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Neonatal parenteral nutrition

[D3] Lipids

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Evidence reviews

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These evidence reviews were developed by the National Guideline Alliance which is part of the Royal College of Obstetricians and Gynaecologists

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Contents

Intravenous lipids

Review questions

This evidence report contains information on two questions conducted as one review relating to the individual constituents (lipids) in parenteral nutrition for preterm and term babies.

- D3a. What is the optimal target for lipid dosage in preterm and term babies who are receiving parenteral nutrition and neonatal care?
- D3b. What is the optimal way (starting dose and approach to increment, if employed) to achieve that?

Introduction

Intravenous lipid emulsion in parenteral nutrition (PN) is a source of energy and prevents essential fatty acid deficiencies. Preterm babies are known to be vulnerable to fat deficiency due to limited stores. Lipid is required as a source of calories for growth, but also provides essential fatty acids which are necessary for brain development. The provision of fats in parenteral nutrition has also been demonstrated to reduce overall energy consumption.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	• Babies born preterm, up to 28 days after their due birth date (preterm babies) • Babies born at term, up to 28 days after their birth (term babies).
Intervention	Optimal target dose • Any amount of IV lipid (g/kg/day) Optimal way to achieve this • Starting dose • Rate of Increase in lipids
Comparison	Optimal target dose • None • Each other Optimal way to achieve this • Different starting doses • Different increases • Different regimens
Outcomes	**Critical** • Neurodevelopmental outcomes (general cognitive abilities at two years corrected age as measured by a validated scale) • Adverse effects of lipids: ○ Infection including sepsis ○ PN related liver disease (abnormal liver function, cholestasis, conjugated Hyperbilirubinaemia) **Important** • Mortality • Growth/Anthropometric measures: ○ Weight gain (g/kg/d)

	○ Linear growth ○ Head circumference (mm) • Adverse effects of lipids: ○ Hypertriglyceridemia • Duration of hospital stay • Nutritional intake (g/kg/day) (defined as proportion of prescribed lipids actually received)

IV: intravenous; PN: parenteral nutrition.

For further details see the review protocol in appendix A.

Clinical evidence

Included studies

Sixteen studies were included in this review, 1 of these studies was reported in 2 articles (Levit 2016, Ong 2016); therefore, 17 articles are included in total (Alwaidh 1996, Brans 1987, Brownlee 1993, Calkins 2017, Drenckpohl 2008, Gilbertson 1991, Gunn, 1978, Hammerman 1988, Kao 1984, Levit 2016, Murdock 1995, Ong 2016, Roelants 2018, Shouman 2012, Sosenko 1993, Wilson 1997, Vlaardingerbroek 2013).

Optimal target dose

Six randomised controlled trials (RCTs) addressed the optimal target dose (review question D3a). Three of these compared the effects of PN which included lipids versus PN without lipids (Gunn 1978, Hammerman 1988, Murdock 1995) and 3 compared different high versus low lipid dose administration (Calkins 2017, Levit 2016, Shouman 2012). The Ong 2016 study provided 2 year follow-up data of the Levit 2016 study, on the cognitive, language and motor skills of the 2 year old children.

How to achieve target dose

Ten RCTs addressed the optimal way to achieve the target dose (review question D3b). Seven of these compared early versus late commencement of intravenous lipids (Alwaidh 1996, Brownlee 1993, Gilbertson 1991, Roelants 2018, Sosenko 1993, Wilson 1997, Vlaardingerbroek 2013) and 3 compared different rates of infusion; 2 studies compared a moderate increase versus a constant rate (Brans 1987, Kao 1984) and 1 compared a short and fast delivery versus a slower increase to peak dose (Drenckpohl 2008).

The included studies are summarised in Table 2.

See the literature search strategy in appendix B, study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E, and GRADE tables in appendix F.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusions are provided, in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Comments
Alwaidh 1996 RCT UK	N=64 Preterm babies <u>Median GA (range)</u> Early: 28 weeks (23 to 31) Late: 28 weeks (23 to 31) <u>Median birth weight (range)</u> Early: 997g (536 to 1353) Late: 1006g (542 to 1486)	<u>Early delivery</u> (n=32) Lipids were started on day 5. Lipids (20% emulsion) were started at 0.5g/kg/day and increased to 3.0g/kg/day over 5 days.	<u>Late delivery</u> (n=32) Lipids were started on day 14. Lipids (20% emulsion) were started at 0.5g/kg/day and increased to 3.0g/kg/day over 5 days.	• Days to regain birth weight • Mortality before discharge	Some babies in the late lipid group received no IV lipid because PN had already been discontinued. Babies started milk feeds at a median of 7 days.
Brans 1987 RCT US	N=38 Low birth weight babies <u>Mean GA (SD; range)</u> Higher infusion rate: 29 weeks (1.3; 29 to 31) Lower infusion rate delivered over 24 hours: 29 weeks (1.7; 27 to 34) Lower infusion rate delivered over 16 hours: 29 weeks (1.3; 27 to 31) <u>Birthweight (SD; range)</u> Higher infusion rate: 1160g (226; 820 to 1500) Lower infusion rate delivered over 24 hours: 1190g (196; 820 to 1480) Lower infusion rate delivered over 16 hours:	<u>Higher infusion rate</u> (n=11) Lipid emulsion was given at a constant rate of 4g/kg/day over 24 hours.	<u>Lower infusion rate delivered over 24 hours</u> (n=14) Lipid emulsion was given at a constant rate of 1g/k/g/day over 24 hours and increased by 1g/kg/day to 4g/kg/day. <u>Lower infusion rate delivered over 16 hours</u> (n=13) Lipid emulsion rate was given at a constant rate of 1g/kg/day over 16 hours followed by no lipids for 8 hours. This was increased by 1g/kg/day to 4g/kg/day.	• Mortality to day 8	All babies received phototherapy from birth. TPN was started on the third postnatal day (unless otherwise indicated). No enteral feedings were provided during the study.

Study	Population	Intervention	Comparison	Outcomes	Comments
	1160g (218; 820 to 1500)				
Brownlee 1993 RCT UK	N=129 Preterm babies, 24-36 weeks gestational age Median GA (range) Early: 29 weeks (23 to 33) Late; 29 weeks (24 to 36) Median birth weight (range) Early: 1144g (539 to 1748) Late: 1147g (415 to 1647)	Early delivery (n=63) Lipids were started within the first 36 hours. Lipids were started at 0.5g/kg/day and increased by 0.5g/kg/day to 3.5g/kg/day.	Late delivery (n=66) Lipids were started on day 6. Lipids were started at 0.5g/kg/day and increased by 0.5g/kg/day to 3.5g/kg/day.	• Mean weight gain/day to discharge • Mortality (before discharge)	In January 1991, surfactant was used regularly. Thirteen babies (10%) were started on enteral feeds within the first 7 days, but were included in the analysis only while receiving full PN.
Calkins 2017 RCT US	N=41 (n=36 analysed) Babies with gastrointestinal disorders. Mean GA (SD) High dose: 36 weeks (2) Low dose: 37 weeks (1) Mean birth weight (SD) High dose: 2.5kg (0.6) Low dose: 2.5kg (0.4)	High dose (n=16) Soybean-based lipid emulsion (20%) was started on day 2 and increased by 0.5-1g/kg/day to ~3g/kg/day.	Low dose (n=20) Soybean-based lipid emulsion (20%) was started on day 2 and increased by 0.5-1g/kg/day ~1g/kg/day.	• Discharge weight • Weight velocity first 28 days • Discharge length cm • Discharge head circumference cm • Sepsis • Cholestasis • Direct bilirubin >1 mg/dL • Length of hospital stay • Necrotising enterocolitis	Enteral feeds were initiated and advanced per routine care. Babies who required an abdominal operation (excluding gastrostomy tubes and rectal biopsies) and received PN for >14 days were included in the final analysis.
Drenckpohl 2008 RCT US	N=110 (n=100 analysed) VLBW babies on NICU; birth weight 750g to 1500g; gestational age 26 to 32 weeks; growth	Higher infusion rate (n=48) Lipids (20% emulsion) were started at 2g/kg/day on the first day of TPN	Lower infusion rate (n=52) Lipids (20% emulsion) were started at 0.5g/kg/day on the first day of TPN and increased	• Time to regain birth weight, days • Weight at discharge • Babies ≥10th percentile for weight • Length at discharge	All TNA solutions, delivered either centrally or peripherally, included 1 U/mL heparin. All babies received

Study	Population	Intervention	Comparison	Outcomes	Comments
	appropriate for gestational age Mean GA (SD) Higher infusion rate: 28.81 weeks (1.72) Lower infusion rate: 28.58 weeks (1.79) Mean birth weight (SD) Higher infusion rate: 1182g (198) Lower infusion rate: 1134g (223)	and increased by 0.5g/kg/day to 3g/kg/day (3 days to reach target dose).	by 0.5g/kg/day to 3g/kg/day (6 days to reach target dose).	• Head circumference • Mortality • Hospital stay • Hypertriglyceridemia • Retinopathy of prematurity • Necrotising enterocolitis	perinatal steroid treatment.
Gilbertson 1991 RCT UK	N=29 Premature babies on NICU, ventilator dependent Mean GA (SD) Early: 28.6 weeks (2.12) Late: 28.8 weeks (2.09) Mean birth weight (SD) Early: 1.15kg (0.24) Late: 1.09kg (0.32)	Early delivery (n=16) Lipids were started on day 1. Lipids (20% emulsion) were started at 1g/kg/day and increased to 3g/kg/day on day 4.	Late delivery (n=13) Lipids were started on day 8. Lipid regimen not reported.	• Days to regain birth weight • Growth in length cm/week • Rate of head circumference growth • Sepsis • Jaundice • Mortality during first 2 weeks • Mortality at day 12 • Hypertriglyceridemia • Hypoglycaemia • Necrotising enterocolitis • ROP	Heparin (1 unit/ml) added to TPN for all babies
Gunn 1978 Randomised trial Canada	N=40 Premature babies with severe respiratory distress	Lipids (n=20) Soybean-based lipid emulsion was started on day 2 at 2g/kg/day and increased to 4g/kg/day.	No lipids (n=20) Babies were given PN consisting of glucose and electrolyte	• Days to regain birth weight • Mortality	All babies received dextrose in water intravenously at a rate of 65 ml/kg for the first 24 hours, prior to randomisation

Study	Population	Intervention	Comparison	Outcomes	Comments
	Mean GA (SD) Lipids: 32.2 weeks (3.2) No lipids: 32.3 weeks (3.5) Mean birth weight (SD) Lipids: 1700g (554) No lipids: 1868g (781)		solution without lipids.		to treatment groups. Heparin was not used. Phytonadione (1 mg) was administered intramuscularly once weekly.
Hammerman 1988 RCT USA	N=42 Preterm babies; birth weight <1750 g Mean GA (SD) Lipids: 30.0 weeks (3.0) No lipids: 29.0 weeks (2.0) Mean birth weight (SD) Lipids: 1166g (431) No lipids: 1086g (384)	Lipids (n=20) Soybean-based lipids emulsion was started at 0.5g/kg/day and increased by 0.5g/kg/day to 2.5g/kg/day for 5 days.	No lipids (n=22) Babies were given PN at similar rates to the intervention arm but without lipids.	• Days to regain birth weight • Mortality • Necrotising enterocolitis • Retinopathy of prematurity	None of the babies received enteral feedings for the duration of the study.
Kao 1984 RCT US	N=43 Preterm babies Mean GA (SD) Continuous infusion rate: 31.0 weeks (0.9) Intermittent infusion rate: 31.3 weeks (0.8) Mean birth weight (SD) Continuous infusion rate: 1.5kg (0.2kg)	Continuous infusion rate (n=19) Lipids were delivered 24hrs/day. Lipids (10% emulsion) were started at 0.5g/kg/day and increased by 0.5g/kg/day to 3g/kg/day (or until fat contributed 40% of daily calories).	Intermittent infusion rate (n=24) Lipids were delivered 8hrs/day. Lipids (10% emulsion) were started at 0.5g/kg/day and increased by 0.5g/kg/day to 3g/kg/day (or until fat contributed 40% of daily calories).	• Sepsis • Mortality	Lipid solution was infused via either a peripheral vein or an umbilical catheter. No enteral feedings were given during the study.

Study	Population	Intervention	Comparison	Outcomes	Comments
	Intermittent infusion rate: 1.6kg (0.1kg)				
Levit 2016 RCT US	N=136 (n=127 analysed) Preterm babies with a GA of ≤29 weeks and <48 hours of life <u>Mean GA (SD)</u> High dose: 26.0 weeks (2.0) Low dose: 27.0 weeks (2.0) <u>Mean birth weight (SD)</u> High dose: 2930g (286) Low dose: 904g (279)	<u>High dose</u> (n=62) Lipids were advanced by 0.5-1g/kg/day to a target dose of 3g/kg/day.	<u>Low dose</u> (n=65) Lipids were given at a maximum dose of 1g/kg/d	• Growth Weight g/week at 28 days of life and at discharge • Growth length cm/week at 28 days of life and at discharge • Growth, head circumference, cm/week at 28 days of life and at discharge • Sepsis • Cholestasis • Mortality • Duration of hospital stay (by treatment group and type of lipid) • Necrotising enterocolitis • Retinopathy of prematurity	For babies in the high dose group, S-IFE dose could be reduced to approximately 1.5g/kg/day if receiving >75% of calories from enteral nutrition (EN). Full enteral feeds were defined as PN discontinuation.
Murdock 1994 RCT Scotland	N=29 Birthweight <2000g; could not receive enteral feeding <u>Mean GA (SD)</u> Lipids: 31.8 weeks (1.7) No lipids; glucose and amino acids: 32.8 weeks (2.8) No lipids; glucose only:	<u>Lipids</u> (n=8) Lipids were given at 1g/kg/day. Glucose was given at 7g/kg/day on day 1 and increased to 10g/kg/day. Amino acids were given at 1g/kg/day and increased to 1.4g/kg/day.	<u>No lipids; glucose and amino acids</u> (n=11) No lipids were given. Glucose was given at 7g/kg/day on day 1 and increased to 10g/kg/day. Amino acids were given at 1g/kg/day and increased to 1.4g/kg/day.	• Hypoglycaemia requiring an increase in glucose	Fluid intakes were altered by the Clinicians if clinically indicated. Babies fed more than 1 ml/hour of expressed breast mild or formula were withdrawn from the study. Phototherapy was administered to babies,

Study	Population	Intervention	Comparison	Outcomes	Comments
	31.0 weeks (2.3) Mean birth weight (SD) Lipids: 1635g (306g) No lipids; glucose and amino acids: 1498g (307g) No lipids; glucose only: 1340g (322g)		No lipids; glucose only (n=10) No lipids or amino acids were give. Glucose was given at 7g/kg/day on day 1 and increased to 10g/kg/day.		where required.
Ong 2016 Prospective follow-up to Levit (2016) US	N=37 (n=30 analysed) Preterm babies with a GA of ≤29 weeks and <48 hours of life Mean GA (SD) High dose: 27 weeks (1) Low dose: 28 weeks (1) Mean birth weight (SD) High dose: 1023g (306) Low dose: 1033g (279)	High dose (n=15) See Levit (2016)	Low dose (n=15) See Levit (2016)	• 2 year follow up on neurodevelopmental outcomes	All babies were receiving full feeds prior to discharge from the NICU.
Roelants 2018 RCT The Netherlands	N=134 Babies with birth weight <1500 g Median GA (IQR) Early; soy: 26^{+2} (25^{+2} to 28^{+1}) Early; mixed: 27^{+1} (25^{+6} to 28^{+6}) Late: 27^{+3} (26^{+2} to 29^{+3})	Early delivery (n=45) Lipids started immediately after birth. Lipids started at 2g/kg/day and increased to 3g/kg/day the next day. Glucose and AA given at 2.4g/kg/day.	Late delivery (n=44) Lipids started on day 2. Lipids started at 1.4g/kg/day and increased to 2.8g/kg/day the next day. Glucose and AA given at 2.4g/kg/day.	• 2 year follow-up on neurodevelopmental outcomes	Immediately after birth, all babies received 6 mg/kg/min glucose and 2.4 g/kg/day) AA as standard care. Enteral feed included minimal enteral feeding at day 1 and a daily increase of approximately

Study	Population	Intervention	Comparison	Outcomes	Comments
	Median birth weight (IQR) Early; soy: 808g (665 to 920) Early; mixed: 846g (726 to 1000) Late: 863g (651 to 1013)				20 mL/kg/day of enteral bolus feeding from day 2 or 3 onwards until 150 to 180 mL/kg/day reached. Early delivery: 24 babies received soy-based lipid emulsions and 25 babies received mixed lipid emulsions.
Shouman 2012 RCT Egypt	N=42 Preterm babies, with blood stream infections Mean GA (SD) High dose: 32.3 weeks (2.15) Low dose: 31.7 weeks (2.6) Mean birth weight (SD) High dose: 1424g (330g) Low dose: 1469g (517g)	High dose (n=22) Lipids started at 0.5g/kg^{-1}/day^{-1} on the first day of TPN and increased by 1g/kg^{-1}/day^{-1} to 3.5 g/kg^{-1}/day^{-1}.	Low dose (n=20) Lipids given at 1g/kg^{-1}/day^{-1} until a negative blood culture was obtained. Then the dose of lipids was modified according to the amount of enteral feed received.	• Daily weight increments (median) • Mortality • Duration of hospitalisation	Antibiotics were started and continued until clinical signs of sepsis subsided, a negative blood culture was obtained and C-reactive protein was normalised (<4.82 mg/l).
Sosenko 1993 RCT US	N=133 Premature babies; birth weight 600-800 and 801-1000g; ventilator dependent Mean birth weight 600 to 800 g weight babies Early; 600g to 800: 709 g	Early delivery (total n=70; 600g to 800g n=42; 801g to 1000g n=28) Lipids started <12 hours postnatally. Soybean-based lipid emulsion (20%) was started at 0.5 g/kg and increased by	Late delivery (total n=63; 600g to 800g n=37; 801g to 1000g n=26) Lipids started on day 7. Soybean-based lipid emulsion (20%) was started at 0.5 g/kg and increased by	• Sepsis • Death before discharge • Necrotising enterocolitis • Retinopathy of prematurity	All babies received vitamin E, 3 units/kg/day, in IV administered multivitamins, consisting of MVI-12 R (Armour), 3 ml/kg/day added to the maintenance fluids, and approximately 990 units of vitamin A.

