Evaluation of the long-term use of soybean oil, medium-chain triglyceride, olive oil and fish oil in patients requiring home parenteral nutrition

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Abbreviations

ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ASPEN	American Society for Parenteral and Enteral Nutrition
BMI	Body Mass Index
BAPEN	British Association for Parenteral and Enteral Nutrition
CINAHL	Cumulative Index to Nursing and Allied Health Literature
ESPEN	European Society for Clinical Nutrition and Metabolism
GGT	Gamma Glutamyl Transferase
HPN	Home Parenteral Nutrition
IFALD	Intestinal Failure Associated Liver Disease
LFT	Liver Function Test
NAS	Non-Alcoholic Fatty Liver Disease Activity Score
NICE	National Institute for Health and Care Excellence
PN	Parenteral Nutrition
PNALD	Parenteral Nutrition Associated Liver Disease

Abstract

Background: Intestinal Failure is a rare form of organ failure which necessitates life sustaining intravenous parenteral nutrition. Lipid emulsions are an important component of parenteral nutrition and include essential fatty acids. Abnormal liver function is common in those receiving long-term parenteral nutrition and can be associated with sustained abnormalities including chronic cholestasis, which can lead to extensive fibrosis and cirrhosis. The causes of Intestinal Failure Associated Liver Disease (IFALD) are multifactorial and include parenteral lipid emulsions. IFALD is both treatable and potentially reversible. A wide variety of parenteral nutrition lipid emulsion formulae are available, though there is a dearth in long-term studies comparing effectiveness in adults.

Aims: To determine the effectiveness of treatment strategies for IFALD in adults. To determine whether the fourth generation soybean oil, medium-chain triglyceride, olive oil and fish oil intravenous lipid emulsion (SMOFlipid®) in home parenteral nutrition is associated with more effective clinical outcomes compared to alternative lipids in adults with Intestinal Failure.

Methods: A systematic review was undertaken to evaluate the effectiveness of strategies to treat IFALD in adults. Studies published between 1970 and 2018 were identified from six bibliographic database platforms: AMED, British Nursing Index, CINAHL, EMBASE, Medline, Web of Science. The Joanna Briggs Institute Critical Appraisal tools were used to assess quality of methodology and potential bias. A single-centre, retrospective cohort study was completed on a sample of adults with Intestinal Failure who received home parenteral nutrition between 1st April 2011 to 31st March 2015. A database of all individuals who received home parenteral nutrition was reviewed. SMOFlipid® was compared with a comparator lipid consisting of either soybean oil, or olive oil combined with soybean oil. Individuals were stratified into two groups based on lipid received over 12 consecutive months. Statistical analysis was completed on SPSS (IBM version 23). Outcomes sought included liver dysfunction, risk of chronic cholestasis, tolerability and clinical signs of essential fatty acid deficiency.

Results: Nine studies, comprising of six case reviews and three intervention studies, were included in the systematic review which found very low quality evidence associating second, third and fourth generation lipid formulae with improved outcomes in adults with IFALD. The studies in the systematic review did not clearly define the clinical parameters which demarcate IFALD. A total of 179 individuals were included in the retrospective cohort study. Gender distribution was 104 (58.1%):75 (41.9%) females to males. Mean admission age 54.58 years (SD 15.21). Only 99 individuals received the same lipid over 12 consecutive months and there were no differences at baseline in gender, admission age, initial primary diagnosis, classification of Intestinal Failure, chronic cholestasis or liver function between in the SMOFlipid® group (n=37) and the comparator lipid group (n=62). At 12 months, those in the SMOFlipid® group did not differ from those receiving comparator lipids in terms of chronic cholestasis prevalence and incidence (p=0.466; p>0.999), liver function (ALP p=0.912, GGT p=0.953, bilirubin p=0.916, ALT p=0.141), mean change in liver function (ALP p=0.273, GGT p=0.373, bilirubin p=0.280, ALT p=0.273), line sepsis (p=0.195) and change in body mass index (p=0.971). There was no difference in group effect for the presence of chronic cholestasis or liver dysfunction after adjusting for confounding variables. SMOFlipid® was tolerated and no clinical signs of essential fatty acid deficiency were observed in either lipid group over the four-year study period; median duration of receiving SMOFlipid® was 238 days (range 1-1044, IQR 112-460.8).

Conclusion: The systematic review found there are limited data to support the use of lipid interventions to treat IFALD. The retrospective cohort study found no clinically relevant differences between SMOFlipid® and the comparator lipids in terms of liver dysfunction, chronic cholestasis, mean difference in body mass index, prevalence of line sepsis and clinical signs of essential fatty acid deficiency. Furthermore, there was no statistical evidence of an effect for lipid group in terms of liver function tests or chronic cholestasis after adjusting for confounding variables. Further high quality studies are required to support the use of lipid formulae in the treatment of IFALD. Additional studies are required to investigate the optimal lipid formulae to manage liver dysfunction while avoiding essential fatty acid deficiency.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright statement

Dedication

For my father.

Acknowledgements

I would like to express my gratitude to my supervisors, Dr Sorrel Burden, Professor Simon Lal and Professor Sarah Tyson for their time, guidance and sharing of expertise throughout this research journey. A special thank you to Dr Sorrel Burden for our regular phone meetings. Also, a very big thank you to Dr Malcolm Campbell, Lecturer in Statistics, who kindly and generously imparted some of his vast statistical knowledge during the analysis process.

Finally, thank you to my loved ones who have not seen enough of me of late: Chris, Papa, Khurshid, Yasmin and little Zain.

The author

I have worked as a clinical dietitian for over 21 years, predominantly managing adult in-patients. After working in the National Health Service for over 19 years and developing a greater appreciation of the preventative nature of diseases that pose a health burden, I embarked on a full-time Master's degree in Public Health in 2016. Having enjoyed the challenge of post-graduate study, the opportunity to undertake research in my own clinical area seemed the most logical way forward to develop research skills.

My specialist area of dietetic expertise is in nutrition support, which includes the management of adults with Intestinal Failure. I have extensive experience in the clinical care of patients with Intestinal Failure receiving parenteral nutrition. I have observed liver dysfunction in this patient group and work within a multi-professional team who advise on the manipulation of parenteral nutrition formulae aiming to minimising its potentially deleterious effects. My professional experience spurred an interest in undertaking this research due to the direct relevance to the patient group I care for. Furthermore, I have often contemplated how to optimally manage liver dysfunction in this patient group when there is a notable lack of long-term studies, specifically in adults, comparing different lipid types in parenteral nutrition formulae.

Chapter 1 Introduction

The term Intestinal Failure is defined as the reduction of gut function below the minimum necessary for the absorption of nutrients with or without water and electrolytes. For those with Intestinal Failure, intravenous supplementation is required to maintain health and or growth (Pironi et al, 2015a).

Parenteral nutrition (PN) is the method by which nutrients are delivered intravenously, or directly into the veins, in those with Intestinal Failure. It is only indicated when it is not possible to attain nutrition through the oral or enteral route, enteral nutrition being the delivery of nutrients through a tube directly into the gut (BAPEN, 2016). For individuals with Intestinal Failure, PN is deployed in both acute or chronic episodes (Pironi et al, 2018). When PN is required beyond an episode of acute hospital care, it can be administered in the home setting, which is known as home parenteral nutrition (HPN) (Staun et al, 2009).

The role of PN can be life sustaining, though abnormal liver function tests (LFTs) commonly occur in those receiving it (Luman and Shaffer, 2002); both having Intestinal Failure and receiving PN are linked to the development of liver dysfunction (Gabe and Culkin, 2010). Known risk factors include the underlying disease condition and having pre-existing liver disease. The components within PN are also important, as overfeeding due to the volume of glucose and lipid components are also factors related to developing liver dysfunction (Staun et al, 2009). Therefore, the term ‘Intestinal Failure Associated Liver Disease’ (IFALD), rather than ‘PN Associated Liver Disease (PNALD), is utilised to describe the occurrence of liver disease in those with Intestinal Failure (Dibb et al, 2013).

It is therefore important that PN meets the nutritional needs of each patient while the long-term effects of PN components, including intravenous lipid emulsion, are evaluated for the role they may have in developing IFALD. Furthermore, knowing how best to optimise PN formulae in those who have established IFALD is important clinically.

Chapter 2 Background

2.1 Intestinal failure

The origins of Intestinal Failure are diverse. It can be acquired from congenital, gastrointestinal, systemic, benign or malignant diseases and it affects all age groups (D'Antiga and Goulet, 2013; O'Keefe et al, 2006). These diseases cause five distinct pathophysiological conditions resulting in the development of Intestinal Failure: mechanical obstruction, short bowel syndrome, intestinal dysmotility, intestinal fistula and extensive small bowel mucosal disease (Pironi et al, 2018). Short bowel syndrome occurs when there is less than 200cm of functional small bowel (Buchman et al, 2003). This is the most frequent pathophysiological cause of Intestinal Failure (Brandt et al, 2017). The functional classification of Intestinal Failure can be categorised into three distinct groups (Lal et al, 2006), as illustrated in Table 2.1 (Pironi et al, 2015a).

Table 2.1: The functional classification of Intestinal Failure

Type I Acute, short-term and usually self-limiting condition
Type II Prolonged acute condition, often in metabolically unstable patients, requiring complex multi-disciplinary care and intravenous supplementation over periods of weeks or months
Type III Chronic condition, in metabolically stable patients, requiring intravenous supplementation over months or years. It may be reversible or irreversible

Intestinal Failure is rare and does not feature in the most recent The World Health Organisation Classification of Diseases, ICD-11 (World Health Organisation, 2018). Its exact incidence and prevalence remain unknown. However, the annual incidence of type II Intestinal Failure in England is ~9 individuals per million based on those receiving PN for 28 days or more (Department of Health, 2008) and ~5-20 individuals per million for Chronic Intestinal Failure caused by benign disease in Europe (Pironi et al, 2016).

Acute Type II Intestinal Failure can progress to Type III (Chronic Intestinal Failure). Type II Intestinal Failure is less likely to progress to Type III Chronic Intestinal Failure when effectively managed (Department of Health, 2008) and multi-disciplinary team input is fundamental to successfully manage Intestinal Failure (Pironi et al, 2018). In those with benign causes of Chronic Intestinal Failure, survival is relatively high. At 5 years, survival is 90% in children and 80% in adults (Pironi et al, 2012). The leading cause of mortality for those with Type II Intestinal Failure is sepsis (Visschers et al, 2008). The resolution of sepsis is also necessary to attain adequate nutritional replenishment in Type II Intestinal Failure (Lal et al, 2006).

2.2 The role of parenteral nutrition in Intestinal Failure

In Type II and Type III Intestinal Failure, PN is required over weeks or months (Pironi et al, 2015a). An expert nutrition support team should advise on the most appropriate prescription of PN formulation (Staun et al, 2009). In addition to fluid, PN can provide macronutrients: carbohydrate, nitrogen and lipid emulsion and micronutrients: vitamins, minerals, trace elements and electrolytes based on individual patient's needs (BAPEN, 2016). Fat soluble vitamins are received within the lipid emulsion component of PN (Calder et al, 2018). Carbohydrate and lipid emulsion serve as the main sources of energy (Staun et al, 2009) and these are received in combination, or in separate PN delivery bags (Dibb et al, 2013). The patient's evolving nutritional needs should be met through PN while avoiding deficiencies in macronutrients and micronutrients.

Long-term HPN is the main treatment for individuals with Intestinal Failure except when the underlying disease, or HPN related complications, warrant intestinal transplantation (Pironi et al, 2012). Despite its life sustaining role, treatment with HPN is associated with complications including those associated with central venous catheters used for its delivery (Allan and Lal, 2018), reduced quality of life (Pironi et al, 2003), metabolic bone disease (Raman et al, 2006) and IFALD (Cavicchi et al, 2000).

2.3 Intestinal failure associated liver disease

The causes of abnormal LFTs in those receiving PN can be multifactorial in origin and are not attributable to PN alone (Gabe and Culkin, 2010). When a liver injury is sustained for reasons related to both Intestinal Failure or the combination of Intestinal Failure and PN, IFALD occurs (Pironi et al, 2016). Pre-existing liver disease and sepsis prior to commencing PN may be significantly influential in the development of IFALD. Additional contributory aetiologies include: a lack of receiving enteral nutrition, gallstones, small intestinal bacterial overgrowth, intestinal anatomy, nutrient toxicity or deficiency, glucose content of PN and lipid emulsion composition (Gabe and Culkin, 2010). Lipid emulsions containing phytosterols, which are plant-derived sterols, have also been associated with the development of liver disease in long-term PN, though further studies are required to confirm causality (Zaloga, 2015). Abnormalities in liver function will usually resolve in those who receive short-term PN (Gabe and Culkin, 2010). Conversely, long-term HPN may be associated with prolonged, problematic liver dysfunction (Cavicchi et al, 2000; Luman and Shaffer, 2002).

Mortality from IFALD in adults receiving long-term HPN is relatively rare and most deaths are attributable to the underlying disease. In a review of eleven studies, only 15 (4%) of 381 HPN related deaths were caused by liver disease in 1310 adults (Pironi et al, 2012). Chronic cholestasis is a frequent histological finding in adults with IFALD, which can progress to extensive fibrosis and cirrhosis (Cavicchi et al, 2000). The presentation of IFALD differs by age, and the deterioration of liver function and presence of cholestasis take place more rapidly in the neonatal population (Sondheimer et al, 1998). In children, liver function abnormalities can occur within 1– 4 weeks of initiating PN (Kelly, 2006). In a systematic review, the incidence of IFALD was 49.8% in infants and children under 18 years old with Intestinal Failure (Lauriti et al, 2014). In contrast with adults, mortality is higher; in two of three studies reviewed, 6 (46%) of 13 PN related deaths in a population of 167 children commencing PN when aged 1 year or younger were attributable to liver disease (Pironi et al, 2012).

Severe, progressing IFALD may be an indication for intestinal transplantation (Buchman et al, 2003). However, IFALD is both treatable and can potentially be reversed with appropriate and timely management (Hvas et al, 2016). Methods to treat IFALD include sepsis prevention and management, avoidance of hepatotoxic medication if possible and the optimisation of PN regime while maintaining oral nutrition, with or without enteral nutrition (Gabe and Culkin, 2010). Key elements to optimising the delivery of PN are related to the duration and content of the infusion received. The delivery of PN should be cyclical, as opposed to via continuous infusion (Pironi et al, 2016) as PN received over a 16-hour period decreases LFTs (Hwang et al, 2000). Overfeeding with excessive glucose and lipid emulsion should be avoided as it is associated with steatosis (Lloyd et al, 2008).

Soybean oil lipid emulsion can cause liver dysfunction in those receiving long-term HPN (Pironi et al, 2015b). Lipid emulsion volume should not exceed 1 gram per kilogram per day of soybean lipid emulsion (Cavicchi et al, 2000; Pironi et al, 2016) due to the risk of developing chronic cholestasis and advanced liver disease (Cavicchi et al, 2000). Liver dysfunction has also been noted to improve when soybean lipid emulsion is substituted with fish oil lipid emulsion (Burns and Gill, 2013; Pironi et al, 2010). However, this finding has yet to be supported by intervention studies and is only based on case reviews to date.

2.4 Lipid formulae and evolution of lipid formulae in parenteral nutrition

Lipid emulsions are oil in water emulsions containing one or more triacylglycerol oil, a phospholipid emulsifier and glycerol (Pironi et al, 2017). There have been changes in the types of lipid emulsions available in PN formulae since its early use. Presently, lipid emulsion formulae are based on four different types of oils: soybean oil, medium-chain triglycerides (from coconut oil), olive oil and fish oil (Wanten and Calder, 2007). The concept of different lipid 'generations' differentiates lipid formulae based on the fatty acid derivative and by the inflammatory response generated on infusion of the lipid (Biesboer and Stoehr, 2016) (Figure 2.2).

First generation lipid emulsions are based on soybean oil. These have a high concentration of polyunsaturated fatty acid, with a high ratio of ω-6 (n-6) linoleic acid to ω-3 (n-3) α-linolenic acid (Table 2.2), which may result in a pro-inflammatory response (Pironi et al, 2017). Inflammatory responses are characteristic of the normal immune response, though this process can be harmful when inappropriate and extreme, resulting in tissue damage (Miles and Calder, 2015). Additional problems with soybean oil lipid emulsion include an inflated systemic inflammatory response in critically ill patients, immune system dysfunction and degradation of the product from lipid peroxidation (Pironi et al, 2015b).

Table 2.2: Oil sources and percentage of fatty acid content of commercial lipid emulsions

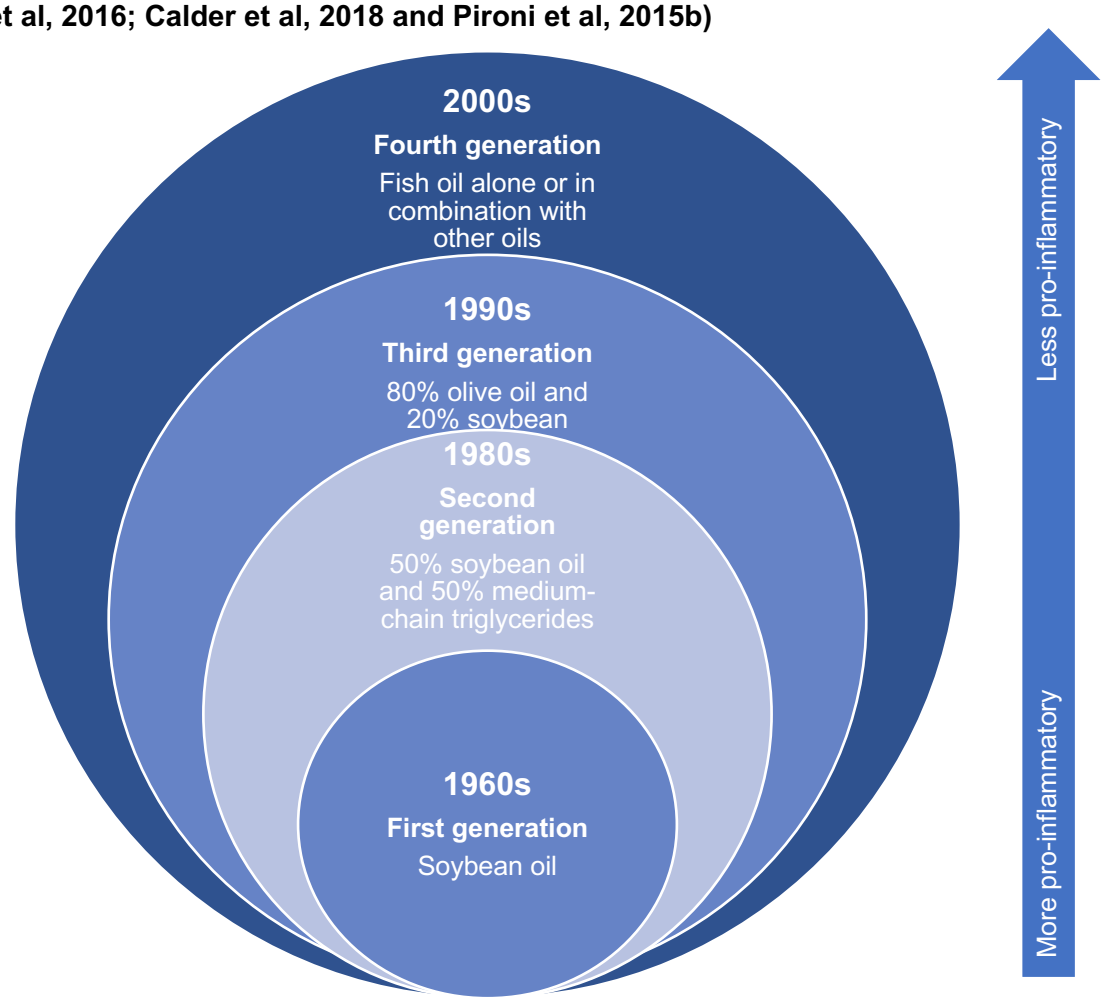
(Data from Cai et al, 2018; Murillo et al, 2015)

Component	SO 100%	SO 50%, MCT 50%	SO 64%, MCT36%	OO 80%, SO 20%	FO 100%	MCT 50%, SO 40%, FO 10%	SO 30%, MCT 30%, OO 25%, FO 15%
Lipid generation	*First*	*Second*	*Second*	*Third*	*Fourth*	*Fourth*	*Fourth*
Commercial name	*Intralipid®*	*Lipofundina®*	*Structolipid®*	*ClinOleic®*	*Omegaven®*	*Lipolus®*	*SMOFlipid®*
Soybean Oil (%)	100	50	64	20	0	40	30
Coconut Oil (%)	0	50	36	0	0	50	30
Olive Oil (%)	0	0	0	80	0	0	25
Fish Oil (%)	0	0	0	0	100	10	15
ω-3 to ω-6	7:1	7:1	7:1	9:1	1:8	2.7:1	2.5:1
*Linoleic acid (%)	44-62	27	35	18.5	4.4	25.7	21.4
*α-linolenic acid *(%)*	4-11	4	2	2	1.8	3.4	2.5
Eico*sapentaenoic acid* (%)	0	0	0	0	19.2	3.7	3
Docosahexaenoic acid *(%)*	0	0	0	0	12.1	2.5	2
Arachidonic acid *(%)*	0.18	0.19	0.24	0.16	1.47	0.52-0.66	0.27-0.5
Phytosterols (mg/L)	348	N/A	0	327 +/- 8	0	N/A	47.6

SO = soybean oil; MCT = medium-chain triglyceride; OO = olive oil; FO = fish oil; * essential fatty acids

Second generation lipid emulsions were created to decrease the ω-6 (n-6) polyunsaturated fatty acid content (Pironi et al, 2015b). These lipids contain medium-chain triglycerides derived from coconut oil, which are not pro-inflammatory and can be easily metabolised. However, medium-chain triglycerides do not contain essential fatty acids and are therefore not suited to use as the sole lipid emulsion (Anez-Bustillos et al, 2016). To overcome this deficiency, third generation lipids were developed which consist of olive oil 80% and soybean oil 20% (Pironi et al, 2015b). Olive oil has a high ω-9 (n-9), non-essential mono-unsaturated fatty acid content. It also has a very low ω-6 (n-6) linoleic acid content and therefore, has to be combined with an oil containing essential fatty acid (Anez-Bustillos et al, 2016). Fourth generation lipid emulsions consist of fish oil, either alone or in combination with one or more of the oils (Pironi et al, 2015b). Only this generation of lipid contains ω-3 (n-3) eicosapentaenoic acid and ω-3 (n-3) docosahexaenoic acid (Raman et al, 2017). Fish oils, like olive oil, have less pro-inflammatory properties than soybean oil (Kalish et al, 2012). The chronological evolution of lipid generations is highlighted in figure 2.1. Oil components in commercial lipid emulsions are shown in Table 2.2.

Figure 2.1: Evolution of intravenous lipid emulsions (data taken from Anez-Bustillos et al, 2016; Calder et al, 2018 and Pironi et al, 2015b)



2.5 Essential fatty acid deficiency and parenteral nutrition

Essential fatty acid deficiency is associated with adverse symptoms which include scaly dermatitis (Press et al, 1974), increased skin permeability, hair loss (Morgensen, 2017) and reduced immunity (Yamanka et al, 1980). When the use of long-term PN was introduced in 1968 (Yamanaka et al, 1980), formulae were lipid emulsion-free initially (Spector and Kim, 2015). Cases of essential fatty acid deficiency in those receiving lipid emulsion-free PN were noted (Collins et al,1971). Subsequently, these deficiencies resolved when soybean lipid emulsion was included in PN (Postuma et al, 1978; Tashiro et al,1976). Additionally, liver dysfunction and fatty liver infiltration were noted in those who developed essential fatty acid deficiency due to receiving fat-free PN (Richardson and Sgoutas, 1975). In these early lipid emulsion-free PN formulae, where dextrose was the sole energy source, additional complications were noted including hyperglycaemia associated immunosuppression, hepatic steatosis and respiratory insufficiency (Raman et al, 2017).

Therefore, when patients are unable to take any food containing fat orally, it should be provided in the form of lipid emulsion in PN. This is because essential fatty acid deficiency will develop in 2-6 months in those receiving lipid emulsion free PN (Staun et al, 2009). Thus, it follows that the fatty acid profile of lipid emulsion formulae is considered to be the most important property (Pironi et al, 2017). Essential fatty acid deficiency occurs due to a lack of the two polyunsaturated fatty acids, ω-3 (n-3) α-linolenic acid and ω-6 (n-6) linoleic acid (Gramlich et al, 2015), which are humans are unable to synthesise (Glick and Fischer, 2013).

These two essential fatty acids yield other ω-3 (n-3) and ω-6 (n-6) polyunsaturated fatty acids through the actions of elongase enzymes. This process results in ω-6 (n-6) linoleic acid generating ω-6 (n-6) arachidonic acid, and ω-3 (n-3) α-linolenic acid generating ω-3 (n-3) eicosapentaenoic acid in addition to ω-3 (n-3) docosahexaenoic acid (Fell et al, 2015). It is of note that very recent evidence has suggested that arachidonic acid and docosahexaenoic acid can also independently meet essential fatty acid requirements in biochemical, animal and human analysis (Anez-Bustillos et al, 2018). Therefore, it may be relevant to consider these components in PN also when evaluating potential for essential fatty acid deficiency based on PN formulae. The differing fatty acid content in commercial lipid emulsions are shown in Table 2.2.

The ‘ESPEN Guidelines on Parenteral Nutrition Home Parenteral Nutrition (HPN) in adult patients’ advise giving 1.2–2.4 g soybean oil per kilogram body weight twice weekly to correct an existing essential fatty acid deficiency (Staun et al, 2009). The guideline also recommends that essential fatty acid deficiency can be prevented with approximately 500–1000 ml of 20% soybean-based lipid emulsion weekly. This recommendation was stated to be based on only two previous findings. Firstly, the presence of essential fatty acid deficiency in patients receiving fat-free HPN formulae (Jeppesen et al, 2000) and secondly, higher essential fatty acid requirements in those with short bowel syndrome receiving it parenterally opposed to via the enteral route (Jeppesen et al, 2000).

The more recent ESPEN guideline ‘ESPEN guidelines on chronic intestinal failure in adults’ differs as it includes a weight-based recommendation for the prevention of essential fatty acid deficiency in HPN-dependent individuals, as opposed to a lipid dose range. A minimum of 1 gram per kilogram body weight essential fatty acid containing lipid emulsion per week is recommended (Pironi et al, 2016). The authors do acknowledge this is based on very low grade evidence from only one observational study in which the plasma phospholipid fatty acid profiles of 56 patients receiving HPN were compared with 37 healthy controls (Jeppesen et al, 1998). The study found the two groups did not have different plasma fatty acid profiles despite 25 of the 56 patients having clinical signs of essential fatty acid deficiency. In all patients receiving HPN, a dose of 500ml soybean-based lipid emulsion once a week was noted to prevent plasma essential fatty acid deficiency according to according to plasma measurements. Importantly, no weight based analysis was completed so it is difficult to relate these findings to the ESPEN recommendations. Interestingly, these ESPEN guidelines do not specify that the lipid must be soybean oil based only. Hence, the full range of commercially available lipid formulae would be suitable (see Table 2.2).

Both of these ESPEN guidelines advise that those receiving HPN for more than 6 months should not receive greater than 1 gram per kilogram body weight soybean-based lipid emulsion per day. This dose limit is due to the risk of developing IFALD in doses which exceed this (Cavicchi et al, 2000). Despite the lack of studies defining the optimal lipid dose to prevent essential fatty acid deficiency in HPN-dependent patients, there is a clear role for lipid formulae for those who are unable to attain fat sources orally. While first generation soybean oil based lipid emulsions have the greatest quantity of essential fatty acids (Table 2.2), its role in development of IFALD strengthen the need to explore how other lipid generations compare in terms of the avoidance of essential fatty acid deficiency.

Interestingly, a recent systematic review, which comprised of three randomised control studies, found lipid emulsions from all four lipid generations were suited to the avoidance of essential fatty acid deficiency in adults on HPN (Jones and Calder, 2018). Furthermore, in one study there was evidence of an increase in ω-3 (n-3) eicosapentaenoic acid and ω-3 (n-3) docosahexaenoic acid in the plasma and red blood cell membranes in those who received soybean 30%, medium-chain triglycerides 30%, olive oil 25% and fish oil 15% lipid emulsion compared to soybean based lipid (Klek et al, 2013). This resulted in a reduced ω-3 to ω-6 ratio (in both plasma and red blood cell membranes) in the latter lipid emulsion compared to soybean lipid emulsion. Klek et al (2013) demonstrated that a fourth generation lipid, with a lower ω-3 to ω-6 ratio, could be a viable alternative to the known pro-inflammatory soybean oil with a higher ω-3 to ω-6 (see Table 2.2). Additionally, this was an important finding given the evolution of lipid generations and known causative role of soybean oil in liver dysfunction discussed in section 2.3.

