Facilitating Clinical Trials of Parenteral Lipid Strategies for the Prevention of Intestinal Failure Associated Liver Disease (IFALD) in Infants

by

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Abstract

Objective

The objective of this thesis was to facilitate clinical trials of the optimal lipid based approach (e.g.: omega-3 containing lipid emulsions or minimization of conventional lipid) for the prevention of Intestinal Failure Associated Liver Disease (IFALD). This was achieved through 3 related projects.

Project 1

The first project examined the risk of advanced IFALD associated with exposure to conventional intravenous lipid in a logistic regression model. The study demonstrated that each day of conventional lipid (> 2.5 g/kg/day) was associated with a significant increase in the risk of advanced IFALD [Odds Ratio: 1.04 95% CI: 1.003 – 1.06].
Project 2

The second project surveyed experts in Intestinal Failure regarding their beliefs of the efficacy of lipid minimization and lipid emulsions containing omega-3 fatty acids relative to conventional emulsions. The goal of the project was to develop prior distributions of the treatment response for these therapies that can be used in Bayesian analyses of clinical trials. Our results demonstrated consistent expert opinion that the novel lipid based approaches are superior to conventional therapy. Estimates of the treatment effect were similar for the two approaches (median elicited treatment response, relative to conventional lipid, was a relative risk of 0.53 for omega-3 lipid and 0.45 for lipid minimization).

Project 3

The final project was a pilot randomized controlled trial of an omega-3 emulsion. The study demonstrated that the randomized design is a feasible strategy for evaluating lipid based approaches for the prevention of IFALD. A Bayesian preliminary assessment of the results of the trial, suggests a high likelihood that the trial will demonstrate a difference between the conventional and omega-3 emulsion evaluated in the trial. However, since the analysis was blinded, the direction of the difference is not known.

Conclusion

This thesis will contribute to the design and analysis of high quality and feasible randomized trials that will allow investigators to address the optimal lipid based approach to the management of IFALD.
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Table of Contents

Abstract ........................................................................................................................................... ii
Acknowledgments .......................................................................................................................... iv
Table of Contents ........................................................................................................................... vi
List of Tables .................................................................................................................................... xi
List of Figures ................................................................................................................................... xiii
List of Appendices .......................................................................................................................... xiv
List of Abbreviations ....................................................................................................................... xv
Thesis Overview ............................................................................................................................ xvi

Chapter 1: Overview of Intestinal Failure Associated Liver Disease ................................. 1
  1.1 Intestinal Failure .................................................................................................................... 1
  1.2 Intestinal Failure Associated Liver Disease......................................................................... 1
    1.2.1 Introduction ................................................................................................................... 2
    1.2.2 Clinical Presentation .................................................................................................. 3
    1.2.3 Epidemiology of PNALD .......................................................................................... 4
    1.2.4 Pathogenesis of PNALD ........................................................................................... 5
    1.2.5 Treatment and Prevention of PNALD ................................................................. 11
    1.2.6 Conclusion ............................................................................................................... 16
    1.2.7 Disclosure ................................................................................................................ 16
    1.2.8 Acknowledgements .................................................................................................. 17
Chapter 2: Lipid Based Approaches to the Management of IFALD ................................. 18

2.1 Review of Dietary Lipids ........................................................................................... 18

2.2 Review of the Role of Parenteral Lipids in IFALD .................................................. 19

2.3 Novel Lipid Based Approaches to the Management of IFALD ................................. 19

2.3.1 Lipid Minimization .............................................................................................. 20

2.3.2 Omega-3 Lipids .................................................................................................. 21

2.3.3 Other Alternate Intravenous Lipid Emulsions ..................................................... 25

2.4 Current Status of Novel Lipid Based Approaches to the Management of IFALD ...... 26

2.4.1 Quality of Evidence ......................................................................................... 27

2.4.2 Safety Concerns ............................................................................................... 28

2.5 Conclusions ............................................................................................................. 29

Chapter 3: Challenges and Solutions in Studying Novel Lipid Based Approaches to the
Management of IFALD – An Introduction to Bayesian Analysis of Clinical Trials ........ 30

3.1 The Role of Randomized Controlled Trials in the Evaluation of the Novel Lipid
Based Approaches ........................................................................................................ 30

3.2 Potential Challenges in Studying Novel Lipid Based Approaches to the Management
of IFALD ........................................................................................................................ 30

3.3 Proposed Solution to the Challenges of Performing Studies of the Novel Lipid Based
Approaches to the Management of IFALD ................................................................. 32

3.4 The Rationale for Bayesian Analyses of Clinical Trials ......................................... 32

3.4.1 Limitations of the Frequentist Approach ............................................................ 32

3.4.2 The Bayesian Approach ................................................................................... 33

3.5 Conclusion .............................................................................................................. 36
5.7.3 Data Analysis........................................................................................................... 57
5.8 Results........................................................................................................................... 58
5.9 Discussion..................................................................................................................... 65
5.10 Conclusion.................................................................................................................. 68
5.11 Acknowledgements ................................................................................................. 68

Preface to Chapter 6 and 7 ............................................................................................ 69

Chapter 6 : The Feasibility of Conducting a Randomized Controlled Trial to Examine a Parenteral Lipid Strategy for the Prevention of Progression of IFALD in Infants with Intestinal Failure ................................................................. 70

6.1 Summary....................................................................................................................... 70
6.2 Objective......................................................................................................................... 70
6.2.1 Specific Objectives .................................................................................................. 70
6.3 Method............................................................................................................................ 71
6.3.1 Trial Overview......................................................................................................... 71
6.3.2 Eligibility Criteria..................................................................................................... 72
6.3.3 Subject Screening and Recruitment......................................................................... 73
6.3.4 Trial Intervention..................................................................................................... 74
6.3.5 Data Collection........................................................................................................ 76
6.3.6 Safety Monitoring.................................................................................................... 76
6.4 Analysis of Feasibility Objectives .............................................................................. 77
6.5 Results of Feasibility Assessment .............................................................................. 78
6.5.1 Recruitment.............................................................................................................. 78
6.5.2 Protocol Compliance ............................................................................................... 79
6.6 Discussion....................................................................................................................... 83
6.7 Conclusion....................................................................................................................... 87
List of Tables

Chapter 1

Table 1-1: Pathogenesis of Parenteral Nutrition Associated Liver Disease............................... 6
Table 1-2: Possible Treatment Strategies for Parenteral Nutrition Associated Liver Disease. 12

Chapter 4

Table 4-1: Surgical Diagnoses in 152 Patients......................................................................... 42
Table 4-2: Univariate Predictors of Conjugated bilirubin > 100 umol/L........................................ 43
Table 4-3: Multiple Variable Models of Conjugated bilirubin > 100 umol/L ......................... 45

Chapter 5

Table 5-1: Center and Participant Characteristics................................................................. 59
Table 5-2: Expert Belief as to the Treatment Effect for the Omega-3 Approach................. 63
Table 5-3: Expert Belief as to the Treatment Effect for the Lipid Minimization Approach.... 64
Table 5-4: Percentage of Experts Recommending Routine Use of the Novel Lipid Based Strategies...................................................................................................................... 65

Chapter 6

Table 6-1: Summary of Significant Protocol Amendments..................................................... 80
Table 6-2: Summary of Deviations.......................................................................................... 82
Table 6-3: Macronutrient Intake .............................................................................................. 82
Chapter 7

Table 7-1: Baseline Characteristics........................................................................................................ 93
Table 7-2: Descriptive Statistics for Variables Used in Linear Regression................................. 95
Table 7-3: Bayesian Estimates of Treatment Efficacy – Conjugated Bilirubin at Trial Completion .............................................................................................................. 96
Table 7-4: Secondary Linear Regression Results ................................................................. 98
Table 7-5: Time to conjugated bilirubin > 50 umol/L analysis .............................................. 100
Table 7-6: Adverse Events ........................................................................................................ 102
List of Figures

Chapter 2

Figure 2-1: Proposed Beneficial Effects of ω3FA in IFALD .................................................. 21

Figure 2-2: Fatty Acid Composition of Intralipid®, SMOFlipid® and Breast Milk .............. 24

Chapter 5

Figure 5-1: Characteristics of the average group of patients ................................................. 56

Figure 5-2: Example scenario provided to participants ............................................................ 56

Figure 5-3: Belief Probability Distributions for each of Conventional Lipid, Omega-3 Lipid, and Lipid Minimization ................................................................. 60

Figure 5-4: Histograms with smoothed curves of the distribution of the expert opinion of the relative risk (RR) of advanced IFALD at 3 months for the novel lipid based approaches compared to conventional lipid ................................................................. 61

Chapter 6

Figure 6-1: Parenteral Nutrition Dosing Nomogram ............................................................. 75

Chapter 7

Figure 7-1: Triplots showing the prior, likelihood and posterior distributions with the uninformative (A), optimistic (B) and sceptical (C) priors for the linear regression .......... 97

Figure 7-2: Triplot showing the prior, likelihood and posterior distribution of the log odds ratio for progressive liver disease ................................................................. 101
List of Appendices

Chapter 4
Appendix A. Code for Bayesian Model Selection Procedure ........................................ 136

Chapter 5
Appendix B. Script for Belief Elicitation Study ............................................................ 137
Appendix C. Code for Low-lipid RR Calculation for a Subject ...................................... 145

Chapter 6
Appendix D. Excerpt from SMOFlipid® Trial Protocol (Version 1.4) ............................. 146

Chapter 7
Appendix E. Code for Bayesian Analysis of Treatment Efficacy .................................. 167
List of Abbreviations

AA: Arachidonic Acid
ALA: Alpha-linolenic Acid
ASPEN: American Society of Parenteral and Enteral Nutrition
CB: Conjugated bilirubin
CB100: Conjugated bilirubin > 100 umol/L
CI: Confidence Interval
CRP: C Reactive Protein
DHA: Docosahexanoic acid
EFA: Essential Fatty Acid
EFAD: Essential Fatty Acid Deficiency
EPA: Eicosapentaenoic Acid
ESLD: End Stage Liver Disease
GCP: Good Clinical Practice
GGT: Gamma-Glutamyl Transferase
IF: Intestinal Failure
IFALD: Intestinal Failure Associated Liver Disease
ILE: Intravenous Lipid Emulsion
LA: Linoleic Acid
LCPUFA: Long Chain Polyunsaturated Fatty Acid
MCID: Minimal Clinically Important Difference
MCMC: Markov Chain Monte Carlo
MCT: Medium Chain Triglyceride
n6:n3 ratio: Ratio of Omega-6 to Omega-3 Fatty Acid
OR: Odds Ratio
ω3FA: Omega-3 Fatty Acid
ω6FA: Omega-6 Fatty Acid
PIFCoN: Paediatric Intestinal Failure Consortium
PN: Parenteral Nutrition
PNAC: Parenteral Nutrition Associated Cholestasis
PNALD: Parenteral Nutrition Associated Liver Disease
RBC: Red Blood Cell
ROBUST: Reporting of Bayes Used in Clinical Studies
RR: Relative Risk
SBS: Short Bowel Syndrome
TPN: Total Parenteral Nutrition
Thesis Overview

The objective of this thesis was to facilitate clinical trials of novel lipid based approaches (alternate intravenous lipid emulsions or minimization of conventional lipid) for the prevention of Intestinal Failure Associated Liver Disease (IFALD) in infants.

Chapter 1 provides an overview of the pathophysiology and current management of paediatric IFALD in order to provide context for the role of the lipid based approaches.

Chapter 2 presents the current evidence for novel lipid based approaches in the treatment of IFALD in infants.

Chapter 3 discusses the potential challenges in conducting clinical trials of the novel lipid based approaches in children with IF. The chapter also reviews the rationale for Bayesian methods for the analysis of data from clinical trials.

Chapters 4 – 7 describe the results of 3 projects designed to achieve the overall aim of the thesis.

The first project (Chapter 4) examined the impact of parenteral lipids on the development of IFALD in a “nested” retrospective cohort study of surgical neonates. The study provides insight into the potential impact that a strategy targeting PN lipids will have on the risk of developing IFALD.

The second project (Chapter 5) determines a distribution of the probability, based on expert opinion, of the novel lipid based approaches being effective for the prevention of IFALD. These distributions can be used as priors in Bayesian analyses of randomized controlled trials of these therapies.

The third project (Chapter 6 and 7) was a pilot multi-centre Canadian randomized controlled trial to evaluate the feasibility of evaluating the lipid based approach in a randomized design.

Chapter 6 presents an assessment of the feasibility of the randomized design for the study of the novel lipid based approach in patients with IF.
Chapter 7 presents a preliminary assessment of the results of the pilot trial that examined an omega-3 containing intravenous lipid emulsion. The analysis was done using Bayesian methods. Data from Chapters 4 and 5 were used as priors for the Bayesian analyses.

Chapter 8 is the concluding chapter that provides a synthesis of the various projects, implications and future research directions.
Chapter 1

1 Overview of Intestinal Failure Associated Liver Disease

1.1 Intestinal Failure

Intestinal failure (IF) is defined as impaired digestion and/or absorption of nutrients resulting in an inadequate intake for the maintenance of health and growth. Short Bowel Syndrome (SBS) is the most common cause of intestinal failure in infants. The incidence of SBS is estimated to be 22.1 per 1000 neonatal intensive care admissions, with a population-based incidence of 24.5 per 100,000 live births.

The major features of IF are dehydration secondary to diarrhoea, malabsorption of macro- and micro-nutrients, malnutrition, and failure to thrive. In those with SBS, after intestinal resection, the residual small bowel undergoes intestinal adaptation, which is the gut’s attempt to optimize its absorptive capacity. Adaptation may take several months or years to complete. Up to 65% of infants with SBS will ultimately adapt and achieve independence from parenteral nutrition (PN). Children with IF from medical causes are less likely to adapt and consequently are more likely to remain on PN with greater risk of morbidity.

Intestinal failure results in a multitude of complications resulting from long-term hospitalization and prolonged PN. The problems include central line complications, sepsis, failure to thrive, and family dysfunction. However, the most serious complication in children with IF is Intestinal Failure Associated Liver Disease (IFALD).

1.2 Intestinal Failure Associated Liver Disease

This chapter will provide an overview of the epidemiology, pathophysiology and current management of paediatric IFALD in order to provide context for the role of the lipid based approaches to the management of IFALD. Although the term Parenteral Nutrition Associated Liver Disease (PNALD) is used in this chapter, we view PNALD and IFALD to be synonymous terms.
1.2.1 Introduction

Parenteral Nutrition (PN) is a life-saving therapy for patients with intestinal failure who are unable to receive sufficient calories enterally. Its development in the late 1960s can be regarded as a significant advance in modern medicine. However, no sooner was PN developed, did reports of the association between PN administration and cholestatic liver disease emerge, with the first publication occurring in 1971. This liver disease, being variously known as PNALD (Parenteral Nutrition Associated Liver Disease) or PNAC (Parenteral Nutrition Associated Cholestasis), is one of the most common complications experienced by patients on long-term PN and is a significant contributor to morbidity and mortality in this patient population.

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1 The term Parenteral Nutrition Associated Liver Disease (PNALD) is used throughout this chapter as this was the term used for the in-press chapter. As discussed we view the terms IFALD and PNALD to be synonymous. The remainder of the thesis will utilize the more contemporary term, IFALD.
While it may be debatable whether the term IFALD (Intestinal Failure Associated Liver Disease) is entirely synonymous with PNALD, this term has recently emerged as the most commonly used term to describe the cholestatic liver disease that occurs in patients with intestinal failure who are on long-term parenteral nutrition. The term IFALD recognizes the multitude of factors at play in the development of this liver disease. Given the multiple etiologic factors, we favour the term IFALD, when discussing liver disease in our intestinal failure patients. For the purposes of this review we view the terms PNALD and IFALD to be interchangeable.

This chapter will consider the clinical presentation, epidemiology, pathogenesis of PNALD, as well as potential treatment strategies. While the review will focus primarily on the paediatric patient, given that this population is most at risk of PNALD, the issues for adult patients are quite similar although the overall risk and incidence of PNALD is lower in adults.

1.2.2 Clinical Presentation

The clinical spectrum of PNALD includes mild to severe cholestasis, hepatic fibrosis to cirrhosis and liver failure. The initial biochemical features are an elevated conjugated serum bilirubin and GGT, which rise within 1 to 4 weeks of initiating PN\textsuperscript{9, 10}. There are age related differences in the presentation of PNALD, with children demonstrating a predominantly cholestatic picture and relatively rapid progression to advanced liver disease, whilst the predominant finding in adults is steatosis\textsuperscript{11, 12}. Biochemically, in adults, transaminitis is the earliest indicator of the disease\textsuperscript{13} with jaundice a late and concerning sign\textsuperscript{14}. Both adults and children develop evidence of biliary sludge and cholelithiasis related to the duration of PN use\textsuperscript{15-17}. It is likely that these processes contribute to PNALD, with evidence that flushing of the biliary system via percutaneous cholangiography improves time to resolution of hyperbilirubinaemia\textsuperscript{18}.

As PNALD progresses, other features of liver disease develop such as synthetic dysfunction and hypersplenism resulting in thrombocytopenia and coagulopathy. We have demonstrated a serum conjugated bilirubin of 100 umol/L (6.7 mg/dl) in neonates to have a sensitivity of 94% and specificity of 87% for later development of end-stage liver disease\textsuperscript{19}. However, the marker occurred late in the disease course and as such was not appropriate to be utilized as a referral criterion for transplantation as wait times for organs were too long. Aside from the risk to life posed by progressive PNALD; the disease likely also significantly impairs quality of life in children by hindering intestinal adaptation and the chance that the child may ultimately be able
to be weaned from PN \textsuperscript{20}. Given the close resemblance of PNALD to other cholestatic and steatotic liver diseases, it is advisable to adequately investigate any patient with suspected PNALD for other causes of liver disease prior to attributing the hepatic dysfunction to PN \textsuperscript{21}.

The histopathological findings of PNALD are variable, with the key features including intracellular and intracanalicular cholestasis, pigmented macrophages, steatosis and periportal fibrosis \textsuperscript{12}. Hepatic steatosis is more common in adults and may occur without associated inflammation, cholestasis, or necrosis. In contrast, infants present with centrilobular cholestasis, portal inflammation and necrosis with steatosis being less prevalent. Other histological features may include signs of hepatocellular injury such as balloon degeneration and multinucleated giant cells.

\textbf{1.2.3 Epidemiology of PNALD}

Descriptions of the epidemiology of PNALD are challenging to interpret as no consistent definitions exist to characterize this condition. While some studies have defined the condition on the basis of consistent elevations in various liver enzymes, recently definitions based only on the serum conjugated bilirubin have become more frequent \textsuperscript{4, 5, 13, 14, 22, 23}. Definition of liver disease will alter the incidence of the disorder with one study showing an incidence of liver disease of 57\% based on a panel of abnormal liver function tests, with the incidence declining to 12\% if only the serum conjugated bilirubin is considered \textsuperscript{24}. Yang et al, also recently demonstrated persistent and prolonged elevations in the transaminase levels in patients with PNALD following achievement of full enteral tolerance despite normalization of serum conjugated bilirubin. This demonstrates that hepatic pathology may occur in the absence of hyperbilirubinaemia \textsuperscript{25}. Depending on definition, the incidence of PNALD lies between 40–60\% of infants on long-term parenteral nutrition and 15–40\% of adults on home parenteral nutrition \textsuperscript{12}. The risk of end-stage liver disease approaches 25\% in paediatric patients with short bowel syndrome \textsuperscript{26} and up to 15\% in adult patients on home PN \textsuperscript{14}. In paediatric patients, the end-stage liver disease is frequently fatal due to a relative unavailability of size appropriate allografts particularly when an intestinal transplant is required. Up to 1.4\% of deaths in children less than 4 years are attributable to short bowel syndrome and most of these deaths are related to liver disease \textsuperscript{4, 5, 11, 26, 27}.

Cohort studies have defined demographic risk factors for PNALD. Overall, premature infants, particularly those < 500 grams, have the greatest risk of PNALD \textsuperscript{5, 9, 28}. Furthermore, preterm
infants with short bowel syndrome, have a significant risk of developing end-stage liver disease from PNALD with incidences as high as 90% in those on PN for greater than 3 months. While short bowel syndrome is a substantial predictor for the development of PNALD, a study from France demonstrated the greatest risk in those with intractable diarrhoea of infancy. Among children with short bowel syndrome, a diagnosis of gastroschisis or jejunal atresia is also associated with an increased risk of PNALD. In adult patients, risk factors for PNALD are related to residual small intestinal length, comorbid liver disease, female gender, and the absence of the colon in continuity.

1.2.4 Pathogenesis of PNALD

In addition to defining risk factors for PNALD, animal models and cohort studies have also elucidated some of the pathophysiologic processes underlying the development of PNALD. The pathophysiology of PNALD is related to both aspects of the parenteral nutrition as well as host factors (Table 1-1).

1.2.4.1 Parenteral Nutrition Related Factors

Hypercaloric feeds, with excess of any of the macronutrients of PN can result in steatosis as well as chronic cholestasis. The mechanism underlying this phenomenon is thought to be related to increased hepatic oxygen demand resulting in relative ischemia. However, specific macronutrient effects also likely result in the development of PNALD as do certain minerals and trace elements.

1.2.4.1.1 Glucose

While glucose is not inherently hepatotoxic, excess glucose administration results in hyperinsulinism. This results in an up regulation of enzymes involved in fatty acid synthesis leading to hepatic steatosis. This issue was particularly germane early in the experience with PN prior to the development of adequate intravenous lipid preparations. However, with an increased focus on the role of lipid in the development of PNALD and strategies to limit lipid use, the issue deserves renewed consideration as calories lost due to lipid minimization are frequently made up by increasing the glucose load.
### Table 1-1: Pathogenesis of Parenteral Nutrition Associated Liver Disease

- **Parenteral Nutrition Associated Factors**
  - Hypercaloric feeds with excess macronutrients
  - Amino Acid
    - Deficiencies of
      - Taurine
      - Cysteine
      - Carnitine
      - Choline
    - Excess Methionine
  - Lipids
    - Phospholipid accumulation
    - Phytosterols
    - Omega-6 long-chain polyunsaturated fatty acids
    - Anti-oxidant imbalance
  - Minerals and Trace Elements
    - Manganese
    - Chromium
    - Copper

- **Host Factors**
  - Prematurity
    - Immaturity of hepatic pathways
  - Intestinal Failure
    - Deranged enterohepatic circulation
    - Stasis
  - Sepsis
    - Catheter related
    - Translocation related
1.2.4.1.2 Amino Acids

Excessive administration of parenteral amino acids has been demonstrated to result in cholestatic jaundice in neonates. This is thought to be related both to cumulative exposure, as well as dose with premature infants who received daily amino acids of 3.6 g/kg/day having a more rapid rise in bilirubin levels than those who received 2.5 g/kg per day\(^23, 36\). However, the notion of amino acid dose-related toxicity is not uniformly accepted\(^37\).

At physiologic doses, it is possible that hepatotoxicity is related to a deficiency of taurine or cysteine. These are considered conditionally essential amino acids in neonates because of the low levels of hepatic cystathionase and cysteine sulfenic decarboxylase which allow for their synthesis from methionine\(^38-40\). Taurine deficiency leads to the inability to form taurine-conjugated bile acids resulting in increased formation of toxic glycine-conjugated bile acids. While taurine supplementation has been shown to improve bile secretion in an animal model, clinical efficacy is limited with taurine containing PN solutions not altering the risk of PNALD\(^41, 42\). Neonates, also have a limited ability to convert lysine and methionine to carnitine which is important for mitochondrial fatty acid oxidation\(^43\). Although carnitine deficiency has been demonstrated in those on PN, normalization of serum carnitine levels has not resulted in improvement of PNALD\(^44\). It has also been suggested that choline deficiency may exacerbate steatosis, with a pilot study demonstrating reduction in steatosis in adults with choline supplementation\(^45\).

A consequence of immaturity of the pathways of methionine metabolism, is accumulation of toxic metabolites of this amino-acid such as 3-methyl propionic acid in the neonate\(^46, 47\). These metabolites are thought to contribute to the development of PNALD with inappropriate methionine load being regarded as important contributor to the development of PNALD in infants.

1.2.4.1.3 Lipids

Lipids have been demonstrated to play a major role in the development of PNALD in both children and adults. In adults, a lipid dose in excess of 1 g/kg/day is related to the development of PNALD\(^22\). In children, Colomb et al. demonstrated that episodes of cholestasis were correlated with lipid concentrations\(^48\). A recent multiple variable study by our group, described
in Chapter 4, examining risk factors for severe PNALD (serum conjugated bilirubin > 100 umol/l) demonstrated that each day of parenteral lipid > 2.5g/kg/day was associated with a 1.04 increase in the odds ratio of developing this outcome. While this risk may seem trivial, it is important to recognize that the risk is expressed per day of lipid, with the odds ratio of severe PNALD approaching 10 with 60-days of PN lipid use at this dose.

The mechanism whereby lipids contribute to PNALD, is likely multi-factorial relating to accumulation of phospholipids, excess phytosterols, predominance of omega-6 fatty acids (ω6FA) leading to a pro-inflammatory state and also anti-oxidant imbalance.

Plant-based, particularly soy, lipid emulsions have been the mainstay of PN to date, with at present no non-plant based lipid emulsions having regulatory approval in North America. These emulsions have high phytosterol and ω6FA content and low anti-oxidant content. Therefore it is likely that intravenous lipid emulsions play a significant role in the development of PNALD.

Serum levels of phytosterols have been demonstrated to be elevated in patients with PNALD, with correlation between these levels and the severity of PNALD. The mechanism whereby phytosterols contribute to PNALD may be related to increased lithogenicity of bile or alterations in the canalicular membrane affecting canalicular flow. More recently a molecular mechanism has been described whereby phytosterols antagonize messenger RNA for critical bile acid homeostatic proteins.

Long-chain polyunsaturated fatty acids (LCPUFA) contained in lipid emulsions, are readily incorporated in a dose dependent manner into cell phospholipid membranes and other tissues, where they are involved in cell signalling, the production of eicosanoids involved in inflammation, blood vessel tone, platelet aggregation, and modulation of the immune system. LCPUFA also directly affect gene transcription and lipid metabolism. LCPUFA provide the substrate for systemic eicosanoid production, with eicosanoids arising from ω6FA (Thromboxane A2, Leukotrienes B4, C4, D4, Prostaglandins D2, E2, and F2, and Prostacyclin I2) having a primarily pro-inflammatory effect which is thought to contribute to the development of PNALD. In addition to being pro-inflammatory, ω6FA also impair bile flow in an animal model of PNALD and induce steatosis.
The final mechanism whereby intravenous lipid emulsions may contribute to the development of PNALD relates to imbalance of anti-oxidants. Anti-oxidants, such as \( \alpha \)-tocopherol are an important addition to lipid emulsions as they prevent lipid peroxidation and free radical generation. However, soy-based lipid emulsions have limited anti-oxidant content, particularly when considering the most biologically active form, \( \alpha \)-tocopherol. This may result in a reduction of this substance in plasma lipoproteins and a resultant decrease in antioxidant defences \(^{21, 64}\). In clinical studies of lipid emulsions containing \( \alpha \)-tocopherol, improved anti-oxidant measures were associated with improvements in liver enzymes \(^{56, 57}\). An additional approach for provision of anti-oxidants is addition of zinc and selenium to the PN solution \(^{65-67}\).

1.2.4.1.4 Minerals and Trace Elements

Trace elements, particularly manganese, have been implicated in the development of PNALD \(^{68-70}\). In a study of 57 children on long-term PN, 45 had evidence of excess blood manganese levels. This is particularly concerning given the adverse neurologic effects of manganese accumulation within the basal ganglia. There was also a correlation between the degree of hypermagnesaemia and PNALD. Furthermore liver disease improved following reduction or elimination of the manganese from the PN. Since manganese is excreted in bile, accumulation of this substance is particularly important in the setting of a cholestatic liver disease such as PNALD. For this reason, we do not add manganese to our PN solutions for infants at risk of PNALD. While aluminum toxicity has been associated with PN induced bone disease, there is no evidence of an association with PNALD \(^{34, 71}\). Similarly, while chromium toxicity, secondary to TPN, has been reported in animals there has been no relation to PNALD in humans although there is evidence of intra-hepatic accumulation of this trace element \(^{72, 73}\). Copper is also potentially hepatotoxic and since its elimination is biliary, it is suggested that monitoring of blood concentrations is justified to prevent hepatic injury \(^{21}\).

1.2.4.2 Host Factors

1.2.4.2.1 Prematurity

Children are at a greater risk of developing PNALD, with the youngest and smallest children being most vulnerable. Beath et al found the highest incidence of PNALD in infants less than 34-week gestation weighing less than 2 kg \(^{74}\). It is logical to assume that this finding relates to
immaturity of the liver, with infants having diminished hepatic synthesis and uptake of bile salts and reduced enterohepatic circulation. This may be due to developmental differences in the regulation of genes involved in this process. Other hepatic functions are also immature with evidence of cystathionase deficiency, glutathione deficiency and a decreased ability for transulfuration of toxic bile salts such as lithocholic acid.

### 1.2.4.2.2 Intestinal Failure

Patients receiving PN for intestinal failure are at much greater risk of PNALD than those who receive PN for other reasons. Stanko et al. demonstrated in a group of patients who received identical parenteral nutrition infusions, that only those with short bowel syndrome developed liver disease. Other studies have shown an increased risk with absence of the colon. Children who are not able to tolerate any enteral feeds are at greater risk of PNALD than those who are partially enterally fed. Degree of bowel loss is also related to outcome, with children with less than 50 centimetres of small bowel being at greatest risk of death from liver failure.

The reason why patients with intestinal failure are at increased risk for PNALD likely relates to both the negative impact of the absence of feeds, impaired enterohepatic circulation, as well as an increased risk for sepsis related to deficiencies in gastrointestinal mucosal integrity and immunity. Absence of enteral feeds, results in alterations in release of gastrointestinal hormones which may affect biliary and intestinal motility. Reduced bile flow is exacerbated by fasting and is a primary factor in the development of biliary sludge and gall stones. Reduced enteral intake also contributes to intestinal hypomotility which may result in bacterial overgrowth due to stasis. Particularly in the setting of a compromised intestine, with increased mucosal permeability, overgrowth may result in translocation of bacteria resulting in sepsis. Intraluminal bacteria have also been implicated in the conversion of chenodeoxycholic acid into the hepatotoxin lithocholic acid.

### 1.2.4.2.3 Sepsis

PNALD has been demonstrated to be associated with recurrent episodes of sepsis in numerous series. Key sources of sepsis in patients on PN relate to both the need for a central venous catheter for PN administration as well as bacterial translocation from bacterial
overgrowth\(^8^7\). Sepsis is frequently contributory to death in patients with advanced PNALD\(^1^1\). Pro-inflammatory cytokines elaborated following endotoxin exposure from a septic insult have been shown to down regulate the molecular mechanisms underlying bile acid transport\(^8^8, ^8^9\). Short bowel syndrome is believed to represent a pro-inflammatory state, with an exaggerated inflammatory response including hepatitis arising from a septic insult\(^9^0\). The fact that the \(\omega6\)FA may result in enhanced levels of pro-inflammatory mediators is intriguing and leads one to speculate whether traditional lipid emulsions potentiate the adverse hepatic response to endotoxin mediated cholestasis.

1.2.5 Treatment and Prevention of PNALD

Table 1-2 provides a summary of the various treatments that can be utilized for PNALD.

1.2.5.1 Nutritional Strategies

The key principle in the nutritional management of a child on PN is to minimize the risk of PNALD by avoiding aspects of the PN that have been associated with this outcome such as overfeeding of parenteral calories as well as addition of detrimental components to the PN such as manganese. Notwithstanding optimal PN management, since PNALD may be reversible if enteral feeding can be resumed prior to the establishment of significant fibrosis or cirrhosis\(^9^1\), encouragement of enteral autonomy is essential. This may be facilitated by multi-disciplinary intestinal rehabilitation teams\(^2^6, ^9^2\). Restoration of gastro-intestinal continuity in those who have proximal enterostomies\(^9^3\) as well as surgical lengthening procedures\(^9^4\) may also play a role. There is evidence that biochemical normalization may occur following a surgical lengthening procedure even in the setting of fibrosis\(^9^5, ^9^6\). However, re-establishment of enteral feeds was important in achieving this outcome, with five out of 8 patients who remained PN dependent after the operation having ongoing cholestasis\(^9^6\).