Study	Population	Intervention	Comparison	Outcomes	Comments
	Early; 801 to 1000g: 915g Late; 600g to 800g: 708 g Late; 801 to 1000g: 888 g	0.5g/kg/day to 1.5g/kg/day.	0.5g/kg/day to 1.5g/kg/day.		Initiation of amino acids was started at days 2 or 3 in both treatment groups. Neither group received enteral feeding until after day 7.
Vlaardingerbroek 2013 RCT The Netherlands	N=144 Very low birth weight babies Mean GA (SD) Early; low AA and glucose: 27.2 weeks (2.2) Early; high AA and glucose: 27.2 weeks (2.1) Late: 27.8 weeks (2.3) Mean birth weight (SD) Early; low AA and glucose: 876g (209g) Early; high AA and glucose: 867g (223g) Late: 843g (224g)	Early delivery; low AA and glucose (n=49) Lipids started immediately after birth. Lipids started at $2g/kg^{-1}/day^{-1}$ and increased to $3g/kg^{-1}/day^{-1}$ the next day. Glucose and AA given at $2.4g/kg^{-1}/day^{-1}$. Early delivery; high AA and glucose (n=47) Lipids started immediately after birth. Lipids started at $2g/kg^{-1}/day^{-1}$ and increased to $3g/kg^{-1}/day^{-1}$ the next day Glucose and AA given at $3.6g/kg^{-1}/day^{-1}$.	Late delivery (n=48) Lipids started on day 2. Lipids started at $1.4g/kg^{-1}/day^{-1}$ and increased to $2.8g/kg^{-1}/day^{-1}$ the next day. Glucose and AA given at $2.4g/kg^{-1}/day^{-1}$.	• Median weight gain $g/kg^{-1}/day^{-1}$ at discharge • Head circumference, at discharge • Late onset sepsis; • Mortality • Duration of hospital stay (days) • Necrotising enterocolitis (≥grade 2) • Retinopathy of prematurity	All babies received glucose (at least 4.0 mg/kg-1/min-1) and 2.4 g/kg-1/day-1 of AA as part of standard clinical care. All babies received minimal enteral nutrition (EN) on the day of birth, which was advanced to full EN, according to the local protocol. After the third day of life, the nutritional regimen, including EN, was at the discretion of the physician.
Wilson 1997 RCT	N=125	Early delivery (n=64)	Late delivery (n=61)	• Median days to regain birth weight	Parenteral vitamins, trace elements, and minerals

Study	Population	Intervention	Comparison	Outcomes	Comments
Northern Ireland	Sick VLBW babies Mean GA (SD) Early: 27.0 weeks (2.4) Late: 27.4 weeks (2.3) Mean birth weight (SD) Early: 925g (221) Late: 933g (242)	Lipids were started on day 2. Lipids (10% emulsion) were started at 0.5g/kg/day and increased to 2g/kg/day. After reaching 2g/kg/day, lipids were changed to a 20% emulsion and increased to 3.5g/kg/day. AA started at 0.5 g/kg/day at 12 h and increased to 2.5-3.5g/kg/day dependent on energy intake. Fluids and carbohydrates administered at increasing dose.	Lipids were started on day 5. Lipids (10% emulsion) were started at 0.5g/kg/day and increased to 2g/kg/day. AA started at day 3 at 1g/kg/day and increased to 2.5g/kg/day. Fluids and carbohydrates administered at increasing dose.	• Mean final weight (at discharge/death) • Mean final length (at discharge/death) • Mean final head circumference (at discharge/death) • Sepsis • Cholestasis • Death before discharge • Hospital stay (days) • Hypertriglyceridemia	similar for both treatment groups. EN administered to all babies.

AA: amino acids; BSID-III: Bayley Scales of Infant and Toddler Development, Third Edition; EN: enteral nutrition; GA: gestational age; IQR: interquartile range; IV: intravenous; IVFE: intravenous fat emulsion; IQR: interquartile range; LCT: long chain triglycerides; MCT: medium chain triglycerides; MIX (mixed fat emulsions); NICU: Neonatal intensive care unit; NR: not reported; PN: parenteral nutrition; RCT: randomised controlled trial; RoP: retinopathy of prematurity; SD: standard deviation; SEM: standard error of the mean; S-IFE: soybean-based intravenous fat emulsions; SOY (soybean); TNA: total nutrient admixtures; TPN: total parenteral nutrition; VLBW: very low birth weight.

See appendix D for full evidence tables.

Quality assessment of clinical outcomes included in the evidence review

GRADE was conducted to assess the quality of outcomes. Evidence was identified for critical and important outcomes. The clinical evidence profiles can be found in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to these review questions. A single economic search was undertaken for all topics included in the scope of this guideline. Please see supplementary material D for details.

Excluded studies

No studies were identified which were applicable to these review questions.

Summary of studies included in the economic evidence review

No economic evaluations were identified which were applicable to these review questions.

Economic model

No economic modelling was undertaken for these reviews because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Clinical evidence statements

Lipids versus no lipids

Days to regain birth weight

- Very low quality evidence from 2 RCTs (n=73) showed no clinically important difference in days to regain birth weight between babies receiving lipids versus no lipids. However, there was high uncertainty around the effect: Mean difference (MD) 0.78 (95% CI -2.27, 3.83).

Mortality

- Very low quality evidence from 2 RCTs (n=82) showed a clinically important difference in mortality rates before discharge between babies receiving lipids versus no lipids. Those babies receiving no lipids had higher rates of mortality as compared to those receiving lipids. However, there was high uncertainty around the effect: Relative risk (RR) 0.64 (95% CI 0.23, 1.78).

Hypoglycaemia requiring glucose

- Very low quality evidence from 1 RCT comparing 3 treatment groups (n=144) showed a clinically important difference in the incidence of hypoglycaemia, with more babies with hypoglycaemia who received no lipids as compared to lipids (i.e. Glucose 10%). However, there was high uncertainty around the effect: RR 0.42 (95% CI 0.11, 1.53; n=18). The same RCT showed a clinically important difference in the incidence of hypoglycaemia, with more babies with hypoglycaemia who received no lipids compared as compared to lipids (i.e. Glucose 10%/Amino acid). However, there was uncertainty around the effect: RR 0.31 (95% CI 0.09, 1.05; n=19).

Necrotising enterocolitis

- Very low quality evidence from 1 RCT (n=42) showed a clinically important difference in the incidence of necrotising enterocolitis, with more babies with necrotising enterocolitis who received lipids as compared to no lipids. However, there was uncertainty around the effect: Peto Odds ratio (POR) 8.61 (95% CI 0.52, 142.87).

Retinopathy of prematurity (ROP)

- Very low quality evidence from 1 RCT (n=28) showed a clinically important difference in the incidence of ROP, with more babies with ROP who received lipids as compared to no lipids. However, there was uncertainty around the effect: RR 3.09 (95% CI 1.22, 7.84).

High versus low dose of lipids

Cognitive skills, number with a SD <1 of norm. 2 year follow up

- Very low quality evidence from 1 RCT (n=30) showed a clinically important difference in the number of babies with cognitive skills <1 SD of the norm at 2 years follow up, with more babies with cognitive skills <1 SD of the norm who received low dose lipids as compared to high dose lipids. However, there was high uncertainty around the effect: RR 0.67 (95% CI 0.13, 3.44).

Language skills, number with a SD <1 of norm. 2 year follow up

- Very low quality evidence from 1 RCT (n=30) showed a clinically important difference in the number of babies with language skills <1 SD of the norm at 2 years follow up, with more babies with language skills <1 SD of the norm who received high dose lipids as compared to low dose lipids. However, there was high uncertainty around the effect: RR 2.00 (95% CI 0.43, 9.32).

Motor skills, number with a SD <1 of norm. 2 year follow up

- Very low quality evidence from 1 RCT (n=30) showed a clinically important difference in the number of babies with motor skills <1 SD of the norm at 2 years follow up, with more babies with motor skills <1 SD of the norm who received low dose lipids as compared to high dose lipids. However, there was high uncertainty around the effect: RR 0.50 (95% CI 0.05, 4.94).

Weight growth in first 28 days (g/day)

- Very low quality evidence from 1 RCT (n=36) showed a clinically important difference in mean weight gain per day in the first 28 days, with greater weight gain in babies that received high dose lipids as compared to low dose lipids. However, there was uncertainty around the effect: MD 6.00 (95% CI -2.59, 14.59).

Weight growth in first 28 days (g/week)

- Low quality evidence from 1 RCT (n=128) showed no clinically important difference in mean weight gain per week in the first 28 days between babies receiving a high dose versus a low dose of lipids: MD 3.00 (95% CI -9.65, 15.65).

Discharge weight (g)

- Very low quality evidence from 1 RCT (n=36) showed no clinically important difference in discharge weight between babies receiving a high dose versus a low dose of lipids. However, there was uncertainty around the effect: MD 0.10 (95% CI -0.42, 0.62).

Discharge weight (g/week)

- Low quality evidence from 1 RCT (n=123) showed no clinically important difference in discharge weight between babies receiving a high dose versus a low dose of lipids: MD 0.00 (95% CI -10.26, 10.26).

Length gain in first 28 days (cm/week)

- Very low quality evidence from 1 RCT (n=122) showed no clinically important difference in length gain in the first 28 days between babies receiving a high dose versus a low dose of lipids. However, there was uncertainty around the effect: MD -0.10 (95% CI -0.28, 0.08).

Discharge length (cm)

- Very low quality evidence from 1 RCT (n=36) showed no clinically important difference in discharge length between babies receiving a high dose versus a low dose of lipids. However, there was uncertainty around the effect: MD -1.00 (95% CI -3.63, 1.63).

Discharge length (cm/week)

- Very low quality evidence from 1 RCT (n=124) showed no clinically important difference in discharge length between babies receiving a high dose versus a low dose of lipids. However, there was uncertainty around the effect: MD -0.20 (95% CI -0.39, -0.01).

Head circumference gain, cm/week

- Very low quality evidence from 1 RCT (n=122) showed no clinically important difference in head circumference between babies receiving a high dose versus a low dose of lipids. However, there was uncertainty around the effect: MD -0.10 (95% CI -0.21, 0.01).

Discharge head circumference (cm)

- Very low quality evidence from 1 RCT (n=36) showed a clinically important difference in discharge head circumference, with larger head circumference in babies who received high dose lipids as compared to low dose lipids. However, there was high uncertainty around the effect: MD 1.00 (95% CI -1.15, 3.15).

Head circumference gain to discharge (cm/week)

- Very low quality evidence from 1 RCT (n=122) showed a clinically important difference in discharge head circumference, with greater head circumference gain in babies who received low dose lipids as compared to high dose lipids. However, there was uncertainty around the effect: MD -0.10 (95% CI -0.21, 0.01).

Sepsis

- Very low quality evidence from 2 RCT (n=172) showed no clinically important difference in on the incidence of sepsis between babies receiving a high dose versus a low dose of lipids. However, there was high uncertainty around the effect: RR 0.84 (95% CI0.31, 2.27).

Cholestasis

- Very low quality evidence from 2 RCT (n=168) showed no clinically important difference in on the incidence of cholestasis between babies receiving a high versus a low dose of lipids. However, there was high uncertainty around the effect: RR 0.98 (95% CI 0.76, 1.27).

Direct bilirubin (>1 mg/dL)

- Very low quality evidence from 1 RCT (n=36) showed no clinically important difference in direct bilirubin (>1 mg/dL) between babies receiving a high dose versus a low dose of lipids. However, there was high uncertainty around the effect: RR 1.12 (95% CI 0.61, 2.08).

Mortality

- Very low quality evidence from 2 RCT (n=178) showed no clinically important difference in mortality rates between babies receiving a high dose versus a low dose of lipids. However, there was high uncertainty around the effect: RR 1.13 (95% CI0.43, 2.98).

Length of hospital stay

- Very low quality evidence from 3 RCT (n=214) showed no clinically important difference in length of hospital stay between babies receiving a high versus a low dose of lipids: MD -0.74 (95% CI -9.95, 8.47).

Necrotising enterocolitis

- Very low quality evidence from 1 RCT (n=135) showed a clinically important difference in the incidence of necrotising enterocolitis, with more babies with necrotising enterocolitis who received low dose lipids as compared to high dose lipids. However, there was high uncertainty around the effect: RR 0.75 (95% CI 0.32, 1.75).

Retinopathy of prematurity (ROP)

- Very low quality evidence from 1 RCT (n=135) showed a clinically important difference in the incidence of ROP, with more babies with ROP who received low dose lipids as compared to high dose lipids However, there was high uncertainty around the effect: RR 0.80 (95% CI0.32, 2.03).

Early versus late delivery of lipids on premature babies with low birth weight

Neurodevelopmental outcomes

- Very low quality evidence from 1 RCT (n=89) showed a clinically important difference in BSID-III motor score <70 between premature babies receiving early delivery of lipids versus late delivery of lipids. Those babies receiving late delivery of lipids were more likely to have a score of less than 70, indicating worse outcome. However, there was high uncertainty around the effect: RR 0.49 (95% CI 0.05, 5.20).
- Very low quality evidence from 1 RCT (n=89) showed a clinically important difference in BSID-III psychomotor score <70 between premature babies receiving early delivery of lipids versus late delivery of lipids. Those babies receiving late delivery of lipids were more likely to have a score less than 70, indicating worse outcome. However, there was high uncertainty around the effect: RR 0.49 (95% CI 0.05, 5.20).

Mean weight gain per day to discharge

- Very low quality evidence from 1 RCT (n=129) showed no clinically important difference in mean weight gain per day to discharge between premature babies receiving early delivery of lipids versus late delivery of lipids. However, there was uncertainty around the effect: MD -2.40 (95% CI -5.30, 0.50).
- Moderate quality evidence from 1 RCT comparing 3 treatment groups (n=144) showed no clinically important difference in mean weight gain per day to discharge between premature babies receiving early delivery of lipids versus late delivery of lipids; n=97 (MD -0.80 [95% CI -3.51, 1.91]).
- Low quality evidence from the same RCT (n=144) showed no clinically important difference in mean weight gain per day to discharge between premature babies receiving early delivery of lipids plus high amino acids versus late delivery of lipids. However, there was uncertainty around the effect: n=95 (MD 1.20 [95% CI -1.90, 4.30]).

Days to regain birth weight

- Low quality evidence from 1 RCT (n=29) showed no clinically important difference in days to regain birth weight between premature babies receiving early delivery of lipids versus late delivery of lipids. However, there was uncertainty around the effect: MD -1.30 (95% CI -5.88, 3.28).

Mean final weight

- Low quality evidence from 1 RCT (n=125) showed no clinically important difference in mean final weight between premature babies receiving early delivery of lipids versus late delivery of lipids: MD 31.00 (95% CI -269.45, 331.45).

Growth in length (cm/week)

- Low quality evidence from 1 RCT (n=29) showed no clinically important difference in length between premature babies receiving early delivery of lipids versus late delivery of lipids. However, there was uncertainty around the effect: MD 0.10 (95% CI -0.18, 0.38).

Mean final length (cm)

- Low quality evidence from 1 RCT (n=125) showed no clinically important difference in mean final length between premature babies receiving early delivery of lipids versus late delivery of lipids: MD 0.20 (95% CI -1.94, 2.34).

Head circumference growth (cm/week)

- Very low quality evidence from 1 RCT (n=29) showed no clinically important difference in weekly head circumference growth between premature babies receiving early delivery of lipids versus late delivery of lipids. However, there was high uncertainty around the effect: MD 0.00 (95% CI -0.28, 0.28).
- Low quality evidence from 1 RCT comparing 3 treatment groups (n=144) showed no clinically important difference in weekly head circumference growth at discharge between premature babies receiving early delivery of lipids (plus glucose and amino acids) versus late delivery of lipids. However, there was uncertainty around the effect; n=97 (MD -0.02 [95% CI -0.08, 0.04]).
- Moderate quality evidence from the same RCT (n=144) showed no clinically important difference in weekly head circumference growth at discharge between premature babies receiving early delivery of lipids (plus glucose and high dose amino acids) versus late delivery of lipids; n=95 (MD 0.01 [95% CI -0.04, 0.06]).

Mean final head circumference (cm)

- Low quality evidence from 1 RCT (n=125) showed no clinically important difference in mean final head circumference between premature babies receiving early delivery of lipids versus late delivery of lipids: MD -0.10 (95% CI -1.77, 1.57).

Sepsis

- Very low quality evidence from 2 RCTs (n=154) showed a clinically important difference in the incidence of sepsis; those babies receiving late delivery of lipids had higher rates of sepsis as compared to those receiving early lipids. However, there was uncertainty around the effect: RR 0.71 (95% CI 0.53, 0.96).
- Low quality evidence from 1 RCT comparing 3 treatment groups (n=144) showed a clinically important difference in the incidence of sepsis, with higher rates of sepsis in those babies who received early lipid delivery (plus glucose and amino acids) as compared to late delivery. However there was uncertainty around the effect: RR 1.96 (95% CI 0.93, 4.15; n=97).
- Low quality evidence from 1 RCT comparing 3 treatment groups (n=144) showed a clinically important difference in the incidence of sepsis, with higher rates of sepsis in those babies who received early delivery of lipids (plus glucose and high dose amino acids) as compared to late delivery. However there was uncertainty around the effect: RR 2.17 (95% CI 1.04, 4.54; n=95).

Cholestasis

- Very low quality evidence from 1 RCT (n=125) showed a clinically important difference in rates of cholestasis between premature babies receiving early delivery of lipids versus late delivery of lipids. Those babies receiving early lipid delivery had higher rates of cholestasis as compared to those receiving late delivery. However, there was high uncertainty around the effect: RR 1.43 (95% CI 0.25, 8.26).

