Winnipeg Regional Health Authority / Office régional de la santé de Winnipeg
Caring for Health / À l'écoute de notre santé

Title:
PRACTICE ISSUE EVIDENCE SUMMARY

Best Practice Issue:

Are there clinically significant advantages and/or disadvantages of alternative lipids Clinoleic® (Baxter) and SMOF Lipid® (Fresenius Kabi) over the current lipid emulsion Intralipid® (Fresenius Kabi) and which patient populations would benefit from these products?

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Date of Final Approval:	To be Reviewed:

Purpose: (goals, scope, intended users, settings, and patient/client groups)

Issue: New alternative lipids (ClinOleic® and SMOF Lipid®) are now available on the Canadian market. Intralipid® is currently being used as the lipid emulsion of choice within the WRHA. Intralipid® is higher in Omega -6 (ω-6) fatty acids (FA) which have been associated with negative immune, hepatic and inflammatory effects. ClinOleic® and SMOF Lipid® have relatively lower ω-6 FA and therefore may have less proinflammatory effects, less hepatic dysfunction and less immune suppression. The WRHA Nutrition Advisory Committee wishes to determine the role of these new alternative lipids and determine which patient populations would benefit from these products.

Goal: To review the evidence-based literature on ClinOleic® and SMOF Lipid® to determine if there are clinically significant advantages and/or disadvantages over the current lipid emulsion Intralipid® (Fresenius Kabi) and determine the patient populations who would benefit from these products.

Intended Users and Settings: WRHA Nutrition and Food Services staff, Manitoba Home Nutrition Program, Nursing staff, Pharmacy staff, Medical staff, Adult patients requiring Parenteral Nutrition support

Scope: Literature review limited to Adults only

Definitions:

α- Linolenic Acid (Omega-3 fatty acid) - essential PUFA of ω-3 family. 18:3n-3; the precursors of EPA/DHA

Arachidonic acid (AA 20:4n-6) – an omega-6 polyunsaturated 20 carbon molecule. It is a precursor in the biosynthesis of the pro inflammatory prostacyclins, prostaglandins, thromboxanes and leukotrienes[51]

Eicosanoids (ie prostaglandins, leukotrienes) – signaling molecules made by oxidation of 20-carbon fatty acids (ie arachidonic acid, EPA), which are synthesized on demand. They are derived from either the ω-3 or ω-6 FA in the cell and nuclear membrane

Eicosapentanoic Acid (EPA 20:5n-3) – an omega -3 polyunsaturated 20 carbon fatty acid molecule derived from α-linolenic acid. It is the precursor in the biosynthesis of the less biologically active and thus less pro- inflammatory prostacyclins, prostaglandins, thromboxanes and leukotrienes[51]

Essential Fatty Acids (EFA) – fatty acids that are required for biological process and cannot be synthesized by body. These include linoleic acid (LA 18:2n-6) and α-linolenic acid (ALA 18:3n-3) which are required for the synthesis of long chain fatty acids especially arachidonic acid and eicosapentanoic acid

Intravenous Fat Emulsion (IVFE) - fat administered intravenously to provide a fat source for biological processes, prevent essential fatty acid deficiency and act as an energy source

Linoleic Acid (Omega-6 fatty acid) - essential PUFA of ω-6 family. 18:2n-6; precursor of arachidonic acid (AA)

Long chain triglyceride (LCT) – greater than 13 carbon molecules in each fatty acid

Medium chain triglyceride (MCT) – 6-12 carbon molecules in each fatty acid

Mono-unsaturated fatty acid (MUFA) – have 1 double bond in the fatty acid

Omega-3 Fatty Acids (ω-3 FA)– first double bond occurs at third carbon molecule of fatty acid from the methyl end

Omega-6 Fatty Acids (ω-6 FA)– first double bond occurs at sixth carbon molecule of fatty acid from the methyl end

Omega-9 Fatty Acids (ω-9 FA) – first double bond occurs at ninth carbon molecule of fatty acid from the methyl end

Phytosterol – a plant sterol naturally occurring in lipid sources with a long carbon chain which is suspected to play a role in parenteral nutrition associated liver dysfunction in adults

Poly-unsaturated fatty acid (PUFA) – have 2 or more double bonds in the fatty acid

Other Abbreviations

ALT - alanine-aminotransferase
AST - aspartate aminotransferase
CRP – C-reactive protein
DHA - docosahexaenoic acid
EFAD – essential fatty acid deficiency
FA - fatty acid
FO – fish oil
IL6 - interleukin 6
LDL – low-density lipoprotein
LT - leukotriene
OO - olive oil
OO/SO - 16% olive oil/4% soybean oil (ClincOleic®)
PG - prostaglandin
PN – parenteral nutrition
RBC – red blood cell
SMOF - SMOFLipid®
SO - soybean oil
TNFα - tumour necrosis factor alpha
ULN – upper limit of normal

Recommendations:

SMOF can be used in all patients who need PN. It is the preferred alternative lipid in patients with the following criteria:

a) Critically ill
b) At risk of developing or have documented liver dysfunction
c) At risk of developing or have documented heightened inflammatory response
d) Documented serious infection

The above patient populations may include (but not limited to) patients in critical care, trauma patients, post-surgical patients, patients requiring long-term PN, patients with hepatic disease and patients with serious infections.

SMOFLipid® should be excluded in the following patient populations:

a) Electrolyte requirements exceeding compatibility information (refer to Appendix 4) (may add extra electrolytes outside the PN)
b) Allergies to Fish or Coconut (SMOFLipid® specific) (egg, soybean or peanut allergy is contraindication to both Intralipid® and SMOFLipid®)

Intralipid® should be retained on contract for those cases where SMOFLipid® would be contraindicated.

Pregnant and Nursing Women: PN may become necessary during pregnancy and lactation. SMOFlipid™ should only be given to pregnant and nursing women after careful consideration as there are no data available on exposure of SMOFlipid™ in these populations.[53]

Rationale

Both ASPEN and ESPEN support the use of alternative lipid emulsions in certain patients requiring IVFE. The alternative IVFEs are metabolized via different pathways, which may lead to less pro-inflammatory effects and less immune suppression, more antioxidant effects and lower the risk of PN associated liver disease (PNALD). Many patients who

require IVFEs are already in a compromised state. Such patients could potentially benefit from one of the alternative IVFEs to diminish the intake of the potentially proinflammatory ω-6 fatty acids.

SMOFLipid® is a balanced lipid emulsion with a reduced ω-6 content. The ω-6 to ω-3 ratio of SMOFLipid® is approximately 2.5:1 which is within the recommended range of 2:1 to 4:1. [39, 13, 53, 54] The potential benefits of Omega-3 fatty acids may include reduced inflammation, improved liver function, and improved antioxidant status.[27] SMOFLipid® has an equivalent safety profile to SO based lipids. SMOFLipid® is also preferred over ClinOleic due to quality of evidence showing an improvement in hepatobiliary function.

Evidence Review: (Please list type and grade of evidence reviewed)

Background:

Traditionally, the WRHA has used Intralipid® (Fresenius Kabi) as the lipid emulsion for PN. Two new alternative parenteral lipid emulsions are now available in Canada (SMOF Lipid®(Fresenius Kabi) and ClinOleic® (Baxter). The alternative lipids reduce the ω-6 content of the lipid emulsion.[17] In addition SMOF provides a source of ω-3 FA.

Intravenous Fat Emulsion (IVFE) is provided to patients receiving PN as an energy source and a source of essential fatty acids. IVFE has the potential to reduce inflammation and immunosuppression with a balanced ω-6 to ω-3 ratio.[39]

Fatty acids (FA) are characterized by **a)** the number of carbons in the FA chain (2–4 carbons = short-chain, 6–12 carbons = medium-chain and ≥14 carbons = long-chain) **b)** number of double bonds in the molecule (saturated FAs have no double bonds, monounsaturated FAs (MUFA) =1 double bond, and polyunsaturated FAs (PUFAs) = 2 or more double bonds) **c)** according to which carbon atom in the chain the first double bond occurs, counting from the methyl end of the molecule, which is referred to as the ω carbon.

There are 3 principal families of unsaturated FAs in humans, ω-3, ω-6, and ω-9, in which the first double bond occurs at the third, sixth or ninth carbon, respectively.[17] The ω-3, ω-6 and ω-9 FAs are metabolized through 3 different pathways. These 3 metabolic pathways use and compete for the same enzymes with a preference of ω-3 > ω-6 > ω-9.[17] (see appendix 1).

Initially PN only provided 2 of 3 macronutrients, carbohydrate and protein. Clinical EFA deficiency was observed in adults receiving lipid free PN during early days. With the availability of parenteral lipid in the mid-1970's, clinical EFA deficiency disappeared. Minimal parenteral requirements for linoleic acid (ω -6 FA) and α-linolenic acid (ω-3 FA) are estimated as 1–4% and 0.5% of total calories respectively. As the enzymes shared by ω 3,6 and 9 pathways have preference on different family of FAs, focus switched to studying how changes in membrane FA composition are affected by changes in fatty acid intake; changes in membrane FA composition in cell signaling and production of less inflammatory and more immune modulating eicosanoids. Dysregulation of EFA metabolism, inflammation, and parenteral fat administration may all play a role in the development of end-stage liver disease that occurs in patients receiving long-term home TPN. It is postulated that the inflammatory potential/response can be directly related to tissue arachidonic acid levels. Potential ways to lower arachidonic acid (ω -6 FA) levels may include reducing parenteral fat and the use of alternative lipids containing less ω -6 FAs or more ω -3 FA.[32]

Table 1. Comparison of the three commercially available intravenous fat emulsion products.