For those patients with limited capacity to adapt, or in whom a prolonged period of adaptation is anticipated, cyclic infusions of PN may be protective. These infusions result in lower insulin levels, less hepatomegaly and improved biochemistry\(^9^7, ^9^8\). Cyclic PN permits a period of free fatty acid mobilization from body stores during the non-infusion period and is thought to protect the liver by promoting more efficient energy utilization, which is important in the setting of hepatotoxic stresses\(^2^1, ^9^9\).
<table>
<thead>
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<th>Treatment Strategies</th>
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<tr>
<td><strong>Nutritional Strategies</strong></td>
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<td>- Encourage enteral autonomy</td>
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<td>▪ Restore continuity</td>
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<td>▪ Intestinal lengthening</td>
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<td>- Multidisciplinary Intestinal Rehabilitation</td>
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<td>- Appropriate PN macronutrients and additives</td>
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<tr>
<td>- Lipid strategies</td>
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<tr>
<td>▪ Omega-3 lipid preparations</td>
</tr>
<tr>
<td>▪ Lipid minimization</td>
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<td><strong>Sepsis Prevention</strong></td>
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<tr>
<td>- Line related sepsis prevention</td>
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<td>▪ Multidisciplinary care and patient education</td>
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<td>▪ Appropriate catheter care</td>
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<td>▪ Antibiotic and ethanol locks</td>
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<td>- Bacterial overgrowth prevention</td>
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<td>▪ Gut decontamination with cyclical antibiotics</td>
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<td>▪ Bulk forming enteral agents</td>
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<td>▪ Glutamine</td>
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<td>▪ Probiotics</td>
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<td><strong>Pharmacologic Therapies</strong></td>
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<td>- N-acetylcysteine</td>
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<td>▪ α-tocopherol</td>
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<td>▪ Zinc, Selenium</td>
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<tr>
<td><strong>Percutaneous cholangiography</strong></td>
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<td><strong>Transplantation</strong></td>
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Given the importance that lipid is thought to play in the pathogenesis of PNALD, there has been an effort to employ lipid minimization strategies for the treatment of PNALD. Colomb et al., demonstrated improvement in serum bilirubin and thrombocytopenia in patients with PNALD with temporary cessation of parenteral lipids 48. Similarly, Rollins demonstrated improvement or resolution of hyperbilirubinaemia with lipid reduction or elimination 100. Ultimately, controlled studies are needed to assess both the safety and efficacy of lipid restriction protocols.

Although the subject will be covered in more detail in the Chapter 2, no review of PNALD will be complete without mentioning the exciting data suggesting that PNALD may be treated by substitution of the \( \omega 6 \)FA containing soy-based lipid emulsion with Omegaven\textsuperscript{®} (Fresenius Kabi, Bad Hamburg, Germany) a lipid emulsion derived from fish-oil with substantial omega-3 fatty acids (\( \omega 3 \)FA). The initial clinical reports of the use of this emulsion originated from Children’s Hospital Boston with a case report published in 2006 of 2 children with severe end-stage PNALD who demonstrated complete reversal of their liver disease after starting Omegaven\textsuperscript{®} 101. The most recent published data from that group demonstrated resolution of PNALD in 45% (19 of 42 cases) while receiving PN compared with 5% in a historic control group who received a soy-based lipid emulsion 102.

Our experience has been similar, with our most recent analysis demonstrating resolution of jaundice in 63% while receiving PN (14 of 22 cases) 103. While the group from Boston have advocated Omegaven\textsuperscript{®} monotherapy at 1 g/kg/day; we have adopted an approach whereby the Omegaven\textsuperscript{®} is initially dosed together with Intralipid\textsuperscript{®} (each at 1g/kg/day). Our practice is based on the belief that this approach should allow for improved nutrition and energy balance, while still providing the anti-inflammatory effect of the omega-3 lipid. We also have significant concerns as to potential adverse long-term neurocognitive outcomes with fat restriction in developing infants. However, in selected instances, the Intralipid\textsuperscript{®} is discontinued due to concern as to the severity of PNALD or as the parenteral lipid is weaned with improved enteral tolerance. We believe that the optimal dosing strategy for Omegaven\textsuperscript{®}, both from an efficacy and safety perspective, is still to be determined.
Although lipid restriction, whether achieved by dose reduction of conventional lipid or dosing Omegaven® at 1 g/kg/day, may be appropriate in a child with advanced liver disease, it may not be appropriate in one with more mild disease where the goal of treatment is preventative. We have held that despite the potential benefit of intravenous lipid emulsions containing ω3FA, at present their use remains investigational and should only be used in those with severe PNALD unless in the context of a randomized trial examining their safety and efficacy as a preventative strategy 104, 105. These preventative randomized trials are ongoing, with one examining Omegaven® and the other SMOFlipid® (a composite lipid emulsion comprised of 30% soybean oil, 30% medium chain triglycerides, 25% olive oil and 15% fish oil) (Fresenius Kabi, Bad Hamburg, Germany) 106.

1.2.5.2 Prevention of Sepsis

Given the key role that sepsis has been shown to play in the development of PNALD, it is logical to assume that prevention of sepsis should be an important factor in the prevention and treatment of PNALD. Sepsis reduction should focus on both care of the central venous catheter, as well as, prevention of bacterial overgrowth and resultant translocation.

Prevention of central venous catheter infections requires individual and team efforts, with data supporting a reduced incidence of catheter infection with dedicated infusion therapy teams 107, 108. In the home setting, education of parents is critical. A meta-analysis has shown that chlorhexidine was superior to povidoneiodine for the prevention of catheter-related infections 109. There is also evidence to suggest that antibiotic and ethanol locks may also be useful 110, 111.

The potential impact that enhanced line care may have, is highlighted by the fact that there is a substantial difference between the incidence and the age of development of liver disease in children whose central line catheter care was managed by a team experienced in this setting 112. There is also a case report of a child with PNALD who demonstrated improvement in their liver disease with change of caregiver presumably secondary to a reduction in the rate of line infection 113.
Treatment of bacterial overgrowth with cycled antibiotics has also been suggested to have a beneficial impact in reducing the risk of sepsis and resultant PNALD\textsuperscript{114}. A randomized trial of prophylactic erythromycin in 182 very low-birth weight neonates demonstrated a significant reduction in liver disease and sepsis. However, since the primary objective was to examine this drug as a motility agent it is not clear as to whether the results were due to the effects on motility or as an antimicrobial\textsuperscript{115}. Given the high prevalence of rapid transit in our patient population, we do not believe that erythromycin is an optimal drug in patients with short bowel syndrome. We generally do not use antibiotics prophylactically but do so for the treatment of clinically significant bacterial overgrowth.

Another strategy that may hold promise are animal models suggesting that bulk-forming enteral agents may limit bacterial translocation\textsuperscript{116, 117}. Glutamine supplementation has also been demonstrated in animal models to limit translocation\textsuperscript{118, 119}. In rats, glutamine reverses the inhibition of hepatocyte mitochondrial metabolism observed following endotoxaemia\textsuperscript{120}. However, a randomized trial of glutamine supplementation in infants did not show substantial benefit\textsuperscript{121}. Finally, the role of probiotics in preventing bacterial overgrowth and translocation needs to be examined further\textsuperscript{114}.

1.2.5.3 Pharmacologic Strategies

Pharmacologic treatments for PNALD are limited. Ursodeoxycholic acid is commonly suggested for PNALD\textsuperscript{122, 123}. A recent randomized trial demonstrated reduction in GGT but not serum bilirubin with its use\textsuperscript{124}. Also, in our experience diarrhoea related to its use limits its applicability in many patients with short bowel syndrome. We recently reported some success with N-acetylcysteine demonstrating normalization of red cell glutathione concentrations\textsuperscript{125}. This therapy requires further evaluation, although we generally employ it in patients with moderate to advanced PNALD given the lack of other options. As discussed earlier there is also evidence that choline supplementation may limit steatosis in adults\textsuperscript{45}.

Other treatments suggested to be beneficial for PNALD that have not been demonstrated to be effective, in controlled studies, have included cholecystokinin\textsuperscript{126, 127} and tauroursodeoxycholic acid\textsuperscript{128}. The fact that these therapies demonstrated promise in the non-controlled setting highlights the importance of adequately powered controlled studies when evaluating therapies for PNALD.
1.2.5.4 Transplantation

Transplantation can be an effective and life-saving therapy for patients with PNALD refractory to other therapies. However, transplantation, in infants, poses a significant challenge because of the shortage of size appropriate grafts particularly when attempting combined liver-intestinal transplantation with significant waitlist mortality \(^4, 5, 11, 26, 27\). Although the outcomes continue to improve, the long-term survival of patients receiving an intestinal transplant remains suboptimal. One and 5 year graft survival for this procedure are 80% and 50% respectively with the poor outcomes primarily related to the significant medical complications associated with small bowel transplantation \(^129\). This has led some to suggest that for patients who are likely to achieve independence from PN once that their liver disease is treated, that isolated liver transplantation be performed\(^130, 131\). While we have adopted this approach occasionally, we believe it is only appropriate in carefully selected patients in whom there is a very high likelihood that the child will achieve nutritional independence.

1.2.6 Conclusion

PNALD is the most common complication arising from prolonged parenteral nutrition use and has the potential for significant morbidity and mortality. Its aetiology is related to both components of the parenteral nutrition as well as host factors. Understanding of the aetiology of PNALD provides targets for intervention. For example, the use of \(\omega3\)FA enriched emulsions have the potential to have a significant impact on the management of patients with PNALD. As well, given the central role of sepsis in the pathogenesis of this condition, optimal patient care to prevent this complication should allow for the best outcome of patients on prolonged parenteral nutrition.

1.2.7 Disclosure

The authors have received Investigator Initiated Trial funding from Fresenius Kabi, the manufacturer of both Omegaven\textsuperscript{®} and Intralipid\textsuperscript{®} to evaluate SMOFlipid\textsuperscript{®} for the prevention of PNALD.
1.2.8 Acknowledgements

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Chapter 2

2 Lipid Based Approaches to the Management of IFALD

The role of intravenous lipids in the pathophysiology of IFALD was introduced in Chapter 1. This chapter will further review the rationale and current evidence for alternate lipid based strategies in the management of IFALD.

2.1 Review of Dietary Lipids

Prior to reviewing the role of lipids in the pathophysiology of IFALD, we shall briefly review the major types of lipids. The primary component of the dietary lipids are fatty acids, which are hydrocarbon chains with a carboxyl group on the one end and a methyl group on the other. The chain length varies in the number of carbons from 2 to 30, with chain lengths of < 6 being termed short chain fatty acids, 6 – 12 medium chain fatty acids and > 18 being termed long chained fatty acids.

Fatty acids also vary in terms of the number and position of double bonds within the chain. Chains with a single double bond are referred to as monounsaturated fatty acids and those with 2 or more double bonds are referred to as polyunsaturated fatty acids. Fatty acids are also classified according to the position of the 1st double bond relative to the methyl end of the chain. Fatty acids with this bond at position 3 are termed omega-3 fatty acids (ω3FA) and those at position 6 are termed omega-6 fatty acids (ω6FA).

The simplest ω6FA is linoleic acid (LA) and the simplest ω3FA is alpha-linolenic acid (ALA). Both of these fatty acids are regarded as essential fatty acids (EFA) as they are not able to be synthesized in humans. However, humans are able to metabolize them further into other longer chain fatty acids. Mediators derived from these longer chain polyunsaturated fatty acids have important biological actions. The primary polyunsaturated fatty acids derived from LA (ω6FA) are arachidonic acid (AA) and dihomo-γ-linoleic acid. The primary polyunsaturated fatty acids derived from ALA (ω3FA) are docosahaexanoic acid (DHA) and eicosapentaenoic acid (EPA). However, it must be noted that infants have limited capacity for the conversion of ALA to DHA and EPA and as such, dietary sources of these fatty acids are required by infants.
2.2 Review of the Role of Parenteral Lipids in IFALD

The precise mechanisms by which Intravenous Lipid Emulsions (ILEs) contribute to IFALD are not well understood and there are likely multiple mechanisms involved \(^{(134)}\) (see Section 1.2.4.1.3).

All ILEs, in North America, are composed of plant-based lipids, primarily soy. The predominant fatty acid source in these emulsions are \(\omega_6\text{FA}\). While plant based ILEs such as Intralipid\(^{\text{®}}\) (Fresenius Kabi, Bad Homburg, Germany) contain \(\omega_3\text{FA}\) in the form of ALA, these emulsions, do not provide a substantial and utilizable source of \(\omega_3\text{FA}\) for the infant \(^{(135,136)}\).

Omega-3 and Omega-6 fatty acids interact with each other through a complex system competing for phospholipid membrane incorporation and eicosanoid synthesis \(^{(137)}\). The \(\omega_6\text{FA}\) are directly and indirectly involved in the synthesis of a number of pro-inflammatory eicosanoids and cytokines including Platelet Activating Factor, Interleukin 1, 2, and 6, and Tumour Necrosis Factor alpha \(^{(138-143)}\). In contrast, \(\omega_3\text{FA}\) are immunomodulatory related to the fact that DHA and EPA are precursors for a group of less inflammatory eicosanoids than those derived from AA \(^{(60,144)}\). As such, an emulsion that has predominantly \(\omega_6\text{FA}\) will support a hyper-inflammatory state.

ILEs from plant sources are also dense in phytosterols and low in anti-oxidants. Phytosterols have been implicated in the development of IFALD, with anti-oxidant imbalance also proposed to be contributory to IFALD \(^{(50-52)}\).

2.3 Novel Lipid Based Approaches to the Management of IFALD

Given the potential role that ILEs play in the pathophysiology of IFALD, there is substantial interest in alternate approaches to provision of intravenous lipids in those with IF. The two main approaches are lipid minimization, as well as, the use of ILEs containing omega-3 fatty acids (\(\omega_3\text{FA}\)) which are derived from fish-oil. Furthermore, there are ILEs, derived from sources other than fish-oil that could be used to replace the soy-based emulsions and theoretically reduce the risk of IFALD.
2.3.1 Lipid Minimization

2.3.1.1 Definition and Rationale

Infants who are dependent on PN are currently recommended to receive between 2-3 g/kg/day of PN lipid \(^{145, 146}\). These recommendations have been revised from historic recommendations with the upper limit previously being 4 g/kg/day. Although a breast fed infant consumes approximately 7 g/kg/day of fat enterally, PN lipid administration is reduced due to the limited ability of the infant to clear intravenous lipid \(^{145}\).

Lipid minimization refers to provision of a soy-based lipid emulsion in doses, significantly lower than these recommendations. While there is no consistent definition for what constitutes lipid minimization, we have defined this to be a lipid dose, in a child on full (> 60% of total calories) parenteral support, of less than 1 g/kg/day of intravenous lipid. However, lipid minimization has sometimes been employed with total intravenous lipid intakes lower than this range. As such, we regard our definition to be the upper range for what constitutes lipid minimization. The rationale for lipid minimization relates to the notion that lowering exposure to these emulsions will result in a lower risk of IFALD \(^{147}\).

2.3.1.2 Clinical Experience with Lipid Minimization

Published evidence regarding the utility of lipid minimization are quite limited and only from retrospective or uncontrolled studies. Despite no data from controlled studies, the weight of evidence suggests that cholestasis may be improved by a reduction in lipid dose. Allardyce et al., demonstrated in adult patients that the risk of developing cholestasis was significantly lower in those who received 1 g/kg/day (1/17) compared with those who received 3 g/kg/day (10/18) \(^{148}\). Colomb et al., demonstrated an association between decreases in lipid therapy and normalization of serum conjugated bilirubin (CB) \(^{48}\). Rollins et al., reported on 6 children with IFALD in whom the soy-based ILE was stopped, with subsequent resolution of cholestasis in all \(^{100}\). However, it is important to note that 4 of the 6 patients received an enteral fish-oil preparation. This raises the possibility of an ω3FA effect or that resolution of cholestasis may be partly related to improved enteral tolerance. Torres et al. reported in abstract form on 32 patients with IFALD, of whom 31 normalized their hyperbilirubinaemia with aggressive intestinal rehabilitation that included restriction of a soy-based ILE to < 1g/kg/day \(^{149}\). Bianchi has suggested improved outcomes with a “hepato-sparing regimen” in which the ILE dose is limited to 1.5 g/kg/day \(^{150}\).
The group from the University of Michigan described a consecutive series of 32 surgical patients on PN, with a CB > 2.5 mg/dl (42.5 umol/L) or a total bilirubin > 5 mg/dl, who were enrolled in a lipid minimization protocol\textsuperscript{147}. Children in this protocol received 1g/kg of a plant based ILE twice a week. Fourteen subjects were compared to 14 matched historical controls, with the results demonstrating a significant reduction in bilirubin between the groups. The average reduction in serum CB was 0.9 mg/dl per week of therapy.

2.3.2 Omega-3 Lipids

2.3.2.1 Rationale

In contrast to $\omega_6$FA, $\omega_3$FA have a number of beneficial effects that are proposed to ameliorate IFALD as described in Figure 2-1\textsuperscript{1}.

![Figure 2-1: Proposed Beneficial Effects of $\omega_3$FA in IFALD.](image)

\textsuperscript{1} From Diamond et al. Ped Surg Int 2008. Reprinted with permission.
Fish-oil derived ILEs have been demonstrated in an animal model not to impair bile flow \(^{50}\). This may be related to either a reduction in phytosterol load or via prostaglandin mediated mechanisms related to the addition of \(\omega3FA\) \(^{50, 62, 151}\). Omega-3 fatty acids have also been demonstrated to reverse hepatic steatosis in both PN and non-PN liver disease \(^{152, 153}\). A number of mechanisms have been proposed including, stimulation of peroxismal and mitochondrial \(\beta\)-oxidation of fatty acids \(^{154-157}\), reduction in de novo lipogenesis \(^{154}\) and providing a poor substrate for esterification to glycerol \(^{158-160}\). Omega-3 fatty acids also decrease oxidative stress, due to a reduction in the activity of superoxide dismutase and glutathione peroxidase \(^{161}\). This effect is also likely augmented by the fact that many of the parenteral ILEs containing \(\omega3FA\) also have significant amounts of the anti-oxidant \(\alpha\)-tocopherol \(^{162, 56, 57}\). Finally, \(\omega3FA\) have important immunomodulatory effects resulting in less pro-inflammatory mediators \(^{53-55, 163}\). Although clinical evidence of immunomodulation in IFALD is limited, evidence for the possible beneficial immunomodulatory impact of \(\omega3FA\) following a cholestatic insult was demonstrated in an animal model of ligation of the common bile duct \(^{164}\).

### 2.3.2.2 Clinical Experience with Omega-3 Containing Intravenous Lipid Emulsions

#### 2.3.2.2.1 Experience with Omegaven®

Gura et al., from Children’s Hospital Boston, published the first report of 2 children with severe end-stage IFALD who demonstrated complete reversal of their liver disease following a change from soy-based Intralipid® (Fresenius Kabi, Bad Hamburg, Germany) to Omegaven® (Fresenius Kabi, Bad Hamburg, Germany), a fish-oil derived ILE, \(^{101}\).

The most recent detailed publication of outcomes from the group in Boston, reported on 42 infants who received Omegaven® compared with 49 subjects from a historic cohort \(^{102}\). Median CB at time of initiation of Omegaven® was 94 umol/L (5.5 mg/dl). Overall resolution of cholestasis while on PN in the Omegaven® group was 19 compared with 2 in the control group. The risk of death or transplantation was also substantially lower in the Omegaven® group relative to the historic cohort (4/42 vs. 17/49). There were 2 patients in the Omegaven® group who developed biochemical evidence of essential fatty acid deficiency (EFAD). A recent review from the group in Boston states that more than 130 children have received Omegaven® with encouraging results \(^{165}\).
To date, 33 patients have received Omegaven® at our institution, with the outcome of the first 22 analysed in detail (12 cases published in full and the remainder in published in abstract form)\textsuperscript{103, 166}. The median age at initiation of Omegaven® was 6.9 (range: 2.2 – 46) months. Median CB at start of therapy was 114 (range: 54 – 231) umol/L (6.7 mg/dl). Sixteen (73%) had complete and sustained resolution of hyperbilirubinaemia, 4 patients received a transplant prior to resolution of hyperbilirubinaemia and two died (1 IFALD; 1 neurological insult). We believe that compared with our historic experience, survival to transplant was facilitated in these children by treatment with Omegaven®. There were no complications attributable to Omegaven®. Also, in contrast to our historic mortality from liver failure of 22% per year of infants with SBS\textsuperscript{26}, only 1 infant has died from IFALD since starting to use Omegaven® rescue therapy in 2006.

Whereas the group in Boston has adopted an approach of utilizing Omegaven® as the sole lipid source in PN, we have treated our patients by combining Omegaven® with Intralipid®. While the group in Boston only provides 1g/kg of Omegaven®, we provide 1g/kg of Intralipid® and 1g/kg of Omegaven®. We believe that this mixture provides improved growth and also that a balanced lipid emulsion makes more sense physiologically than a lipid that is composed entirely of primarily ω3FA or ω6FA. As well, there is emerging evidence that supplementation of infant formulas with both ω3FA and ω6FA has beneficial effects on visual, somatic, and neural development\textsuperscript{167, 168}.

Other evidence for the use of Omegaven® in paediatric IFALD are limited to case series and single patient reports with outcomes similar to that noted in our and the Boston experience\textsuperscript{169-175}. There has also been discussion of the possible beneficial effects of enteral fish-oils\textsuperscript{176}. While we recognize that the use of enteral preparations is partly related to the difficulty of obtaining Omegaven® in North America, these reports are substantially confounded by the fact that children with sufficient intestinal function to tolerate enteral fish-oil are likely demonstrating adequate intestinal adaptation. As such, they could be expected to have resolution of IFALD on the basis of improved enteral tolerance alone\textsuperscript{177}.
2.3.2.2.2 Experience with SMOFlipid®

SMOFlipid® (Fresenius Kabi, Bad Hamburg, Germany) is a composite emulsion lipid that contains Soy Bean Oil (30%), Medium Chain Triglycerides (MCT) (30%), Olive Oil (25%) and Fish Oil (15%). The product therefore contains both ω3FA and ω6FA with a n6:n3 ratio (ratio of ω6FA to ω3FA) of 2.5:1, which is within the optimal range of 1:1 – 4:1 as established in the literature for immunomodulatory effects 55, 178, 179.

SMOFlipid® also contains MCTs (30%). MCTs are more water soluble than longer chain triglycerides. They are more readily hydrolyzed and eliminated from the blood stream 180. MCTs have also not been associated with hepatic steatosis 181, 182 and do not serve as precursors for free radical formation 181, 182. MCTs also prevent beta-oxidation of ω6FAs 183.

SMOFlipid® also contains olive oil that is rich in the monounsaturated fatty acid, oleic acid. This lipid is a major component of the Mediterranean diet and is associated with significant cardiovascular benefits 184-186. Monounsaturated lipids are less prone to peroxidation, and do not alter lymphocyte function like ω6FAs 187.

The lipid composition of SMOFlipid® more closely approximates the fatty acid composition of Breast Milk than does Intralipid® (Figure 2-2). Note that although Intralipid® contains ω3FA, this is all ALA which, as previously discussed, is not biologically useful in the infant 135, 136.

![Figure 2-2: Fatty Acid Composition of Intralipid®, SMOFlipid® and Breast Milk.](image-url)
A number of European studies have examined SMOFlipid® relative to standard soy-based lipids in paediatric populations, including preterm infants, at dosages up to 3.5g/kg/day of lipid. These studies were primarily focused on safety. The results of these studies confirmed the safety of the product, as well as, it being a suitable replacement for a soy-based lipid. Furthermore, SMOFlipid® was eliminated faster than the soy-based lipid. Similarly, there were changes in the membrane phospholipid profiles of patients which would likely lead to a decrease in pro-inflammatory eicosanoids.

Some of the outcomes from these trials are of direct relevance to children with IFALD. Skouroliakou et al., demonstrated reduced oxidative stress with SMOFlipid® relative to Intralipid® in a randomized controlled trial of 38 pre-term infants. However, serum bilirubin did not differ at Day 14 of treatment. Tomsits et al. compared SMOFlipid® to Intralipid® in a randomized sample of 60 premature neonates and demonstrated improvements in serum GGT (gamma-glutamyl transferase) in the SMOFlipid® group. Goulet et al., studied 28 children on home parenteral nutrition, randomized to SMOFlipid® vs. Intralipid® for a month. At the end of this period, the change in serum total bilirubin was significantly lower in the SMOFlipid® group. Whereas the SMOFlipid® group experienced a decline in bilirubin over the trial, bilirubin levels increased in the Intralipid® group. These results are congruent with 2 randomized controlled trials in adults. One of these studies was in surgical patients in the post-operative period that demonstrated improved hepatic parameters with SMOFlipid® relative to Intralipid®. The other examined adult patients with IF who demonstrated improved hepatic function after a month of treatment with SMOFlipid®. Finally, there are 3 case series, from Europe of SMOFlipid® being employed for the management of advanced IFALD, much in the same way that Omegaven®, has been employed in North America. Of the 23 patients treated across these 3 series, 18 demonstrated complete resolution of their conjugated hyperbilirubinaemia despite receiving conventional doses of lipid.

2.3.3 Other Alternate Intravenous Lipid Emulsions

Outside of North America, there are other emulsions including mixtures of soy/coconut (Lipofundin® MCT, B Braun, Melsungen, Germany) and olive/soy (Clinoleic®, Baxter, Berkshire, United Kingdom). Theoretically, by reducing the exposure to ω6FA, these emulsions may play a role in the management of IFALD.
There is one randomized study of Lipofundin® MCT in paediatric surgical patients that is not of particular relevance to those with IF. There was also a 3-day trial of Lipofundin® MCT vs. a soy-based emulsion that did not demonstrate differences in total bilirubin, although the duration of study was too short for a difference to be expected. However, based on fatty acid profiles, the authors concluded that the conventional emulsion may be preferred from a nutritional perspective. A recent 7-day randomized study of Lipofundin® MCT vs. Lipoplus® (B Braun, Melsungen, Germany), an emulsion with similar composition to SMOFlipid® although with less fish-oil (10% vs. 15%), demonstrated increased levels of fatty acids associated with reduced inflammation with the fish-oil ILE, but no difference in total bilirubin.

In an adult study, Clinoleic® was demonstrated to be associated with stable liver function over a 3-month treatment period. There are 5 paediatric randomized studies that examined the safety of Clinoleic® in pre-term infants over a short period of time. Given the time-period as well as objectives of these studies, they did not specifically address changes in liver function in a meaningful way. However the olive-oil emulsions were associated with improved anti-oxidant measures with one study showing decreases in pro-inflammatory cytokines. One medium term study (60-days) of children with stable liver function at trial enrolment, did not demonstrate any adverse hepatic consequences with Clinoleic®. Trials comparing Clinoleic® to SMOFlipid® are ongoing. The hepatic outcomes from these studies will be of particular interest.

2.4 Current Status of Novel Lipid Based Approaches to the Management of IFALD

While the novel lipid based may be appropriate for those with advanced IFALD, given the dearth of alternative therapies, in those with early or no liver disease, they should only be used in the context of randomized controlled trials. Our caution relates primarily to the lack of high quality evidence for the efficacy of these approaches and the limited safety data including an understanding of the impact on growth and development. Our concern is further highlighted by a recent publication from our group showing that should the threshold for initiation of a novel lipid based approach be set at 34 umol/L (2 mg/dl), as is already occurring at some centers, only 10% of surgical infants managed with the novel approach would benefit. The reason for this assertion was that only 10% of the subjects in this cohort, who received a conventional ILE, progressed to more advanced IFALD, defined as a serum CB > 100 umol/L.
2.4.1 Quality of Evidence

It is critical to recognize that all experience with lipid minimization as well as Omegaven® and SMOFlipid® in established IFALD, come from retrospective or uncontrolled studies. Furthermore, while SMOFlipid® has been suggested on the basis of the randomized trials to be associated with improved hepatic outcomes, the patient populations in these studies were either normal pre-term infants or children on home PN with stable liver function and not patients with IF at high risk of progressive IFALD. While the magnitude of differences in terms of hepatic outcomes between SMOFlipid® and Intralipid® were statistically significant, they were not of clinical relevance. This is not surprising given the patient populations in which these studies were done, as well as, the short duration of study.

Uncontrolled studies are subject to the impact of both known and unknown confounders. As such, inferences about the potential efficacy of these therapies must be tempered by this fact. The most prevalent confounder in the setting of patients with IF is the degree of enteral support with weaning of the PN concomitant with the novel lipid based therapy. However, in our experience, there was only a median 10% increase in enteral tolerance in our patients who responded to Omegaven®. Resolution of advanced cholestasis in this setting based on our historical experience is highly unusual.

Uncontrolled studies also do not allow one to assign causality, which is a particular issue when one considers the impact of Omegaven®. Omegaven® as it has been used in those with advanced IFALD represents both an alternate lipid source but also a form of lipid minimization. The lipid dose employed by the group in Boston and most of the other publications was 1g/kg/day and the mean lipid dose in our cohort was 1.4 g/kg/day. These doses are substantially lower than that typically used for parenteral lipids in infants (2-3g/kg/day) and within the range of lipid intake that we regard as lipid minimization. Therefore, the apparent beneficial effect of Omegaven® may be related to reduced lipid dose rather than a qualitative change in lipid source. The experience with SMOFlipid® in advanced IFALD as well as experience from the use of omega-3 lipids in animal models of IFALD, argue against the impact of Omegaven® as being only one of dose restriction. However, until controlled data exist that examines both dose and source, this question remains unanswered. However, both Omegaven® and SMOFlipid® contain more \textit{α}-tocopherol than Intralipid® with this anti-oxidant, being another potential confounder.
2.4.2 Safety Concerns

2.4.2.1 Concerns Related to Lipid Restriction

The long-term implications of a reduction in lipid dose on growth and development are unknown. Therefore, while dose restriction may be appropriate for the treatment of advanced liver disease, it may not be acceptable in the preventative setting. We believe that there needs to be a higher level of evidence in terms of long-term safety and efficacy before substantially altering recommended parenteral fat and energy intake in infants given the critical role that lipids play in neurodevelopment. There is also evidence that both $\omega_6$FA and $\omega_3$FA are important for development \(^{154, 155}\).

Reducing lipid intake also has the potential to result in EFAD. In the series of 32 patients managed with lipid minimization by Cober et al., biochemical evidence of EFAD, was noted in 8. Although the group in Boston have reported on patients with biochemical evidence of EFAD, they have stated that clinically significant EFAD has not been noted in patients managed with Omegaven\(^{\text{®}}\) \(^{165}\). Other groups have however noted this complication \(^{174}\). Although we agree with de Meijer et al., that the 0.1 to 0.7\% linoleic acid content of Omegaven\(^{\text{®}}\) may be sufficient to prevent EFAD, we maintain that further evidence is needed regarding the use of any ILE at a lipid dose of $< 1\text{g/kg/day}$ over a prolonged period in developing infants, especially in those with minimal or no liver disease.

2.4.2.2 Omega-3 Specific Concerns

The major theoretical concerns regarding an imbalance between $\omega_3$FA and $\omega_6$FA intake, relates to the ability of $\omega_3$FA to down regulate Arachidonic Acid (AA). Although down-regulation of AA may be a major mechanism to explain the beneficial effects of $\omega_3$FA, the possible risks of AA inhibition include growth suppression, immunesuppression, increased lipid peroxidation and delayed haemostasis \(^{209, 210}\). Despite these concerns, neonatal animal models have not demonstrated any impairment in bone composition or growth \(^{211}\). One study in fact demonstrated a beneficial impact of $\omega_3$FA on bone formation \(^{212}\). In human studies, $\omega_3$FA PN supplementation has not been associated with any adverse consequences in lipid parameters \(^{213-217}\).
There have been no reported significant complications associated with Omegaven® use in children in either the Boston or Toronto experience. There is a case report, from another center, of a Burr cell haemolytic anaemia in a child with IF treated with Omegaven® that resolved following discontinuation. Given that ω3FA are known to alter Red Blood Cell (RBC) membrane dynamics it is likely that this adverse effect was related to Omegaven®.