Jaundice

- Very low quality evidence from 1 RCT (n=29) showed no clinically important difference in rates of jaundice between premature babies receiving early delivery of lipids versus late delivery of lipids. However, there was high uncertainty around the effect: RR 1.14 (95% CI 0.47, 2.75).

Mortality during the first 28 days

- Very low quality evidence from 2 RCTs (n=162) showed no clinically important difference in mortality during the first 28 days between premature babies receiving early delivery of lipids versus late delivery of lipids. However, there was high uncertainty around the effect: RR 1.03 (95% CI 0.32, 3.30).

Mortality before discharge

- Very low quality evidence from 5 RCTs (n=481) showed no clinically important difference in mortality before discharge between preterm babies receiving early versus late delivery of lipids. However, there was high uncertainty around the effect: RR 0.81 (95% CI 0.53, 1.26).
- Very low quality evidence from 1 RCT comparing 3 treatment groups (n=144) showed a clinically important difference in mortality before discharge between preterm babies receiving early (plus glucose and amino acids)versus late delivery of lipids. Those babies receiving early lipid delivery had higher rates of mortality as compared to those receiving late delivery. However, there was high uncertainty around the effect: RR 1.37 (95% CI 0.47, 4.02; n=97).
- Very low quality evidence from 1 RCT comparing 3 treatment groups (n=144) showed a clinically important difference in mortality before discharge between preterm babies receiving early (plus gludocse and high dose amino acids) versus late delivery of lipids. Those babies receiving early lipid delivery had higher rates of mortality as compared to those receiving late delivery. However, there was high uncertainty around the effect: RR 2.04 (95% CI 0.75, 5.53).

Hospital stay

- Low quality evidence from 1 RCT (n=125) showed no clinically important difference in duration of hospital stay between preterm babies receiving early versus late delivery of lipids: MD 1.00 (95% CI -3.97, 5.97).
- Moderate quality evidence from 1 RCT comparing 3 treatment groups showed no clinically significant difference in duration of hospital stay between preterm babies receiving early (plus glucose and amino acids or high dose amino acids) versus late delivery of lipids: MD 3.30 (95% CI -10.99, 17.59; n=97) and MD -4.50 (95% CI -18.52, 9.52; n=95), respectively.

Hypertriglyceridemia

- Very low quality evidence from 2 RCTs (n=154) showed no clinically important difference on the incidence of hypertriglyceridemia between premature babies receiving early delivery of lipids versus late delivery of lipids. However, there was high uncertainty around the effect: RR 1.24 (95% CI 0.75, 2.04).

Hypoglycaemia

- Very low quality evidence from 1 RCT (n=29) showed no clinically important difference in rates of hypoglycaemia between premature babies receiving early delivery of lipids versus late delivery of lipids. However, there was high uncertainty around the effect: RR 1.14 (95% CI 0.47, 2.75).

Necrotising enterocolitis

- Very low quality evidence from 2 RCTs (n=162) showed a clinically important difference in rates of necrotising enterocolitis between premature babies receiving early delivery of lipids versus late delivery of lipids. Those babies receiving late lipid delivery had higher rates of necrotising enterocolitis as compared to those receiving early delivery. However, there was high uncertainty around the effect: RR 0.59 (95% CI 0.22, 1.58).
- Very low quality evidence from 1 RCT comparing 3 treatment groups showed clinically important differences in rates of necrotising enterocolitis between premature babies receiving early delivery of lipids (plus glucose and amino acids: n=97; or high dose amino acids: n=95) versus late delivery of lipids. However, there was high uncertainty around the effects: RR 0.49 [95% CI 0.05, 5.23; n=97] (higher rates with late lipid delivery) and RR 2.04 [95% CI 0.39, 10.63; n=95] (higher rates with early lipid delivery), respectively.

Retinopathy of prematurity (ROP)

- Very low quality evidence from 1 RCT (n=29) showed a clinically important difference in the rates of ROP between premature babies receiving early delivery of lipids versus late delivery of lipids. Those babies receiving late lipid delivery had higher rates of ROP as compared to those receiving early delivery. However, there was uncertainty around the effect: POR 0.11 (95% CI 0.00, 5.53).

Higher or continuous infusion rate versus lower or intermittent infusion rate

Time to regain birth weight (days)

- Moderate quality evidence from 1 RCT (n=100) showed no clinically important difference in time to regain birth weight between babies receiving a higher infusion rate (shorter and moderate increase) versus lower infusion rate (longer and moderate increase): MD -0.36 (95% CI -1.82, 1.10).

Weight at discharge (g)

- Moderate quality evidence from 1 RCT (n=100) showed no clinically important difference in weight at discharge between babies receiving a higher infusion rate (shorter and moderate increase) versus lower infusion rate (longer and moderate increase): MD -52.17 (95% CI -289.29, 184.95).

Infant's ≥10th percentile for weight

- Low quality evidence from 1 RCT (n=100) showed a clinically important difference in the number of infant's in ≥10th percentile for weight, with more babies ≥10th percentile who received higher infusion rate (shorter and moderate increase) as compared to lower infusion rate (longer and moderate increase). However, there was uncertainty around the effect: RR 2.41 (95% CI 1.22, 4.76).

Length at discharge (cm)

- Moderate quality evidence from 1 RCT (n=100) showed no clinically important difference in length at discharge between babies receiving a higher infusion rate (shorter and moderate increase) versus lower infusion rate (longer and moderate increase): MD -0.54 (95% CI -2.00, 0.92).

Head circumference at discharge (cm)

- Moderate quality evidence from 1 RCT (n=100) showed no clinically important difference in head circumference at discharge between babies receiving a higher infusion rate (shorter and moderate increase) versus lower infusion rate (longer and moderate increase): MD -0.25 (95% CI -1.17, 0.67).

Sepsis

- Very low quality evidence from 1 RCT (n=43) showed a clinically important difference in the rate of sepsis, with more babies with sepsis who received intermittent infusion rates as compared to continuous infusion rates. However, there was high uncertainty around the effect: RR 0.32 (95% CI 0.04, 2.60).

Mortality

- Lowquality evidence from 1 RCT (n=100) showed a clinically important difference in mortality rates between babies receiving a higher versus a lower infusion rate. Those babies receiving lower infusion rates had higher rates of mortality as compared to those receiving higher infusion rates. However, there was h uncertainty around the effect: POR 0.14 (95% CI 0.01, 1.38).
- Lowquality evidence from 1 RCT (n=43) showed a clinically important difference in mortality rates between babies receiving intermittent versus continuous infusion rates. Those babies receiving continuous infusion rates had higher rates of mortality as compared to those receiving intermittent infusion rates. However, there was uncertainty around the effect: POR 0.17 (95% CI 0.00, 8.63).
- Low quality evidence from 1 RCT comparing 3 treatment groups (n=38) showed clinically important differences in mortality rates between babies receiving higher versus lower infusion rate over 24 hours or higher infusion rates over 24 hours versus lower infusion rates over 16 hours. Those babies receiving lower infusion rates had higher rates of mortality as compared to those receiving higher infusion rates. However, there was uncertainty around the effects: POR 0.17 [95% CI 0.00, 8.69; n=25] and POR 0.16 [95% CI 0.00, 8.06; n=24], respectively.

Duration of hospital stay

- Low quality evidence from 1 RCT (n=100) showed no clinically important difference in the duration of hospital stay between babies receiving a higher infusion rate (shorter and moderate increase) versus lower infusion rate (longer and moderate increase). However, there was uncertainty around the effect: MD -6.93 (95% CI -17.39, 3.53).

Hypertriglyceridemia

- Low quality evidence from 1 RCT (n=100) showed a clinically important difference in the rate of hypertriglyceridemia between babies, with more babies with hypertriglyceridemia who received higher infusion rates (shorter and moderate increase) as compared to lower infusion rates (longer and moderate increase). However, there was uncertainty around the effect: RR 3.79 (95% CI 0.83, 17.37).

Necrotising enterocolitis

- Moderate quality evidence from 1 RCT (n=100) showed there is a clinically important difference in the rate of necrotising enterocolitis, with more babies with necrotising enterocolitis who received a lower infusion rate (longer and moderate increase) compared to a higher infusion rate (shorter and moderate increase): Peto odds ratio (POR) 7.75 (95% CI 1.68 to 35.77).

Retinopathy of prematurity (ROP)

- Low quality evidence from 1 RCT (n=100) showed there is a clinically important difference in rates of ROP, with more babies with ROP who received higher infusion rates (shorter and moderate increase) as compared to lower infusion rates (longer and moderate increase). However, there was uncertainty around the effect: RR 0.27 (95% CI 0.08, 0.90).

Economic evidence statements

No economic evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee discussed the importance and relevance of various outcomes when assessing the effectiveness of lipids for PN in neonates. The committee agreed the critical outcomes are neurodevelopmental outcomes (general cognitive abilities at two years corrected age as measured by a validated scale), adverse effects of lipids (including sepsis, PN related liver disease such as abnormal liver function, cholestasis and conjugated hyperbilirubinaemia), and growth/anthropometric measures (weight gain, linear growth and head circumference). These were agreed to be critical because they are directly affected by the amount of lipids that a baby receives. Other outcomes of lesser importance for decision making but nevertheless important are mortality, duration of hospital stay, hypertriglyceridemia and nutrition intake (defined as the proportion of prescribed lipids actually received). These were agreed to be important rather than critical because they would be influenced by nutrition but also by other complications of being born preterm.

The quality of the evidence

The quality of evidence was assessed using GRADE methodology. The quality of the evidence ranged from very low to moderate quality. Outcomes were downgraded for risk of bias because of uncertainty surrounding the methods of randomisation and whether allocation concealment was performed. In most cases, only the investigator or assessor were blinded. A number of outcomes showed high imprecision, a small number of studies were found for some comparisons and often only one study was available per outcome. Numerous studies reported results using intention to treat analysis, for others it was either unclear or the authors used per protocol analysis. Few studies reported the actual amount of lipids delivered to the babies. This is an important factor in order to ascertain the effectiveness of the intervention, for instance, a high dosage intervention may not have achieved its target dosage and any benefit detected in fact be in response to a lower dosage.

Benefits and harms

The committee discussed the findings of the evidence review. As the evidence was of low to moderate quality and formulations were commonly different from current practice. The committee therefore used the evidence together with their knowledge and experience to reach agreement by informal consensus on a starting and maintenance range.

Starting lipids

The committee took into account the evidence which showed that slowly increasing lipids from a low starting dosage (for example, 0.5 g/kg/day) to a target dosage (for example, 3 g/kg/day), using an infusion rate of 0.5 g/kg/day, may be associated with a reduced number of babies with retinopathy of prematurity and hypertriglyceridemia compared with those who start at a higher dosage (2 g/kg/day) and have a shorter time to the same target dosage. A benefit on the number of babies who are equal to or greater than the 10th percentile for weight was found in the higher starting dosage and shorter time to target dosage. There was some evidence of reduced mortality with higher infusion rates and with intermitted delivery of lipids; however, there was evidence of reduced sepsis with continuous delivery. Therefore, the committee agreed by informal consensus that lipids should be increased gradually from the starting range to the maintenance range to ensure the baby tolerates any change in PN and suggested incrementing by 0.5g/kg/day as an example.

There was some alternate evidence of increased retinopathy of prematurity and necrotising enterocolitis when babies were given PN containing lipids compared with no lipids. However, there was some benefit of giving lipids in terms of lower incidence of mortality and hypoglycaemia. The committee noted that retinopathy of prematurity, necrotising enterocolitis and mortality were secondary outcomes in the included studies and that the studies were underpowered to detect differences in these outcomes. And the generally accepted benefits of providing intravenous lipid outweighs these possible risks. The committee noted that one study by Vlaardingerbroek 2013 most closely reflects current practice when it comes to the timing of delivering lipids. One group received lipids soon after birth and was compared to lipids being delivered on day 2. The majority of outcomes showed no difference between the early versus late delivery of lipids. The committee were, aware of evidence to suggest that delaying lipid results in fatty acid deficiency within the first two days of life in the vulnerable preterm population. There was some evidence of increased cholestasis when lipids were given on the first day compared to day 2; however, there was some evidence of reduced retinopathy of prematurity and improved neurodevelopmental outcomes. Evidence regarding sepsis, mortality and necrotising enterocolitis was inconsistent. Therefore, the committee agreed by informal consensus that there was not sufficient evidence to delay starting lipids.

For preterm and term babies, 1g/kg/day was chosen as the lower starting dosage threshold. Some studies started lipids at 0.5g/kg/day but the committee agreed that there may be greater weight gain with higher doses and it was important to maintain proportions with other macronutrients recommended in this guideline. The upper starting dosage threshold of 2g/kg/day was selected because this was the maximum starting dosage used in included studies that gradually increased lipid intake.

Maintaining Lipids

The evidence showed that a higher target dosage of lipids was associated with a higher mean weight gain in the first 28 days, and lower rates of retinopathy or prematurity and necrotising enterocolitis compared with a lower dosage of lipids. However, the majority of growth outcomes did not show clinically important differences based on lipid dosage. Evidence regarding neurodevelopmental outcomes was inconsistent. Therefore, the committee agreed that that the range of lipids given in the included studies (3-4g/kg/day at maximum) are safe and effective and recommended 3g/kg/day as the lower dosage threshold for the maintenance range and 4g/kg/day as the upper dosage threshold for the maintenance range.

The committee discussed, based on knowledge and experience that babies starting PN after the first 4 days after birth should start PN based on the recommended maintenance range. Babies starting PN after this time point may have already made progress with incrementing up to the maintenance levels of macronutrients required for growth from their enteral nutrition. If that enteral nutrition has to be stopped (for example, due to development of necrotising enterocolitis) and PN started the committee felt that returning to starting doses of macronutrients would likely lead to nutritional deficit. Alternatively, babies may be starting PN after this time point as they have not made sufficient progress with enteral fees within the first 72 hours after birth. However, the committee agreed by informal consensus, and based on their expertise, that the quantity of macronutrients that can be tolerated is closely linked to the postnatal age of the baby, with older babies able to tolerate greater nutritional intake.

Therefore, the committee agreed starting on the maintenance range would be appropriate even if progress has not been made with enteral feeds. The committee agreed to use the same approach for other constituents whenever there is an absence of evidence.

Cost effectiveness and resource use

No economic studies were identified which were applicable to this review question.

The committee explained that recommendations pertaining to an optimal target dosage of lipid in preterm and term babies who are receiving PN or neonatal care and the optimal way of achieving this target dosage would not incur extra resource implications to the health care system.

The committee noted that getting the amount of lipid for neonatal PN may result in avoiding additional costs associated with adverse effects to the NHS (e.g. incorrect amounts of lipid can result in adverse events such as hypoglycaemia which may require resource-intensive management).

The committee explained that recommendations in this area reflect practice across many units and as such cost savings to the NHS, if any, are likely to be negligible.

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Appendices

Appendix A – Review protocols

Review protocol for review question: What is the optimal target for lipid dosage in preterm and term babies who are receiving parenteral nutrition and neonatal care? and What is the optimal way (starting dose and approach to increment, if employed) to achieve that?

Table 3: Review protocol for intravenous lipids

Field (based on PRISMA-P)	Content
Review question	D3a. What is the optimal target for lipid dosage in preterm and term babies who are receiving parenteral nutrition and neonatal care? D3b. What is the optimal regimen (starting dose and approach to increment, if employed) to achieve that?
Type of review question	Intervention
Objective of the review	To determine what quantity of intravenous lipids should be provided.
Eligibility criteria – population/disease/condition/issue/domain	• Babies born preterm, up to 28 days after their due birth date (preterm babies) • Babies born at term, up to 28 days after their birth date (term babies)
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	D3a. • Any amount of IV lipid (g/kg/day) D3b. • Starting dose • Rate of Increase in lipids
Eligibility criteria – comparator(s)/control or reference (gold) standard	D3a. • None • Each other D3b.

Field (based on PRISMA-P)	**Content**
	• Different starting doses • Different increases • Different regimens

Outcomes and prioritisation	**Critical**
	• Neurodevelopmental outcomes (general cognitive abilities at two years corrected age as measured by a validated scale)
	• Growth/Anthropometric measures:
	  ○ Weight gain (g/kg/d)
	  ○ Linear growth
	  ○ Head circumference (mm)
	• Adverse effects of lipids:
	  ○ Infection (including sepsis)
	  ○ PN related liver disease (abnormal liver function, cholestasis, conjugated Hyperbilirubinaemia)
	
	Important
	• Mortality
	• Duration of hospital stay
	• Necrotising enterocolitis
	• Hypertriglyceridemia
	• Hypoglycaemia
	• Retinopathy of prematurity (RoP)
	• Nutritional intake (g/kg/day) (defined as proportion of prescribed lipids actually received)

Eligibility criteria – study design	Only published full text papers: • Systematic reviews of RCTs • RCTs • Comparative cohort studies (only if RCTs unavailable or limited data to inform decision making) • Non-comparative studies (only if no evidence from RCTs or comparative cohort studies, limited data on critical outcomes to inform decision making) No date restriction needed. Participant numbers (no restrictions for observational studies).