2.6 Optimal lipid formulae in PN

The risk factors for IFALD in adults have been identified and its occurrence can be reversed with appropriate and timely management (Hvas et al, 2016). Lipid emulsions are an essential component of PN formulae for those with Intestinal Failure, whether these are received either short-term, or long-term in HPN. Lipid emulsions have a role in providing energy, fat soluble vitamins and in avoiding essential fatty acid deficiency (sections 2.2 and 2.5). Conversely, they are potentially harmful due to pro-inflammatory properties and have a role in the development of IFALD (sections 2.2-2.4). While the function of lipid formulae is clearly defined, there is a paucity of studies comparing the safety and efficacy of different lipid types in those receiving long-term HPN. Irrespective of whether HPN is received solely in the home setting or accompanied by hospital admissions, the optimal lipid emulsion has yet to be identified.

The longest study comparing different lipid formulae was published recently by Klek et al (2018). In this randomised control trial, 67 patients starting HPN received one of four different lipid formulae spanning four lipid generations. These were: soybean oil 100%; medium-chain triglyceride 50% and long-chain triglyceride 50%; olive oil 80% and soybean oil 20%; or soybean oil 30%, medium-chain triglyceride 30%, olive oil 25% and fish oil 15% (see Table 2.2). At 12 months, 65 individuals were included in the analysis and LFTs normalised in all groups, there were no between group differences. Additionally, essential fatty acid deficiency was not observed in any of the lipid emulsion groups. While lipids emulsions across all four generations were comparable in this study, further exploration is clearly required. Furthermore, it remains unknown which lipid emulsion formula, if any, is best suited to treating established IFALD.

There is only limited evidence suggesting that fourth generation fish oil formulae may have a contributory role in improving established IFALD (section 2.3). There is an imperative need for further clinically relevant studies to determine which lipid emulsion formulae optimally prevent and treat IFALD, while avoiding essential fatty acid deficiency in those receiving long-term HPN. The proposed study aims to evaluate a lipid emulsion comprising fourth generation soybean oil 30%, medium-chain triglyceride 30%, olive oil 25% and fish oil 15% in a long-term HPN cohort. The study will evaluate clinical outcomes pertaining to liver function, tolerability and symptoms of essential fatty acid deficiency. Whether stated as PN or HPN, this study's aim is to examine specific outcomes in relation to the duration received in a cohort of individuals receiving HPN.

Chapter 3 Systematic literature review: The treatment of Intestinal Failure Associated Liver Disease in adults

3.1 Systematic review protocol

A protocol was developed to outline the remit of the systematic review and methodology a priori (Appendix 1). Items included were based on 'The PRISMA-P 2015 Explanation and Elaboration paper' to support rigour and credibility (Shamseer et al, 2015). The protocol met peer review approval prior to the systematic review commencing, thereby reinforcing research integrity and transparency of the process (Moher et al, 2015). The protocol, entitled 'Factors associated with the prevention and treatment of intestinal failure associated liver disease in adults' was submitted for registration on the international register International Prospective Register of Ongoing Systematic Reviews (PROSPERO) on 15th March 2017 and registered on 24th March 2017 (registration number 42017058963). The protocol included two research questions; the question considered most appropriate to the present research was completed for the thesis. The remaining question was included in the protocol as directly relevant to this field of research, though deferred with a view to completion by the researcher and/ or a member of the clinical team at Salford Royal Hospital.

3.2 Research question, aim and objective

The PICO framework (Richardson et al, 1995) was used to devise the research question. Population, Intervention, Comparison and Outcomes were each considered to ensure the question was focused. The research question was:

Which interventions are effective in the treatment of IFALD adults?

3.2.1 Aim of systematic review

To determine the effectiveness of treatment strategies for IFALD in adults.

3.3 Information sources

Electronic databases were selected to retrieve published articles pertaining to the treatment of IFALD. Six bibliographic database platforms were included to capture medicine, complementary medicine and nursing including Medline, EMBASE, AMED, British Nursing Index, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and social sciences and conference proceedings (Web of Science). Relevant published abstracts from conferences held by the European Society for Clinical Nutrition and Metabolism (ESPEN), the British Association for Parenteral and Enteral Nutrition (BAPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN) were also included as information sources to capture additional pertinent studies.

3.4 Literature search strategy

The literature search strategy was also devised with the use of The PICO framework (Richardson et al, 1995) by considering the Population, Intervention, Comparison and Outcomes using key words and search terms to identify research related to IFALD. This approach was deployed to ensure the literature search had the sensitivity to identify relevant studies and specificity to limit irrelevant search results. The search strategy had three categories of search terms: therapeutic options, liver dysfunction and the population of interest (Table 3.1). The therapeutic options reflected modes of nutrition (cyclic, parenteral, PN, intravenous, enteral, oral), components of PN (fish oil, omega, soybean, lipid, glucose, carbohydrate, taurine, choline, amino acid, aluminium, manganese), a clinical diagnosis bacterial overgrowth and therapeutic treatments (teduglutide, ursodiol, transplant). Search terms for comparison (or control group) interventions were not specified as this would have reduced the sensitivity of the search.

The search terms were combined using the Boolean operators “AND” and “OR.” Terms were nested by being enclosed in parentheses. Words beginning with “Cyclic”, “Carbohydrate”, “URSO”, “Amino acid”, “Transplant” and “Adult” were truncated by the asterisk (*) Search terms are detailed in Table 3.1. In Medline, the search was limited to: human age groups: young adult, adult, middle aged, aged, aged 80 and over, date: 1970-2017. In EMBASE, the search was limited to: human age groups: adult 18-64 years, aged 65+ years, language: English. In AMED, the search was limited to: date: 1970-2017, language: English language. In British Nursing Index, the following limit was set: date: 1992-2017. In CINAHL the search was limited to: human age groups: adult 19-44 years, middle aged 45-64 years, aged 65+ years, aged 80 or over, all adult. In Web of Science, the search was not limited.

Web of Science was searched on 13th March 2017. Medline, EMBASE, AMED, British Nursing Index, CINAHL were searched on 22nd March 2017. Email ‘alerts’ were set at the time of conducting electronic database searches. This enabled the author to receive details of subsequent potentially relevant studies which were reviewed until 6th October 2018. Additionally, all database searches were repeated on 6th October 2018. Titles and abstract files were imported from each electronic database to Elsevier Mendeley reference manager (version 1.17.10).

Table 3.1: Search terms for the systematic review

Intervention: terms for therapeutic options	Outcome: terms for liver dysfunction	Population: term for the population of interest
"Cyclic*" **OR** "Parenteral" **OR** "PN" **OR** "Intravenous" **OR** "Enteral" **OR** "Oral" **OR** "Fish Oil" **OR** "Omega" **OR** "Soybean" **OR** "Lipid" **OR** "Glucose" **OR** "Carbohydrate*" **OR** "Bacterial Overgrowth" **OR** "URSO*" **OR** "Teduglutide" **OR** "Taurine" **OR** "Choline" **OR** "Amino acid*" **OR** "Aluminium" **OR** "Manganese" **OR** "Transplant*"	"Intestinal Failure" **OR** "Intestinal Failure Associated Liver Disease" **OR** "IFALD" **OR** "Parenteral Nutrition Associated Liver Disease" **OR** "PNALD"	Adult*

3.5 Study selection criteria

Studies on adults (≥18 years old) with Intestinal Failure in both genders were eligible for inclusion. Studies addressing both adults and children were considered suitable if data for adults were reported separately to avoid excluding potentially relevant data. Studies on individuals with pre-existing cholestasis or liver disease prior to developing Intestinal Failure were excluded as potential effects from interventions would introduce bias. Randomised controlled trials, quasi-randomised trials, prospective studies, retrospective case control studies and case reviews were included. Articles published in English between January 1970 and 6th October 2018 were eligible. There was no restriction on the type of study setting to acknowledge that IFALD is not location specific. Individuals identified to have Intestinal Failure receiving one or more of the interventions were sought: cyclical infusion of PN, continuous infusion of PN, intake of enteral/oral nutrition, fish oil PN formulae, soybean PN formulae, glucose in PN.

3.5.1 Primary and secondary outcome measures

Primary outcome measures were chosen to reflect measurable outcomes reflecting liver function (Table 3.2). A standard definition of chronic cholestasis was pre-defined to allow consistent comparisons between studies for this outcome: the persistent elevation greater than 1.5 times the upper limit of the normal range for more than 6 months of two of the following: alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and total bilirubin (Cavicchi et al, 2000). Secondary outcome measures reflected the potentially deleterious impact of IFALD in terms of mortality and morbidity. Furthermore, the secondary outcomes were also chosen to explore and evaluate the impact on the health service and potential economic consequences of IFALD (Table 3.2).

Table 3.2: Primary and secondary outcome measures

Outcome measures
Primary outcome measures: Elevated LFTs Variation in LFTs Chronic cholestasis (defined by Cavicchi et al, 2000)
Secondary outcome measures: Mortality attributable to IFALD Length of hospital stay (days) Number of admissions to hospital due to IFALD

IFALD = intestinal failure associated liver disease, LFTs = liver function tests

3.5.2 Screening and study selection process

The titles and abstracts of studies identified in the literature search were screened for studies that potentially met the systematic review protocol selection criteria. A proportion were checked by a second person (SB). Full texts of potentially suitable literature were retrieved. Full texts were also obtained where the title and abstract provided insufficient information for an assessment to be made. The reference lists of retrieved full text articles were reviewed for potentially relevant studies not identified in the database searches. A shortlisting form (Appendix 2) was completed to verify suitability for inclusion and to specify the reason for rejection. A second reviewer (SB) verified the selection of full texts by reviewing the studies.

3.6 Data extraction

A data extraction form was produced to facilitate data collection (Appendix 3). The form was piloted on an initial sample of studies and revised to facilitate ease of data collection. Data abstracted included:

- Title, journal, year of studies and funding sources.
- Study design, setting, duration and method of randomisation/blinding.
- Sample size.
- Inclusion and exclusion criteria.
- Patient characteristics: age, gender, functional classification of Intestinal Failure (if stated).
- Interventions received, duration of intervention, quantity and dose of intervention, comparison group.
- Characteristics of adults stated to have ‘IFALD’ to produce a narrative synthesis of defining features; parameters sought included (but were not be limited to): age, gender, intestinal anatomy, the presence or absence of sepsis, small bowel bacterial overgrowth and use of hepatotoxic medication.
- Study outcomes pertinent to the defined primary and secondary outcome measures including the time when outcomes were reported.

3.7 Data analysis and synthesis

Extracted data were reviewed to compare and interpret the findings. Study interventions were analysed to assess outcome effect size. Due to heterogeneity and lack of studies suited to pooling results, a meta-analysis could not be performed. The results are presented narratively.

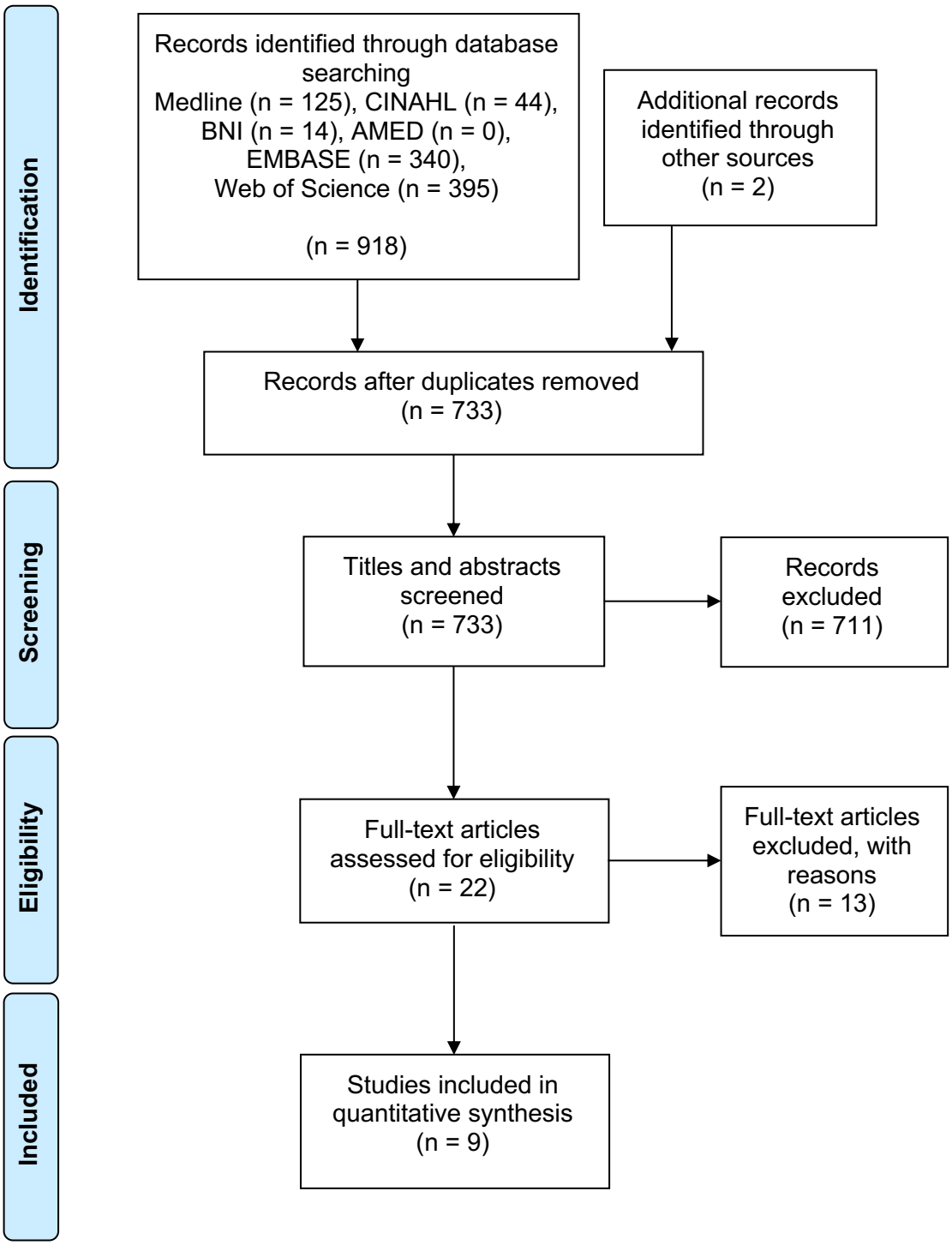
3.8 Quality assessment

The Joanna Briggs Institute Critical Appraisal tools were used to assess the quality of methodology and potential bias in design, conduct and analysis (The Joanna Briggs Institute, 2017). The checklists for ‘case reports’ were used for case reviews and ‘cohort studies’ for the remaining studies as deemed the most suitable (Tables 3.4 and 3.5).

3.9 Systematic literature review findings

The search strategy identified 733 studies after duplicates had been removed. Figure 3.1 details the numbers of studies included and excluded at each stage of the review.

Figure 3.1: Review stages based on PRISMA flow diagram (Moher et al, 2009)



3.9.1 Overview of studies included in the systematic review

Nine studies were included in the review that recruited 44 participants, 20 were male and 24 were female (Appendix 3). Six were individual case reviews (Burns and Gill, 2013; Halliken et al, 2008; Hvas et al, 2016; Moyes et al, 2012; Pironi et al, 2010; Venecourt-Jackson et al, 2013). Two were pre and post treatment cohort studies (Pastor-Clerigues et al, 2014; Xu et al, 2012). The remaining study was a prospective study combined with a case note review (Thomas-Gibson et al, 2004).

Two of the six case reviews were conducted in the United Kingdom (Hvas et al, 2016; Moyes et al, 2012), one in Finland (Halliken et al, 2008), one in Italy (Pironi et al, 2010), one in New Zealand (Venecourt-Jackson et al, 2013) and one in the United States of America (Burns and Gill, 2013). One pre and post treatment cohort study was based in Spain (Pastor-Clerigues et al, 2014) and the remaining in in China (Xu et al, 2012). The prospective study combined with case review was conducted in the United Kingdom (Thomas-Gibson et al, 2004).

Six of the studies did not state a funding source (Burns and Gill, 2013; Halliken et al, 2008; Hvas et al, 2016; Thomas-Gibson et al, 2004; Venecourt-Jackson et al, 2013; Pironi et al, 2010) of which, Hvas et al (2016) declared no competing interests. One stated the research was not commissioned (Moyes et al, 2012). The remaining studies were funded by government (Pastor-Clerigues et al, 2014) and a natural science foundation (Xu et al, 2012).

All of the studies were on adults only with no mixed populations of adults and children. Ages of participants receiving interventions ranged from 25 to 59 years old. In the case reviews, median age was 46.5 years. In the remaining studies, two specified the median ages and ranges of intervention groups as 37 years (range 22-45) (Xu et al, 2012) and 44 years (range 25–68) (Thomas-Gibson et al, 2004). The remaining study stated mean age of 28.5 years (SD 0.75) (Pastor-Clerigues et al, 2014). The total sample from all the included studies receiving interventions was 36, with an approximately even gender distribution of 17 males to 19 females. One study featured comparator groups, with a ratio of intervention group to comparator of 2 to 8 (Pastor- Clerigues et al, 2014).

None of the studies deployed classification of Intestinal Failure outlined by the ESPEN endorsed recommendations by Pironi et al (2015). The diagnoses of all subjects were stated, and the most predominant diagnosis was short bowel syndrome. The aforementioned diagnosis was the only participant diagnosis in six of the nine studies (Burns and Gill, 2013; Halliken et al, 2008; Hvas et al, 2016; Pastor-Clerigues et al, 2014; Xu et al, 2012; Pironi et al, 2010) and one further study together with 'other causes of Intestinal Failure' and 'pseudo-obstruction' (Thomas-Gibson et al, 2004). Other study participants had multiple enterocutaneous fistulae (Venecourt-Jackson et al, 2013) and a mesenteric infarction duodenostomy (Moyes et al, 2012).

There was a wide range in intervention duration varying from one month (Xu et al, 2012) to seventeen months (Halliken et al, 2008). In one case review, intervention duration was not stated (Hvas et al, 2016). Participant inclusion and exclusion criteria were clear in all studies where this was applicable. All three intervention studies pre-defined homogenous groups based on age, clinical parameters and length of receiving HPN. Two studies excluded those with liver dysfunction not aligned to parenteral nutrition associated liver disease; Xu et al (2012) excluded those with other stated established causes of liver disease and Pastor-Clerigues et al (2014) excluded those without non-alcoholic steatohepatitis and other coexistent causes of liver disease differing from parenteral nutrition associated liver disease. Thomas-Gibson et al (2004) excluded those with established cholestasis (bilirubin >0.03 mmol/l) prior to exposure to the intervention.

Only Hvas et al (2016) and Pironi et al (2010) included specific defining characteristics of IFALD detailed in the data extraction Table (Appendix 3). The Hvas et al (2016) report suggested the clinical features of IFALD in adults vary from having 'mild cholestasis or steatosis to cirrhosis and decompensated liver disease' (Hvas et al, 2016, p.115). In this particular case, the IFALD diagnosis was supported with elevated LFT results with a bilirubin of 96 μmol/L, ALT 161 IU/L and ALP 300 IU/L. Furthermore, the report detailed additional confirmatory investigations stating, 'tests for viral and autoimmune hepatitis and cross-sectional imaging including magnetic resonance cholangiopancreatography were normal except for liver steatosis' and 'a liver biopsy revealed focal interface hepatitis and perivascular cholestasis, consistent with IFALD' (Hvas et al, 2016, p.115).

Pironi et al (2010) described a case review in which parenteral nutrition associated liver disease was reversed. The report stated 'The pathogenesis is multifactorial, including parenteral nutrition, intestinal failure and systemic related factors' when explaining the use of the two distinct defining terms: parenteral nutrition associated liver disease and IFALD (Pironi et al, 2010, p. 243). Of interest is the acknowledgement of IFALD as a clinical occurrence, though the case features the reversal of parenteral nutrition associated liver disease and not IFALD per se. This suggests the patient's liver disease was attributable to receiving PN and not due to having Intestinal Failure. As per Hvas et al (2016), elevated liver function tests were used as markers of its incidence. In similarity to Hvas et al (2016), liver biopsies were utilised to measure steatosis and fibrosis.

Hence, both studies demonstrate parallels in diagnostic tests used to identify both IFALD and parenteral nutrition associated liver disease. Both studies also explore the potential role of hepatotoxic drugs in the presented cases. Hvas et al (2016) state catheter sepsis was a causal factor in the development of IFALD. Though not stated as causal in Pironi et al (2010), catheter sepsis and post-operative systemic inflammation were also mentioned when describing the patient's history of liver dysfunction. Hvas et al (2016) reported that IFALD is multifactorial, additionally stating its treatment should be multidisciplinary, suggesting that even advanced cases of IFALD are potentially reversible.

The treatment of parenteral nutrition associated liver disease, opposed to IFALD featured, in six of the included studies (Burns and Gill, 2013; Moyes et al, 2012; Pastor-Clerigues et al, 2014; Pironi et al, 2010; Venecourt-Jackson et al, 2013; Xu et al, 2012). Therefore, it can be postulated that PN was viewed as the more likely origin to liver dysfunction compared to Intestinal Failure in these studies.

The studies in this review did not provide a consensus on which clinical parameters clearly define IFALD. Subsequently, it was not possible to demarcate common features of IFALD objectively in terms of age, gender, intestinal anatomy, the presence (or absence) of sepsis, small bowel bacterial overgrowth, or other clinical parameters. Despite search terms for liver dysfunction including both IFALD and parenteral nutrition associated liver disease, the studies in this review used term IFALD less frequently compared to parenteral nutrition associated liver disease. However, the diagnostic techniques used to diagnose both of these conditions were similar.

Sasdelli et al (2018) concluded the occurrence of IFALD varied greatly according to the criteria on which it is diagnosed in a report which included 113 adults managed at a single-centre. Cases were categorised using nine known diagnostic criteria for IFALD at the start of commencing HPN (+/- 3 months). This range of criteria featured across the sample, though prevalence varied from 5% to 43% depending on the criteria used for diagnosis; the most frequent diagnosis was steatosis based on ultrasound scan, and the least frequent was cholestasis based on total bilirubin >1 mg/dL and conjugated bilirubin >0.3 mg/ 83 dL for > 6 months. It was suggested there is a need for a consensus definition between national and international intestinal failure units. The findings of this systematic review also support the need for clear defining criteria; this review sought to determine the effectiveness of treatment strategies for IFALD in adults, though none of the included studies had a clear definition which compromised the direct comparison of treatment efficacies.

In addition to improvements relating to the primary and secondary outcomes to be discussed in section 3.9.5 and 3.9.6, progress was reported with other nutrition-related parameters. These included enteral feeding (fistuloclysis via distal limb) combined with a reduction in PN volume (Hvas et al, 2016) and solely enteral (naso-jejunal) feeding (Moyes et al, 2012). Burns and Gill (2013) reported symptomatic improvements including increased energy, appetite, decreased abdominal pain, decreased nausea, vomiting and diarrhoea. These details provided additional context to the improvements in clinical status.

Table 3.3: Intervention and generation of lipid emulsions in included studies

Author	Intervention lipid emulsion	Generation of lipid
Halliken et al, 2008 Thomas-Gibson et al, 2004	Olive oil (ω-9) 80%, soybean oil (ω-6) 20%	Third
Xu et al, 2012	Soybean (ω-6) 50% and medium-chain triglycerides (coconut oil) 50% AND fish oil (ω-3) 100%	Second and Fourth
Burns and Gill, 2013 Pironi et al, 2010 Venecourt-Jackson et al, 2013	Fish oil (ω-3) 100%	Fourth
Pastor-Clerigues et al, 2014	Fish oil (ω-3) 100% followed by Soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15%	Fourth and Fourth
Hvas et al, 2016 Moyes et al, 2012	Soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15%	Fourth

3.9.2 Authors' study aims

The studies measured variation in liver function and extent of liver disease while receiving the lipid intervention. The reversal of parenteral nutrition associated liver disease was described in four of the single case reviews (Burns and Gill, 2013; Moyes et al, 2012; Pironi et al, 2010; Venecourt-Jackson et al, 2013) and in the two pre and post treatment cohort studies, featuring two (Pastor-Clerigues et al, 2014) and fifteen individuals respectively (Xu et al, 2012). Hvas et al (2016) reported on the successful reversal of IFALD in a single case review. Halliken et al (2008) investigated the effect of differing amounts of plant sterols in parenteral nutrition on serum plant sterol concentration and liver function tests. This study reported plant sterol concentrations in parenteral nutrition solution and serum by using gas-liquid chromatography. Thomas-Gibson et al (2004) primarily investigated the safety of the lipid intervention. This included the recording of clinical parameters of liver dysfunction and adverse events, while comparing it to usual lipid received.

Table 3.4: Quality assessment for case reviews

Author, year	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Comments
Hvas et al, 2016	Yes	Yes	Yes	Yes	Yes*	Yes	No	Yes	*Lipid dose not specified. Glucose dose not stated. Hours of PN administration not stated. Soybean oil, medium-chain triglyceride, olive oil and fish oil (SMOFlipid®) one of multiple featured interventions to reverse IFALD.
Burns and Gill, 2013	Yes	Yes	Yes	Yes	Yes*	Yes	No	Yes	Glucose dose not stated. PN given over 16 hours. Changing to intervention of fish oil (Omegaven®) from soybean-based lipid tolerated. By three months, all symptoms absent and liver function normalised.
Venecourt-Jackson et al, 2013	Yes	Yes	Yes	Yes	Yes*	Yes	No	Yes	*Unclear if duration of PN was over 18 hours as per pre-treatment. Changing from soybean and olive oil-based emulsion (ClinOleic®) to fish oil-based lipid emulsion (Omegaven®) improved liver function.

Hallikainen et al, 2008	Yes	Yes	Yes	Yes*	Yes**	Yes	No	Yes	*Data on patient's energy intake included. Glucose dose stated. Plant sterol and liver enzyme values decreased on changing from soybean-based to soybean and olive oil-based lipid emulsion (ClinOleic®). **Hours of administration not stated.
Moyes et al, 2012	Yes	Yes	Yes	Yes	Yes*	Yes	No	Yes	*Hours of administration not stated. Glucose dose not stated First publication demonstrating resolution of parenteral nutrition associated liver disease on changing from soybean and olive oil-based lipid emulsion (ClinOleic®) to soybean oil, MCT, olive oil and fish oil (SMOFlipid®).
Pironi. et al, 2010	Yes	Yes	Yes	Yes	Yes*	Yes	No**	Yes	Hours of administration not stated. **'No PN-related complications, no adverse events on receiving fish oil-based lipid (Omegaven®), liver histology changed from NASH grade 2 steatosis and inflammation and stage 3 fibrosis to grade 1 steatosis and inflammation and stage 3 fibrosis.

IFALD = intestinal failure associated liver disease, MCT = medium-chain triglyceride, NASH = non-alcoholic steatohepatitis, PN = parenteral nutrition

Table 3.5: Quality assessment for pre and post treatment cohort studies and prospective study combined with case note review

Author, year	Were the two groups similar and recruited from the same population?	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Was the exposure measured in a valid and reliable way?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)?	Were the outcomes measured in a valid and reliable way?	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Were strategies to address incomplete follow up utilised?	Was appropriate statistical analysis used?
Pastor-Clerigues et al, 2014	No*	Yes*	Yes	No	No	No**	Yes	Yes	Yes	N/A	Yes
Comments	Glucose dose not stated. *Comparator group had soybean oil and medium-chain triglycerides (Lipofundin®) (n=1), soybean and olive oil-based lipid emulsion (ClinOleic®) (n=4), soybean oil, medium-chain triglyceride, olive oil and fish oil (SMOFlipid®) (n=3). No baseline LFTs for comparator groups. Non Alcoholic Fatty Liver Disease Activity Score (NAS)> 6 due to PNALD received fish oil (Omegaven®) intervention**All subjects had PNALD.										
Xu et al, 2012	N/A	N/A	Yes	Yes*	Yes*	No**	Yes	Yes	Yes***	N/A	Yes
Comments	Hours of administration not stated. *Confounding factors included: Resting energy expenditure measured every week and non-protein energy changed in PN AND patients received a lipid to sugar ration of 1:1 in PN **Subjects had cholestasis at the outset. Direct bilirubin and total bilirubin significantly decreased after 4 weeks, liver biopsies showed histological improvement with fish oil lipid emulsion (Omegaven®) ***Authors do not state why 4 of the 15 subjects did not receive liver biopsy pre and post intervention.										
Thomas-Gibson et al, 2004	N/A	N/A	Yes	Yes*	No	Yes	Yes**	Yes	No***	Yes	Yes
Comments	Hours of administration not stated *Glucose median 20.3 kilocalories per kilogram per day (range 11.1–38.5) Lipid median 4.3 kilocalories per kilogram per day (range 1.23–8.63) **Authors do not state actual liver function results or reference ranges ***Reasons for four patients not completing study stated. Study focus was the safety and efficacy of soybean and olive oil-based lipid emulsion (ClinOleic®).										

LFTs = liver function tests, NAS = non-alcoholic fatty liver disease activity score, PN = parenteral nutrition, PNALD = parenteral nutrition associated liver disease

3.9.3 Quality assessment for case reviews

The results of the quality assessment are detailed in Table 3.4. Patient demographic characteristics were described in all cases. All reports clearly described and presented the patient's history on a timeline. The current clinical condition of patients was presented in all reports, enabling the reader to evaluate results from the point at which the interventions were initiated.