Another theoretical concern is that of increased hepatic fibrosis on the basis of a rabbit model of IFALD. One of the limitations in assessing this issue clinically is that liver biopsies are rarely performed in patients with IFALD, especially when the child is demonstrating biochemical evidence of resolution. However, in a report of 2 cases, Soden et al., demonstrated progressive fibrosis with Omegaven® use despite biochemical normalization. It is also important to recognize that while Omegaven® may result in normalization of hyperbilirubinaemia, a biochemical improvement in serum CB does not rule out ongoing liver injury contributing to progressive fibrosis. Therefore it is unclear whether the progressive fibrosis was related to the fact that the child remained on PN with ongoing liver injury, was the result of healing of the injury inflicted prior to the start of Omegaven® therapy, or that fibrosis is a specific adverse consequence of treatment with Omegaven®.

Despite the apparent safety of Omegaven®, we believe that further experience with this and other related emulsions such as SMOFlipid® are needed to ensure that the preparations are not associated with rare but serious adverse events. This is especially important when one considers their use in patients with no or early IFALD, where the risk-benefit ratio is different from those with advanced IFALD. It must be recognized that overall the risk attributable to ω3FA with a composite emulsion such as SMOFlipid® are likely to be lower than those with Omegaven® given the balanced lipid composition of these emulsions.

### 2.5 Conclusions

Novel lipid based approaches seem, on the basis of the uncontrolled data presented in this chapter to be very promising for the management of IFALD. However, there is a lack of high quality evidence on which to base treatment recommendation. Therefore more research is needed to better evaluate the efficacy of these approaches. Furthermore, additional safety parameters including the potential impact of these therapies on long-term growth and development need to be assessed.
Chapter 3

3 Challenges and Solutions in Studying Novel Lipid Based Approaches to the Management of IFALD – An Introduction to Bayesian Analysis of Clinical Trials

3.1 The Role of Randomized Controlled Trials in the Evaluation of the Novel Lipid Based Approaches

The strongest evidence for the efficacy of a treatment is derived from well designed and performed randomized controlled trials, either singly or combined in appropriate metanalyses. In a review of adult therapies that were suggested to be beneficial in uncontrolled studies, Sacks et al., demonstrated that only 20% were effective when studied in a randomized design. Therefore, as promising as the novel lipid based approaches may seem, randomized trials are required to appropriately evaluate their efficacy and safety prior to recommending wide-spread adoption of these therapies in those with early or mild IFALD. There are, however, a number of characteristics of patients with IF that may make these trials challenging to perform.

3.2 Potential Challenges in Studying Novel Lipid Based Approaches to the Management of IFALD

Intestinal Failure is a rare disease, with Canadian population level estimates of 24.5 / 100 000 live births and only 384 paediatric cases of established IF requiring long-term PN in the United Kingdom. Due to the rarity of IF, trials will probably need to be multi-center in order to accrue sufficient patients to be adequately powered.

The fact that multi-center trials will be required and also that such studies may be methodologically complex, is compounded by the limited experience with randomized controlled trials in children with IF. Two recent systematic reviews highlight the paucity of controlled trials in this area. Klein et al., reviewed the literature with the goal of providing data on the pathophysiology of IFALD, as well as, to document prospective randomized controlled trials of therapies in this area. They identified 12 clinical trials examining potential therapeutic options for IFALD. Only 1 of these studies enrolled patients with documented IF, with 9 enrolling pre-term/low-birth weight infants and 2 enrolling surgical neonates.
et al. performed a similar review, but limited their search to studies that enrolled patients with established IF in the past decade. This review yielded 2 randomized controlled trials. The findings of these systematic reviews are not surprising, given the paucity of randomized controlled trials in the field of paediatric surgery as a whole.

All of the studies evaluating the novel lipid based approaches to date have focused on the serum CB as the end-point. Conjugated bilirubin is a biomarker for a number clinically important outcomes including portal hypertension, liver failure, transplantation or death. These outcomes are both more infrequent and also take longer to develop, which is likely why current studies have focused on the serum CB. Given the more infrequent nature of these outcomes, large studies will be required in order to be sufficiently powered to demonstrate an impact on these outcomes. Such studies will also require a much longer follow-up period (years), than the short term (months) duration of studies published to date.

One of the limitations of relying on the CB is that there has been a suggestion that progressive IFALD may develop in the absence of rising CB. However, liver biopsies, which would allow one to diagnose hepatic fibrosis early, are infrequently done clinically in the IF population and would not likely be appropriate, for ethical reasons, in clinical trials. Dynamic tests of liver function are still in development in the IF population but may be more appropriate outcomes for clinical trials in the future. However, the acceptability to participants of these tests that may be invasive will need to be evaluated.

Children with IF have a variety of aetiologies as well as associated co-morbidities. This heterogeneity has implications in terms of the medical and surgical management of these patients. Since a clinical trial of a novel lipid based approach will require standardization of the PN, the heterogeneity of children with IF may make this aspect of the trial unfeasible. Furthermore, it is not known whether participation in randomized controlled trials will be acceptable to the parents of these complex children.

Finally, most of the experience with the novel lipid based approaches in children with IFALD has focused on those with advanced disease. Thus there is a paucity of data on which to base estimates of the potential magnitude of the treatment response with the novel lipid based approaches in those with early IFALD. Such estimates are critical in sample size calculations in order to ensure that future trials are adequately powered.
3.3 Proposed Solution to the Challenges of Performing Studies of the Novel Lipid Based Approaches to the Management of IFALD

This thesis presents a three component strategy to facilitate clinical trials of novel lipid based approaches for prevention of IFALD. First, we further examined the role of parenteral lipid in the pathophysiology of IFALD in order to determine the potential magnitude of benefit that a lipid based approach may have. Bayesian analysis of randomized trials has been suggested as a strategy for trials in rare diseases such as IFAD. Bayesian analyses, as will be described in the subsequent section require estimates of the effect size, from data external to the trial, to be used as a prior distribution. However, there is a paucity of data on which to base these prior distributions. Therefore, as our second project, we performed an expert belief elicitation study to determine the distribution of the probability, based on expert opinion, of the novel lipid based approaches being effective for the prevention of IFALD. These distributions can be used as priors in Bayesian analyses of randomized controlled trials of these approaches. Finally, given the specific challenges of performing clinical trials in this area, we performed a pilot multi-center randomized controlled trial of a novel lipid based strategy.

3.4 The Rationale for Bayesian Analyses of Clinical Trials

3.4.1 Limitations of the Frequentist Approach

The traditional, or frequentist paradigm for the analysis of data from clinical trials, focuses on the probability that the observed data or values more extreme, were obtained by chance alone. The p-value is a quantification of the probability that the results obtained could be due to chance. By convention, when the probability that the results were obtained by chance is less than 5%, we conclude that the difference observed is “statistically significant”. The 5% chance of incorrectly concluding that there is a treatment effect is known as a Type I error. Therefore, the question answered by the p-value is merely whether there is any treatment effect, rather than how large that treatment effect might be. Estimates of the magnitude of treatment effects are however of most relevance to decision makers including patients, clinicians and funders.

The magnitude of the p-value is not only related to the effect size, but also the sample size from which the results are drawn. As such, the frequentist approach is not ideally suited to the study of rare diseases, where larger clinical trials may not be feasible.
3.4.2 The Bayesian Approach

In contrast to the frequentist approach, a Bayesian analysis allows for maximal information to be gained from the limited number of subjects enrolled in a study. The Bayesian approach achieves this through formal incorporation of prior information into the analysis which may reduce sample size requirements \(^{240}\). A Bayesian analysis also provides a meaningful estimate of the probability a treatment response. According to Spiegelhalter et al., Bayesian approaches to assessment of a health technology can be defined as “explicit and qualitative use of external evidence in the design, monitoring, analysis, interpretation and reporting of the results” \(^{241}\). While the Bayesian approach can be utilized in the design and monitoring of clinical trials \(^{241},^{242}\), including for sample size estimation \(^{243}\) and stopping rules \(^{244}\), this chapter will focus on the use of the Bayesian approach for the analysis of data from a randomized controlled trial.

3.4.2.1 The Prior, Likelihood and Posterior Distribution

Central to a Bayesian analysis, is the notion of the prior distribution which is a probability distribution of the variable of interest from data external to the study. This prior may be based on previous studies or, in the absence of higher levels of evidence, on expert opinion \(^{245}\). A Bayesian analysis is a formal method of integrating the prior distribution with the distribution of the new data, known as the likelihood, to yield a posterior distribution \(^{241}\).

The posterior distribution reflects the variable of interest taking both the prior information and the data into account. For example, in the analysis of a clinical trial, the prior distribution may be an estimate of the treatment effect from previous studies. This is then combined with the new data from the trial, to yield a posterior distribution. The posterior distribution provides the updated probability of the treatment response based on both the external information and the current study. The posterior distribution can be utilized to make inferences as to the probability of a treatment response of a particular magnitude. Therefore, the Bayesian approach yields a direct estimate of the probability of there being a meaningful treatment effect \(^{246}\). This notion is expanded in ongoing trial monitoring by a Bayesian approach, whereby the posterior distribution is updated as subjects are accrued and the trial stopped once the posterior distribution yields convincing evidence of either a meaningful difference between treatments or that such a difference is unlikely to be achieved \(^{247},^{248}\). This is done without increasing the error rate.
3.4.2.1.1 Types of Prior Distributions

Prior distributions may be uninformative or informative.

3.4.2.1.1.1 Uninformative Priors

Uninformative priors are priors which have little intrinsic information with the goal of the analysis being a posterior distribution that reflects the likelihood. This is achieved by specifying a prior with low precision. While the posterior from the analysis mirrors the likelihood, it is important to recognize that the posterior distribution allows one to directly estimate the probability of a meaningful treatment effect. This can be illustrated with data from a hypothetical placebo trial with 30 participants (15 in each group) of a drug for symptom management of particular disorder. The outcome of this study was a disease specific quality of life instrument. A difference of 2-points on this measure is believed to be clinically important. The mean value in the experimental arm was 13.6 units (standard deviation: 4.97) and in the control arm 10.5 units (standard deviation: 4.36). A frequentist analysis with a t-test provided insufficient evidence to conclude that there was a difference between the treatments (t-statistic 1.797, df = 28, p = 0.083, mean difference 3.06: 95% confidence interval: -0.42 to 6.56). An uninformative Bayesian analysis provides very similar estimates for the difference in means between the groups (median value: 3.05, 95% credible interval -0.58 to 6.61). However, unlike the frequentist analysis, the Bayesian analysis allows one to ascertain the probability of a clinically important difference 74%, or 96% for any difference. Therefore, this small study that would have likely been regarded as “negative” with the frequentist approach, may provide useful information when analyzed by the Bayesian approach.

3.4.2.1.1.2 Informative Priors

Informative priors are those with information that may alter the likelihood. The goal of the analysis is a posterior distribution that combines both the prior and the likelihood. Formal incorporation of data from previous studies, may allow investigator to address questions meaningfully with fewer subjects. However, inclusion of prior information is one of the aspects of the Bayesian approach that is most controversial. The primary argument is that one can’t be certain that the information contained in the prior is correct. To address this issue, sensitivity analyses can be performed whereby the impact of alterations in the prior distribution, including the use of sceptical priors as will be elaborated in the next paragraph, is assessed.
When analysing data from clinical trials, optimistic and sceptical priors, are specific types of informative priors. Optimistic priors are constructed to demonstrate a high probability of a meaningful treatment response. Sceptical priors are constructed to have a high probability of there not being a treatment response. Spiegelhalter et al., suggest that optimistic priors should be centered on the point estimate for the treatment response on the basis of the prior information, with the variance of the distribution specified to include only a 5% chance of a null effect. Similarly, sceptical priors are suggested to be centered on a treatment effect of 0, with an only 5% chance of a treatment effect at least as large as the point estimate for the treatment effect.

The posterior distribution of an analysis utilizing a sceptical prior is particularly important when considering the results of a clinical trial. Since the sceptical prior reflects a low probability of a meaningful treatment response, the posterior distribution updates this probability on the basis of the data. It is suggested that this posterior distribution reflects what an individual who holds a sceptical view of the treatment prior to the trial should believe with knowledge of the data.

The question being addressed by this analysis therefore is whether the data from the trial are sufficiently strong to convince a sceptic to adopt the treatment.

3.4.2.2 Reporting of the Results of Bayesian Studies

Generally, the results of a Bayesian analysis are reported in terms of a measure of central tendency (median or mean value) of the parameter (variable) of interest. The 95% credible interval for the variable of interest is also typically reported. This interval represents the range between the 2.5th and 97.5th percentile for the variable of interest.

Plots of the various distributions may also be provided, with a triplot being a plot of the prior, likelihood and posterior. The posterior distribution can be utilized to make inferences as to the probability of a treatment response of a particular magnitude. Recommendations regarding adoption or avoidance of the therapy are based on the probability of benefit being sufficiently high or low.

Sung et al., surveyed experts in Bayesian analytic techniques in order to develop criteria for reporting of the results of Bayesian studies. Their criteria, termed ROBUST (Reporting of Bayes Used in clinical STudies), consists of 7 items. The items comprise: (1) specification and (2) justification of the prior distribution, as well as, (3) a sensitivity analysis if alternate priors are
used, (4) details regarding the statistical model employed, as well as, (5) the analytic technique. The details of the analytic technique may include the number of concurrent analyses (chains) that were run for the analysis using a Bayesian analysis of complex statistical models using Markov chain Monte Carlo (MCMC) simulator such as Winbugs (MRC Biostatistics Unit Cambridge, UK)\textsuperscript{251} in order to ensure stability (convergence) of the model, the values (initial values) used to begin the analysis, and the number of times the MCMC simulator was run (iterations).

In terms of presentation of the results, authors are recommended to report measures of (6) central tendency, such as the mean or median, as well as, a measure of (7) dispersion such as the standard deviation or credible interval.

3.5 Conclusion

Randomized controlled trials of the novel lipid based approaches are required prior to their widespread adoption in children with IF who have minimal liver dysfunction. However, these trials may be challenging to perform given the rarity of the condition, heterogeneity and complexity of the patient population and limited experience with clinical trials in these patients. Therefore, a pilot study was performed to evaluate the feasibility of this design (Chapter 6). Also, the Bayesian approach has possible advantages over the frequentist paradigm in the analysis trials of rare diseases such as IF. We therefore surveyed experts in order to develop prior distributions to be used in such analyses (Chapter 5). A blinded Bayesian analysis of data from the pilot trial was performed that included use of the priors obtained from the group of experts (Chapter 7).
Chapter 4

4 The Role of Parenteral Lipids in the Development of Advanced Intestinal Failure Associated Liver Disease in Infants – A Multiple Variable Analysis

THE ROLE OF PARENTERAL LIPIDS IN THE DEVELOPMENT OF ADVANCED INTESTINAL FAILURE ASSOCIATED LIVER DISEASE IN INFANTS

- A MULTIPLE VARIABLE ANALYSIS

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4.1 Précis

A serum conjugated bilirubin greater than 100 umol/L (5.9 mg/dl) (CB100), in infants who receive parenteral nutrition (PN), has been demonstrated to be a predictor of end-stage liver disease requiring transplantation. This multiple variable analysis demonstrates that days of PN lipid >2.5g/kg and intercurrent septic episodes are important predictors for CB100 development.

4.2 Abstract

Background: Given the recent interest in the role of omega-6 lipids in the development of Intestinal Failure Associated Liver Disease (IFALD), we sought to examine the role of parenteral lipids in the development of a serum conjugated bilirubin greater than 100 umol/L (5.9 mg/dl) [CB100] in infants. Method: Between 2003 and 2004, data were collected prospectively on infants undergoing an abdominal surgical procedure. Univariate logistic regression models for the prediction of CB100 by 1-year post-operatively were developed. Predictors significant at the 0.2 level on univariate analysis were entered into a backward stepwise multiple variable logistic regression. Results: 152 infants received parenteral nutrition post-operatively, and 22 developed CB100. Predictors that met criteria for consideration in the multiple-variable model were: age, weight, small bowel length, presence of a stoma, proportion of enteral feeds post-operatively, septic episodes, days of maximal PN amino acid (> 2.5g/kg/day), days of maximal lipid (> 2.5 g/kg/day), and PN duration. The final model included septic episodes [Odds Ratio (OR): 3.23 95% Confidence Interval (CI): 1.8 - 5.9] and days of lipid > 2.5g/kg/day [OR: 1.04 95%CI: 1.003 – 1.06]. At 60-days of maximal lipid, the odds of advanced IFALD were increased 10-fold.

Conclusions: Our model suggests a key role of parenteral lipids and septic events in the development of CB100 from IFALD. These data may provide targets, such as careful line care, reduction in maximal lipid dose, or the use of alternate lipids such as Omega-3 fatty acids, to prevent CB100 an identified marker of subsequent liver failure from IFALD.

Keywords: Intestinal Failure Associated Liver Disease
Parenteral Lipids
Sepsis
4.3 Introduction

Intestinal Failure Associated Liver Disease (IFALD) is the most common complication of prolonged parenteral nutrition support in children with an incidence of up to 90% in infants with Short Bowel Syndrome (SBS) who remain dependent on parenteral nutrition (PN) in excess of 3-months \(^{29}\). While for some the condition is self-limited, up to 25% of children with IFALD will advance to end-stage liver disease requiring transplantation \(^{26}\). Historically, the disease has often been fatal, due to a relative unavailability of size-appropriate allografts when intestinal transplantation is required \(^{4, 5, 11, 26, 27}\). However, there is increasing evidence from uncontrolled studies that omega-3 lipids, may be beneficial for the treatment of advanced IFALD and improve survival up to 90% \(^{102, 166, 176}\).

The rationale for the use of parenteral omega-3 lipids, such as Omegaven\(^{®}\) (Fresenius Kabi, Bad Homburg, Germany) is based on the fact that available parenteral lipid emulsions in North America are plant-derived and contain hepatotoxic phytosterols \(^{50-52, 59}\) and a predominance of omega-6 long-chain polyunsaturated fatty acids that are pro-inflammatory \(^{53-55}\) and pro-steatotic \(^{62, 63}\). In contrast, fish-derived lipid emulsions do not contain phytosterols and have a predominance of omega-3 fatty acids that are thought to not have the same adverse hepatic effects and therefore may be useful in treating advanced IFALD \(^{102, 166}\).

Given the recent increased focus on the role of omega-6 lipids in the development of IFALD we sought to quantify the impact of parenteral lipids in the development of advanced IFALD as defined by the development of a serum conjugated bilirubin exceeding 100 umol/L (5.9 mg/dl) based on previous data showing this to be an important marker for progressive liver disease \(^{19}\). The data for this study were collected during a period when the only available lipid emulsion at our institution was a soy-based lipid.

4.4 Method

4.4.1 Subjects

Between 1 January 2003 and 31 December 2004 data were collected prospectively on all infants (< 3 months of age) undergoing abdominal surgical procedures on our quaternary paediatric General Surgical service. Follow-up of enrolled cases continued until 31 December 2005. The objective of this cohort study was to determine risk factors for intestinal failure as well as
predictors of outcome in children undergoing abdominal surgical procedures. To that end
detailed demographic, surgical, nutritional, biochemical, and therapeutic data were collected on
all subjects. Subjects from our database were selected for inclusion in this analysis if they
received PN for greater than 1 day post-operatively. All subjects during the time period covered
by this study received as their primary parenteral lipid, Intralipid® (Fresenius Kabi, Bad
Hamburg, Germany) which is derived from soy-bean oil. The primary amino acid solution
employed over this time-period was Primene® (Baxter, Mississauga, Canada).

4.4.2 Study Design and Analysis

This paper represents a retrospective analysis of our prospectively collected data with the
specific goals of determining risk factors for the development of a conjugated serum bilirubin
exceeding 100 umol/L (CB100) by 1-year post-operatively with a particular interest in
examining the role of parenteral lipid. All statistical analyses were performed using SPSS (SPSS
Corporation, Chicago IL - Version 14). Approval for this study was obtained from the Research
Ethics Boards at The Hospital for Sick Children and University of Toronto.

In order to develop predictive models for CB100, initial univariate logistic regression models
were performed with a number of predictors. Predictors were chosen a priori and included:
corrected gestational age in weeks at the time of surgery, percentile weight for gestational age at
the time of surgery, percent predicted residual small bowel and colon length following surgery
using normative values established by Toloukian et al 252, preservation of the ileoceleal valve,
presence of an ostomy, the number of septic episodes, maximal percent enteral feeds post-
operatively, and details of PN. The specific aspects of PN treatment that were considered were
the number of days of maximal lipid and amino acid as defined by a dose exceeding 2.5g/kg/day
as well as the total number of days with any amount of PN. Time dependent variables (e.g.: PN
duration and number of septic episodes) were right censored for patients who developed CB100,
such that events occurring after the development of CB100 were not included.

Following the univariate analyses, multiple variable logistic regression was performed with
consideration of all variables with a p-value < 0.2 in the univariate analyses. Our initial approach
was to perform a backward stepwise multiple variable logistic regression using the log-likelihood
option for model selection. A priori we had also specified that we would examine a model with
maximum days of PN lipid “forced-in” to the final model should this variable not appear in our model based on stepwise selection.

During the development of our multiple variable model by stepwise regression, we acknowledged that some of the predictors considered in this model were collinear. Collinearity was defined as any two variables with a Pearson correlation exceeding 0.8. Therefore, additional multiple variable models were developed by substituting the collinear terms with each other.

As a post-hoc analysis we also performed a Bayesian Logistic Regression model selection procedure. The objective of this analysis was to determine the probability of each of the models with collinear terms as being the optimal model for CB100 prediction. The analysis was performed using Winbugs (MRC Biostatistics Unit Cambridge, UK) [Code in Appendix A].

Equal prior probabilities were assigned to the various models at the outset of the analysis reflecting that it was assumed to be equally likely that the various models could be optimal for CB100 prediction. The analysis was performed with 3 chains to allow for assessment of convergence of the Bayesian simulation during a “burn-in” of 10,000 iterations of the analysis. The posterior probability, reflecting the probability that each model was optimal following the analysis, was ascertained following a further 10,000 iterations of the Bayesian simulation.

4.5 Results

One-hundred and fifty two infants met inclusion criteria and were included in this analysis. The median gestational age at the time of surgery was 37.4 (range: 24.5 – 45.4) weeks. Eighty three (54.6%) of the subjects were male. The primary surgical diagnoses are listed in Table 4-1. Overall, 22 of the infants developed a conjugated serum bilirubin exceeding 100 umol/L (CB100) and 130 did not. The median time to CB100 was 11 (range: 1 - 26) weeks. Median total duration of follow-up was 35.5 (range 0 - 145) weeks for those who did not develop CB100 and 38.5 (range 1 - 103) weeks for those who did develop CB100. Overall, 8 (36.4%) children who developed CB100 died during the follow-up period in contrast to 11 (8.5%) children who did not develop CB100. Sepsis was the most common cause of death in both groups (3/8 in the CB100 group and 5/11 in the group who did not develop CB100). One patient in the CB100 group died from liver failure.
Table 4-1: Surgical Diagnoses in 152 Patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal Atresia</td>
<td>35 (23%)</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis</td>
<td>31 (20.4%)</td>
</tr>
<tr>
<td>Abdominal Wall Defects</td>
<td>24 (15.8%)</td>
</tr>
<tr>
<td>Spontaneous Perforation</td>
<td>18 (11.8%)</td>
</tr>
<tr>
<td>Malrotation/Volvulus</td>
<td>11 (7.2%)</td>
</tr>
<tr>
<td>Anorectal Malformations</td>
<td>11 (7.2%)</td>
</tr>
<tr>
<td>Hirschprungs Disease</td>
<td>10 (6.6%)</td>
</tr>
<tr>
<td>Meconium Ileus</td>
<td>4 (2.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (5.3%)</td>
</tr>
</tbody>
</table>

4.5.1 Univariate Predictors of CB100

Univariate predictors of CB100 are listed in **Table 4-2**. In terms of demographic characteristics, the only statistically significant predictor of CB100 was percent predicted small bowel length with children who developed CB100 having a shorter intestinal length (83.5% vs. 96.2%; p=0.001). As well, children who developed CB100 tended to be more premature (34.7 vs. 36.5 weeks gestational age at surgery; p = 0.074), as well as heavier for gestational age (41.7%tile vs. 29.5%tile; p =0.059) than those who did not develop CB100. Colon length, resection of the ileocecal valve and presence of an ostomy were not useful in predicting the development of CB100. Septic events were clearly associated with the development of CB100 with each septic event being associated with a 4.2 times increase in the odds ratio of developing CB100 (p <0.001). Infants who developed CB100 also received fewer of their feeds enterally in the post-operative period (81.6% vs. 93.6%) than those who did not develop CB100 (p = 0.049). PN was a significant predictor for the development of CB100 with days of maximal (>2.5g/kg/day) lipid [Odds Ratio (OR) = 1.06 per day], days of maximal (>2.5g/kg/day) amino acid [OR = 1.05 per day], and total duration of PN [OR = 1.03 per day] being significant risk factors at the p <0.001 level.
### Table 4-2: Univariate Predictors of Conjugated bilirubin > 100 umol/L

<table>
<thead>
<tr>
<th></th>
<th>CB100&lt;sup&gt;1&lt;/sup&gt;</th>
<th>no CB100</th>
<th>OR&lt;sup&gt;2&lt;/sup&gt; (95%CI&lt;sup&gt;3&lt;/sup&gt;)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>22</td>
<td>130</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational Age at Surgery</td>
<td>34.7 (4.0)</td>
<td>36.5 (4.4)</td>
<td>0.91 (0.83 – 1.01)</td>
<td>0.074</td>
</tr>
<tr>
<td>Weight Percentile at Surgery</td>
<td>41.7 (29.5)</td>
<td>29.5 (25.5)</td>
<td>1.02 (0.99 – 1.03)</td>
<td>0.059</td>
</tr>
<tr>
<td>Small Bowel Remaining – percentile</td>
<td>83.5 (25.9)</td>
<td>96.2 (9.2)</td>
<td>0.95 (0.93 – 0.98)</td>
<td>0.001</td>
</tr>
<tr>
<td>Colon Remaining – percentile</td>
<td>96.7 (11.6)</td>
<td>95.8 (13.1)</td>
<td>1.01 (0.97 – 1.05)</td>
<td>0.768</td>
</tr>
<tr>
<td>Proportion with Ileocecal valve resection</td>
<td>4.7%</td>
<td>4.7%</td>
<td>0.99 (0.11 – 8.7)</td>
<td>0.994</td>
</tr>
<tr>
<td>Proportion with ostomy</td>
<td>45.5%</td>
<td>30.2%</td>
<td>0.52 (0.21 – 1.30)</td>
<td>0.163</td>
</tr>
<tr>
<td>Number of Septic Episodes</td>
<td>3.8 (1.7)</td>
<td>1.2 (1.1)</td>
<td>4.23 (2.3 – 7.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent Enteral Feeds post-operatively</td>
<td>81.6 (30.8)</td>
<td>93.6 (23.1)</td>
<td>0.99 (0.97 – 1.0)</td>
<td>0.049</td>
</tr>
<tr>
<td>Days with PN Amino Acid &gt;2.5g/kg/day</td>
<td>33.3 (32.7)</td>
<td>6.7 (12.4)</td>
<td>1.05 (1.03 – 1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days with PN Lipid &gt;2.5g/kg/day</td>
<td>48.3 (38.8)</td>
<td>10.0 (14.1)</td>
<td>1.06 (1.04 – 1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Number of Days on PN&lt;sup&gt;4&lt;/sup&gt;</td>
<td>83.0 (49.7)</td>
<td>28.7 (34.1)</td>
<td>1.03 (1.02 – 1.04)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All values are mean (standard deviation) unless indicated by a %.

<sup>1</sup>Conjugated Serum bilirubin > 100umol/L (5mg/dl) ; <sup>2</sup>Odds Ratio; <sup>3</sup>Confidence Interval; <sup>4</sup>Parenteral Nutrition.
4.5.2 Multiple Variable Predictors of CB100

Variables significant at the 0.2 level were considered for inclusion in the multiple variable model. The variables that met this criterion included: gestational age at surgery, percentile weight, percent predicted small bowel length, presence of a stoma, proportion of enteral feeds post-operatively, number of septic episodes, days of PN amino acid > 2.5g/kg/day, days of lipid > 2.5 g/kg/day, and total days of PN. These variables were entered into a backward stepwise multiple variable logistic regression, using the likelihood ratio option for model selection. The final model obtained by step-wise selection (Table 4-3: Model 1) included days of PN lipid >2.5g/kg/day as well as the number of suspected septic episodes (Overall Model Chi-square = 61.494 p < 0.001). Both predictors were associated with an increased risk of CB100 with each day of parenteral lipid >2.5g/kg/day being associated with a 1.04 fold increase in the odds of developing CB100 and each septic event being associated with a 3.2 fold increase in the odds of developing CB100.

Collinearity with Pearson correlations exceeding 0.8 was identified between days of maximum lipid and days of maximum amino acid (r = 0.853), as well as between days of maximum lipid and total PN days (r = 0.827); all other variable combinations had a correlation < 0.8. Two other potential models with these variables substituted for the number of days of maximum lipid were considered. These models are listed in Table 4-3 and are termed Model 2 (days of maximum amino acid, septic episodes) and Model 3 (total days of PN, septic episodes). In neither of these models, did the PN term (maximum amino acid or total days of PN) achieve statistical significance at the 0.05 level. This is in contrast to Model 1, the model derived by the stepwise regression process, where days of lipid >2.5g/kg/day was a statistically significant predictor of the development of CB100.

In order to further ascertain which of the 3 models had the optimal predictive properties, we performed a post-hoc Bayesian Model Selection analysis whereby each model was assigned an equal prior probability and the posterior probability of each model being the optimal model for the prediction of CB100 was assessed. Model 1 had the greatest posterior probability (77%) followed by Model 2 (16%) and Model 3 (7%).
Table 4-3: Multiple Variable Models of Conjugated bilirubin > 100 umol/L

<table>
<thead>
<tr>
<th>Term</th>
<th>OR(^1)</th>
<th>95% CI(^2)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Septic Episodes</td>
<td>3.23</td>
<td>1.77 – 5.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days of Maximum Lipid</td>
<td>1.04</td>
<td>1.003 – 1.06</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Septic Episodes</td>
<td>3.56</td>
<td>1.99 – 6.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days of Maximum Amino Acid</td>
<td>1.03</td>
<td>0.99 – 1.05</td>
<td>0.070</td>
</tr>
<tr>
<td><strong>Model 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Septic Episodes</td>
<td>3.47</td>
<td>1.90 – 6.33</td>
<td>0.001</td>
</tr>
<tr>
<td>Total Days of Parenteral Nutrition</td>
<td>1.01</td>
<td>0.99 – 1.03</td>
<td>0.187</td>
</tr>
</tbody>
</table>

\(^1\)Odds Ratio \(^2\)Confidence Interval

4.6 Discussion

The objective of this study was to examine the role of lipid in the development of advanced IFALD in infants. We defined advanced IFALD as a serum conjugated bilirubin of 100 umol/L (CB100). This definition is based on a publication from our group that found CB100 to be a useful indicator of subsequent liver failure requiring transplantation with a sensitivity of 94% and specificity of 87% and negative and positive predictive values of 98% and 70% respectively. The median time from CB100 to liver failure was 60 days highlighting the fact that CB100 is an important marker of severe IFALD.
While our primary focus was on the role of lipids in the development of advanced IFALD, we decided to perform the study on a number of predictors. We included in our multiple variable analysis both host and PN-related factors that could be associated with advanced IFALD, rather than focus on the PN lipids in isolation. The model identified by the multiple variable process included only parenteral lipids and septic episodes. However, due to collinearity between the PN terms in the model (maximum lipid, maximum protein and total duration of PN), prior to selecting our “final” model, we examined 2 alternate models with each of these terms in addition to sepsis. In neither of these alternate models did the PN term achieve statistical significance. A subsequent post-hoc Bayesian analysis, which assessed given equal probabilities prior to the analysis, the probability of each model being the optimal model for CB100 prediction, suggested that the posterior probability for the model selected by the multiple variable process of being the optimal model for prediction approached 80%. Therefore, we believe that the model obtained from the multiple variable processes can be regarded as a robust model in terms of understanding risk factors for advanced IFALD.