Field (based on PRISMA-P)	Content
	Conference abstracts of RCTs will only be considered if no evidence is available from full published RCTs (if no evidence from RCTs or comparative cohort studies available and are recent i.e., in the last 2 years-authors will be contacted for further information).
Other inclusion exclusion criteria	**Inclusion**: Clinical settings that provide neonatal care or specialist paediatric care. UK and non-UK studies (non-UK studies from middle and high income countries according to WHO/World Bank criteria).
Proposed sensitivity/sub-group analysis, or meta-regression	• Parents or carers whose first language is not English • Parents or carers who have learning difficulties or disabilities There are inequalities that have been identified relating to how information is provided to them and the type of support they need. • It is known that being a young woman (aged 17 years or under) or a woman with a low socioeconomic status increases the risk of giving birth to a baby preterm. These groups could require particular support and specific recommendations may be required to address their particular needs. Stratified analysis: • Babies born preterm, up to 28 days after their due birth date (preterm babies) • Babies born at term, up to 28 days after their birth (term babies) • Critically ill babies or those requiring surgery (for example, inotropic support, therapeutic hypothermia, fluid restriction) Subgroup analysis: • Population subgroups: o Age of baby o Preterm (extremely preterm <28 weeks' GA; very preterm: 28-31 weeks' GA; moderately preterm: 32-36 weeks' GA) o Birthweight: low birthweight (<2500g); very low birthweight (<1500g) and extremely low birthweight (<1000g) Important confounders (when comparative observational studies are included for interventional reviews):

Field (based on PRISMA-P)	Content

	• Age of baby
	• Birthweight: low birthweight (<2500g); very low birthweight (<1500g) and extremely low birthweight (<1000g)
	• Continuous IV lipid versus intermittent IV lipid
	• Actual dose received
	• Sex of baby
	• Gestation (preterm versus term)
	• For neurodevelopmental outcomes:
	  ○ Biological (sex, small for gestational age, ethnicity)
	  ○ Neonatal (PVL, IVH, infarct, sepsis, ROP, NEC, antenatal/postnatal steroids, BPD at 36 weeks)
	  ○ Social (SES, substance abuse, alcohol abuse, multiple pregnancy, chorioamnionitis, neglect, maternal age, maternal mental health disorder)

Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. A random sample of the references will be sifted by a second reviewer. This sample size will be 10% of the total, or 100 studies if the search identified fewer than 1000 studies. All disagreements will be resolved by discussion between the two reviewers. The senior systematic reviewer or guideline lead will act as arbiter where necessary.
Data management (software)	Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. Low income countries will be downgraded for indirectness. NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists (ROBIS (systematic reviews and meta-analyses); Cochrane risk of bias tool (RCTs or comparative cohort studies); Cochrane risk of bias tool (Non-randomised studies); Newcastle-Ottawa scale (Non-comparative studies).
Information sources – databases and dates	A search strategy will be developed to include medical subject headings and free text terms based on the eligibility criteria: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase databases will be searched. The search will be limited to human studies and those conducted in the English language.
Identify if an update	This is not an update.
Author contacts	Developer: The National Guideline Alliance https://www.nice.org.uk/guidance/indevelopment/gid-ng10037

Field (based on PRISMA-P)	Content
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014.
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see appendix B.
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual 2014. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/.
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual 2014.
Methods for analysis – combining studies and exploring (in)consistency	For details of the methods please see supplementary material C.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014.
Rationale/context – current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Alliance (NGA) and chaired by Dr Paul Eunson in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details of the methods please see supplementary material C.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.

Field (based on PRISMA-P)	Content
Roles of sponsor	NICE funds the NGA to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	This review is not registered with PROSPERO.

BPD: bronchopulmonary dysplasia; CDSR: Cochrane Database of Systematic Reviews; CCTR: Cochrane Controlled Trials Register; DARE: Database of Abstracts of Reviews of Effects; GA: gestational age; GAS: Goal Attainment Scale; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; IV: intravenous; IVH: intraventricular haemorrhage; NEC: necrotising enterocolitis; NGA: National Guideline Alliance; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PN: Parenteral nutrition; PRISMA-P: preferred reporting items for systematic review and meta-analysis protocols; PVL: periventricular leukomalacia; RCT: randomised controlled trial; RoB: risk of bias; ROBINS-I: risk of bias in non-randomised studies of interventions; ROBIS: risk of bias in systematic reviews; ROP: retinopathy of prematurity; SD: standard deviation; SES: socioeconomic status; UK: United Kingdom; WHO: World Health Organisation.

Appendix B – Literature search strategies

Literature search strategies for review question: What is the optimal target for lipid dosage in preterm and term babies who are receiving parenteral nutrition and neonatal care? and What is the optimal way (starting dose and approach to increment, if employed) to achieve that?

One combined search was conducted for the research questions.

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

#	Searches
1	INFANT, NEWBORN/
2	(neonat$ or newborn$ or new-born$ or baby or babies).ti,ab.
3	PREMATURE BIRTH/
4	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 (birth? or born)).ab,ti.
5	exp INFANT, PREMATURE/
6	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 infan$).ti,ab.
7	(pre#mie? or premie or premies).ti,ab.
8	exp INFANT, LOW BIRTH WEIGHT/
9	(low adj3 birth adj3 weigh$ adj5 infan$).ti,ab.
10	((LBW or VLBW) adj5 infan$).ti,ab.
11	INTENSIVE CARE, NEONATAL/
12	INTENSIVE CARE UNITS, NEONATAL/
13	NICU?.ti,ab.
14	or/1-13
15	PARENTERAL NUTRITION/
16	PARENTERAL NUTRITION, TOTAL/
17	PARENTERAL NUTRITION SOLUTIONS/
18	ADMINISTRATION, INTRAVENOUS/
19	INFUSIONS, INTRAVENOUS/
20	CATHETERIZATION, CENTRAL VENOUS/
21	exp CATHETERIZATION, PERIPHERAL/
22	(parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?).ti,ab.
23	((peripheral$ or central$) adj3 (line? or catheter$)).ti,ab.
24	drip?.ti,ab.
25	or/15-24
26	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp.
27	(g adj3 kg adj3 (d or day) adj5 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric

#	Searches
	Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp.
28	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)).mp.
29	(g adj3 kg adj3 (d or day) adj5 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)).mp.
30	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or

#	Searches
	Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM$ Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)).mp.
31	(g adj3 kg adj3 (d or day) adj5 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM$ Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)).mp.

#	Searches
32	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 macronutrient?).mp.
33	exp AMINO ACIDS/ad [Administration & Dosage]
34	exp LIPIDS/ad [Administration & Dosage]
35	exp PROSTAGLANDINS/ad [Administration & Dosage]
36	34 not 35
37	exp CARBOHYDRATES/ad [Administration & Dosage]
38	exp HEPARIN/ad [Administration & Dosage]
39	exp GLYCOPEPTIDES/ad [Administration & Dosage]
40	exp AMINOGLYCOSIDES/ad [Administration & Dosage]
41	or/38-40
42	37 not 41
43	FAT EMULSIONS, INTRAVENOUS/
44	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 36 or 42
45	14 and 25 and 44
46	14 and 43
47	45 or 46
48	limit 47 to english language
49	LETTER/
50	EDITORIAL/
51	NEWS/
52	exp HISTORICAL ARTICLE/
53	ANECDOTES AS TOPIC/
54	COMMENT/
55	CASE REPORT/
56	(letter or comment*).ti.
57	or/49-56
58	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
59	57 not 58
60	ANIMALS/ not HUMANS/
61	exp ANIMALS, LABORATORY/
62	exp ANIMAL EXPERIMENTATION/
63	exp MODELS, ANIMAL/
64	exp RODENTIA/
65	(rat or rats or mouse or mice).ti.
66	or/59-65
67	48 not 66

Databases: Embase; and Embase Classic

#	Searches
1	NEWBORN/
2	(neonat$ or newborn$ or new-born$ or baby or babies).ti,ab.
3	PREMATURITY/
4	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 (birth? or born)).ab,ti.
5	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 infan$).ti,ab.
6	(pre#mie? or premie or premies).ti,ab.
7	exp LOW BIRTH WEIGHT/
8	(low adj3 birth adj3 weigh$ adj5 infan$).ti,ab.
9	((LBW or VLBW) adj5 infan$).ti,ab.
10	NEWBORN INTENSIVE CARE/
11	NEONATAL INTENSIVE CARE UNIT/
12	NICU?.ti,ab.
13	or/1-12
14	PARENTERAL NUTRITION/
15	TOTAL PARENTERAL NUTRITION/
16	PERIPHERAL PARENTERAL NUTRITION/
17	PARENTERAL SOLUTIONS/
18	INTRAVENOUS FEEDING/
19	INTRAVENOUS DRUG ADMINISTRATION/
20	exp INTRAVENOUS CATHETER/
21	(parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?).ti,ab.
22	((peripheral$ or central$) adj3 (line? or catheter$)).ti,ab.
23	drip?.ti,ab.
24	or/14-23
25	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or

#	Searches
	Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp.
26	(g adj3 kg adj3 (d or day) adj5 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp.
27	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)).mp.
28	(g adj3 kg adj3 (d or day) adj5 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or

#	Searches
	Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)).mp.
29	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM$ Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)).mp.
30	(g adj3 kg adj3 (d or day) adj5 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM$ Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide?

#	Searches
	or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)).mp.
31	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 macronutrient?).mp.
32	exp AMINO ACIDS/do [Drug Dose]
33	exp LIPID/do [Drug Dose]
34	exp PROSTAGLANDIN/do [Drug Dose]
35	33 not 34
36	exp CARBOHYDRATE/do [Drug Dose]
37	exp HEPARIN/do [Drug Dose]
38	exp GLYCOPEPTIDE/do [Drug Dose]
39	exp AMINOGLYCOSIDE/do [Drug Dose]
40	or/37-39
41	36 not 40
42	exp AMINO ACIDS/
43	exp LIPID/
44	exp PROSTAGLANDIN/
45	43 not 44
46	exp CARBOHYDRATE/
47	exp HEPARIN/
48	exp GLYCOPEPTIDE/
49	exp AMINOGLYCOSIDE/
50	or/47-49
51	46 not 50
52	OPTIMAL DRUG DOSE/
53	RECOMMENDED DRUG DOSE/
54	DRUG DOSE REGIMEN/
55	DOSE CALCULATION/
56	DRUG DOSE COMPARISON/
57	DRUG DOSE ESCALATION/
58	DRUG DOSE INCREASE/
59	DRUG DOSE INTENSIFICATION/
60	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 35 or 41
61	42 or 45 or 51
62	52 or 53 or 54 or 55 or 56 or 57 or 58 or 59
63	13 and 24 and 60
64	13 and 24 and 61 and 62
65	or/63-64
66	limit 65 to english language
67	letter.pt. or LETTER/
68	note.pt.
69	editorial.pt.
70	CASE REPORT/ or CASE STUDY/
71	(letter or comment*).ti.
72	or/67-71
73	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
74	72 not 73

#	Searches
75	ANIMAL/ not HUMAN/
76	NONHUMAN/
77	exp ANIMAL EXPERIMENT/
78	exp EXPERIMENTAL ANIMAL/
79	ANIMAL MODEL/
80	exp RODENT/
81	(rat or rats or mouse or mice).ti.
82	or/74-81
83	66 not 82

Databases: Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; and Health Technology Assessment

#	Searches
1	MeSH descriptor: [INFANT, NEWBORN] this term only
2	(neonat* or newborn* or new-born* or baby or babies):ti,ab
3	MeSH descriptor: [PREMATURE BIRTH] this term only
4	((preterm* or pre-term* or prematur* or pre-matur*) near/5 (birth* or born)):ti,ab
5	MeSH descriptor: [INFANT, PREMATURE] explode all trees
6	((preterm* or pre-term* or prematur* or pre-matur*) near/5 infan*):ti,ab
7	(pre#mie? or premie or premies):ti,ab
8	MeSH descriptor: [INFANT, LOW BIRTH WEIGHT] explode all trees
9	(low near/3 birth near/3 weigh* near/5 infan*):ti,ab
10	((LBW or VLBW) near/5 infan*):ti,ab
11	MeSH descriptor: [INTENSIVE CARE, NEONATAL] this term only
12	MeSH descriptor: [INTENSIVE CARE UNITS, NEONATAL] this term only
13	NICU?:ti,ab
14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
15	MeSH descriptor: [PARENTERAL NUTRITION] this term only
16	MeSH descriptor: [PARENTERAL NUTRITION, TOTAL] this term only
17	MeSH descriptor: [PARENTERAL NUTRITION SOLUTIONS] this term only
18	MeSH descriptor: [ADMINISTRATION, INTRAVENOUS] this term only
19	MeSH descriptor: [INFUSIONS, INTRAVENOUS] this term only
20	MeSH descriptor: [CATHETERIZATION, CENTRAL VENOUS] this term only
21	MeSH descriptor: [CATHETERIZATION, PERIPHERAL] explode all trees
22	(parenteral* or intravenous* or intra-venous* or IV or venous* or infusion*):ti,ab
23	((peripheral* or central*) near/3 (line? or catheter*)):ti,ab
24	drip?:ti,ab
25	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26	((Dose? or Dosage? or Regimen? or Amount? or Optimal* or Optimis* or Requir* or Target? or Rate? or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/5 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)) :ti,ab
27	(g adj3 kg adj3 (d or day) near/5 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or

#	Searches
	Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)) :ti,ab
28	((Dose? or Dosage? or Regimen? or Amount? or Optimal* or Optimis* or Requir* or Target? or Rate? or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/5 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)) :ti,ab
29	(g adj3 kg adj3 (d or day) near/5 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)) :ti,ab
30	((Dose? or Dosage? or Regimen? or Amount? or Optimal* or Optimis* or Requir* or Target? or Rate? or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/5 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or

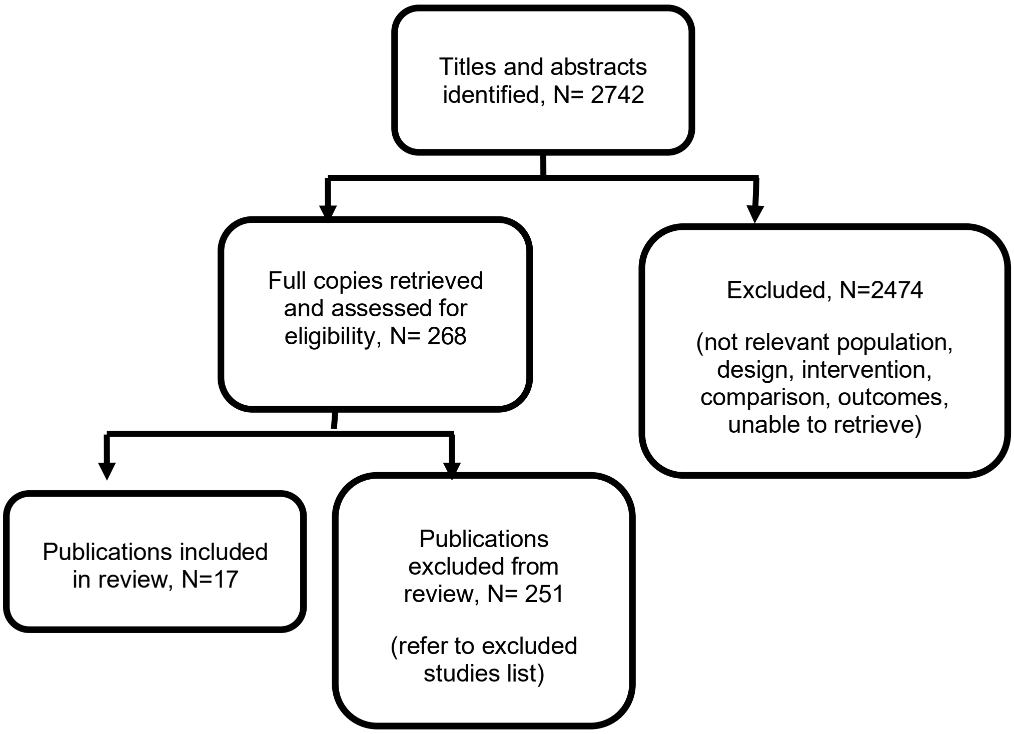
#	Searches
	Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM* Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)) :ti,ab
31	(g adj3 kg adj3 (d or day) near/5 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM* Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)) :ti,ab
32	((Dose? or Dosage? or Regimen? or Amount? or Optimal* or Optimis* or Requir* or Target? or Rate? or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/5 macronutrient?) :ti,ab

#	Searches
33	MeSH descriptor: [AMINO ACIDS] explode all trees and with qualifier(s): [Administration & dosage - AD]
34	MeSH descriptor: [LIPIDS] explode all trees and with qualifier(s): [Administration & dosage - AD]
35	MeSH descriptor: [PROSTAGLANDINS] explode all trees and with qualifier(s): [Administration & dosage - AD]
36	#34 not #35
37	MeSH descriptor: [CARBOHYDRATES] explode all trees and with qualifier(s): [Administration & dosage - AD]
38	MeSH descriptor: [HEPARIN] explode all trees and with qualifier(s): [Administration & dosage - AD]
39	MeSH descriptor: [GLYCOPEPTIDES] explode all trees and with qualifier(s): [Administration & dosage - AD]
40	MeSH descriptor: [AMINOGLYCOSIDES] explode all trees and with qualifier(s): [Administration & dosage - AD]
41	#38 or #39 or #40
42	#37 not #41
43	MeSH descriptor: [FAT EMULSIONS, INTRAVENOUS] this term only
44	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #36 or #42
45	#14 and #25 and #44
46	#14 and #43
47	#45 or #46

Appendix C – Clinical evidence study selection

Clinical study selection for review question: What is the optimal target for lipid dosage in preterm and term babies who are receiving parenteral nutrition and neonatal care? and What is the optimal way (starting dose and approach to increment, if employed) to achieve that?

Figure 1: PRISMA Flow chart of clinical article selection for review question on individual constituents (intravenous lipids) in PN for preterm and term babies.



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is the optimal target for lipid dosage in preterm and term babies who are receiving parenteral nutrition and neonatal care? and What is the optimal way (starting dose and approach to increment, if employed) to achieve that?

