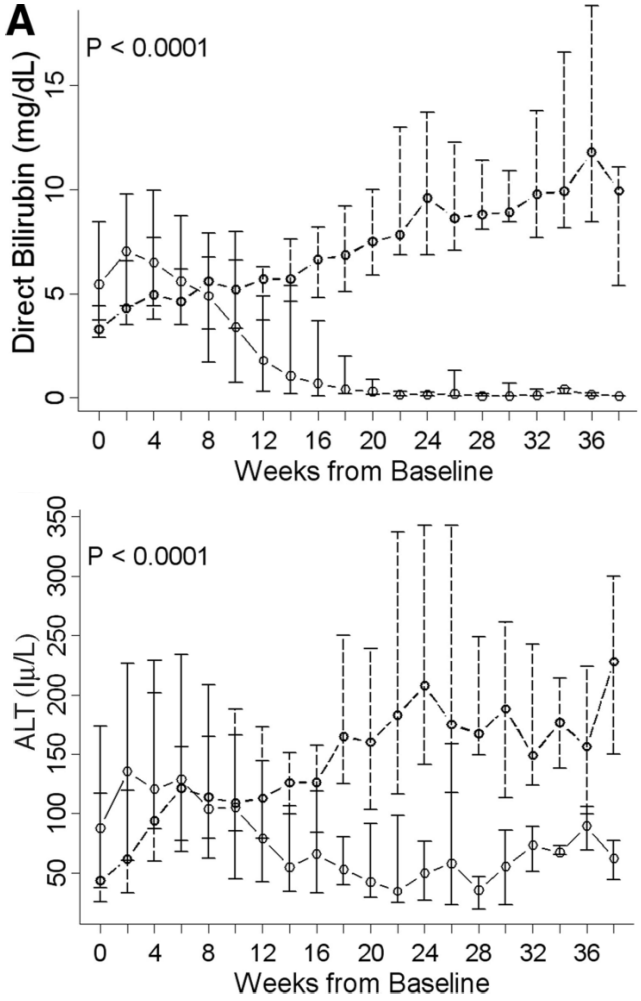
Figure Direct bilirubin and ALT in the fish oil group, and the historical controls (from Puder 2009).



Cholestasis resolved in 45% (19/42) of the fish oil group while still on PN, compared to 4% (2/46) of the historical cohorts.

The rate of the combined outcome of death or required liver transplant was significantly lower in the fish oil group (9.5%) than in the historical controls (34.7%, p=0.0005). The crude rate of reversal of cholestasis in subjects who did not die or require liver transplants was 8.6x greater in the fish oil group than in the historical controls. This increased to 17.4x higher rate once differences in baseline characteristics were accounted for.

The main safety measures followed (hypertriglyceridemia, and coagulopathy) significantly favored the fist oil group.

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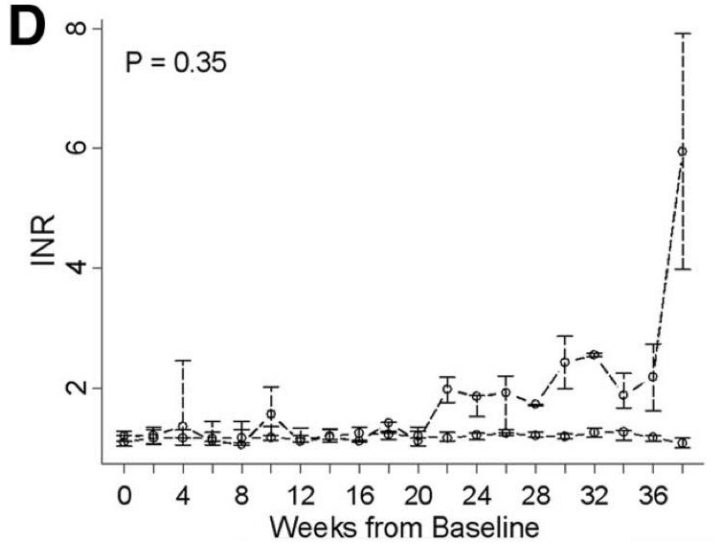
Table Incidence of hypertriglyceridemia and coagulopathy in fish oil group, and the historical controls (from Puder 2009).