Product Name	High in	Lipid Source	Concentrations of Selected FA, % by weight				n6:n3 Ratio	A-Tocopherol mg/L	Phytosterols mg/L[61]	Vitamin K mcg/ 100 mL
			Linoleic	A-Linolenic	EPA	DHA				
Intralipid 20%®	ω-6	100% soybean oil	44-62	4-11	0	0	7:1	38	343-439	59-72
ClinOleic® 20%	ω-9	20%soybean oil 80%olive oil	18.5	2	0	0	9:1	32	227-274	5.9
SMOF Lipid® 20%	ω-3	30%soybean oil 30% MCT oil 25% olive oil 15% fi h oil	21.4	2.5	3	2	.5:1	200	179-207	20-25

Adapted from Adapted from Vanek et al[17] and Ellegard et al [38] (phytosterol amounts) [59, 60, 61]

The vitamin K content of SMOFLipid® and ClinOleic® is not sufficient to meet the daily requirement and supplemental vitamin K may be required (refer for Appendix 4 for compatibility).

The alternative agents have an equivalent safety profile to soybean oil. [17] These alternative IV fat emulsions (IVFE) are metabolized via different pathways, which may lead to less pro-inflammatory effects and less immune suppression. [17]

Inflammation
Although individual immune function tests may show variable results, clinically, ω-3 FAs are relatively less pro-inflammatory than ω-6 FAs. In addition, some ω-3 FAs may actually have anti-inflammatory effects.[17] Many patients who require IVFEs are already in a compromised state. Such patients could potentially have better clinical outcomes when receiving one of the alternative IVFEs to diminish the intake of the potentially pro-inflammatory ω-6 fatty acid (linoleic acid) which comprises more than 50% of the fatty acid profile in SO. [17]ω-6 FAs are preferentially metabolized to arachidonic acid (AA) producing more pro- inflammatory prostanoids (E2, I2, A2) and leukotrienes (B4, C4, E4) while ω-3 FAs are preferentially metabolized to eicosapentanoic acid (EPA) producing less pro-inflammatory prostanoids (E3, I3, A3) and leukotrienes (B5, C5, E5).[17] A decreased ratio of ω-6 to ω-3 fatty acid intake inhibits the metabolism of arachidonic acid and results in reduced production of pro-inflammatory mediators.[55]

Immune Suppression
Some evidence suggests that certain long chain fatty acids may impair immune function by interfering with phagocytosis and chemotaxis and may result in an increased risk of infection.[17] High amounts of ω-6 FAs (SO) can affect neutrophil, lymphocyte, monocyte and macrophage function.[40]

Lipid Peroxidation
Unsaturated fatty acids (particularly PUFA) can undergo lipid peroxidation that involves the incorporation of an oxygen molecule in the fatty acid when breaking down the double bonds. [17] This produces lipid peroxides (unstable molecules) that are converted to volatile metabolites that can trigger chain reactions resulting in inactivation of enzymes, proteins and other elements. [17] ω -6 FA has been associated with peroxidation and oxidative stress leading to premature cell death and linked to immune depression.[21] Most SO based lipid emulsions have limited amounts of α-tocopherol (vitamin E) (a potent antioxidant) and prolonged use is thought to lead to a depletion of antioxidant defences due to a reduced content of α-tocopherol in plasma lipoproteins.[17] ClinOleic®, an OO based IVFE contains 60% MUFA and 20% PUFA. MUFA is less prone to lipid peroxidation and the risks associated with excessive intake of PUFA.[55] SMOFLipid® also has the benefit of containing olive oil and is supplemented with α-tocopherol (vitamin E) which reduces oxidation of ω-3 FA.[14]

Hepatic function
PN has been associated with effects on the liver including cholestasis, liver fibrosis and liver failure.[40] Although the exact etiology is unknown, there is evidence lipid emulsions contribute to hepatobiliary dysfunction.[40] Phytosterols found in SO are thought to have a deleterious effect on hepatic function. Animal studies have demonstrated that intravenous phytosterol injections alone markedly reduced bile acid excretion (increasing risk of cholestasis), increased bile cholesterol and phospholipid levels. [40] Refer to Table 1 for phytosterol content of the three IVFE.

Nutrition Organization Alternative Lipid Statements:

ASPEN (2012)[17,26]
A.S.P.E.N.'s position is that the currently available SO IVFE in the U.S. meets the requirements to prevent EFAD and provide a caloric alternative to dextrose in most patients receiving PN. However, the newer, alternative IVFEs offer similar safety and efficacy profiles as the SO IVFE with additional benefits. Based on substantial biochemical and clinical evidence, the newer, alternative IVFEs have:
1. Less pro-inflammatory effects
2. Less immune suppression
3. More antioxidant effects
4. Act as a better alternative energy source than standard SO IVFE for many critically-ill patients
5. Lower the risk of PN-associated liver disease (PNALD) [26]

There are alternative oil-based fat emulsions, such as medium-chain triglycerides (MCTs), olive oils (OOs), and fish oils (FOs), that, based on extensive usage in Europe, have an equivalent safety profile to SO. These alternative IVFEs are metabolized via different pathways, which may lead to less proinflammatory effects and less immune suppression. Many patients who require IVFEs are already in a compromised state. Such patients could potentially have better clinical outcomes when receiving one of the alternative IVFEs to diminish the intake of the potentially proinflammatory ω-6 fatty acid (linoleic acid) which comprises more than 50% of the fatty acid profile in SO. ASPEN's position paper on alternative

lipids recommends further research to determine which IVFE may be most clinically useful for specific patient populations.[17]

Critical Care Patients

ESPEN (2009)[18]
Lipids should be an integral part of PN for energy and to ensure essential fatty acid provision in long-term ICU patients (Grade B). Intravenous lipid emulsions (LCT, MCT or mixed emulsions) can be administered safely at a rate of 0.7 g/kg up to 1.5 g/kg over 12 to 24 h (Grade B). The tolerance of mixed LCT/MCT lipid emulsions in standard use is sufficiently documented. Several studies have shown specific clinical advantages over soybean LCT alone but require confirmation by prospective controlled studies (Grade C). Olive oil-based PN is well tolerated in critically ill patients. (Grade B). Fish oil-enriched lipid emulsions probably decrease length of stay in critically ill patients (Grade B).[18]

ASPEN(2009)[25]
"In the first week of hospitalization in the ICU, when PN is required and EN is not feasible, patients should be given a parenteral formulation without soy-based lipids (SO). (Grade D)"
This recommendation was based on the Canadian Clinical Practice Guidelines 2001. It is controversial and is supported by two level II studies. [57, 58] It should be applied with caution as full dose PN without lipids might exacerbate stress-induced hyperglycemia. While 2 level 2 studies would generate a grade C recommendation, the implications from the practical standpoint led to a downgrade of the recommendation to D.[25]

Canadian Clinical Practice Guidelines (2013)[16]
When PN with intravenous lipid is indicated, IVFE that reduce the load of ω-6 FA/SO **should be considered**. However, there are insufficient data to make a recommendation on the type of lipids to be used that reduce the n-6 FAs/SO load in critically ill patients receiving PN. [16]

Recommendation: Based on 2 level 2 studies, in critically ill patients who are not malnourished, are tolerating some EN, or when PN is indicated for short term use (< 10 days), withholding lipids high in SO should be considered. There is insufficient data to make a recommendation about withholding lipids high in SO in critically ill patients who are malnourished or those requiring PN for long term (> 10 days). Practitioners will have to weigh the safety and benefits of withholding lipids high in soybean oil on an individual case-by-case basis in these latter patient populations.[24]

Home Nutrition and Hepatology

ESPEN (2009)[20]
Lipid emulsion based on olive oil appears to be equally safe as those based on SO for long term home PN.[19] In liver cirrhosis, use lipid emulsions with a content of ω-6 unsaturated fatty acids lower than in traditional pure SO emulsions.[20]

Summary of In-vivo Human Study Information SMOFLIpid® 20% (Soybean Oil 6%, Medium Chain Triglycerides 6%, Olive oil 5%, Fish oil 3%) (Refer to Appendix 3 for review of Individual Studies)

SMOFLipid® is a 4th generation IVFE that is a mixture of soybean oil, MCT oil, olive oil and fish oil (30%/30%/25%/15%) which provides a balanced fatty acid profile.

Fish oil provides a high content of the ω-3 fatty acids, EPA and DHA. DHA is an important structural component of cell membranes whereas EPA is a precursor of less pro-inflammatory eicosanoids (prostaglandins (E2, I2, A2), thromboxanes and leukotrienes (B4, C4, E4). Olive oil replaces some of the PUFA with MUFA which is less prone to peroxidation than PUFA.[39] MCT provides the body with an immediate energy source sparing larger amounts of essential fatty acids for incorporation into cell membranes. Soybean oil provides the necessary amount of EFA (linoleic (ω-6) and α-linolenic (ω-3)).[53] SMOFLipid® may have less pro-inflammatory effects, less immune suppression, more antioxidant effects, act as a better alternative energy source for many critically-ill patients and lower the risk of PN-associated liver disease compared to Intralipid®.[17] SMOF is supplemented with α-tocopherol (vitamin E) which reduces oxidation of ω-3 FAs.[14]

SMOF appears safe and well tolerated by various patient populations. [10, 11, 13, 39, 50] SMOF increases EPA/DHA concentrations in cell membranes and plasma α-tocopherol levels.[13, 55] Significantly lower triglyceride levels were found in SMOF treated patients. [41, 49] The use of SMOF is associated with smaller changes in liver enzymes in surgery, home TPN, and critically ill patients.[12, 55, 15] This was confirmed by several meta-analysis.[34, 41, 27, 41]The impact of SMOF on inflammatory response is not consistent which may be potentially due to differences in endpoints (CRP, IL-6, TNFα) and study design, but it does tend to favour less pro-inflammatory effects with SMOF overall.[13, 29, 37] Two meta-analyses found significant reductions in infection rate in fish oil containing IVFE, but SMOF was not used in all the studies included. [27, 34]