Our final model suggested that for each septic episode, the odds of developing CB100 were increased by 3.23 and for each day of PN lipid >2.5 g/kg/day the odds of developing CB100 were increased by 1.04. While the odds associated with the lipid term were only 1.04, which is very small, it is critical to recognize that this is per day of “maximal” lipid and at 60-days of such exposure the odds ratio approached 10 for the development of CB100. While we believe that our results represent the first quantification of the impact of sepsis and maximal lipid exposure in the development of advanced IFALD, the results of our analysis are in keeping with the existing literature. Sepsis has long been recognized as a key factor for IFALD with recent advances in understanding the molecular mechanisms of this.

Lipid dose is also well recognized as a risk factor for IFALD, with an adult study demonstrating that a lipid dose in excess of 1 g/kg/day being related to the development of IFALD. In children, Colomb et al. demonstrated that episodes of cholestasis were correlated with lipid concentrations and that improvement in serum bilirubin and thrombocytopenia were noted with temporary cessation of parenteral lipids. Cober et al, also demonstrated improvement or resolution of hyperbilirubinaemia with lipid reduction. However, while it is believed that lipids play a deleterious role in terms of liver function, it remains unclear as to whether these effects relate to the dose of lipid irrespective of type of lipid or due to specific lipids such as
phytosterols $^{50-52, 59}$ or omega-6 fatty acids $^{53-55, 62, 63}$. It has also been proposed that one of the mechanisms whereby lipids contribute to IFALD is by overwhelming hepatic reticuloendothelial clearance capacity $^{48}$, and the fact that maximal lipid rather than total lipid was included in the model provides some support for this theory.

Despite using prospectively collected data, our study is subject to limitations. The low rate (22/152) of subjects who developed CB100 may have resulted in reduced power in fitting the various models. This may have been further compounded by the issues regarding collinearity between the PN predictors, although we believe that our evaluation of the alternate models including the Bayesian analysis addresses this concern. Ultimately, larger studies would be ideal for external validation of our findings; although with current alterations in lipid dosing and composition, it is unclear if such studies would be possible due to bias from care providers. While the cohort included all surgical infants who received PN for at least 1-day, we recognize that the risk of IFALD is primarily related to prolonged treatment with PN. For this reason, we performed an additional analysis including only those children who received PN for > 14 days. The results of that analysis were equivalent to our primary analysis with the final model including only septic episodes [OR: 2.68 95% CI: 1.5 – 4.9] and days of lipid > 2.5g/kg/day [OR: 1.04 95%CI: 1.006 – 1.07]. Also, PN exposure was only expressed as number of treatment days. This was related to the availability of the data from our prospective database. It is possible that more granular data such as cumulative exposure may have resulted in different estimates as to the relative effects of the various components of the PN. Our definition of maximal (>2.5 g/kg/day) lipid and amino acid, was based on the mid-range for appropriate intakes for full-parenteral support for developing infant based on classic studies as well as American Society of Enteral and Parenteral Nutrition (ASPEN) recommendations $^{145, 146}$. While we recognize that there is a recent tendency to limit lipid intake for infants at high risk of intestinal failure, it must be acknowledged that our lipid risk estimates pertain to a dose exceeding 2.5g/kg/day and therefore may not be applicable to lower doses of lipid. Notwithstanding the fact that lower lipid doses are being employed at some centers, our views on the limited data regarding the long-term safety of lipid restriction have prevented us from recommending such an approach at this time $^{104, 105}$ and overall believe that a lipid dose between 2-3 g/kg/day is appropriate for most surgical infants. However, we have altered our dosing and tend to use 2.5 g/kg/day as maximum dose in infants with SBS who are likely to require PN for an extended duration.
Notwithstanding the limitations of the present study, we believe that our results have important clinical implications namely confirming the key role that parenteral lipids and sepsis play in the development of advanced IFALD. The findings are also robust after performing both post hoc and Bayesian analyses. This observation provides targets for intervention in terms of prevention of sepsis and alternate lipid based strategies in attempting to reduce the risk of advanced IFALD and its devastating consequences.

Prevention of sepsis in the SBS population should focus on both care of the central catheter as well as prevention of bacterial overgrowth and resultant translocation. Prevention of catheter infections requires individual and team efforts, with a reduced incidence of catheter infection with dedicated infusion therapy teams. The potential impact that enhanced line care may have, is highlighted by the fact that there is a substantial difference between the incidence and the age of development of liver disease in children whose central line catheter care was managed by a team experienced in this setting. Ethanol locks have recently been suggested to have promise in the prevention of line sepsis in uncontrolled studies. Treatment of bacterial overgrowth with cycled antibiotics has also been suggested to have a beneficial impact in reducing the risk of sepsis and resultant IFALD.

In terms of lipid based strategies, the alternatives are the use of omega-3 lipid or lipid minimization. When evaluating the existing literature regarding both omega-3 lipids and lipid minimization, it is critical to recognize that all available studies were uncontrolled and therefore subject to confounding. Most notably, it is unclear as to whether the beneficial impact of the omega-3 lipids relates solely to a change in lipid source or is also related to decreased lipid dosing as Omegaven® is typically dosed at a maximum of 1 g/kg/day. Additionally, these uncontrolled studies do not afford the optimal opportunity to evaluate the safety of the intervention. We have therefore argued that in the absence of adequate long-term growth and neurodevelopmental data on the safety of alternate lipid based strategies such as Omega-3 lipids or lipid restriction, such strategies should not be widely adopted until the necessary studies are completed. This is of particular relevance when one considers that to prevent advanced IFALD, one would need to implement the strategy in those with early liver disease, with data from our group suggesting that only 10% of infants with a bilirubin of 34 umol/L (2 g/dl) will develop CB100. Therefore, despite the conclusions of our analysis, we believe that despite the promise that alternate lipid strategies may have, at present their use remains investigational.
and should only be used in those with severe IFALD unless in the context of a randomized trial examining their safety and efficacy as a preventative strategy.

4.7 Clinical Relevancy

Our findings suggest that the primary predictors for the development of advanced IFALD (Intestinal Failure Associated Liver Disease) in infants on parenteral nutrition (PN) were days of PN lipid >2.5g/kg and intercurrent septic episodes. This suggests that strategies to reduce the incidence of sepsis such as careful line care, as well as novel parenteral lipid based approaches (reduction in maximal lipid dose or the use of alternate lipids such as Omega-3 fatty acids) should be considered as key targets in the prevention and management of advanced IFALD. However, ultimately the utility and safety of these approaches, particularly the novel lipid based approaches for the prevention of IFALD, should be assessed in well designed randomized controlled trials that consider both short and long-term implications.

4.8 Disclosure

The authors, with the exception of Ms de Silva and Dr Tomlinson, have received Investigator Initiated Trial funding from Fresenius Kabi, the manufacturer of both Omegaven® and Intralipid® to evaluate SMOFlipid® for the prevention of IFALD.

4.9 Acknowledgements

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Chapter 5

5 Expert Beliefs Regarding Novel Lipid Based Approaches to Paediatric Intestinal Failure Associated Liver Disease

EXPERT BELIEFS REGARDING NOVEL LIPID BASED APPROACHES TO PEDIATRIC INTESTINAL FAILURE ASSOCIATED LIVER DISEASE.

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Ivan Diamond was supported by a Fellowship award from the Canadian Institutes of Health Research with additional support from the Surgeon Scientist Training Program, Department of Surgery, University of Toronto. Ivan Diamond is also the recipient of a Graduate Studentship Award from the Canadian Liver Foundation and the Chisholm Memorial Fellowship, Post Graduate Medical Education Office, the University of Toronto.

Brian Feldman is supported by a Canada Research Chair in Childhood Arthritis
5.1 Contributors Statement

Drs. Diamond, Feldman and Wales were primarily responsible for the design of the study in consultation with Drs. Pencharz, Moore and Ling. Dr. Diamond conducted all of the interviews. Dr. Diamond was primarily responsible for the analysis and received critical input in this regard from Dr. Tomlinson and Mr. Grant. Drs. Wales, Feldman, Pencharz, Ling and Moore provided input into the interpretation of the data. Dr. Diamond wrote the 1st draft of this manuscript that was subsequently revised by all of the other authors. All authors approved the final version of the manuscript.

5.2 Disclosure

The authors, with the exception of Mr. Grant and Dr. Tomlinson, have received Investigator Initiated Trial funding from Fresenius Kabi, to evaluate the role of SMOFlipid®, an omega-3 containing Intravenous Lipid Emulsion, for the prevention of IFALD.

5.3 What’s Known on this Subject

Lipid minimization and the use of Omega-3 Intravenous Lipid Emulsions have shown promise in uncontrolled studies of paediatric Intestinal Failure Associated Liver Disease (IFALD). However, clinical trials are needed to determine the efficacy and safety of these novel lipid based approaches.

5.4 What this Study Adds

Experts believed that the novel-lipid based approaches would lower the risk of IFALD relative to conventional emulsions. Distributions of the expert opinion of the treatment effect can be used to facilitate Bayesian analyses of clinical trials of these therapies.
5.5 Abstract

Objective: To determine expert beliefs regarding the probability of Intestinal Failure Associated Liver Disease (IFALD) with novel lipid based approaches (Lipid minimization / Omega-3 lipids) to the management of IFALD in order to facilitate Bayesian analyses of clinical trials of these therapies. Method: Structured interviews were conducted using a validated approach to belief elicitation with 60 Intestinal Failure (IF) experts from across North America. Participants were asked to estimate in an average population of infants referred for management of IF with early IFALD, the probability of advanced IFALD at 3 months following referral in each of 3 scenarios: 1. conventional lipid 2. omega-3 lipids 3. lipid minimization. Probability distributions of the risk of advanced IFALD with each strategy were developed. Distributions of the elicited treatment effect for the novel approaches, relative to conventional lipid, were calculated. Results: Median duration of experience of participants managing patients with IF was 8.5 (range 2-35) years. The median probability of advanced IFALD using Conventional Lipid was 32.5%, Omega-3 lipids 17.5% and Lipid minimization 13%. The median of the elicited treatment effects relative to conventional lipid, was a relative risk of 0.53 for the Omega-3 lipid and 0.45 for Lipid minimization. Conclusions: There was consistent expert opinion that the novel lipid based approaches are superior to conventional therapy, with similar estimates of treatment efficacy for the two approaches. The distributions of the elicited treatment effects can be used as prior distributions in Bayesian analyses of clinical trials of these novel strategies.

Keywords: Intestinal Failure Associated Liver Disease
Parenteral Lipids
Expert Opinion
5.6 Introduction

Intestinal Failure Associated Liver Disease (IFALD) is a devastating complication that develops in up to 60% of infants on long-term parenteral nutrition (PN) \(^6, ^7, ^12\). The risk of end-stage liver disease (ESLD) approaches 25%. Historically, ESLD was fatal in up to 90% due to unavailability of size appropriate allografts particularly when an intestinal transplant is required \(^4, ^5, ^11, ^26, ^27\). While the pathophysiology of IFALD is multi-factorial \(^12, ^21\), recently there has been much interest in the critical role that Intravenous Lipid Emulsions (ILEs) play in the pathophysiology of IFALD \(^134\).

There are data from uncontrolled studies that alternative novel lipid based approaches [lipid minimization \(^48, ^100, ^147, ^149\) or the use of ILEs containing omega-3 fatty acids \(^101-103, ^165, ^166, ^169-175\)] may be beneficial in the treatment of patients with established IFALD. Colomb et al., described an association between decreases in lipid therapy and normalization of serum conjugated bilirubin \(^48\). Rollins et al., published a series of 6 children with IFALD in whom the soy-based ILE was stopped, with subsequent resolution of cholestasis in all \(^100\). Torres et al. reported on 32 patients with IFALD, of whom 31 normalized their hyperbilirubinaemia with aggressive intestinal rehabilitation that included restriction of a soy-based ILE to < 1g/kg/day \(^149\). Cober et al., reported on 32 children who were enrolled in a lipid minimization protocol that consisted of 1g/kg of a plant based ILE twice a week \(^147\). The subjects were compared to a historical cohort, with the results demonstrating a significant reduction in bilirubin between the groups.

In 2006, Gura et al., from Children’s Hospital Boston, published the first report of 2 children with severe end-stage liver IFALD who demonstrated complete reversal of their liver disease following a change from Intralipid\(^\text{®}\) (Fresenius Kabi, Bad Hamburg, Germany) a soy-based ILE to Omegaven\(^\text{®}\) (Fresenius Kabi, Bad Hamburg, Germany) fish-oil derived ILE \(^101\). The most recent detailed publication of outcomes from this group, reported on 42 infants who received Omegaven\(^\text{®}\) compared with 49 subjects from a historic cohort \(^102\). Overall, resolution of cholestasis while on PN in the Omegaven\(^\text{®}\) group was 19 compared with 2 in the control group. A recent review from the group in Boston reports that in excess of 130 children have received Omegaven\(^\text{®}\) with encouraging results \(^165\). A number of other case series and reports, including those from the authors’ institution have demonstrated similar outcomes with Omegaven\(^\text{®}\) in children with advanced IFALD \(^103, ^166, ^169-175\).
We have argued that despite the promise of the novel lipid based approaches to the management of IFALD, these treatments remain experimental. We believe that these therapies may be appropriate for those with advanced IFALD given the limited alternatives and historically poor outcomes. However, in those with early or no liver disease, they should only be used in the context of randomized controlled trials that appropriately evaluate their efficacy and safety both in the short and long-term. Given the rarity of IF with Canadian population level estimates of 24.5 / 100 000 live births and only 384 paediatric cases of established IF requiring long-term PN in the United Kingdom, these trials will be challenging to perform to ensure that they are adequately powered.

An alternate strategy that has been suggested for the analysis of clinical trials of rare diseases, is the Bayesian approach. The Bayesian method has the advantage of formally integrating prior information into the analysis allowing for questions to be addressed with smaller sample sizes. While Bayesian priors are typically derived from previous studies, in the absence of such information, expert belief can be sought in order to develop prior distributions for such analyses. According to Johnson et al., in addition to forming priors to estimate the treatment response, these expert beliefs can be used to document equipoise, be used in sample size calculations and used for interim study monitoring.

The objective of this study was to survey expert opinion as their beliefs surrounding the risk of progressive IFALD with the novel lipid based approaches in the management of paediatric patients with early IFALD. Distributions of the relative risk of advanced IFALD with the novel approaches, relative to conventional therapy can then be calculated. These distributions of the treatment effect can be used as prior distributions for Bayesian analyses of clinical trials of the novel lipid based approaches.

## 5.7 Methods

We conducted an expert belief elicitation study using a method that was developed and validated by Johnson et al. Ethical approval for this study was obtained from the research ethics boards at the Hospital for Sick Children and the University of Toronto.
5.7.1 Participants

All centers that participated in PIFCon (Paediatric Intestinal Failure Consortium) were invited by email to participate in this study. At the time the study was conducted, PIFCon consisted of 22 centers including the authors’ institution. If agreeable, the PIFCon investigator was requested to provide the name of 3 members of their multi-disciplinary IF team, one from the paediatric disciplines (Paediatric Gastroenterology Hepatology and Nutrition, or Neonatology), one from the surgical disciplines (Paediatric General or Transplant Surgery) and one from the allied health team (Dietitian or Advanced Care Nurse, although we specified a preference for a Dietitian), who would be willing to be interviewed as the expert panel from that center. Although additional participants were not solicited, in the event that a center indicated that additional members of their team wished to participate, this was allowed up to a maximum of 5 participants per program. Centers were also asked to provide data on their experience with lipid minimization and ILEs containing omega-3 fatty acids.

5.7.2 Belief Elicitation Interview

In person interviews were conducted on a single day at each site by a single interviewer (IRD). All interviews took place over a 7-week period during the summer of 2010. The interviews were conducted using a standardized script (Appendix B). The survey instrument and script was piloted amongst the members of the investigator group (BMF, SCL, AMM, RCG) to ensure usability. Two of the authors (PWW, PBP) participated in the study and thus did not participate in piloting the instrument.

5.7.2.1 Worked Example

At the outset of the survey, participants were introduced to the concept of an average group of patients with IF on which to base their answers (Figure 5-1). Participants were provided with a worked example of the survey method (Figure 5-2). Participants were asked to provide a point estimate for the risk of an outcome, the plausible range for this outcome and then to create a distribution of their beliefs for values within that range. The belief distribution was done by placing magnets, each of which represented 5% weight of belief, in 5-point “bins” along the plausible range. Participants were informed once their belief distribution was created, to review the distribution to ensure that it accurately reflected their belief prior to proceeding to the next scenario. Photographs were taken of the distributions for data capture purposes.
<table>
<thead>
<tr>
<th><strong>Age</strong></th>
<th>0 – 12 months corrected gestational age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PMHx</strong></td>
<td>Abdominal Surgical procedure within the last 6-months, since which the child has received parenteral nutrition.</td>
</tr>
<tr>
<td><strong>Nutrition</strong></td>
<td>40-100% of calories obtained from parenteral nutrition</td>
</tr>
<tr>
<td></td>
<td>PN macronutrient composition</td>
</tr>
<tr>
<td></td>
<td>o Fat: 2 - 3g/kg/day</td>
</tr>
<tr>
<td></td>
<td>o Protein: 2 - 4 g/kg/day</td>
</tr>
<tr>
<td></td>
<td>o Glucose: 5 – 14 mg/kg/min</td>
</tr>
<tr>
<td><strong>Labs</strong></td>
<td>Serum conjugated bilirubin 1-2 mg/dl (17-34 umol/l)</td>
</tr>
</tbody>
</table>

**Figure 5-1:** Characteristics of the average group of patients on which scenarios were based.

---

**EXAMPLE**

Assume that you are seeing some of these patients during your November clinic.

1. In this hypothetical situation, what is your best estimate of the proportion of patients who will develop a viral respiratory infection within the next 60-days?

![Proportion Graph]

2. There may be some uncertainty around your estimate of the proportion who will develop a viral respiratory infection. Using an X in the interval, indicate the upper and lower limits of your estimate.

![Proportion Graph]

3. Using the magnetic board, you have been given 20 magnets. Each magnet represents 5% probability. Placing the magnets in the intervals, indicate the weight of belief for your estimates of the proportion who will develop a viral infection.

![Magnetic Board]

**Figure 5-2:** Example scenario provided to participants to demonstrate method. The inserted image shows the magnetic board that was used for the study.
5.7.2.2 Belief Elicitation

The survey consisted of 3 scenarios. In each scenario participants were asked to estimate the proportion of the average group of patients with IF (Figure 5-1), who 3-months following referral for management of IF, would develop advanced IFALD (serum conjugated bilirubin > 6 mg/dl). In each scenario, only the type of lipid emulsion that the group of patients received differed. In first scenario, termed “conventional lipid” the group continued to receive Intralipid® (Fresenius Kabi, Bad Hamburg, Germany) as their parenteral lipid source at a dose of 2-3 g/kg/day. In the second scenario, termed “omega-3 lipid”, the groups ILE was changed from Intralipid® to a lipid source containing a substantial source of omega-3 fatty acids at a dose of 2-3 g/kg/day. In the third scenario, termed “lipid minimization”, the PN prescription was modified such that the lipid received was <1 g/kg/day of Intralipid®. Participants were informed that aside from weaning of parenteral nutrition with changes in enteral tolerance, no other changes were made to the care of the patient.

5.7.2.3 Secondary Questions

Following the final scenario, participants were asked to complete 6 questions on a paper survey. The first 2 questions asked participants whether based on their understanding of the literature as well as their clinical experience there was sufficient justification to routinely recommend the use of either novel lipid based strategy in patients with IF. Participants were asked to specify how this changed based on the degree of liver dysfunction. The final 4 questions addressed demographics including: sex, specialty, duration of experience managing patients with IF and formal statistical training.

5.7.3 Data Analysis

Center and participant characteristics were summarized with frequency counts or median values as appropriate. Answers to our secondary question were summarized using frequency counts.

5.7.3.1 Distributions of the Risk of Liver Disease with Each Strategy

Photographs of the belief distributions were examined and the number of magnets in each bin counted by a research assistant, ensuring that the sum of magnets was 20. These counts were entered into a database in 5-point ranges to form individual belief distributions. The individual belief distributions for each strategy were averaged to create a population wide distribution.
5.7.3.2 Distributions of the Elicited Treatment Response

A distribution of the elicited treatment response for each novel strategy relative to conventional lipid was calculated for each participant. This was done in R (The R Project for Statistical Computing) by treating each participant’s belief distributions as a continuous distribution (Appendix C). Values were sampled sequentially from each participant’s distribution for the novel approach and conventional lipid and a relative risk (RR) value calculated. This was done 100 000 times for each of the novel approaches, in order to calculate a distribution of the RR for each participant for that approach. The distributions of the RR for each participant were then averaged to create a population wide distribution.

In addition to calculating RR distributions for the entire sample, we also created distributions for the various disciplines as well as for those participants from centers with experience of less than and greater than 15 patients treated with either of the novel approaches. We also created distributions for the most optimistic and sceptical quartile of respondents, based on the RR calculated from the participants point estimates. The RR of advanced IFALD for lipid minimization relative to the omega-3 approach was also assessed.

5.8 Results

5.8.1.1 Participants

Eighteen centers out of a total of 22, including the investigators’ institution, participated in this study. One center declined to participate, for unspecified reasons. Three centers did not respond to the invitation, despite telephone and fax follow-up.

Sixty expert interviews were conducted. The median number of participants per center was 3 (range: 2-5).

Table 5-1 describes center and participant characteristics. Centers had more experience with the lipid minimization approach, with all but 1 center having utilized this approach. Six of the centers had no experience with the omega-3 approach. Five centers had experience with > 15 cases of both novel approaches.
Table 5-1: Center and Participant Characteristics

**Center Characteristics (Number = 18)**

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Years with IF&lt;sup&gt;1&lt;/sup&gt; program</td>
<td>4.5 (0 – 29)&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Average Number of New Patients per year</td>
<td>20 (6 – 90)&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prior experience with Omega-3 lipids</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>6 (33.3%)</td>
</tr>
<tr>
<td>&lt; 15 cases</td>
<td>5 (27.8%)</td>
</tr>
<tr>
<td>&gt; 15 cases</td>
<td>7 (38.9%)</td>
</tr>
<tr>
<td>Prior experience with Lipid Restriction</td>
<td></td>
</tr>
<tr>
<td>&lt; 15 cases</td>
<td>7 (38.9%)</td>
</tr>
<tr>
<td>&gt; 15 cases</td>
<td>11 (61.1%)</td>
</tr>
</tbody>
</table>

**Participant Characteristics (Number = 60)**

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number Male</td>
<td>27 (45%)</td>
</tr>
<tr>
<td>Specialty</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>18 (30%)</td>
</tr>
<tr>
<td>Paediatric Surgery</td>
<td>14</td>
</tr>
<tr>
<td>Transplant Surgery</td>
<td>4</td>
</tr>
<tr>
<td>Paediatrics</td>
<td>23 (38.3%)</td>
</tr>
<tr>
<td>Neonatology</td>
<td>2</td>
</tr>
<tr>
<td>Paediatric GI&lt;sup&gt;3&lt;/sup&gt; / Nutrition</td>
<td>21</td>
</tr>
<tr>
<td>Dietitian</td>
<td>16 (26.7%)</td>
</tr>
<tr>
<td>Nurse Practitioner</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Number of years treating patients with IF</td>
<td>8.5 (0 – 29)&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Number with prior formal statistical training</td>
<td>29 (48.3%)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Intestinal Failure  
<sup>2</sup> Data represent median and range  
<sup>3</sup> Gastroenterology
5.8.1.2 Risk of Advanced IFALD

Figure 5-3 plots the average of the experts’ beliefs about the risk of advanced IFALD for the three strategies. The experts believed that the median risk of advanced IFALD was 37.5% with conventional therapy. This was substantially higher than for either novel approach. The experts believed that the median risk of advanced IFALD with lipid minimization was 13% and 17.5% with the omega-3 approach. There was substantially more uncertainty around the risk of advanced IFALD with conventional therapy than with the novel approaches.

Figure 5-3: Belief Probability Distributions for each of Conventional Lipid, Omega-3 Lipid, and Lipid Minimization. The x-axis specifies the percentage of patients who are expected to develop advanced IFALD within 3 months. The y-axis provides the weight of expert belief for the percentage who develop advanced IFALD. This axis is proportional to the probability, based on the expert opinion, that the incidence of advanced IFALD is within the particular range for the percentage who will develop advanced IFALD. The values of the y-axis have no intrinsic meaning, but the area under each curve equals 1.
5.8.1.3 Elicited Treatment Effect

Figure 5-4 demonstrates the elicited distribution of the experts’ belief as to the treatment effect, compared to conventional lipid, for the lipid minimization and the omega-3 approaches. These distributions reflect the prior distribution for the treatment effect for the prevention of IFALD based on the experts’ views.

The experts’ median RR for the omega-3 approach was 0.53 and 0.45 for lipid minimization.

![Figure 5-4: Histograms with smoothed curves of the distribution of the expert opinion of the relative risk (RR) of advanced IFALD at 3 months for the novel lipid based approaches compared to conventional lipid. Panel A – Lipid Minimization. Panel B – Omega-3 approach. Values less than 1 favour the novel therapy whereas those greater than 1 favour conventional therapy. The y-axis provides the weight of belief, although there is no intrinsic meaning to the values on the axis. The area under each curve equals 1.](image)

Given the similar magnitude of the treatment effect, we assessed the treatment effect for these strategies relative to one another. The expert belief of the median RR for advanced IFALD (lipid minimization vs. omega-3 approach) was 0.93 [Inter Quartile Range: 0.48 – 1.87].
Table 5-2 lists the median and Inter Quartile Range for the RR for the omega-3 approach. The table, also includes the experts opinion as to the probability that the RR would be above or below various threshold values. Table 5-3 provides the same information for the lipid minimization approach. These tables stratify the likelihood of benefit by discipline, center experience and whether the participant’s RR estimate was in the lower quartile (optimist), middle two quartiles (average) or upper quartile (sceptic).

The experts believed that there was an 87% chance that the omega-3 approach and 85% chance that lipid minimization would be superior to conventional treatment (RR < 1). The experts believed that there was less than a 10% chance that either approach would be associated with a meaningfully increased risk of advanced IFALD (RR > 1.2).

There were no relevant differences in the distribution of the elicited treatment response between the various disciplines. The overall estimates of benefit (RR < 1) were higher for those with greater experience with either novel approach relative to those with less experience. For the omega-3 approach, estimates of treatment efficacy did not differ meaningfully between those with little (< 15 cases) and no experience. In terms of the most sceptical participants, the majority of expert belief still supported the notion that the novel treatments would likely be more effective than the conventional approach.

5.8.1.4 Opinion Regarding Current Role of Novel Approaches

Table 5-4 presents the experts’ opinion regarding whether the novel approaches should be considered routine based on their experience and understanding of the literature.

While only 35% of experts felt that the routine use of omega-3 lipid was justified at this time in those with early IFALD, 68% of experts felt that lipid minimization was routinely justified in these patients. Eighty-five percent of experts believed in routine use of omega-3 lipids and 92% in the routine use of lipid minimization in those with advanced IFALD.
<table>
<thead>
<tr>
<th></th>
<th>Median RR(^1)</th>
<th>IQR(^2)</th>
<th>PROBABILITY THAT THE RELATIVE RISK IS WITHIN THE SPECIFIED RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td><strong>Entire Sample</strong></td>
<td>0.53</td>
<td>0.27 – 0.81</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Discipline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>0.53</td>
<td>0.24 – 0.86</td>
<td>9%</td>
</tr>
<tr>
<td>Surgical</td>
<td>0.59</td>
<td>0.30 – 0.84</td>
<td>7%</td>
</tr>
<tr>
<td>Dietitian</td>
<td>0.50</td>
<td>0.28 – 0.72</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Center Experience</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No experience</td>
<td>0.61</td>
<td>0.31 – 0.85</td>
<td>6%</td>
</tr>
<tr>
<td>&lt; 15 cases</td>
<td>0.62</td>
<td>0.36 – 0.87</td>
<td>5%</td>
</tr>
<tr>
<td>&gt; 15 cases</td>
<td>0.41</td>
<td>0.20 – 0.68</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Based on RR point estimate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most optimistic</td>
<td>0.21</td>
<td>0.11 – 0.34</td>
<td>21%</td>
</tr>
<tr>
<td>Average</td>
<td>0.53</td>
<td>0.33 – 0.73</td>
<td>4%</td>
</tr>
<tr>
<td>Most sceptical</td>
<td>0.85</td>
<td>0.71 – 1.05</td>
<td>7%</td>
</tr>
</tbody>
</table>

\(^1\) Relative Risk.

\(^2\) Inter Quartile Range
Table 5-3: Expert Belief as to the Treatment Effect for the Lipid Minimization Approach

<table>
<thead>
<tr>
<th></th>
<th>Median RR(^1)</th>
<th>IQR(^2)</th>
<th>Probability that the Relative Risk is within the specified range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Entire Sample</td>
<td>0.45</td>
<td>0.26 – 0.76</td>
<td>7%</td>
</tr>
<tr>
<td>Discipline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>0.39</td>
<td>0.18 – 0.73</td>
<td>14%</td>
</tr>
<tr>
<td>Surgical</td>
<td>0.54</td>
<td>0.34 – 0.91</td>
<td>30%</td>
</tr>
<tr>
<td>Dietitian</td>
<td>0.41</td>
<td>0.27 – 0.70</td>
<td>5%</td>
</tr>
<tr>
<td>Center Experience</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 15 cases</td>
<td>0.47</td>
<td>0.30 – 0.76</td>
<td>5%</td>
</tr>
<tr>
<td>&gt; 15 cases</td>
<td>0.42</td>
<td>0.22 – 0.71</td>
<td>11%</td>
</tr>
<tr>
<td>Based on RR point estimate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most optimistic</td>
<td>0.18</td>
<td>0.09 – 0.28</td>
<td>27%</td>
</tr>
<tr>
<td>Average</td>
<td>0.46</td>
<td>0.32 – 0.65</td>
<td>2%</td>
</tr>
<tr>
<td>Most sceptical</td>
<td>0.86</td>
<td>0.59 – 1.30</td>
<td>1%</td>
</tr>
</tbody>
</table>

\(^1\) Relative Risk.

\(^2\) Inter Quartile Range
Table 5-4: Percentage of Experts Recommending Routine Use of the Novel Lipid Based Strategies

<table>
<thead>
<tr>
<th></th>
<th>Omega-3</th>
<th>Lipid Minimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Liver Function (CB$^1 &lt; 1$ mg/dl)</td>
<td>15%</td>
<td>35%</td>
</tr>
<tr>
<td>Early IFALD$^2$ (CB 1 – 3 mg/dl)</td>
<td>35%</td>
<td>68%</td>
</tr>
<tr>
<td>Moderate IFALD (CB 4-6 mg/dl)</td>
<td>75%</td>
<td>87%</td>
</tr>
<tr>
<td>Advanced IFALD (CB &gt; 6 mg/dl)</td>
<td>85%</td>
<td>92%</td>
</tr>
</tbody>
</table>

$^1$Conjugated Bilirubin  $^2$Intestinal Failure Associated Liver Disease

5.9 Discussion

This study demonstrates that experts believed the incidence of advanced IFALD would be lower with the novel lipid based approaches (omega-3 lipids and lipid minimization) than with conventional ILE. Overall, experts believed that the incidence of advanced IFALD with the novel approaches would be approximately 50% of that with conventional therapy. When the novel approaches were compared to one, the risk of liver disease was essentially equivalent, suggesting equipoise in terms of the novel therapies included in the survey. This may provide justification for a clinical trial comparing these strategies. The experts were consistent in their opinion that the novel therapies should be considered routine in advanced IFALD. However, there was less support for their use outside of clinical trials in early liver disease at this time.