TABLE 3. Safety of Fish Oil From Baseline Until the End of Follow-Up*

Safety Marker	Fish Oil (n = 42)	Soybean Oil (n = 49)	*P*
Triglycerides (mg/dL), mean ± SD†	105	166	0.0002
Hypertriglyceridemia (>400), rate (weeks of observation)	0.3	8.8	0.0003
INR, mean†	1.2	1.6	0.004
INR >2, rate (weeks of observation)‡	1.5	3.6	0.08
Platelets, mean†	192	174	0.44
T/T ratio, mean†	0.032	—	—
T/T ratio >0.2, rate (weeks of observation)‡	0.5	—	—

Although there was no significant difference in INR between the groups over the entire study, INR began to increase in the controls near the end of the study as they developed worsening end-stage liver disease. In the fish oil group, INR remained low during the entire study.

Figure INR in the fish oil group, and the historical controls (from Puder 2009).



References

Puder 2009. Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. Ann Surg 2009;250:395-402.

Gura 2006. Reversal of parenteral nutrition-associated liver disease in two infants with

short bowel syndrome using parenteral fish oil: implications for future management. Pediatrics 2006;118:e197-201.
Gura 2008. Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. Pediatrics 2008;121:e678-86.
Diamond 2009. Changing the paradigm: omegaven for the treatment of liver failure in pediatric short bowel syndrome. J Pediatr Gastroenterol Nutr 2009;48:209-15.

3.0 STUDY DESIGN

Compassionate use, single cohort, observational study.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

Infants on parenteral nutrition who have congenital or acquired gastrointestinal diseases that place them at risk of short bowel syndrome (SBS) or prolonged parenteral-nutrition-dependence, will be considered eligible for the study if either (1) they remain cholestatic (bilirubin > 2 mg/dL) after 4wks of reduced lipids and trace elements, or (2) If their direct bilirubin is > 6 mg/dL in the absence of suspected or proven infection.

4.2 Exclusion Criteria

Subjects will be considered ineligible for the study if they are felt unlikely to survive more than 30d, or unlikely to require parenteral nutrition for at least 30d.

4.3 Study Enrollment Procedures

Clinical nutrition rounds, between the PI and the NICU dietician, occur every 1-2wk as part of the routine clinical care of the infants. As part of the clinical care of the infants, and infant identified as having cholestasis or PNALD (direct bilirubin ≥2 mg/dL on two consecutive occasions ≥8d apart) have their intralipid infusion rate reduced to 1 g/kg/d and have the trace elements added to their parenteral nutrition reduced. The current protocol will not alter this.

5.0 STUDY TREATMENT (*OR INTERVENTION*)

5.1 Regimens (*or Intervention*), Administration, and Duration

The intervention is the use of omegaven (an intravenous fish oil emulsion) in place of intralipid (the currently used soybean oil intravenous lipid emulsion, until parenteral nutrition is discontinued, or until cholestasis resolves.

Parents of eligible patients will be approached for consent for their infants to take part in the study. If they agree, the PI will contact the FDA to receive an IND number for the infant (copies of the required FDA paperwork will be sent to the IRB). Omegaven will be ordered from the manufacturer. Once the IND number is received, the IRB will be informed of the subjects IND number. Once the IND number is received, and communicated with the IRB, and the omegaven is received, intralipid infusions will be

stopped and omegaven will be infused at the rate of 1 g/kg/d. Clinically-indicated labs will be monitored, as for all patients on prolonged parenteral nutrition, i.e. CBC, electrolytes, BUN, Creatinine, ALT, AST, Alkaline phosphatase, albumin, total bilirubin, direct bilirubin and serum triglycerides will be measured at least every 2 weeks. No additional labs will be required as part of the study.

Adjustment of Omegaven Dosage
Hypertriglyceridemia: If serum triglycerides are > 400, other causes will be excluded (e.g. renal disease, medications). If no other causes can be found, the clinical team caring for the baby may decide to reduce the infusion of omegaven by 25%, depending on their clinical assessment of risk and benefits.
Essential Fatty Acid Deficiency: If there are concerns that essential fatty acid deficiency may be occurring (characteristic skin rash plus unexplained thrombocytopenia), the clinical team caring for the baby may decide to discontinue omegaven and re-start infusion of intralipid at a rate of 0.5 – 1 g.kg/d.
Other: The clinical team caring for the baby will be allowed to withhold the omegaven infusion or restart the intralipid infusion for any reason if they believe that to be in the best interests of the patient.

Discontinuation of Omegaven
Omegaven will be discontinued either (1) once parenteral nutrition is discontinued, irrespective of the direct bilirubin level, or (2) once the direct bilirubin has been below 2 mg/dL for more than 2weeks. In the later case, if the direct bilirubin rebounds above 2 mg/dL at anytime the omegaven can be restarted. If omegaven is re-started, the discontinuation criteria will be the same as before: i.e. it will be discontinued when parenteral nutrition is discontinued or when the direct bilirubin has been below 2 mg/dL for more than 2 weeks.