FO containing IVFE may reduce the length of hospital stay [12, 27, 34, 55] and ICU length of stay. [27, 32] FO containing IVFE has not been shown to impact mortality to date. [27, 34]

Studies Reviewed: 18 studies (including 4 meta-analysis)

Number of patients in each study: 12 -199 patients (meta-analysis 306-1502 patients)

Populations Studied:
Healthy Volunteers 1 study[10]
Long-Term PN (intestinal failure) - 1 study[11]
Critical Care – 4 studies[14,29] (including 2 meta-analysis[32, 27])
Surgery - 11 studies[12,13,14,15, 30,29,55,37] (including 3 meta-analysis [27,34,41])

Parameters Studied (main criteria only):
Safety and tolerability – 6 studies[10,11,12,13,14,50]
Hepatobiliary function - 11 studies[11,12,14,15,27,28,30,34,41,50,12]
Plasma and Lymphocyte Composition/ Fatty Acid Composition - 3 studies[11,13,14]
Length of ICU Stay, Length of Ventilation, other ICU parameters – 2 studies[27,32]
Inflammatory Response/Triglyceride Levels - 2 studies [29,49]
Phytosterols (ClinOleic® and SMOF Lipid®) 1 study[38]

Population Groups
Safety and Tolerability

a) **Healthy Individuals** - Short-term infusions (6 hours) of SMOF in healthy volunteers induced a less marked increase in serum triglyceride concentrations and shorter triglyceride half-life in healthy volunteers compared to SO IVFE.[10]

b) **Long term (Intestinal failure) –** After 4 weeks, mean concentrations of ALT, AST and total bilirubin were significantly lower with SMOF compared to SO (both within the reference range).[11] EPA, DHA and ω -3 to ω -6 fatty acid ratio increased in the SMOF group while they remained unchanged in SO in both plasma and RBC phospholipids.[11] Serum α-tocopherol concentrations significantly increased with SMOF compared to SO.[11]

c) **General** - No difference between SMOF and SO (Lipovenoes®) after 7 days in respect to plasma triglycerides, cholesterol, glucose and liver enzyme levels[50] A review of 4 studies comparing SMOF to SO demonstrated no negative effects associated with SMOF.[39]

Surgery

a) **Elective abdominal or thoracic surgery –** Concentrations of serum triglycerides, phospholipids, and total cholesterol were comparable between SMOF and SO. Mortality, laboratory and clinical parameters were not different. Trends toward a reduced length of hospital stay as well as reduced liver enzymes (AST, ALT, GGT, ALP) were observed with SMOF.[12,55] In the SMOF group, EPA and DHA were rapidly incorporated into the plasma phospholipid fatty acid pattern resulting in an increased EPA:AA ratio.[55] Phospholipid–derived fatty acid pattern of leukocytes and platelets were similar to those seen in plasma phospholipids. On day 6, the ratio of LTB5:LTB4 was more favorable in the SMOF group and α-tocopherol levels were significantly higher in SMOF.[55]

In a subsequent economic evaluation of the total cost of hospital stay, patients receiving SMOF lipid® incurred a cost of $15,303 per patient while patients receiving SO emulsion incurred a cost of $17,331 per patient. The use of SMOF lipid® was associated with an incremental cost savings of $2,028 due to decreased length of stay .[28]

b) **Abdominal Surgery –**, A trial of 233 patients demonstrated that treatment with SMOF lipid® is well tolerated and modulates FA and leukotriene patterns suggesting favourable anti-inflammatory effects.[13] On day 6, plasma α-

tocopherol levels, content of ω-3 FA in plasma phospholipids and ratio of ω-3 to ω-6 FA were elevated in SMOF compared to SO.[13] The total ω-6 content in plasma phosholipids was lower in SMOF compared to SO.[13] A prospective randomized study of 41 patients compared 4 days of SMOF and LCT/MCT on hepatobiliary function in patients who underwent elective gastrointestinal surgery. There were no differences between the SMOF and LCT/MCT group.[30] However, the lipid dose (1.4g/kg/BW) was higher than current practice and the study duration was only 5 days.[30]

c) **Major abdominal or large cranial-maxillo-facial resection for cancer -** A prospective, randomized, double blind trial compared SMOF and OO/SO for 5 days. At day 2 and day 5, the SMOF group had significantly lower AST, ALT and α-glutathione S-transferase levels compared with OO/SO. [15]

d) **Meta-analysis # 2 – (23 studies, 1502 patients)** see critical care below.[27]

e) **Meta-analysis # 3 – (21 studies, 1487 patients) (includes all FO lipid emulsions – <u>not</u> specific to SMOFLipid®)**

Aim: Comprehensive meta-analysis of 21 RCTs to evaluate the effects of <u>fish oil</u> containing lipid emulsions compared to standard soybean oil/soybean oil-MCT-based emulsions on infection, length of stay, liver dysfunction in post-surgery patients.

Results: FO was associated with a significant reduction in the length of hospital stay, infections, ALT, GGT, and total bilirubin without significant changes in mortality and postoperative medical costs. This review employed rigorous article selection process. The quality of evidence of each clinical outcome was assessed as high.

Limitations: SMOF lipid®used in 4 out of 21 studies.[34]

f) **Meta-analysis 4 - (6 studies, 306 patients) – SMOFLipid®**
Aim: To assess the safety and efficacy of SMOF versus other parenteral lipid emulsion (including OO/SO-based (ClinOleic®) and SO-based (Lipoven 20%®)) in post-operative patients
Results: SMOF was associated with a lower change in hepatic enzymes (↓ change in AST, ALT, ALP and GGT compared to Lipoven 20%®- not for other comparators) and LDL-Triglycerides (vs ClinOleic® and Lipoven 20%®). No significant differences in adverse events and length of hospital stay.
Limitations: a) **statistical inconsistencies with statements** (p value did not meet significance when making statements about CRP and hepatic enzymes (compared to ClinOleic®)) b) several IVFE used as comparators[41]

g) **Inflammatory Response/Triglyceride Levels –** In a trial of post-operative ICU patents comparing the inflammatory response of SMOF and ClinOleic®, the SMOF group had significantly lower IL-6, TNFα and soluble E-selectin concentrations (by day 5).[29] In a follow-up study, triglyceride levels were significantly lower in the SMOF group than the ClinOleic® group on day 2 and day 5. By day 5 the incidence of a pathological triglyceride level (defined as 3.4 mmoL/L or greater) was significantly lower in SMOF (0%) compared to ClinOleic® (31.8%).[49] In a study of 40 patients undergoing gastrointestinal surgery, the SMOF group had lower triglycerides on day 6 compared to MCT/LCT.[37] The inflammatory markers, superoxide radical and total oxygen radical were not different between groups.[37]

Critical Care

a) **Abdominal Surgery: -** Liver enzymes were increased in both SO and OO in patients being treated for at least 5 days. The increases in liver enzymes and phospholipid /apo A1 ratio (indicator of alterations in liver function) were significantly lower in the SMOF group (except AST). Changes in CRP were not significant, but there was a significant improvement in plasma lipophilic antioxidant vitamins and LDL-α-tocopherol levels in the SMOF group.[14]

b) **Meta-analysis # 1 – None of the trials contained SMOFLipid® specifically but several contained the constituents of SMOFLipid® (MCT, OO, FO)**

Aim - systematic review/meta-analysis of 12 RCTs (806 patients) to evaluate the effect of various parenteral alternative oil-based IVFE (SO–sparing strategies) on mortality, ICU and hospital length of stay, infections, and mechanical ventilation days in critically ill adult patients.[36]
Results: SO-sparing strategies were associated with clinically important reductions in mortality, duration of ventilation, and in ICU length of stay, but none of these were statistically significant. Soybean oil-sparing strategies had no effect on infectious complications.[36]
Limitations: a) This review excluded studies that reported only biochemical, metabolic, immunologic, or nutritional outcomes. b) No attention paid to the dose and the length of intervention. c) Patient populations in the studies were heterogeneous.[36] **c) None of the trials contained SMOFLipid® specifically**

c) **Meta-analysis # 2 – (Surgery and ICU patients) (includes all ω-3 PUFA lipid emulsions – not specific to SMOFLipid®)**

23 studies reviewed; N= 1502 pts; N= 762 ICU pts

Aim: to analyze literature (RCT's) comparing ω-3 enriched PUFA lipid emulsions (including SMOF) with standard non-enriched lipid emulsions (SO, MCT/LCT or OO/SO emulsions) in surgical and ICU patients receiving PN.

Results: No statistical difference in mortality (RR 0.89) (0.59-1.33). ω-3PUFA lipid emulsions are associated with statistically and clinically significant reduction in infection rate (RR 0.61) (0.45-0.84).), reduction in ICU length of stay by 1.92 days (-3.27 to -0.58 days) and reduction in hospital length of stay by 3.29 days (-5.13 to -1.45 days). Other beneficial effects included improved lung exchange (oxygenation index (PO_2: FiO_2 ratio), liver function (ALT -10.05 units/L (-18.81 to –1.29)) (AST -9.85 units/L (–17.49 to -2.21)) and a trend towards less impairment of kidney function (sCr -0.03 umol/L (-0.08 to 0.01). Improved antioxidant status (α-tocopherol + 12.33 umol/L (8.73 to 15.93) and fatty acid / plasma phospholipid composition (increased DHA and EPA, decreased IL- 6) are also reported. No improvements in triglycerides (0.12 mmol/L (-0.15 to 0.39), bilirubin, CRP, platelet count or coagulation time.