It must be recognized that the focus of our survey was on the efficacy of the novel lipid based approaches, rather than other issues such as safety that are critical to be evaluated and considered in the adoption of a novel therapy. We firmly believe that optimal patient care is provided by therapies that have been evaluated in well performed controlled trials that consider both safety and efficacy. In terms of the novel lipid based approaches, this is particularly important in those with early IFALD$^{104,105}$. We believe that one of the key messages of our finding that experts believe that the novel lipid based approaches are likely to be superior to conventional therapy is an urgent need to confirm these views with high quality and definitive data from clinical trials. There are presently 2 randomized controlled trials in progress, examining the role of the omega-3 lipid approach for the prevention of IFALD$^{106}$. 
Given the rarity of IFALD, clinical trials may be challenging to perform. We propose that Bayesian analysis of these trials may be an excellent strategy to adopt as they allow for the assessment of the probability of treatment responses of varying magnitudes. The expert beliefs elicited in this study, can also be utilized as priors in these Bayesian analyses. This will allow for formal incorporation of the expert opinion into the analysis of the trials. By including data from experts in the analysis, one may be able to obtain a more precise estimate of the treatment response than from the trial alone. This is suggested to be a major advantage of the Bayesian approach in the analysis clinical trials of rare diseases as it allows one to address the question with fewer subjects. The sceptical priors can be utilized to determine whether the results of the trials would alter the view of a sceptic to the extent that they would be likely to adopt the therapy.

The wide variability of expert belief as to the risk of advanced IFALD with conventional lipid was somewhat unexpected. We speculate that this is due to the multi-factorial nature of IFALD. Lipid likely interacts with other important etiologic factors such as prematurity and sepsis. However, the finding that expert opinion is divergent as to the baseline risk of advanced IFALD with conventional lipid, has important implications in terms of sample size calculations in designing clinical trials to evaluate novel lipid based strategies.

We adopted an inclusive approach in terms of identifying experts via the PIFCON consortium. Since PIFCON includes the majority of centers in North America with established intestinal rehabilitation teams, our study sample includes the majority of key stakeholders in the management of paediatric IF across the continent.

While our results represent the collective views of paediatric IF practitioners, we recognize that sites and participants may have had variable experience with the novel lipid based approaches. We attempted to examine the impact that this had on the results by providing a breakdown of the distribution of the elicited treatment response by center experience. Centers with and without experience with the novel lipid based approaches had very similar estimates for the likely treatment response suggesting that this was not a significant issue.
In addition to variable participant experience, it is important to recognize the other key limitations of this study. Participants were asked to estimate the risk of advanced IFALD with each therapy rather than the relative treatment efficacy. The relative treatment efficacy was calculated from the individual distributions. The reasons for doing so was that relative risks distributions are difficult for participants to directly specify as they are not directly observable\textsuperscript{257}. An expert can reflect on experience to estimate the probability of IFALD, however, it is a much more difficult task to abstract that information and compute the relative probabilities for different values of the ratio of these probabilities. This is further compounded by the fact, that relative risks are not normally distributed, but rather their distribution is normal on the log relative risk scale.

It is possible with the method that we used to compute the RR distributions that values at the extremes of the calculated RR distributions are over-weighted and would not have been included to the same extent had the participants been able to directly specify a RR distribution. This has to do with the fact that the two risk distributions were assumed to be independent. However there is likely some degree of correlation between the estimates of risk of IFALD with various therapies. In order to address this issue, the interquartile range is provided for each treatment response distribution.

The distributions of the treatment response primarily apply to clinical trials having as their outcome advanced IFALD as defined by a serum conjugated bilirubin of 6 mg/dl (100 umol/l). Despite this, we believe that the distributions reflect reasonable approximations for the distribution of the risk of progressive IFALD should another threshold be specified in the design of the study. Therefore, we believe that they can reasonably be used in clinical trials with other definitions for progressive liver disease.

It is also important to recognize that most of the experience with the novel lipid based approaches is in patients with advanced IFALD and there are currently no data from controlled trials in this area. As such, the distributions of the risk of IFALD and the treatment response are based on belief rather than objective data. Therefore, while expert opinion suggests that the novel lipid based approaches are superior to the conventional approach this notion is based on level 5 evidence\textsuperscript{258} and should not be regarded as definitive for making decisions regarding patient care without further study.
5.10 Conclusion

This study is the first study to formally survey expert beliefs regarding the efficacy of the novel lipid based approaches in the management of IFALD. Overall, there was consistent expert opinion that the novel lipid based approaches are superior to conventional therapy. Furthermore, the experts believed that the lipid minimization and omega-3 approaches would have similar treatment effects when compared with conventional therapy. This highlights the need for well designed studies in order to confirm the expert beliefs as to the superiority of the novel lipid based approaches relative to conventional therapy. There was no meaningful difference in the novel treatments when compared with one another. A trial comparing the novel lipid based approaches can therefore be justified on the basis of this finding of equipoise. The distributions of the treatment effects from this study, can be used a prior distributions in Bayesian analyses of clinical trials of these novel therapies.

5.11 Acknowledgements

This paper was presented in part at Clinical Nutrition Week, the meeting of ASPEN (American Society of Parenteral and Enteral Nutrition), Vancouver, British Columbia (January 29 – February 1, 2011).

The authors wish to acknowledge the assistance of Dr. Sindhu Johnson.

The authors wish to acknowledge our colleagues across the PIFCon sites (Alberta Children’s Hospital, Calgary, AB, Children’s Hospital, St Louis, MO, Children’s Hospital Boston, Boston, MA, Children’s Hospital of Pittsburgh, Pittsburgh, PA, Children’s National Medical Center, Washington, DC, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, Comer Children’s Hospital, Chicago, IL, Duke University Medical Center, Durham, NC, Mattel Children’s Hospital at UCLA Medical Center, Los Angeles, CA, Nationwide Children’s Hospital, Columbus, OH, Riley Children’s Hospital, Indianapolis, IN, Seattle Children’s Hospital, Seattle, WA, Texas Children’s Hospital, Houston, TX, The Children’s Hospital, Denver, CO, University of Miami Medical Center, Miami, FL, University of Michigan, C.S. Mott Children’s Hospital, Ann Arbor, MI, University of Nebraska Medical Center, Omaha, NB) who participated in this study.
Preface to Chapter 6 and 7

The following 2 chapters will present data from a pilot trial designed to evaluate the feasibility of conducting a randomized controlled trial of a novel lipid based therapy for the prevention of IFALD in infants. **Chapter 6** will consider the overall feasibility of the study design and **Chapter 7** will present the results of a blinded Bayesian analysis of a limited number of outcomes from the trial.

Disclosure

Investigator Initiated Clinical Trial Funding for this project was obtained from Fresenius Kabi (Bad Hamburg, Germany) the manufacturer of Intralipid®, SMOFlipid® and Omegaven®. The funder was not involved in the design of the trial nor will they participate in the data analysis. The study investigators have primary ownership of the data and the right to publish the results.

Acknowledgements

The trial would not have been possible without the assistance and support of a number of people. At the Hospital for Sick Children: Clinical Research Office/ Research Institute (Julie Gibson, Rita Street, Shauna Kirk, Jason McGuire, Velma Marzinotto, Desta Ramlackhansingh, Aaron Leahy, Brian Rousson), Research Support Pharmacy (Mark Bedford, Darcy Nicksy, Sandra Judd, Lynn England), Core Lab (Daksha Jadav, Peggy Gallella), Data Safety Monitoring Board (Dr. Annie Fecteau, Dr. Nicola Jones, Derek Stephens), Database support and data entry (Loreto Lecce, Robert Grant), Research Nurse Co-ordinators (Nicole de Silva, Eveline Lapidus-Krol), GIFT Team (Christina Kosar, Karen Lang, Glenda Courtney-Martin, Kathryn Cormier, Megan Carricato, Joan Brennan-Donnan, Laura Coxson, Penni Kean, Janice Bowers). At McMaster Children’s Hospital - Dr. Peter Fitzgerald, Dr. Chris Fusch, Julia Pemberton. At The University of Alberta – Dr. David Sigalet, Dr. Mary Brindle, Dr. Dana Boctor, Dr. Jill Boulton, Viona Lam, Sandra Young. At Stollery Children’s Hospital – Dr. Bryan Dicken, Dr. Justine Turner. At St. Justine Hospital – Dr. Valerie Marchand, Maxime Thibault, Guylaine Aubé, Julie Lavoie, Nathalie Bureau. Analysis of RBC phospholipids (Dr. Tom Clandinin, Kelly Leonard).
Chapter 6

6 The Feasibility of Conducting a Randomized Controlled Trial to Examine a Parenteral Lipid Strategy for the Prevention of Progression of IFALD in Infants with Intestinal Failure

6.1 Summary

The objective of this project was to determine the feasibility of conducting a randomized controlled trial of a novel lipid based strategy for the prevention of IFALD in infants. Between January 2009 and June 2010, a pilot multi-center randomized controlled trial, of SMOFlipid® vs. Intralipid®, was conducted at 4 Canadian centers. Screening data were available from the 3 sites that enrolled subjects during this time period. One-hundred and eighty-two infants were screened, of whom 27 were potentially eligible for the study. Sixteen of these children were enrolled and 11 refused participation in the study. Two of the 16 enrolled subjects did not meet the a priori protocol definition of a valid participant as they stopped PN due to early achievement of full enteral tolerance. Analysis of feasibility focused on the first 15 enrolments. Twenty-four protocol deviations occurred in these subjects. The most common deviation (8/24) was related to the standardized approach for prescribing PN. An amendment was made to the PN dosing nomogram which reduced the incidence of this deviation. Overall, we conclude that it is feasible to evaluate a novel lipid based approach in a randomized trial.

6.2 Objective

The goal of this project was to explore the feasibility of conducting a randomized controlled trial of a novel lipid based strategy for the prevention of IFALD in infants with intestinal failure.

6.2.1 Specific Objectives

The specific feasibility issues that we aimed to address were as follows:

i. The ability to recruit patients.

ii. Feasibility and compliance with the protocol.
6.3 Method

An excerpt of the trial protocol (Version 1.4; 8 January 2010) is included in Appendix D.

6.3.1 Trial Overview

The trial was designed as a multi-center parallel group randomized controlled trial comparing SMOFlipid® versus Intralipid® (Clinicaltrials.gov Registration #: NCT00793195). Approval for the study was obtained from the Research Ethics Board at the Hospital for Sick Children as well as the University of Toronto. Approval from the local Research Ethics Board at each external site was also obtained.

Planned enrolment was for 24 subjects. Since the trial was designed as a pilot study, the sample size was not based on an estimate of treatment effect, but rather a reasonable size to ensure good feasibility data. At the proposed sample size, the trial had 80% power to detect a 60 point difference in serum CB. This difference was felt to be a reasonable treatment effect for SMOFlipid® given our experience with Omegaven® in those with advanced IFALD.\(^\text{103, 166}\)

Since duration of PN is challenging to predict, we included a provision for replacement of subjects who discontinued PN prior to the 2nd week on the study due to achievement of full enteral tolerance, but not for reasons of safety or efficacy. By design, these subjects were not to be included in the analysis of trial outcomes or count toward recruitment targets.

Enrolment was to close 24-months after the 1st site was opened. However, if after 18-months from the time the 1st site was opened, less than 16-valid subjects (i.e. those who did not end early due to achievement of full enteral tolerance) had been enrolled in the trial, the enrolment was to close at that time.

The centers that participated in the study were The Hospital for Sick Children in Toronto, McMaster Children’s Hospital in Hamilton, University of Calgary (Alberta Children’s Hospital / Foothills Medical Center) in Calgary, Stollery Children’s Hospital in Edmonton and Ste Justine Hospital in Montreal. Enrolment at each site was opened as soon as approval was obtained from that site’s local research ethics board. Prior to opening enrolment at each site, a site-visit was undertaken for the purposes of training the local site investigator and their team.
6.3.2 Eligibility Criteria

6.3.2.1 Inclusion Criteria

1. ≤ 24 months of age at enrolment
2. Evidence of early hepatic dysfunction
   a. Serum conjugated bilirubin ≥ 17 umol/L on 2 consecutive readings 7 days apart
      i. No evidence of sepsis
         1. Normal temperature (T between 35.5°C and 38.0°C)
         2. Normal leukocyte count
         3. Normal platelet count
         4. No systemic septic symptoms
      ii. No prior administration of Omegaven®
   3. ≥ 40% of total calories administered by PN
   4. Meet one of the following diagnostic categories
      a. Short Bowel Syndrome
         i. Abdominal surgical procedure including gastroschisis/omphalocele closure by any means and percutaneous drainage procedures within the past 6 months and has been receiving PN since surgery
      b. Intestinal Failure
         i. One of the following diagnoses for which the child is dependent on PN
            1. Gastrointestinal Motility Disorder
            2. Mucosal Enteropathy
   5. Expectation of the treating physician that the patient will require PN for at least 3 weeks following enrolment.
   6. Parents willing to participate including randomization

6.3.2.2 Exclusion Criteria

1. Sepsis or Hemodynamic Instability of any cause
2. Coagulopathy (Platelets ≤ 150 000, or INR ≥ 1.4)
3. Hypersensitivity to fish-, egg- or soy protein or to any of the active substances or excipients

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1 Inclusion criterion was added in January 2010 with protocol amendment.
4. Current enrolment in another clinical trial involving a surgical or pharmacologic intervention
5. Serum conjugated bilirubin > 50 umol/L
6. Hyperlipidaemia (any of)
   a. LDL ≥ 4 mmol/L
   b. HDL ≥ 2 mmol/L
   c. Total cholesterol ≥ 5 mmol/L
   d. Triglycerides ≥ 1.5 mmol/L
7. Treatment with intravenous N-Acetylcysteine or oral Ursodeoxycholic acid
8. Renal insufficiency
   a. Creatinine ≥ 80 umol/L
9. Disorders of Fluid Balance (any of)
   a. Serum Sodium < 130 mmol/L
   b. Serum Sodium > 145 mmol/L
10. Unstable conditions
    a. Acute pulmonary oedema
    b. Decompensated cardiac insufficiency
    c. Severe post-traumatic conditions
    d. Uncompensated diabetes mellitus
    e. Acute myocardial infarction
    f. Stroke within 3 months
    g. Thromboembolic event within 3 months
    h. Metabolic acidosis
       i. Serum Bicarbonate < 17 mmol/L

6.3.3 Subject Screening and Recruitment

At each site, the health records of infants on PN were reviewed weekly to identify patients who were potentially eligible for the study. Patients were included in the screening log if they had received PN for > 6 days following a surgical procedure or were receiving PN due to an intestinal motility disorder. The serum CB and degree of enteral support were examined for each patient who met the screening criteria. A notation was made in the log whether the CB was above (> 50 umol/L) or below (< 17 umol/L) the threshold for enrolment in the study and whether the degree of parenteral support was ≥ 40% of total caloric intake. If the patient’s values were outside of these ranges, a decision was made whether to continue following them based on the chance they would meet criteria for the study at a later date.
6.3.4 Trial Intervention

The trial intervention was modification of the type of ILE received by the subject (SMOFlipid® or Intralipid®).

6.3.4.1 Randomization

Subjects were randomly assigned to receive SMOFlipid® or Intralipid® in a 1:1 manner.

Randomization was done centrally by the research support pharmacy at the Hospital for Sick Children. The randomization sequence was developed by the research support pharmacy using a random number table prior to enrolment of the first subject. To ensure that treatment assignment was balanced over the duration of the study, the sequence was developed in blocks of variable size without investigator input or knowledge.

Allocation concealment was achieved by the randomization sequence only being known to the research support pharmacy at the Hospital for Sick Children. The group assignment was relayed to the dispensing pharmacist only after enrolment had occurred. This was done immediately prior to dispensing of the first dose of study medication. Notification of treatment assignment for participants’ will be done at the conclusion of the entire study.

6.3.4.2 Blinding

The study lipid was administered in a blinded manner, by dispensing the trial lipid in an identical container (syringe or infusion bag). All participants, treating clinicians and investigators were blinded to the treatment assignment. Only the research support pharmacist at the Hospital for Sick Children and the dispensing pharmacist at the subject’s institution were aware of the group assignment.

6.3.4.3 Duration of Treatment

Subjects were to be treated with study lipid for a maximum of 12 weeks at which time they resumed Intralipid®. Other trial end-points included full tolerance of enteral feeds or the development of a serum CB >100 umol/L for at least 14 days. The reason for having CB > 100 umol/L as a trial end-point was to allow the patient with progressive liver disease to be considered for alternate therapies such as Omegaven®.
6.3.4.4 Lipid Dosing

The PN solution was formulated according to a nomogram (Figure 6-1) that takes into account the proportion of caloric intake received parenterally. The feasibility of formulating PN according to a nomogram was an objective of the pilot study. Based on initial experience the nomogram was modified 12-months into the study.

<table>
<thead>
<tr>
<th>% of calories administered by PN</th>
<th>Lipid (g/kg/day)</th>
<th>Protein (g/kg/day)</th>
<th>Carbohydrate (g/kg/day)</th>
<th>GIR* (mg/kg/min)</th>
<th>PN Calories Range** (kcal/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 – 100 %</td>
<td>2.5 – 3</td>
<td>3 – 4</td>
<td>15 – 20</td>
<td>10.4 - 13.9</td>
<td>88 – 114</td>
</tr>
<tr>
<td>60 – 80 %</td>
<td>2.5 – 3</td>
<td>2.5 – 3.5</td>
<td>9 – 15</td>
<td>6.3 - 10.4</td>
<td>66 – 95</td>
</tr>
<tr>
<td>50 – 60 %</td>
<td>2 – 3</td>
<td>2 – 2.5</td>
<td>7 – 11</td>
<td>4.9 - 7.6</td>
<td>52 – 77</td>
</tr>
<tr>
<td>40 – 50 %</td>
<td>1.5 – 2.5</td>
<td>1.5 – 2</td>
<td>6 – 9</td>
<td>4.2 - 6.3</td>
<td>41 – 69</td>
</tr>
<tr>
<td>30 – 40 %</td>
<td>1.0 – 2.5</td>
<td>1 – 1.5</td>
<td>5 – 7</td>
<td>3.5 - 4.9</td>
<td>31 – 55</td>
</tr>
<tr>
<td>20 – 30 %</td>
<td>0.7 – 2</td>
<td>0.7 – 1</td>
<td>3 – 4</td>
<td>2.1 - 2.8</td>
<td>20 – 38</td>
</tr>
<tr>
<td>10 – 20 %</td>
<td>0.3 – 1.5</td>
<td>0.5 – 1</td>
<td>1 – 2</td>
<td>0.7 - 1.4</td>
<td>8 – 28</td>
</tr>
<tr>
<td>&lt; 10 %</td>
<td>0 – 1</td>
<td>0 – 1</td>
<td>0 – 1</td>
<td>0 - 0.7</td>
<td>0 – 17</td>
</tr>
</tbody>
</table>

**PN Dosing Nomogram – Revised January 2010**

<table>
<thead>
<tr>
<th>% of calories administered by PN</th>
<th>Lipid (g/kg/day)</th>
<th>Protein (g/kg/day)</th>
<th>Carbohydrate (g/kg/day)</th>
<th>GIR* (mg/kg/min)</th>
<th>PN Calories Range** (kcal/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 – 100 %</td>
<td>2 – 3</td>
<td>3 – 4</td>
<td>10 – 20</td>
<td>6.9 - 13.9</td>
<td>64 – 111</td>
</tr>
<tr>
<td>60 – 80 %</td>
<td>2 – 3</td>
<td>2.5 – 3.5</td>
<td>8 – 16</td>
<td>5.6 - 11.1</td>
<td>55 – 95</td>
</tr>
<tr>
<td>50 – 60 %</td>
<td>2 – 3</td>
<td>2 – 2.5</td>
<td>6 – 12</td>
<td>4.2 - 8.3</td>
<td>46 – 78</td>
</tr>
<tr>
<td>40 – 50 %</td>
<td>1.5 – 2.5</td>
<td>1.5 – 2</td>
<td>5 – 10</td>
<td>3.5 - 6.9</td>
<td>37 – 65</td>
</tr>
<tr>
<td>30 – 40 %</td>
<td>1.0 – 2.5</td>
<td>1 – 1.5</td>
<td>4 – 8</td>
<td>2.8 - 5.6</td>
<td>27 – 56</td>
</tr>
<tr>
<td>20 – 30 %</td>
<td>0.7 – 2</td>
<td>0.7 – 1</td>
<td>2 – 6</td>
<td>1.4 - 4.2</td>
<td>16 – 42</td>
</tr>
<tr>
<td>10 – 20 %</td>
<td>0.3 – 1.5</td>
<td>0.5 – 1</td>
<td>1 – 4</td>
<td>0.7 - 2.8</td>
<td>8 – 31</td>
</tr>
<tr>
<td>&lt; 10 %</td>
<td>0 – 1</td>
<td>0 – 1</td>
<td>0 – 2</td>
<td>0 - 1.4</td>
<td>0 – 20</td>
</tr>
</tbody>
</table>

*GIR: Glucose Infusion Rate – this value reflects the GIR for a 24 period based on the total daily glucose intake. It does not reflect a maximum GIR in the setting of a PN cycle of less than 24 hours.

**Provided for reference only with rounding to whole numbers. Lower limit calculated using the minimum macronutrient values and the Upper limit using the maximum values for each macronutrient. Caloric densities for the macronutrients used in the calculations were as follows: lipid = 9kcal/g, protein = 4kcal/g, carbohydrate = 3.4 kcal/g.

Figure 6-1: Parenteral Nutrition Dosing Nomogram
6.3.4.5 Management of Enteral and Parenteral Feeds

Over the course of the trial, it was anticipated that adjustments would be made to the proportion of feeds received enterally and parenterally by each participant according to their clinical needs. These adjustments were expected to include increases and decreases in the proportion of parenteral to enteral intake. Choice of feeds, timing of the adjustment of the enteral feeds, ratio of enteral to parenteral feeds was to be at the discretion of the treating physician. Initially we had provided a specific list of enteral feeds to choose from. However, due to poor buy-in from the treating physicians this provision was removed from the protocol 12-months into the study. The only enteral formula that was still not allowed while on trial was a fish-oil solution.

6.3.5 Data Collection

Outcomes that were collected at baseline (Week 0), weekly while on the trial and 4 weeks following trial completion (referred to as “Week 16” irrespective of when the child ended the trial) included: serum CB (considered to be the primary clinical outcome of the pilot trial), electrolytes, albumin, liver enzymes, parenteral intake, enteral intake, stool output, weight, length, and head circumference (week 0, 6, 12, and 16 only). A complete blood count was done at weeks 0, 4, 8, 12, and 16. An international normalized ratio, RBC phospholipids, CRP, immunologic markers (Interleukins 1, 6, 8, 10, 12, Tumour Necrosis Factor α), nephelometry, serum cholesterol and serum triglyceride and were assessed at weeks 0, 6, and 12 and 16.

6.3.6 Safety Monitoring

6.3.6.1 Assessment of Adverse Events

Adverse events were handled according to the principles of Good Clinical Practice (GCP) as adopted by Health Canada. Adverse events were graded by the investigator according to severity and classified as expected and unexpected based on a listing provided in the protocol. Adverse events were recorded irrespective of whether the adverse event was believed to be related to the subject’s participation in the trial.

All unexpected adverse events were reported to the local Research Ethics Board as well as to the Data Safety Monitoring Board (DSMB).
6.3.6.2 Data Safety Monitoring Board

The DSMB included a paediatric surgeon, a paediatrician with expertise in nutrition and gastroenterology, and a biostatistician. All members of the DSMB were independent from the trial to the extent that they were not investigators, nor will they be included in any publications arising from the trial.

By protocol, the DSMB met to review the records of the first 4 subjects within 6 weeks of the 4th subject’s post-trial assessment and again within 6 weeks of the 14th subject’s post-trial assessment. No further scheduled meetings were held, although a meeting of the DSMB could be called by any DSMB member or one of the investigators. The DSMB members were provided monthly with a de-identified listing of all unexpected adverse events as well as expected serious adverse events.

6.4 Analysis of Feasibility Objectives

In June 2010, an amendment was made to continue the trial beyond the feasibility period. Although the trial had not met its objective of 16 enrolments within 18-months, it was felt that such a target could still be achieved within a reasonable time period. The amendment included a provision to analyze limited data on subjects who were enrolled and had completed their participation in the study by June 30, 2010.

The feasibility objectives were assessed by examining the screening logs from each site, the amendments made to the protocol during the 1st 18-months that the trial was open, as well as the list of protocol deviations from each site. These logs included deviations that were recorded by the investigators during the subject’s participation in the trial as well as those identified during site visits to each of the external sites that enrolled subjects (Summer 2010).

The logs also included deviations identified during an internal audit by the Clinical Research Office at the Hospital for Sick Children of that site’s records (May 2010) as well as a GCP inspection by Health Canada at the Hospital for Sick Children (July 2010). The reports from the site visits as well as the audit and inspection were reviewed to identify common issues with the conduct of the study.
6.5 Results of Feasibility Assessment

The trial opened to enrolment at the Hospital for Sick Children in January 2009. Enrolment was opened at the Hamilton sub-site in July 2009, Calgary Sub-site in September 2009, and Edmonton sub-site in November 2009. The trial opened at the Montreal sub-site in October 2010 and therefore data from that site are therefore not included in this analysis.

All sites were provided with the Hospital for Sick Children approval in December 2008 in order to begin the local approval process. The duration between December 2008 and the time the site was opened was related to the time that it took for the trial to receive local ethics approval as well as to complete the sub-site agreement. The Montreal site experienced an additional delay related to the need to obtain a waiver from the provincial health authority for insurance issues.

Over the 18-months covered by the present analysis, 15 subjects completed participation in the study (12 Toronto, 3 Hamilton and 1 Calgary). Two of these subjects discontinued PN prior to the 2\textsuperscript{nd} trial week due to early achievement of enteral tolerance. There was one subject still on trial at the Toronto site at the time of data closure for this analysis. This subject was not included in the analyses presented in this thesis.

In the 10 months since data closure for this pilot analysis ended, a further 7 subjects have been enrolled (7 Toronto, 1 Hamilton, 2 Calgary and 1 Edmonton). No subjects have been enrolled at the Montreal sub-site to date. At present, 3 subjects remain to meet the recruitment target.

6.5.1 Recruitment

Data on patients screened was available from 3 of the sites (Toronto, Hamilton and Calgary). Although screening occurred in Edmonton, the site did not begin recording screening data until mid 2010, after data closure for this analysis had occurred. A total of 182 patients were screened (128 Toronto, 22 Hamilton, 32 Calgary). The duration that screening occurred at each site was 18 months Toronto, 12 months Hamilton and 9 months Calgary.

Of the 182 patients who were screened, 27 were found to be potentially eligible. Sixteen of these patients were enrolled in the study. The remaining 11 refused participation. Seven of the refusals occurred in the first 6-months that the trial was open.
Of the 155 subjects who were not eligible, 127 were excluded because they were not within the range for serum CB (CB between 17-50 umol/L) for at least a week while receiving > 40% of their calories parenterally.

Five patients were excluded because they had previously received Omegaven®. Four of these patients were at the University of Calgary. The remaining patient was a patient who was transferred to the Hospital for Sick Children from another institution at which Omegaven® had been started. The remaining 23 patients were excluded because they had significant septic issues or thrombocytopenia while their CB was in range for the study.

6.5.2 Protocol Compliance

One substantive amendment was made 12 months into the study to address a number of issues identified in the 1st year that the trial was open. Table 6-1 lists the major changes that were made with this amendment.

Table 6-2 provides a listing of all protocol deviations. The most common deviation was related to the PN composition being outside of macronutrient ranges specified in the dosing nomogram (Figure 6-1).

The nomogram was amended 1 year after the study was started. In the 10 subjects enrolled prior to the amendment, nomogram deviations occurred in 6. In the 5 subjects enrolled after the amendment, 2 experienced a deviation related to the PN dosing.

The average and range of macronutrient intake for subjects enrolled in the study are included in Table 6-3.
Table 6-1: Summary of Significant Protocol Amendments

<table>
<thead>
<tr>
<th>Number</th>
<th>Change</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Added expected duration of 3 weeks of PN to eligibility criteria.</td>
<td>The original protocol that was approved by the REB(^2) (Version 1.2) did not include a requirement to be on parenteral nutrition for an extended period of time. This was done as it was felt to be challenging to accurately predict the expected duration of PN. However, with increasing experience, and 2 children who ended the trial prior to the 2(^{nd}) week due to early enteral tolerance – one of whom likely would not have been enrolled had this provision been specified, it was felt that such a restriction was needed to attempt to limit enrolment of subjects who will not be on trial for a sufficient duration to allow for adequate data capture.</td>
</tr>
<tr>
<td>2</td>
<td>Clarified that administration of Omegaven(^®) would preclude participation.</td>
<td>This was done in response to a query from an external site, asking whether it would be possible to enrol a child who following Omegaven(^®) treatment for more advanced disease, had an improvement in liver function such that their bilirubin is within the range for this study. The stated goals of the current study are to examine whether SMOFlipid(^®) prevents progression of IFALD(^3) in patients who are receiving a standard lipid emulsion. Therefore, and enrolling patients who received Omegaven(^®) would be contrary to that objective.</td>
</tr>
<tr>
<td>3</td>
<td>Removed list of allowed enteral feeds.</td>
<td>The original protocol had a list of allowed enteral formulas. The objective of this list was to try and avoid the use of formulas that were fortified with omega-3 fatty acids. However, in the 2-years since the protocol was developed most infant formulas had these fatty acids added making this limitation unfeasible. As well, restriction of the allowed enteral feeds was one of the areas of the protocol to which there was significant opposition from the clinical teams.</td>
</tr>
<tr>
<td>4</td>
<td>Altered duration of time, once at full feeds for discontinuation of lipid.</td>
<td>The original protocol stated that PN was not to be stopped unless there was maintenance of growth over a 1 week period. The intention of this requirement was to ensure that the subject was tolerating enteral feeds well prior to stopping PN. However, since implementing the study, it has became clear that a fixed time requirement is not feasible given that such a requirement would unnecessarily prolong hospital stay and is inconsistent with clinical practice.</td>
</tr>
<tr>
<td></td>
<td>Added provision to allow patients to continue the trial at home.</td>
<td>In the original version of the protocol, we mentioned the possibility of sending patients home on PN while still on the trial. While we viewed this outcome as unlikely, it became evident that subjects would be ready for discharge, on home PN, while still on trial. A number of logistic, drug safety and regulatory issues had to be resolved in order to implement this provision.</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Modified schedule of blood work.</td>
<td>The blood work schedule specified in version 1.2 of the protocol was considered and agreed to by the site investigators. However, clinicians at one of the sites, expressed concern over the frequency of the CBC and INR. Following DSMB consultation, we modified the CBC frequency, from every 2 weeks, to monthly and the INR frequency, from every 2 weeks, to every 6 weeks.</td>
</tr>
<tr>
<td></td>
<td>Added Anaemia to Expected list of adverse events.</td>
<td>Anaemia was omitted as an oversight in the original version of the protocol. This issue was discussed with the members of our DSMB who agreed that anaemia is considered to be an expected adverse event in our patient population.</td>
</tr>
<tr>
<td></td>
<td>Modification of PN dosing nomogram</td>
<td>The PN nomogram was adjusted to reflect the trend to decreased intravenous lipid dose in neonates at high risk of IFALD given the increasing recognition of the role that lipids play in the pathogenesis of IFALD. In Version 1.2, the range for lipids in the nomogram for those above 60% PN calories was 2.5-3 g/kg/day; this has been adjusted to 2-3 g/kg/day to reflect changing clinical practice. Minor adjustments to the carbohydrate dosing were also made as per the recommendations of the dietitian group.</td>
</tr>
</tbody>
</table>

1Parenteral Nutrition, 2Research Ethics Board, 3Intestinal Failure Associated Liver Disease, 4Complete Blood Count, 5International Normalized Ratio, 6Data Safety Monitoring Board.
### Table 6-2: Summary of Deviations

<table>
<thead>
<tr>
<th>Deviation</th>
<th>Number with Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral Nutrition outside of nomogram</td>
<td>8</td>
</tr>
<tr>
<td>Enrolment deviation</td>
<td>2</td>
</tr>
<tr>
<td>Variation in timing of blood work</td>
<td>2</td>
</tr>
<tr>
<td>Drug administration issue</td>
<td>4</td>
</tr>
<tr>
<td>Variation in method for nutritional calculation</td>
<td>3</td>
</tr>
<tr>
<td>Deviation in reporting of adverse event</td>
<td>2</td>
</tr>
<tr>
<td>Data not collected due to subject instability</td>
<td>3</td>
</tr>
</tbody>
</table>

### Table 6-3: Macronutrient Intake

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median Weekly Intake</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid (g/kg/day)</td>
<td>2.3</td>
<td>0 – 2.7</td>
</tr>
<tr>
<td>Protein (g/kg/day)</td>
<td>3.1</td>
<td>0 – 4.0</td>
</tr>
<tr>
<td>Carbohydrate (g/kg/day)</td>
<td>14.2</td>
<td>0 – 19.0</td>
</tr>
<tr>
<td>Parenteral Calories (kcal/kg/day)</td>
<td>84.4</td>
<td>0 – 101.4</td>
</tr>
</tbody>
</table>
Monitoring visits were made to the external sites that enrolled subjects for this analysis. There were 2 common issues identified. The first issue pertained to adverse events that had not been recorded in the subject’s adverse event log. This was due to a misunderstanding of the GCP definition of an adverse event versus what is considered to be a complication by clinicians.