The diagnostic tests, assessment methods and results were clearly described for all studies. Objective, valid and reliable tests were used though being retrospective cases, different investigative methods and timing of outcome measures were deployed to assess outcomes. These different practices reflect individual clinical condition and clinician choice but make it difficult to compare studies. Most presented LFT results at baseline and thereafter, detailed in the data extraction Table (Appendix 3). Instrument error, which indicates the difference between actual values and recorded values, cannot be excluded from any of the studies as there was no reporting of instrument calibration. If this had been done, the use of different instruments, laboratories and staff compromise comparison and are potential sources of bias.

Intervention lipids were described clearly in all reports, though variation in how the doses were reported was evident. Wide differences in dose, duration and quantity limited comparison of findings between studies (Table 3.6). Only two reports included energy from oral intake (Halliken et al, 2008; Pironi et al, 2010). Furthermore, carbohydrate content of PN in the form of glucose, was stated in three reports (Halliken et al, 2008; Pironi et al, 2016; Venecourt-Jackson et al, 2013). These factors are relevant to the interpretation of results and omission compromises quality; lack of enteral nutrition and glucose in PN could be contributory to the development of IFALD (Gabe and Culkin, 2010). Only one report included the number of hours of PN administration (Burns and Gill, 2013). Delivery of PN should ideally cyclical, opposed to via a continuous infusion (Pironi et al, 2016) as delivery over a 16-hour period decreases LFTs (Hwang et al, 2000). Complete reporting on PN components and delivery would have provided a more accurate reflection of the PN intervention and improved the quality of reporting.

Only Hvas et al (2016) detailed hepatoxic drugs received by the patient. Burns and Gill (2013), Halliken et al (2008) and Pironi et al (2010) acknowledge drug toxicity as a potential cause of liver dysfunction. These drugs should be avoided where possible in patients with IFALD (Gabe and Culkin, 2010). Lack of clarity regarding intake of these drugs in the remaining studies compromised quality as it was impossible to exclude their contributory role in the presented liver dysfunction. All reports described post intervention clinical condition clearly. There were no adverse events or unanticipated events identified in the case reviews.

3.9.4 Quality assessment for pre and post treatment cohort studies and prospective study combined with case note review

The results of the quality assessment are detailed in Table 3.5. In Pastor-Clerigues et al (2014), those receiving the intervention lipid were deemed to have a Non-Alcoholic Fatty Liver Disease Activity Score (NAS) > 6 caused by parenteral nutrition associated liver disease which was determined by liver biopsy. The comparator group had NAS ≤ 6 (Kleiner et al, 2005). Despite the report stating this to be usual clinical practice, the two groups having differing degrees of liver disease at the outset would result in selection bias. Although the report states the duration the three different comparator lipids were received over, baseline LFT results were not provided. This compromised quality as the variation in LFTs from baseline to the end of the study could not be compared between the intervention and comparator groups.

The title of Xu et al (2012) stated the study was to investigate ‘biopsy proven parenteral nutrition associated liver disease’, though it is not exactly clear how parenteral nutrition associated liver disease was defined, or if all subjects had a liver biopsy at the outset. Only eleven of the fifteen patients are stated to have had a liver biopsy both pre and post intervention. Liver histology is ambiguously detailed to have shown cholestasis and inflammation in ‘most’ cases pre-treatment. Post intervention histology, after one month, is included to illustrate a decrease in cholestasis and inflammation pictorially. However, it is not clear how many individuals were included in these specimens, or in box and whisper plots depicting pre and post intervention cholestasis, fibrosis, steatosis or inflammatory changes. There was clearly no overall loss to follow up as other biochemical data, for example LFTs, were included for all fifteen individuals included in the statistical analysis. As these data are not reported, the study may be subject to reporting bias.

Exposures were measured in a valid manner in all three studies (Pastor-Clerigues et al, 2014; Thomas Gibson et al, 2004; Xu et al, 2012). Thomas Gibson et al (2004) substantiated intervention delivery details with data from patient diaries. Compliance exceeded 90% of the intended administration in twelve of thirteen patients completing more than 2 months (range 75–100%). Complete intervention delivery would be difficult to accurately confirm outside controlled trial settings, though Pastor-Clerigues et al (2014) and Xu et al (2012) do not support the delivery of reported parenteral lipids in the reports or acknowledge this as a study limitation.

No confounding variables were acknowledged in the Pastor-Clerigues et al (2014) study. Xu et al (2012) adjusted for potential overfeeding as a confounding variable. Resting energy expenditure was measured every week to adjust non-protein energy in PN on a weekly basis. However, the report failed to detail how resting energy expenditure was measured. Thomas Gibson et al (2004) also acknowledged confounding variables by stating median (and range) of glucose and lipid provided by the intervention. None of these studies specified if any patients were in receipt of hepatotoxic drugs; the relevance of including these has been highlighted in section 3.9.3. In all studies, follow-up time was sufficient for the sought outcomes to occur. None of the reports mention instrument calibration, which would pose the same potential errors identified in section 3.9.3. Xu et al (2012) acknowledge the potential for inter-observer error by stating the interpretation of liver biopsies was undertaken by one, experienced pathologist. Pastor-Clerigues et al (2014) and Thomas Gibson et al (2004) did not state how many clinicians, or researchers, determined NAS scores or completed anthropometric measurements respectively.

There was no loss to follow up in the Pastor- Clerigues et al (2014) and Xu et al (2012). In Thomas Gibson et al (2004), four patients did not complete the study. The reasons were specified; one patient withdrew consent (after 15 days), one developed abnormal liver function and sepsis and two patients developed sepsis, one of which was fatal. Pastor-Clerigues et al (2014) state the study was a ‘proof of concept observational follow up’. Appropriate statistical analysis was completed though with a small overall sample size, and only two individuals receiving the intervention, inferential tests have limited value. The results should be interpreted with caution. Another flaw of this study is that it is not possible to know if by chance, those with higher NAS scores who received the intervention, were going to improve over time more than those with lower scores; the results may be biased in favour of the intervention group, which may not have been better than the comparators.

3.9.5 Quality assessment conclusion

The overall quality of evidence from all of the included studies was very low. The improvements in liver dysfunction in individual case reviews provide an insight to potential benefits in deploying lipid emulsions as a treatment. They also reflect clinicians' decision-making by presenting how individual cases of liver dysfunction were managed. However, case review findings have low generalisability and it is not possible to establish cause and effect; statistical analysis and adjustments for confounding variables are not possible with case reviews. There were no high-quality randomised control trials identified in this review. In the absence of large, adequately powered intervention studies, the three intervention studies do add to the limited evidence supporting the use of lipid manipulation as a treatment for IFALD in adults. Findings in these studies are relevant, though inferences are compromised by small sample sizes and thus are inadequately powered. Additionally, interventions and reporting outcomes pertinent to this review were not standardised across studies, making it difficult to infer definitive conclusions.

3.9.6 Primary outcome measures

Elevated LFTs and variation in LFTs

The primary outcome measures of this systematic review by intervention and generation of lipid emulsions are summarised in Table 3.6 and detailed further in the data extraction table (Appendix 3).

Table 3.6: Summary of primary and secondary outcomes by intervention and generation of lipid emulsions

Author, year	Intervention lipid, generation of lipid	Duration, Quantity, Dose	Primary outcome measures: Elevated LFTs, variation in LFTs	Secondary outcome measures: Mortality, length of hospital stay (days), number of admissions
Halliken et al, 2008	Olive oil (ω-9) 80%, soybean oil (ω-6) 20% Third	17 months 20 grams per day for 12 months, then 35 grams per day	Baseline: ALP *205 U/L, GGT no baseline, ALT* 95 U/L Approximately 8 weeks: ALP* 200 U/L, GGT no result, ALT 60* U/L Approximately 5 months: ALP *145 U/L, GGT* 110 U/L, ALT *80 U/L	No mortality
Thomas-Gibson et al, 2004		6 months 500ml/100g 2-3 times per week	In 12 patients, baseline Bil fell within normal range and AST no more than 15% outside In 2 patients ALP, GGT or ALT was elevated > twice normal range at baseline with otherwise normal laboratory parameters Transient rises in some LFTs in 4 patients-not stated which, remained persistently abnormal in one severely septic patient who had abnormal baseline LFTs	No mortality One patient left trial due to abnormal liver function tests and sepsis
Xu et al, 2012	Soybean (ω-6) 50% and medium-chain triglycerides (coconut oil) 50% AND fish oil (ω-3) 100% Second and Fourth	One month Up to 10 grams ω-3 per day 0.15-0.20 grams per kilogram per day 'ω-3/ω6 ratio approximately 1:4'	Baseline (median and IQR): Direct Bil 43.7 umol/L (37.4-105.5), Total Bil 65.9 μmol/L (48.5-150.5), ALT 73.1 U/L (35.3-111.3), ALP 150.0 U/L (65.5-334.0), GGT 166.0 U/L (98.3-395.5) 4 weeks (median and IQR): Direct Bil *11.0 umol/L (0.0-31.0) $p \leq 0.001$, Total Bil 26.4 μmol/L (10.0-63.4) $p \leq 0.001$, ALT 55.7 U/L (23.5-103.7) p 0.039, ALP 146.0 U/L (65.0-253.5), GGT 165.6 U/L (62.5-296.0) *approximate value taken from line graph Within 4 weeks, normal direct Bil in 12/15 patients	No mortality

Burns and Gill, 2013	Fish oil (ω-3) 100% Fourth	4 months 45 grams per day 5 times per week	Baseline: Total Bil 12.4mg/dl, ALP 239 IU/L, AST 225 IU/L, ALT 124 IU/L Week 5: Total Bil* 4.2mg/dl and remained in normal reference range, ALP* 510 IU/L, AST* 100 IU/L, ALT* 80 IU/L Week 16: Total Bil 0.9mg/dL, ALP 423 IU/L, AST 87 IU/L, ALT 93 IU/L, all except Total Bil remained above upper limit of reference range	No mortality One planned admission to hospital for first ω-3 infusion, length of stay not stated
Pironi et al, 2010		8 months 75ml/7.5grams lipid per day Approximately 0.20 grams per kilogram per day 6 days per week (5 days per week for the last 2 months)	Baseline: Total Bil 0.69 mg/dL (0.20-1.10), Conjugated Bil mg/dL 0.25 U/L (<0.30), AST 41 U/L (<32), ALT 25 U/L (<31), GGT 129 U/L (<36), CRP 0.10 mg/dL (<0.80) 1 month: Total Bil 0.40 mg/dL, Conjugated Bil mg/dL 0.16 U/L, AST 33 U/L, ALT 22 U/L, GGT 89 U/L, CRP 0.04 mg/dL 3 months: Total Bil 0.60 mg/dL, Conjugated Bil mg/dL 0.25 U/L, AST 44 U/L, ALT 33 U/L, GGT 100, CRP 0.16 mg/dL 7 months: Total Bil 0.44 mg/dL, Conjugated Bil mg/dL 0.16 U/L, AST 24 U/L, ALT 13 U/L, GGT 38, CRP 0.97 mg/dL	No mortality No hospital admissions reported
Venecourt-Jackson et al, 2013		2 ½ months 80g 6 days per week	Baseline: Bil 535 μmol/litre (reference range 0-20), ALT 141 IU/litre (reference range 0-45), ALP 161 IU/L (reference range 40-120), GGT 77 IU/L (reference range 0-60) Week 8: Bil 63, ALT 38*, ALP 60*, GGT 38* Week 10: Normal ALT	No mortality No hospital admissions reported
Pastor-Clerigues et al, 2014	Fish oil (ω-3) 100% followed by Soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15% Fourth and Fourth	6 months 1 gram per kilogram 5 times per week for 4 months followed by 4 times per week for 2 months	Baseline: AST (11-39 IU/L) 97.5 +/- 33.2, ALT (7-33 IU/L) 179 +/- 70.71, GGT (8-55 IU/L) 73.5 +/- 65.7, ALP (50-300 IU/L) 150.5 +/- 58.6, Total bilirubin (<2.5mg/dL) 0.76 +/- 0.05 Week 4: AST (11-39 IU/L) 38.5 +/- 24.7, ALT (7-33 IU/L) 41.5 +/- 23.3, GGT (8-55 IU/L) 28.5 +/- 2.1, ALP (50-300 IU/L) 116 +/- 57.9, Total bilirubin (<2.5mg/dL) 0.66 +/- 0.48 Week 8: AST (11-39 IU/L) 38.4 +/- 9.1, ALT (7-33 IU/L) 36 +/- 7, GGT (8-55 IU/L) 21.5 +/- 6.3, ALP (50-300 IU/L) 98 +/- 36.7, Total bilirubin (<2.5mg/dL) 0.75 +/- 0.4 Week 12: AST (11-39 IU/L) 30.5 +/- 2.1, ALT (7-33 IU/L) 30.5 +/- 7.7, GGT (8-55 IU/L) 31 +/-25.4, ALP (50-300 IU/L) 115 +/- 9.8, Total bilirubin (<2.5mg/dL) 0.53 +/- 0.01 Week 16: AST (11-39 IU/L) 27.5 +/- 6.3, ALT (7-33 IU/L) 30.5 +/- 1.9, GGT (8-55 IU/L) 35.5 +/- 19, ALP (50-300 IU/L) 113.5 +/- 7.7, Total bilirubin (<2.5mg/dL) 0.8 +/- 0.3	No mortality No hospital admissions reported

Hvas et al, 2016	Soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15% Fourth	Duration not stated Dose not stated Twice per week	Baseline: Bil 96 μmol/l, ALT 161 IU/L, ALP 300 IU/L Liver function tests reported to 'slowly improved'	No mortality One admission due to fungal catheter infection and abnormal liver function-length of stay not stated
Moyes et al, 2012		1 year and 4 months 500ml Once per week	Baseline: Bil* μmol/L 145, AST* IU/L 95, ALP* IU/L 195 12 weeks: Bil 100 μmol/L, AST* 55 IU/L, ALP* 420 IU/L 14 months: Bil* μmol/L 10, AST* 40 IU/L, ALP* 145 IU/L	No mortality One admission with jaundice and cholestatic LFTs-length of stay not stated

ALP = alkaline phosphatase, ALT = alanine aminotransferase, Bil = bilirubin, Direct Bil = direct bilirubin, GGT = gamma-glutamyl transferase, IFALD = intestinal failure associated liver disease, IQR = interquartile range, LFTs = liver function tests, LCT = long-chain triglyceride, MCT = medium-chain triglyceride, PN = parenteral nutrition *approximate values taken from line graphs

All studies included LFTs, reporting an improvement in LFTs with values decreasing following the intervention lipid. Of the nine studies, all except two included laboratory baseline values for each of the LFTs analysed (Halliken et al, 2008; Thomas-Gibson et al; 2004). Two studies did not illustrate the improvements in liver dysfunction with actual laboratory values of LFTs (Hvas et al, 2016; Thomas Gibson et al, 2004). Hvas et al (2016) reported 'liver function tests slowly improved' while on the intervention, though the focus of this report was on multiple contributory factors relating to the reversible character of IFALD, opposed to solely focusing on lipid as an intervention and LFT related outcomes.

Halliken et al (2008) reported, approximately 5 months after receiving the 17-month intervention, ALP decreased from approximately 205 to 145 U/L, ALT from approximately 95 to 80 U/L and GGT to 110 U/L, though no baseline GGT result was provided. Also using olive oil (ω-9) 80%, soybean oil (ω-6) 20%, Thomas-Gibson et al (2004) also noted improved LFTs. The ALP, GGT and ALT were reported to have been elevated more than twice that of normal levels at baseline in two patients. The bilirubin was reported to have fallen within the normal range, and AST no more than 15% outside it in twelve of the thirteen patients who received more than two months treatment.

In the study by Thomas-Gibson et al (2004), one patient left the trial prematurely due to 'abnormal liver function tests and sepsis'. It was not stated exactly when the patient left the trial, though on investigation, no definitive cause was found. The LFT abnormalities are reported to have continued over the next 2 years of follow-up. The report states examination of four years biochemistry results did not reveal a 'frameshift' of deterioration while receiving the lipid, which is presented as supportive evidence for the author's conclusion of the intervention lipid being a safe alternative to usual care which, at the time of publication, was soybean oil emulsions. The two aforementioned studies were the only ones that used solely third generation lipids for the intervention, which is reflective of the age of the studies.

Comparing the Halliken et al (2008) single case review with the thirteen-participant study by Thomas-Gibson et al (2004) is difficult as differing lipid dosage, frequency and intervention duration hinder fair comparison. In Thomas-Gibson et al (2004), the dose was five-fold greater compared to the initial starting dose in Halliken et al (2008). The higher dose in Thomas-Gibson et al (2004) was only received 2-3 times per week for six months, compared to daily for 12-months in Halliken et al (2008) (Table 3.6). Thomas-Gibson et al (2004) report usual practice is not to exceed 1 gram per kilogram body mass per day, but do not provide data on the intervention lipid dosage in this format. Halliken et al (2008) also omit lipid dose per body mass. These data would provide more detail on dose by individual study participant body mass.

The Xu et al (2012) study was the only one that combined two intervention lipids in individuals who had developed cholestasis when previously receiving solely soybean based PN (Table 3.6). The lipid dosage was only up to 10 grams per day and the length of time the intervention was given was only one month, which is a relatively short period. Dosage was individualised, as resting energy expenditure was measured weekly with non-protein calorie delivery from PN adjusted accordingly. This ranged from 0.15-0.20 grams per kilogram per day, which was stated as 'ω-3/ω-6 ratio of approximately 1:4'. In one month, a decrease in total bilirubin from a median of 65.9 μmol/L (IQR 48.5-150.5) to 26.4 μmol/L (IQR 10.0-63.4), ($p \leq 0.001$) and direct bilirubin from 43.7 umol/L (IQR 37.4-105.5) to approximately 11.0 umol/L (IQR 0.0-31.0), ($p \leq 0.001$) was noted. Direct bilirubin was also reported to have normalised in 12 of the 15 participants. Direct bilirubin was illustrated in graphical form and the median values presented (with interquartile ranges) reflecting the wide range in values, though outliers would be excluded with results presented in this manner. Additionally, the baseline upper interquartile range value of 105.5 contradicted the line graph of results which appeared to be closer to 86.0.

In the three studies with only fish oil (ω-3) 100% as an intervention, duration varied from two and a half months (Venecourt-Jackson et al, 2013) to 8 months (Pironi et al, 2010), and dose widely from only 7.5g per day, approximately 0.20 grams per kilogram per day, (Pironi et al, 2010) to 80grams per day (Venecourt-Jackson et al, 2013). Frequency of intervention also varied in each of these case reviews (Table 3.6). These differences and the variations in timing of outcomes make it difficult to compare the intervention across the studies. The baseline LFTs were notably lower in Pironi et al, (2010) compared to the other two studies. Modest decreases were noted across the presented LFTs (Table 3.6).

A decrease in bilirubin from a baseline of 535 μmol/litre to 63 μmol/litre at week 8 in Venecourt-Jackson et al, (2013) was the most notable LFT improvement in this study despite remaining above the reference range (Table 3.6). In Burns and Gill (2013), total bilirubin normalised by week 5 and remained in the normal reference range at the end of the study. Though other LFTs showed an improvement, all remained above the upper reference range at week 16. Additionally, it is notable that ALP increased from 239 to approximately 510 IU/L in five weeks and at week 16, remaining higher than intervention outset at 423 IU/L (Burns and Gill, 2013). The authors do acknowledge this, but also state the ALP subsequently declined to pre-treatment value without giving any indication of the timeframe for this resolve.

Pastor-Clerigues et al (2014) infused fish oil 100% in two individuals for four months. Baseline AST, ALT and GGT were elevated at the outset but each showed a decrease each month for the total period of intervention (Table 3.6) ($p<0.05$). On changing to soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15% for the following two months, AST, ALT and GGT were noted to increase at 5 months, 5 and 6 months and 6 months respectively. Comparator groups were already receiving three different lipid types. Baseline LFT results were not provided for comparator groups limiting further interpretation.

In the two case reviews in which soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15% was the intervention, improvements were noted universally (Table 3.6). Duration, dose and variation in LFTs were not stated in Hvas et al (2016). Moyes et al (2012) administered a 500ml dose, for a long duration period of 1 year and 4 months, but lipid was only given once per week. The LFT results over approximately 14 months demonstrated decreases in AST, ALP and a marked decrease in bilirubin from 145 μmol/litre to 10 μmol/litre (Table 3.6).

Chronic cholestasis

Chronic cholestasis was not defined in any of the reports using the pre-specified definition of the persistent elevation > 1.5 times the upper limit of the normal range for > 6 months of two of the following: alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and total bilirubin) (Cavicchi et al, 2000) (Appendix 3 Data extraction table). Thus, it was not possible to directly compare the prevalence of chronic cholestasis across any of the studies. Where cholestasis was described, it was identified by histology from liver biopsies (Burns and Gill, 2013; Hvas et al, 2016; Moyes et al, 2012; Xu et al, 2012). When seeking a confirmatory diagnosis of parenteral nutrition associated liver disease, Venecourt-Jackson et al (2013) reported the patient declined a liver biopsy. Pironi et al (2010) also took liver biopsies prior to and post treatment, though results were not used to classify cholestasis initially, but to assess non-alcoholic steatohepatitis. Pastor-Clerigues et al (2014) also took liver biopsies to determine non-alcoholic steatohepatitis and hepatic fibrosis scores.

Xu et al (2012) reported soybean (ω-6) 50% and medium-chain triglycerides (coconut oil) 50% and fish oil (ω-3) 100% resulted in an improvement in cholestasis confirmed with liver biopsies. Burns and Gill (2013) demonstrated improvements in cholestasis with fish oil (ω-3) 100% with the normalisation of total bilirubin in 16 weeks from 12.4 to 0.9 mg/dL and of the inflammatory marker C-reactive protein. Pironi et al (2010) and Venecourt-Jackson et al (2013) noted cholestasis improved measured by liver histology and normalised LFTs respectively using fish oil (ω-3) 100% (Appendix Table 3). Moyes et al (2012) demonstrated an improvement in cholestasis with a fibroscan which showed decreased liver stiffness with soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15%. This lipid also improved cholestasis reportedly measured by improved liver function in Hvas et al (2016).

3.9.7 Secondary outcome measures

Mortality attributable to IFALD, length of hospital stay, number of admissions to hospital due to IFALD

Secondary outcomes for lipid emulsions are summarised in Table 3.6 and detailed further in the data extraction table (Appendix 3). None of the studies reported any mortality attributable to IFALD or indeed liver dysfunction of any other description. Only one study detailed a hospital admission due to IFALD prior to the participant receiving an IFALD diagnosis (Hvas et al, 2016). Here, the admission was due to a fungal catheter infection and abnormal liver function, though the length of stay was not reported. Only two other studies included details of hospital admissions caused by liver dysfunction (Burns and Gill, 2013 and Moyes et al, 2012). The first reported a case of a patient who underwent a planned hospital admission for observation when receiving the first of three intervention lipid infusions, but the length of stay was not reported (Burns and Gill, 2013). The second reported a case of a patient who had one admission with jaundice and cholestatic LFTs of which, the length of stay was not clear from the report. The lead author for this study (Moyes et al, 2012) was emailed for clarity, but a response was not received. Thomas-Gibson et al (2004) state one patient left the trial due to abnormal liver function tests and sepsis. This required further investigation, which one can assume would have required hospital admission as the patient was septic, though no details are included for this assumption to be confirmed.

3.10 Discussion of the systematic review findings

The systematic review sought to determine the effectiveness of treatment strategies for IFALD in adults. The findings were limited by the small number of very low-quality studies identified. No randomised control trials were included, and six of the nine studies were case reviews. The three intervention studies were inadequately powered and were not suited to pooling for meta-analysis. Therefore, it was not possible to make meaningful inferences regarding the effectiveness of the treatment strategies identified. Despite these limitations, the studies unanimously featured lipid manipulation, highlighting both its contributory role and its importance as a potential treatment for IFALD.

Five different types of lipid treatment formulae were evaluated (Table 3.3). Each of these demonstrated an improvement in LFTs. None of the studies measured improvements in cholestasis using the pre-specified definition (Cavicchi et al, 2000). Liver histology was most commonly deployed to measure cholestasis. Improvements in cholestasis were noted with three lipid types: soybean (ω-6) 50% and medium-chain triglycerides (coconut oil) 50% and fish oil (ω-3) 100% (Xu et al, 2012); fish oil (ω-3) 100% (Burns and Gill, 2013; Pironi et al, 2010 and Venecourt-Jackson et al, 2013); and soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15% (Hvas et al, 2016; Moyes et al, 2012).

The clinical improvements in LFTs and cholestasis, using these predominantly fourth generation lipids, lacked consistency in duration, quantity and dosage. These variations hindered the comparison of interventions. Additionally, markers of clinical improvement, including the range and timing of LFTs measured, differed across the studies. These findings suggest that while lipids are used as a treatment for liver dysfunction, there is a diversity in current clinical practice. This is unsurprising given the paucity of studies pertaining to the use of lipid as an intervention for IFALD.

Although the presence of liver disease in those receiving long-term HPN is well established (Cavicchi et al, 2000; Kumpf, 2006), previous intervention studies have not evaluated the efficacy of the lipid emulsions in adults with established IFALD. Furthermore, in view of the serious health consequences which IFALD may potentially lead to, which include liver transplantation and death (Pironi et al, 2012), it is imperative that both the preventative and treatment role of lipid emulsions are fully explored.

In the absence of studies specifically focussing on resolving IFALD with lipids as the intervention, other studies pertaining to those with Intestinal Failure receiving lipid interventions were explored. These were reviewed for relevant findings relating to the primary and secondary outcomes of this systematic review (Table 3.2). Studies comparing lipids in adults with Intestinal Failure in the absence of IFALD are also limited, and the longest study duration to date is 12-months. Klek et al (2018) evaluated long-term safety and efficacy in terms of managing liver function and IFALD prevention, as previously stated in section 2.6. In this randomised control trial, it was hypothesised that third generation lipid, olive oil (ω-9) 80%, soybean oil (ω-6) 20%, would improve liver test results and decrease bilirubin. In this lipid group, the GGT and bilirubin did show a decrease over the 12 months ($p=0.0079$; $p=0.0023$ respectively). However, as all groups showed a normalisation of LFTs, the study demonstrated that lipids from all four generations were largely comparable across the cohort.

Another recent study was completed by Osowska et al (2018) on a cohort of 32 patients with Intestinal Failure receiving HPN. Individuals did not have liver disease and had been in receipt of first generation soybean lipid emulsion HPN for at least two years previously. An intervention of either third generation olive oil (ω-9) 80%, soybean oil (ω-6) 20%, or fourth generation soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15% was then received for 60 days. In the olive oil (ω-9) 80%, soybean oil (ω-6) 20% group, GGT decreased ($p=0.044$), and there were and no changes in the soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15% group. As per Klek et al (2018), these findings would suggest third generation (olive oil (ω-9) 80%, soybean oil (ω-6) 20%) has a modest superiority in terms of reducing LFTs. These findings add some strength to support the use of this lipid in the management of liver dysfunction as noted in two of the papers identified in this review (Halliken et al, 2008; Thomas-Gibson et al, 2004).

There have been systematic reviews and meta-analyses featuring parenteral lipids previously, but these have not solely featured adult populations with established Intestinal Failure receiving long-term HPN. Lauriti et al (2014) performed a systematic review to determine the incidence of parenteral nutrition associated cholestasis and IFALD in children receiving PN for ≥14 days, and to review the efficacy of measures used to prevent and treat these. In this report, only prospective cohort studies and randomised control trials were included in those <18 years old, without cholestasis or liver disease at the outset, who received PN for ≥14 days. The incidence of cholestasis was high and directly proportional to the duration on PN; 15.7% for PN ≤1 month up to 60.9% for PN ≥2 months ($p<0.0001$). These high rates of cholestasis may relate to the immaturity of the neonatal liver in which the uptake and synthesis of bile salts and enterohepatic circulation are compromised (Watkins et al, 1975). Hence, there is a more rapid progression to clinically relevant liver disease in children, as discussed in section 2.3. The authors stated that fish oil (ω-3) 100% and soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15% may be beneficial in both the prevention and treatment of IFALD, but there was insufficient evidence to support using them. These findings have limited direct comparability to adults in whom IFALD presents and progresses differently.

Tian et al (2013) evaluated soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15% in the post-operative period following elective thoracic or abdominal surgery (n=306). In this systematic review and meta-analysis of adults, only randomised control trials were included. Compared with soybean oil, this lipid resulted in reductions in AST, ALT, GGT and ALP; the corresponding relative effects were -5.25, 95% CI -8.52, -1.98 ($p=0.02$); -8.92, 95% CI -14.23, -3.60 ($p= 0.001$); -23.46, 95% CI -40.13, -6.79 ($p=0.006$); -19.56, 95% CI -29.85, -9.28 ($p=0.0002$) respectively. However, these findings were based on only two studies, in which each lipid was received for 6 days only (Antebi et al, 2004; Mertes et al, 2006). Not only was the population different from adults with IFALD, the intervention was very short and not in a population with any form of known liver disease. These findings do, however, suggest that soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15% is effective in reducing LFTs in a different population to adults with Intestinal Failure or indeed IFALD.