Limitations : 1) Meta-analysis – lots of heterogeneity - Varied doses and formulations of ω-3 PUFAs (SMOF, SO/MCT/ω-3 TGs, SO + FO) and comparators (SO, OO/SO) 2) Improvements in some parameters (ie LFTs) only marginal[27]

Hepatobiliary function
In a trial of 73 long term PN patients with intestinal failure, mean concentrations of ALT, AST and total bilirubin were significantly lower with SMOF compared to SO (both within the reference range).[11] A trend towards reduced liver enzymes was observed with SMOFLipid® in 199 surgical patients[12] A prospective, randomized, double blind trial in post-operative (major abdominal or large cranial-maxillo-facial resection for cancer) patients compared 5 days of SMOF and OO/SO. At day 2 and 5, the SMOF group had significantly lower AST, ALT and α-glutathione S-transferase levels compared with the OO/SO. [15] A short (5 days) prospective randomized study of 41 patients compared 4 days of SMOF and LCT/MCT on hepatobiliary function in patients who underwent elective gastrointestinal surgery. There was no difference between the SMOF and LCT/MCT group.[30] In a trial comparing 7 days of SMOF and SO (Lipovenoes®), there was no difference in respect to liver enzyme levels[50]

In a meta-analysis of 1502 patients receiving ω-3 enriched PUFA lipid emulsions (not necessarily SMOF), there was a statistically and clinically significant reduction in liver function tests (ALT -10.05 units/L (-18.81 to –1.29)) (AST -9.85 units/L (–17.49 to -2.21))[27] In a meta-analysis of 1487 patients receiving FO IVFE (not necessarily SMOF) in post-surgery patients, FO was associated with a significant reduction in ALT, GGT, and total bilirubin.[34] In a meta-analysis of 306 post-surgical patients, SMOF was associated with a lower change in the level of hepatic enzymes (↓ change in AST, ALT, ALP and GGT compared to SO (Lipoven 20%®); not for other comparators).[41] However, there were statistical inconsistencies within statements in the study.[41]

Phytosterols (ClinOleic® and SMOF Lipid®)
Phytosterols in PN solutions may have a role in cholestasis development.[17, 38] Phytosterol and cholesterol levels were higher in Intralipid® (348 mg/L phytosterol; 292 mg/L cholesterol) than in Clinoleic® (237 mg/L phytosterol; 98 mg/L cholesterol) and SMOF Lipid® (phytosterol 47.6 mg/L)[38]

Limitations of Evidence
Many trials were small (less than 50 patients).[10,13,14,15,29,30,37,49,50] There were flaws in the statistical analysis of some studies.[41]

Quality of Evidence (Summary of all evidence available)

Safety and Tolerability - Grade B
Multiple studies demonstrating consistency in outcomes despite differences in design, sample size and outcome measures.

Clinical Outcomes (hepatobiliary function) – Grade B
Multiple studies demonstrating consistency in outcomes despite differences in design, sample size and outcome measures.

Clinical Outcomes (infection, immunomodulatory effects, length of stay) – Grade C
Multiple studies with a trend towards favourable outcomes have been conducted. However, there is a lot of heterogeneity among the patient populations and outcomes and further study is required to confirm the results.

Summary of In-vivo Human Study Information Clinoleic® 20% (Olive Oil 16%/Soybean Oil 4%)
(Refer to Appendix 2 for review of Individual Studies)

ClinOleic® contains a low ω-6 PUFA (20%), high ω-9 MUFA (60%), and low saturated fatty acid content which closely matches international dietary recommendations for the fatty acid ratio.[40,55] Potential negative immune, hepatic, and inflammatory effects observed in SO based Intralipid® are linked to its high ω-6 PUFA content which are precursors to pro-inflammatory eicosanoids.

Clinoleic® is composed predominantly of ω-9MUFA which are not involved in production of eicosanoids and are therefore neutral to inflammatory process. Therefore, ClinOleic®, with less PUFA and more MUFA is thought to be less prone to lipid peroxidation; induce few or no immunomodulatory effects; not distort intrinsic host inflammatory response; and more effectively preserves the integrity of cholestatic markers.[40]

Our literature review concludes that ClinOleic® appears safe to use and is well tolerated in various patient populations studied.[1,2,6,7,8,9,33] It is demonstrated that ClinOleic® has a similar nutritional efficacy to SO IVFE with no development of EFA deficiency after 3 months as demonstrated by a triene:tetraene ratio which remained stable and below the threshold of 0.2.[8] Biochemical evidence of EFA deficiency occurs within 4 weeks of **fat-free** TPN.[32] In addition, no significant changes in lipid profiles or liver function have been reported.[4,8,9,23,52] Compared with SO-based IVFEs, ClinOleic® resulted in membrane phospholipid changes reflective of the infused lipid and consistent with improved membrane fluidity.[8] Alteration of membrane fluidity may affect the function of membrane-bound signaling cytokines and improve immune function.[54] Comparative studies using SO based IVFE and OO based IVFE demonstrate no differences in inflammatory or immunologic markers.[1,2,5,8,33] One study reporting significantly shorter length of ICU stay and shorter duration of ventilation had major limitations.[3] A RCT with 100 medical and surgical ICU patients reported no difference in mortality and ICU length of stay between OO and SO groups.[33] A meta-analysis reviewed SO – sparing strategies and found these strategies which included, but not exclusive to use of ClinOleic®, were associated with clinical reductions in mortality, duration of ventilation and ICU length of stay however none of the results were statistically significant.[36]

Studies Reviewed: 16 studies (including 1 meta-analysis)

Number of patients in each study: 13 - 100 patients

Populations Studied:
Home PN - 4 studies [1,2,8,35]
Critical Care – 3 studies (1 meta-analysis) [3,5,33,36]

Dialysis Patients - 1 study[6]
Burn Patients - 1 study[7]
Surgery - 2 studies[9, 23]

Parameters Studied (main criteria only):
Safety and tolerability – 6 studies[1,2,6,7,8,9,33]
Length of ICU Stay, Length of Ventilation, other ICU parameters - 2 studies[3, 33, 36]
Hepatobiliary function - 5 studies[4,7,9,23, 52]
Infection rate, New Infection, WBC's – 1 study[5,35, 33]
Plasma and Lymphocyte Composition/ Fatty Acid Composition - 1 study[8, 23]
Lipid Peroxidation - 1 study[9, 35]
Short-term Vascular, Metabolic, Immune and Inflammatory effects - 1 study[21]
Phytosterols (ClinOleic® and SMOF Lipid®) 1 study[38]

Population Groups
Home PN Patients

a) **Safety and efficacy** – Clinical, nutritional and inflammatory parameters did not differ between OO based and SO based lipid products over 3-6 months[1,2, 8] No differences in liver function tests between OO and SO.[8]

b) **Plasma and Lymphocyte Composition** – Fatty acid composition changed over time. OO had increased plasma oleic acid, γ-linoleic acid and Mead's acid. Lymphocyte cell membranes showed γ-linolenic acid unchanged in OO and decreased in SO. For both SO and OO, plasma and lymphocyte EFA remained in normal ranges without EFA deficiency. No difference in arachidonic acid changes between groups[8]

c) **Infection -** No evidence of compromised immune function in patients on long term OO IVFE.[35]

Critical Care

a) **Trauma patients** – Study showed a shorter length of ICU stay, shorter duration of ventilation, lower energy intake, lower blood glucose, CO_2 production and minute volume. However, there were several limitations with this trial which included (a) small trial (33 patients) (b) trial did not really compare OO to SO lipids as glucose/lipid ratio was different (lipid group (75% lipid (OO)/ 25% glucose) and glucose group (37% lipid (SO)/63% glucose), therefore the effect may be due to lower glucose load rather than a lipid emulsion effect[3]

b) **Infection -** No differences between infection rate/new infections, acute phase proteins and major health outcomes, length of ICU/hospital stay and mortality. There was a decrease in WBC in the SO group and an increase in the OO group. Author theorized there is less immune suppression in OO group[5]

c) **Medical / Surgical ICU** – A study of 100 patients compared the differences in hospital clinical outcomes (nosocomial infections and noninfectious complications), hospital length of stay, glycemic control, inflammatory and oxidative stress markers, and granulocyte and monocyte functions between SO and OO.[33] SO and OO showed similar rates of infectious and noninfectious complications, no differences in glycemic control, inflammatory and oxidative stress markers and immune function, mortality rates and ICU length of stay.[33]

d) **Meta-analysis # 1 – Not specific to ClinOleic®**

Aim - systematic review/meta-analysis of 12 RCTs (806 patients) to evaluate the effect of various parenteral SO-sparing strategies (including ClinOleic®) on mortality, ICU and hospital length of stay, infections, and mechanical ventilation days in critically ill adult patients.[36]
Results: SO-sparing strategies were associated with clinically important reductions in mortality, duration of ventilation, and in ICU length of stay, but none of these were statistically significant. SO-sparing strategies had no effect on infectious complications.[36]

Limitations: a) This review excluded studies that reported only biochemical, metabolic, immunologic, or nutritional outcomes. b) No attention paid to the dose and the length of intervention. c) Patient populations in the studies were heterogeneous.[36]

Hepatobiliary function – OO based lipids had less deterioration in cholestatic enzymes and triglycerides in a small trial of 21 patients with no difference in cytolytic enzymes.[4] However, there were some limitations with this trial which included a) small trial (22 patients) (b) individual enzyme results or mean results in each arm were not provided (c) significant deterioration was defined as number of patients who move to a more abnormal category after starting PN, (< ULN, 1-2x ULN and > 2 x ULN). However, since baseline results were not reported, a patient's result may have been just below the cut off and then deteriorated slightly to be included in a more abnormal group.[4]

In a trial of 22 burn patients, abnormalities of cholestatic enzymes occurred more frequently in MCT/LCT based IVFE compared to OO based group.[7] In a study of 13 home PN patients, there were no difference in liver function tests between OO and SO.[8] In a study of 20 patients who underwent abdominal surgery for cancer, the only statistically significant difference between SO and OO was the decrease in AST in the SO group.[9] One trial of 28 patients demonstrated no difference in any of the hepatic function parameters after a minimum of 5 days.[23] One trial of 70 patients reported biliary tolerance (assessed by repeated ultrasounds, changes in AST, ALT, ALP, GGT and total bilirubin) with either SO or OO IVFE.[52] Ultrasounds on day 15 and day 30 (in 36 patients with a normal baseline) showed presence of gallbladder sludge in similar numbers of patients. No difference was found enzyme activity between day 0 to day 60 between the groups.[52]