Table 4: Clinical evidence tables for included studies

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Alwaidh, M. H., Bowden, L., Shaw, B., Ryan, S. W., Randomised trial of effect of delayed intravenous lipid administration on chronic lung disease in preterm neonates, Journal of pediatric gastroenterology and nutrition, 22, 303-6, 1996 Ref Id 606279 Country/ies where the study was carried out UK Study type Randomised controlled trial	Sample size N=64 (n=32 early, n=32 late) Characteristics Gestational age (weeks) - median (range) Early: 28 (23 to 31) Late: 28 (23 to 31) Birthweight (g) - median (range) Early: 997 (536 to 1353) Late: 1006 (542 to 1486) Number ventilated Early: 26 Late: 22 Duration of assisted ventilation (days) - median (range) Early: 15 (2 to 91) Late: 13 (2 to 60)	Interventions Early: Intravenous (IV) lipids began on day 5. All neonates had started PN at 48 hours of age. Late: IV lipids began on day 14. All neonates had started PN at 48 hours of age.	Details IV lipids (Intralipid Kabivitrum 20%) was administered in an initial dose of 0.5 g/kg/day, increasing over 5 days to 3.0 g/kg/day. IV lipid was discontinued when at ≥50% of fluid requirements were met by milk feeds.* Power analysis Not reported (sample size was based on a predicted distribution of 67% of neonates weighing <1000 g). Statistical analyses Continuous outcomes were reported as median (range) and comparisons made using Mann-Whitney U test. Categorical	Results Age regaining birth weight (days) - median (range) Early: 15 (0 to 21) Late: 16 (8 to 30) Mortality (between 5 and 28 days of age) - n/N Early: 1/32 Late: 1/32	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: The authors stated that infants were randomised (via sealed envelopes, but no other details were provided on methods used to generate and allocate the allocation sequence (unclear risk of bias). Performance bias: The authors did not report on blinding of personnel; participants were neonates and blinding was therefore not applicable (unclear risk of bias).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess whether early intravenous lipid (IVL) increases the incidence of chronic neonatal lung disease (CNLD) in preterm neonates. Study dates Not reported. Source of funding Not reported.	<u>Age at starting milk feeds (days) - median (range)</u> Early: 7 (2 to 24) Late: 7 (2 to 20) Inclusion criteria • Infants with a birth weight of <1,500 g who were admitted to the intensive care unit and required parenteral nutrition (PN). Exclusion criteria Not reported.		outcomes were analysed using contingency tables and compared using relative risk (RR) and 95% confidence intervals (CIs). Intention-to-treat (ITT) analysis Analyses was conducted on an ITT basis.		Detection bias: The authors did not report on blinding of outcome assessors (unclear risk of bias). Attrition bias: The authors stated that there were no withdrawals from the study, but consent was withheld for two infants (low risk of bias). Reporting bias: Pre-specified outcomes reported; attrition/exclusions discussed (low risk of bias). Other bias: There was insufficient information to determine whether an important risk of bias exists (unclear risk of bias). Other information *Thirteen infants in the late lipid group received no IV lipid because PN had already been discontinued by day 14.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Brans, Y. W., Ritter, D. A., Kenny, J. D., Andrew, D. S., Dutton, E. B., Carrillo, D. W., Influence of intravenous fat emulsion on serum bilirubin in very low birthweight neonates, Archives of disease in childhood, 62, 156-60, 1987 Ref Id 606314 Country/ies where the study was carried out USA Study type Randomised controlled trial Aim of the study To compare the effects of three different intravenous fat emulsion regiments on serum bilirubin in very low birth weight neonates. Study dates Not reported.	Sample size N=38 Group 1: N=14 Group 2: N=13 Group 3: N=11 Characteristics Gestational age (weeks) - mean ±SD (range) Group 1: 29 (1.7) (820 to 1480) Group 2: 29 (1.3) (27 to 31) Group 3: 29 (1.3) (28 to 31) Postnatal age (days) - mean ±SD (range) Group 1: 4 (1.9) (1 to 9) Group 2: 3 (1.6) (2 to 7) Group 3: 3 (1.4 (2 to 5) Sex (male/female) - number Group 1: 10/4 Group 2: 8/5 Group 3: 4/7 Birth weight (g) - mean ±SD (range) Group 1: 1190 (196) (820 to 1480) Group 2: 1160 (218) (820 to 1500) Group 3: 1160 (226) (820 to 1500)	Interventions Group 1: Fat emulsion at a constant rate over 24 hours, starting at a daily dosage of 1 g/kg and increasing by 1 g/kg on each successive day to a daily maximum of 4 g/kg. Group 2: Fat emulsion at a constant rate over 16 hours followed by 8 hours without infusion of fats; daily dosage as per group 1. Group 3: Fat emulsion at a constant rate over 24 hours with a daily dosage of 4 g/kg at the start of infusion.	Details All neonates received phototherapy from birth. Total PN was started on the third postnatal day (unless otherwise indicated). Total PN fluids, fat emulsion excepted, were administered through an arterial umbilical catheter as long as the neonate required the catheter for blood gas monitoring. If the catheter was removed the fluids were administered through peripheral veins. No enteral feedings were provided during the study. Power analysis Not reported. Statistical analyses Data were analysed using one way analysis of variance to detect differences between treatment groups. Duncan's multiple range test was applied to significant	Results Mortality up to day 8 - N Group 1: 1 Group 2: 1 Group 3: 0	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: The authors did not provide details on methods used to generate and allocate the allocation sequence (unclear risk of bias). Performance bias: The authors did not report on blinding of personnel; participants were neonates and blinding was therefore not applicable (unclear risk of bias). Detection bias: The authors did not report on blinding of outcome assessors (unclear risk of bias). Attrition bias: The authors stated that 9 neonates (23%) did not complete the study due to death, necrotising enterocolitis, severe

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Supported in part by the National Institute of Child Health and Human Development.	Inclusion criteria • Neonates weighing ≤1500 g at birth and receiving parenterally administered fat emulsions. Exclusion criteria • Neonates weighting <750 g at birth; • Estimated gestational age <27 weeks.		differences. Within each group, the mean value for each day of study (which lasted for 8 days) was compared with the pre-infusion value using one tailed Student's paired t test. Intention-to-treat (ITT) analysis Not reported. Data from babies who did not complete the 8 day trial were included in the analysis up to the time of stopping the study.		hyperlipidaemia, withdrawal of consent, interruption of lipid infusion, or start of enteral feedings; these babies were included in analysis up to the time of stopping the study (high risk of bias). Reporting bias: Pre-specified outcomes reported; attrition/exclusions discussed (low risk of bias). Other bias: There was insufficient information to determine whether an important risk of bias exists (unclear risk of bias). Other information
Full citation Brownlee, K. G., Kelly, E. J., Ng, P. C., Kendall-Smith, S. C., Dear, P. R., Early or late parenteral nutrition for the sick preterm infant?, Archives of disease in childhood, 69, 281-3, 1993	Sample size N=129 (early n=63, late n=66) Characteristics <u>Gestational age (weeks) - median (range)</u> Early: 29 (23 to 33) Late: 29 (24 to 36)	Interventions Early: PN administered within the first 36 hours. Late: PN administered on the sixth complete day.	Details PN included Intralipid 20% (KabiVitrum) and either Vamin 9 glucose or Vamin Infant (KabiVitrum), started at a dose of 0.5 g/kg/day and increasing daily by this amount to a maximum of 3.5 g/kg/day.	Results <u>Weight gain/day (g) to discharge - mean ±SD</u> Early: 18.6 (7.7) Late: 21 (9.1) <u>Mortality (before discharge)* - number (%)</u> Early: 11 (17) Late: 14 (21)	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: The authors did not describe methods

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 606318 Country/ies where the study was carried out UK Study type Randomised controlled trial Aim of the study To assess the value of early introduction of lipids into parenteral nutrition (PN) in preterm infants. Study dates January 1990 and November 1991. Source of funding Not reported.	<u>Birth weight (g) - median (range)</u> Early: 1144 (539 to 1748) Late: 1147 (415 to 1647) <u>Pressure shunt product - mean ±SD</u> Early: 478 (292) Late: 518 (301) <u>Intermittent positive pressure ventilation (days) - median (range)</u> Early: 4.5 (1 to 29) Late: 6.0 (1 to 25) Inclusion criteria • Infants with a birth weight equal to or less than 1750 g; • Still requiring intermittent positive pressure ventilation (IPPV) at 12 hours of age; • Radiographic features of respiratory distress syndrome.		Lipid infusions were continuous over 24 hours. The fluid regimen was the same for the early and late groups; infants were started on 75 ml/kg/day of 10% dextrose solution and this was increased daily in increments to 165 to 180 ml/kg/day. Power analysis Not reported. Statistical analyses Non-normally distributed data were analysed using the Mann-Whitney U test, and Student's t test was used for normally distributed data. Intention-to-treat (ITT) analysis Not reported.	*4 (3%) infants died after sepsis.	used to generate and conceal allocation sequence (unclear risk of bias). Performance bias: The authors did not state whether personnel were blind to treatment allocation; participants were neonates and blinding was therefore not applicable (unclear risk of bias). Detection bias: The authors did not provide details on blinding of outcome assessors (unclear risk of bias). Attrition bias: Twenty five (19%) infants died after entry into the trial and were excluded from analysis; no other loss to follow-up reported (low risk of bias). Reporting bias: Pre-specified outcomes reported; attrition/exclusions discussed (low risk of bias). Other bias: Unclear whether enteral

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria • Infants with severe congenital abnormalities; • Infants with pulmonary hypoplasia.				feedings may have impacted on outcomes for babies receiving this (unclear risk of bias). Other information In January 1991, surfactant was used regularly. Thirteen infants (10%) were started on enteral feeds within the first 7 days, but were included in the analysis only while receiving full PN.
Full citation Calkins, K. L., Havranek, T., Kelley-Quon, L. I., Cerny, L., Flores, M., Grogan, T., Shew, S. B., Low-dose parenteral soybean oil for the prevention of parenteral nutrition-associated liver disease in neonates with gastrointestinal disorders, Journal of Parenteral and Enteral Nutrition, 41, 404-411, 2017 Ref Id 688623	Sample size N=41 (N analysed: n=16 standard dose; n=20 low dose) Characteristics Gestational age (weeks) - mean ±SD Standard dose: 36 (2) Low dose: 37 (1) Sex (male) - N (%) Standard dose: 10 (63) Low dose: 8 (40) Birth weight (kg) - mean ±SD Standard dose: 2.5 (0.6) Low dose: 2.5 (0.4)	Interventions Standard dose: Approximately 3 g/kg/day of S-ILE (20% Intralipid). Low dose: Approximately 1 g/kg/day of S-ILE (20% Intralipid).	Details S-ILE was initiated in all neonates in the first 24 to 48 hours of age and advanced by 0.5 to 1 g/kg/day to the target dose depending on triglyceride tolerance. The intervention continued until the patient reached approximately 100 days of age, was weaned from PN, discharged from the hospital, or died, whichever came first. Patients received PN composed of dextrose and amino acids (10% Premasol). Goal	Results Discharge weight (g) - mean ±SD Standard dose: 3.5 (0.7) Low dose: 3.4 (0.9) Weight velocity (g/day) in first 28 days - N (%) Standard dose: 24 (16) Low dose: 18 (8) Discharge length (cm) - mean ±SD Standard dose: 50 (4) Low dose: 51 (4) Discharge head circumference (cm) - mean ±SD Standard dose: 36 (4)	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: Randomisation stratified by site and blocks of 4 using opaque sealed envelopes (low risk of bias). Performance bias: The authors stated that infants were randomised in an unmasked fashion;

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA Study type Randomised controlled trial Aim of the study To assess whether a lower dose compared with a higher dose of Soybean-based intravenous lipid emulsions (S-ILE) prevents cholestasis without compromising growth in neonates with gastrointestinal disorders. Study dates October 2010 and February 2014. Source of funding Authors received funding from the National Institute for Health, Today's and Tomorrow's Children Fund, Mattel Children's Hospital, University of California, National Centre for Advancing Translational Sciences.	Birth length (cm) - mean ±SD Standard dose: 45 (4) Low dose: 45 (3) Birth head circumference (cm) - mean ±SD Standard dose: 33 (4) Low dose: 32 (2) Gastroschisis - N (%) Standard dose: 12 (75) Low dose: 15 (75) Omphalocoele - N (%) Standard dose: 1 (6) Low dose: 4 (20) Atresia - N (%) Standard dose: 3 (19) Low dose: 0 Meconium disease - N (%) Standard dose: 0 Low dose: 1 (5) Inclusion criteria • Neonates with gastrointes tinal disorders (gastr oschisis, omphalocoele, small bowel atresia,		calories and amino acid doses for term and low-birth-weight neonates were approximately 100 and 120 kcal/kg/day and 3 g/kg/day and 3 to 4 g/kg/day, respectively. Goal glucose infusion rates were increased to a maximum of 12 to 16 mg/kg/min and adjusted at the discretion of the primary medical team based on glucose tolerance, goal calories, and growth. Power analysis To achieve 80% power, approximately 60 patients per arm were required. Statistical analyses Categorical data were analysed using Fisher exact test; for continuous data differences were assessed using the Student t test. Repeated measures with an autoregressive covariance structure were used to compare longitudinal data on	Low dose: 35 (2) Late-onset sepsis - N (%) Standard dose: 3 (19) Low dose: 3 (15) Cholestasis - N (%) Standard dose: 6 (38)* Low dose: 6 (30) Direct bilirubin (>1 mg/dL) - N (%) Standard dose: 9 (56) Low dose: 10 (50) Length of hospital stay (days) - mean ±SD Standard dose: 58 (47) Low dose: 54 (38)	participants were neonates and blinding was therefore not applicable (high risk of bias). Detection bias: The authors did not provide details on blinding of outcome assessors (unclear risk of bias). Attrition bias: 5 infants (12%) were excluded from analysis because they received ≤14 days of PN and/or did not have an abdominal operation (low risk of bias). Reporting bias: Pre-specified outcomes reported and attrition/exclusions discussed. However, the study was underpowered (high risk of bias). Other bias: Unclear whether enteral feedings may have impacted on the outcomes (unclear risk of bias). Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	intestinal perforation, Hirschsprung disease, volvulus, or meconium ileus and/or peritonitis); • ≤5 days of age at enrolment. Patients who required an abdominal operation (excluding gastrostomy tubes and rectal biopsies) and received PN for >14 days were included in the final analysis. Exclusion criteria • Informed consent not provided; • Neonates with a primary liver disorder excluding parenteral nutrition-associated liver disease (PNALD), congenital intrauterine		growth, PN and enteral nutrition, and laboratory values. No adjustments were made for multiple comparisons. Intention-to-treat (ITT) analysis Not reported.		Enteral feeds were initiated and advanced per routine care. *In patients receiving PN for >28 days, the incidence of cholestasis was 30% for the low dose group and 40% for the standard dose group.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	infection, metabolic disorder, or terminal illness.				
Full citation Gunn, T, Reaman, G, Outerbridge, EW, Peripheral total parenteral nutrition for premature infants with the respiratory distress syndrome: a controlled study, The Journal of Pediatrics, 92, 608-613, 1978 Ref Id 1007715 Country/ies where the study was carried out Canada Study type Randomised trial Aim of the study To compare the effects of different peripheral total parenteral nutrition (PN) regimens in the treatment of premature	Sample size N=40 consecutively enrolled infants (PN group: n=20; control group: n=20) Characteristics Gestational age (weeks) - mean ±SD PN: 32.2 (3.2) Control: 32.3 (3.5) Birth weight (g) - mean ±SD PN: 1700 (554) Control: 1868 (781) Sex (male) - n PN: 9 Control: 8 Inclusion criteria • Infants with radiologically confirmed respiratory distress syndrome;	Interventions PN: Infants received PN starting on day 2 of life. A soybean emulsion (Intralipid Vitrum) supplying 1.1 calories/ml was started at 2 g/kg/day of fat, increasing, as tolerated to a maximum of 4 g/kg/day in 40 ml. Control: Infants received parenteral fluids consisting of glucose and electrolyte solution (Ionosol MB with glucose supplementation to achieve a concentration of 10%).	Details All infants received dextrose in water intravenously at a rate of 65 ml/kg for the first 24 hours, prior to randomisation to treatment groups. Heparin was not used. Any infant who was receiving glucose and was unable to feed orally by 2 weeks of age was transferred to total PN. Power analysis Not reported. Statistical analyses Not reported. Intention-to-treat (ITT) analysis Not reported.	Results Days to regain birth weight (survivors) - mean ±SD PN (n=17): 12.8 (9.0) Control (n=14): 13.8 (4.1) Mortality - n/N PN: 3/20 Control: 6/20	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: Infants were randomised using a random card selection; no other details provided (unclear risk of bias). Performance bias: The authors did not mention blinding of personnel; participants were neonates and blinding was therefore not applicable (unclear risk of bias). Detection bias: The authors did not mention blinding of outcome assessors (unclear risk of bias). Attrition bias: The authors reported that 1