A systematic review and meta-analysis comparing third generation olive oil (ω-9) 80%, soybean oil (ω-6) 20% and fourth generation soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15% to first generation soybean oil (ω-6) was completed by Dai et al (2016). The report included 15 randomised control trials, in a population with mean treatment ages ranging from 26.14 weeks to 73.2 years. Reasons for receiving parenteral lipid included: premature birth, short bowel syndrome, surgical interventions, haemodialysis, intractable diarrhoea, critical illness and pseudo-obstruction combined with short bowel syndrome. The report found both lipids similar to first generation soybean oil (ω-6) in terms of safety. The meta-analysis, which included studies that ranged from 5-90 days, found ALP was higher in the olive oil (ω-9) 80%, soybean oil (ω-6) 20% group compared to soybean oil ($p<0.00001$), whereas in the soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15%, both AST and ALP concentrations were lower than the first generation soybean oil (ω-6) ($p= 0.004$; $p=0.02$ respectively). When the meta-analysis was performed on adults only, it showed that ALT and ALP were lower in those in the soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15% group than in those given soybean oil ($p=0.004$; $p=0.03$ respectively).

The Dai et al (2016) report did include individuals with short bowel syndrome, a known pathophysiological condition resulting in the development of Intestinal Failure (Pironi et al, 2018). The improvements in ALT and ALP would suggest that soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15% warrants further investigation in those with Intestinal Failure receiving long-term HPN, as the report only accounted for LFT benefits in the first 90 days of receiving PN. The report did not account for any sepsis or other inflammatory processes, such as surgical interventions, that may have contributed to liver dysfunction which one could postulate are less likely to be seen in a more stable, established HPN population.

In the present review, there was no reported mortality attributable to IFALD or any other form of liver dysfunction in those receiving the lipid interventions. Knowing the number of admissions and length of stay attributable to IFALD in the identified studies would aid the evaluation of its health economic impact. IFALD can be potentially fatal (De Meijer et al, 2010), though the findings of this review suggest this is not common. This concurs with Pironi et al (2012), whose review of eleven studies cited only 15 (4%) of 381 PN related deaths were attributed to liver disease in a mixed patient population of 1310 adults. The reports did not include data on length of hospital stay pertaining to IFALD, or indeed any other form of liver dysfunction. Knowing the number of admissions and length of stay attributable to IFALD would have provided an insight into the health economic impact.

3.11 Protocol amendment

One amendment was submitted on 10th July 2017 to correct an error in the originally stated study eligibility criteria; the protocol had initially stated 'prospective and retrospective case control studies' instead of 'prospective studies and case control studies'.

3.12 Limitations of systematic review

The systematic review was limited by excluding articles not in English language. One study was eliminated at shortlisting due to being in Chinese (see Appendix 2 shortlisting form). As stated in section 3.1, only one of the two systematic review protocol questions is included in the present thesis. The years of inclusion were another limitation, though including earlier search years would be unlikely to increase the number of studies found due to the use of parenteral lipid only commencing relatively recently (section 2.5). Furthermore, parenteral lipid formulae and dosage have only been investigated independently for liver dysfunction since Cavicchi et al's (2000) study of permanent Intestinal Failure. In this study parenteral lipid of greater than 1 gram per kilogram per day and the presence of cholestasis were associated with the incidence of complicated liver disease related to parenteral nutrition.

The comparison of efficacy of each lipid intervention was compromised due to the poor study quality. The review lacks high quality studies to conclude which lipid had the greatest effect on LFTs and chronic cholestasis. The quality of evidence is poor being predominantly based on individual case reviews in which statistical analysis is not possible. Furthermore, the included intervention studies featured very small samples. No randomised control trials or adequately powered intervention studies were identified. As no studies were suited to pooling results, a meta-analysis could not be performed. The wide variation in dose, frequency and length of treatment in included studies may reflect the lack of clear guidance on the use of lipids to treat of IFALD.

3.13 Future research

The evolution of lipid has widened clinicians' choice of PN formulae. However, there is a clear gap in the literature on the optimal type of lipid to both prevent and treat liver dysfunction while avoiding essential fatty acid deficiency in adults receiving long-term HPN. In order to compare which lipid emulsions are most effective for these outcomes, adequately powered randomised controlled studies would be hierarchically superior to observational studies (Guyatt et al, 1995). Randomised control trials have the advantage of a prospective design with pre-defined interventions and end-points for populations that fall within the inclusion criteria (Sørensen et al, 2006). An adequately powered randomised controlled study would minimise bias and provide strong primary evidence to support lipid choice and dosage. However, this type of study would be expensive and would also pose ethical challenges in deciding on control group lipid in those with established IFALD. In comparison, an observational study, such as a retrospective cohort study, would be disadvantageous in terms of being more prone to biases (Thiese, 2014). However, existing large cohorts in receipt of lipid containing HPN do provide a ready source of clinical data which can be analysed retrospectively. Unlike a randomised control study, such analyses could be undertaken without the need to enrol patients, provided patients agreed to their data being used for research. Furthermore, such studies can be undertaken with a priori parameters to measure liver dysfunction and chronic cholestasis.

A retrospective cohort study on those with established Intestinal Failure comparing HPN lipid type would support a comparison of liver dysfunction, risk of chronic cholestasis and tolerability. Furthermore, the impact of changing lipid type in HPN could be evaluated for each of these outcomes. These data could contribute to evidence guiding clinicians on how to treat IFALD with lipid as an intervention. This study will compare adults receiving HPN with soybean oil or olive oil 80% and soybean oil 20% with soybean 30%, medium-chain triglycerides 30%, olive oil 25%, fish oil 15%.

Chapter 4 Empirical research question, aim and objectives

4.1 Research question

Do patients with Intestinal Failure who receive fourth generation intravenous lipid emulsion (soybean oil, medium-chain triglyceride, olive oil and fish oil) in home parenteral nutrition have different health outcomes to those receiving alternative lipids?

4.2 Aim

To determine whether fourth generation (soybean oil, medium-chain triglyceride, olive oil and fish oil) intravenous lipid emulsion is associated with more effective clinical outcomes compared with earlier generation lipids.

4.3 Objectives

Objective 1: To identify whether the type of parenteral lipid emulsion received long-term (twelve consecutive months) increases the risk of chronic cholestasis.

Objective 2: Identifying differences in liver dysfunction between lipid groups.

Objective 3: To identify the impact of changing lipid group from earlier generation lipids to soybean oil, medium-chain triglyceride, olive oil and fish oil emulsion on chronic cholestasis and liver dysfunction.

Objective 4: Identifying whether there are differences in body mass index by lipid group.

Objective 5: To determine whether the prevalence of line sepsis differs by lipid group.

Objective 6: Identifying whether there were any clinical signs of essential fatty acid deficiency in those receiving soybean oil, medium-chain triglyceride, olive oil and fish oil.

Chapter 5 Methods

5.1 Research design

The study design was a retrospective longitudinal cohort study of adults with established intestinal failure to assess the impact of different lipids on their health status in terms of chronic cholestasis, liver dysfunction, body mass index, line sepsis and clinical signs of essential fatty acid deficiency. The type of lipid emulsion received by the patient had previously been decided by clinicians caring for those in the study. Individuals were stratified into two groups: those who received SMOFlipid® and a comparator group, those who received standard lipid (Intralipid® or ClinOleic® lipid) both over 12 consecutive months. The components of parenteral nutrition in the two lipid groups are shown in Table 5.1.

Table 5.1: Components and lipid generation of parenteral nutrition in the two comparison groups

SMOFlipid® group (Fourth generation lipid)	Standard lipid group	
	Intralipid® (First generation lipid)	ClinOleic® (Third generation lipid)
Soybean oil (ω-6) 30% Medium-chain triglycerides 30% Olive oil (ω-9) 25% Fish oil (ω-3) 15%	Soybean oil (ω-6) 100%	Olive oil (ω-9) 80% Soybean oil (ω-6) 20%

5.2 Research setting

This research was based at Salford Royal NHS Foundation Trust. This 728-bed teaching hospital, based in the North West of England, is one of only two UK centres for specialised Intestinal Failure care. Services are provided for both in-patients (in a 21-bed unit) and out-patients with Intestinal Failure by an expert multi-disciplinary team. The very specific clinical features of this patient group with established Intestinal Failure provided a cohort suited to this research in a single location. A database on all patients receiving PN was commenced in 2011. The present research period spanned from 1st April 2011 to 31st March 2015.

5.3 Inclusion and exclusion criteria

The inclusion criteria were for patients (in or out-patients), in receipt of PN for > 90 days and over 18 years old. These criteria ensured the research only included adults receiving parenteral nutrition for a length of time that would support the comparison of the two lipid groups under analysis. Individuals only receiving intravenous fluids and electrolytes were excluded as these individuals did not receive lipids.

5.4 Minimising bias

Potential sources of bias were considered and reduced where possible prior to commencing data collection and analysis. Selection bias was minimised as the entire study population had established Intestinal Failure and were in receipt of HPN and therefore, at risk of developing the pre-defined outcomes of interest. It was, however, not possible to adjust for selection bias that may have occurred due to the clinician's choice of a particular lipid type that may have been based on assessment of baseline liver function or a prediction of future liver dysfunction, as these variables were unknown. Bias from confounding variables were included in the regression analysis where possible, though it was not possible to include all confounding variables, for example lack of enteral nutrition, as these data were not available to the researcher.

The variables analysed and outcomes sought were specific and clearly defined prior to collating data. For example, by outlining the parameters of liver function test results for chronic cholestasis a priori, data could be objectively retrieved. Similarly, channelling bias in the analysis was minimised by having two defined lipid groups and those not falling into these groups being excluded from the lipid group analysis.

5.5 Data collection

For the cohort who received lipid in HPN, the following baseline characteristics were extracted: gender (male/female), age at admission (years), initial primary diagnosis, classification of Intestinal Failure prior to commencing HPN (type 2, type 3) and duration of HPN (days). Individuals were grouped as follows: those receiving HPN, those receiving HPN > 90 days, those not receiving SMOFlipid® or standard lipid for 12-months, those receiving SMOFlipid® or standard lipid for 12-months, those receiving SMOFlipid® for 12-months and those receiving standard lipid for 12-months.

For individuals meeting the study inclusion criteria, the following characteristics were also extracted: small bowel length (cm) and baseline liver function (alkaline phosphatase (ALP) (U/L), gamma-glutamyl transferase (GGT) (U/L), bilirubin (U/L), alanine aminotransferase (ALT) (U/L)) (+/-2 weeks). Individuals were grouped as follows: those who received SMOFlipid® or standard lipid for 12 consecutive months and those who did not receive SMOFlipid® or standard lipid for 12 consecutive months.

The numbers in each group with chronic cholestasis were selected from LFT results by noting if the following criteria were satisfied: *the persistent elevation greater than 1.5 times the upper limit of the normal range for more than 6 months of two of the following: alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and total bilirubin* (Cavicchi et al, 2000). Liver function tests results from 10 weeks before, or 2 weeks after the completion of the 12-month of lipid PN were included in the analysis. The range in inclusion dates was decided as individuals were infrequently observed to have liver function tests within a close margin of starting each lipid though frequently coinciding with the 12-month date.

Further exploration was undertaken to determine if those with chronic cholestasis had it on commencing either lipid. It was not possible to define chronic cholestasis on the persistent elevation of liver function parameters for more than 6 months as these data pre-dated the individuals' transfer to Salford Royal Hospital and were not available. Subsequently, a pragmatic definition was used: *the persistent elevation greater than 1.5 times the upper limit of the normal range at baseline (+/- 4 weeks) for two of the following: alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and total bilirubin.*

Individuals in the standard lipid group with chronic cholestasis were reviewed to establish if they subsequently received SMOFlipid®. For these individuals, the duration of receiving SMOFlipid® was noted (in months). Liver function test results were reviewed at 6 months, 12 months (+/- 4 weeks) and the presence of chronic cholestasis within the subsequent 12-months of commencing SMOFlipid® determined. The following confounding variables, known to be associated with liver dysfunction and chronic cholestasis, were also collated: gender (male/female), admission age (years), mean glucose energy (kilocalories per kilogram per day), mean lipid energy (kilocalories per kilogram per day), total number of days on HPN (or end of study), receiving hepatotoxic drugs and the presence of sepsis (on starting the lipid or between 10 and 12 months). Mean glucose and lipid energy were manually calculated by reviewing prescription dates and changes during the 12-month lipid period.

Liver function tests results were noted in both lipid groups at baseline, as previously detailed, and at 12-months (+/- 6 weeks). These data enabled analysis of liver function on commencing either lipid, variations over the 12-month period and an end point of 12-months post continuous lipid delivery. Liver function test results at 12-months were correlated with mean lipid doses (kilocalories per kilogram per day) on scatterplots for both lipid groups. The range in inclusion dates was decided as individuals were observed to have liver function tests within a close margin of starting each lipid though infrequently coinciding with the 12-month date. Subsequently, a wider margin was chosen to obtain data to include analysis at 12 months. All liver function tests were analysed at the same laboratory at Salford Royal Hospital. Data on hospital re-admissions directly attributable to liver dysfunction within 12 months of lipid commencement were noted for both groups.

Body mass index values for those in both lipid groups were noted at baseline and at 12-months after commencing either lipid. Values included in the analysis were +/- six weeks actual HPN dates. The presence of line sepsis was also noted, and values included in the analysis were +/- four weeks actual HPN dates. Data on clinical signs of essential fatty acid deficiency during the four-year study period in those who received SMOFlipid® were noted.

The following variables were not available: PN infusion period, enteral intake, anthropometric measurements of mid-arm muscle circumference or hand-grip strength. The following variables were available but not extracted to be included in any of the analyses: total energy and total nitrogen.

5.6 Statistical analysis

5.6.1 Descriptive statistics

Categorical variables were summarised using frequency counts and percentages. Continuous variables with approximately symmetrical distributions were summarised using mean and standard deviations; 95% confidence intervals were estimated for means and differences between means. Skewed continuous variables were summarised using medians, ranges and interquartile ranges. Scatterplots were used to display the relationship between two continuous variables with points identified by categorical variables.

Throughout, analysis was performed using as many data values as possible for each analysis, and numbers of individuals included in or missing from each analysis were clearly reported in tables.

5.6.2 Hypothesis tests

Categorical variables were compared between two groups using Pearson's chi-square test or Fisher's exact test when expected cell counts were less than 5. Continuous variables were compared using independent samples-t-tests unless variables were skewed in which case, the Mann Whitney test was used. When the degree of skewness was uncertain, both tests were completed, and the results were compared to determine whether the two tests agreed on the statistical significance of the difference between the two groups. If the tests agreed, then the skewness present did not have an impact on the comparison; if the tests disagreed, the skewness present did have an impact and the Mann-Whitney test results were considered to have greater validity. A significance of α = 0.05 was used.

5.6.3 Regression techniques

Multiple logistic regression was used to assess the association between type of lipid received and chronic cholestasis within twelve months (dependent variable) adjusted for a number of confounding variables (detailed above). All available data were collected.

Sample sizes for using logistic regression to identify factors associated with chronic cholestasis were based on Peduzzi et al (1996), who derived a rule-of-thumb for estimation of parameters based on the number of explanatory variables and prevalence of the outcome. Sample sizes for using multiple linear regression to identify factors associated with liver function were based on Tabachnick and Fidell (2001, p 117) and Miles and Shevlin (2001, pp 119-125), who derived rules-of-thumb for 80% power and moderate effect sizes. The figures were provided by Dr Malcolm Campbell, Lecturer in Statistics at The University of Manchester. Sample sizes needed to predict chronic cholestasis assumed a prevalence of 18.2%, which was the prevalence found in this study. The logistic regression model fitted in the analysis has eight explanatory variables which required a sample size of 440. An alternative approach would be to look at lipid type in combination with each confounding variable in turn. This would have required a sample size of 110.

Multiple linear regression was used to assess the association between type of lipid received and liver function tests at twelve months (dependent variable) adjusted for a number of confounding variables (detailed above). The multiple regression model fitted in the analysis has nine explanatory variables which required a sample size of 122. An alternative approach would be to look at lipid type in combination with each confounding variable in turn. This would have required a sample size of 106. Multiple linear regression was also used to assess the association between liver function tests at twelve months (dependent variable) and dose and type of lipid received. The number of explanatory variables in these models was three (lipid dose, lipid type and their interaction). The multiple regression model for liver function tests fitted in the analysis required a sample size of 107. In addition to p-values being interpreted, effect sizes and confidence intervals for the multiple regression coefficients for the dummy variable defining lipid group were also assessed.

5.7 Ethical considerations

It was essential to ensure that research integrity was maintained prior to and during all stages of the research process. According to the four principles of The Singapore Statement, honesty, accountability, professionalism and good stewardship are central to attaining research integrity (World Conference on Research Integrity, 2010). Adherence to these principles was central to the ethical considerations for this research. Individual consent was not required as the research was based on secondary data analysis and did not entail the recruitment of study participants. Nonetheless, appropriate measures were taken to ensure patient data were safeguarded to maintain confidentiality. The researcher only had access to fully pseudo-anonymised data as there were no identifiable patient details in the data set transferred to the researcher. Only the clinical team were aware of the patients' details.

An application outlining details of the intended research was approved by The Health Service Health Research Authority prior to commencing data analysis (Integrated Research Application System ID 214468). This approval, which was submitted by an academic supervisor, ensured the research was compliant with the approval process for NHS organisations providing a duty of care to patients. This includes the legal compliance, evaluation of governance and the opinion of an independent research ethics committee (Health Research Authority, 2018).

Patient data was extracted from an Excel® (Microsoft version 16.10) spreadsheet compiled specifically for this research by a data project manager at Salford Royal Hospital. Data included in the Excel® spreadsheet were taken from a number of sources pertaining to patients at Salford Royal Hospital therefore, protecting superfluous patient data beyond the scope of this research being shared. The Excel® spreadsheet was accessed on a secure encrypted university laptop, via a password, only disclosed to the researcher. Patient data were pseudo-anonymised with each individual recognisable by a unique number only. Data taken from the Excel® spreadsheet and subsequently analysed on SPSS (IBM version 23) were stored on The University of Manchester's secure and backed up 'P-drive'. These measures ensured secure access and storage of sensitive patient data.

The researcher also undertook additional training to attain a greater awareness in the principles of ethical practice and research integrity prior to undertaking the analysis. This included The National Institute for Health Research 'Introduction to Good Clinical Practice eLearning Secondary Care' and Epigeum 'Research Integrity – Biomedical Sciences Online Course'.

The research was sponsored by Fresenius Kabi Limited, the company who manufacture SMOFlipid®. Neither the researcher or any of the supervisors had any personal association or employment with this company. It could be argued that a hypothetical conflict of interest, for example, favouring outcomes related to SMOFlipid® could be postulated should such links exist. Conversely, even without such associations, it has been noted that positive bias does exist for the product of interest in industry sponsored research when compared with non-industry sponsored research (Mandrioli et al, 2016). Therefore, declaring all funding sources in any study is key to ensuring transparency.

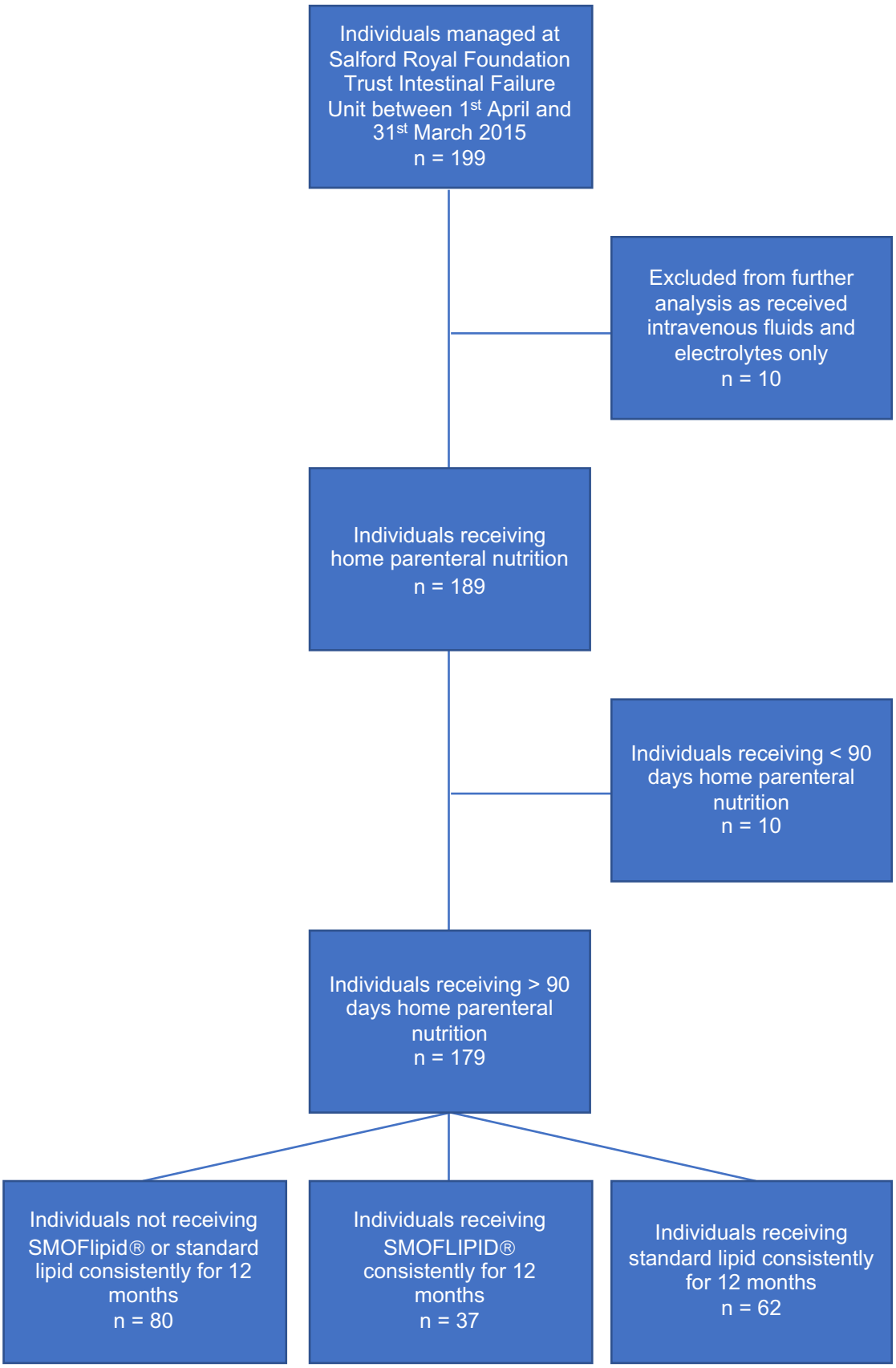
Chapter 6 Results

6.1 Sample characteristics

6.1.1 Characteristics of the sample

One hundred and ninety-nine individuals were managed at Salford Royal NHS Foundation Trust Intestinal Failure Unit between 1st April 2011 and 31st March 2015. Ten individuals received intravenous fluids and electrolytes only and were excluded. One hundred and eighty-nine individuals received HPN, ten for less than 90 days. Of the people receiving HPN for > 90 days, 80 did not receive SMOFlipid® or standard lipid, 37 received SMOFlipid® and 62 standard lipid for 12 consecutive months (Figure 6.1).

Figure 6.1: Flow diagram



Gender, admission age, initial primary diagnosis classification of Intestinal Failure prior to commencing HPN and duration on HPN across the total sample and by subgroup are shown in Table 6.1.

Table 6.1: Categorical baseline characteristics and duration on home parenteral nutrition of sample by group

	Individuals receiving HPN (n=189)	Individuals receiving HPN > 90 days (n=179)	Individuals not receiving SMOFlipid or standard lipid for 12 months (n=80)	Individuals receiving SMOFlipid or standard lipid for 12 months (n=99)	Individuals receiving SMOFlipid for 12 months (n=37)	Individuals receiving standard lipid for 12 months (n=62)
Gender						
Male	78 (41.3%)	75 (41.9%)	31 (38.8%)	44 (44.4%)	21 (56.8%)	23 (37.1%)
Female	111 (58.7%)	104 (58.1%)	49 (61.3%)	55 (55.6%)	16 (43.2%)	39 (62.9%)
Admission age (mean; SD)	54.53 (SD 14.99)	54.58 (SD 15.21)	54.83 (SD 14.68)	54.38 (SD 15.70)	51.57 (SD 16.09)	56.06 (SD 15.34)
Initial primary diagnosis						
Vascular	26(13.8%)	26 (14.5%)	11 (13.8%)	15 (15.2%)	8 (21.6%)	7 (11.3%)
Surgical Complications	78 (41.3%)	71 (40.0%)	34 (42.5%)	37 (37.4%)	17 (45.9%)	20 (32.3%)
Crohn's Disease	32 (16.9%)	31 (17.3%)	10 (12.5%)	21 (21.2%)	6 (16.2%)	15 (24.2%)
Motility Disorders	18 (9.5%)	17 (9.5%)	6 (7.5%)	11 (11.1%)	2 (5.4%)	9 (14.5%)
Radiation Enteritis	5 (2.7%)	5 (2.8%)	2 (2.5%)	3 (3.0%)	1 (2.7%)	2 (3.2%)
Active Malignancy	16 (8.5%)	16 (8.9%)	11 (13.8%)	5 (5.1%)	1 (2.7%)	4 (6.5%)
Scleroderma	2 (1.1%)	1 (0.6%)	1 (1.3%)	0 (0.0%)	0 (0%)	0 (0%)
Other	12 (6.4%)	12 (6.7%)	5 (6.3%)	7 (7.1%)	2 (5.4%)	5 (8.1%)
Classification of Intestinal Failure prior to commencing HPN						
Type 2	150 (79.4%)	143 (79.9%)	66 (82.5%)	77 (77.8%)	33 (89.2%)	44 (71.0%)
Type 3	39 (20.6%)	36 (20.1%)	14 (17.5%)	22 (22.2%)	4 (10.8%)	18 (29.0%)
Duration on HPN (days; median, range, IQR)	476, 6-1474, 261.5-793.5	513, 99-1474, 307-813	273, 99-1112, 194.25-357.75	724, 377-1474, 536-949	599, 381-1273, 475.5-823.5	795, 5377-1474, 604.75-1075.75

HPN = home parenteral nutrition

6.1.2 Characteristics of individuals receiving home parenteral nutrition for >90 days

One hundred and seventy-nine individuals received HPN for > 90 days and were included in further analysis. Gender, admission age, initial primary diagnosis classification of Intestinal Failure prior to commencing HPN and duration on HPN closely matched the whole sample (Table 6.1).

Ninety-nine individuals received either SMOFlipid® or standard lipid for 12 consecutive months and were included in further analysis (Table 6.1). There was no statistical evidence of an association between gender (p=0.443), admission age (t-test p=0.848, Mann U Whitney test p=0.925), initial primary diagnosis (p=0.327) or classification of Intestinal Failure (p=0.443) and whether or not individuals received SMOFlipid® or standard lipid emulsion for 12 consecutive months. Continuous baseline characteristics of individuals receiving SMOFlipid® or standard lipid emulsion for 12 consecutive months or not are shown in Table 6.2. The only observed difference was that GGT results were higher in excluded versus included individuals (121.60 U/L versus 44.20 U/L respectively) (t-test p=0.039, Mann Whitney U test p=0.031) (Table 6.2).

Table 6.2: Continuous baseline characteristics of individuals receiving SMOFlipid® or standard lipid emulsion for 12 consecutive months (n=99) or not (n=80)

Continuous baseline characteristic	Lipid received for 12 consecutive months				t-test p-value	Mann-Whitney U test p-value
	No		Yes			
	n	Mean (SD)	n	Mean (SD)		
Small bowel length (cm)	34	99.56 (58.13)	41	91.22 (61.45)	0.551	0.405
ALP (U/L) (30-130 U/L)	77	202.49 (209.24)	99	169.47 (106.11)	0.209	0.986
GGT (U/L) (<38 U/L)	10	121.60 (102.44)	10	44.20 (40.37)	0.039	0.031
Bil (U/L) (0-20 umol/L)	71	7.34 (4.93)	84	8.79 (7.34)	0.159	0.326
ALT (U/L) (7-40 U/L)	77	46.92 (50.91)	99	45.33 (37.42)	0.812	0.458

ALP = alkaline phosphatase, ALT = alanine aminotransferase, Bil = bilirubin, GGT = gamma-glutamyl transferase

6.1.3 Characteristics of individuals receiving SMOFlipid® or standard lipid emulsion for 12 consecutive months

Two individuals received both lipid types for 12 consecutive months. Analysis was based on the first lipid received (in both cases this was standard lipid). Thirty-seven individuals received SMOFlipid® and 62 received standard lipid (Table 6.1). A lower proportion of males received standard lipid (n=23, 37.1%) compared to SMOFlipid® (n=21, 56.8%) (p=0.057) but there was no clear evidence of a statistical effect. There was no difference between lipid groups in admission age (t-test p=0.169, Mann Whitney U test p=0.202) and initial primary diagnosis (p=0.438).