Dialysis Patients (Intradialytic) – OO and SO based IVFE similarly improved nutritional status and influenced plasma lipid, oxidative, inflammatory and immune parameters.[6]

Burn Patients No fatty acid deficiencies were observed. Abnormalities of cholestatic enzymes occurred more frequently in MCT/LCT based IVFE compared to OO based group [7]

Surgery

a) **Abdominal with cancer** One trial examined glucose, LFT's, albumin, triglycerides, cholesterol, BMI and body temperature and lipid peroxidation in SO and OO. The only statistically significant difference between the SO and OO group was the decrease in AST in the SO group. All other parameters were not statistically significant.[9]

b) **Digestive surgery –**One trial of 28 patients demonstrated no difference in any of the hepatic function parameters or plasma lipid levels between the groups. (MCT/LCT, oleic, LCT and structured lipid). The change in serum fatty acids reflected the pattern of fatty acids administered with different lipid emulsion used.[23]

Phytosterols (ClinOleic® and SMOF Lipid®)
Phytosterols in PN solutions may have a role in cholestasis development.[17, 38] Phytosterol and cholesterol levels were higher in Intralipid® than ClinOleic® (refer to page 5)

Limitations of Evidence
Most trials were very small (less than 40 patients)[1-12] Some trials had flaws in their methodology (see critical care and hepatobiliary function above).[3,4]

Quality of Evidence (Summary of all evidence available)

Safety and Tolerability - Grade B
Multiple studies demonstrating consistency in outcomes despite differences in design, sample size and outcome measures.

Clinical Outcomes (hepatobiliary function) – Grade C
Limited number of studies with small sample sizes and some studies with research design flaws.

Clinical Outcomes (infection, immunomodulatory effects, length of stay) – Grade C
Limited number of studies with small sample sizes and some studies with research design flaws.

Other Information

Compatibility Information (see Appendix 4)

Cost Information (see Appendix 5)

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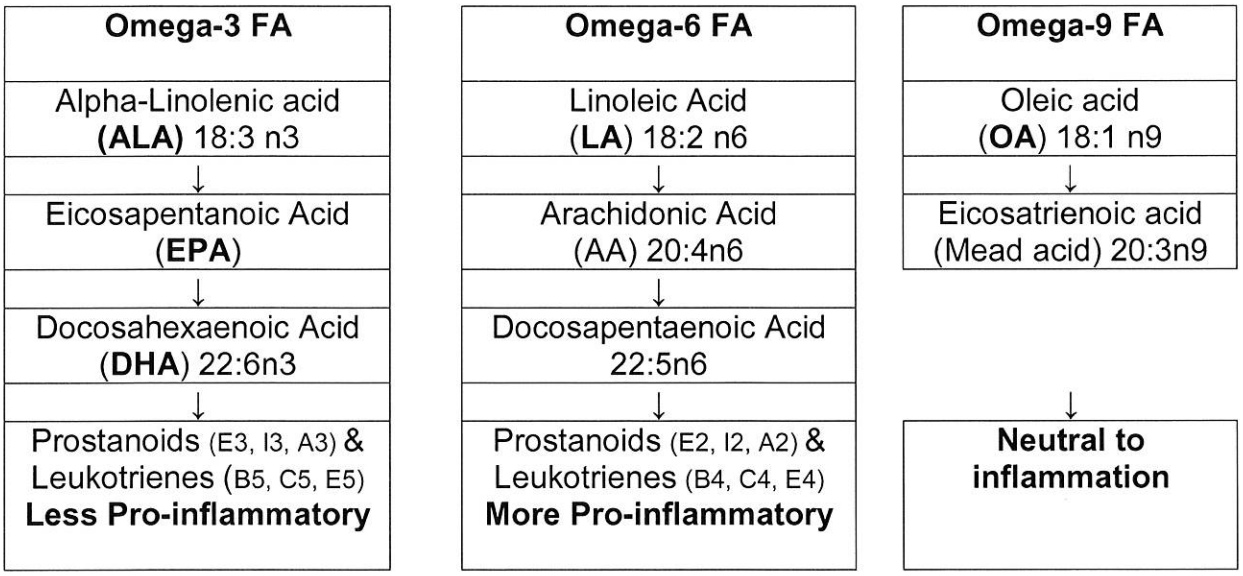
Practice Implications:
A formulary submission for SMOFLipid® will be completed. It will be reviewed by the WRHA Adult Pharmacotherapy Committee. Once added to the WRHA formulary, education about appropriate use will be undertaken with relevant users/stakeholders.
Recommendation for implementation:
These recommendations are being reviewed by:

Name and Credentials	Date Review Complete

Appendix 1

Fatty Acid Composition

Metabolic pathways of ω-3, ω-6, ω-9 fatty acids and their relative pro-inflammatory properties.
Adapted from Vanek et al[17]



Appendix 2

In vivo Human Study Information - Clinoleic® (Olive Oil 16%/Soybean Oil 4%)

N = 14 (Home PN) (Reimund)[1]
Aim: An open label, prospective study to assess ClinOleic® 20% in respect to efficacy, safety and effect on systemic inflammatory parameters in stable patients on home PN. Nutritional status, clinical and biologic tolerance and effect upon systemic inflammatory parameters were analyzed at the following times: a) before switching to ClinOleic® b) after 1 month and c) after 3 months
Results: Clinical and nutritional markers and inflammatory parameters did not differ between day 0 and month 3, no essential fatty deficiency and no side effects (8 pts with remote history of PN cholestatic liver disease)
Limitations: (a) small trial

N = 13 (Home PN) (Thomas-Gibson)[2]
Aim: An open label, prospective study /retrospective study to evaluate the efficacy and safety of ClinOleic® 20% in home PN patients (adults) already receiving PN; comparing it to their usual lipid (soybean oil based). Assessments were bimonthly up to 6 months and retrospective adverse events were recorded 6 months prior to study, during the study and after the study was completed.
Results: Four patients ended treatment prematurely (2 sepsis , 1 abnormal LFT's and sepsis, 1 withdrew consent). The study did not identify any problems with tolerability or safety in prolonged use of ClinOleic®. The retrospective review revealed similar complication rates in the 6 months before, during and after the trial. (6 pts with pre-existing biliary disease (Ultrasound showed no significant change in outflow)
Limitations: (a) small trial

N = 33 (Trauma Patients) (Huschak)[3]
Aim: An open label, prospective, randomized trial of severe multiple trauma patients receiving a parenteral lipid-based (63% glucose/37% lipid (soybean)) nutrition and parenteral glucose-based (40% glucose/60% lipid ClinOleic®))nutrition comparing the following parameters: energy expenditure, mean energy intake, energy intake/energy expenditure ratio, triglycerides, nitrogen balance, blood glucose, CO_2 production, minute volume, length of ventilation, length of ICU stay.
Results: No difference in energy expenditure and energy intake/expenditure ratio, triglycerides or nitrogen balance. Lower mean energy intake in lipid group, lower blood glucose, CO_2 production, minute volume and shorter duration of ventilation and length of stay in ICU.
Limitations: (a) small trial (18 vs 15 pts) (b) did not really compare olive oil to soybean oil lipids as glucose/lipid ratio was different (lipid group (75% lipid/ 25% glucose) and glucose group (37% lipid/63% glucose). The effect may be due to lower glucose load rather than a lipid emulsion effect.

N = 21 (Hepatobiliary Function) (Palova)[4]
Aim: A retrospective trial to compare the effects of soybean oil versus olive oil lipid emulsions on hepatobiliary function and serum triglycerols. Cholestatic and cytolytic enzymes, conjugated bilirubin and serum triglycerols were sampled before and 1 day after nutrition PN (minimum of 2 weeks duration). Baseline results must be < 2x upper limit limit of normal (ULN).
Results: Significant deterioration of cholestatic enzymes in 5 of 10 pts in soybean oil group and 1 of 11 in olive oil group. Serum triglycerols significantly deteriorated in 7 of 10 pts in soybean oil group and 1 of 11 in olive oil group. No differences in cytolytic enzymes **(NOTE LIMITATIONS)**
Limitations(a) small trial (10 vs 11 pts) (b) olive oil group was older (50 vs 33) (c) baseline - all enzymes < 2 x ULN, however individual enzyme results or mean results in each arm were not provided (d) significant deterioration defined as number of patients who move to a more abnormal category after starting PN (< ULN, 1-2x ULN and > 2 x ULN). However, since baseline results were not reported, a patient's result may have been just below the cut off and then deteriorated slightly to be included in a more abnormal group.