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
infants with respiratory distress syndrome. Study dates September 1974 to May 1975. Source of funding Not reported.	• Unable to tolerate oral feeding. Exclusion criteria Not reported.				infant was lost to follow-up (low risk of bias). Reporting bias: Pre-specified outcomes were reported in surviving infants (unclear risk of bias). Other bias: There was insufficient information to determine whether an important risk of bias exists (unclear risk of bias). Other information All intravenous bottles and tubing were changed daily. No catheters were used. Phytonadione (1 mg) was administered intramuscularly once weekly.
Full citation Drenckpohl, D., McConnell, C., Gaffney, S., Niehaus, M., Macwan, K. S., Randomized trial of very low birth weight	Sample size N=110 (N=100 infants completed the study: Higher rate of infusion n=48; Lower rate of infusion n=52) Characteristics	Interventions Higher rate of infusion: 2 g/kg/ day of 20% intravenous fat emulsion (IVFE) on the first day of total parenteral nutrition (TPN).	Details The IVFE level in the TPN was increased by 0.5 g/kg/day daily, until all infants in each group achieved 3 g/kg/day. Total nutrient admixtures (TNAs)	Results <u>Time to regain birth weight (days) - mean ±SD</u> Higher rate of infusion: 12.5 (3.68) Lower rate of infusion: 12.86 (3.76)	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
infants receiving higher rates of infusion of intravenous fat emulsions during the first week of life, Pediatrics, 122, 743-751, 2008 Ref Id 688862 Country/ies where the study was carried out USA Study type Randomised controlled trial Aim of the study To determine whether very low birth weight infants are able to tolerate higher rates of infusion of intravenous fat emulsion during the first week of life and maintain their serum triglyceride levels at ≤200 mg/dL. Study dates June 2005 to September 2006. Source of funding	Gestational age (weeks) - mean ±SD Higher rate of infusion: 28.81 (1.72) Lower rate of infusion: 28.58 (1.79) Birth weight (g) - mean ±SD Higher rate of infusion: 1182.44 (197.93) Lower rate of infusion: 1134.00 (223.49) Sex (male) - % Higher rate of infusion: 58.3 Lower rate of infusion: 55.8 Inclusion criteria • Infants with gestational ages between 26 and 32 weeks; • Birth weights between 750 and 1500 g, and were classified as appropriate for gestational age (AGA) on the basis of the approved growth chart;	Lower rate of infusion (control): 0.5 g/kg/ day of 20% IVFE on the first day of total TPN.	were used to deliver PN to each infant; compounded from 70% dextrose, Trophamine, and 20% Intralipid emulsion. Macronutrients were blended together while the electrolytes, vitamins, minerals, cysteine (75 mg/kg/day), carnitine (25 mg/kg/day), and heparin (1 U/mL) were added manually. Power analysis A sample size of 82 (41 infants in each treatment arm) was required to achieve 80% power. Statistical analyses Secondary outcomes were assessed using independent, 2-sample, t tests or Pearson X^2 tests. Intention-to-treat (ITT) analysis Not reported.	Weight at discharge (g) - mean ±SD Higher rate of infusion: 1894.27 (392.05) Lower rate of infusion: 1946.44 (771.10) Infants in ≥10th percentile for weight for age - n (%) Higher rate of infusion: 20 (42) Lower rate of infusion: 9 (17); p=0.007 Length at discharge (cm) - mean ±SD Higher rate of infusion: 42.6 (3.02) Lower rate of infusion: 43.14 (4.35) Head circumference at discharge (cm) - mean ±SD Higher rate of infusion: 30.92 (2.20) Lower rate of infusion: 31.17 (2.49) Mortality - n (%) Higher rate of infusion: 0 (0) Lower rate of infusion: 3 (6)	Selection bias: The authors stated that sealed envelopes were shuffled and used to allocate treatment assignment; no other details were provided (unclear risk of bias). Performance bias: The authors stated that the study was not blinded as NICU was experiencing a shortage of neonatologists to monitor babies; participants were neonates and blinding was therefore not applicable (unclear risk of bias). Detection bias: The authors did not provide details on blinding of outcome assessors (unclear risk of bias). Attrition bias: The authors reported that 10 infants (9%) were excluded from analysis due to deviation from protocol, triglycerides not drawn, TPN prematurely stopped,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Children's Miracle Network.	• Singletons, twins, or triplets who met the weight and AGA status criteria. Exclusion criteria • Infants who were small for gestational age at birth; • Infants with serious congenital anomalies, and/or developed early sepsis.			Length of hospital stay (days) - mean ±SD Higher rate of infusion: 43.65 (19) Lower rate of infusion: 50.58 (33) Hypertriglyceridemia - n (%) Higher rate of infusion: 7 (15) Lower rate of infusion: 2 (4) Necrotising enterocolitis - n (%) Higher rate of infusion: 0 (0) Lower rate of infusion: 7 (14); p=0.008 Retinopathy of prematurity - n (%) Higher rate of infusion: 3 (6) Lower rate of infusion: 12 (23); p=0.019	early sepsis, incorrect birth weight used (low risk of bias). Reporting bias: Pre-specified outcomes reported; exclusions were discussed (low risk of bias). Other bias: No other bias detected (low risk of bias). Other information All TNA solutions, delivered either centrally or peripherally, included 1 U/mL heparin. All infants received perinatal steroid treatment.
Full citation Gilbertson, N., Kovar, I. Z., Cox, D. J., Crowe, L., Palmer, N. T., Introduction of intravenous lipid administration on the first day of life in the	Sample size N=29 (early n=16; late n=13) Characteristics Gestational age (weeks) - mean ±SEM Early: 28.6 (0.53) Late: 28.8 (0.58)	Interventions Early: Received TPN with IVL increasing from 1 g/kg/day on the first day of life to 3 g/kg/day by day 4. Late: Received an isocaloric, isovolumetric	Details Lipid was administered as Intralipid 20% which provides 2.0 kcal per $m1^{-1}$. IVL was infused at a constant rate during a 20-hour period, with a 4-hour lipid-free interval	Results Days to regain birth weight -mean ±SEM Early: 10.1 (1.33) Late: 11.4 (1.92) Growth in length (cm/week) - mean ±SEM	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
very low birth weight neonate, Journal of Pediatrics, 119, 615-623, 1991 Ref Id 688997 Country/ies where the study was carried out UK Study type Randomised controlled trial Aim of the study To assess the tolerance of intravenous lipid (IVL) in sick, ventilator-dependent, very low birth weight infants from the first day of life and the effect on glucose homeostasis. Study dates Not reported. Source of funding Sir Jules Thorn Trust.	 Birth weight (kg) - mean ±SEM Early: 1.15 (0.06) Late: 1.09 (0.09) Days ventilation - mean ±SEM Early: 9.92 (3.68) Late: 15.90 (4.53) Inclusion criteria • Infants aged <6 hours on admission to the neonatal intensive care unit; • Ventilator dependent; • Requirement for intensive medical and nursing care as defined by the criteria of the British Paediatric Association; • Estimated need for total parenteral nutrition (TPN) for at least 1 week.	regimen that differed only in that it contained no lipid until the eighth day and had a higher glucose concentration.	between 4 and 8 AM daily. Heparin (1 unit/ml) was added to the TPN for all infants. Fluid recommendations used to permit isocaloric and isovolumetric administration in both groups were from 83 ml/kg/day on day 1 increasing to 150 ml/kg/day by day 4 onward. Amino acid intake was increased progressively to reach a total of 2.6 g/kg/day (as Vamin Infant; KabiVitrum) by day 4. Power analysis The authors stated that the number of infants in the study provided 80% power. Statistical analyses Two-way analysis of variance used to compare outcomes between groups (time and type of treatment as factors and metabolites as dependent variables). Intention-to-treat (ITT) analysis	Early: 0.7 (0.1) Late: 0.6 (0.1) Growth in head circumference (cm/week) - mean ±SEM Early: 0.5 (0.1) Late: 0.5 (0.1) Sepsis - n (%) Early: 2 (12.5*) Late: 5 (38.5*) Jaundice - n (%) Early: 7 (43.8*) Late: 5 (38.5*) Mortality in the second week - n (%) Early: 1 (6.25*) Late: 1 (7.7*) Mortality at day 12 - n (%) Early: 0 (0) Late: 1 (7.7*) Hypertriglyceridemia - n (%) Early: 3 (18.8*) Late: 1 (7.7*) Hypoglycaemia - n (%) Early: 7 (43.8*) Late: 5 (38.5*)	Selection bias: The authors stated that infants were alternately assigned to treatment groups; no other details were provided (unclear risk of bias). Performance bias: The authors did not provide details on blinding of personnel; participants were neonates and blinding was therefore not applicable (unclear risk of bias). Detection bias: The authors did not provide details on blinding of outcome assessors (unclear risk of bias). Attrition bias: The authors reported that data were not included for 3 infants (10%) who required TPN for <1 week (low risk of bias). Reporting bias: Pre-specified outcomes reported; exclusions were discussed (low risk of bias). Other bias: There was insufficient information to determine whether

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria • Infants with major congenital abnormalities; • Infants of diabetic mothers.		Not reported.	<u>Necrotising enterocolitis - n/N (%*)</u> Early: 1/16 (6.3) Late: 1/13 (7.7) <u>Retinopathy of prematurity - n/N (%*)</u> Early: 0/16 (0) Late: 1/13 (7.7)	an important risk of bias exists (unclear risk of bias). Other information Infants did not receive enteral feeding during the first week. *calculated.
Full citation Gunn, T, Reaman, G, Outerbridge, EW, Peripheral total parenteral nutrition for premature infants with the respiratory distress syndrome: a controlled study, The Journal of Pediatrics, 92, 608-613, 1978 Ref Id 1007715 Country/ies where the study was carried out Canada Study type Randomised trial Aim of the study	Sample size N=40 consecutively enrolled infants (PN group: n=20; control group: n=20) Characteristics <u>Gestational age (weeks) - mean ±SD</u> PN: 32.2 (3.2) Control: 32.3 (3.5) <u>Birth weight (g) - mean ±SD</u> PN: 1700 (554) Control: 1868 (781) <u>Sex (male) - n</u> PN: 9 Control: 8 Inclusion criteria	Interventions PN: Infants received PN starting on day 2 of life. A soybean emulsion (Intralipid Vitrum) supplying 1.1 calories/ml was started at 2 g/kg/day of fat, increasing, as tolerated to a maximum of 4 g/kg/day in 40 ml. Control: Infants received parenteral fluids consisting of glucose and electrolyte solution (Ionosol MB with glucose supplementation to achieve a concentration of 10%).	Details All infants received dextrose in water intravenously at a rate of 65 ml/kg for the first 24 hours, prior to randomisation to treatment groups. Heparin was not used. Any infant who was receiving glucose and was unable to feed orally by 2 weeks of age was transferred to total PN. Power analysis Not reported. Statistical analyses Not reported. Intention-to-treat (ITT) analysis Not reported.	Results <u>Days to regain birth weight (survivors) - mean ±SD</u> PN (n=17): 12.8 (9.0) Control (n=14): 13.8 (4.1) <u>Mortality - n/N</u> PN: 3/20 Control: 6/20	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: Infants were randomised using a random card selection; no other details provided (unclear risk of bias). Performance bias: The authors did not mention blinding of personnel; participants were neonates and blinding was therefore not applicable (unclear risk of bias). Detection bias: The authors did not mention

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To compare the effects of different peripheral total parenteral nutrition (PN) regimens in the treatment of premature infants with respiratory distress syndrome. Study dates September 1974 to May 1975. Source of funding Not reported.	• Infants with radiologically confirmed respiratory distress syndrome; • Unable to tolerate oral feeding. Exclusion criteria Not reported.				blinding of outcome assessors (unclear risk of bias). Attrition bias: The authors reported that 1 infant was lost to follow-up (low risk of bias). Reporting bias: Pre-specified outcomes were reported in surviving infants (unclear risk of bias). Other bias: There was insufficient information to determine whether an important risk of bias exists (unclear risk of bias). Other information All intravenous bottles and tubing were changed daily. No catheters were used. Phytonadione (1 mg) was administered intramuscularly once weekly.
Full citation	Sample size	Interventions	Details	Results	Risk of bias assessed with Cochrane risk of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Hammerman, C., Aramburo, M. J., Decreased lipid intake reduces morbidity in sick premature neonates, The Journal of pediatrics, 113, 1083-8, 1988 Ref Id 606399 Country/ies where the study was carried out USA Study type Randomised controlled trial Aim of the study To assess the effects of lipid infusion on clinical outcomes in sick premature neonates in the first week of life. Study dates May 1986 to May 1987. Source of funding Not reported.	N=42 (lipids n=20; no lipids n=22) Characteristics Gestational age (weeks) - mean ±SD Lipids: 30 (3) No lipids: 29 (2) Birth weight (g) - mean ±SD Lipids: 1166 (431) No lipids: 1086 (384) Inclusion criteria • Premature neonates admitted to intensive care; • Birth weight <1750 g); • Respiratory distress syndrome; • Had not received any nutrition by day 3 of life; • Expected to receive parenteral nutrition (PN) for at least 5 subsequent days.	Lipids: Total PN started with 0.5 g/kg/day of Vitrum (isotonic, 10 g/dl emulsion of soybean oil, with glycerol as the aqueous phase, supplying 1100 calories per litre), which was increased at a rate of 0.5 g/kg/day to 2.5 g/kg/day) for 5 days. No lipids: Total PN at a similar rate to the lipids group, but without the lipid infusion for 5 days.	All infants were given 1 ml/day of a multivitamin preparation (LyphoMed). Power analysis Not reported. Statistical analyses Continuous data were reported as means (SDs); differences between treatment groups were analysed using analysis of variance. Where significant differences were observed, intergroup differences for a given variable were compared using one-tailed Student t test. Categorical data were compared between groups by means of chi-square test. Intention-to-treat (ITT) analysis Not reported.	Days to regain birth weight - mean ±SD Lipids: 19 (7) No lipids: 17 (6) Mortality - n (%) Lipids: 2 (10*) No lipids: 2 (9.1) Necrotising enterocolitis - n (%) Lipids: 2 (10*) No lipids: 0 (0) Retinopathy of prematurity - n/N Lipids: 8/11 No lipids: 4/17; p<0.05	bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: The authors stated that infants were randomised using a computer-generated randomisation procedure; treatment assigned using sealed envelopes from a group of previously randomised cards (low risk of bias). Performance bias: The authors stated that due to the obvious recognisability of the Vitrum, the study could not be conducted in a double-blind fashion; participants were neonates and blinding was therefore not applicable (high risk of bias). Detection bias: The authors did not provide details on blinding of outcome assessors (unclear risk of bias).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria • Infants who were expected to receive enteral nutrition within the first week of life; • Infants who were not candidates for Vitrum infusion (e.g. severe hyperbilirubinaemia); • Receiving indomethacin.				Attrition bias: The authors did not report attrition rates or exclusion of infants (unclear risk of bias). Reporting bias: Pre-specified outcomes reported; it was unclear why some outcomes were only reported in a proportion of participants (unclear risk of bias). Other bias: There was insufficient information to determine whether an important risk of bias exists (unclear risk of bias). Other information None of the infants received enteral feedings for the duration of the study. *calculated.
Full citation Kao, L. C., Cheng, M. H., Warburton, D., Triglycerides, free fatty acids, free fatty acids/albumin molar ratio, and cholesterol levels in serum of	Sample size N=43* (continuous infusion: n=19; intermittent infusion: n=24) Characteristics <u>Sex (males) - n</u>	Interventions Continuous: As per intermittent infusion, but over 24 hours per day. Intermittent: 8 hrs/day lipid infusion (Intralipid 10%) at a starting dose	Details Lipid solution was infused via either a peripheral vein or an umbilical catheter. All neonates had umbilical catheters in place and received a continuous	Results <u>Sepsis - n/N (%)</u> Continuous: <32 weeks: 1/9 (11.11**); ≥32 weeks: 0/10 (0) Intermittent: <32 weeks: 3/14 (21.4**); ≥32 weeks: 1/10 (10**)	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
neonates receiving long-term lipid infusions: controlled trial of continuous and intermittent regimens, The Journal of pediatrics, 104, 429-35, 1984 Ref Id 606432 Country/ies where the study was carried out USA Study type Randomised controlled trial Aim of the study To compare the effects of two different lipid infusion regimens in neonates and to determine the optimal regimen. Study dates January 1982 to September 1982.	13 Gestational age (weeks) - mean ±SD Continuous: <32 weeks: 28.3 (0.3); ≥32 weeks: 33.5 (1.2) Intermittent: <32 weeks: 28.4 (0.4); ≥32 weeks: 35.3 (1.4) Birth weight (kg) - mean ±SD Continuous: <32 weeks: 1.1 (0.1); ≥32 weeks: 1.9 (0.2) Intermittent: <32 weeks: 1.1 (0.1); ≥32 weeks: 2.3 (0.2) Inclusion criteria • Neonates with weight appropriate for gestational age; • Had not been fed; • Tolerated intravenous parenteral nutrition consisting of glucose and amino acids solutions;	of 0.5 g/kg/day, increasing incrementally by 0.5 g/kg/day to either 3 g/kg/day or until fat contributed to 40% of daily calories.	low dose of heparin (1 U/ml infusate). Power analysis Not reported. Statistical analyses Serum triglycerides were compared at different timepoints using the Student unpaired t test. Differences in rates of complications in infants <32 and ≥32 weeks post-conception receiving intermittent or continuous regimens was assessed using the chi-square test. Intention-to-treat (ITT) analysis Not reported.	Mortality - n (%) Continuous: <32 weeks: 0/9 (0); ≥32 weeks: 0/10 (0) Intermittent: <32 weeks: 1/14 (7.14**); ≥32 weeks: 0/10 (0)	Selection bias: The authors did not provide details on methods used to generate and conceal allocation sequence (unclear risk of bias). Performance bias: The authors did not provide details on blinding of personnel; participants were neonates and blinding was therefore not applicable (unclear risk of bias). Detection bias: The authors did not provide details on blinding of outcome assessors (unclear risk of bias). Attrition bias: It was unclear how many infants were included in the study; the authors stated that 28 infants were included in the study, but data also suggests a total of 43 infants (unclear risk of bias). Reporting bias: Pre-specified outcomes were reported; attrition and exclusions were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding One author supported in part by the National Institutes of Health.	• Stable or improving respiratory status for at least 48 hours; • Serum total bilirubin concentration <6 mg/dl and platelet count >100,000/μL. Exclusion criteria Not reported.				not discussed (unclear risk of bias). Other bias: There was insufficient information to determine whether an important risk of bias exists (unclear risk of bias). Other information *Authors report n=28, but Table 1 (characteristics of neonates) suggests n=43. **calculated. No enteral feedings were given during the study.
Full citation Levit, O. L., Calkins, K. L., Gibson, L. C., Kelley-Quon, L., Robinson, D. T., Elashoff, D. A., Grogan, T. R., Li, N., Bizzarro, M. J., Ehrenkranz, R. A., Low-dose intravenous soybean oil emulsion for prevention of cholestasis in preterm neonates, Journal of Parenteral	Sample size N=136 (High dose: n=67; Low dose: n=69) N= 127 analysed for primary outcome (High dose: n=62; Low dose: n=65) Characteristics <u>Gestational age (weeks) - mean ±SD</u> High dose: 26 (2) Low dose: 27 (2) <u>Birth weight (g) - mean ±SD</u>	Interventions High dose: Received S-IFE advanced by 0.5 to 1 g/kg/day to a target dose of approximately 3 g/kg/day. Low dose: Received a maximum of S-IFE dose of 1 g/kg/day.	Details S-IFE provided as Liposyn II 20% or Intralipid 20%. Parenteral nutrition (PN) prescribed according to routine practice. For infants in the control group, S-IFE dose could be reduced to approximately 1.5 g/kg/day if receiving	Results <u>Weight (g/week) at day 28 - mean ±SD</u> High dose (n=61): 66 (34) Low dose (n=67): 63 (39) <u>Weight at discharge (g/week) - mean ±SD</u> High dose (n=61): 140 (30) Low dose (n=62): 140 (28)	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: The authors stated that treatment assignment was conducted using sequentially numbered, sealed opaque envelopes containing