There was a difference between groups in classification of Intestinal Failure (p=0.035), the SMOFlipid® group containing proportionally more Type 2 patients than the standard lipid group (n=33, 89.2% versus n=44, 71.0%). Median duration on HPN for individuals on SMOFlipid® was 599 days (range 381-1273, IQR 475.5-823.5) and 795.5 days (range 377-1474, IQR 604.75-1075.75) for individuals on standard lipid which was a difference (p=0.002). The only observed difference in continuous baseline characteristics was that ALT results were higher in the SMOFlipid® compared to the standard lipid group (56.51 U/L versus 38.66 U/L respectively) (t-test p=0.042, Mann Whitney U test p=0.090) (Table 6.3).

Table 6.3: Continuous baseline characteristics of individuals receiving SMOFlipid® (n=37) or standard lipid emulsion (n=62) consistently for 12 months

Continuous baseline characteristic	SMOFlipid®		standard lipid		t-test p-value	Mann-Whitney U test p-value
	n	Mean (SD)	n	Mean (SD)		
Small bowel length (cm)	18	86.94 (62.50)	23	94.57 (61.81)	0.699	0.664
ALP (U/L) (30-130 U/L)	37	178.46 (111.71)	62	164.11 (103.18)	0.518	0.615
GGT (U/L) (<38 U/L)	2	39.00 (16.97)	8	45.50 (45.22)	0.852	0.793
Bil (U/L) (0-20 umol/L)	30	9.67 (6.70)	54	8.30 (7.69)	0.416	0.247
ALT (U/L) (7-40 U/L)	37	56.51 (47.02)	62	38.66 (28.70)	0.042	0.090

ALP = alkaline phosphatase, ALT = alanine aminotransferase, Bil = bilirubin, GGT = gamma-glutamyl transferase

6.2 Objective 1: To identify whether the type of parenteral lipid emulsion received long-term (twelve consecutive months) increases the risk of chronic cholestasis

6.2.1 Lipid group comparison on the prevalence of chronic cholestasis within 12 months

It was not possible to establish the presence of confirmed chronic cholestasis in all individuals due to missing data (see Table 6.4). Chronic cholestasis was observed in 18 individuals. Although the proportion of individuals with chronic cholestasis was higher in those receiving standard lipid (n=13, 25.0%) compared to SMOFlipid® (n=5, 17.9%), this did not reach statistical significance (p=0.466 Table 6.4).

Table 6.4: Prevalence of confirmed chronic cholestasis

	SMOFlipid® (n=37)		standard (n=62)		Chi ^{2} (p-value)
	Yes	No	Yes	No	
Confirmed chronic cholestasis Missing data 9 SMOFlipid®, 10 standard	5 (17.9%)	23 (82.1%)	13 (25.0%)	39 (75.0%)	0.533 (p=0.466)

6.2.2 Liver dysfunction by lipid group in individuals with confirmed chronic cholestasis

Table 6.5 presents the change in liver function from baseline to 12 months in the 18 individuals with confirmed chronic cholestasis (+/- 2 weeks). A decrease in mean ALP was noted in the standard lipid group. A greater decrease in mean bilirubin and ALT was noted in SMOFlipid® compared with standard lipid. No GGT results were available. No association was found between mean changes in liver function and lipid type (ALP p=0.742, bilirubin p=0.621, ALT p=0.563). However, it should also be noted that sample sizes were small (see Table 6.5).

Table 6.5: Change in liver function in individuals with chronic cholestasis over 12 months

	SMOFlipid® Mean difference (SD) n=5	standard Mean difference (SD) n=13	t	df	Mean difference (p-value)	95% Confidence Interval
ALP (30-130 U/L) Missing data 1 Standard	0.80 (114.36)	-31.17 (197.40)	-0.335	15	-31.97 (p=0.742)	-235.13, 171.19
GGT (<38 U/L)	-	-	-	-	-	-
Bil (0-20 umol/L) Missing data 3 standard	-5.20 (6.22)	-2.00 (13.22)	0.507	13	3.20 (p=0.621)	-10.45, 16.85
ALT (7-40 U/L) Missing data 2 standard	-28.60 (62.08)	-13.09 (41.90)	0.593	14	15.50 (p=0.563)	-40.63, 71.65

ALP = alkaline phosphatase, ALT = alanine aminotransferase, Bil = bilirubin, GGT = gamma-glutamyl transferase

6.2.3 Incidence of chronic cholestasis in twelve months

Table 6.6 presents baseline cholestasis status in the 18 individuals with confirmed chronic cholestasis (see Table 6.4). Chronic cholestasis was confirmed (at baseline) in only one individual receiving standard lipid; the incidence was 5/28 (17.9%) for SMOFlipid® and reduced to 12/52 (23.1%) for standard lipid. Thus, incidence remained comparable to prevalence (Table 6.4). Incomplete liver function test results lead to chronic cholestasis status being unknown in 3 individuals receiving SMOFlipid® and 8 receiving standard lipid (11 (61.1%) of the 18 individuals who had chronic cholestasis at 12 months). Cholestasis status was not associated with lipid type ($p > 0.999$) (Table 6.6).

Table 6.6: Baseline chronic cholestasis status

	SMOFlipid® (n=5)	standard (n=13)	Fisher's exact (p-value)
No chronic cholestasis	2 (40.0%)	3 (23.1%)	>0.999
Confirmed chronic cholestasis	0 (0%)	1 (7.7%)	>0.999
Incomplete results to define chronic cholestasis status	3 (60.0%)	8 (61.5%)	>0.999
No data available for analysis	0 (0%)	1 (7.7%)	>0.999

6.2.4 Effect of confounding variables on prevalence of chronic cholestasis at 12 months

Table 6.7 presents the logistic regression analysis comparing the prevalence of chronic cholestasis within 12 months of receiving SMOFlipid® or standard lipid. The analysis included the following confounding variables: gender (male/female), admission age (years), mean glucose energy (kilocalories per kilogram per day), mean lipid energy (kilocalories per kilogram per day), total number of days on HPN (or end of study), whether the individual had sepsis and whether the individual took hepatotoxic drugs. The results indicate the effect of individual variables when adjusted for all other confounding variables. A test of the model against a constant only model (Likelihood ratio Chi square=7.005, df=8, p=0.536) indicated the confounding variables do not reliably account for the prevalence of cholestasis at 12 months. The regression model found that none of the confounding variables were predictors of chronic cholestasis at 12 months. Chronic cholestasis was less likely in the SMOFlipid® group compared with the standard lipid group though there was no evidence of a statistical effect (OR = 0.646, p = 0.532) (Table 6.7). Although the odds ratio was not itself close to 1.0, its 95% confidence interval (0.164, 2.545) was relatively wide.

Table 6.7: Logistic regression analysis on prevalence of chronic cholestasis at 12 months in SMOFlipid® (n=27) or standard lipid emulsion (n=51)

Independent variable	Odds Ratio	95% Confidence Interval	p-value
(Intercept)	0.153	0.001, 2.901	0.057
Gender (Male/Female)	0.747	0.218, 2.562	0.747
Admission age (Years)	1.020	0.974, 1.067	0.405
Glucose (kilocalories per kilogram per day)	1.061	0.989, 1.139	0.099
Lipid (kilocalories per kilogram per day)	1.127	0.846, 1.501	0.414
Number of days on HPN (or end of study)	0.999	0.997, 1.001	0.386
Sepsis at start date or approximately 12 months later	1.732	0.377, 7.957	0.480
Hepatotoxic drugs during 12 months SMOFlipid® / standard lipid	0.582	0.128, 2.643	0.484
SMOFlipid® / standard lipid for 12 consecutive months	0.646	0.164, 2.545	0.532

HPN = home parenteral nutrition

6.3 Objective 2: Identifying differences in liver dysfunction between lipid groups

6.3.1 Liver dysfunction at twelve months

Table 6.8 presents liver function results at 12 months (+/- six weeks). Mean ALP, GGT and bilirubin were similar in the two groups. Mean ALT was higher in the SMOFlipid® group compared to standard lipid. However, the large standard deviations in all the liver function test results reflect a wide variation from the mean. No association was found between mean liver function and lipid type (ALP p=0.912, GGT p=0.953, bilirubin p=0.916, ALT p=0.141) (Table 6.8).

Table 6.8: Liver function at 12 months

	SMOFlipid® Mean (SD) n=37	standard Mean (SD) n=62	t	df	Mean difference (p-value)	95% Confidence Interval
ALP (30-130 U/L) Missing data 6 SMOFlipid®, 8 standard	165.06 (98.14)	167.26 (81.27)	.111	83	2.195 (p=0.912)	-37.129, 41.519
GGT (<38 U/L) Missing data 15 SMOFlipid®, 22 standard	121.59 (146.21)	123.85 (142.12)	.059	60	2.259 (p=0.953)	-73.964, 78.483
Bil (0-20 umol/L) Missing data 7 SMOFlipid®, 11 standard	9.00 (6.38)	9.24 (11.06)	.106	79	0.235 (p=0.916)	-4.167, 4.638
ALT (7-40 U/L) Missing data 7 SMOFlipid®, 13 standard	47.70 (37.76)	36.29 (22.62)	-1.499	41.927	-11.414 (p=0.141)	-26.780, 3.951

ALP = alkaline phosphatase, ALT = alanine aminotransferase, Bil = bilirubin, GGT = gamma-glutamyl transferase

6.3.2 Change in liver dysfunction over 12 months

Table 6.9 presents changes in liver function from baseline (+/- 2 weeks) to 12 months. A decrease in mean ALP and bilirubin was noted in SMOFlipid® only. The ALT decreased with both types of lipid though to a larger extent in SMOFlipid®. Mean GGT decreased in standard lipid only though baseline GGT results were only available for 2 individuals on SMOFlipid® and 5 on standard lipid. No association was found between these mean changes in liver function test result and lipid type (ALP p=0.273, GGT p=0.373, bilirubin p=0.280, ALT p=0.273).

Table 6.9: Changes in liver function from baseline to 12 months

	SMOFlipid® Mean difference (SD) n=37	standard Mean difference (SD) n=62	t	df	Mean difference (p-value)	95% Confidence Interval
ALP (30-130 U/L) Missing data 6 SMOFlipid®, 8 standard	-20.84 (85.92)	4.93 (112.25)	1.105	83	25.765 (p=0.273)	-20.628, 72.157
GGT (<38 U/L) Missing data 35 SMOFlipid®, 57 standard	9.50 (14.85)	-14.00 (31.22)	-.978	5	-23.500 (p=0.373)	-85.241, 38.241
Bil (0-20 umol/L) Missing data 11 SMOFlipid®, 18 standard	-1.81 (7.36)	1.18 (12.76)	1.090	68	2.990 (p=0.280)	-2.484, 8.463
ALT (7-40 U/L) Missing data 7 SMOFlipid®, 13 standard	-15.67 (52.96)	-3.88 (30.42)	1.112	40.886	11.789 (p=0.273)	-9.623, 33.201

ALP = alkaline phosphatase, ALT = alanine aminotransferase, Bil = bilirubin, GGT = gamma-glutamyl transferase

6.3.3 Lipid dose and liver dysfunction over 12 months by lipid emulsion

Liver function at 12 months and lipid dose (of individuals included in the analysis) are shown by lipid group in Table 6.10. Mean liver function tests results and mean lipid doses were both slightly higher in the SMOFlipid® group.

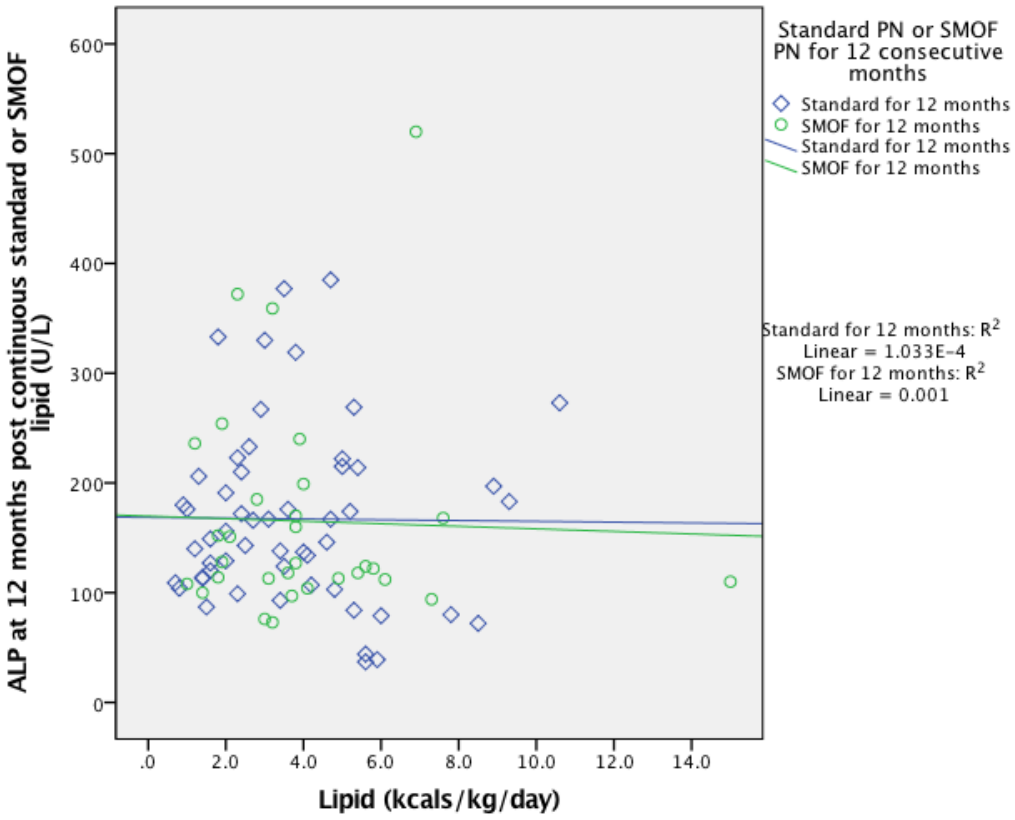
Table 6.10: Liver function at 12 months by lipid dose and lipid group

	SMOFlipid® Mean (SD) (n=38)	standard Mean (SD) (n=62)	t	df	Mean difference (p-value)	95% Confidence Interval
ALP (30-130 U/L)	174.22 (109.55)	167.26 (81.27)	0.363	84	6.96 (0.737)	-31.17, 48.09
Lipid (kcal/kg/day)	4.18 (2.75)	3.72 (2.30)				
Lipid (g/kg/day*) Missing data 6 SMOFlipid®, 8 standard	0.46 (0.31)	0.36 (0.26)	1.604	84	0.10 (0.113)	-0.02, 0.22
GGT (30-130 U/L)	126.65 (144.89)	123.85 (142.12)	0.075	61	2.80 (0.940)	-71.76, 77.36
Lipid (kcal/kg/day)	4.24 (2.99)	3.67 (2.33)				
Lipid (g/kg/day*) Missing data 15 SMOFlipid®, 22 standard	0.47 (0.33)	0.41(0.26)	0.798	61	0.06 (0.428)	-0.09, 0.21
Bil (30-130 U/L)	9.29 (6.48)	9.24 (11.06)	0.022	80	0.05 (0.982)	-4.30, 4.40
Lipid (kcal/kg/day)	4.27 (2.74)	3.59 (2.22)				
Lipid (g/kg/day*) Missing data 7 SMOFlipid®, 11 standard	0.47 (0.30)	0.40 (0.25)	1.139	80	0.07 (0.258)	-0.05, 0.19
ALT (30-130 U/L)	47.39 (37.16)	36.29 (22.62)	1.663	78	1.10 (0.100)	-2.19, 24.39
Lipid (kcal/kg/day)	4.27 (2.74)	3.65 (2.24)				
Lipid (g/kg/day*) Missing data 7 SMOFlipid®, 13 standard	0.47 (0.30)	0.41 (0.25)	0.967	78	0.06 (0.337)	-0.06, 0.18

ALP = alkaline phosphatase, ALT = alanine aminotransferase, Bil = bilirubin, GGT = gamma-glutamyl transferase, kcal/kg/day = kilocalories per kilogram per day, g/kg/day = grams per kilogram per day
*based on 1gram = 9 kilocalories energy taken from British Nutrition Foundation, 2018

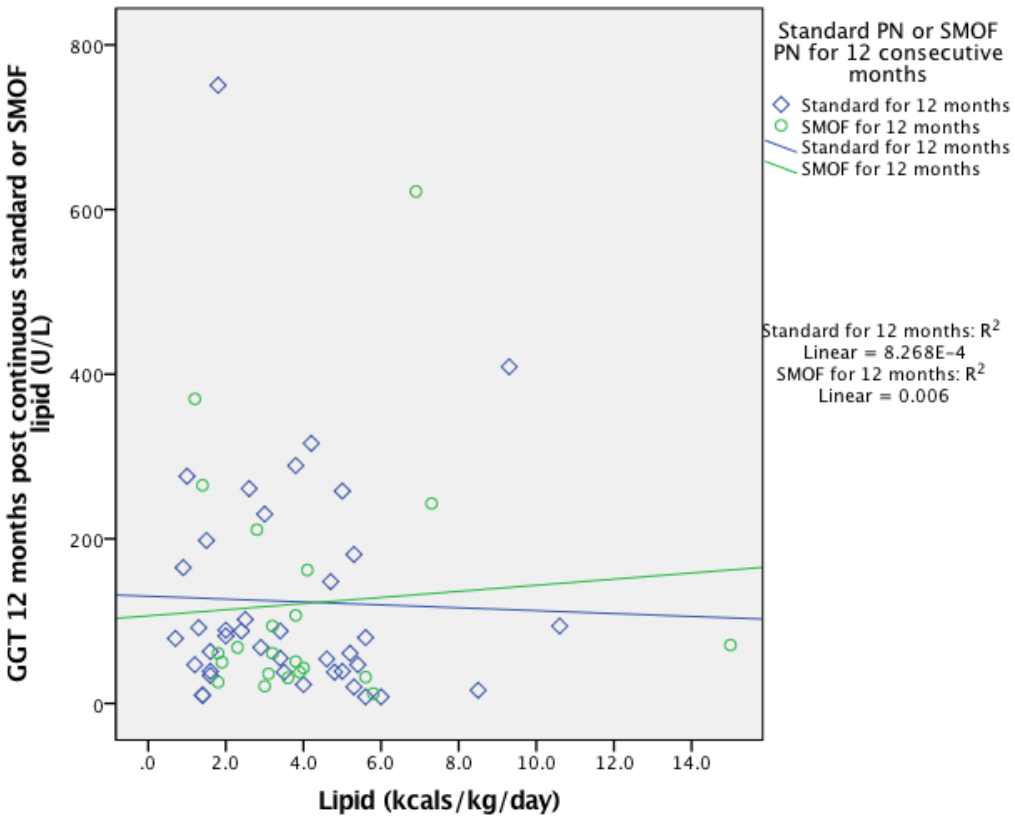
The regression model for ALP displayed a weak negative trend of ALP decreasing as both standard lipid and SMOFlipid® dose increased. The regression model was not significant (F=0.018, df=3 and 81, p=0.997) and neither were either of their slopes. Less than 0.1% of the variance of ALP at 12 months was explained by the lipid type and dose (figure 6.2).

Figure 6.2: Scatterplot of ALP 12 months post continuous SMOFlipid® (n=31) or standard lipid (n=54) against mean lipid energy dose (kilocalories per kilogram per day) by lipid



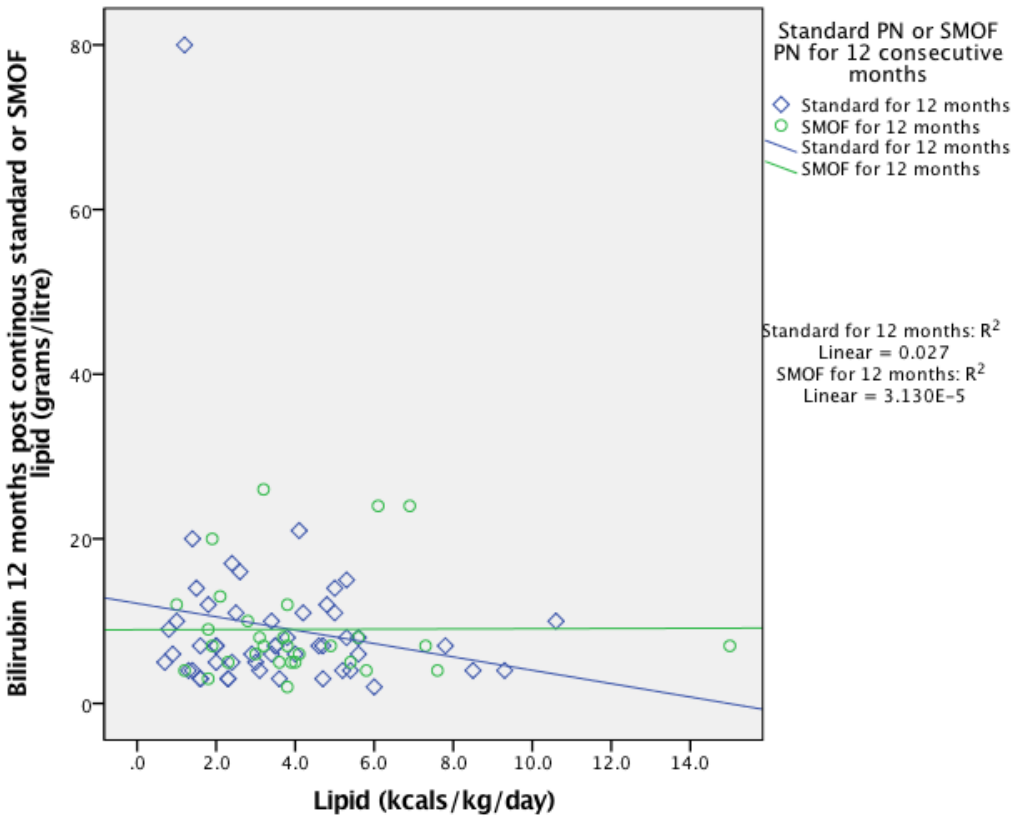
The regression model for GGT displayed a weak negative trend of GGT decreasing as standard lipid dose increased and a weak positive trend of GGT increasing as SMOFlipid® dose increased. The model was not significant (F=0.051, df=3 and 58, p=0.985) and neither were either of the slopes. Less than 0.1% of the variance of GGT at 12 months was explained by the lipid type and dose (figure 6.3).

Figure 6.3: Scatterplot of GGT 12 months post continuous SMOFlipid® (n=22) or standard lipid (n=39) against mean lipid energy dose (kilocalories per kilogram per day) by lipid



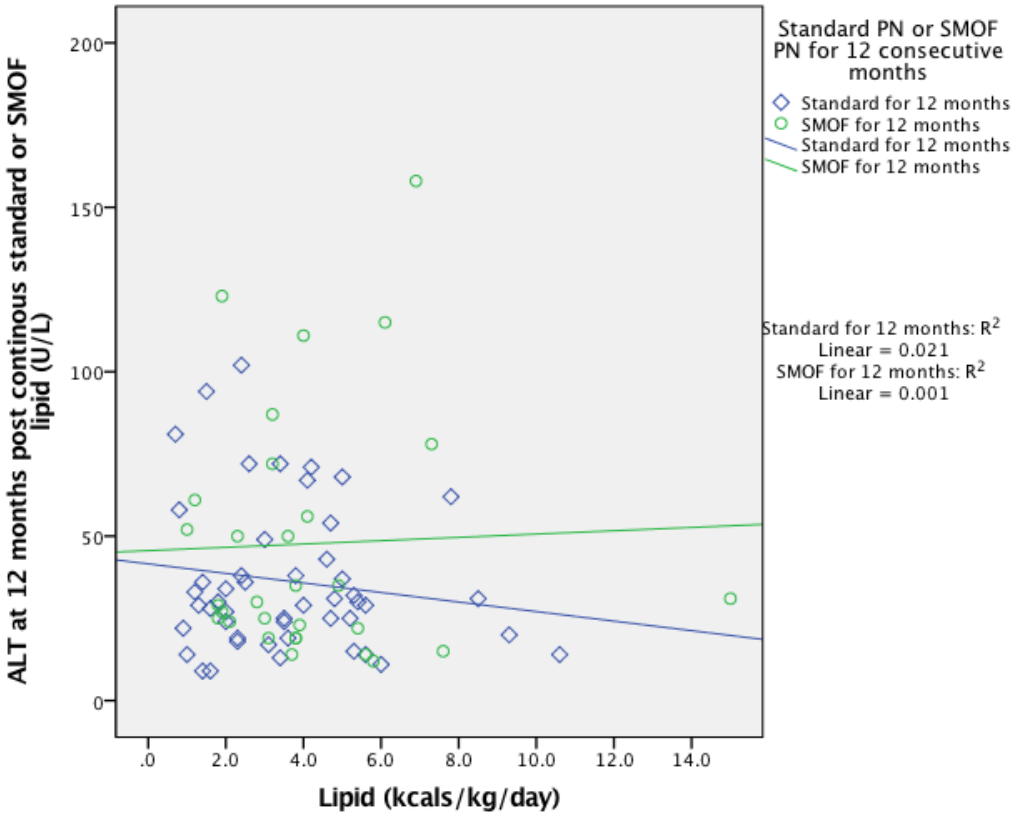
The regression model for bilirubin displayed a weak negative trend of bilirubin decreasing as standard lipid dose increased and a weak positive trend of bilirubin increasing as SMOFlipid® dose increased. The model was not significant (F=0.588, df=3 and 77, p=0.625) and neither were either of the slopes. Less than 0.1% of the variance of bilirubin at 12 months was explained by the lipid type and dose (figure 6.4).

Figure 6.4: Scatterplot of bilirubin 12 months post continuous SMOFlipid® (n=30) or standard lipid (n=51) against mean lipid energy dose (kilocalories per kilogram per day) by lipid



The regression model for ALT displayed a weak negative trend of ALT decreasing as standard lipid dose increased and a weak positive trend of ALT increasing as SMOFlipid® dose increased. The model was not significant (F=1.143, df=3 and 75, p=0.338) and neither were either of the slopes. Only 0.5% of the variance of ALT at 12 months was explained by the lipid type and dose (figure 6.5).

Figure 6.5: Scatterplot of ALT 12 months post continuous SMOFlipid® (n=30) or standard lipid (n=49) against mean lipid energy dose (kilocalories per kilogram per day) by lipid



None of the scatterplots displayed strong correlations and all four had distributed data with outliers displayed as liver function test plot values that fell away from the trend line. The scatterplots (and linear regression) provide an analysis of the trends in liver function as mean lipid dose increased without accounting for any confounding variables, for example, glucose dose or the presence of sepsis. None of the regressions suggest the variation in liver function were attributable to lipid type or lipid dose (ALP: R^2 = 0.006, p=0.929; GGT: R^2 = 0.006, p=0.954; bilirubin R^2 = 0.023, p=0.613; ALT: R^2 = 0.042, p=0.350).

6.3.4 Hospital re-admission due to liver dysfunction

Data on re-admission to Salford Royal Hospital directly attributable to liver dysfunction were available for all individuals in the two lipid groups; 2/62 individuals (3.2%) receiving standard lipid and 3/37 individuals receiving SMOFlipid® (8.1%) were re-admitted due to liver dysfunction. No association was noted between lipid type and re-admission rate ($p=0.359$).

6.3.5 Effect of confounding variables on liver dysfunction at 12 months

Multivariable analysis compared the results of liver function tests after 12 months of receiving SMOFlipid® or standard lipid; multiple linear regression models for each liver function test included the following confounding variables: gender, admission age, mean energy from glucose (kilocalories per kilogram per day), mean energy from lipid (kilocalories per kilogram per day), total number of days on HPN (or end of study), whether the individual had sepsis and whether the individual took hepatotoxic drugs. It was not possible to include small bowel length in circuit due to only having data for 41 of the 99 individuals who received standard or SMOFlipid® for 12 consecutive months. The results indicate the effect of individual variables when adjusted for all other confounding variables. Total energy received from HPN was excluded from the regression models due to having an almost perfect correlation with energy from glucose ($r = 0.960$).

The regression model for ALP (Table 6.11) was significant (F=3.295, df=9 and 73, p=0.002) accounting for 20.1% of the variance of ALP at 12 months. An increment of one U/L increase in baseline ALP was associated with an increased ALP at 12 months of 0.403 U/L; baseline ALP was a predictor of ALP at 12 months. The model predicted a non-significant decrease in ALP at 12 months of -17.203 U/L for SMOFlipid® compared with standard lipid. The 95% confidence interval for the regression coefficient was relatively wide (-57.549, 23.143). There was no evidence that gender, admission age, mean energy from glucose (kilocalories per kilogram per day), mean energy from lipid (kilocalories per kilogram per day), total number of days on HPN (or end of study), sepsis and hepatotoxic drugs were predictors of ALP at 12 months (Table 6.11).