N = 39 (Immune Function) (Mateu—de Antonio)[5]
Aim: An observational retrospective trial comparing the effects of soybean based oil (SO) to olive oil emulsion (OO) on infection rate, appearance of new infections, leukocyte count, acute phase proteins (albumin, fibrinogen CRP) and major health outcomes in ICU patients receiving PN > 5 days.
Results: No differences were observed in infection rate/ new appearance, acute phase proteins and major health outcomes. At the end of PN, blood leukocyte count **decreased** by 3.25 x 10^9 in the **SO** group and

increased by 4.51 x 10^9 in the **OO** group from baseline (P = 0.036). Peak leukocyte count presented a trend (p= 0.078) for a higher value in the OO vs SO group (18.86 vs 15.28 x 10^9). Length of ICU stay, hospital stay and mortality were not statistically different . (proposed mechanism of effect on leukocytes - SO emulsions promote lymphocyte and neutrophil death by apoptosis)
Limitations: (a) small study (b) leukocyte count is a variable parameter (usually to infectious or inflammatory processes)[5]

N = 35 (Dialysis Patients) (Cano)[6]
Aim: A 5 week randomized, double blind trial comparing the efficacy and tolerance of soybean based oil (SO) to olive oil emulsion (OO) during intradialytic PN. On days 0 and 35, **nutritional status** was assessed by BMI, normalized protein catabolic rate, pre-dialytic sCr, albumin, transthyretin;; **lipid metabolism** was assessed by LDL, HDL, TG's, phospholipids , various apo and lipo proteins;; **oxidative status** by α tocopherol , retinol, selenium , glutathione peroxidase, malondialdehyde and advanced oxidized protein products;; **inflammatory status** by CRP, orosmucoid, IL-2 and IL-6
Results: No serious adverse event was observed. Nutritional criteria improved. From the data, it was concluded that OO and SObased intradialytic PN similarly improved nutritional status and influenced plasma lipid, oxidative, inflammatory and immune parameters.
Limitations: (a) small study

N = 20- 22 (Burn Patients) (Garcia-de-Lorenzo)[7]
Aim: A prospective, randomized, double blind trial comparing the tolerability and effects on fatty acids of medium chain/long chain triglycerol (50:50) (MCT/LCT) to olive oil emulsion (OO) in severely burned patients treated for 6 days. Plasma fatty acids, LFT's and plasma cytokines were assessed before and after TPN. Adverse events and clinical outcomes within the subsequent 6 months were recorded.
Results: With both lipid emulsions the conversion of linoleic acid in its higher derivatives improved and essential fatty acid deficiency did not appear. Abnormalities of LFT's (cholestasis) occurred in 9/11 patients in the (MCT/LCT) vs 3/9 pts in the OO group. (most levels between 1-2x and 2-5 x ULN). Seven patients died of sepsis (3 MCT/LCT and 4 OO)
Limitations: (a) small study (b) did not show actual LFT values (baseline and day 6) (broken down into 1-2 x ULN;; 2-5 x ULN and > 5 x ULN) and worsening levels

N = 13 (Effects on Plasma and Lymphocyte Lipid composition) (Vahedi)[8]
Aim: A prospective, randomized double blind trial comparing the clinical and metabolic effects of olive oil (OO) emulsion with a standard soybean oil (SO) administered to home PN adult patients over a 3 month period. There was a 30 day run-in with medium chain triglycerides/ long chain triglycerides prior to randomization. Patient demographics, nutritional intake, adverse events and phospholipid fatty acid profiles in plasma and lymphocyte cell membrane were compared.
Results: No differences in patient demographics. One case of pneumonia in the OO group vs 0 in SO group. Liver function tests remained unchanged. OO has similar nutritional efficacy compared to SO with no deficiency in essential fatty acids during the study period. Lymphocytes cell membranes showed γ-linolenic acid unchanged in OO and decreased in SO. For both SO and OO, plasma and lymphocyte EFA remained in normal ranges without EFA deficiency. No difference in arachidonic acid changes between groups
Limitations: (a) small study (b) hard to understand clinical impact of different fatty acid composition

N =20 (Effects on Temp, BMI, LFT's) (Onar)[9]
Aim: To compare the effects of 0.75g/kg/day of soybean based fat emulsion (n=10) with soybean/olive oil (n=10) based fat emulsion in patients undergoing abdominal surgery for cancer with respect to the following parameters: glucose, LFT's, albumin, triglycerides, cholesterol, BMI and body temperature, lipid peroxidation (TBARS- indicator of free radical production).
Results: Soybean oil group had significant increase (Day 0 to Day 7) in ALP and GGT and body temp. In the olive oil/soybean group (Day 0 to Day 7), ALP, GGT, total protein and albumin all increased after 7 days whereas bilirubin was decreased. The only statistically significant difference between the soybean and olive oil group was the decrease in AST in the soybean group (30.1 to 27 units/L) compared with the olive oil group (44.9 to 57.6 units/L). All other parameters were not statistically significant.
Limitations: a) small sample size b) short follow up (7 days) c) statistics in study hard to interpret

N= 28 (Puiggròs)[23]
Aim: A prospective randomized double-blind study to compare the effect of different lipid emulsions (MCT/LCT, oleic, LCT, and structured lipid) on liver function, lipid profile, and fatty acid disturbances in adult patients post digestive surgery. Patients treated for at least 5 days with 1.1-1.2g/kg/day of lipids.
Results: On day 6, there was no difference observed in any of the hepatic function parameters or plasmatic lipid

levels between the groups. The change in serum fatty acids reflected the pattern of fatty acids administered with different lipid emulsion used.

N = 42 (Olthoff)[35]

Study Design:20 pts on ClinOleic®, 21 controls; on ClinOleic® for ≥ 6 months; open study.
Background: Pts on HPN are at increased risk for infectious complications particularly catheter related infection. It remains unknown if components of the TPN solutions, especially lipids, play a role.
Aim: Compare the first line, "innate" immune function of pts on ClinOleic® with healthy controls to measure any impairment in capacity to eliminate Strep. Pneumoniae, any difference in the expression of activation and degranulation markers, oxygen radical production or in the oxidant-antioxidant balance.
Results: No evidence of compromised immune function in pts on long term olive-oil based IVFE.
Of interest, there were some differences in oxidant-antioxidant balance. HPN pts had significantly lower selenium and vitamin C levels and a five-fold increase in oxidized glutathione levels which the authors postulate may be explained in part by fact that selenium is contained in glutathione peroxidase and is involved in oxidation reactions of glutathione. Vitamin C levels were below normal range in 5% of HPN pts; selelnium levels were below normal in 30% of HPN pts.Other laboratory findings in HPN pts: 35% had mildly elevated triglyceride levels, 20% had elevated ALT and AST, 50% had elevated ALP and/or GGT. Hgb levels were significantly lower than controls but were within normal range. Vitamin E, total bilirubin and CRP levels were not different.

N= 12. (Siqueira)[21]

Study Design: prospective randomized controlled crossover trial; Subjects admitted on 4 different occasions to receive in random order 24 hour infusions of either normal saline, Lipid-free PN, Intralipid or ClinOleic® PN. Also given oral 400 kcal low fat chicken salad at lunch and supper during infusions.
Aim: Compare vascular, metabolic, immune, inflammatory effects of Intralipid vs ClinOleic®vs normal saline in normotensive, healthy subjects.
Results: Systolic blood pressure was increased and endothelial function was impaired during Intralipid® infusion and not during ClinOleic® infusion. No significant changes in plasma free fatty acids, lipid profile, inflammatory and oxidative stress markers, immune function parameters or sympathetic activity between Intralipid and ClinOleic®.
Limitations: a) Small trial in healthy subjects. b) short duration to see effect - Authors recommend study in hospitalized pts under stress. c) oral intake may have affected results

N = 100 (Umpierrez)[33]

Aim: A prospective, double-blind, randomized, controlled trial compared the differences in hospital clinical outcomes (nosocomial infections and noninfectious complications), hospital length of stay, glycemic control, inflammatory and oxidative stress markers, and granulocyte and monocyte functions between 2 study groups receiving PNcontaining soybean oil-based (intralipid) or olive oil-based (ClinOleic®)lipid emulsions in the medical-surgical intensive care units at a major urban teaching hospital and a tertiary referral university hospital.
Results: The administration of PNcontaining soybean oil-based and olive oil-based lipid emulsion resulted in similar rates of infectious and noninfectious complications and no differences in glycemic control, inflammatory and oxidative stress markers and immune function in critically ill adults and similar overall rates in mortality and ICU length of stay. Patients in both groups had a similar length of stay 47 vs 41 days and mortality 16.3% and 9.8% respectively.
Limitations: a) Small number of patients b) preponderance of surgical ICU subjects and c) the study was not powered to demonstrate differences in mortality between treatment groups.

N = 70 (Bouletreau)[52]

Aim: A randomized open label, prospective study comparing the effects of ClinOleic® (OO) 20% and Intralipid 20%® (SO) on biliary tolerance (assessed by repeated ultrasounds, changes in ALT, AST, ALP, GGT, and total bilrubin). Patients were treated for at least 15 days (range15 – 438 days).
Results: Biliary complications as assessed by repeated ultrasound on day 15 and day 30 in 36 patients with a normal baseline ultrasound showed presence of gallbladder sludge in 6/17 (OO) and 7/19 (SO). Twenty-six to 40% of all patients had mild increases in one or more hepatic enzymes (1.1 - 2 times upper limit of normal). In the group treated for 15- 60 days, no difference was found in enzyme activity between day 0 to day 60 between the groups.
Conclusion: Hepatic and biliary tolerance of SO and OO in prolonged PN appear to be equivalent
Limitations: (a) small trial (b) article translated from French with very little information on the methodology (c) some patients were taking oral nutrition (11patients SO and 10 patients 00)

SMOF Lipid® and ClinOleic®

N = 43 (Ellegard)[38]
Study Design: Observational study; 24 short bowel syndrome (SBS); 16 without TPN, 8 with TPN; 9 ileostomomy; 21 controls. **Type of IVFE in the TPN was not specified**.
Background: Phytosterols in PN solutions may have role in cholestasis development. Phytosterol and cholesterol levels were higher in Intralipid® (348 mg/L phytosterol; 292 mg/L cholesterol) than in Clinoleic® (237 mg/L phytosterol; 98 mg/L cholesterol) and SMOF Lipid® (phytosterol 47.6 mg/L)
Aim: Quantify concentration of phytosterols in different IVFEs. Also measured blood phytosterol levels in adult pts with SBS with and without TPN compared with controls.
Results: Pts with SBS on TPN had serum phytosterol levels that were 174% higher than controls; SBS pts not on TPN had serum phytosterol levels 54% lower than controls. There was no correlation found between calculated intake of phytosterol and serum levels. Serum cholesterol levels in SBS pts regardless of nutrition were 21% lower than controls. All levels in pts with ileostomy were similar to controls.
Lab results: Slightly elevated liver enzymes (specified only that <2 times normal range) in 7/16 SBS without TPN and 6/8 with TPN. Alkaline Phosphatase levels were correlated with borderline significance to serum phytosterol levels but not to phytosterol intake. Only 1/8 SBS with TPN had slightly elevated bilirubin. No other levels specified.
Limitations:1) Observational, small study – only 8 TPN pts. 2) Type of IVFE was not specified 3) no data correlating low levels of phytosterol in ClinOleic® with clinical effects in patients.