The other issue centered on minor variations in the method for nutritional calculations, such as caloric and macronutrient intakes, between the sites. The magnitudes of these deviations were small. Although training had been provided at the site initiation visits, in response to the issue identified during the site visits, we developed a Case Report Form (CRF) completion guide. At the time of the visits, the adverse event logs were updated to include all adverse events. The nutritional calculations on the CRFs were verified and corrected where necessary.

An audit of the trial by Health Canada in early July 2010, found the trial to be in compliance with GCP as adopted by Health Canada 259.

6.6 Discussion

The objective of this project was to determine the feasibility of conducting a randomized controlled trial of a novel lipid based strategy for the prevention of IFALD in infants. The specific feasibility objectives that we assessed were the ability to recruit subjects and compliance with the protocol. The trial experienced slower than expected recruitment as well as a number of problems with protocol compliance. However, on the whole, our results demonstrate that it is possible to examine the efficacy of a novel lipid based approach using a randomized design. Although the study examined an omega-3 containing ILE, SMOFlipid®, we believe that the results of this trial are applicable to trials of any lipid based intervention for IFALD. This includes other ILEs, as well as, lipid minimization.

Three possible reasons for the poor recruitment have been identified. First it took longer than anticipated to launch the external sites. This was related to the variable length of time to complete execution of the sub-site agreements. The sub-site investigators all had limited experience with randomized controlled trials and as such we suspect that part of the delay was related to unfamiliarity of the structures and processes for clinical trials at their institutions. This issue can be addressed in future studies by providing specific guidance to sub-site investigators regarding the process for launching a clinical trial, as well as, anticipating and planning for a
likely delay in achieving approval at the external sites. In terms of IF studies, the investigator group involved in the current study will likely collaborate on future IF trials, with the experience from the current study facilitating these trials.

The second recruitment issue was refusal of 11 of the 27 potentially eligible subjects to participate. The majority of these refusals were in the first 6 months that the trial was open. Unfortunately, few of the parents provided a reason for refusal. Literature on reasons for refusal to participate in clinical trials include: specific problems with the protocol including randomization, inconvenience of participation including the potential for side effects, financial disincentives to participate, concern as to the role of the funder in the study, as well as participation in multiple studies. While we were not able to address the specific reasons for issues with recruitment in this study, we can speculate that the fact that the refusals primarily occurred early in the conduct of the study, suggests that reluctance of health care professionals to endorse a new study, as well as, parental reluctance for their child to participate in a new trial may have played a role. Anecdotally, as the trial proceeded, clinical teams increasingly referred potential candidates for the trial, even though the child had not yet developed a conjugated hyperbilirubinaemia, but were thought to likely remain on PN for a prolonged period and therefore believed to be at high risk of IFALD.

The final recruitment issue was that 23 patients had another exclusion, typically sepsis or thrombocytopenia at the time that their CB was within range (17 – 50 umol/L) for the study. Most of the infants who were excluded for this reason were preterm or low-birth weight infants. Despite the medical issues experienced by these subjects, because of the volume of additional blood work required for the study (12cc / 3 months) it is possible that many of these infants would not have been enrolled as paediatric research ethics boards typically limit research bloods to < 5% predicted blood volume per 3 month period (10.5 cc for a 2.5kg infant). In designing future studies, it would be ideal to include these infants as they are known to be at highest risk of progressive IFALD. Their inclusion is important to ensure that the results of the study can be generalised to these high risk patients. Investigators should therefore reconsider thrombocytopenia as an exclusion criterion. Coagulopathy is largely a theoretical consideration with an ILE that is exclusively comprised of ω3FA and therefore is not particularly germane when considering a composite emulsion such as SMOFlipid. The additional blood volume was related to further examining the mechanism of action (cytokines and red blood cell
phosopholipid composition). Such outcomes will likely not be included in future studies given improved neonatal animal models of IF. 

Overall compliance with the trial protocol was adequate, with 24 deviations over the 18 months. The most common reason for protocol deviation was PN composition outside of the range specified in the PN dosing nomogram. There were also deviations related to variations in calculation of nutritional data based on patient characteristics. For example, one of the subjects had an obstructed proximal gastro-intestinal tract that was drained via a gastrostomy tube. This subject was allowed to eat by mouth but received additional enteral feeds via a jejunostomy tube. Given that the oral feeds were not absorbed, these were not included in calculations of enteral intake. This highlights the need in a patient population as complex as children with IF to build flexibility into trial procedures to account for these clinical issues. However, in developing these strategies, investigators need to be cautious to ensure that the overall scientific integrity of the study is not compromised.

We believe that in order to study a novel lipid based approach, PN dosing needs to be standardized. The reason for this is to ensure that for various degrees of parenteral support, the PN macronutrient intake is balanced between treatments. However, based on discussions with experienced clinicians, it was unclear if such standardization was feasible given the complexity of the nutritional management of children with IF. Therefore, while the protocol included a nomogram for PN dosing (Figure 6-1), we explicitly stated that the use of the nomogram constituted a feasibility outcome. The nomogram was the main reason for protocol deviations. Minor modifications to the nomogram were made as the trial progressed which decreased the incidence of protocol deviations around PN dosing. This suggests that the current version of the nomogram is more appropriate for future studies.

Modifications to the protocol were made 10-months after the trial was started. Two of the first 15-subjects discontinued PN prior to the 2nd trial week due to early enteral tolerance. By protocol, these children will not be included in the analyses or count toward recruitment targets. The inclusion criteria were modified to specify that a participant had to be expected to remain on PN for > 3 weeks in order to enrol. Since the amendment was implemented, none of the children who were excluded for this reason received PN for > 3 weeks. As such, this additional inclusion criterion did not appear to jeopardize recruitment.
We also modified the schedule of blood work that would routinely be done each week. This was in response to concern of some of the clinicians at one of our external sites. This highlights the need, at the time of trial design, to not only ensure that there is buy-in from the sub-site investigators but also key stakeholders at the various sites.

When the protocol was developed we also acknowledged that a mechanism to allow for a child to go home while on trial PN may be needed. However, we did not include this provision in the original version of the protocol as it was felt that there may be significant regulatory issues. However, one subject ended participation at week 10 as he was discharged. Therefore at the time of the amendment we implemented a home PN provision that required additional stability data from the manufacturer as home PN is dispensed a week in advance. While none of the 15 subjects included in this analysis were discharged home while on the trial, two subsequent subjects, completed the trial at home without any major issues. We believe that a home PN provision is important for future studies as it allows for the duration of the study to be extended beyond 12 weeks. This will be especially important when designing trials to evaluate more rare and longer-term outcomes other than the CB such as liver failure, transplantation and death.

At the time of routine monitoring visits to the external sites, we identified minor issues related to the calculation of the nutritional information (macronutrient and caloric intake), as well as, capture of adverse events. Although, site initiation visits and training were done prior to launching the trial, we had not provided written instructions to the sites at the time that the trial was launched. Following the monitoring visits, such guidelines were developed. Provision of a manual of procedures is supported by the literature as a mechanism for facilitating multi-site studies. Its absence was an oversight on behalf of the investigators. Furthermore, a web based clinical trial protocol, including educational resources, has been suggested in order to facilitate randomized trials in paediatric surgery. We believe that the issues with regards to adverse event capture were related to a misunderstanding of the definition of an adverse event under the GCP guidelines relative to what is considered to be a complication by clinicians. This highlights the need to specifically ensure that the research team received training in GCP.
The primary limitation of the present analysis is related to fact that the trial, although multi-centered, was performed at a small number of Canadian centers. Therefore, one cannot be certain that the randomized design will be acceptable to parents and physicians of children with IF in other jurisdictions, given that multi-national trials will likely be required to further address this issue. Also, the impact of specific center and investigator characteristics contributing to the success of the trial cannot be evaluated. However, it must be recognised, that all sites participating in the trial had limited experience with randomized controlled trials. Therefore, we do not think that specific center or investigator characteristics are the primary reason that the design was deemed to be feasible. It is possible that at centers with greater experience with randomized trials, including those who gained experience through the present study, that subsequent studies will experience fewer issues with protocol compliance.

6.7 Conclusion

In conclusion, it is possible to evaluate a novel lipid based approach in a randomized controlled trial. However, recruitment in the present study was slower than had been anticipated when the trial was designed. Modifications were required to the protocol, that will allow for a more robust study design for future studies. Although the current study focused on a novel ILE, we believe that the results of this feasibility assessment also apply to trials of other lipid based approaches including lipid minimization. The experience gained from this trial, may facilitate clinical trials of other therapies that may be beneficial for children with IFALD.
Chapter 7

7 Preliminary Assessment of the Results of the Pilot Randomized Controlled Trial

7.1 Summary

We obtained blinded group assignments and limited data on subjects who had completed participation in the trial prior to June 30, 2010. These data were analyzed within a Bayesian framework in order to determine whether the pilot trial is likely to yield a meaningful difference between the treatments. Preliminary evidence of safety was also assessed based on the adverse event profile in each group. The results of the analysis suggest a high probability of a meaningful difference in serum CB between treatments. However, since the analysis was blinded one cannot determine which treatment is more effective. There were no meaningful differences in terms of adverse events.

7.2 Objective

The objective of this chapter is to examine whether the pilot trial is likely to demonstrate a difference between the treatments evaluated. Preliminary evidence of safety of the intervention will also be addressed.

7.3 Method

7.3.1 Assessment of Efficacy

In July 2010, we obtained blinded group assignments (Group A and B) for subjects who had completed participation in the trial prior to June 30, 2010. Group assignment was not released for subjects who were enrolled prior to July 2010, but were still on the trial at the time the blinded group assignment was released.

The primary clinical outcome of the pilot trial was the serum CB during the final trial week. The present analyses will focus on the CB, rather than other measures of liver function. These outcomes, such as liver enzymes and markers of synthetic function, as well as, markers of inflammation, will be analysed when the trial is completed.
In addition to analyses of the CB, we performed a limited number of analyses of potential confounders including degree of enteral tolerance, degree of hepatic dysfunction at trial enrolment, duration of time on the study, average macronutrient and caloric intake.

Assessment of efficacy was done within a Bayesian framework using a variety of analytic techniques. All Bayesian analyses were done in Winbugs (MRC Biostatistics Unit Cambridge, UK). Initial values were system generated with the exception of the initial values for the time to event and logistic regression analyses. In general, 3 chains were run for each analysis to allow for assessment of model convergence by examining the Gelman-Rubin plots following 10 000 iterations. The model was run for a further 10 000 iterations prior to assessment of the model parameters. The code for all Bayesian analyses can be found in Appendix E.

A limited number of frequentist analyses were also done for illustrative purposes in R (The R Project for Statistical Computing).

**7.3.1.1 Linear Regression**

**7.3.1.1.1 Primary Analyses**

A Bayesian linear regression model was fitted to the CB in the final week that the subject was on the trial using Winbugs (Appendix E.). The purpose of this analysis was to determine whether the mean CB at the time of trial completion differed between the groups.

The linear regression was also performed in a frequentist framework using R.

**7.3.1.1.1 Priors**

When specifying priors for the linear regression and Analysis of Covariance (ANCOVA), the group with the higher mean value for serum CB formed the reference group.

Three different priors were utilized for the treatment effect:

- **Uninformative prior:** Normal distribution with a mean of 0 and standard deviation of 100. Since the precision for this prior is low, the posterior distribution will reflect the likelihood (Section 3.4.2.1.1).

- **Optimistic prior:** Normal distribution with a mean of -60 umol/L (a change of 60 umol/L was the difference proposed at the time the trial was designed (Section 6.3.1) and a
standard deviation of 36.5. This prior specifies a 95% chance that there would be at least some benefit to treatment A. The choice of this prior is based on the recommendation of Spiegelhalter et al., who suggest that an optimistic prior should include a 5% probability of a negative treatment effect.

- **Sceptical prior**: Normal distribution with a mean of 0 umol/L and a standard deviation of 36.5. This prior specifies that the treatment response will be centered on 0, with a less than 5% chance that the treatment effect would be better than -60 umol/L. This prior also follows the recommendations of Spiegelhalter et al. 242.

### 7.3.1.1.2 Secondary Linear Regression Analyses

We also examined, in univariate models, the differences between groups in terms of:

1. 4-week post-trial CB
2. Change in CB while on the study adjusted for length of time on trial
3. Change in enteral tolerance on trial
4. Duration of time on trial
5. Average weekly macronutrient doses
   a. Lipid
   b. Carbohydrate
   c. Protein
6. Average weekly parenteral caloric intake

All of these secondary analyses were done using the uninformative prior specified in section 7.3.1.1.1.1.

### 7.3.1.2 Analysis of Covariance

In order to adjust the treatment effect for potential confounders, an analysis of covariance (ANCOVA) model was fitted to the CB in the final trial week using Winbugs (Appendix E). The variables that were included in the model were the change in enteral tolerance, CB at trial enrolment and the duration of time on the study. Uninformative priors were placed on all the model parameters with the exception of the treatment effect. For this variable, the model was examined using the same uninformative, optimistic and sceptical priors as specified in Section 7.3.1.1.1.
7.3.1.3 Longitudinal Data Analysis

A linear random effects model was fitted using Winbugs (Appendix E). The serum CB from each trial week was included in the analysis. Data from the 2 participants who ended the trial early were included in this analysis. This analysis was done using an uninformative prior only. The objective of this analysis was to determine whether the rate of change in serum CB per week over the course of the trial differed between treatment groups.

7.3.1.4 Time to Event Analysis

A time to event model was fitted (Appendix E). Data from the 2 participants who ended the trial early were included in this analysis. The outcome of this analysis was time to a CB of 50 umol/L. This threshold was chosen, as this was the level above which the subject would no longer be eligible to participate in the study.

In addition to performing the analysis with an uninformative prior, we also utilized the priors from our expert belief elicitation study (Chapter 5). Three distributions for the Relative Risk (RR) of progressive liver disease with the omega-3 approach, were used as priors for the Hazard Ratio (HR). The specific priors used were the distribution from the entire group of experts, as well as, those designated as optimists and sceptics (Section 5.8.1.3).

The priors were entered into the model as normal distributions on the log scale. When specifying the priors, the treatment with the lower risk of advanced liver disease was assumed to reflect the novel treatment.

A Cox proportional hazard time to event analysis was also done in a frequentist framework using R.

7.3.1.5 Logistic Regression

A logistic regression model was fitted (Appendix E). Data from the 2 participants who ended the trial early were included in this analysis. The outcome of the analysis was progressive liver disease, defined by development of a serum CB > 50 umol/L.
The analysis was initially performed using an uninformative prior. However, we also used the final model of the risk of advanced IFALD from Chapter 4 to develop a distribution for the risk of progressive liver disease at 7 weeks exposure to conventional lipid > 2.5 g/kg/day. The rationale for choosing 7 weeks was that this was the mean duration on study for the participants. This odds ratio (OR) distribution at this time point was used as a prior for the risk of progressive liver disease.

The posterior distribution from this analysis reflects the updated risk of progressive liver disease based on the data from Chapter 4 as well as the trial.

7.3.2 Assessment of Safety

Assessment of safety focused on an assessment of the adverse events for subjects in each of the groups. Adverse events from each subject were tallied into categories.

No statistical comparisons were made in terms of the frequency of the adverse events in each group.

7.4 Results

7.4.1 Assessment of Efficacy

Of the 15 subjects who completed participation in the trial prior to data closure for this analysis, 2 discontinued PN prior to the end of the 1st week of participation in the trial. By protocol, these subjects, who achieved full enteral tolerance early, did not have any trial assessments completed after that time. Also a priori it was specified that, unless the reason for early trial termination was related to efficacy or safety, they would not be included in the analyses. These subjects were both assigned to Group A. Notwithstanding the fact that by protocol, these subjects were not to be included in the analysis, we did include them in certain analyses.

Of the 13 valid subjects, 5 were assigned to group A and 8 were assigned to group B. Baseline characteristics of these participants are included in Table 7-1.
<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td><strong>Age (weeks – mean/sd)</strong></td>
<td>6.2 (1.4)</td>
<td>4.1 (2.1)</td>
</tr>
<tr>
<td><strong>Gestational Age (weeks – mean/sd)</strong></td>
<td>35.8 (3.0)</td>
<td>36.0 (1.7)</td>
</tr>
<tr>
<td><strong>Birth Weight (grams)</strong></td>
<td>2516 (639)</td>
<td>2708 (699)</td>
</tr>
<tr>
<td><strong>Gender (% male)</strong></td>
<td>3 (60%)</td>
<td>6 (75%)</td>
</tr>
<tr>
<td><strong>Aetiology (N, %)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrotizing Enterocolitis</td>
<td>2 (40%)</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal Wall Defect</td>
<td>1 (20%)</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>Small Bowel Atresia</td>
<td>1 (20%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Diaphragmatic Hernia</td>
<td>1 (20%)</td>
<td>-</td>
</tr>
<tr>
<td>Motility Disorder</td>
<td>-</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Volvulus</td>
<td>-</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td><strong>Weight at Enrolment (gram)</strong></td>
<td>3365 (675)</td>
<td>3214 (791)</td>
</tr>
<tr>
<td><strong>Ileocecal Valve (N, % with)</strong></td>
<td>3 (60%)</td>
<td>7 (87.5%)</td>
</tr>
<tr>
<td><strong>Stoma (N, % with)</strong></td>
<td>3 (60%)</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td><strong>Duration of PN(^1) prior to trial</strong> (days – mean, sd)</td>
<td>41 (9)</td>
<td>27 (13)</td>
</tr>
</tbody>
</table>

\(^1\) Parenteral Nutrition
7.4.1.1 Linear Regression

Means and standard deviations of variables that were used in the linear regression analyses are included in Table 7-2.

7.4.1.1.1 Primary Outcome - Bayesian Analysis

Table 7-3 presents the results of the linear regression analysis that examined the impact of treatment on CB in the final week on trial.

Triplots showing the distributions of the prior, likelihood and posterior from the linear regression analysis are shown in Figure 7-1.

The overall probability of a treatment effect as defined by the CB at trial completion for group A being smaller than group B approached 100% for all analyses.

The posterior probability of a treatment effect lower than -60 umol/L was 43% with the uninformative, 48% with the optimistic prior and 22% with the sceptical prior. The prior probability of a treatment effect of this magnitude with the sceptical prior was 5%.

Table 7-3 also presents the probability of a treatment effect better than -30 umol/L. The reason for reporting this value is that we regard a difference in serum CB of -30umol/L to reflect the minimally clinical important difference (MCID). The posterior probability of this difference with the uninformative prior was 93%, 96% with the optimistic prior and 85% with the sceptical prior.

7.4.1.1.2 Primary Outcome - Frequentist Analysis

The estimate of the treatment response from the frequentist analysis was a -59.65 umol/L difference in serum CB between treatment A and B (95% confidence interval: -95.5 to -22.8, p = 0.004).
Table 7-2: Descriptive Statistics for Variables Used in Linear Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (N = 5)</th>
<th>Group B (N = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>Initial CB (umol/L)</td>
<td>27.4</td>
<td>9.2</td>
</tr>
<tr>
<td>Final CB (umol/L)</td>
<td>9.6</td>
<td>16.7</td>
</tr>
<tr>
<td>Post-trial CB (umol/L)</td>
<td>7.4</td>
<td>10.6</td>
</tr>
<tr>
<td>Change in Enteral tolerance (%)</td>
<td>56.8</td>
<td>43.4</td>
</tr>
<tr>
<td>Trial duration (weeks)</td>
<td>7.8</td>
<td>4.0</td>
</tr>
<tr>
<td>Average Lipid Dose (g/kg)</td>
<td>2.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Average Carbohydrate Dose (g/kg/day)</td>
<td>11.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Average Protein Dose (g/kg/day)</td>
<td>2.8</td>
<td>1.05</td>
</tr>
<tr>
<td>Average Parenteral Caloric Intake (kcal/kg/day)</td>
<td>72.3</td>
<td>23.7</td>
</tr>
</tbody>
</table>
### Table 7-3: Bayesian Estimates of Treatment Efficacy – Conjugated Bilirubin at Trial Completion

<table>
<thead>
<tr>
<th>Prior</th>
<th>Unadjusted Analysis</th>
<th>Adjusted Analysis(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median(^2)</td>
<td>95% CI(^3)</td>
</tr>
<tr>
<td>Uninformative</td>
<td>-57.2</td>
<td>-92.1 to -19.8</td>
</tr>
<tr>
<td>Optimistic</td>
<td>-59.1</td>
<td>-90.7 to -27.3</td>
</tr>
<tr>
<td>Sceptical</td>
<td>-47.9</td>
<td>-78.5 to -10.8</td>
</tr>
</tbody>
</table>

\(^1\) Adjusted for conjugated bilirubin at enrolment, duration of time on trial and change in enteral tolerance on trial.

\(^2\) Treatment effect - Difference in mean conjugated bilirubin (umol / L) between treatment A minus treatment B

\(^3\) Credible Interval

\(^4\) Probability that the treatment effect is greater than – 60 umol/L difference in serum conjugated bilirubin

\(^5\) Probability that the treatment effect is greater than – 30 umol/L difference in serum conjugated bilirubin

\(^6\) Probability of any treatment effect
Figure 7-1: Triplots showing the prior, likelihood and posterior distributions with the uninformative (A), optimistic (B) and sceptical (C) priors for the linear regression analysis examining final trial week serum conjugated bilirubin (CB) in umol/L.
7.4.1.1.3 Secondary Outcomes - Bayesian Analysis

The results of the secondary linear regression analyses can be found in Table 7-4. The 95% credible intervals for the posterior distribution for the two analyses that examined treatment efficacy (CB at post trial visit and change in CB per week on trial) were all negative and did not include 0. This suggests a high probability of benefit with treatment A.

For the most part, the analyses that examined potential confounders (change in enteral tolerance, duration of time on the trial, average macronutrient and caloric intake) had median values close to 0. This suggests that the groups did not appear to differ in a meaningful way in terms of the distribution of these confounders. The only variables that appeared to differ between groups were the average carbohydrate and parenteral caloric intake, for which group A appeared to receive more than B.

Table 7-4: Secondary Linear Regression Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median$^1$</th>
<th>95% CI$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 week post trial CB (umol/L)</td>
<td>-45.8</td>
<td>-81.1 to -9.2</td>
</tr>
<tr>
<td>Change in bilirubin per week on trial (umol/L/week)</td>
<td>-9.3</td>
<td>-17.9 to -0.7</td>
</tr>
<tr>
<td>Change in enteral tolerance on trial (%)</td>
<td>-4.9</td>
<td>-36.2 to 45.4</td>
</tr>
<tr>
<td>Duration of time on trial (week)</td>
<td>0.28</td>
<td>-5.1 to 5.7</td>
</tr>
<tr>
<td>Average Lipid Dose (g/kg/day)</td>
<td>0.32</td>
<td>-0.31 to 0.95</td>
</tr>
<tr>
<td>Average Carbohydrate Dose (g/kg/day)</td>
<td>2.97</td>
<td>-3.1 to 8.7</td>
</tr>
<tr>
<td>Average Protein Dose (g/kg/day)</td>
<td>0.78</td>
<td>-0.6 to 2.1</td>
</tr>
<tr>
<td>Average Parenteral Caloric Intake (kcal/kg/day)</td>
<td>17.4</td>
<td>-13.3 to 46.2</td>
</tr>
</tbody>
</table>

$^1$ Difference in means between treatment A minus treatment B

$^2$ Credible Interval
7.4.1.2 Analysis of Covariance

The results of the ANCOVA, controlling for starting CB, duration of time on trial and change in enteral tolerance are also presented in Table 7-3.

The adjusted analysis confirmed the main findings of the unadjusted linear regression demonstrating an advantage to treatment A. However, the magnitude of the treatment response was lower with the adjusted analysis. This is related to inclusion of the covariates in the model.

For the ANCOVA analysis using the sceptical prior, the posterior probability of a treatment response exceeding the MCID, in favour of treatment A, was 63%.

7.4.1.3 Longitudinal Data Analysis

The results of the linear random effects model confirmed the finding of a benefit in favour of treatment A. The median value of the difference in rate of change in serum CB per week between the groups was -6.67 umol/l/wk (95% credible interval: -14.6 to 1.8). The probability that this response was < 0, reflecting a greater decline with treatment A was 94%.

7.4.1.4 Time to Event Analysis

Three of the 7 subjects assigned to Treatment A and 6 of the 8 subjects assigned to Treatment B developed a serum CB > 50 umol/L at some point during the trial. Two of the participants in group A who experienced this outcome ended the trial prior to the 2\textsuperscript{nd} week due to achievement of enteral tolerance.

7.4.1.4.1 Time to Event - Bayesian Analysis

Table 7-5 summarizes the results of the time to event analysis examining the risk of progressive liver disease in group A relative to group B.

The posterior probability that the HR was less than 1 (i.e.: a benefit to treatment A) was 93% with the uninformative prior and 95% with the prior from the entire group of experts.

Using the sceptical prior, there was an 83% posterior probability of benefit to treatment A. The prior probability of the sceptics for such a benefit was 73%.
Table 7-5: Time to conjugated bilirubin > 50 umol/L analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Median HR¹</th>
<th>95% CI²</th>
<th>p HR &lt; 1³</th>
<th>p HR &lt; 0.5⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninformative</td>
<td>0.36</td>
<td>0.07 – 1.44</td>
<td>93%</td>
<td>68%</td>
</tr>
<tr>
<td>Entire Sample</td>
<td>0.39</td>
<td>0.12 - 1.18</td>
<td>95%</td>
<td>67%</td>
</tr>
<tr>
<td>Optimists</td>
<td>0.29</td>
<td>0.08 – 0.93</td>
<td>98%</td>
<td>82%</td>
</tr>
<tr>
<td>Sceptics</td>
<td>0.71</td>
<td>0.36 – 1.42</td>
<td>83%</td>
<td>15%</td>
</tr>
</tbody>
</table>

¹Hazard Ratio, a value < 1, implies that the risk of progressive IFALD was lower in Group A.
²Credible Interval
³Probability that the Hazard Ratio is less than 1
⁴Probability that the Hazard Ratio is less than 0.5

7.4.1.4.2 Time to Event - Frequentist Analysis

The HR for the development of progressive liver disease from the frequentist analysis was 0.53 (95% confidence interval 0.13 to 2.14, p = 0.376).

7.4.1.5 Logistic Regression

The odds ratio of progressive liver disease (as defined by a serum CB > 50 umol/L) was higher in group B relative to group A using an uninformative prior: median 4.9 (95% credible interval: 0.5 to 67.9).

Figure 7-2 demonstrates the triplot for the analysis with the informative prior on the log odds ratio scale.

The prior odds ratio of progressive liver disease at 7 weeks from the final model in Chapter 4 was a median of 5.2 (95% credible interval: 1.5 – 21.1, log scale: mean 1.654, standard deviation: 0.6871). The posterior odds ratio of progressive liver disease was a median of 5.03 (95% credible interval: 1.6 to 16.2). This odds ratio reflects the estimate of the risk of progressive liver disease in group B versus group A, taking into account both information from Chapter 4 as well as the data from the trial.
Figure 7-2: Triplot showing the prior, likelihood and posterior distribution of the log odds ratio for progressive liver disease.

7.4.2 Safety Assessment

Table 7-6 lists adverse events experienced by the subjects enrolled in the trial. All subjects experienced at least 1 adverse event. There was one serious, but expected adverse event in a subject assigned to treatment B (severe sepsis). There were no serious unexpected adverse events or any unexpected adverse drug reactions.

With the exception of a scalp rash in a subject assigned to treatment B and a red man syndrome following administration of Vancomycin in a subject assigned to treatment A, all other adverse events were expected according to the listing of adverse events in the protocol.

Although a formal analysis was not done, there did not seem to be any meaningful differences in the adverse event profile between treatment A and B.
7.5 Discussion

The objective of this project was to determine whether the pilot trial is likely to demonstrate a meaningful difference between the treatments evaluated. The analysis was performed in a Bayesian framework using a variety of techniques, including linear regression to examine for the difference in mean CB at trial completion, ANCOVA to provide an adjusted estimate of the mean difference in CB, a longitudinal analysis to compare rate of change in serum CB, a time to event analysis and a logistic regression. Overall, the results of our analysis, which focused on the serum CB, suggest that the risk of IFALD progression was substantially lower with treatment A than treatment B.

### Table 7-6: Adverse Events

<table>
<thead>
<tr>
<th>Number with Event (%)</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>5 (100%)</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>Any Serious Adverse Event</td>
<td>-</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Infectious Complication</td>
<td>3 (60%)</td>
<td>7 (87.5%)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>2 (40%)</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>3 (60%)</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Nutritional Abnormality</td>
<td>3 (60%)</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Line complication</td>
<td>1 (20%)</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>Electrolyte Disturbance</td>
<td>5 (60%)</td>
<td>7 (87.5%)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>3 (60%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>1 (20%)</td>
<td>1 (12.5%)</td>
</tr>
</tbody>
</table>
Since the analysis was blinded, we do not know which of the treatments is more effective. The reason why a blinded analysis was performed was that the trial still remains open to enrolment and we did not want to influence recruitment. However, there seems to be a high likelihood that the current trial will demonstrate a meaningful difference between SMOFlipid® and Intralipid®. However, the direction of this effect is not known. Given the small number of subjects, it is not possible to make any definitive statements regarding the safety of the intervention, although there appears to be little difference between the treatments. Therefore, even though we do not know which treatment was superior, the present analysis cannot be regarded definitive in terms of making treatment recommendations.

While the results of the current analysis will be presented to the DSMB, the trial will not be stopped early. The rationale behind this provision in the protocol was that in trials that stopped early for benefit, typically the large effect size turns out to be smaller in subsequent studies 269. This is particularly relevant to positive results from small trials 270. However, we must acknowledge that stopping rules for benefit are ethically complex 271.

One of the advantages of the Bayesian approach is the formal incorporation of data external to the trial as priors. Unfortunately, data on which to base priors, other than extrapolation from studies of children with advanced IFALD are quite limited. We therefore used a number of sources for priors, including our views on the likely treatment effect based on our clinical experience with Omegaven® in those with advanced IFALD, data from a previous multiple variable model of advanced IFALD (Chapter 4) and also priors from our expert belief elicitation study (Chapter 5).

The reason for using multiple sources for the priors was twofold. First the types outcomes (continuous vs. binary) were different necessitating different priors. Second, one of the major criticisms of the Bayesian approach is the fact that the prior may not be correct leading to an erroneous conclusion 249. We believe that by using priors from different sources, one would be able to get a more accurate picture of the treatment effect than with an analysis with a prior from a single source. The fact that the results of the analyses with the various priors are consistent provides support for the notion that the results are not the consequence of a poor choice of prior. Furthermore, inclusion of the prior did not alter the direction of the treatment response relative to that obtained from the likelihood.
The model from Chapter 4 and the prior distributions from Chapter 5 used a threshold CB of 100 umol/L (6mg/dl) to indicate progressive IFALD. However, progressive IFALD for the trial analysis was defined as a CB > 50 umol/L. The reason for choosing the lower threshold was based on the fact that no subject on the trial had met the higher outcome. While the definition of progressive IFALD was less stringent in the trial than those in Chapter 4 and 5 we felt it reasonable to use these priors, despite the differences in the threshold for classification of progressive disease.

For both the logistic regression and time to event analysis, while inclusion of the informative prior increased the precision for the estimate of the HR or OR, the overall conclusions of the informative analysis were not different from the uninformative analysis. The likelihood, in these analyses had low precision due to the small sample size. Therefore the posterior distribution for these studies was largely influenced by the more precise prior. The fact that the magnitude of the treatment response for the likelihood and prior were similar, provides some support that our assumption that these priors are acceptable markers for the risk of progressive liver disease despite the difference in how progressive disease was quantified.