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and Enteral Nutrition, 40, 374-382, 2016 Ref Id 689356 Country/ies where the study was carried out USA Study type Randomised controlled trial Aim of the study To investigate whether low dose soybean-based intravenous fat emulsions (S-IFE) is safe and effective in preventing cholestasis in preterm neonates. Study dates May 2009 to November 2012. Source of funding Partially supported by the National Institute for Health. Authors received funding from	High dose: 930 (286) Low dose: 904 (279) Small for gestational age - n (%) High dose: 11 (16) Low dose: 17 (25) Multiple gestation - n (%) High dose: 13 (19) Low dose: 21 (30) Inclusion criteria • Infants with a gestational age ≤29 weeks; • <48 hours of age. Exclusion criteria • Infants with known chromosomal abnormality; • Congenital intrauterine infection; • Structural liver abnormality;		>75% of calories from enteral nutrition (EN). Full enteral feeds were defined as PN discontinuation. Power analysis To achieve 80% power, 65 infants were required in each treatment group; to account for early deaths and loss to follow-up, the sample size required was 136. Statistical analyses Categorical data were analysed using the Chi-square test or Fisher exact test. Differences in continuous data were assessed using the Student t test or Wilcoxon rank sum test. Intention-to-treat (ITT) analysis ITT analysis conducted.	Length (cm/week) at day 28 - mean ±SD High dose (n=61): 0.8 (0.5) Low dose (n=61): 0.9 (0.5) Length at discharge (cm/week) - mean ±SD High dose (n=61): 0.9 (0.3) Low dose (n=63): 1.1 (0.7) Head circumference at day 28 (cm/week) - mean ±SD High dose (n=61): 0.5 (0.3) Low dose (n=61): 0.6 (0.3) Head circumference at discharge (cm/week) - mean ±SD High dose (n=61): 0.7 (0.2) Low dose (n=61): 0.8 (0.4) Sepsis - n/N High dose: 3*/67 Low dose: 5*/69 Cholestasis** - n/N (%) High dose: 39/67 (63) Low dose: 45/69 (69)	computer-generated random numbers with a block size of 4 (low risk of bias). Performance bias: The authors did not provide details on blinding of personnel; participants were neonates and blinding was therefore not applicable (unclear risk of bias). Detection bias: The authors did not provide details on blinding of outcome assessors (unclear risk of bias). Attrition bias: The authors stated that 1 infant was lost to follow-up, 9 infants (total n=7.4%) did not have laboratory data available for the primary outcome (low risk of bias). Reporting bias: Pre-specified outcomes were reported; attrition/exclusions were discussed; however, it was unclear why outcomes were not always reported in all

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
the National Institute for Health, Today's and Tomorrow's Children Fund, Mattel Children's Hospital, University of California, the National Centre for Advancing Translational Sciences.	• Terminal illness.			Mortality - n/N High dose: 5*/67 Low dose: 5*/69 Duration of hospital stay (days) - mean ±SD High dose: Liposyn II 20% (n=48) 84 (38); Intralipid 20% (n=19) 84 (30) Low dose: Liposyn II 20% (n=49) 91 (43); Intralipid 20% (n=20) 104 (68) Necrotising enterocolitis - n/N High dose: 8*/67 Low dose: 11*/69 Retinopathy of prematurity - n/N High dose: 7*/67 Low dose: 9*/69	infants (unclear risk of bias). Other bias: Unclear whether enteral feedings may have impacted on outcomes in babies receiving this (unclear risk of bias). Other information *calculated. **Defined as serum direct bilirubin [DB]/total bilirubin [TB] ≥15% after 14 PN days) at day of life (DOL) 28 or full enteral feeds, whichever was later.
Full citation Murdock, N., Crighton, A., Nelson, L. M., Forsyth, J. S., Low birthweight infants and total parenteral nutrition immediately after birth. II. Randomised study of biochemical tolerance of intravenous glucose, amino acids, and lipid, Archives of disease in	Sample size N=44 (n=29 analysed) Glucose 10%/amino acids/lipid: n=8 Glucose 10%: n=10 Glucose 10%/amino acids: n=11 Characteristics Sex (male/female) - number	Interventions Glucose 10%/amino acids/lipid (Vamin 9): Lipids were given at 1g/kg/day. Glucose was given at 7g/kg/day on day 1 and increased to 10g/kg/day. Amino acids were given at 1g/kg/day and increased to 1.4g/kg/day.	Details Infants were randomised to one of three intravenous fluid regimens; fluid intakes were altered by the Clinicians if clinically indicated. Infants fed more than 1 ml/hour of expressed breast milk or formula	Results Hypoglycaemia requiring an increase in glucose* - number of days during each regimen in which hypoglycaemia protocol initiated Glucose 10%/amino acids/lipid: 2 Glucose 10%: 6 Glucose 10%/amino acids: 9	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: The authors did not provide details on methods used to generate and conceal allocation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
childhood. Fetal and neonatal edition, 73, F8-12, 1995 Ref Id 606507 Country/ies where the study was carried out Scotland Study type Randomised controlled trial Aim of the study To compare the tolerance of three parenteral nutrition regimens within the first 48 hours of life in low birth weight infants. Study dates Not reported. Source of funding Chest, Heart and Stroke Association (Scotland) and the Scottish Home and Health Department.	Glucose 10%/amino acids/lipid: 4/4 Glucose 10%: 7/4 Glucose 10%/amino acids: 9/1 Gestational age (weeks) - mean (SE) Glucose 10%/amino acids/lipids: 31.8 (0.6) Glucose 10%: 31.0 (0.7) Glucose 10%/amino acids: 32.8 (0.9) Birth weight (g) - mean (SE) Glucose 10%/amino acids/lipids: 1635 (108) Glucose 10%: 1340 (97) Glucose 10%/amino acids: 1498 (97) Inclusion criteria • Infants weighing <2000 g at birth; • Cannot receive enteral feeds immediately after birth. Exclusion criteria	Glucose 10%/amino acids (Vamin 9): No lipids were given. Glucose was given at 7g/kg/day on day 1 and increased to 10g/kg/day. Amino acids were given at 1g/kg/day and increased to 1.4g/kg/day. Glucose 10%: No lipids or amino acids were give. Glucose was given at 7g/kg/day on day 1 and increased to 10g/kg/day.	were withdrawn from the study. Power analysis Not reported. Statistical analyses Not reported. Intention-to-treat (ITT) analysis Not reported.		sequence (unclear risk of bias). Performance bias: The authors did not provide details on blinding of personnel; participants were neonates and blinding was therefore not applicable (unclear risk of bias). Detection bias: The authors did not provide details on blinding of outcome assessors (unclear risk of bias). Attrition bias: The authors stated that 15 infants (34%) were withdrawn due to rapid progression to milk feeding (high risk of bias). Reporting bias: Pre-specified outcomes were reported; attrition/exclusions were discussed (low risk of bias). Other bias: There was insufficient information to determine whether an important risk of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Not reported.				bias exists (unclear risk of bias). Other information *Days on which intervention initiated used a proxy measure for number of infants with hypoglycaemia requiring an increase in glucose. Phototherapy was administered to infants, if required: Glucose 10%/amino acids/lipids: n=5 Glucose 10%: n=9 Glucose 10%/amino acids: n=8
Full citation Ong, Margaret L., Purdy, Isabell B., Levit, Orly L., Robinson, Daniel T., Grogan, Tristan, Flores, Martiniano, Calkins, Kara L., Two-Year Neurodevelopment and Growth Outcomes for Preterm Neonates Who Received Low-Dose Intravenous Soybean Oil, JPEN. Journal of	Sample size N=30 (high dose: n=15; low dose: n=15) Characteristics Gestational age (weeks) - mean ±SD High dose: 27 (1) Low dose: 28 (1) Birth weight (g) - mean ±SD High dose: 1023 (306) Low dose: 1033 (279)	Interventions High dose: see Levit (2016) Low dose: see Levit (2016)	Details The primary medical team, using standard NICE guidelines, dictated medical care, enteral nutrition (EN), parenteral nutrition (PN) prescription, with the exception of SO dose. PN was infused continuously for 24 hours. Maternal breast milk encouraged, or donor	Results Neurodevelopment at 2 years follow-up Frequency of low developmental domain scores <1 SD below the normative mean (composite score <85) - n (%) Cognitive High dose: 2 (14) Low dose: 3 (27) Language High dose: 4 (29) Low dose: 2 (18)	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: See Levit (2016). Performance bias: See Levit (2016). Detection bias: The authors stated that

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
parenteral and enteral nutrition, 2016 Ref Id 689598 Country/ies where the study was carried out USA Study type Prospective follow-up study to Levit 2016 (randomised controlled trial) Aim of the study To investigate the impact of low dose soybean-based intravenous fat emulsions (S-IFE) on neurodevelopment and growth over the first 2 years of age in preterm neonates. Study dates Not reported. Source of funding	<u>Length (cm) - mean ±SD</u> High dose: 36 (5) Low dose: 36 (3) <u>Head circumference (cm) - mean ±SD</u> High dose: 25 (2) Low dose: 25 (2) <u>Sex (male) - n (%)</u> High dose: 12 (63) Low dose: 14 (78) <u>Small for gestational age - n (%)</u> High dose: 3 (16) Low dose: 2 (11) <u>Sepsis - n (%)</u> High dose: early onset: 0 (0); late onset: 2 (11) Low dose: early onset: 0 (0); late onset: 1 (6) Inclusion criteria • ≤29 weeks gestational age; • <48 hours of age; • Infants with neurodevelopment and growth data points available for at least 1		breast milk until approximately 34 weeks corrected GA and/or a weight of 1500 g achieved. All infants received approximately 2 to 4 mg/kg/d of iron, along with 800 IU of vitamin D via EN and/or supplements. At discharge from the NICU, infants received fortified premature formula and breast mild or fortified premature formula exclusively (if breast milk not available), in addition to iron and vitamin D supplements. Power analysis See Levit (2016). Statistical analyses Continuous outcomes were analysed using the Student's t test. Categorical data were analysed using the Fisher's exact test. Comparative analyses between the 2 treatment groups for growth over time (from	<u>Motor</u> High dose: 1 (7) Low dose: 2 (18)	healthcare professionals performing the follow-up evaluations were unaware of treatment assignment (low risk of bias). Attrition bias: The authors stated that only 1 of 3 originally participating sites participated in the follow-up study; n=30 of 37 infants originally participating at this site completed follow-up (high risk of bias). Reporting bias: Pre-specified outcomes were reported; attrition/exclusions were discussed (low risk of bias). Other bias: See Levit (2016). Other information All infants were receiving full feeds prior to discharge from the NICU.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Support received from the University of California. Financial disclosures were reported by authors.	outpatient visit after discharge from the neonatal intensive care unit (NICU). Exclusion criteria • Congenital intrauterine infection; • Hepatic structural abnormalities; • Genetic disorders; • In-born errors of metabolism; • pH <6.8 at birth.		birth to 24 months), and total and parenteral energy, glucose infusion rates, and soybean oil dose over the first 28 days of age, were conducted using an autoregressive regression model with analysis of variance set up for time. To maximise the statistical power (given the small sample size), no additional confounding variables were included in the models. Univariate regression models were used to assess the association between birth weight and gestational age with Bayley Scales of Infant Development III (BSID-III) scores. Intention-to-treat (ITT) analysis ITT analysis conducted.		
Full citation Roelants, Jorine A., Vlaardingerbroek, Hester, van den Akker,	Sample size N=144 included in original trial (control group, n=48; AA plus lipids group, n=49; high	Interventions Control (Late): Glucose and standard AA continued during the first 2 days of life.	Details Immediately after birth, all infants received 6 mg/kg/min glucose and	Results <u>BSID-III motor score <70 - n/N</u> AA plus lipids: 1/45 Control: 2/44	Risk of bias assessed with Cochrane risk of bias tool for randomised trials

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Chris H. P., de Jonge, Rogier C. J., van Goudoever, Johannes B., Vermeulen, Marijn J., Two-Year Follow-up of a Randomized Controlled Nutrition Intervention Trial in Very Low-Birth-Weight Infants, JPEN. Journal of parenteral and enteral nutrition, 42, 122-131, 2018 Ref Id 1008764 Country/ies where the study was carried out The Netherlands Study type RCT Aim of the study To determine the effect of early and aggressive parenteral nutrition on long term (2 year) outcomes in very low birth weight (VLBW) babies. Study dates	AA plus lipids group, n=47 - high AA + lipid group is not relevant for this review question) N=134 included in follow-up (control group, n=44; AA plus lipids group, n=45; high AA plus lipids group, n=45; 2 infants excluded due to congenital anomaly, 8 infants lost to follow-up - high AA + lipid group is not relevant for this review question) Characteristics <u>Gestational age (weeks) - median (IQR)</u> AA + soybean (soy): 26^{+2} (25^{+2} to 28^{+1}) AA + mixed fat emulsions (mix): 27^{+1} (25^{+6} to 28^{+6}) Control: 27+3 (26^{+2} to 29^{+3}) <u>Small for gestational age at birth (<-2 standard deviation for weight) - number (%)</u> AA + soy: 0 (0) AA + mix: 0 (0) Control: 6 (14)	Lipids started at 1.4 g/kg/day on the second day of life and increased to 2.8 g/kg/day the next day. AA + lipids (Early): Glucose and AA continued during the first 2 days of life. Lipids started at 2 g/kg/day immediately after birth and increased to 3 g/kg/day on the second day of life.	2.4 g/kg/day) AA as standard care. Enteral feed included minimal enteral feeding at day 1 and a daily increase of approximately 20 mL/kg/day of enteral bolus feeding from day 2 or 3 onwards until 150 to 180 mL/kg/day reached. Power analysis Based on Vlaardingerbroek 2013; to achieve 80% power, 30 infants per treatment group were required. Accounting for expected losses to follow-up, 50% more infants per group were included. Statistical analyses Multivariate logistic or linear regression analysis used where appropriate to assess associations between interventions and outcomes; expressed as odds ratios (ORs) or effect sizes (β) with 95% confidence intervals (CIs). If count of outcomes was zero,	<u>BSID-III psychomotor score <70 - n/N</u> AA plus lipids: 1/45 Control: 2/44	Cochrane risk of bias tool Selection bias Random sequence generation: A computer-generated block randomisation list with variable block sizes was provided by a statistician. (Taken from Vlaardingerbroek 2013) (low risk). Allocation concealment: Sealed, opaque randomisation envelopes created by a research pharmacist (Taken from Vlaardingerbroek 2013) (low risk). Performance bias Blinding of participants and personnel: Study group randomisation was open after inclusion; participants were neonates and blinding was therefore not applicable. (Taken from Vlaardingerbroek 2013) (high risk). Detection bias Blinding of outcome assessment: Outcome assessors were blinded