Meta-analysis (12 RCTs) - Alternative lipid emulsions in the critically ill. (Manzanares)[36]
Aim:systematic review and meta-analysis of 12 RCTs to evaluate the effect of parenteral soybean oil-sparing strategies (LCT+MCT vs LCT, fish oil containing emulsions vs LCT or LCT+MCT, Olive oil containing emulsions vs LCT or LCT+MCT) on mortality, ICU and hospital length of stay, infections, and mechanical ventilation days in critically ill adult patients.
Results: Soybean oil-sparing strategies were associated with clinically important reductions in mortality, duration of ventilation, and in ICU length of stay, but none of these were statistically significant. Soybean oil-sparing strategies had no effect on infectious complications.
Limitations: This review only included studies with mortality, ICU and hospital length of stay, infections and mechanical ventilation days as outcomes and excluded the ones that reported only biochemical, metabolic, immunologic, or nutritional outcomes. Hence no attention paid to the dose and the length of intervention. The patient populations in the studies were heterogeneous. There were three subgroups (LCT+MCT vs LCT, fish oil containing emulsions vs LCT or LCT+MCT, Olive oil containing emulsions vs LCT or LCT+MCT) and there is small number of studies under each subgroup.

Appendix 3

In vivo Human Study Information – SMOF Lipid® (Soybean Oil 6%, Medium Chain Triglycerides 6%, Olive oil 5%, Fish oil 3%)

N=12 (Schlotzer)[10]
Methods: Randomized double blind cross-over study of healthy subjects receiving SMOFlipid® or Lipovenoes® over 6 hours.
Aim: to investigate plasma elimination and tolerance of a new lipid emulsion based on soybean oil, medium chain triglycerides (MCT), olive oil and fish oil (SMOF Lipid®).
Results: Infusion of SMOF induced a less marked increase of serum triglyceride concentration. At the end of the infusion, mean serum triglyceride concentration was significantly lower with SMOF ($p<0.05$). Triglyceride half life was significantly shorter for SMOF than for Lipovenoes® (p,0.001).
Conclusion: SMOF was eliminated significantly faster than the standard lipid emulsion. The safety evaluation revealed a good systemic and local tolerance of SMOF.
Limitations: a) small trial b) healthy volunteers c) short time of infusion

N=73 (Klek)[11]
Methods: Randomized, controlled, double-blind, multicentre study in patients with stable intestinal failure, requiring PN with SMOF or SO for 4 weeks. Safety and tolerance, fatty acid pattern in red blood cell phospholipids and plasma lipoproteins, serum Vitamin E, Interleukin (IL-6), and soluble tumour necrosis (s-TNF)-receptor(R)II were also evaluated
Aim: To evaluate the safety and tolerance of a soybean/MCT/olive/fish oil emulsion in intestinal failure patients on long-term PN.
Results: Mean concentrations of ALT, AST and total bilirubin, whilst remaining within the reference range, were significantly lower with (SMOF) oil emulsion after the treatment period compared to control. EPA, DHA and n-3/n-6 fatty acid ratio increased in the SMOF group while they remained unchanged in the control in plasma and RBC. Serum a-tocopherol concentrations significantly increased in the study group compared to the control. IL-6 and sTNF-RII levels did not change during the study period. Serious adverse affects occurred in 2 SMOF patients and in 8 control patients. SMOF emulsion was safe and well tolerated over 4 weeks and leads to positive changes in fatty acid profiles.

N=199 (Mertes)[12]
Methods: A prospective, double blind, multicenter study of post-operative patients (elective abdominal or thoracic surgery) randomized to SMOF of Lipovenoes® for at least 5 days. Parameters examined included triglycerides, phospholipids, cholesterol, hospital length of stay and mortality as well other safety/tolerance measurements.
Aim: SMOFlipid® was tested for safety, tolerance and metabolic and clinical efficacy in surgical patients.
Results: Concentrations of serum triglycerides, phospholipids, and total cholesterol were comparable in both groups and within the expected ranges. Laboratory and clinical parameters were not different. A trend towards a reduced length of hospital stay was observed with SMOFlipid®. SMOFlipid® is clinically safe and well tolerated in postoperative patients. There are indications that SMOFlipid® may be associated with a better liver tolerance and shorter length of hospitalization.

Note: In a subsequent economic evaluation, patients receiving SMOF lipid® incurred a cost of $15,303 per patient while patients receiving SO emulsion incurred a cost of $17,331 per patients. The use of SMOF lipid® was associated with an incremental cost saving of $2,028.[28]

N=33 (Grimm)[13]
Methods: Double blind, randomized trial of SMOF or Lipovenoes® for at least 5 days following major abdominal surgery. Lipid biochemistry, plasma tocopherol, fatty acid pattern in plasma, leukocyte and platelet phospholipids were reviewed.
Aim: To assess the effects of a novel lipid emulsion with reduced content of n-6 fatty acids, increased share of MUFA and n-3 fatty acids and supplemental vitamin E on fatty acid and leukotriene pattern in surgical patients.
Results: Treatment with the new emulsion SMOF lipid® is well tolerated and modulates FA and leukotriene pattern suggesting favourable anti-inflammatory effects and further clinical benefits. On day 6, plasma α-

tocopherol levels, content of ω-3 FA in plasma phospholipids and ratio of ω-3 to ω-6 FA were elevated in SMOF compared to SO. The total ω-6 content in plasma phosholipids was lower in SMOF compared to SO.

N=20 (Antebi)[14]
Background: Double blind study of adult ICU patients undergoing major surgery randomly assigned to SO (Lipoven®) or SMOF with treatment of at least 5 days. Liver enzymes, C-reactive protein, antioxidant capacity, α-tocopherol levels and LDL–lipid oxidation (incubation of the LDL in the presence of a pro-oxidant) were measured.
Aim: Efficacy and safety of an α-tocopherol-enriched emulsion incorporating soybean, coconut, olive and fish oils (SMOF) are compared in terms of biologic parameters to those of soybean oil-based emulsion (Lipoven®).
Results: The plasma activities of liver enzymes and phospohlipids/apo A1ratio (indicator of alterations in liver function) were increased in both groups. However, in the SMOF group, the increases were lower than in the Lipoven® group except AST. Changes were non-significant for the CRP plasma levels. The antioxidant capacity and amount of LDL-derived oxidation by-products were comparable in both groups. There was a significant improvement in plasma lipophilic antioxidant vitamins and LDL-α-tocopherol levels only in the SMOF group.

N=44 (Piper)[15]
Background: Prospective, randomized, double blind trial in post-operative (major abdominal or large cranial-maxillo-facial resection for cancer) patients comparing SMOF and OO/SO for 5 days. AST, ALT, α glutathione S-transferase were measured at baseline, day 2 and day 5.
Aim: To assess the effects of SMOF compared with a lipid emulsion based on olive and soybean oil on hepatic integrity.
Results: There was no significant difference at d0, but at d2 and d5, significantly lower aspartate aminotransferase, alanine-aminotransferase, and a-glutathione S-transferase levels were found in soybean oil, medium-chain triglycerides, olive oil and fish oil group compared with the control group. Hepatic integrity was well retained with the administration of SMOF lipid® whereas in patients receiving a lipid emulsion based on olive and soybean oil liver enzymes were elevated indicating a lower liver tolerability.

Meta-analysis (23 studies);; N= 1502 pts N= 762 ICU (Pradelli)[27]
Aim: to analyze literature (RCT's) comparing ω-3PUFA lipid emulsions with standard non-enriched lipid emulsions (soybean oil, MCT/LCT or olive/soybean oil emulsions) in surgical and ICU patients receiving PN.
Results: No statistical difference in mortality (RR 0.89) (0.59-1.33). ω-3PUFA lipid emulsions are associated with statistically and clinically significant reduction in infection rate (RR 0.61) (0.45-0.84),), reduction in ICU length of stay by 1.92 days (-3.27 to -0.58 days) and reduction in hospital length of stay by 3.29 days (-5.13 to -1.45 days). Other beneficial effects included improved lung exchange (oxygenation index (PO_2: FiO_2ratio), liver function (ALT -10.05 units/L (-18.81 to –1.29)) (AST -9.85 units/L (–17.49 to -2.21)) and a trend towards less impairment of kidney function (sCr -0.03 umol/L (-0.08 to 0.01). Improved antioxidant status (α-tocopherol + 12.33 umol/L (8.73 to 15.93) and fatty acid / plasma phospholipid composition (increased DHA and EPA, decreased IL- 6) are also reported. No improvements in triglycerides (0.12 mmol/L (-0.15 to 0.39), bilirubin, CRP, platelet count or coagulation time.
Limitations : 1) Meta-analysis – lots of heterogeneity - Varied doses and formulations of ω-3 PUFAs (SMOF, SO/MCT/ω-3 TGs, SO + FO) and comparators (SO, OO/SO) 2) Improvements in some parameters (ie LFTs) only marginal

N=41 (Hallay)[30]
Aim: A prospective randomized study to compare the effect of 4-day post-operative use of SMOF and LCT/MCT on hepatobiliary function in patients who underwent gastrointestinal surgery.
Results: there was no difference between SMOF and LCT/MCT group.
Limitations: Experimental dose of lipid is 1.4g/kg/BW which is higher than current practice. The study only observed 5 days post op and more prominent changes were seen on Day 4, but not statistically significant. The study may not be long enough to show a difference.