While the majority of our analyses were done using Bayesian methods, we did 2 frequentist analyses for illustrative purposes. The first analysis was a linear regression examining difference in final trial week CB. On the surface, the results of the frequentist analysis seem identical to the uninformative Bayesian analysis. Although the p-value was “statistically significant”, it is important to remember that the p-value is merely the probability of obtaining the data or values more extreme by chance alone, rather than a statement about the magnitude of the treatment response (Section 3.4). On the other hand, the distributions obtained from the Bayesian analysis allow one to assess the probability of a treatment response of various magnitudes. This is particularly germane to the frequentist Time to Event analysis, where the p-value was > 0.05. Therefore, assuming a Type I error rate of 5%, this result would be regarded as reflecting insufficient evidence to conclude that there was a difference between the groups. However, by employing the Bayesian approach, one is able to demonstrate a high probability that there is a meaningful benefit to treatment A.
The fact that no patient developed a CB > 100 umol/l while on the study was somewhat surprising. There are a number of possible reasons for this. First, the median duration on study was 7 weeks. This reflects that the some of the subjects enrolled in the study were weaned from PN over the course of the trial. In contrast, the time point for estimation of the risk of liver disease in the expert study was 3 months. Therefore, had children been enrolled who remained on PN for longer, we may have seen more children with severe IFALD. Second, in our expert belief study (Chapter 5), there was greater than expected uncertainty as to the baseline risk of IFALD with conventional therapy. It is therefore possible that the risk of IFALD with conventional therapy is lower than what we thought. Finally, exclusion of pre-term neonates due to sepsis and coagulopathy, may have played a role in decreasing the incidence of CB > 100 umol/L by limiting enrolment of patients at highest risk of progressive IFALD.

Despite the fact that the subjects in our trial may have had less severe IFALD based on the shorter duration on PN after enrolment than we had anticipated, there still seems to be significant benefit to one of the treatments. It is therefore possible, that the magnitude of the treatment effect will be even greater in those at higher risk of IFALD although this assertion will need to be formally evaluated in subsequent studies.

Subsequent studies as well as animal models, should also investigate the potential impact that the novel lipid emulsions may have on intestinal adaptation. There is evidence from animal models that PN impacts intestinal mucosal and absorptive function\(^ {272, 273}\) and therefore theoretically, there may be an impact of the novel ILEs on adaptation. However, this issue will be challenging to address given the multitude of factors influencing intestinal adaptation and the probability of being weaned from PN\(^ {274}\).

Although the trial had a small sample size, the treatment groups seemed to be reasonably well balanced in terms of the limited number of confounders examined. The only substantive difference was a higher glucose and parenteral caloric intake in group A. We speculate that reason for this difference is random and may be related to the small sample size. Furthermore, higher PN support is believed to increase the risk of IFALD. Therefore these imbalances do not appear to have affected the overall conclusion that treatment A seems to have a lower risk of IFALD.
The present analysis has a number of limitations. First, one must recognise that our conclusions are based on a small number of subjects resulting in low precision for the likelihood with certain of the more complex analyses. Second, at the time the trial was designed we had planned not to do any interim analyses. Therefore, the current analyses were not determined at the time that the study was designed. Furthermore, the thresholds for the MCID or definition of advanced liver disease were also done post hoc. Notwithstanding these concerns, since this analysis was only to determine whether the trial is likely to yield a meaningful result and not make treatment recommendations, these concerns can be partly allayed.

Our final limitation is the same limitation of all studies to date evaluating the novel lipid based approaches, namely, reliance on serum CB (Section 3.2). Serum CB is an imperfect biomarker for what are believed to be the primary outcomes of interest. While we acknowledge this issue, until larger scale and longer term studies are performed, clinical trials will likely focus on the CB. Despite its limitations, we also believe that the CB still provides important data regarding the impact of these therapies on the risk of IFALD.

7.6 Conclusion

Although the results of this analysis do not allow one to conclude which of SMOFlipid® or Intralipid® lowers the risk of IFALD, there is a high probability that the trial will yield a meaningful treatment effect. The fact that one can draw this conclusion on the basis of an analysis of between 13 and 15 subjects highlights both the large magnitude of the treatment effect as well as the advantages of the Bayesian approach. Therefore, on the basis of the results of the previous and this chapter, one can conclude that not only is it feasible to evaluate a novel lipid based approach in a randomized design, it is also worthwhile to pursue further evaluation of these approaches given the difference noted between the treatments evaluated in this study.
Chapter 8

8 Concluding Remarks

8.1 Review of Thesis Rationale

Intestinal Failure Associated Liver Disease is the greatest contributor to the morbidity experienced by children with IF \(^3\), \(^7\). Historically, IFALD was the primary cause of death of children with IF. However, IFALD is also believed to impair intestinal adaptation. Children with progressive IFALD therefore remain dependent on PN for longer, exposing them to a greater risk of complications including worsening liver disease \(^{20}\). As such, strategies to reduce the risk of IFALD should have a significant impact on the management of children with IF.

While the pathophysiology of IFALD is multifactorial, recently much attention has been devoted to the critical role that \(\omega_6\)FA containing ILEs play in the development of IFALD \(^{134}\). Understanding the role that ILEs play in the development of IFALD may allow the use of targeted therapies \(^{104}\), \(^{105}\). The two approaches that have been advanced are that of lipid minimization and alternate ILEs including those containing \(\omega_3\)FA. These therapies have, however, only been studied in uncontrolled settings, primarily in children with advanced IFALD. Therefore, we have argued that there is insufficient evidence to recommend these novel therapies in children with early or no IFALD in order to prevent the progression to advanced IFALD \(^{104}\), \(^{105}\).

While the randomized controlled trial provides the best evidence for the efficacy and safety of an intervention \(^{223}\), these trials may be challenging to perform in children with IF. First, IF is a rare disease and therefore trials will need to be performed across multiple centers. Second children with IF are a heterogeneous group of patients who typically have multiple additional comorbidities and the standardization of management required in a clinical trial may be difficult to achieve. Also, it is unclear if randomized studies would be acceptable to the caregivers of these complex children. There is also little evidence on which to base estimates of treatment efficacy with the novel lipid based approaches for use in sample size calculation. Finally, there is limited experience with clinical trials in the IF population.
8.2 Review of Thesis Objective

The objective of this thesis was to facilitate clinical trials of novel lipid based strategies for the prevention of IFALD. This was achieved through three related projects. The first of these projects examined the risk of progressive IFALD to better quantify the role of ILEs in the development of this disorder. The second project surveyed experts as to their opinion of the risk of progressive liver disease with conventional therapy, lipid minimization and an ω3FA containing ILE. This exercise allowed for the development of prior distributions in order to facilitate Bayesian analyses of clinical trials of these treatments. The final project was a pilot multi-center randomized controlled trial of an ω3FA containing ILE. The objective of this project was to explore the feasibility of the randomized design in this patient population. In addition to exploring the feasibility of the randomized design, we also explored the likelihood that the current pilot trial would yield a meaningful treatment response.

8.3 Synthesis of Thesis Findings

In Chapter 4, we developed a multiple variable model examining risk factors for the development of advanced IFALD. Of the variables considered, the final model contained 2 variables – septic episodes and exposure to conventional lipid > 2.5 g/kg/day. As such, the analysis provides targets for intervention in order to reduce the risk of IFALD. The role of sepsis prevention in the management of IFALD, through strategies such as the use of ethanol or antibiotic locks, requires formal evaluation. Ideally this evaluation should be done in a randomized manner. Although this thesis focused on the lipid based approach, it is hoped that the experience gained with the trial performed as part of this thesis will help facilitate such studies.

Although sepsis was demonstrated to be an important factor in the development of progressive IFALD, we specifically chose to focus on facilitating clinical trials of lipid based strategies for the prevention of IFALD. The reason for doing so was that we believed that targeting lipids would have the greatest impact. In our multiple variable model, each day of conventional lipid > 2.5 g/kg/day was associated with a 1.04 increase in the odds of advanced IFALD. At 60-days, which is a conservative estimate for the duration of time on PN for a child with severe IF, the odds ratio of advanced IFALD is increased almost 10-fold. Therefore, the results of this study confirmed our impression that novel lipid based therapies may have a significant impact in the prevention of IFALD.
In Chapter 5 we explored expert belief of the efficacy of the novel lipid based approaches (ω3FA containing ILEs and lipid minimization) for the prevention of advanced IFALD. This study demonstrated that experts believed that the novel approaches would lessen the risk of IFALD progression. There was also a greater than expected degree of uncertainty around the baseline risk of advanced IFALD with conventional lipid. This has implications for sample size calculations for clinical trials.

Although, experts believed that both ω3FA containing ILEs and lipid minimization should be regarded as routine for those with advanced IFALD, there was less support for their use in those with minimal or early IFALD. This uncertainty suggests that clinical trials of these therapies in those with early IFALD are appropriate.

Clinical trials of novel lipid based therapies in IF are likely to be challenging to perform given the small heterogeneous patient populations. Therefore, one of the major goals of the belief elicitation study was to provide priors that can be used in Bayesian analyses of trials of these therapies. As outlined in Chapter 3, we believe that the Bayesian approach should be considered in the analysis of trials in patients with rare diseases such as IFALD.

Given the potential for challenges in performing such randomized studies, we felt in prudent to evaluate the feasibility of the randomized controlled design for the evaluation of a novel lipid based strategy for the prevention of advanced IFALD. This objective was assessed in Chapter 6 which presented a feasibility assessment of a pilot multi-center randomized controlled trial to evaluate the role of SMOF lipid® in this regard. While recruitment was slower than anticipated, primarily due to the delay in launching external sites and a number of refusals early in the trial, the overall design was assessed to be feasible.

Aside from overall feasibility, one of the specific issues that we sought to address was the feasibility of standardizing the administration of PN for subjects enrolled in the trial. We believed this aspect of the design to be important to allow the groups to be balanced from a nutritional perspective and facilitate optimal assessment of efficacy of the therapy. Although the PN dosing nomogram was the most common reason for deviations in the pilot study, with minor adjustments, we were able to substantially reduce the incidence of such deviations. Therefore, we conclude that it is feasible to standardize dosing of PN in the context of a randomized controlled trial.
In Chapter 7 we performed a blinded Bayesian analysis of data from the pilot trial. The median reduction in serum CB between the groups was -57.2 umol/L. The Bayesian approach allows one to directly estimate the probability of a treatment response of a particular magnitude. Based on the unadjusted linear regression with an uninformative prior, the posterior probability of the treatment response exceeding 60 umol/L was 43%. The probability of a treatment response greater than what we view to be the MCID (30 umol/L) was 93%.

The analysis was performed using a number of statistical techniques, which confirmed that the pilot trial has a high likelihood of yielding a meaningful treatment effect. In addition to performing uninformative Bayesian analyses and analyses with priors based what we believed to be optimistic and sceptical treatment responses; we also used priors from Chapter 4 and 5. By using a prior that was developed from the model in Chapter 4, we were able to integrate data from the trial and our model in order to provide a more precise estimate for the odds ratio of progressive liver disease with conventional lipid. Also, by using priors from the expert belief elicitation study, we were able to integrate the results of the trial with the views of the experts in a time to event analysis. When considering these priors, one must acknowledge that the outcome used to generate the priors in both the multiple variable model (Chapter 4) and the expert belief elicitation study (Chapter 5) was more advanced IFALD (CB > 100 umol/L) than that utilized for the trial outcomes (CB > 50 umol/L). However, for both of these analyses, the median value for the prior and the likelihood were of similar magnitude which lends support to the appropriateness of these priors despite this limitation.

8.4 Implications

Although the pilot trial remains ongoing, with no plan to halt the trial on the basis of the interim analysis, likely the greatest issue that this thesis raises is what will the results of pilot trial mean for patients with IF?

If Group A, represents the active treatment (SMOFlipid®), would the results of the final analysis of the trial, provided that the treatment effect is maintained and that other outcomes are favourable, be sufficiently convincing to convince clinicians to adopt the therapy without further study? We suspect that, on the basis of the expert belief elicitation study, with 35% of experts already believing that an ω3FA approach can be routinely justified in those with IF prior to being aware of the trial outcomes, it is possible that such a study will alter practice. However, it is
important to note that the pilot trial is too small to adequately address the safety of the intervention, given possible rare adverse events.

On the other hand, should the conventional approach prove to be the more efficacious strategy, the results of the trial would significantly challenge the current understanding of the role of lipids in the pathophysiology of IFALD. The study would also highlight the need to evaluate therapies, despite their promise in uncontrolled studies, in the context of a randomized trial.

### 8.5 Future Research Directions

While the results of the ongoing pilot trial may provide evidence of efficacy for the ω3FA approach, the immediate research priority remains definitive trials of various strategies for the prevention of IFALD. As well, since the current pilot trial is examining a composite emulsion, that has both reduced ω6FA and additional ω3FA, a positive result does not necessarily mean that the addition of ω3FA is the reason for a beneficial effect. Therefore in concert with the clinical trials, animal models are required to investigate ILEs of varying composition and their role in the management of IFALD. These studies will also allow investigators to further delineate the mechanism of action of these therapies.

As evidence of the efficacy of either novel lipid based approach as a preventative strategy from clinical trials accumulates, trials directly comparing these strategies should be performed. In our expert belief elicitation study, there already appears to be evidence of equipoise in terms of expert opinion of the relative efficacy of the alternate approaches explored in this study. This may provide justification for a trial that would directly compare the ω3FA approach to lipid minimization.

We anticipate that early clinical trials will focus on short term outcomes. However, given the critical role that lipids play in growth and development, particularly of the central nervous system, subsequent studies should focus on the longer term outcomes. These outcomes should include the impact of the novel lipid based strategies on growth and cognitive development.
The bulk of the evidence to date for the novel lipid based approaches has focused on their impact on serum CB. Conjugated bilirubin is an important, yet imperfect biomarker, for clinically important outcomes. Therefore, future trials should also consider the impact of the novel lipid based approaches on these outcomes including liver failure resulting in death or the need for transplantation. Dynamic tests of liver function in IF patients may also play a role in assessment of the degree of hepatic dysfunction. Finally, the impact of novel ILEs on intestinal adaptation should be considered.

8.6 Final Thought

We believe that the optimal care of children with IFALD will be achieved through therapies that have been evaluated in well-designed randomized controlled trials. It is believed that the knowledge gained from this thesis will facilitate such studies. While this thesis focus on lipid based approaches, by demonstrating the feasibility and acceptability of the randomized design in the IF population and by developing expertise in this area, this thesis should also facilitate for trials of other therapies that may be beneficial to children with IF. These therapies may include those to reduce the risk of sepsis or approaches that may be useful for improving intestinal adaptation.
References


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Appendices
Appendix A. Code for Bayesian Model Selection Procedure

model
{
    sd[1] <- sd(sepsis[])
    sd[2] <- sd(lipid[])
    sd[3] <- sd(amino[])
    sd[4] <- sd(total[])

    for (i in 1:n)
    {
        c.sepsis[i]  <- (sepsis[i] - mean(sepsis[]))/sd(sepsis[])
        c.lipid[i]  <-  (lipid[i] - mean(lipid[]))/sd(lipid[])
        c.amino[i] <- (amino[i] - mean(amino[]))/sd(amino[])
        c.total[i]  <- (total[i] - mean(total[]))/sd(total[])
    }

    for (i in 1:n)
    {
        b100[i] ~ dbern(p[i])
        logit(p[i]) <- alpha + b[1]*c.sepsis[i] + b[2]*c.lipid[i] + b[3]*c.amino[i] + b[4]*c.total[i]
    }

    prior[1] <- 1/3
    prior[2] <- 1/3
    prior[3] <- 1/3

    k ~ dcat(prior[])
    alpha ~ dnorm(0.0, tau)
    tau <- 1
    tau.1 <- tau
    tau.2 <- 1000*tau.1

    for (j in 1:4) {
        del[j] <- delval[j,k]
        b[j] ~ dnorm(0,tau.b[j])
        #pick the spike or slab prior for b[j]
        tau.b[j] <- equals(del[j],1)*tau.1+equals(del[j],0)*tau.2
        beta.orig[j] <- b[j]/sd[j]
        best[j] <- equals(k,j)
    }

    delval[1,1] <- 1; delval[2,1] <- 1; delval[3,1] <- 0; delval[4,1] <- 0;
    delval[1,2] <- 1; delval[2,2] <- 0; delval[3,2] <- 1; delval[4,2] <- 0;
    delval[1,3] <- 1; delval[2,3] <- 0; delval[3,3] <-0; delval[4,3] <- 1;
}
Appendix B. Script for Belief Elicitation Study

Thank you for agreeing to meet with me. The purpose of this study is to document experts’ beliefs as to the efficacy of novel lipid based strategies for the prevention of Parenteral Nutrition Associated Liver Disease. I am a Surgical Resident and a PhD Clinical Epidemiology candidate. This study will form part of my PhD thesis work. This questionnaire includes 15 questions and will take approximately 25 minutes.

Your responses will be kept anonymous, and will only be used for research purposes. You have been assigned a unique identifier code which will be written at the top of your questionnaire. The code will be kept confidential. Your identity will be protected when the results of this study are published. If you do not wish to participate in this study, please feel free to decline. (For Sickkids participants: Participation or decision not to participate in this survey will not impact your professional relationship with the Hospital for Sick Children in anyway.) Are you agreeable to participation in this study?

*If no* - thank the participant for their time.

*If yes* - proceed to the example.

Before we begin the questionnaire, I have an example of what will be asked of you. For each scenario, we will be considering an average group of patients with the following clinical characteristics who are seen for evaluation of management by your intestinal failure program?

**Age** 0 – 12 months corrected gestational age

**PMHx** Abdominal Surgical procedure within the last 6-months, since which the child has received parenteral nutrition.

**Nutrition** 40-100% of calories obtained from parenteral nutrition

**PN macronutrient composition**

- **Fat:** 2 - 3g/kg/day
- **Protein:** 2 - 4 g/kg/day
- **Glucose:** 5 – 14 mg/kg/min

**Labs** Serum conjugated bilirubin 1-2 mg/dl (17-34 umol/l)
I am going to provide you with a laminated card, with these patient characteristics.

*Provide laminated card*

For the example, assume that you are seeing some of these patients during your November clinic. The first question that was asked is: In this hypothetical situation, what is the best estimate of the proportion of patients who will develop a viral respiratory infection within the next 60-days? In this example, the participant thought that the proportion of patients who would develop viral respiratory infection within the next 60-days was 20% so he put an X on the line at 20%.

The second question that was asked is: There may be some uncertainty around the estimate of the proportion who will develop a viral respiratory infection. Using an X in the interval, indicate the upper and lower limits of the estimate.

In this example, the participant put an X at 10% because he thought the probability could be as low as 10%. He put an X at 30% because he thought the probability could be as high as 30%.

The third question that was asked is that in the last question, the participant indicated a range for the probability of survival. However, he may believe in some proportions more than others. Using magnets that represent 5% probability, he was then asked to placed the magnets in the bins to indicate his weight of belief. Once the magnets are placed, you can see that it creates a shape and distribution. After you place the magnets, you will be asked to take a moment and check if the shape and distribution of your magnets placement reflects what you truly believe. If you feel that the placement of the magnets does not reflect what you believe, you will be able to rearrange your magnets until you are satisfied that the magnet placement reflects your true belief. I will then take a photograph of the distribution of your magnets prior to proceeding with the next question.

Do you have any questions?

*If yes – investigator to answer any questions. Once all questions have been addressed, then ask the participant to proceed.*

*If no – investigator to continue.*
For the following 3 scenarios you will be asked to estimate the proportion of patients who develop more advanced liver disease with various lipid treatments. For each scenario the specific structure of the 3 questions will be identical to those in the example.

When answering these questions remember you are considering an average group of patients with the following clinical characteristics who are seen for evaluation of management by your intestinal failure program?

- **Age**: 0 – 12 months corrected gestational age
- **PMHx**: Abdominal Surgical procedure within the last 6-months, since which the child has received parenteral nutrition.
- **Nutrition**: 40-100% of calories obtained from parenteral nutrition
- **PN macronutrient composition**
  - Fat: 2 - 3g/kg/day
  - Protein: 2 - 4 g/kg/day
  - Glucose: 5 – 14 mg/kg/min
- **Labs**: Serum conjugated bilirubin 1-2 mg/dl (17-34 umol/l)

In each scenario, I will ask you what proportion of this group will develop more advanced liver disease, then to provide me with the upper and lower limits of your estimate, and finally using the magnets to create a distribution of your belief.

Do you have any questions?

*If yes – investigator to answer any questions. Once all questions have been addressed, investigator to give the participant the study questionnaire.*

*If no – investigator to give the participant the study questionnaire.*

As you complete this survey, I will be here to assist you if you have any questions. I will read each of the questions aloud. Remember, the laminated card you have been given has the characteristics for the group of patients we are considering in each example.
Scenario 1

Assume that the patients continue to receive Intralipid as their parenteral lipid source without any changes to the macronutrient composition. Aside from gradual weaning of parenteral nutrition if the child demonstrates improved enteral tolerance no other changes are made to the care of this patient.

Question 1: In this hypothetical situation, what is your best estimate of the proportion of patients who will develop a serum conjugated bilirubin exceeding 6mg/dl (100 umol/l) within 3-months? Please indicate your answer by putting an X on the line.

Question 2: There may be some uncertainty around your estimate of the proportion who will develop a serum conjugated bilirubin exceeding 6mg/dl (100 umol/l). Using an X in the interval, indicate the upper and lower limits of your estimate.

Question 3: You have indicated that the lower boundary is X% and the upper boundary is Y%. I will place one 5% magnet at each of these bins. I will give you 18 more magnets, each of which represent 5% probability and totals 100%. Using these magnets, please indicate the weight of belief for your estimates of the proportion who will develop a serum conjugated bilirubin exceeding 6mg/dl (100 umol/l).

Do you have any questions?

If yes – investigator to answer any questions. Once all questions have been addressed, then investigator to continue.

If no – investigator to continue.

Once all the magnets have been placed:

Please take a moment to review the shape and distribution of your answer. Does this reflect what you truly believe? If not, please feel free to revise the magnet placement.

Do you have any questions?
If yes – investigator to answer any questions. Once all questions have been addressed, then
investigator to ask the participant to proceed to Scenario 2.

If no – investigator to ask the participant to proceed to Scenario 2.

Scenario 2

Assume that, at the time you evaluate the patient, the main lipid source is changed from
Intralipid to a lipid source containing a substantial source of omega-3 fatty acids although the
PN macronutrient composition is not changed (2-3g/kg/day). Aside from gradual weaning of
parenteral nutrition if the child demonstrates improved enteral tolerance no other changes are
made to the care of this patient.

Question 4: In this hypothetical situation, what is your best estimate of the proportion of
patients who will develop a serum conjugated bilirubin exceeding 6mg/dl (100 umol/l) within
3-months? Please indicate your answer by putting an X on the line.

Question 5: There may be some uncertainty around your estimate of the proportion who will
develop a serum conjugated bilirubin exceeding 6mg/dl (100 umol/l). Using an X in the interval,
indicate the upper and lower limits of your estimate.

Question 6: You have indicated that the lower boundary is X% and the upper boundary is Y%. I
will place one 5% magnet at each of these bins. I will give you 18 more magnets, each of which
represent 5% probability and totals 100%. Using these magnets, please indicate the weight of
belief for your estimates of the proportion who will develop a serum conjugated bilirubin
exceeding 6mg/dl (100 umol/l).

Do you have any questions?

If yes – investigator to answer any questions. Once all questions have been addressed, then
investigator to continue.

If no – investigator to continue.

Once all the magnets have been placed:
Please take a moment to review the shape and distribution of your answer. Does this reflect what you truly believe? If not, please feel free to revise the magnet placement.

Do you have any questions?

If yes – investigator to answer any questions. Once all questions have been addressed, then investigator to ask the participant to proceed to Scenario 3.

If no – investigator to ask the participant to proceed to Scenario 3.

**Scenario 3**

Assume that, at the time you evaluate the patient, you modify the lipid composition of the PN solution such that the range is <1 g/kg/day. However, the patient continues to receive Intralipid. Aside from gradual weaning of parenteral nutrition if the child demonstrates improved enteral tolerance no other changes are made to the care of this patient.

Question 7: In this hypothetical situation, what is your best estimate of the proportion of patients who will develop a serum conjugated bilirubin exceeding 6mg/dl (100 umol/l) within 3-months? Please indicate your answer by putting an X on the line.

Question 8: There may be some uncertainty around your estimate of the proportion who will develop a serum conjugated bilirubin exceeding 6mg/dl (100 umol/l). Using an X in the interval, indicate the upper and lower limits of your estimate.

Question 9: You have indicated that the lower boundary is X% and the upper boundary is Y%. I will place one 5% magnet at each of these bins. I will give you 18 more magnets, each of which represent 5% probability and totals 100%. Using these magnets, please indicate the weight of belief for your estimates of the proportion who will develop a serum conjugated bilirubin exceeding 6mg/dl (100 umol/l).

Do you have any questions?

If yes – investigator to answer any questions. Once all questions have been addressed, then investigator to continue.
If no – investigator to continue.

Once all the magnets have been placed:

Please take a moment to review the shape and distribution of your answer. Does this reflect what you truly believe? If not, please feel free to revise the magnet placement.

Do you have any questions?

If yes – investigator to answer any questions. Once all questions have been addressed, then investigator to ask the participant to proceed to Questions 10 and 11.

If no – investigator to ask the participant to proceed to Questions 10 and 11.

Please proceed to the following page and answer questions 10 and 11. Please ask me any questions that you may have.

Once questions 10 and 11 are completed ask, Do you have any questions?

If yes – investigator to answer any questions. Once all questions have been addressed, then investigator to ask the participant to proceed to Questions 10 and 11.

If no – investigator to ask the participant to proceed to Questions 10 and 11.

Please proceed to the following page and answer questions 10 and 11. Please ask me any questions that you may have.

Once questions 10 and 11 are completed ask, Do you have any questions?

If yes – investigator to answer any questions. Once all questions have been addressed, then investigator to ask the participant to proceed to Questions 12-15

If no – investigator to ask the participant to proceed to Questions 12-15

Please proceed to the following page and answer questions 12 to 15. Please ask me any questions that you may have.
Once questions 12 -15 are completed ask, Do you have any questions?

If yes – investigator to answer any questions.

If no – investigator to proceed to closing

After completion of the questionnaire:

Thank you very much for sharing your beliefs with us and participating in this study.

When the study is completed, we will email you the results of the study for your interest.

All of your responses will be kept anonymous. Thank you for your time.
Appendix C. Code for Low-lipid RR Calculation for a Subject

```r
PConv <- d[1,1:20]  
PConv <- PConv/sum(PConv)  
PLowLip <- d[1,41:60]  
PLowLip <- PLowLip/sum(PLowLip)  
PROBS <- seq(.025,0.975,by=0.05)  
P1 <- unlist(PLowLip)  
P2 <- unlist(PConv)  
B <- 100000  
eps <- 0.024  
sampleProb1 <- sample(PROBS,size=B, prob=P1, replace=T) + runif(B, -eps, eps)  
sampleProb2 <- sample(PROBS,size=B, prob=P2, replace=T) + runif(B, -eps, eps)  
RRO <- sampleProb1/sampleProb2  
RR[,1]<-RRO
```
Appendix D. Excerpt from SMOFlipid® Trial Protocol (Version 1.4)

**Trial Population**

**Trial Sites and Population**

This study shall be performed at the Hospital for Sick Children in Toronto, University of Calgary (Alberta Children’s Hospital/Foothills Medical Center - Qualified Site Investigator: Dr D Sigalet), McMaster Medical Centre in Hamilton (Qualified Site Investigator: Dr Peter Fitzgerald), and Stollery Children’s Hospital in Edmonton (Qualified Site Investigator: Dr Justine Turner). Other sites, including St Justine Hospital in Montreal (Qualified Site Investigator: Dr Valérie Marchand) may be added at a later date.

At the Hospital for Sick Children, neonates for this study will primarily be recruited from the patients in the Division of General Surgery and those followed by the GIFT (Group for Improvement of Intestinal Function and Treatment) team at the Hospital for Sick Children in Toronto. Approximately 20 incident cases of SBS per year are assessed by GIFT. It is anticipated that the majority (>80%) of incident cases referred to GIFT will meet criteria for participation in this study, and given the burden of liver disease in SBS, the absence of a “back door”, and potential benefits of the SMOFlipid®, most parents will agree to participate in the trial. It is therefore anticipated that enrolment of all of subjects can be achieved within 18-months.

Definition of SBS is controversial with a number of definitions suggested, based on both anatomic and functional characteristics. Traditionally, we have employed the definition espoused by the Canadian Association of Paediatric Surgeons namely that following resection of a portion of the gastrointestinal tract a child has ≤ 25th percentile of predicted bowel length for gestational age or those with >25th percentile of bowel length who remain on parenteral nutrition 42 days post-operatively. However, such a definition is unfeasible in the context of this trial for a number of reasons. First, accurate quantification of bowel length is infrequently available. Second, even when length is available it reflects the length measured at a prior time point and may not reflect the current length. Third, requiring 42 days of PN prior to a diagnosis of SBS may mean that some children may have a serum conjugated bilirubin higher than the range for consideration of participation in the trial. For these reasons, we will employ a clinical definition of SBS based on
the fact that an infant has had gastrointestinal surgery and remains on substantial PN support (≥ 40%) at the time that liver function develops. We will also include children who have medical causes of intestinal failure who are dependent on PN.

In order to exclude children from the trial who are close to being weaned from PN, we will require that, prior to enrolment; the treating physician informs the investigator that s/he believes that the patient will require PN for at least 3 weeks following enrolment. We will track, the actual subsequent duration of PN for those excluded by this criterion, as one of the pilot trial feasibility outcomes in order to ascertain the impact on subject accrual.

**Inclusion and Exclusion Criteria**

**Inclusion Criteria**

1. ≤ 24 months of age at enrolment
2. Evidence of early hepatic dysfunction
   a. Serum conjugated bilirubin ≥ 17 umol/L on 2 consecutive readings 7 days apart
      i. No evidence of sepsis
         1. Normal temperature (T between 35.5°C and 38.0°C)
         2. Normal leukocyte count
         3. Normal platelet count
         4. No systemic septic symptoms
      ii. No prior administration of Õmegaven®
3. ≥ 40% of total calories administered by PN
4. Meet one of the following diagnostic categories
   a. Short Bowel Syndrome
      i. Abdominal surgical procedure including gastroschisis/omphalocele closure by any means and percutaneous drainage procedures within the past 6 months and has been receiving PN since surgery
   b. Intestinal Failure
      i. One of the following diagnoses for which the child is dependent on PN
         1. Gastrointestinal Motility Disorder
         2. Mucosal Enteropathy
5. Expectation of the treating physician that the patient will require PN for at least 3 weeks following enrolment.
6. Parents willing to participate including randomization
**Exclusion Criteria**

1. Sepsis or Hemodynamic Instability of any cause.
2. Coagulopathy (Platelets ≤ 150 000, or INR ≥ 1.4)
3. Hypersensitivity to fish-, egg- or soy protein or to any of the active substances or excipients
4. Current enrolment in another clinical trial involving a surgical or pharmacologic intervention
5. Serum conjugated bilirubin > 50 umol/L
6. Hyperlipidaemia (any of)
   a. LDL ≥ 4 mmol/L
   b. HDL ≥ 2 mmol/L
   c. Total cholesterol ≥ 5 mmol/L
   d. Triglycerides ≥ 1.5 mmol/L
7. Treatment with intravenous N-Acetylcysteine or oral Ursodeoxycholic acid
8. Renal insufficiency
   a. Creatinine ≥ 80 umol/L
9. Disorders of Fluid Balance (any of)
   a. Serum Sodium < 130 mmol/L
   b. Serum Sodium > 145 mmol/L
10. Unstable conditions
    a. Acute pulmonary edema
    b. Decompensated cardiac insufficiency
    c. Severe post-traumatic conditions
    d. Uncompensated diabetes mellitus
    e. Acute myocardial infarction
    f. Stroke within 3 months
    g. Thromboembolic event within 3 months
    h. Metabolic acidosis
       i. Serum Bicarbonate < 17 mmol/L

**Methods of Recruitment**

Parents of eligible subjects will be informed of the study by a physician, dietician or nurse practitioner who is involved in their clinical care. If the parents are interested in learning more about the trial, an arrangement will be made for an investigator or study coordinator, who is not involved in the clinical care of the patient, to speak with them about the trial.