Table 6.11: Multiple linear regression analysis of ALP at 12 months post continuous SMOFlipid® (n=30) or standard lipid emulsion (n=53)

Independent variable	Unstandardised Coefficient	95% Confidence Interval	p-value
(Constant)	126.846	16.692, 237.001	0.025
Gender (Male/Female)	-31.243	-68.428, 5.942	0.098
Admission age (Years)	0.128	-1.083, 1.339	0.834
Glucose (kilocalories per kilogram per day)	0.336	-1.995, 2.666	0.755
Lipid (kilocalories per kilogram per day)	3.001	-5.143, 11.145	0.465
Number of days on HPN (or end of study)	-0.034	-0.101, 0.033	0.289
Sepsis at start date or approximately 12 months later	3.810	-45.933, 53.553	0.879
Hepatotoxic drugs during 12 months SMOFlipid® / standard lipid	-22.650	-64.935, 19.635	0.289
SMOFlipid® / standard lipid for 12 consecutive months	-17.203	-57.549, 23.143	0.398
Baseline ALP (U/L)	0.403	0.242, 0.563	<0.001

Adjusted R^2 = 0.201, ALP = alkaline phosphatase, HPN = home parenteral nutrition

The regression model for GGT (Table 6.12) with adjustment for baseline liver function only included 7 subjects and was too small for meaningful statistical analysis. Therefore, GGT was re-analysed without baseline values (Table 6.12). This model was not significant (F=0.998, df=8 and 52, p=0.449) accounting for less than 0.1% of the variance of GGT at 12 months. The model predicted a non-significant decrease in GGT at 12 months of -29.757 U/L for SMOFlipid® compared with standard lipid. The 95% confidence interval for the regression coefficient was very wide (-118.669, 59.156). Female gender was associated with a decreased GGT of -103.535 U/L compared with males at 12 months. Admission age, mean energy from glucose (kilocalories per kilogram per day), mean energy from lipid (kilocalories per kilogram per day), total number of days on HPN (or end of study), sepsis and hepatotoxic drugs were not predictors of GGT at 12 months (Table 6.12).

Table 6.12: Multiple linear regression analysis of GGT at 12 months post continuous SMOFlipid® (n=22) or standard lipid emulsion (n=39)

Independent variable	Unstandardised Coefficient	95% Confidence Interval	p-value
(Constant)	108.357	-135.589, 352.304	0.377
Gender (Male/Female)	-103.535	-183.739, -23.332	0.012
Admission age (Years)	1.225	-1.622, 4.072	0.392
Glucose (kilocalories per kilogram per day)	1.732	-3.965, 7.429	0.544
Lipid (kilocalories per kilogram per day)	5.654	-11.129, 22.419	0.502
Number of days on HPN (or end of study)	-0.063	-0.224, 0.098	0.437
Sepsis at start date or approximately 12 months later	33.684	-77.084, 144.453	0.544
Hepatotoxic drugs during 12 months SMOFlipid® / standard lipid	28.854	-65.246, 122.954	0.541
SMOFlipid® / standard lipid for 12 consecutive months	-29.757	-118.669, 59.156	0.505
Baseline GGT (U/L)	-	-	-

Adjusted $R^2 < 0.001$, GGT = gamma-glutamyl transferase, HPN = home parenteral nutrition

The regression model for bilirubin (Table 6.13) was not significant (F=1.209, df=9 and 58, p=0.307) accounting for only 2.7% of the variance of bilirubin at 12 months. The model predicted a non-significant decrease in bilirubin at 12 months of -0.812 U/L for SMOFlipid® compared with standard lipid. The 95% confidence interval for the regression coefficient was again very wide in terms of the scale of values for bilirubin (-6.447, 4.832). Gender, admission age, mean energy from glucose (kilocalories per kilogram per day), mean energy from lipid (kilocalories per kilogram per day), total number of days on HPN (or end of study), sepsis and hepatotoxic drugs were not predictors of bilirubin at 12 months (Table 6.13).

Table 6.13: Multiple linear regression analysis of bilirubin at 12 months post continuous SMOFlipid® (n=25) or standard lipid emulsion (n=43)

Independent variable	Unstandardised Coefficient	95% Confidence Interval	p-value
(Constant)	13.603	-1.405, 28.611	0.075
Gender (Male/Female)	-3.935	-9.226, 1.355	0.142
Admission age (Years)	-0.044	-0.235, 0.146	0.642
Glucose (kilocalories per kilogram per day)	-0.139	-0.487, 0.209	0.427
Lipid (kilocalories per kilogram per day)	-0.284	-1.456, 0.888	0.630
Number of days on HPN (or end of study)	0.003	-0.007, 0.012	0.587
Sepsis at start date or approximately 12 months later	-2.174	-9.167, 4.819	0.536
Hepatotoxic drugs during 12 months SMOFlipid® / standard lipid	-1.598	-7.411, 4.245	0.586
SMOFlipid® / standard lipid for 12 consecutive months	-0.812	-6.447, 4.832	0.774
Baseline bilirubin (U/L)	0.287	-0.036, 0.611	0.081

Adjusted R^2 = 0.027, HPN = home parenteral nutrition

The regression model for ALT (Table 6.14) was significant (F=2.164, df=9 and 67, p=0.036) accounting for 12.1% of the variance of ALT at 12 months. An increment of one U/L increase in baseline ALT was associated with an increased ALT at 12 months of 0.189 U/L at 12 months; baseline ALT was a predictor of ALT at 12 months. The model predicted a non-significant increase in ALT at 12 months of 10.489 U/L for SMOFlipid® compared with standard lipid. The 95% confidence interval for the regression coefficient was relatively wide (-4.519, 25.497). Female gender was associated with a decreased ALT of -15.178 U/L. Admission age, mean energy from glucose (kilocalories per kilogram per day), mean energy from lipid (kilocalories per kilogram per day), total number of days on HPN (or end of study), sepsis and hepatotoxic drugs were non-significant predictors of ALT at 12 months (Table 6.14).

Table 6.14: Multiple linear regression analysis of ALT at 12 months post continuous SMOFlipid® (n=29) or standard lipid emulsion (n=48)

Independent variable	Unstandardised Coefficient	95% Confidence Interval	p-value
(Constant)	20.088	-20.101, 60.277	0.322
Gender (Male/Female)	-15.178	-28.865, -1.491	0.030
Admission age (Years)	-0.036	-0.516, 0.444	0.881
Glucose (kilocalories per kilogram per day)	-0.168	-1.105, 0.768	0.721
Lipid (kilocalories per kilogram per day)	0.772	-2.297, 3.842	0.617
Number of days on HPN (or end of study)	0.024	-0.002, 0.051	0.072
Sepsis at start date or approximately 12 months later	-0.213	-18.664, 18.238	0.982
Hepatotoxic drugs during 12 months SMOFlipid® / standard lipid	-3.319	-19.023, 12.384	0.674
SMOFlipid® / standard lipid for 12 consecutive months	-10.489	-4.519, 25.497	0.168
Baseline ALT (U/L)	0.189	0.013, 0.365	0.036

Adjusted R^2 = 0.121, ALT = alanine aminotransferase, HPN = home parenteral nutrition

6.4 Objective 3: To identify the impact of changing lipid group from earlier generation lipids to soybean oil, medium-chain triglyceride, olive oil and fish oil emulsion on chronic cholestasis and liver dysfunction

Thirteen individuals had cholestasis within 12 months of continuous standard lipid (Table 6.4). Five individuals received SMOFlipid® following standard lipid. However, none of these individuals received SMOFlipid® immediately after receiving standard lipid for 12 consecutive months. The duration of receiving SMOFlipid® varied between 1 month and 14.5 months. No liver function results were available at 12 months (Table 6.15).

One individual had chronic cholestasis within 12 months (individual C). The presence or absence of chronic cholestasis could not be determined in two individuals (B and D) due to insufficient liver function test results. Further exploration of baseline liver function (on commencing SMOFlipid®) would aid establishing mean differences in liver function after commencing SMOFlipid®. However, the cohort was too small for meaningful statistical analysis.

Table 6.15: Liver function tests at 6 months (+/- 4 weeks) and presence of cholestasis within 12 months of commencing SMOFlipid®

Individual	Duration on SMOFlipid® (months)	ALP at 6 months (30-130 U/L)	GGT at 6 months (<38 U/L)	Bilirubin at 6 months (0-20 grams/L)	ALT at 6 months (7-40 U/L)	Cholestasis within 12 months of commencing SMOF
A	14.5	-	51	6	31	No
B	17	-	-	-	-	-
C	7	340	264	5	54	Yes
D	11	45	-	-	-	-
E	1	-	-	-	-	-

ALP = alkaline phosphatase, ALT = alanine aminotransferase, GGT = gamma-glutamyl transferase

6.5 Objective 4: Identifying whether there are differences in body mass index by lipid group

BMI data had a margin of +/- six weeks actual HPN dates. Individuals in both lipid groups had similar mean BMI results at the outset and at 12 months. No notable differences were observed between lipid groups though the standard deviation for standard lipid at baseline was greater than that of the other results (Table 6.16).

Table 6.16: Comparison of mean BMI on commencing SMOFlipid® or standard lipid and at 12 months

BMI (kg/m^2)	Mean (SD)	95% confidence interval
Baseline BMI SMOFlipid® (n=37) Missing data 1	23.29 (4.60)	21.735, 24.849
BMI at 12 months SMOFlipid® (n=37) Missing data 8	24.96 (4.16)	23.381, 26.544
Baseline BMI standard (n=62) Missing data 4	23.47 (7.74)	21.439, 25.508
BMI at 12 months standard (n=62) Missing data 16	24.13 (4.62)	22.760, 25.505

BMI = body mass index

The lipid groups were compared for mean difference in BMI at baseline and at 12 months (Table 6.17). No association was noted between mean differences in BMI with lipid type (p=0.971).

Table 6.17: Comparison of difference in mean BMI on commencing SMOFlipid® and standard lipid and at 12 months

	SMOFlipid® Mean (SD) (n=37)	standard Mean (SD) (n=62)	Mean Difference (p-value)	t	df	95% Confidence Interval
Difference between baseline BMI and BMI at 12 months (kg/m^2) Missing data 8 SMOFlipid®, 19 standard	1.72 (2.75)	1.69 (3.17)	-.026 (p=0.971)	-.037	70	-1.468, 1.415

BMI = body mass index

6.5 Objective 5: To determine whether the prevalence of line sepsis differs by lipid group

Data included for analysis had a margin of +/- four weeks of actual HPN dates. Line sepsis was proportionally higher in the individuals receiving SMOFlipid® (n=4, 10.8%) compared with standard lipid (n=2, 3.3%) (Table 6.18). No association was noted between lipid type and line sepsis status (p=0.195). The incidence for the SMOFlipid® group was 0.30 per 1000 catheter days and 0.09 per 1000 catheter days in the standard lipid group.

Table 6.18: Comparison of prevalence of line sepsis within 12 months of receiving SMOFlipid® or standard lipid emulsion

	SMOFlipid® (n=37)	standard (n=62)	Fisher's Exact p-value
Line sepsis Missing data 1 standard	4 (10.8%)	2 (3.3%)	p=0.195

6.6 Objective 6: Identifying whether there were any clinical signs of essential fatty acid deficiency in those receiving soybean oil, medium-chain triglyceride, olive oil and fish oil

SMOFlipid® was well tolerated in the cohort as there was no report of it being discontinued at any point during the four-year study period due to intolerance. No clinical signs of essential fatty acid deficiency were reported by the clinical team at Salford Royal NHS Foundation Trust in those who were included in the 12-h lipid analyses or those who received it at any point during the entire study time-frame. The median duration of receiving SMOFlipid® was 238 days (range 1-1044, IQR 112-460.8).

Chapter 7 Discussion

7.1 Main research aims

The empirical research conducted for this thesis aimed to determine whether fourth generation SMOFlipid® (soybean oil, medium-chain triglyceride, olive oil and fish oil) intravenous lipid emulsion was associated with more effective clinical outcomes compared with earlier generation lipids. Existing evidence had established causality between soybean oil lipid emulsion and IFALD in those receiving long-term HPN in doses exceeding 1 gram per kilogram per day (Cavicchi et al, 2000), though further exploration was clearly required on other lipid formulae. The systematic review sought to determine the effectiveness of treatment strategies for IFALD in adults (Chapter 3). The findings identified a limited number of studies which provided very low quality evidence for the use of predominantly fourth generation lipids. The research question led on to address the use of a fourth generation lipids from a lack in literature.

No clinically relevant differences in outcomes were found between those who received SMOFlipid® compared with those who received standard lipid. The analysis was limited by small sample sizes which led to underpowered analysis and wide estimates of variability.

7.1.1 Empirical research

Characteristics of the sample and interpreting baseline findings

Before reviewing the findings of the research objectives further, it is important to understand the characteristics of the sample included in the analyses.

Despite the majority of the sample meeting the study inclusion criteria (n=179/189), the proportion in the two lipid groups compared in the main analyses was considerably lower (n=99). These individuals had better baseline GGT (Table 6.2). These data would suggest those not included in the analyses, who had poorer liver function in terms of GGT, were more likely to change HPN lipid emulsion formulae over the subsequent 12 months. This LFT can reflect hepatobiliary disease, including cholestasis when accompanied with other liver enzyme abnormalities (Limdi and Hyde, 2003). Mean ALP and ALT levels were also raised, though importantly, data availability was limited and GGT results were only available for ten individuals. Furthermore, the standard deviations for all three of these LFTs were large indicating a wide variation in results and these findings were not substantive enough for inferences to be made.

At baseline, another important variable where data was notably incomplete across the sample was small bowel length (Table 6.2). In those who received either lipid for 12 months, these data were only available for 41 of the 99 individuals included in the analyses. The importance of small bowel anatomy is two-fold. Firstly, the greater the length of residual small bowel, the greater the patient's capacity will be to absorb nutrition via the oral or enteral route, which in theory, would reduce the amount of HPN required. This could have an impact on the patient's risk of developing liver dysfunction attributable to receiving nutrient components in HPN including lipid and glucose (Gabe and Culkin, 2010). Secondly, ESPEN strongly recommend that clinicians attempt to preserve small bowel intestinal length and retain the colon in continuity with small bowel where possible as a means to prevent IFALD (Pironi et al, 2010).

In a study of adult patients on HPN for more than six months, Lloyd et al (2018) found those with larger small bowel lengths had a reduced prevalence of cholestasis. Among 113 adults receiving HPN containing energy or fluid and electrolytes only, the odds ratio for cholestasis in those with a small bowel length of >200 cm compared with those with a small bowel length <50 cm was 0.07 (95% CI 0.01, 0.63); among 98 receiving HPN containing energy only, the corresponding odds ratio was 0.08 (95% CI 0.01, 0.70). Odds ratios for the other two ranges (50cm-100cm and 100-200cm) compared to <50cm were also less than 1.0 but in both analyses, the overall association with cholestasis was not clinically relevant when all ranges were included (p=0.09 and p=0.13 respectively).

In a more recent study of 634 adults with irreversible Intestinal Failure in those receiving HPN, Cazals-Hatem et al (2018) found a short bowel length of <20cm was an independent risk factor for IFALD. This was confirmed in those who had liver biopsies (n=32) with the presence of liver fibrosis, risk ratio 12.4 (95% CI 3.5, 44.1) (p<0.001). Therefore, missing bowel length data has implications beyond comparing the characteristics of those included in the present study; it could not be included in later analysis including being accounted for as a confounding variable in the regression analyses.

The baseline ALT differed between the two lipid groups, being higher in the SMOFlipid® group, Table 6.3. Standard deviations were high in each group compared to the means, suggesting that the non-parametric test might be more reliable. This liver function test, together with ALP, which was also raised, are makers of liver injury, including non-alcoholic fatty liver disease (Limdi and Hyde, 2003). Unlike IFALD, in which cholestasis is a frequent finding (Cavicchi et al, 2000), this type of liver disease has a different presentation as cholestasis does not occur (Buchman et al, 2017). It could be postulated that these patients, who may have been showing signs of non-alcoholic fatty liver disease, may have prompted the clinicians to choose a the less pro-inflammatory lipid emulsion SMOFlipid® to avoid potentially contributing to existing liver disease at the outset. The large variations from the presented mean values make this inference speculative only.

7.1.2 Study objectives

This study showed the incidence and prevalence of chronic cholestasis to be comparable between lipid groups with no association between lipid received (Tables 6.4, 6.6 and sections 6.2.2, 6.2.3). These findings suggest the least pro-inflammatory fourth generation SMOFlipid® did not have a greater protective effect to developing chronic cholestasis compared to the more pro-inflammatory standard lipid, which comprised of first and third generation lipids (Figure 2.1).

It is difficult to compare these findings for the SMOFlipid® group with previous findings due to paucity of data. The prevalence of cholestasis (17.9% in the SMOFlipid® and 25% cholestasis in the standard lipid groups respectively) were both lower than the 28% noted by Lloyd et al (2008) who used the same standard lipid as the present study and the same definition of chronic cholestasis. In an earlier report by Cavicchi et al (2000), the same diagnostic criteria found the prevalence was notably higher at 65% (28 of 90 individuals) after a median of 6 months HPN. These patients were receiving the most pro-inflammatory first generation soybean oil lipid emulsion. Both of these studies differed from the present study as they excluded other causes of liver disease and therefore, cholestasis could be attributed to HPN alone. Klek et al (2018) reported no cholestasis over 12 months in in a cohort of 67 individuals who received one of four lipid types from all four generations of lipid, which included the lipids in the present study. A different definition for cholestasis was used, however, in which either conjugated bilirubin was greater than 3 times the upper limit of normal and either GGT or ALP greater than 3 times the upper limit of normal, or conjugated bilirubin alone greater than 2mg/dL. Furthermore, the study also excluded those with any pre-existing liver dysfunction, further compromising comparability.

Closer inspection of the 18 patients in the present study deemed to have chronic cholestasis demonstrated that LFTs improved in both groups from baseline over 12 months, though there was no difference between groups on different lipid emulsions (Table 6.5). Additionally, the similar incidence to prevalence rates suggest that cholestasis status did not improve in either lipid group over this time period. Therefore, in this analysis, though the sample size receiving SMOFlipid® was small, it did not demonstrate improvements in cholestasis as per the three fish oil containing lipid combinations identified in the thesis systematic review which each improved cholestasis. These were second and fourth generation soybean (ω-6) 50% and medium-chain triglycerides (coconut oil) 50% and fish oil (ω-3) 100% respectively (Xu et al, 2012), fourth generation fish oil (ω-3) 100% (Burns and Gill, 2013; Pironi et al, 2010 and Venecourt-Jackson et al, 2013) and fourth generation soybean (ω-6) 30%, medium-chain triglycerides 30%, olive oil (ω-9) 25%, fish oil (ω-3) 15% (SMOFlipid®) (Hvas et al, 2016; Moyes et al, 2012).

Unfortunately, as none of those in the standard lipid group identified to have cholestasis received SMOFlipid® immediately afterwards and the numbers who did receive this were so small (n=5), (Table 6.15), it was not possible to draw any conclusions based on changing lipid type. As none of the confounding variables predicted the presence of cholestasis at 12 months, this finding would suggest that receiving parenteral lipid per se does not have to impact adversely on cholestasis status in long-term HPN. Glucose was the confounding variable with the lowest p-value (0.099) and the 95% confidence interval for its odds ratio (0.989 to 1.139) almost contained 1.0, suggesting a potential association with chronic cholestasis, hidden perhaps by the small sample size, though glucose was being treated in this analysis as a confounder. Once again, outcome was not associated to lipid group, though the SMOFlipid® group were less likely to develop cholestasis as the odds ratio was 0.646, 95% CI 0.164, 2.545, though no association was noted (p=0.532) (Table 6.7).

Recently, ESPEN published a document titled ‘Clinical approach to the management of Intestinal Failure Associated Liver Disease (IFALD) in Adults: A position paper from the Home Artificial Nutrition and Chronic Intestinal Failure Specialist Interest Group of ESPEN’ (Lal et al, 2018). In this report, it was stated that there are no long-term data to support the use of ‘novel lipid emulsions’ in the treatment of IFALD and described these lipids by stating the examples: medium-chain triglyceride and long-chain triglyceride mixtures, olive oil and fish oils. These are second, third and fourth generation lipids respectively. The expert group recommended that although the current evidence is only based on case reports and case series, the advice would be to limit parenteral lipid to less than 1g per kilogram body weight per day and to reduce the omega 3 to omega 6 ratio where possible when treating IFALD.

This implies using fourth generation lipids such as SMOFlipid®, at a dose of less than 1g per kilogram body weight per day, is advisable for IFALD due to the low omega 3 to omega 6 ratio (see Table 2.2). Interestingly, the reports ESPEN included as evidence of the limited studies in this area were Burns and Gill (2013); Pironi et al (2010); Venecourt-Jackson et al (2013) and Xu et al (2012), each of which were included in the thesis systematic review. The present findings do not contribute further to the limited data supporting the use of fourth generation lipids as a treatment for IFALD if cholestasis is used to define its presence.

The two lipid groups were comparable at 12-months in terms of liver function and dose of lipid received (Table 6.8 and Table 6.10), though in both groups, the wide 95% confidence intervals reflect the inadequate sample size, which is an important consideration in interpreting the results. The elevated LFTs in both groups were not an unexpected finding given that long-term HPN was being received. For the mean changes in liver function at 12-months, data were missing for virtually all individuals in both groups for GGT, limiting the analysis. SMOFlipid® did show superiority in terms of decreases in ALP, Bilirubin and ALT, though no association was noted to lipid type (Table 6.9).

In this thesis, analyses were performed using only complete cases with individuals with no missing data on the variables included in the analysis. This means that reduced numbers of individuals were included in the analyses, reducing the statistical power and introducing a potential for bias if the individuals excluded were different in any relevant characteristics. Sterne et al (2009) describe three types of missing data. Data are said to be 'missing completely at random' if there are no systematic differences between observed values and missing values, when the loss of data is purely random; data are said to be 'missing at random' if there are systematic differences due to observed values; and data are said to be 'missing not at random if there are systematic differences due to unobserved causes. Sterne et al (2009) describe how in the case of data that are assumed to be 'missing at random', observed values may be used to impute missing values using multiple imputation methods so that no individuals are omitted from the analysis. In a follow-up study, multiple imputation could be considered to overcome the problem of missing data, but Sterne et al (2009) note that specialist statistical help is required.

It is difficult to compare these findings with previous studies due to the paucity of data comparing long-term parenteral lipids in HPN in adults. Klek et al (2018), performed a single-centre randomised control trial which included individuals receiving lipids from four generations. As in the present study, bilirubin decreased in the SMOFlipid® group from a mean of 18.4 (SD 16.7) at baseline to 14.0 (SD 10.9) at 12 months, although the median GGT increased from 74 (IQR 27.5-94.6) to 78 (IQR 27.5-80). Associations were noted in the decreases in mean bilirubin and GGT from baseline to 12 months from 23.1 to 11.1 for bilirubin ($p=0.002$) and from 222.5 to 146.6 for GGT ($p=0.008$) in only one lipid, the olive oil 80% and 20% soybean oil. It is not possible to compare these improvements directly to the standard lipid group in the present study as individuals in this comparator group received either soybean oil or olive oil 80% and 20% soybean oil-the two were not differentiated in the present study.

Benefits with olive oil 80% and soybean oil 20% were also noted in a two-centre study of 32 adults with Intestinal Failure and no pre-existing liver disease receiving soybean oil parenteral nutrition between 2 and 12 years. In those who received olive oil 80% and soybean oil 20%, GGT levels decreased from the start to the end-point of the 60-day study ($p=0.044$) compared with SMOFlipid®. The beneficial effects of olive oil 80% and soybean oil 20% in the Klek et al (2018) and Osowska et al (2018) studies may provide some explanation as to why the standard lipid group and SMOFlipid® did not differ in terms of liver dysfunction in the present study, though further supportive evidence is needed to substantiate this.

Parenteral SMOFlipid® was evaluated by Daoud et al (2018) in a retrospective cohort study on those with Chronic Intestinal Failure who had been receiving HPN for a median of five years. In this study, those who previously received soybean oil or fish oil 100% then received SMOFlipid® (n=30) were included. Liver function test results were reported to be stable at 6, 12 and 24 months after starting SMOFlipid® but no association noted ($p>0.05$). The actual LFT results were not reported but as per the present study, these findings would suggest SMOFlipid® does not induce worsening of LFTs. Nine of the individuals in the study had an ultra-short bowel, which is as previously discussed is a risk for liver dysfunction (Cazals-Hatem et al, 2018), though the authors did not state if they had adjusted for this confounding variable which as previously stated, was not possible in the present study.

The Daoud et al (2018) study was recently presented as a conference poster abstract and this reflects the fact that long-term studies on parenteral lipids in the adult Intestinal Failure population are lacking and this area of research is still at an embryonic stage. In the present study, SMOFlipid® did not replicate improvements in LFT's reported in studies of post-operative populations (Tian et al, 2013) and mixed populations (Dai et al, 2016) discussed in section 3.10.

The present study found the SMOFlipid® group showed weak positive associations between GGT, bilirubin and ALT and lipid dose, and a weak negative association between ALP and lipid dose; all of the LFTs decreased as doses increased in the standard lipid group. The analyses showed outliers in each scatterplot and all of the trends were weak and non-linear (Figures 7.2-7.5). Furthermore, none of the underlying regression models were significant. It might be expected that LFTs would increase and not decrease as lipid doses increased, but in this analysis, confounding variables were not accounted for. It should be remembered that the analysis in this study were underpowered with the sample sizes being too small to reliably demonstrate statistical effects.

As stated previously, Cavicchi et al (2000) linked lipid doses of greater than 1 gram per kilogram per day to deleterious outcomes in terms of chronic cholestasis and advanced liver disease. Also, the 'ESPEN guidelines on chronic Intestinal Failure in adults' advise soybean oil dose should not exceed 1 gram per kilogram per day in those receiving HPN for more than 6 months (Pironi et al, 2016). In the present study, the dose of lipid received in each group was well below these recommendations, ranging from 0.46 to 0.47grams per kilogram per day in the SMOFlipid® group and 0.36 to 0.41grams per kilogram per day in the standard lipid group (Table 6.10). Therefore, the recommended soybean oil dose was not exceeded in either lipid group. It could be postulated that these low doses would make either lipid less likely to be the cause of any liver dysfunction noted in this study. It is also worth noting that there was no statistical evidence of a difference in dose between lipid groups.

In the multiple linear regression analyses (Tables 6.11-6.14), only the overall models for ALP and ALT were significant. The baseline levels of these two LFTs were the only independent predictors of their respective levels at 12-months after adjustment for all other confounding variables. As discussed in section 7.1.1, these two LFTs were already raised at baseline, though it was not known if any individuals included in the study had been diagnosed with any co-existing liver disease at any point either during, or prior to the analysis period. These findings highlight the importance of targeting raised baseline LFTs as potential predictors of ongoing future liver dysfunction. Neither being in the SMOFlipid® or standard lipid group were predictors of these two LFTs at 12 months and no other confounding variable at baseline predicted LFT results at 12 months. However, as previously stated in section 7.1.1, an important confounding variable of small bowel length was missing from these analyses. Furthermore, it was unknown if any of those in the analysis were maintaining an oral or enteral intake which would be protective of liver dysfunction (Gabe and Culkin, 2010).

While the presence of co-existing liver disease in individuals in the two lipid groups was an unknown, the number of admissions due to liver dysfunction was known (Section 6.3.4); no association was noted between type and admission (p=0.359). For the present study, the length of stay for each of these admissions was unknown but clearly, this is an important factor in terms of the patient having to experience a hospital admission and the potential for IFALD, which can lead to liver transplantation (Lal et al, 2018). Furthermore, the economic impact of providing in-patient hospital care for Intestinal Failure is an important factor also being estimated to have an average price of £600 per bed day (NHS England, 2017).