Meta-analysis (21 RCTS - Does intravenous fish oil benefit patients post-surgery? (N-N Li)[34]
Aim: Comprehensive meta-analysis of 21 RCTs to evaluate the effects of fish oil containing lipid emulsions compared to standard soybean oil/soybean oil-MCT-based emulsions on infection, length of stay, liver dysfunction in post-surgery patients.
Results: FO was associated with a significant reduction in the length of hospital stay, infections, ALT, GGT, and total bilirubin without significant change in mortality and postoperative medical cost. This review employed rigorous article selection process. The quality of evidence of each clinical outcome was accessed as high.
Limitations: SMOF lipid®used in 4 out of 21 studies.

Meta-analysis (6 RCTs) (n= 306 pts)(Tian)[41]
Aim: To assess the safety and efficacy of a new parenteral lipid emulsion (SMOF) versus other parenteral lipid emulsions in post-operative patients.
Results: SMOF was associated with a lower change in level of hepatic enzymes (↓ change in AST, ALT, ALP and GGT vs Lipoven 20%®- not for other comparators) and LDL-Triglycerides (vs ClinOleic® and Lipoven20%®). No significant differences in adverse events and length of hospital stay.
Limitations: a) **statistical inconsistencies with statements** (p value did not meet significance when making statements about CRP, hepatic enzymes (vs ClinOleic®)) b) several drugs used as comparators

N= 44 (Schade)[29]
Aim: Compare SMOF to ClinOleic® on inflammatory response in post-op ICU pts.
Study Design:prosective randomized controlled trial;. Pts allocated to group A (SMOF) or group B (ClinOleic®) administered over 5 days. Inflammatory response indicators, IL-6, TNFα, and soluble E-selectin were measured on Day 0, 2, and 5.
Results: There was no significant difference until Day 5. SMOF group had significantly lower ($P<0.05$) IL-6 (group A: 73 ± 58 vs group B: 123 ± 107 pg/ml), TNFα (group A: 15.2 ± 7.9vs group B: 22.6 ± 12.9 pg/nl), and soluble E-selectin concentrations (group A: 21.5 ± 13.7 vs group B: 32.6 ± 21.2 ng/ml).
Conclusion: The administration of SMOF within a PN regimen led to a significantly lower inflammatory response at day 5 compared to ClinOleic®.

N= 44 (Piper)[49] (same population as Schade[29])
Aim: Compare SMOF to ClinOleic® for lipid utilization.
Study design: Same study as **Schade[29]**. Triglyceride levels were measured Day 0, 2, 5. A pathological triglyceride level was defined at 300 mg/dl and a significance level at $P<0.05$.
Results: No significant differences at baseline (Day 0 group A: 119mg/dl ± 35 vs group B: 120 ± 45 mg/dl; $P=0.87$). Triglyceride levels were significantly lower in SMOF group than ClinOleic® group on day 2 (group A: 151 ± 52 vs group B: 202 ± 108 mg/dl; $P<0.03$) and day 5 (group A: 163 ± 72 vs group B: 233 ± 94 mg/dl; $P<0.01$). At day 5 the incidence of pathological triglyceride level (defined as 3.4 mmoL/L or greater) was significantly lower in SMOF (0%) compared to ClinOleic® (31.8%).
Conclusion: SMOF resulted in better utilization (clearance) of triglycerides than ClinOleic®.

N=24 (Genton)[50]
Aim: Compare metabolic and clinical tolerance of SMOF to Soybean oil lipid, Lipovenoes® in pts using TPN for at least 7 days.
Results: No differences in plasma triglyceride, cholesterol, glucose and liver enzyme levels.
Conclusion: SMOF is well tolerated metabolically and clinically.

Review of 4 Clinical Studies comparing SMOF to Soy Oil based lipid (Grimm)[39]
Aim: To compare SMOF to Soy Oil based lipid to assess safety, tolerance, effect on liver function and immune function in healthy volunteers, surgical and hospital patients.
Study Design:TPN with SMOF infused over 5 to 14 days for 6 to 24 hours/day with 0.125 g fat/kg up to 2 g fat/kg BW per day compared to soy based IVFE. Included 2 previously reviewed (Schlotzer 2004 and Antebi 2004; Genton 2004 Schulzki 1999)
Results: No study demonstrated any negative effects associated with SMOF.

N= 199 (Shulzki)[55] (may be same population studied in Mertes[12])
Study Design: double blind randomized European multicenter trial in surgical pts for 5 days of either SMOF or Soybean IVFE.
Results: Analysis showed slightly lower increases in liver enzymes (AST, ALT, GGT, ALP) in the SMOF group. Other parameters including adverse events showed no differences. A subgroup analyses of 99 SMOF and 100 Soybean oil showed both IVFE induced a modest increase of serum triglyceride levels (not statistically significant) and in both groups levels reached steady state early and remained within normal range (max TG levels SMOF 1.99 ± 0.98 mg/dl and 2.00 ±0.83 mg/dl). No differences in mortality; a trend towards reduced length of stay observed in SMOF group (15.7±6.3 days vs 17.8±13.2 days in SO). A third subgroup of 33 pts, SMOF n=19, SO n=14) demonstrated in the SMOF group, EPA and DHA were rapidly incorporated into plasma phospholipid fatty acid pattern resulting in an increased EPA:AA ratio ($p<0.05$). Phospholipid –derived fatty acid pattern of leukocytes and platelets were similar to those seen in plasma phospholipids. The modified fatty acid pattern changed the eicosanoid pattern suggesting beneficial effects on the immune system. On day

6 the ratio of LTB5:LTB4 was more favorable in the SMOF group ($p<0.05$). The 7 day reduction of hospital stay may be a result of the anti-inflammatory shift in the LT pattern. Furthermore plasma α-tocopherol levels were significantly higher in SMOF group (34.2 ± 10.3 umol/L) vs the soy oil group (17.6 ± 2.9 umol/L; $p<0.05$).
Conclusions: in future soybean oil IVFE will be used in uncomplicated pts; SMOF is safe and well tolerated; is associated with improved liver tolerance and immune function; maintains plasma alpha-tocopherol levels and may be particularly suitable for use in patients with hyperinflammatory diseases and/or stressed immune systems.

N=40 (Wu)[37] (5 did not complete)
Aim: Randomized clinical trial's aim was to assess the efficacy of the new SMOFlipid® in gastrointestinal surgery compared with MCT/LCT.
Results: SMOFlipid® was well tolerated in adult patients undergoing gastrointestinal surgery. The increment of triglyceride on day 6 from baseline was significantly lower in SMOFlipid® group than in MCT/LCT group. Inflammatory markers, as well as superoxide radical and total oxygen radical were not different between groups.
Limitations: Small sample size.

SMOF Lipid® and ClinOleic®

N = 43 (Ellegard)[38] **- refer to page 20**

Meta-analysis (12 RCTs) - Alternative lipid emulsions in the critically ill. (Manzanares)[36] **– refer to page 20**

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Appendix 4

Compatibility Information

	WRHA Guidelines (Intralipid) – Abacus Soft Limits (HSC/St B)	ClinOleic®[43]	SMOFLipid®[44]
Potassium	200 mmol/day 80 mmol/L 10 mmol/hr	150 mmol/L	100-150 mmol/L
Sodium	154 mmol/L	150 mmol/L	150 mmol/L
Magnesium	20 mmol/day 12 mmol/L	5.6 mmol/L	5 mmol/L
Calcium (independent of Ca+/PO4 curve)	14 mmol/day 10 mmol/L	5 mmol/L	5 mmol/L
Phosphate (independent of Ca+/PO4 curve)	60 mmol/day 60 mmol/L	30 mmol/L (includes PO_4 from both ClinOleic® 20% - (1.5 mmol PO_4/100 mL of lipid) and supplemental PO_4)	15 mmol/L
Chloride	300 mmol/L	- No data on the maximums - Acetate and chloride may be added as long as the ion coupled to them (ie K+) does not exceed the amount specified above - Do not exceed Acetate 140 mmol/L (previous maximum)	300 mmol/L
Acetate	140 mmol/L		150 mmol/L (do not exceed previous maximum of 140 mmol/L)

	WRHA Guidelines (Intralipid) – Abacus Soft Limits (HSC/St B)	ClinOleic®[43]	SMOFLipid®[44]
Ascorbic Acid 250 mg/mL	500 mg/day	No info for TNA	No info for TNA
Dextrose 70%	9 g/kg	170g/L	220 g/L
Fish Oil Emulsion 10%	1 g/kg	No info for TNA	No info for TNA
Folic Acid 5 mg/mL	1 mg/day	No info for TNA	No info for TNA
Lipid	2.5 g/kg Intralipid	65g/L of ClinOleic® 20%	38 g/L(stability get better as concentration increases)
Iron Dextan 50 mg/mL	100 mg/day (2 in 1) 0 mg/day (TNA)	0 mg/day (TNA)	0 mg/day (TNA)
MVI Adult/9+3	10 mL/day	10 mL/day	10 mL/L
Pyridoxine 100 mg/mL	100 mg/day	No info for TNA	No info for TNA
Ranitidine 25 mg/mL	300 mg/day	300 mg/day	100 mg/L
Thiamine 100 mg/mL	100 mg/day	No info for TNA	No info for TNA
Micro +6 Adult	2 mL/day	2 mL/day	1 mL/L
Travasol 10%	2 g/kg	50 g/L	55g/L
Vitamin B12 1000 mcg/mL	100 mcg/day	No info for TNA	No info for TNA
Vitamin K 10 mg/mL	10 mg/day	No info for TNA	10 mg/L
Zinc sulfate 1 mg/mL	10 mg/L	10 mg/day (including Trace)	No information

Appendix 5

Cost Information (January 2014)

Intralipid = 250 mL - $10.91 500 mL - $11.16

SMOFLipid®= 250 mL - $11.00 500 mL - $13.50

ClinOleic®= 250 mL - $10.91 500 mL - $11.16