A log will be kept of all patients who are potentially eligible for the trial, and who are provided with information, as such information on all eligible subjects will be kept and we shall be able to accurately document rates of recruitment.
**Replacement of Subjects Dropping Out**

Subjects who drop out between the time that consent is obtained and randomization will be replaced. These subjects will be grouped with those who declined to participate in the trial for the purposes of the subject flow diagram.

Subjects who drop out between randomization and the end of their 12th day of trial lipid for reasons other than adverse events will also be replaced. The reason for the choice of the end of the 12th day of treatment, is that this time will occur prior to the 2nd week’s blood work, and as such by only replacing subjects who drop out prior to this time point, we shall limit bias that may be introduced by replacing subjects who drop out due to a perception of treatment efficacy. Data from these subjects will not be included in the data for analysis, although a log of their participation and reasons for termination will be kept and reported with the trial results.

Subjects who drop out or are withdrawn from the trial due to adverse events, will not be replaced, and the data from these subjects will be included as part of the analysis in an intention to treat manner.

**Allocation of Interventions**

**Methods for Randomization**

To prevent attrition from the time of consent to randomization, subjects will be randomly assigned to either the treatment (SMOFlipid® or Intralipid®) immediately prior to dispensing the first dose of study medication. Randomization will be done in blocks by the study pharmacist at The Hospital for Sick Children using a random number table generated by the pharmacy. The block size will be determined by the pharmacist and may be variable.

In the event that a subject drops out and is to be replaced, the “replacement” subject will be randomized without regard to the group that the participant they are replacing was assigned to.

For subjects enrolled at external sites, the study pharmacist at The Hospital for Sick Children will relay the group assignment to a research pharmacist at the subjects’ institution. This will be done in writing, by faxing or emailing the study pharmacist at the institution where the subject is being treated.
Methods for Concealment of Allocation

Only the study pharmacist at the Hospital for Sick Children will have access to the randomization sequence, and randomization will occur centrally for all subjects enrolled. As well, the study will be conducted in a multiple blind manner. Notification of treatment assignment will only be done at the conclusion of the entire study to maintain integrity of the randomization blocks.

The Intervention

Dosing

The PN solution will be formulated according to a nomogram (Figure 4-1) which takes into account the percentage of the subject’s caloric intake that they are taking parenterally. The specific parenteral to enteral mix will be at the discretion of the treating physician, but the PN shall be formulated according to the ranges on the nomogram as adjustments are made. The minimum PN intake for consideration of enrolment in the trial is 40% of caloric intake; however, with development of enteral intake, the subject may receive less than this level during the trial.

The PN solution will be infused continuously over 12-24 hours by the infusion pump. The duration of PN support each day will depend on the enteral tolerance of the child, and shall be at the discretion of the treating physician. However, orders for PN shall be only written by one of the qualified investigators, unless the pharmacy is provided, in writing, with a list by the PI of qualified individuals (Physicians, Registered Dieticians or Advanced Practice Nurses) to whom they have delegated this task.

Since both SMOFlipid® and Intralipid® are 20% lipid solutions, they contain the same lipid concentration per volume. Therefore, enrolment in the trial will not require any adjustments to the infant’s total fluid intake which shall be established at the discretion of the treating physician.

Management of Enteral to Parenteral Mix

Over the course of the trial, it is anticipated that there will be adjustments made to the enteral and parenteral mix. These adjustments may involve both increases and decreases in the proportion of parenteral to enteral intake, and shall be done at the discretion of the treating physician based on
the clinical needs of the subject. Each time a change is made, the specific formulation of the various components of the PN solution shall be established by the ranges specified on the nomogram (Figure 6-1). If a clinician does not feel that the suggested dosing on the nomogram is appropriate for the degree of PN the child is receiving, they shall provide the PI with the reasons for this in writing, and it shall be at the PI’s discretion whether the subject will be allowed to continue as part of the trial, or if they should be withdrawn.

**Enteral Feeds**

Management of Enteral Feeds, including choice of feeds, timing of the adjustment of the enteral feeds, ratio of enteral to parenteral feeds will be at the discretion of the treating physician. The only formula that is not allowed while on trial is a pure ω3FA enteral lipid solution.

PN shall not be discontinued, unless the patient is taking 95% of calories enterally with good tolerance and growth as evidence by appropriate weight gain. This will be determined by the treating physician in consultation with the trial/qualified site investigator.

Enteral tolerance and specific formula utilized shall be tracked throughout the trial. In the analysis and interpretation of the data, consideration will be given to the ω3FA content received via the enteral route.

**Administration**

The intravenous study lipid will be administered as part of a PN solution, although the lipid and amino acid / glucose components shall be administered in separate containers. The amino acid solution to be used will be Primene® 10% (Baxter). The concentration of the amino acid and glucose component of the parenteral nutrition solution shall be determined by the nomogram (Figure 4-1) for the subjects’ percent parenteral intake. Addition of vitamins, minerals, and micronutrients to the PN shall be not be standardized, although all PN solutions shall be manganese free. Excessive Vitamin E shall also not be added. During administration a 1.2 micron filter will be placed on the intravenous line between the PN solutions (lipid and amino acid / glucose) and the patient.
All Intralipid® shall be acquired and dispensed from the pharmacy at the site that the subject is enrolled at or via the homecare pharmacy for subjects who go home on PN while still on the trial. Since this product forms part of routine clinical care, the costs for inpatients shall be borne by the regular mechanisms for acquiring this lipid. All SMOFlipid® will be acquired from the manufacturer (Fresenius Kabi) and dispatched from the manufacturer to the dispensing pharmacy as “unblinded lipid”.

It is anticipated that the vast majority of participants in the trial will be inpatients. However, in the event that a patient is discharged during the study period, the investigator in concert with the pharmacy at the institution that the subject is enrolled at will co-ordinate with the home PN pharmacy and supply study lipid in order that the patient can continue in the trial. Subjects will only be discharged home, following extensive parenteral education, as is normal practice for patients on home PN.

The pharmacy at the site which the subject is enrolled will notify the home PN pharmacy of the group to which the subject is assigned at least 7-days prior to the patient being discharged home. The pharmacy at that site will arrange for the home PN pharmacy to collect sufficient lipid (Intralipid® or SMOFlipid®) for the remainder of the subject’s participation in the trial, with a 5 day excess to account for breakages etc. Such lipid will be sequestered by the home PN pharmacy and be exclusively used for the intended subject while on the trial with remaining lipid being destroyed following the end of the subject’s trial participation. In the event that Intralipid® is sent to the home PN pharmacy, the pharmacy at the site which the subject is enrolled will invoice the principal investigator for the Intralipid® on a cost recovery basis. To avoid unblinding, such billing shall occur no sooner than 1-month following the subject’s final day on trial lipid. The pharmacy at the Hospital for Sick Children will supply the home PN pharmacy with the necessary documentation to ensure regulatory compliance as well as templates for labels for use on the blinded lipid bags.

Blinded lipid bags as well as the PN glucose/amino acid solution, will be delivered to the subject’s home by the home PN pharmacy as is usual practise. Frequency of delivery will be at the discretion of the home PN pharmacy, but will occur at least every 7 days. When delivered, the PN solutions will be stored in a fridge until administration as is routinely done in home PN patients.
In general, only sufficient volume of PN solution for administration with minimal overfill is provided in the PN bags for use at home, and this practice will continue so that there will be minimal residual lipid following each day’s administration. Residual PN solutions will be disposed of together with the PN container in the manner that patients at home typically discard these items.

Parents of subjects of home PN will be provided with a “flowsheet” that will be used to record data on volumes of PN infused, issues with administration, weights, inputs and outputs. The flowsheet will also have a section to document disposal of the residual trial lipid solution after each dose is administered. These flowsheets will form part of the trial record. For subjects who are managed at home, data on the case report forms will be collected either by telephone or by visit to the hospital (minimum frequency q 4 weeks). Bloodwork will be performed either at an external laboratory or at the site at which the subject is enrolled for routine blood work and at the site at which the subject is enrolled for “special trial blood work”.

The degree to which patients are discharged during the trial, as well as feasibility of coordination with home PN pharmacies will be tracked as pilot trial outcome measures. These outcomes are critical to understand, as it is likely that in a subsequent trial of longer duration, there will likely be a significant number of subjects who will be discharged still on PN, and such coordination will be necessary for the success of that trial.

**Blinding**

The lipid shall be administered in a blinded manner, with all participants, treating clinicians and investigators being blinded to the treatment assignment. Only the study pharmacist at the Hospital for Sick Children and the research pharmacist at the subject’s own institution or the home PN pharmacist will be aware of the group to which the subject is assigned. In order to maintain integrity of the randomization sequence and to avoid premature analysis of the data, next of kin or legal guardians of subjects will not be informed of the lipid to which they were assigned until the conclusion of the entire trial.

Blinding will be done at the time the lipid is dispensed by the pharmacy and shall be achieved by using an identical container (60cc Monoject or B-D Luer Lock syringe or Baxter All-In-One Empty EVA bags) for the lipid solution. The lipid will be administered as a stand-alone solution
without any additions, with the carbohydrate and amino acid solutions together with the micronutrients being provided in a separate infusion bag/syringe.

In the event a syringe is used, trial parenteral lipid will be placed in the syringe on the day that the product is to be used, and an expiry no longer than 36 hours after the syringe is prepared shall be placed on the container. In the event that an EVA bag is used, an expiry date no longer than 8-days after the bag is prepared shall be placed on the container.

Unused lipid will be discarded by the nursing staff in an incineration bag or in the garbage as is usual practise for subjects who receive trial PN at home.

**Duration of Treatment**

Subjects will be treated with study lipid for a maximum of 12 weeks at which time they will resume Intralipid® at the same dose as the lipid used during the trial.

However, if a patient develops a sustained conjugated hyperbilirubinaemia >100 umol/L, for at least 14 days, they will be withdrawn from the trial. The rationale behind this is to allow for the patient to be considered for alternate therapies such as Omegaven®. Subjects who develop full tolerance of enteral feeds and have their PN stopped will end the trial at the point that the PN is stopped.

**Co-intervention and Contamination**

Since the majority of patients will be in-patients for the duration of the trial, it is unlikely that enteral ω3FA lipids will be administered. In the event that subjects are discharged, parents will be made aware that enteral ω3FA lipids should not be administered. Other hepatoprotective strategies, such as treatment with intravenous N-acetylcysteine or oral Ursodeoxycholic acid, will be prohibited during the trial. Neither have definitive evidence of efficacy or are considered to be standard of care. Other treatments, common in infants with SBS such as use of prokinetics, antidiarrheals and oral antibiotics for gut decontamination, should not impact the outcome of the trial, and as such will be allowed, however, their use will be tracked.

In the event that a patient in the trial undergoes a surgical procedure, the PN will be held during the immediate peri-operative period as is the standard procedure. This is typically done for the hours immediately preceding the operation, the time within the operating room, with the PN
resuming post-operatively. However, once the PN is resumed, the child will resume the trial PN solution. The nature of the operation will be tracked on the weekly datasheet, and also any missed doses of PN shall be recorded on the weekly trial data capture sheet.

**Outcome Assessment**

*Outcome Measures Specific to Pilot Study*

Pilot trial outcome measures will be tracked continuously through the trial, with a formal analysis of recruitment at 4, 12, 18 and 24 months following the initiation of the study. A recruitment log will be kept, at each centre, of all patients who were screened but who did not enrol in the study, with the reasons for non-enrolment recorded in this log.

If, at 18 months from full approval of the trial at the Hospital for Sick Children, there are less than 16 patients recruited and enrolled, no further enrolment will take place, and the trial will be terminated once all subjects already enrolled have completed their assessment and data will be analyzed. For the purposes of this recruitment target, cases who meet the criterion for early replacement will not be included in the count of enrolled subjects.

Furthermore, no additional enrolment will take place 24-months after full approval of the trial at the Hospital for Sick Children. The rationale behind these criteria are that the overall aim of the study is to pilot the intervention, with data obtained from this trial to be used to design a definitive trial. As such, prolongation of the pilot due to poor enrolment cannot be justified; rather these issues need to be taken into account in designing a more definitive trial that will likely need to be extended to other centres.

Compliance with study protocols will be assessed by reviewing the clinical records following completion of the first 4 patients, and again following 12 patients, and at the completion of the study. At least one site visit per external centre that enrolls patients will also be planned to ensure consistency of application of the trial protocol across the centres. During these visits, data quality checks will be done by comparing the data entered on the study datasheets with information in the clinical records.
Assessment of Clinical Outcome Measures

The objective of tracking these clinical outcome measures is primarily so that estimates of efficacy can be determined. These data will be critical in designing a more definitive trial.

Primary Clinical Outcome

The primary clinical outcome will be mean serum conjugated bilirubin (umol/L) at trial completion.

Secondary Clinical Outcomes

Secondary clinical outcomes will include: proportion with the development of cholestasis (sustained serum conjugated bilirubin >50 umol/L for greater than 2 weeks in absence of sepsis), proportion with progression of liver disease (sustained serum conjugated bilirubin >100 umol/L), degree of enteral tolerance (%), and growth parameters.

Other Biochemical Outcomes

Other biochemical outcomes shall include assessment of mean levels of “hepatic markers” (AST, ALT, ALP, GGT), coagulation parameters (PT, PTT, INR, platelets, serum lipid levels (triglycerides and cholesterol), serum albumin, and nephelometry (measure of lipid clearance).

Immunologic Outcomes

Immunologic outcomes shall include assessment of RBC phospholipids composition, C-reactive Protein (CRP) and serum immunologic marker (IL-1b, IL-2R, IL-6, IL-8, IL-10, TNF-α) assessment.

Safety Outcomes

Safety outcomes shall include assessment of adverse events.
Timing of Outcome Assessment

Data will be collected weekly during the trial for “routine” clinical and biochemical trial outcomes with “special” biochemical outcomes assessed at baseline (week 0), 6 weeks after starting the trial lipid, trial conclusion (12 weeks in most cases) and 4 weeks after completion of the trial (week 16). The rationale behind the 4 week post-trial measurement is to assess for durability of response, as well as to obtain additional safety data.

In the event that a subject stops parenteral nutrition prior to week 12 or if the study medication is stopped early because of development of a serum bilirubin >100 µmol/L, then the “special” outcomes which would normally be done at week 6 or 12 will be done the week the study lipid or PN is stopped. The patient will then enter the “Post-study phase” and the post-trial assessment will be done 4 weeks after stopping the study lipid or PN.

The outcomes that are considered “routine” trial outcomes that will be collected at baseline and then weekly while on the trial and once at 4 weeks following trial completion include: serum bilirubin, electrolytes, albumin, AST, ALT, ALP, GGT, Total Fluid Intake, Type of enteral feed, % enteral intake, % stool output, weight, length, and head circumference (week 0, 6, 12, and 16 only). A complete blood count will be done at weeks 0, 4, 8, 12, and 16 and an INR at weeks 0, 6, and 12 and 16. These items all constitute components of the routine care of infants with SBS who are on parenteral nutrition. The frequencies of the blood-work, are at or below the frequency that are done for clinical care; as such the treating clinician may perform these tests more frequently than required for the trial. However, these additional test results will not be recorded unless they meet the definition of an adverse event.

The outcomes that are considered “special” trial outcomes and will be measured at baseline, 6 weeks, trial completion, and 4 weeks post completion include: RBC phospholipids, CRP, Serum Immunologic Markers (IL-1b, IL-2R, IL-6, IL-8, IL-10, TNF-α), and Nephelometry (“Intralipid level” - measure of lipid clearance), Serum Cholesterol and Serum Triglycerides. The total volume of blood to be taken each time will be 4cc (2.5cc for CRP, immunologic markers, Intralipid, Cholesterol and Triglycerides and 1.5cc for the RBC phospholipid levels).

In general, all biochemical outcomes will be assessed on the same day each week for each subject with whenever possible serum being sampled in the morning. Clinical outcomes will also
be captured that day. However, in order to avoid additional blood-work, if a child had blood-
work within 48 hours that measured the same parameters as required by the trial, the results from
that blood-work may be used. Similarly, trial blood-work may be advanced/delayed by 48-hours
for clinical reasons (e.g.: a neonate who requires multiple blood-tests). However, for the
purposes of the baseline blood-work, all blood-work must occur prior to the subject starting on
the trial lipid. Similarly, all week 12 (final week) blood-work must occur prior to the subject
resuming Intralipid®. Lipid levels (Cholesterol and Serum Triglycerides) done within a week of
enrolment to ensure eligibility may be used as the subjects baseline assessment for those
parameters. In the event that these bloods have already been done, the 2.5cc of blood that is
usually drawn for CRP, immunologic markers, Intralipid, Cholesterol and Triglycerides can be
reduced to 2 cc as the Cholesterol and Serum Triglycerides will not be measured on that sample.
Similarly, in the event that an external site runs Cholesterol and Serum Triglycerides at another
study time point (i.e.: week 6, 12, or 16), then the volume of “special” blood drawn will be
reduced to 2cc from the usual 2.5cc for CRP, immunologic markers, Intralipid, Cholesterol and
Triglycerides.

All adverse events will be entered into an adverse event log every time a child suffers any
adverse event whether or not it is believed to be related to the subjects’ participation in the trial.
All adverse events will be reviewed by the principal investigator and the DSMB, as will be
described in the safety section of the protocol.

Analysis of Laboratory Measures

All laboratory measures with the exception of the “special” trial blood work will be measured at
the child’s home institution. However, external sites have the option to measure Cholesterol and
Triglycerides at their site, or to have the analysis done at the Hospital for Sick Children. In the
event that the analysis of Cholesterol and Triglycerides is done at the external site, the volume of
blood drawn/serum shipped to The Hospital for Sick Children will be reduced as previously
described. While analysis of the samples will be done at The Hospital for Sick Children, when
the “special” trial blood work; is drawn, the blood will be spun and separated at each site and red
blood cells and serum will be frozen and stored at -70C with batch shipments made to the
Hospital for Sick Children. The “special” trial blood work will be analyzed centrally in the
Department of Paediatric Laboratory Medicine at The Hospital for Sick Children in batches.
The RBC phospholipids will be analyzed in the laboratory of Dr Tom Clandinin at the University of Alberta in Edmonton in batches.

**Safety Monitoring**

**Data and Safety Monitoring**

An independent DSMB (Data Safety Monitoring Board) shall be constituted with composition including a paediatric surgeon, a paediatrician with expertise in nutrition and gastroenterology, and a biostatistician. All members of the DSMB shall be independent from the trial to the extent that they are not investigators, nor shall be included in any publications arising from the trial.

The DSMB will meet to review the records of the first 4 subjects within 6 weeks of the 4th subject’s post-trial assessment. The DSMB will convene again within 6 weeks of the 14th subject’s post-trial assessment to review selected records of subjects up until that point. No further scheduled meetings will be held, although a meeting of the DSMB can be called to meet by any DSMB member or by one of the investigators. The chair of the DSMB shall submit a brief report to the REB at the Hospital for Sick Children within 10-days of each meeting.

Adverse event datasheets will be reviewed by the DSMB at their discretion as well as on request of the PI. To facilitate review, the DSMB members shall be provided monthly with a de-identified listing of all unexpected adverse events as well as any expected but serious adverse events, unless required sooner under the SickKids guidelines as described below. The DSMB may request further information from the investigators, and the DSMB shall have the authority to request the group assignment of a particular patient from the study pharmacist, and to halt the trial due to safety concerns. The DSMB however, will not have the authority to halt the trial for perceived benefit, and shall only be able to request an interim analysis in the event that harm of SMOFlipid® treatment is suspected.

In the event that the trial is terminated or unblinding of any subject occurs, the trial funder will be informed within 3 days.
Adverse Events Definitions

Adverse Event (AE)

An Adverse Event is any unfavourable or unintended clinical or other occurrence during the study period that may or may not be the result of participation in the research study. The ICH-Drug trial definition of AE will be employed namely any untoward medical occurrence

- In a patient or clinical investigation subject
- Following administration of a product or use of a medical device
- The event need not necessarily have a causal relationship with the treatment or usage.
- Includes adverse reactions which are a noxious and unintended response to a medicinal product or to a medical or surgical device.

Examples of Adverse Events include;

- Clinically significant signs and symptoms
- Abnormal test findings e.g., laboratory, x-ray, ECG
- Mild reactions or side effects that do not require treatment intervention e.g., mild skin rash, mild headache, slight nausea
- A study interview that causes an unexpected emotional reaction
- Complaints about alleged research misconduct

Each Adverse Event can be classified according to severity or intensity and in relation to the study treatment;

Intensity Grades

- Mild: Does not interfere with subject’s usual function
- Moderate: Interferes to some extent with usual function
- Severe: Interferes significantly with usual function
Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence that:
- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
  - Is a congenital anomaly/birth defect
- Includes serious adverse reactions to drugs

Serious Unexpected Adverse Drug Reaction (S-UADR)

A S-UADR is a serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out in the investigator’s brochure or on the label of the drug.

Related Adverse Event

A Related Adverse Event is any AE or SAE that in the professional opinion of the investigator, treating physician, or member of the DSMB is the result of participation in the trial. Related Adverse Events in the context of a drug trial such as the current study are termed Adverse Drug Reactions (ADR). Related Adverse Events may then be further classified to be expected or unexpected on the basis of the listing contained in the protocol below. Note that unexpected and related serious adverse events will meet the criteria for a S-UADR as defined above.

Expected Adverse Events

Expected Adverse Events are those adverse events which are listed below and can be classified as those which are unrelated to the experimental treatment and related i.e.: those which may be attributed to the PN lipid.
The Expected Adverse Events in patients with SBS unrelated to PN or the experimental treatment include:

1. Septic episodes (intra-abdominal collections, wound, intravenous site, skin, urosepsis, pneumonia) including progression to severe sepsis which may necessitate admission to a critical care unit
2. Bowel obstructions/ileus
3. Nausea or vomiting
4. Fistula formation
5. Stoma problems
6. Dumping/Diarrhoea
7. Anastomotic leaks
8. Wound problems (e.g.: dehiscence, incisional hernias)
9. Anaemia
10. Elevated markers of Inflammation (e.g.: CRP)

The Expected Adverse Events in patients with SBS related to PN but unrelated to the experimental treatment include:

1. Septic episodes (line sepsis, bacteremia) including progression to severe sepsis.
2. Line complications (thrombosis, breakage, dislodgement, extravasation)
3. Fluid, acid-base, electrolyte and mineral disturbances
4. Volume overload (edema, pulmonary edema)
5. Hypo/Hyperglycaemia
6. Malnutrition/Failure to Thrive

The Expected Adverse Events which may be attributed to the PN lipid include:

1. Liver disease (including hemorrhage from portal hypertension)
2. Hyperlipidemia
3. Transient elevations in serum lipid components
4. Fat overload syndrome
5. Temperature Instability
6. Chills
7. Hypotension
8. Hypertension
9. Nausea, vomiting
10. Anorexia
11. Headache
12. Back or chest pain with dyspnea
13. Cyanosis
14. Hypersensitivity reactions including anaphylaxis

**Adverse Event Reporting Requirements**

Adverse event reporting will adhere to The Hospital for Sick Children’s adverse event (AE) reporting requirements as well as Health Canada’s regulations. Definition and Grading of the event will be done according to the definitions noted above.

A qualified investigator will assess and grade the severity of the AE or ADR and document the results in the patient’s case record form and health record. In event of an unexpected AE or ADR occurring at an external site, the qualified site investigator shall be responsible for notifying the principal investigator as soon as possible but no later than 48-hours of becoming aware of such. The responsibility for notifying the local REB shall fall on the qualified site investigator within the time frame established by that REB.

If an unexpected SAE (S-UADR) occurs, the principal investigator/study sponsor will notify the SickKids Research Ethics Board, SickKids Clinical Research Monitors and Data Safety Monitoring Board, Health Canada, and the patient’s physician within the required time frame as specified below. For non-serious unexpected adverse events, the principal investigator will notify the SickKids Research Ethics Boards, SickKids Clinical Research Monitors and Data Safety Monitoring Board, and the patient’s physician within the required time frame as specified below.

**Reporting to the SickKids REB**

In reporting adverse events, the investigator shall:

Report all local unexpected adverse events (not just unexpected, *serious* events) on the standard REB AE reporting form.
Report all unexpected serious drug reactions experienced at study sites external to SickKids.

When follow-up reports are necessary, they must be clearly indicated as such on the AE form. The initial report should be appended to the follow-up report to facilitate review.

For unexpected adverse events, investigators are obliged to inform the REB, in addition to their clinical chief within 7 days of learning of the event.

For unexpected serious adverse events, investigators are obliged to inform the REB, in addition to their clinical chief immediately i.e., within 48 hours of learning of the event (by AE form, telephone or email) even if the information is incomplete. A complete follow-up AE report should be submitted as soon as possible but no later than 7 days after the initial reporting.

Report all AEs that fall under these guidelines to the members of the DSMB within the timeframe required for REB reporting.

**Reporting to the Participant’s Physician**

All AE and SAEs shall be reported to the clinician who has primary responsibility for the participant no later than 48-hours after the investigator becoming aware of the AE.

**Reporting to Health Canada**

All S-UADRs occurring in the context of this trial (both inside and outside of Canada) are subject to expedited reporting to Health Canada.

These include reactions;

- Where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information

- A complete follow up report within 8 days which includes an assessment of the importance and implication of any findings including relevant previous experience with the same or similar drugs

- Where it is neither fatal nor life-threatening within 15 days after becoming aware of the information
Each ADR which is subject to expedited reporting should be reported individually in accordance with the data element(s) specified in the Health Canada/ICH Guidance Document E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

**Reporting to the Manufacturer**

All S-UADRs, related but expected SAEs, and unexpected AEs related to the study medication (SMOFlipid® or Intralipid®) will be reported to Fresenius Kabi, the manufacturer of both products, no later than 3 days after becoming aware of the information. All remaining adverse events and all other safety information relevant, will be reported to Fresenius Kabi at the conclusion of the trial.

**Data Collection and Management**

**Responsibility for Data Collection**

The responsibility for data entry shall fall to the principal investigator for subjects enrolled at the Hospital for Sick Children, and to the qualified site investigator at external sites. The investigator may designate a data entry co-ordinator. Training for that data co-ordinator will be done by the Principal Investigator or his delegate. Ongoing support and monitoring with respect to data collection and completion will also be done by the Principal Investigator or his delegate.

**Data Collection**

Data will be collected on paper Case Report Forms (CRFs) created for the study. Each subject will be identified by a unique study ID in the database that will not allow identification of the subject. A master list of subject names / IDs will be maintained by the qualified site investigator at each site participating in the study. The research pharmacy shall also have access to the list of subject names/study IDs for purposes of randomization and dispensing study lipid.

Relevant study records will be archived for 25 years following completion of the study, as per the requirements of the Food & Drug Act, Division 5. Once the study is complete and the final report has been published, the records will be retained and destroyed in accordance with the SickKids Record Retention and Destruction policy.
Each external centre shall fax their datasheets to a secure fax line at the Hospital for Sick Children weekly. In the event that a site misses ≥ 2 weeks of data on a subject, or has significant missing fields on a patient on more than 2 occasions, no further enrolment will occur at that site until such a time that the data on the subjects that are already enrolled and the issues behind the data capture problems are addressed.

External sites will only have access to the patients enrolled at their center. The investigator group at the Hospital for Sick Children and members of the DSMB shall have access to records of all subjects enrolled in the trial.

**Data Quality Control**

Data will be entered into a secure database designed for the purposes of the study. Consistency checks will be performed during data entry and warnings will be displayed. The data will be checked to make certain that entered values are acceptable, and that all required fields are entered. After initial entry of the data, modifications shall be recorded, including identifying information about the person who made the update, the date, changed values, and comments.

Random checks will be done throughout the trial to ensure accuracy of the data on the CRFs. These checks will be done at the same time as the protocol compliance checks after subjects 4, 12, and 20, with additional checks done randomly throughout the study and particularly during visits to other sites enrolling patients.
Appendix E. Code for Bayesian Analysis of Treatment Efficacy

**Linear Regression Analysis with an Uninformative Prior**

```r
model {

  for (i in 1:13) {

    CBf[i] ~ dnorm(final[i], tau)
    final[i] <- beta0 + beta1 * group[i]
  }

  beta0 ~ dnorm(0, tau.op)
  beta1 ~ dnorm(0, tau.rx)

  tau ~ dgamma(0.01, 0.001)
  tau.op <- 1/(sd.op*sd.op)
  sd.op <- 100
  tau.rx <- 1/(sd.rx*sd.rx)
  sd.rx <- 100

  prob.g60 <- (1 - step(beta1 + 60))
  prob.g30 <- (1 - step(beta1 + 30))
  prob.g0 <- (1 - step(beta1))
}
```
Analysis of Covariance with an Uninformative Prior

model {

  for (i in 1:13) {
    CBf[i] ~ dnorm(final[i], tau)

    final[i] <- beta0 + beta1 * group[i] + beta2 * CBp[i] + beta3 * wk[i] + beta4 * enc[i]
  }

  beta0 ~ dnorm(0, tau.op)
  beta1 ~ dnorm(0, tau.rx)
  beta2 ~ dnorm(0, tau.op)
  beta3 ~ dnorm(0, tau.op)
  beta4 ~ dnorm(0, tau.op)

  tau ~ dgamma(0.01, 0.001)
  tau.op <- 1/(sd.op*sd.op)
  sd.op <- 100
  tau.rx <- 1/(sd.rx*sd.rx)
  sd.rx <- 100

  prob.g60 <- (1 - step(beta1 + 60))
  prob.g30 <- (1 - step(beta1 + 30))
  prob.g0 <- (1 - step(beta1))
}

**Linear Random Effects Model**

model {

for (i in 1:116) {

    CB[i] ~ dnorm(CBt[i], tau1)

    CBt[i] <- alpha[ID[i]]
    + beta[ID[i]]*time[i]
    + beta.gp*gp[i]
    + beta.gptm*(time[i]*gp[i])

}

for(j in 1:15){

    alpha[j] ~ dnorm(alpha0, tau.alpha)
    beta[j] ~ dnorm(beta0, tau.beta)

}

tau.alpha <- 1/(sd.alpha*sd.alpha)
tau.beta <- 1/(sd.beta*sd.beta)
sd.alpha ~ dunif(0,30)
sd.beta ~ dunif(0,30)

tau1<-1/(sd1*sd1)
sd1~dunif(1, 40)

alpha0 ~ dnorm(0, tau2)
beta.gp ~ dnorm(0, tau2)
beta0 ~ dnorm(0, tau2)
beta.gptm ~ dnorm(0, tau2)
tau2<-1/(sd2*sd2)
sd2<-36.25
prob.rx <- (1 - step(beta.gptm))

}
Time to Event Model

model{
  for(i in 1:15) {
    time[i] ~ dweib(r, mu[i])l(cens[i],)
    log(mu[i]) <- beta1 + beta2*group[i]
  }

  #prior on shape parameter
  r ~ dexp(0.001)

  #priors on regression parameters
  beta1 ~ dnorm(0.0, 0.001)
  beta2 ~ dnorm(m, v)
  v <- 1/(sd*sd)
  sd <-
  m <-

  #values for uninformative: m = 0, sd = 36.12
  #values for informative: m = -0.84, sd = 0.97
  #values for optimistic: m = -1.68, sd = 1.05
  #values for sceptical: m = -0.12, sd = 0.4

  HRgp <- exp(beta2)
  p.eff <- 1 - step(HRgp - 1)
  p.eff5 <- 1 - step(HRgp - 0.5)

}
**Logistic Regression**

model
{
  for (i in 1:15)
  {
    b50[i] ~ dbern(p[i])
    logit(p[i]) <- alpha + b1*gp[i]
  }
  b1 ~ dnorm(m, t)
  t <- 1/(sd*sd)
  m <-
  sd <-
    # Uninformative prior: m = 0, sd = 36.25
    # Informative prior: m = 1.654, sd = 0.6871
  alpha ~ dnorm(0.0, 0.001)
  ORrisk <- exp(b1)
}
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**Figure 2-1** - From Diamond IR, Sterescu A, Pencharz PB, Wales PW. The Rationale for the Use of Parenteral Omega-3 Lipids in Children with Short Bowel Syndrome and Liver Disease. Paediatric Surgery International. 2008; 24: 773-8. Reprinted with permission of Springer, New York, NY.

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