Safety Assessment
Routine clinical labs will be used to monitor for the principal side effects of omegaven (thrombocytopenia, hypertriglyceridemia), and the response to treatment (direct bilirubin, ALT). INR and triene:tetrene ratio will be assessed as clinically indicated if coagulopathy or essential fatty acid deficiency are suspected.

5.2 Study Product Formulation and Preparation
Omegaven intravenous lipid emulsion as supplied by the manufacturer.

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition

Parents of eligible patients will be approached for consent for their infants to take part in the study. If they agree, the PI will contact the FDA to receive an IND number for the infant (copies of the required FDA paperwork will be sent to the IRB). Omegaven will be ordered from the manufacturer. Once the IND number is received, the IRB will be

informed of the subjects IND number. Once the IND number is received, and communicated with the IRB, and the omegaven is received, intralipid infusions will be stopped and omegaven will be infused at the rate of 1 g/kg/d.

5.3.2 Study Product Accountability

The FDA permits the cost of omegaven to be billed to insurance carriers, or to public insurance. These costs will be largely, but not completely offset by the reduction in cost as the standard intravenous lipid (intralipid) will not be given. No addition laboratory tests will be carried out. If the relevant private or public insurance provider refuses to cover the additional cost of omegaven (approx $50-75/d) we would expect that costs will be absorbed by either the UCDMC pharmacy. In the unlikely event that this does not prove possible, and alternative coverage for omegaven can not be found (e.g. internal NICU funds) the parents will be asked to pay for omegaven. The IRB will be informed of this eventuality should it occur. The consent form will clearly state the plans regarding charging for omegaven, and that the family would be payers of last resort if alternative methods of funding the omegaven are not successful.

5.4 Concomitant Medications

5.4.1 Required Medications

Current receipt of parenteral nutrition (including iv lipids), are required for the diagnosis of PNALD, and therefore for enrollment in the study

5.4.2 Prohibited Medications

None

5.4.3 Precautionary Medications

None

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.2 Timing of Evaluations

6.2.1 Screening and Pre-Entry Evaluations

Clinical nutrition rounds, between the PI and the NICU dietician, occur every 1-2wk as part of the routine clinical care of the infants. As part of the clinical care of the infants, and infant identified as having cholestasis or PNALD (direct bilirubin ≥2 mg/dL on two consecutive occasions ≥8d apart) are identified.

6.2.2 Entry Evaluations

Clinical nutrition rounds, between the PI and the NICU dietician, occur every 1-2wk as part of the routine clinical care of the infants. As part of the clinical care of the infants, and infant identified as having cholestasis or PNALD (direct bilirubin ≥2 mg/dL on two consecutive occasions ≥8d apart) have their intralipid infusion rate reduced to 1 g/kg/d and have the trace elements added to their parenteral nutrition reduced. The current protocol will not alter this. If they remain cholestatic (bilirubin > 2 mg/dL) after 4wks of reduced lipids and trace elements, or (2) if their direct bilirubin is > 6 mg/dL in the absence of suspected or proven infection they will be considered eligible for the study.

6.2.3 Post-Entry Evaluations

Will continue as part of the clinical nutrition rounds

6.2.4 Discontinuation Evaluations

Will continue as part of the clinical nutrition rounds. Omegaven will be discontinued either (1) once parenteral nutrition is discontinued, irrespective of the direct bilirubin level, or (2) once the direct bilirubin has been below 2 mg/dL for more than 2 weeks. In the later case, if the direct bilirubin rebounds above 2 mg/dL at anytime the omegaven can be restarted. If omegaven is re-started, the discontinuation criteria will be the same as before: i.e. it will be discontinued when parenteral nutrition is discontinued or when the direct bilirubin has been below 2 mg/dL for more than 2 weeks. Omegaen may also be discontinued at any time is desired by the family, the attending physician or the study PI.

7.0 CLINICAL MANAGEMENT ISSUES

7.1 Toxicity

Routine clinical labs will be used to monitor for the principal side effects of omegaven (thrombocytopenia, hypertriglyceridemia), and the response to treatment (direct bilirubin, ALT). INR and triene:tetrene ratio will be assessed as clinically indicated if coagulopathy of essential fatty acid deficiency are suspected. If serum triglycerides are > 400, other causes will be excluded (e.g. renal disease, medications). If no other causes can be found, the clinical team caring for the baby may decide to reduce the infusion of omegaven by 25%, depending on their clinical assessment of risk and benefits. If there are concerns that essential fatty acid deficiency may be occurring

(characteristic skin rash plus unexplained thrombocytopenia), the clinical team caring for the baby may decide to discontinue omegaven and re-start infusion of intralipid at a rate of 0.5 – 1 g/kg/d.