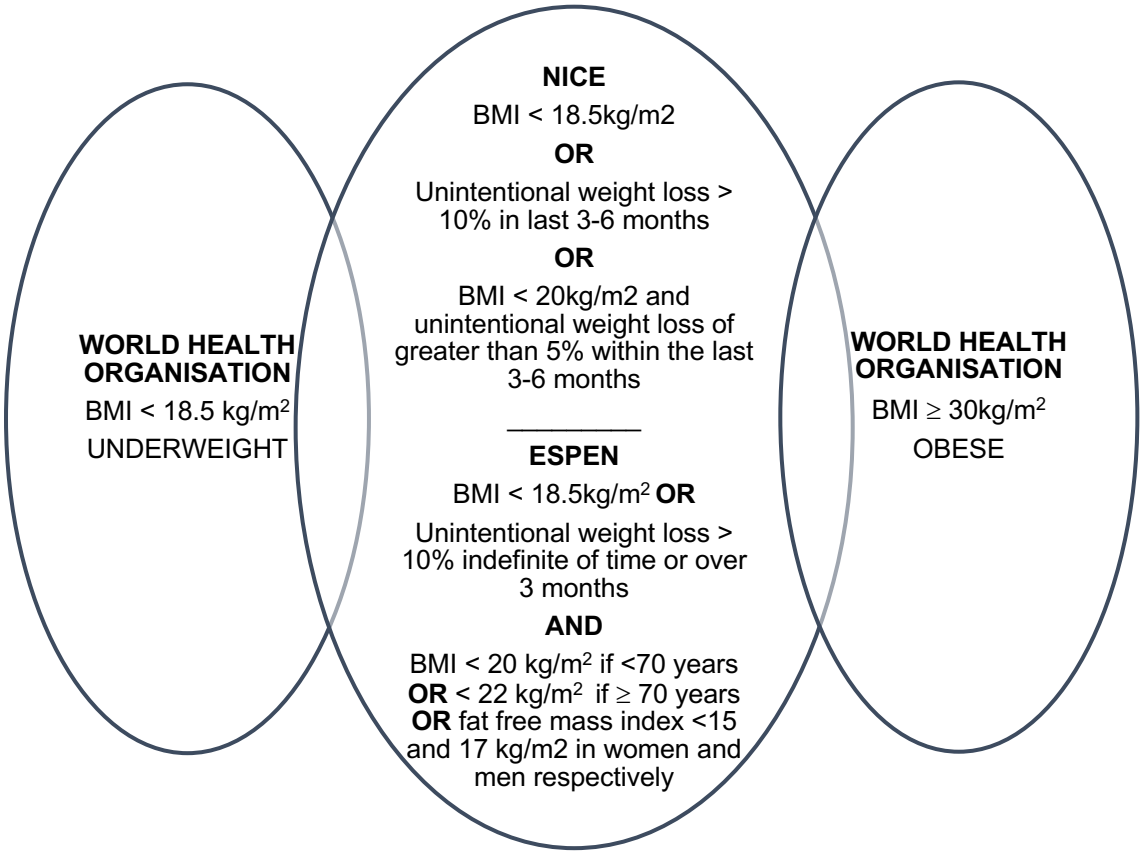
In the Tian et al (2013) systematic review, no difference in length of hospital stay was found between the SMOFlipid® and the soybean lipid groups (-2.10, 95% confidence interval -4.97, 0.77) (Mertes et al, 2006). However, the study included in this study reported data on post-operative elective abdominal and thoracic surgery patients receiving the lipids for only 6 days (Mertes et al, 2006). Thus, comparability with the population in the present study is of limited value due to the difference type of patients being studied and the standard lipid group comprising of two lipid types.

The incidence of catheter related sepsis in both groups was lower than previously noted in a systematic review of catheter-related infections in adults receiving HPN (Dreesen et al, 2013). In the report, which included 39 studies, the catheter-related infection rate ranged between 0.38 and 4.58 episodes per 1000 catheter days. This was notably higher than the present study, in which incidence was only 0.30 and 0.09 episodes per 1000 catheter days in the SMOFlipid® group and standard lipid groups respectively (calculated with an assumed prevalence of line sepsis throughout the study). The present study was also lower than that of Klek et al (2018) which ranged from 0.35 to 0.667 per 1000 days.

These were not an unexpected finding, as the study took place at one of the only two UK centres for specialised Intestinal Failure care; as catheter-related infections are a surrogate marker of the quality of parenteral nutrition care (Dibb et al, 2016), low rates would be expected. Though the rate was higher rate in SMOFlipid® group, no association was noted between lipid type. Lipid emulsions are not causal of catheter related line sepsis, though exploration of any potential group differences were important as this known complication can lead to severe sepsis and is potentially fatal (Dibb et al, 2017). Furthermore, the resolution of any form of sepsis is required to attain adequate nutritional replenishment in Type II Intestinal Failure (Lal et al, 2006), and 77 (77.8%) of the individuals in the two lipid groups were classed as having Type II Intestinal Failure on commencing HPN (Table 6.1).

In this study, data relating to nutritional status were limited to BMI only. In adults, underweight is classified with a BMI of < 18.5 kg/m^2, and conversely, obesity is classified with a BMI of ≥ 30 kg/m^2 (World Health Organisation, 2015). Contrary to the public health perception that those who are obese are not at risk of malnutrition, or malnourished, the ESPEN and National Institute for Health and Care Excellence (NICE) classifications both illustrate that obese and underweight individuals can be malnourished (Figure 7.1). The monitoring of this parameter as a baseline characteristic in studies and indeed in the clinical setting is usual practice.

Figure 7.1: Classification of malnutrition (data taken from Cederholm et al, 2015; National Institute of Health and Clinical Excellence, 2006 and World Health Organisation, 2015)



The findings relating to BMI are not unexpected (Table 6.17). Those in the sample, and within the two lipid groups, had a low prevalence and incidence of line sepsis, so it would follow that adequate nutritional replenishment could be achieved with low levels of sepsis (Lal et al, 2006). The subsequent increase in BMI would be also be expected given the low levels of sepsis from any source and consistent receipt of parenteral nutrition over 12 months in a clinically stable population. As the two groups did not differ, it cannot be hypothesised that either lipid had benefits to nutritional status measured by BMI only.

An interesting finding in this study was that none of the cohort receiving SMOFlipid® across the four-year study period exhibited clinical signs of essential fatty acid deficiency. No clinical signs of essential fatty acid deficiency were observed in the comparator group either, who received first generation soybean oil based lipids or third generation olive oil (ω-9) 80% and soybean oil (ω-6) 20%. As the use of the newer generation of lipids continue to be a key focus of both the cause and the potential treatment for IFALD, it is important that their clinical efficacy is understood in terms of avoiding any nutrient deficiency. Traditionally, soybean oil based lipids have been perceived to be required to meet essential fatty acid needs, due to having the greatest quantity of ω-6 (n-6) linoleic acid to ω-3 (n-3) α-linolenic acid compared with other PN formulae (Table 2.2). Indeed, this is reflected in ESPEN guidelines which stipulate soybean oil containing parenteral nutrition should be administered to correct essential fatty acid deficiencies (Staun et al, 2009; Pironi et al, 2016). In this study, the median duration of receiving SMOFlipid® was 238 days and more importantly, the maximum duration of 1044 days (approximately 2.9 years) which is supportive the evidence that using SMOFlipid® for long-term parenteral nutrition will not result in clinical signs of essential fatty acid deficiency.

Jones and Calder (2018) recently published a systematic review on adults receiving HPN in which fatty acid status, laboratory and clinical outcome alterations on receiving different intravenous lipid emulsions were reviewed. In the report, which included three randomised control trials and 110 adults, the levels of ω-3 (n-3) eicosapentaenoic acid and ω-3 (n-3) docosahexaenoic acid, increased in the SMOFlipid® group (n=20) from baseline to 4 weeks compared to the soybean oil group (n=20) in both plasma and red blood cells. Thus, omega-6 to omega-3 fatty acid ratio was favourably lower after 4-weeks in those receiving SMOFlipid® compared to the soybean oil in both plasma and red blood cells ($p=<0.0001$; $p=0.003$ respectively). These findings were based on a sub-group analysis of one study over a period of only four weeks (Klek et al, 2013). Therefore, further evidence is needed in larger samples over longer periods of time to strengthen the evidence that SMOFlipid® is suited to avoiding essential fatty acid deficiency in long-term HPN. An important unknown factor in the Klek et al (2013) study, and the present research, was not measuring how much fat was being taken through oral diet and therefore, it is not possible to conclusively attribute these favourable outcomes to parenteral lipid alone.

7.2 Implications of research findings for clinical practice

This study adds strength to the evidence that SMOFlipid® is suited for long-term use in HPN. As stated in section 7.1.2, the median duration of receiving SMOFlipid® was 238 days and the maximum duration of 1044 days (approximately 2.9 years). The findings do not suggest that SMOFlipid® is superior to the comparator first and third generation lipids in the prevention or treatment of cholestasis, or the management of liver dysfunction in long-term HPN. Conversely, the findings do not suggest that SMOFlipid® is inferior to the comparator lipids in terms of these outcomes.

7.3 Limitations and strengths of study

There are some key limitations to these study findings, each of which must be acknowledged when interpreting the results. The retrospective nature of the study resulted in a large volume of missing data which limited the scope of all analyses. Another contributory factor which reduced the sample size was patients not receiving a lipid type for 12 consecutive months and thus being excluded from comparative lipid analyses. Careful consideration was given to the study design to optimise the sample included in the analyses across the 4-year study period. However, as data were collected retrospectively from existing patient care, such sample losses were unavoidable.

The reduction in the sample suitable for analyses contributed to the study being inadequately powered for each of the analyses. A retrospective cohort study of this nature with heterogeneity in lipid prescription, duration and timing of measuring the key study variables does impede sample suitability. The two lipid groups comprised of lipids from three different generations of lipid (Table 5.1). If the two lipids in the ‘standard’ lipid group had been analysed separately, this would have compromised the group sample size but enabled analyses of SMOFlipid® against two comparators. Overall, this study found no differences between SMOFlipid® and standard lipid in outcome variables. This does not demonstrate that the lipid formulations were equivalent, just that there was no evidence of a difference between the lipid formulations. The analyses were underpowered so there is a possibility of type II errors occurring, in which statistical tests fail to detect a real difference at the population level because the sample sizes were not large enough.

In the multiple regression analyses in particular, after adjusting for confounding variables, there was no clear statistical evidence of a difference between SMOFlipid® and standard lipid in the prevalence of chronic cholestasis or mean values for the liver function variables ALP, GGT, bilirubin and ALT at 12 months. Effect sizes (odds ratio and unstandardised linear regression coefficients respectively) were generally small (relatively near 1.0 or 0.0 respectively) with wide confidence intervals. One exception was the linear regression model for ALT, where the relatively wide 95% confidence interval contained 0.0 near its lower end. This suggested that lipid group might be associated with ALT at 12-months but this would need to be confirmed in a larger study.

As previously highlighted, two important confounding variables were unknown: whether patients were maintaining oral or enteral diet and small bowel length. Also, no data were available on the patient's actual oral, enteral or parenteral nutrition received versus their individual nutritional needs. Therefore, it was not possible to comment on whether patients were exceeding their energy requirements at any point. Additionally, those with existing liver disease were unknown throughout the analyses and therefore, not excluded from the study at the outset, so this could be contributory to the liver dysfunction observed in this study. Analyses were also based primarily on 12 months of receiving a particular lipid, though this does not account for any effect that previously received lipids may, or may not, have had on liver function. It was not possible to have a 'washout' period or knowledge that the outcomes were not related to a previously received lipid.

The data utilised for the analyses were reliant on HPN volume reportedly received by each patient. As this data was obtained in a non-trial setting, it was not possible to substantiate accuracy, for example with patient diaries or by using pumps that record volume of parenteral nutrition delivery. The study was performed on patients at a UK based single centre, so the findings are less generalisable to global Intestinal Failure patients than a multi-centre global study. Finally, as no individuals received SMOFlipid® immediately after standard lipid, it was not possible to observe the effect of changing lipid. The third study objective sought to determine the impact of changing from standard to SMOFlipid®, though this analysis was subsequently very limited.

Despite the stated limitations, the main strengths of the research are the inclusion of the systematic review (which was preceded by a peer reviewed protocol), the moderately large sample size and long study duration. Though unable to clearly define optimal treatment strategies, the very low quality studies unanimously featured lipid manipulation, highlighting both its contributory role and its importance as a potential treatment for IFALD. The findings demonstrate that while lipids are used as a treatment for liver dysfunction, there is a paucity of studies pertaining to the effective use of lipid as an intervention for IFALD. The findings strengthen the need for well-designed intervention studies to compare the efficiency of different lipids as a treatment for IFALD. The total sample was 179 but the number of individuals who had received either the standard lipid comparator or SMOFlipid® was only 99. To the author's knowledge, only the Klek et al (2018) study to date has evaluated SMOFlipid® in adults in terms of long-term safety and efficacy in terms of managing liver function and essential fatty acid deficiency over 12-months. In their randomised control trial, the total sample size included in analysis was 65 across four lipid groups and 16 individuals received SMOFlipid®. In the present study, although the study was not adequately powered, it was still possible to perform statistical analyses for most of the study objectives to give indications of associations. There is dearth of literature in this area and further research is needed to support the presented findings.

Chapter 8 Conclusion and recommendations

8.1 Conclusion

While minor differences were observed between lipid groups, no clinically relevant effects were found in the analyses for liver dysfunction, chronic cholestasis, body mass index or line sepsis. Furthermore, there was no evidence of a difference between lipid groups in liver function tests or chronic cholestasis after adjusting for confounding variables. No clinical signs of essential fatty acid deficiency were reported to have been observed by the clinical team at Salford Royal NHS Foundation Trust in those receiving SMOFlipid® or the comparator lipid across the sample. While the findings of this empirical research reveal very little difference between the two groups, this in itself is an important finding given the limited existing literature examining long-term tolerability of lipid emulsions in HPN.

8.2 Recommendations

8.2.1 Recommendations pertinent to lipid composition of parenteral nutrition

The study did not identify clinically relevant differences between lipid groups in terms of liver dysfunction, chronic cholestasis, body mass index or line sepsis. Therefore, the findings of this study are not supportive of the use of solely fourth generation SMOFlipid® over either first generation soybean oil lipid or third generation olive oil 80% and soybean oil 20%, or vice versa, in those receiving long-term HPN. Thus, the recommendation would be to continue adhering to ESPEN advice giving those who are dependent on parenteral nutrition a minimum of 1 gram per kilogram body weight essential fatty acid containing lipid emulsion per week to prevent essential fatty acid deficiency (Pironi et al, 2016) (Table 2.2). Additionally, to use fourth generation lipids only to ensure the omega 3 to omega 6 ratio is low (Table 2.2) in cases where IFALD has been diagnosed, based on liver function test results and possible histology. This advice is based on recently published ESPEN position paper ‘Clinical approach to the management of Intestinal Failure Associated Liver Disease (IFALD) in Adults: A position paper from the Home Artificial Nutrition and Chronic Intestinal Failure Specialist Interest Group of ESPEN’ (Lal et al, 2018).

8.2.2 Recommendations for further research

While this study included a large initial sample size with data collected retrospectively over a four-year period, missing data were a considerable problem in the analyses. This compromised the sample size, reduced the statistical power of analyses and may have introduced a potential bias. Data collection for the retrospective cohort study was particularly problematic as extensive cleaning of data was required prior to analysis. The data needed for the study existed in a complex spreadsheet taken from an existing Microsoft Excel® spreadsheet used for data collection at Salford Royal Hospital. Data for study individuals had to be collected at different time points and were placed in SPSS by the researcher. Some variables had to be calculated by hand, for example mean glucose and lipid doses.

In view of this, recommendations for further research are firstly, a multi-centre randomised control trial which would make findings more generalisable to the global population of adults with Intestinal Failure. Three pre-specified variables would measure the primary outcomes of firstly, a change in all LFTs over 18 months and secondly, a diagnosis of cholestasis based on the same Cavicchi et al (2000) criteria used in this study. The secondary outcomes would be a diagnosis of IFALD based on a pre-defined standard definition and, signs of essential fatty acid deficiency, based on physical signs and serum markers. It would be important in the development of this research that a standard definition for IFALD was defined with some consensus within the clinical and research communities. The intervention lipids would be four separate groups: standard care comprising of first generation soybean oil, and three comparator groups: second generation soybean oil 50% and medium-chain triglycerides 50%, third generation olive oil 80% and soybean oil 20% and fourth generation SMOFlipid® as per Klek et al (2018). The study would include a cost effectiveness analysis which is important as lipid prices vary considerably; the soybean oil in the present study was Intralipid® which at £13.52 per 500ml is vastly cheaper than SMOFlipid® at £174.30 per 500ml (National Institute for Health and Care Excellence, 2019).

The analysis would take place on an intention to treat basis. The study would run over 18-months which would exceed the existing time of studies to date, and closer reflect the longevity of receiving HPN, which has an approximate 80% 5-year survival in adults (Pironi et al, 2012). A longer trial could not be justified given the cost of randomised control trials. Prior to undertaking this type of study, a feasibility randomised control trial is needed to test the viability of prospective data collection across different study sites, to assess the potential for recruitment of suitable individuals in a full randomised control trial and to inform sample size calculation. Such a trial would enable comparison analysis of lipid effect at an individual level in addition to the group effects as per the present research.

The second set of recommendations are for clinical practice is that this analysis could be replicated in the future with the ongoing retrospective data collection by stratifying new patients into groups based on lipid received over a 12-month consecutive time period in the patient database. By including new patients only, there would be no need to consider the potential effects of lipids received previously on liver function at baseline. This analysis could be completed with each generation of lipid, or commercial lipid, in separate groups to attain greater differentiation of the outcomes per individual lipid. A greater retrospective study duration than the present study would however, be required to attain a large enough sample to adequately power statistical validity. Finally, the absence of one liver function test (GGT) was most notable throughout the analyses, even when other liver function test results were available. Therefore, it may be beneficial for clinicians to consider why GGT is not routinely in LFT analysis and agree whether it would be beneficial to have GGT collected as frequently as the other LFTs for ongoing patient care in addition to long-term analysis of practice.

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Appendix 1: Systematic review protocol

Prevention and treatment of intestinal failure associated liver disease in adults: protocol for a systematic review

Background

Intestinal failure (IF) is defined as 'the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth' (1). The causes of IF are varied; it can originate from acquired congenital, gastrointestinal, systemic, benign or malignant diseases and affects all age categories (2) (3). The functional classification of IF falls within three distinct groups (4), as illustrated in table 1 (1).

Table 1. Functional classification of IF

Type I Acute, short-term and usually self-limiting condition
Type II Prolonged acute condition, often in metabolically unstable patients, requiring complex multi-disciplinary care and intravenous supplementation over periods of weeks or months
Type III Chronic condition, in metabolically stable patients, requiring intravenous supplementation over months or years. It may be reversible or irreversible

Parenteral nutrition (PN) is required over weeks or months in Type II IF and typically long-term in Type III IF (1). PN has a life sustaining role, though abnormal liver function tests (LFTs) commonly occur in individuals receiving it (5). The causes of abnormal LFTs are multifactorial and not solely attributable to PN such that the term 'Intestinal Failure Associated Liver Disease or IFALD' rather than 'PN Associated Liver Disease' is now used to describe the occurrence of liver disease in individuals with IF (6). Thus, the presence of pre-existing liver disease and sepsis may be significantly influential prior to commencing PN. Further contributory aetiological factors include intestinal anatomy, lack of enteral nutrition, gallstones, small intestinal bacterial overgrowth, nutrient toxicity or deficiency, PN glucose content and lipid composition (7). Abnormal LFTs typically resolve in short-term PN (7). However, long-term PN may be associated with sustained abnormalities in liver function (5) (8).

In adults, chronic cholestasis is a frequent histological finding that can lead to extensive fibrosis and cirrhosis (8). Mortality from IFALD in adults receiving long-term PN is, however, relatively rare and the majority of deaths occur due to underlying disease; a review of eleven studies cited only 15 (4%) of 381 PN related deaths were attributed to liver disease in a mixed patient population of 1310 adults (9). IFALD is not limited to the adult population, though the presence of cholestasis and the deterioration of liver function occur more rapidly in the neonatal population (10). This may reflect the immaturity of the neonatal liver, in which the uptake and synthesis of bile salts and enterohepatic circulation are compromised (11). A recent systematic review noted the incidence of IFALD to be 49.8% in infants and children with IF (age < 18 years) (12). Furthermore, in contrast with adults, mortality is higher; in two of three studies reviewed, 6 (46%) of 13 PN related deaths in a mixed patient population of 167 children (commencing PN ≤ 1 year old) were attributed to liver disease (9).

Progressive severe IFALD may be an indication for intestinal transplantation (13). However, with appropriate and timely management, IFALD is both treatable and can potentially be reversed (14). Measures to address IFALD include the prevention and management of sepsis; avoidance of hepatotoxic medication wherever possible; optimisation of PN regime while maintaining oral/enteral nutrition (7). PN should also be delivered cyclically, opposed to via a continuous infusion (15); delivery over a 16-hour period decreases LFTs (16). Overfeeding with excessive volumes of glucose and lipid are associated with steatosis, and should therefore be avoided in PN infusions (17) (18). PN Lipid composition should not exceed >1 gram per kilogram per day of soybean emulsion (8) (15) due to the associated risk of chronic cholestasis and advanced liver disease (8). Improved LFTs have also been noted when soybean emulsion based PN is substituted with fish oil formulae (19) (20).

Consolidating existing literature

Although IFALD and its associated deleterious effects have been identified in the literature, defining parameters of IFALD and clinical stratification have not been clearly demarcated. Furthermore, there is notable heterogeneity in relevant studies to date, leading to an unknown true prevalence of IFALD. A systematic review of literature relating to the prevention, treatment and identification of IFALD in adults has not previously been undertaken; synthesis of evidence will enable optimal management strategies to be postulated.

Title: Factors associated with the prevention and treatment of intestinal failure associated liver disease in adults

Aim

To determine the effectiveness of prevention and treatment strategies for IFALD in adults.

Objectives

1. To assess strategies used to prevent IFALD in adults and review their efficacy.
2. To assess strategies used to treat IFALD in adults and review their efficacy.

Research questions

1. Which interventions are effective in the prevention of IFALD in adults?
2. Which interventions are effective in the treatment of IFALD adults?

Methodology

Information sources

The search strategy will be agreed by the authors and use keywords and search terms related to IFALD. Studies will be identified by searching electronic databases and reviewing reference lists of relevant articles. The following databases will be searched: Medline (Ovid), EMBASE, AMED, British Nursing Index, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Web of Science. Published abstracts from conferences held by the European Society for Clinical Nutrition and Metabolism (ESPEN), the British Association for Parenteral and Enteral Nutrition (BAPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN) will also be searched. Articles published in English between January 1970 and January 2017 will be included.

Search strategy (key words/search terms)

Research question 1

"Antibiotic*" **OR** "Cyclic*" **OR** "Parenteral" **OR** "PN" **OR** "Intravenous" **OR** "Enteral" **OR** "Oral" **OR** "Fish Oil" **OR** "Omega" **OR** "Soybean" **OR** "Lipid" **OR** "Glucose" **OR** "Carbohydrate*" **OR** "Bacterial Overgrowth" **OR** "URSO*" **OR** "Teduglutide" **OR** "Taurine" **OR** "Choline" **OR** "Amino acid*" **OR** "Aluminium" **OR** "Manganese"

AND

"Intestinal Failure" **OR** "Intestinal Failure Associated Liver Disease" **OR** "IFALD" **OR** "Parenteral Nutrition Associated Liver Disease" **OR** "PNALD"

Research question 2

"Cyclic*" **OR** "Parenteral" **OR** "PN" **OR** "Intravenous" **OR** "Enteral" **OR** "Oral" **OR** "Fish Oil" **OR** "Omega" **OR** "Soybean" **OR** "Lipid" **OR** "Glucose" **OR** "Carbohydrate*" **OR** "Bacterial Overgrowth" **OR** "URSO*" **OR** "Teduglutide" **OR** "Taurine" **OR** "Choline" **OR** "Amino acid*" **OR** "Aluminium" **OR** "Manganese" **OR** "Transplant*"

AND

"Intestinal Failure" **OR** "Intestinal Failure Associated Liver Disease" **OR** "IFALD" **OR** "Parenteral Nutrition Associated Liver Disease" **OR** "PNALD"

AND

"Adult*"

Search limits

Humans

Selection criteria

Participants: Inclusion criteria-Adults (> 18 years) with IF, all genders. Studies addressing both adults and children will be included if data for adults are reported separately.

Exclusion criteria-Individuals with pre-existing cholestasis or liver disease prior to developing IF.

Study eligibility criteria: Randomised controlled trials (RCTs), quasi-randomised trials, prospective studies, retrospective case control studies, case reviews.

Setting: There will be no restrictions based on the type of study setting.

Interventions: Interventions received by individuals identified to have IF will include one or more of the following:

Research question 1: Antibiotics, cyclical infusion of PN, continuous infusion of PN, intake of enteral/oral nutrition, fish oil PN formulae, soybean PN formulae, glucose in PN.

Research question 2: Cyclical infusion of PN, continuous infusion of PN, intake of enteral/oral nutrition, fish oil PN formulae, soybean PN formulae, glucose in PN.

Research question 1

Primary outcome measures: Elevated LFTs, variation in LFTs, chronic cholestasis (defined as the persistent elevation > 1.5 times the upper limit of the normal range for > 6 months of two of the following: alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and total bilirubin.

Secondary outcome measures: Length of hospital stay (days), number of admissions due to IFALD.

Research question 2

Primary outcome measures: Elevated LFTs, variation in LFTs, chronic cholestasis (defined as the persistent elevation > 1.5 times the upper limit of the normal range for > 6 months of two of the following: alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and total bilirubin).

Secondary outcome measures: Mortality attributable to IFALD, length of hospital stay (days), number of admissions due to IFALD.

Screening and study selection process

Inclusion will be based on study eligibility and selection criteria. One reviewer (TK) will screen titles and abstracts retrieved to determine relevance. Full texts will be retrieved where the title and abstract provide insufficient information. A second reviewer (SB) will verify suitability for inclusion (and exclusion). Full texts of potentially relevant literature will be retrieved and eligibility reviewed by one reviewer (TK). Inclusion (and exclusion) of full texts in the systematic review and meta-analysis (if appropriate) will be verified by the second reviewer (SB). Reasons for excluding full texts reviewed will be documented.

Data extraction

A data collection form will be produced to facilitate data collection. The form will be piloted on an initial sample of studies and revised if required. Data abstracted will include:

- Title, journal, year of publication and funding sources.
- Study design, method of randomisation and blinding.
- Patient characteristics: age, gender, functional classification of IF (if stated).
- Interventions received, duration of intervention, quantity/dose of intervention, comparison group.
- Study outcomes pertinent to the defined primary and secondary outcome measures including the time when outcomes were reported.

Study interventions will be analysed to measure outcome effect size in the prevention and treatment of IFALD. The defining characteristics of individuals deemed to have IFALD will also be sought; this may include (but will not be limited to) age, gender, intestinal anatomy, the presence (or absence) of sepsis, small bowel bacterial overgrowth and use of hepatotoxic medication. The reviewers will resolve disagreements through discussion. If required, two attempts to contact study authors will be made (via email) if clarity is required on any aspect of the publication.

Quality assessment

The risk of bias in included studies will be assessed using the Cochrane Collaboration's tool (21).

Data analysis and presentation

Statistical analysis will be performed for primary and secondary outcomes. The relative risk (for categorical outcome data) and standardised mean differences (for continuous data) and 95% confidence intervals will be calculated. The defining characteristics of individuals stated to have IFALD will be presented narratively. Studies will be assessed for heterogeneity using an appropriate statistical model. If appropriate, the results from comparable groups of studies will be pooled and statistical meta-analysis completed for the outlined primary outcome measures. A solely narrative analysis will be completed if heterogeneity between studies prevents suitability for meta-analysis.

References

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20. Burns DL, Gill BM. Reversal of parenteral nutrition-associated liver disease with a fish oil-based lipid emulsion (Omegaven) in an adult dependent on home parenteral nutrition. JPEN J Parenter Enteral Nutr 2013 Mar;37(2):274-280.