An external Data Safety Monitor (Dr. Steven A. Abrams, Professor of Pediatrics, Section of Neonatology, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX) will be informed of all subjects recruited to the protocol. He will be informed, by e-mail, of any laboratory results on the subjects at least monthly, or within 7d of any significant change in biochemical data. He will have the authority to withdraw a subject from the protocol at any time. He will be unaware of the subjects name, but will be made aware of any pertinent clinical data relevant to lab interpretation (e.g. presence or absence of infection, underlying GI diagnosis, amount of enteral feeds etc). Subjects will be identified by an anonymous number when communicating with the external safety monitor.

7.2 Other Diseases
N/A

7.3 Pregnancy
N/A

7.4 Breast-feeding (if applicable)
N/A

8.0 CRITERIA FOR DISCONTINUATION

8.1 Permanent Treatment Discontinuation
Omegaven will be discontinued either (1) once parenteral nutrition is discontinued, irrespective of the direct bilirubin level, or (2) once the direct bilirubin has been below 2 mg/dL for more than 2 weeks. In the later case, if the direct bilirubin rebounds above 2 mg/dL at anytime the omegaven can be restarted. If omegaven is re-started, the discontinuation criteria will be the same as before: i.e. it will be discontinued when parenteral nutrition is discontinued or when the direct bilirubin has been below 2 mg/dL for more than 2 weeks.

8.2 Premature Study Discontinuation
As for 8.1

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues
This is a compassionate use, non-hypothesis testing protocol. Summary descriptive statistics will be generated, e.g. time to resolution of cholestasis.

9.2 Endpoints

9.2.1 Primary Endpoints *(including definitions)*

Time to resolution of cholestasis (direct bilirubin < 2 mg/dL without subsequent rebound above 2 mg/dL).

9.2.2 Secondary Endpoints (*including definitions*)

None

9.2.3 Substudy Endpoints (*as required)*

None

9.3 Randomization and Stratification

N/A

9.4 Sample Size and Accrual

Up to 25 subjects recruited

(For main study and substudies.)

9.5 Monitoring

As above

9.5 Analyses

As above

10.0 PHARMACOLOGY PLAN

N/A

11.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1 Records to Be Kept

The patient's participation will be documented in the EMR. All labs will be measured for clinical reasons, not for reasons related to the study. They will stay in the EMR. A list of patients on the study will be kept in a secure filing cabinet by the PI.

11.2 Role of Data Management

N/A.

11.3 Clinical Site Monitoring and Record Availability

N/A

11.4 Expedited Adverse Event Reporting to

An external Data Safety Monitor (Dr. Steven A. Abrams, Professor of Pediatrics, Section of Neonatology, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX) will be informed of all subjects recruited to the protocol. He will be informed, by e-mail, of any laboratory results on the subjects at least monthly, or within 7d of any significant change in biochemical data. He will have the authority to withdraw a subject from the protocol at any time. He will be unaware of the subject name, but will be made aware of any pertinent clinical data relevant to lab interpretation (e.g. presence or absence of infection, underlying GI diagnosis, amount of enteral feeds etc). Subjects will be identified by an anonymous number when communicating with the external safety monitor.

The IRB will also be informed of any adverse events. The FDA will be informed of any adverse events only to the extent required by law.

12.0 HUMAN SUBJECTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (pending) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the subject (or parent, legal guardian, or person with power of attorney for subjects who cannot consent for themselves, such as those below the legal age of consent). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, parent, or legal guardian, and this fact will be documented in the subject's record.

12.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain subject confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the , the OHRP, or the pharmaceutical supporter(s) or designee.

12.3 Study Discontinuation

The study may be discontinued at any time by the IRB, the pharmaceutical supporter(s), the FDA, the OHRP, or other government agencies as part of their duties to ensure that research subjects are protected.

13.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by policies.

15.0 REFERENCES

Puder 2009. Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. Ann Surg 2009;250:395-402.
Gura 2006. Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. Pediatrics 2006;118:e197-201.
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APPENDIX I

This format will allow the title and first page number of each appendix to appear in the Table of Contents.

The Sample Informed Consent will continue to be numbered as it has been (i.e., Page 1 of X).