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Appendix 2: Shortlisting form

Reference Title author, year	**Inclusion criteria** 1. > 18 years old with IF 2. All genders 3. Studies including adults and children if adults reported separately	**Exclusion criteria** Pre-existing cholestasis or liver disease prior to developing IF	**Study eligibility criteria** 1. Randomised controlled trials (RCTs), quasi-randomised trials 2.Prospective studies 3. Retrospective case control studies 4. Case reviews 5. Pre and post treatment cohort study	**Interventions** 1. Cyclical infusion of PN 2. Continuous infusion of PN 3. Enteral/oral nutrition 4. Fish oil PN formulae 5. Soybean PN formulae 6. Glucose in PN	**Accept/Reject** (including reason for rejection)
1. Reversal of intestinal failure-associated liver disease (IFALD): emphasis on its multifactorial nature Hvas et al, 2016	1. 25-year old 2. Male 3. N/A	Not categorically stated. Abnormal LFT's at 3 month outpatient follow up	4	3 4	Accept
2. Impact of intravenous lipid emulsions on liver function tests: Contribution of parenteral fish oil Badia-Tahull et al, 2015	1. No > 17 years old 2. Yes, 66% male 3. N/A	Not stated	2	1/2 not stated which 4	Reject Prevention rather than treatment
3. Transient Elastography (FibroScan) Is Not Correlated With Liver Fibrosis but With Cholestasis in Patients With Long-Term Home Parenteral Nutrition Van Gossum et al, 2015	1. 43 (18-73 years) 2. Male and female 3. N/A	Intrahepatic mass detected by hepatic ultrasonography, ongoing alcohol abuse (female, 140 g/wk; male, 210 g/wk); known chronic viral hepatitis B or C; any other known chronic hepatic disease (diagnosed prior to starting HPN); human immunodeficiency virus infection, previous liver transplantation	2	1 2	Reject Investigation into Transient elastography as a non-invasive alternative to liver biopsy for assessment of the progression of hepatic fibrosis to cirrhosis-not relevant

4. The relationship between the parenteral dose of fish oil supplementation and the variation of liver function tests in hospitalized adult patients Badia-Tahull et al, 2015	1. > 17 years old median age 68 (range 24-90) 2. Yes, 68% male 3. N/A	Liver disease previous to PN excluded	2	4	Reject Prevention rather than treatment
5. Anti-inflammatory and anti-fibrotic profile of fish oil emulsions used in parenteral nutrition-associated liver disease Pastor-Clerigues et al, 2014	1. >18 years old 2. Gender not stated 3. N/A	Not stated	5	3	Accept
6. Four-week parenteral nutrition using a third generation lipid emulsion (SMOFlipid) – A double-blind, randomised, multicentre study in adults Klek et al, 2013	1. 18-85 years old 2. Male and female 3. N/A	Severe liver insufficiency	1	1 2 4 5	Reject Not treatment of IFALD
7. Successful treatment of parenteral nutrition--associated liver disease in an adult by use of a fish oil--based lipid source Crook and Sriram, 2013	N/A	N/A	N/A	N/A	Reject Editorial not empirical research
8. Reversal of Parenteral Nutrition–Associated Liver Disease With a Fish Oil–Based Lipid Emulsion (Omegaven) in an Adult Dependent on Home Parenteral Nutrition Burns and Gill, 2013	1. 50-year old 2. Female 3. N/A	Not stated	4	1 (12 hours) pre-intervention and post-intervention (16 hours) 4	Accept
9. Successful treatment of parenteral nutrition-associated liver disease in an adult by use of a fish oil-based lipid source Venecourt-Jackson et al, 2013	1. 53-year old 2. Male 3. N/A	Not stated	4	4	Accept

10. Effect of omega-3 polyunsaturated fatty acids to reverse biopsy-proven parenteral nutrition-associated liver disease in adults Xu et al, 2012	1. Adults (20-45 years) 2. Males and females 3. N/A	Patients with other liver diseases (e.g., cystic fibrosis, metabolic dysfunction, hepatitis C) excluded	5	4	Accept
11.Phytosterolemia in parenteral nutrition patients: Implications for liver disease development Llop et al, 2008	1. 20-79 years old 2. Male and female 3. N/A	Eligibility criteria included 'no medical history suggesting liver disease and normal liver parameters at the start of PN'	1	N/A	Reject Intervention does not meet protocol criteria
12. Effect of Parenteral Serum Plant Sterols on Liver Enzymes and Cholesterol Metabolism in a Patient With Short Bowel Syndrome Hallikainen et al, 2008	1. 38-year old 2. Female 3. N/A	Not stated	4	1/2 (not stated which) olive oil (Clinoleic)	Accept
13. Safe and efficacious prolonged use of an olive oil-based lipid emulsion (ClinOleic) in chronic intestinal failure Thomas-Gibson, S. et al, 2004	1. Adults 25-68 years old 2. Males and female 3. N/A	Not stated but established cholestasis (bilirubin > 0.03 mmols/litre) prior to exposure to treatment (clinoleic)	2 and 4	1/2 (not stated which) olive oil (Clinoleic)	Accept
14. Preventative effects of omega-3 fish oil emulsions on parenteral nutrition-associated liver disease Ma et al, 2014					Reject Article in Chinese. Protocol states articles in English only
15. Lipid emulsion containing fish oil in adults with parenteral nutrition-associated liver disease: A case report and review of literature Chaiyasoot et al, 2014	1. 42-year old 2. Male 3. N/A	Not stated	4	1 4	Reject Poster abstract

16. Improvement of parenteral nutrition-associated cholestasis in an adult using fish oil-based parenteral nutrition Moyes et al, 2012	1. 43-year old 2. Male 3. N/A	Not stated	4	4	Accept
17. Prevention effects of omega-3 fish oil emulsions on parenteral nutrition-associated liver disease Cao et al, 2012	1. Not stated 2. Not stated 3. Not stated	Not stated	1	4	Reject Age of subjects not stated Poster abstract
18. In patients on long-term home parenteral nutrition (HPN), transient elastography (FibroScan) correlates with cholestasis but not with liver fibrosis Van Gossum et al, 2011	1. Adults (ages not stated) 2. Male and female 3. N/A	Not stated	2	1/2 (not stated which)	Reject Correlation of transient elastography with cholestasis and liver fibrosis-not relevant
19. Fish oil-based emulsion for the treatment of parenteral nutrition associated liver disease in an adult patient Pironi et al, 2010	1. 58-year old 2. Female 3. N/A	Not stated except steatosis on ultrasound scan (2004 and 2005)	4	4	Accept

20. Intravenous lipid emulsions and liver function in adult patients with chronic intestinal failure: Results from a randomized clinical trial Klek et al, 2018.	1. Adults mean age 53.9 years 2. Male and female. 3. N/A.	Pre-existing liver dysfunction history of cancer and anticancer treatment within the last 5 years, severe hyperlipidaemia, severe coagulopathy, severe renal insufficiency, acute thromboembolic events, positive test for HIV, Hepatitis B or C known or suspected drug or alcohol abuse, participation in another interventional clinical trial in parallel or within 3 months prior. Women with childbearing potential, of childbearing potential who tested positive on a standard pregnancy test and/or those who are lactating		1/2 (not stated which) 4 5	Reject. Not treatment of IFALD.
21. Lipid emulsion based exclusively on omega-3 fatty acids for abnormal liver functioning associated with total parenteral nutrition Romero et al, 2018	1. 47-year old 2. Female 3. N/A	Not stated	4	1 or 2 (not stated) 4	Reject Poster abstract
22. *Is ursodeoxycholic acid an effective therapy for total parenteral nutrition-related liver disease? Beau et al, 1994	1. 20-68 years 2. Male and female 3. N/A		2	1 5 6	Reject Intervention in study, ursodeoxycholic acid, is not one of the interventions included in systematic review protocol

23. *Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury Puder et al, 2009	1. No 2. Male and female 3. N/A		1	5	Reject Infants not adults

*Identified through reviewing reference lists

HPN = home parenteral nutrition, IF = Intestinal Failure LFT's = liver function tests, PN = parenteral nutrition

Appendix 3: Data extraction form

Title, Journal, Authors, Year, Funding source	Study design, Study setting	Population: Adults or Adults and Children Age Gender Diagnosis Classification of IF	Sample size Intervention/ Control population	Duration of study-pre and post intervention Timeframe for follow-up	Inclusion /Exclusion criteria	Intervention (s): Duration/ Quantity/ Dose	Comparator (s): Duration/ Quantity/ Dose	Authors' main outcome measures
Reversal of intestinal failure-associated liver disease (IFALD): emphasis on its multifactorial nature Frontline Gastroenterology Hvas et al, 2016 No funding source declared Authors state no competing interests	Case review Salford Royal Hospital, Salford, UK	Adult 25 years Male Short bowel syndrome No functional classification by authors (#Type III)	1	5 years Final surgery in 2007, intervention in February 2012 Intervention duration not stated	N/A	Soybean (30%), medium-chain triglycerides (30%), olive oil (25%) and fish oil (15%) Duration not stated Twice per week Dose not stated	None	Reversal of IFALD
Defining characteristics of individuals with IFALD? Yes 'The presentations of IF- associated liver disease (IFALD) range from mild cholestasis or steatosis to cirrhosis and decompensated liver disease' 'On admission, Bil was 96 µmol/L, alanine aminotransferase (ALT) 161 IU/L and alkaline phosphatase (ALP) 300 IU/L' 'Tests for viral and autoimmune hepatitis and cross-sectional imaging including magnetic resonance cholangiopancreatography were normal except for liver steatosis' 'A liver biopsy revealed focal interface hepatitis and perivascular cholestasis, consistent with IFALD', 'IFALD is multifactorial and requires multidisciplinary treatment. Patients may benefit from care in a dedicated IF unit, and even advanced liver disease may be reversible' **Primary outcome measures:** Elevated LFTs, variation in LFTs, chronic cholestasis Baseline: Bil 96 µmol/l, ALT 161 IU/L, ALP 300 IU/L on commencing intervention, perivascular cholestasis confirmed by liver biopsy Liver function tests reported to 'slowly improved' **Secondary outcome measures:** Mortality attributable to IFALD, length of hospital stay (days), number of admissions due to IFALD No mortality, one admission due to fungal catheter infection and abnormal liver function, length of stay not stated								

Title, Journal, Authors, Year, Funding source	Study design, Study setting	Population: Adults or Adults and Children Age Gender Diagnosis Classification of IF	Sample size Intervention/ Control population	Duration of study-pre and post intervention Timeframe for follow-up	Inclusion /Exclusion criteria	Intervention (s): Duration/ Quantity/ Dose	Comparator (s): Duration/ Quantity/ Dose	Authors' main outcome measures
Anti-inflammatory and anti-fibrotic profile of fish oil emulsions used in parenteral nutrition-associated liver disease PLOS ONE Pastor-Clerigues et al, 2014 Funding from Spanish Government, research grants from Regional Government	Pre and post treatment cohort study General University Hospital, Valencia, Spain	Adults Intervention group: 28.5 +/- 0.75 years, 1 male, 1 female Comparator groups: Lipofundin® 71 years 1 female ClinOleic® 35 +/- 23.8 years 2 male, 2 female SMOFlipid® 46+/- 26 years 1 male, 2 female Short bowel syndrome No functional classification by authors (#Type II/III)	10 Intervention (n=2) Comparator groups (n=8)	Intervention group: HPN for 8 years +/- 1.4 years- soybean (20%) olive oil (80%) (ClinOleic®) for two years prior to study intervention period of 6 months Comparator groups: Lipofundin® HPN for 2 years and during 6 months study AND HPN for 9.5 years +/- 1.9 years and ClinOleic® 2 years before study AND HPN for 6 years +/- 1.2 years and SMOFlipid® 1 year before study	Inclusion: > 18 years old, presence of non-alcoholic steatohepatitis (NASH), PNALD (after excluding other stated causes of liver disease), HPN ≥ 2 years, Lipofundin®, ClinOleic® or SMOFlipid® Exclusion: < 18 years old, absence of NASH, other coexistent cause of liver disease differing from PNALD, ≤ 2 years PN	Fish oil (100%) (Omegaven®) 1gram per kilogram 5 times per week for 4 months followed by: Soybean (30%), medium-chain triglycerides (30%), olive oil (25%) and fish oil (15%) (SMOFlipid®) 1 gram per kilogram 4 times per week for 2 months (Hours of PN administration not stated)	MCT/ LCT (Soybean 50%, MCT 50%) (Lipofundin®) 1gram per kilogram 4 times a week OR Soybean (20%) olive oil (80%) (ClinOleic®) 1.2 grams per kilogram 4 times a week OR SMOFlipid® 1gram per kilogram 4 times a week	Reversal of PNALD-variation in LFT's, NAS and fibrosis scores, in vitro inflammatory and profibrotic markers

Defining characteristics of individuals with IFALD? No, the authors describe PNALD
Primary outcome measures: Elevated LFTs, variation in LFTs, chronic cholestasis
Baseline
AST (11-39 IU/L) 97.5 +/- 33.2; ALT (7-33 IU/L) 179 +/- 70.71; GGT (8-55 IU/L) 73.5 +/- 65.7; ALP (50-300 IU/L) 150.5 +/- 58.6;
Total bilirubin (<2.5mg/dL) 0.76 +/- 0.05
Week 4:
AST (11-39 IU/L) 38.5 +/- 24.7; ALT (7-33 IU/L) 41.5 +/- 23.3; GGT (8-55 IU/L) 28.5 +/- 2.1; ALP (50-300 IU/L) 116 +/- 57.9;
Total bilirubin (<2.5mg/dL) 0.66 +/- 0.48
Week 8:
AST (11-39 IU/L) 38.4 +/- 9.1; ALT (7-33 IU/L) 36 +/- 7; GGT (8-55 IU/L) 21.5 +/- 6.3; ALP (50-300 IU/L) 98 +/- 36.7; Total bilirubin (<2.5mg/dL) 0.75 +/- 0.4
Week 12:
AST (11-39 IU/L) 30.5 +/- 2.1; ALT (7-33 IU/L) 30.5 +/- 7.7; GGT (8-55 IU/L) 31 +/-25.4; ALP (50-300 IU/L) 115 +/- 9.8;
Total bilirubin (<2.5mg/dL) 0.53 +/- 0.01
Week 16:
AST (11-39 IU/L) 27.5 +/- 6.3; ALT (7-33 IU/L) 35.5 +/- 19; GGT (8-55 IU/L) 113.5 +/- 7.7; ALP (50-300 IU/L) 113.5 +/- 7.7;
Total bilirubin (<2.5mg/dL) 0.8 +/- 0.3
Secondary outcome measures: Mortality attributable to IFALD, length of hospital stay (days), number of admissions due to IFALD
No mortality, no hospital admissions reported

Title, Journal, Authors, Year, Funding source	Study design, Study setting	Population: Adults or Adults and Children Age Gender Diagnosis Classification of IF	Sample size Intervention/ Control population	Duration of study-pre and post intervention Timeframe for follow-up	Inclusion /Exclusion criteria	Intervention (s): Duration/ Quantity/ Dose	Comparator (s): Duration/ Quantity/ Dose	Authors' main outcome measures
Reversal of Parenteral Nutrition–Associated Liver Disease with a Fish Oil–Based Lipid Emulsion (Omegaven®) in an Adult Dependent on Home Parenteral Nutrition Journal of Parenteral and Enteral Nutrition Burns and Gill, 2013 No financial disclosure declared	Case review Burlington, Massachusetts, USA	Adult Female 50-year old Short bowel syndrome No functional classification by authors by authors (#Type III)	1	Exact duration not stated, approximately 5 years and 7 months plus 16 months on intervention	N/A	16 months ω-3 fish oil based PN 45grams over 16 hours, 2 litres, 90 gram amino acid, dextrose 1354 kilocalories energy 5 times per week Patient was on soybean-based lipid emulsion for duration prior to ω-3 fish oil intervention	None	Reversal of parenteral nutrition associated liver disease (PNALD) Tolerance to intervention lipid
Defining characteristics of individuals with IFALD? No. The authors describe PNALD **Primary outcome measures:** Elevated LFTs, variation in LFTs, chronic cholestasis Baseline: Total Bil 12.4mg/dl, ALP 239 IU/L, AST 225 IU/L, ALT 124 IU/L Week 5: Total Bil* 4.2mg/dl and remained in normal reference range, ALP* 510 IU/L, AST* 100 IU/L, ALT* 80 IU/L Week 16: Total Bil 0.9mg/dL, ALP 423 IU/L, AST 87 IU/L, ALT 93 IU/L, all except Total Bil remained above upper limit of reference range A liver biopsy confirmed moderate to severe hepatocanalicular and ductal cholestasis, portal expansion with bile ductular proliferation and mild acute on chronic inflammation pre-intervention **Secondary outcome measures:** Mortality attributable to IFALD, length of hospital stay (days), number of admissions due to IFALD No mortality, one planned admission to hospital for first ω-3 infusion, length of stay not stated								

Title, Journal, Authors, Year, Funding source	Study design, Study setting	Population: Adults or Adults and Children Age Gender Diagnosis Classification of IF	Sample size Intervention/ Control population	Duration of study-pre and post intervention Timeframe for follow-up	Inclusion /Exclusion criteria	Intervention (s): Duration/ Quantity/ Dose	Comparator (s): Duration/ Quantity/ Dose	Authors' main outcome measures
Successful treatment of parenteral nutrition-associated liver disease in an adult by use of a fish oil-based lipid source Nutrition Venecourt-Jackson et al, 2013 No funding source declared	Case review North Shore Hospital, Auckland, New Zealand	Adult 53 years Male Multiple enterocutaneous fistulas No functional classification by authors (#Type III)	1	29 ½ months 27 months before intervention (consisting of 18-month admission and 9 months on pre-intervention lipid and 2 ½ months intervention)	N/A	Fish oil (100%) (Omegaven®) 2 ½ months 80g 6 days per week (? over 18 hours as per pre-treatment PN)	None	Reversal of parenteral nutrition associated liver disease (PNALD)
Defining characteristics of individuals with IFALD? No. Presumptive diagnosis of PNALD made with defining characteristics **Primary outcome measures:** Elevated LFTs, variation in LFTs, chronic cholestasis Baseline: Bil 535 μmol/litre (reference range 0-20), ALT 141 IU/litre (reference range 0-45), ALP 161 IU/L (reference range 40-120), GGT 77 IU/L (reference range 0-60) Week 8: Bil 63, ALT 38*, ALP 60*, GGT 38* (*approximate values) Week 10: Normal ALT **Secondary outcome measures:** Mortality attributable to IFALD, length of hospital stay (days), number of admissions due to IFALD No mortality, no hospital admissions reported								

Title, Journal, Authors, Year, Funding source	Study design, Study setting	Population: Adults or Adults and Children Age Gender Diagnosis Classification of IF	Sample size Intervention/ Control population	Duration of study-pre and post intervention Timeframe for follow-up	Inclusion /Exclusion criteria	Intervention (s): Duration/ Quantity/ Dose	Comparator (s): Duration/ Quantity/ Dose	Authors' main outcome measures
Effect of omega-3 polyunsaturated fatty acids to reverse biopsy-proven parenteral nutrition-associated liver disease in adults Clinical Nutrition Xu et al, 2012 Grant from the National Natural Science Foundation of China	Pre and post treatment cohort study Jinling Hospital, Nanjing University School of Medicine, China	Adults 9 male,6 female Median age: 37 years (range: 22-45) Short bowel syndrome No functional classification by authors (#Type II/III)	15 No control	Approximately 17 months (16 months recruitment, at least 1 month intervention)	Inclusion: Adults receiving 100% PN with soybean oil emulsion (aged 20-45 years) with short bowel syndrome defined as small bowel remnant ≤100 cm, serum direct Bil μ34 mmol/L (2 mg/dL) and predicted PN duration ≥30 days due to congenital or acquired GI disease Exclusion: Patients with other liver diseases and obvious evidence of infection	Soybean (50%) and coconut (50%) (Lipofundin®) MCT/LCT) AND fish oil (100%) (Omegaven®) One month Up to 10g ω-3/day 0.15-0.20gram per kilogram/ day 'ω-3/ω6 ratio approximately 1:4'	None	Presence or improvement of cholestasis (liver biopsy before and after intervention) Variation in fatty acid composition and liver function

Defining characteristics of individuals with IFALD? No. Authors describe features of PNALD
Primary outcome measures: Elevated LFTs, variation in LFTs, chronic cholestasis
Within 4 weeks, normal direct Bil in 12/15 patients. Other patients continued to decrease to normal levels after censoring-data not shown, significant decrease in direct Bil ($p \leq 0.001$)-values illustrated on line graph
Baseline and 4 weeks median and interquartile range:
Direct Bil umol/L
43.7 (37.4-105.5), *11.0 (0.0-31.0), approximately 11.0 umol/L (0.0-31.0), $p \leq 0.001$
Total Bil μmol/L
65.9 (48.5-150.5), 26.4 (10.0-63.4), $p \leq 0.001$
ALT U/L
73.1 (35.3-111.3), 55.7 (23.5-103.7), $p \leq 0.039$
ALP U/L
150.0 (65.5-334.0), 146.0 (65.0-253.5), not significant
GGT U/L
166.0 (98.3-395.5), 165.6 (62.5-296.0), not significant
11/15 patients had liver biopsy pre-intervention and 'liver histology and inflammation' present in 'most' cases pre-treatment
Illustrations of histology after 1 month to demonstrated decreases in cholestasis and inflammation, no data on individual numbers
Secondary outcome measures: Mortality attributable to IFALD, length of hospital stay (days), number of admissions due to IFALD
No mortality, no hospital admissions reported

Title, Journal, Authors, Year, Funding source	Study design, Study setting	Population: Adults or Adults and Children Age Gender Diagnosis Classification of IF	Sample size Intervention/ Control population	Duration of study-pre and post intervention Timeframe for follow-up	Inclusion /Exclusion criteria	Intervention (s): Duration/ Quantity/ Dose	Comparator (s): Duration/ Quantity/ Dose	Authors' main outcome measures
Effect of Parenteral Serum Plant Sterols on Liver Enzymes and Cholesterol Metabolism in a Patient With Short Bowel Syndrome Nutrition in Clinical Practice Hallikainen et al, 2008 No financial disclosure declared	Case review Kuopia University Hospital, Finland	Adult Female 38 years Short bowel syndrome No functional classification by authors (#Type III)	1	22 years on soy oil-based lipid and 17 months on intervention	N/A	Olive oil (80%) and soy oil (20%) 17 months 20g/day for twelve months, then increased to 35g/day Oral intake averaged 1000-1500kcal/ day during 'follow up period'	None	Variation in serum lipid, plant sterol and LFT's
Defining characteristics of individuals with IFALD? No. Authors describe features of PNALD **Primary outcome measures:** Elevated LFTs, variation in LFTs, chronic cholestasis Baseline: ALP *205 U/L, GGT no baseline, ALT* 95 U/L Approximately 8 weeks: ALP* 200 U/L, GGT no result, ALT 60* U/L Approximately 5 months: ALP *145 U/L, GGT* 110 U/L, ALT *80 U/L *timelines and results approximate-taken from line graph **Secondary outcome measures:** Mortality attributable to IFALD, length of hospital stay (days), number of admissions due to IFALD Two attempts to email author to determine if any admissions and length of stay both emails not accepted for 'security or policy reasons'								

Title, Journal, Authors, Year, Funding source	Study design, Study setting	Population: Adults or Adults and Children Age Gender Diagnosis Classification of IF	Sample size Intervention/ Control population	Duration of study-pre and post intervention Timeframe for follow-up	Inclusion /Exclusion criteria	Intervention (s): Duration/ Quantity/ Dose	Comparator (s): Duration/ Quantity/ Dose	Authors' main outcome measures
Safe and efficacious prolonged use of an olive oil-based lipid emulsion (ClinOleic®) in chronic intestinal failure. Clinical Nutrition Thomas-Gibson et al, 2004 No funding source declared	Prospective study and case review St Marks Hospital, Harrow, UK	Adults 9 females, 4 males median age 44 years (range 25–68) Short bowel syndrome n=9 Other intestinal failure (scleroderma and visceral myopathy n=3) Pseudo-obstruction n=1 No functional classification by authors (#Type II/III)	13 No control	18 months consisting of 6-month trial and three (retrospective) 6-month case note reviews (before, during and after trial)	Inclusion: 18–80 years; anticipated need of HPN for at least 6 months from trial start; greater than 50% of the total energy requirement provided by PN and lipid required ≥ twice per week Exclusion: active malignant disease or acquired immunodeficiency syndrome; pregnancy or lactation; serious disease other than that for which PN required; established cholestasis (Bil >0.03 mmol/l); prior exposure to intervention; and expected survival of less than 6 months from trial start	6 months Olive oil (80%) and soy oil (20%) (ClinOleic®) 500ml 2-3 times per week 11 of the 13 patients were on soybean oil-based lipids prior to intervention. All had 15 days lipid free prior to intervention	None	Changes in anthropometric data (weight, body mass index, mid arm circumference and triceps skinfold). Adverse events, events responsible for an unscheduled hospital visits, infectious complications, central vein thrombosis. Serum full blood count, lipid profile, urea and electrolytes, liver function. Presence of gallstones and/or sludge, Gallbladder motility and biliary outflow. Sepsis, thrombotic episodes, admissions to hospital and admission duration, blood results considered

Defining characteristics of individuals with IFALD? No
Primary outcome measures: Elevated LFTs, variation in LFTs, chronic cholestasis
In 12 patients, baseline Bil within normal range and AST no more than 15% outside
In 2 patients ALP, GGT or ALT was elevated > twice normal range at baseline with otherwise normal laboratory parameters
Transient rises in some LFTs in 4 patients, not stated which, remained persistently abnormal in one severely septic patient who had abnormal baseline LFTs
One patient left the trial prematurely due to 'abnormal liver function tests and sepsis'. Not stated when patient left the trial. On investigation, no definitive cause was found, but the abnormalities continued in over the next 2 years of follow-up
Secondary outcome measures: Mortality attributable to IFALD, length of hospital stay (days), number of admissions due to IFALD
No mortality
No reported hospital admissions due to IFALD but authors state one patient left trial due to abnormal liver function tests and sepsis

Title, Journal, Authors, Year, Funding source	Study design, Study setting	Population: Adults or Adults and Children Age Gender Diagnosis Classification of IF	Sample size Intervention/ Control population	Duration of study-pre and post intervention Timeframe for follow-up	Inclusion /Exclusion criteria	Intervention (s): Duration/ Quantity/ Dose	Comparator (s): Duration/ Quantity/ Dose	Authors' main outcome measures
Improvement of parenteral nutrition-associated cholestasis in an adult using fish oil-based parenteral nutrition Frontline Gastroenterology Moyes et al, 2012 Authors declared not commissioned	Case review Glasgow Royal Infirmary, Glasgow, UK	Adult 43 years Male Mesenteric infarction, duodenostomy No functional classification by authors (#Type II)	1	2 years and 3 months; 11 months on pre-intervention lipid, 1 year and 4 months on intervention lipid (Authors also mention no longer on lipid in parenteral nutrition 12 weeks post operatively after above study duration) Main author emailed to confirm study duration-no response	N/A	Soybean (30%), medium- chain triglycerides (30%), olive oil (25%) and fish oils (15%) SMOFlipid® 20% 1 year and 4 months 500ml Once per week	None	Reversal of PNALD
Defining characteristics of individuals with IFALD? No. Authors describe features of PNALD **Primary outcome measures:** Elevated LFTs, variation in LFTs, chronic cholestasis Baseline: Bil* μmol/L 145, AST* IU/L 95, ALP* IU/L 195 12 weeks: Bil 100 μmol/L, AST* 55 IU/L, ALP* 420 IU/L 14 months: Bil* μmol/L 10, AST* 40 IU/L, ALP* 145 IU/L *timelines and results approximate - taken from line graph Patient was identified to have jaundice and cholestatic liver blood tests and confirmation of severe acute cholestasis prior to intervention lipid **Secondary outcome measures:** Mortality attributable to IFALD, length of hospital stay (days), number of admissions due to IFALD No mortality, one admission with jaundice and cholestatic LFT's, length of stay not clear from text-main author emailed for clarity-no response								

Title, Journal, Authors, Year, Funding source	Study design, Study setting	Population: Adults or Adults and Children Age Gender Diagnosis Classification of IF	Sample size Intervention/ Control population	Duration of study-pre and post intervention Timeframe for follow-up	Inclusion /Exclusion criteria	Intervention (s): Duration/ Quantity/ Dose	Comparator (s): Duration/ Quantity/ Dose	Authors' main outcome measures
Fish oil-based emulsion for the treatment of parenteral nutrition associated liver disease in an adult patient The European e-Journal of Clinical Nutrition and Metabolism Pironi et al, 2010 No funding source declared	Case review St. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy	Adult 59 Female Short bowel syndrome No functional classification by authors (#Type III)	1	Approximately 10 years and 8 months exact pre-intervention dates not provided; 8 months intervention	N/A	Fish oil (Omegaven® 10%)* 8 months 75ml/7.5g lipid/day, approximately 0.20g/kg/day 6 days per week, *5 days per week for the last 2 months * in addition to olive oil (80%) and soy oil (20%), ClinOleic® 20%, 50g, 6 days/week approximately 1g/kg first 3 months then increased to 1.5g/kg, mild increase in oral intake observed during first 3 months,160g glucose infusion 6 days per week	None	Reversal of PNALD, variation in LFT's

Defining characteristics of individuals with IFALD? Yes. The authors acknowledge the prevalence of hepatic dysfunction in patients receiving HPN for intestinal failure and subsequently differentiate clinical features in neonates and children and adults. The authors then state 'The pathogenesis is multifactorial, including parenteral nutrition, intestinal failure and systemic related factors. Thus, both the definitions of parenteral nutrition associated liver disease (PNALD) and of intestinal failure associated liver disease (IFALD) are used **Primary outcome measures:** Elevated LFTs, variation in LFTs, chronic cholestasis Baseline: Total Bil 0.69 mg/dL (0.20-1.10), Conjugated Bil mg/dL 0.25 U/L (<0.30), AST 41 U/L (<32), ALT 25 U/L (<31), GGT 129 U/L (<36), CRP 0.10 mg/dL (<0.80) 1 month: Total Bil 0.40 mg/dL, Conjugated Bil mg/dL 0.16 U/L, AST 33 U/L, ALT 22 U/L, GGT 89 U/L, CRP 0.04 mg/dL 3 months: Total Bil 0.60 mg/dL, Conjugated Bil mg/dL 0.25 U/L, AST 44 U/L, ALT 33 U/L, GGT 100, CRP 0.16 mg/dL 7 months: Total Bil 0.44 mg/dL, Conjugated Bil mg/dL 0.16 U/L, AST 24 U/L, ALT 13 U/L, GGT 38, CRP 0.97 mg/dL Biopsy pre and post treatment, reduction in cholestasis post intervention **Secondary outcome measures:** Mortality attributable to IFALD, length of hospital stay (days), number of admissions due to IFALD No mortality No hospital admissions reported

ALP = alkaline phosphatase, ALT = alanine aminotransferase, Bil = bilirubin, GGT = gamma-glutamyl transferase, HPN = home parenteral nutrition, IF = intestinal failure, IFALD = intestinal failure associated liver disease, LCT = long-chain triglyceride, MCT = medium-chain triglyceride, NAS = Non-alcoholic fatty liver disease activity score, NASH = Non-alcoholic steatohepatitis, PN = parenteral nutrition, PNALD = parenteral nutrition associated liver disease
# Classification of IF according to systematic review author