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
December 2008 to January 2012. Source of funding MJN, Nestle Nutrition Institute, Danone, Nutricia, Hipp, Baxter, and United Pharmaceuticals.	Birth weight (g) - median (IQR) AA + soy: 808 (665 to 920) AA + mix: 846 (726 to 1000) Control: 863 (651 to 1013) Sex (male) - number (%) AA + soy: 10 (48) AA + mix: 11 (46) Control: 23 (52) Prenatal steroids (0/1/2 doses) - number (%) AA + soy: 1/2/18 (5/9/86) AA + mix: 0/9/15 (0/38/62) Control: 1/5/38 (2/11/87)* *1 mother received 4 doses of prenatal steroids. Inclusion criteria Inborn babies with birth weight <1500g. Exclusion criteria • Congenital anomalies; • Metabolic diseases;		univariate analysis was performed using Fisher's exact test. Confounders included in multivariate regression model were: gestational age at birth, birth weight standard deviation (SD) score, sex, and socioeconomic status SD scores. Differences between groups in mental and psychomotor scores were assessed using univariate analysis (Kruskal-Wallis) and multivariate analysis (linear regression). No correction for multiple testing was applied. Intention-to-treat (ITT) analysis ITT analysis conducted.		to treatment allocation (low risk). Attrition bias Incomplete outcome data: Number of infants lost to follow-up were minimal and similar between groups (low risk). Reporting bias Selective reporting: Protocol registered and pre-specified outcomes are reported (TrialRegister.nl: NTR1445) (low risk). Other bias Other sources of bias: It is unclear what effect the use of enteral feeds may have had on the outcomes (unclear risk) Other information Long term follow-up of Vlaardingerbroek 2013. Study underpowered and intervention may have been too short to produce lasting differences in neurodevelopmental outcomes.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Renal, hepatic or endocrine ano malies; • Other disorders interfering with growth or neurodevelopm ent.				
Full citation Shouman, B., Abdel-Hady, H., Badr, R. I., Hammad, E., Salama, M. F., Dose of intravenous lipids and rate of bacterial clearance in preterm infants with blood stream infections, European Journal of Pediatrics, 171, 811-6, 2012 Ref Id 668007 Country/ies where the study was carried out Egypt Study type Randomised controlled trial	Sample size N=42 (standard dose: n=22; restricted dose: n=20) Characteristics Gestational age (weeks) - mean ±SD Standard dose: 32.3 (2.51) Restricted dose: 31.7 (2.6) Birth weight (g) - mean ±SD Standard dose: 1423.6 (330.3) Restricted dose: 1469.0 (517.0) Sex (male) - n (%) Standard dose: 14 (63.6) Restricted dose: 9 (45)	Interventions Standard dose: IV lipids according to unit's standard protocol (starting at 0.5 $g/kg^{-1}/day^{-1}$ on first day of TPN and gradually increasing by 1 $g/kg^{-1}/day^{-1}$ to a maximum of 3.5 $g/kg^{-1}/day^{-1}$. Restricted dose: IV lipids 1 $g/kg^{-1}/day^{-1}$ until a negative blood culture was obtained where the dose of IV lipids was modified according to the amount of enteral feed received.	Details TPN prepared by a designated nurse and administered as an "all-in-one" admixture prepared daily following usual hospital practices, except for intravenous lipid emulsion (IVLE). Admixtures were delivered through peripheral or central catheters at a constant (pump-controlled) rate for 24 hours per day. All patients received similar amino acid solutions and the same amounts of vitamins. IV lipids were SMOF lipid 20% containing soybean oil, medium-chain triglycerides, olive oil, and fish oil.	Results Daily weight gain (g/day) - median (interquartile range; IQR) Restricted dose: 0.9 (-3.3 to 11.7) Standard dose: 25 (6.9 to 31.9); p=0.0001 Mortality - n (%) Restricted dose: 2 (10) Standard dose: 3 (13.6); p=0.72 Duration of hospitalisation (days) - mean ±SD Restricted dose: 31.4 (20.2) Standard dose: 37.3 (22.5); p=0.38	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: Infants were randomised using cards provided in consecutively numbered, opaque, sealed envelopes (low risk of bias). Performance bias: Nurses and doctors caring for infants were blind to treatment allocation; participants were neonates and blinding was therefore not applicable (low risk of bias).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess whether a restricted dose of intravenous (IV) lipids reduces the time of clearance of bacteria in preterm infants with blood stream infections (BSI). Study dates September 2008 to April 2010. Source of funding None stated.	Weight at randomization (g) - mean ±SD Standard dose: 1415.5 (361.2) Restricted dose: 1502.3 (471.7) Length at randomisation (cm) - mean ±SD Standard dose: 39.1 (2.3) Restricted dose: 38.8 (4.6) Head circumference at randomisation (cm) - mean ±SD Standard dose: 29 (2.1) Restricted dose: 28.5 (3.1) Inclusion criteria • Consecutive preterm infants meeting the criteria for BSI*; • Receiving total parenteral nutrition (TPN). Exclusion criteria Newborns with:		Power analysis Not reported. Statistical analyses Group comparisons of normally distributed data were analysed using independent t tests. The Mann-Whitney U-test was used to compare non-normally distributed data. Comparisons of categorical data were analysed using the chi-square test or Fisher's exact test. Intention-to-treat (ITT) analysis Not reported.		Detection bias: The authors did not provide details on blinding of outcome assessors (unclear risk of bias). Attrition bias: No loss to follow-up reported (low risk of bias). Reporting bias: Pre-specified outcomes were reported; no attrition/exclusions were reported (low risk of bias). Other bias: It is unclear what effect the use of different antibiotic treatments for early or late sepsis, or the use of enteral feeds may have had on the outcomes (unclear risk of bias). Other information *Defined according to Centre for Disease Control criteria as manifested by clinical evidence of sepsis in the presence of a documented positive blood culture. Antibiotics were started; including combinations of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Severe malformations; • Inborn errors of metabolism; • Symptoms of congenital infection.				penicillin with gentamicin in early-onset sepsis, and flucloxacillin with either gentamycin or cefotaxime in late-onset sepsis. Antibiotics continued until clinical signs of sepsis subsided, a negative blood culture was obtained and C-reactive protein was normalised (<4.82 mg/l). The authors stated that hypertriglyceridemia was not detected in preterm infants with BSI who received full-dose IV lipids.
Full citation Sosenko, I. R., Rodriguez-Pierce, M., Bancalari, E., Effect of early initiation of intravenous lipid administration on the incidence and severity of chronic lung disease in premature infants, The Journal of pediatrics, 123, 975-82, 1993	Sample size N=133 600 to 800 g weight infants Early Intralipids: n=42 Control: n=37 801 to 1000 g weight infants Early Intralipids: n=28 Control: n=26 Characteristics Birth weight (g) - mean	Interventions Early Intralipids: 20% Intralipid starting at <12 postnatal hours at 0.5 g/kg for the first 24 hours and increasing by 0.5 g/kg every 24 hours until reaching 1.5 g/kg, and then maintained to day 7. Lipid infusions were maintained for a 24 hour period.	Details All infants received vitamin E, 3 units/kg/day, in IV administered multivitamins, consisting of MVI-12 R (Armour), 3 ml/kg/day added to the maintenance fluids, and approximately 990 units of vitamin A. Initiation of amino acids was started at days 2	Results Mortality during first 28 days - n/N (%)* 600 to 800 g Early Intralipids: 18/42 (42.9**) Control: 7/37 (18.9**) 801 to 1000 g Early Intralipids: 3/28 (10.7**) Control: 5/26 (19.2**) Mortality >28 days - n (%)	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: Infants were randomised using cards provided in consecutively numbered, opaque,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 606587 Country/ies where the study was carried out USA Study type Randomised controlled trial Aim of the study To assess the effects of intravenous (IV) lipids in the first 12 hours after birth on the incidence and/or severity of chronic lung disease in oxygen and/or ventilator-dependent premature infants. Study dates March 1990 to December 1991. Source of funding March of Dimes and University of Miami Project Newborn.	600 to 800 g Early Intralipids: 709 Control: 708 801 to 1000 g Early Intralipids: 915 Control: 888 Sex (male) - % 600 to 800 g Early Intralipids: 40 Control: 49 801 to 1000 g Early Intralipids: 64 Control: 65 Illicit drug use - % 600 to 800 g Early Intralipids: 24 Control: 11 801 to 1000 g Early Intralipids: 7 Control: 11 Tocolytic administration - % 600 to 800 g Early Intralipids: 36 Control: 46 801 to 1000 g Early Intralipids: 39 Control: 42 Maternal corticosteroids - % 600 to 800g Early Intralipids: 7 Control: 30; p=0.016 801 to 1000g Early Intralipids: 11	Control: Received Intralipids from day 7.	or 3 in both treatment groups. Neither group received enteral feeding until after day 7. Power analysis To achieve 80% power, 46 infants were required in each group for infants weighing 600 to 800 g, and 95 infants in group for infants weighing 801 to 1000 g. Statistical analyses Treatment group comparisons, stratified by birth weight, were analysed using Student t test for unpaired data. The chi-square test was used to identify any differences in proportions. Mantel-Haenszel adjustment was performed to correct for effects of inequality of confounding variables between groups. Multivariate logistic regression analyses were performed to assess all variables simultaneously and	600 to 800 g Early Intralipids: 2/42 (4.8**) Control: 2/37 (5.4**) 801 to 1000 g Early Intralipids: 0/28 (0) Control: 2/26 (7.7) Necrotising enterocolitis - n (%) 600 to 800 g Early Intralipids: 3/42* (7) Control: 5/37* (14) 801 to 1000 g Early Intralipids: 2/28* (7) Control: 3/26* (11)	sealed envelopes (low risk of bias). Performance bias: The authors stated that the study was not blinded; participants were neonates and blinding was therefore not applicable (high risk of bias). Detection bias: The authors stated that personnel involved in data analysis, and chest x-ray interpretation were not aware of treatment group assignment (low risk of bias). Attrition bias: No loss to follow-up (other than deaths) reported (low risk of bias). Reporting bias: Data for certain outcomes (e.g. amount of weight lost after birth, duration of hospital stay) were not presented in the paper, reasons for this were not provided; 1 infant not included for mortality in 600 to 800 g early lipids treatment

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Control: 19 Inclusion criteria • Inborn infants weighing between 600 and 1000 g at birth; • Requiring mechanical ventilation at 6 postnatal hours for infants weighing 600 to 800 g; • Requiring mechanical ventilation plus supplemental oxygen at 6 postnatal hours for infants weighing 801 to 1000g. Exclusion criteria • Infants weighing <600 g due to high mortality rates; • Infants weighting >1000g due to low incidence		determine possible interactions. Intention-to-treat (ITT) analysis ITT analysis performed.		group (high risk of bias). Other bias: The study was terminated due to the higher mortality rate in infants weighing 600 to 800 g and receiving Intralipid (unclear risk of bias). Other information Due to the potential role that fluid intake in the first week may play in the development of chronic lung disease, infants received the minimal total daily fluid intake (e.g. infants started on daily fluid intake between 80 and 100 ml/kg/day); increases were based on assessments of their fluid and electrolyte balance to ensure adequate hydration and electrolyte status. *Causes of death included respiratory failure, CNS haemorrhage, asphyxia, pulmonary haemorrhage,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	of chronic lung disease (<6% at the study institution); • Major congenital anomalies; • Clinical evidence of congenital infection; • Previability or terminal condition or both; • Lack of informed consent from parents.				pneumothorax, sepsis, necrotising enterocolitis, undiagnosed congenital anomaly, renal failure, hepatobiliary disease. **Calculated.
Full citation Vlaardingerbroek, H., Vermeulen, M. J., Rook, D., Van Den Akker, C. H. P., Dorst, K., Wattimena, J. L., Vermes, A., Schierbeek, H., Van Goudoever, J. B., Safety and efficacy of early parenteral lipid and high-dose amino acid administration to very low birth weight infants, Journal of	Sample size N=144 (Intervention 1: n=49; Intervention 2: 47; control: n=48) Characteristics Gestational age (weeks) - mean ±SD Intervention 1: 27.2 (2.2) Intervention 2: 27.2 (2.1) Control: 27.8 (2.3)	Interventions Intervention group 1: Infants received glucose and amino acids (AA) 2.4 g/kg^{-1}/day^{-1}, with lipids started soon after birth (starting dose of 2 g/kg^{-1}/day^{-1}, increased the next day to 3 g/kg^{-1}/day^{-1}). Intervention group 2: In addition to glucose from birth, infants received high-dose AA	Details All infants received glucose (at least 4.0 mg/kg^{-1}/min^{-1}) and 2.4 g/kg^{-1}/day^{-1} of AA as part of standard clinical care. Infants in the control group received Intralipid 20%; infants in the intervention groups were randomised to receive	Results Weight gain at discharge (g/kg^{-1}/day^{-1}) - mean ±SD Intervention 1: 25.0 (5.2) Intervention 2: 27.0 (7.3) Control: 25.8 (8.1) Head circumference gain at discharge (mm/week) - mean ±SD Intervention 1: 8.1 (1.5) Intervention 2: 8.4 (1.3)	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: Infants were randomised using opaque, sealed envelopes stratified for weight and sex; envelopes were created by a research

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Pediatrics, 163, 638, 2013 Ref Id 690133 Country/ies where the study was carried out The Netherlands Study type Randomised controlled trial Aim of the study To evaluate the safety and efficacy in providing early parenteral lipid and high-dose amino acid to very low birth weight infants. Study dates December 2008 to January 2012. Source of funding Not reported.	Birth weight (g) - mean ±SD Intervention 1: 876 (209) Intervention 2: 867 (223) Control: 843 (224) Sex (male/female) n/n Intervention 1: 19/30 Intervention 2: 21/25 Control: 25/23 Small for gestational age* - n (%) Intervention 1: 18 (37) Intervention 2: 20 (43) Control: 25 (52) *Birth weight z-score <-2. Inclusion criteria • Inborn, very low birth weight (VLBW) infants; • Birth weight <1500 g; • Central venous catheter in place to allow for more concentrated glucose solutions and	(3.6 $g/kg^{-1}/day^{-1}$ from birth onwards) and lipids (starting dose of 2 $g/kg^{-1}/day^{-1}$, increased the next day to 3 $g/kg^{-1}/day^{-1}$). Control: Infants received glucose and amino acids (AA) (2.4 $g/kg^{-1}/day^{-1}$) during the first 2 days of life. Lipids were started on day 2 of life at 1.4 $g/kg^{-1}/day^{-1}$ and increased the following day to 2.8 $g/kg^{-1}/day^{-1}$.	either Intralipid 20% or SMOFlipid 20%. Power analysis To achieve 80% power, 30 infants per treatment group were required. Accounting for expected losses to follow-up and practical limitations, 50% more infants per group were included. Statistical analyses Linear regression analysis was conducted to calculate mean length gain (mm/day) for each infant. Between group differences were analysed using chi-square test and a one-way ANOVA with Bonferroni correction for multiple testing, as appropriate. Mixed models and logistic regression analyses were used to test for significant changes in time and to correct for the potential influence of sex, gestational age, and small for gestational age.	Control: 8.3 (1.3) Late-onset sepsis - n (%) Intervention 1: 16 (34) Intervention 2: 17 (35) Control: 8 (17) Mortality - n (%) Intervention 1: 7 (15) Intervention 2: 10 (21) Control: 5 (10) Duration of hospital stay (days) - mean ±SD Intervention 1: 94.3 (31.3) Intervention 2: 86.5 (29.1) Control: 91.0 (39.9) Necrotising enterocolitis (≥grade 2) - n (%) Intervention 1: 1 (2) Intervention 2: 4 (8) Control: 2 (4) Retinopathy of prematurity ≥grade 3 - n (%) Intervention 1: 0 (0) Intervention 2: 2 (4) Control: 2 (4)	pharmacist not involved in the care of infants and were based on computer-generated block randomisation lists with variable block sizes (low risk of bias). Performance bias: The authors stated that all technicians were blinded for study group treatment throughout the study and analyses; participants were neonates and blinding was therefore not applicable (low risk of bias). Detection bias: The authors stated that all technicians were blinded for study group treatment throughout the study and analyses (low risk of bias). Attrition bias: 2 infants (1.4%) discontinued interventions at follow-up (low risk of bias). Reporting bias: Pre-specified outcomes were reported; attrition/exclusions

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	to restrict total fluid intake. Exclusion criteria • Infants with congenital anomalies (including chromosome defects and known metabolic diseases; • Infants with endocrine, renal, or hepatic disorders.		Intention-to-treat (ITT) analysis ITT analysis conducted.		were reported (low risk of bias). Other bias: It is unclear what effect the use of enteral feeds may have had on the outcomes (unclear risk of bias). Other information All infants received minimal enteral nutrition (EN) on the day of birth, which was advanced to full EN, according to the local protocol. After the third day of life, the nutritional regimen, including EN, was at the discretion of the physician. Repeated blood glucose concentrations >10 mmol/L (180 mg/dL) were treated with continuous intravenous insulin (starting dose 0.1 U/kg^{-1}/hour^{-1}), if reducing the glucose infusion rate to a minimal intake of 4 mg/kg^{-1}/min^{-1} was not effective.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Wilson, DC, Cairns, P, Halliday, HL, Reid, M, McClure, G, Dodge, JA, Randomised controlled trial of an aggressive nutritional regimen in sick very low birthweight infants, Archives of Disease in Childhood, 77, F4-F11, 1997 Ref Id 1007716 Country/ies where the study was carried out Northern Ireland Study type Randomised controlled trial Aim of the study To compare the effects of two different nutritional interventions in sick very low birth weight (VLBW) infants. Study dates	Sample size N=125 (Aggressive PN: n=64; control: n=61) Characteristics <u>Gestational age (weeks) - mean ±SD</u> Aggressive PN: 27.0 (2.4) Control: 27.4 (2.3) <u>Birth weight (g) - mean ±SD</u> Aggressive PN: 925 (221) Control: 933 (242) <u>Sex (male) - n (%)</u> Aggressive PN: 34 (53) Control: 32 (52) <u>Small for gestational age (<10th percentile) - n (%)</u> Aggressive PN: 19 (30) Control: 19 (31) <u>Maternal steroids - n (%)</u> Aggressive PN: 33 (52) Control: 41 (67) Inclusion criteria	Interventions Aggressive PN: Fluid intake similar to control group. Carbohydrates started at 4.2 to 5.5 mg/kg/min on day 1, with small increments permitted until PN fluids maximally equivalent to 12.5% dextrose solution by peripheral catheter or 15% dextrose solution by central catheter. AA started at 0.5 g/kg/day at 12 hours, increasing by 0.5 g/kg/day to a maximum of 2.5 g/kg/day (if energy intake <80 kcal/kg/day) or 3.5 g/kg/day (if energy intake >80 kcal/kg/day). Lipid emulsion started at 0.5 g/kg/day on day 2 (10% Lipofundin medium chain triglyceride/long chain triglyceride; MCT/LCT), increased by a maximum of 0.5 g/kg/day to 2 g/kg/day. Emulsion then changed to 20% Lipofundin MCT/LCT and dose	Details Aggressive PN: EN given at 0.5 ml/hour on day 1 and gradually increased as clinical state improved. Control: Enteral feed of choice was mother's milk, or if not available, preterm formula was used. Enteral nutrition (EN) started when infants clinically stable, and stopped in the event of respiratory deterioration or abdominal distension. Power analysis To achieve 80% power, and with an estimated survival rate of 75% for sick VLBW infants, 130 infants were required. Statistical analyses Normally distributed data were analysed using Student's t test and other continuous data were analysed using the Mann-Whitney U test.	Results <u>Time to regain birth weight (days) - median (interquartile range; IQR)</u> Aggressive PN (n=64): 9 (6 to 11) Control (n=61): 12 (9 to 17); p<0.001 <u>Final weight (g) (at discharge/death) - mean ±SD</u> Aggressive PN: 2111 (904) Control: 2080 (809) <u>Final length (cm) (at discharge/death) - mean ±SD</u> Aggressive PN: 43.0 (6.3) Control: 42.8 (5.9) <u>Final head circumference (cm) (at discharge/death) - mean ±SD</u> Aggressive PN: 31.4 (5.0) Control: 31.5 (4.5) <u>Sepsis - n (%)</u> Aggressive PN: 32 (50) Control: 40 (66) <u>Cholestasis - n (%)</u>	Risk of bias assessed with Cochrane risk of bias tool for randomised trials Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: Infants were randomised through computer generation with stratification to ensure equal numbers of extremely low birth weight and small for gestational age infants in each treatment group; sealed envelopes used to randomise infants by stratified group (low risk of bias). Performance bias: The authors stated that it was not possible to blind treatment group assignment; participants were neonates and blinding was therefore not applicable (unclear risk of bias).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
April 1990 (for 25 months). Source of funding One author was supported by a Royal Belfast Hospital for Sick Children Research Fellowship and grants from the Northern Ireland Mother and Baby Appeal, Perinatal Trust Fund of Northern Ireland, the Bryson Bequest and the Dina Kohner Fund of the Queen's University of Belfast and B Braun Melsungen AG.	• Infants weighing <1200 g at birth, born in or transferred to a neonatal intensive care unit on the first postnatal day; • Infants weighing 1200 to 1499 g requiring mechanical ventilation within 24 hours of birth. Exclusion criteria • Infants with major congenital anomalies.	increased by 0.5 g/kg/day to a maximum of 3.5 g/kg/day. Parenteral vitamins, trace elements, and minerals similar to control group. Control: Fluids started at 60 to 80 mg/kg/day and increased to 150 to 180 ml/kg/day by day 6. Carbohydrates were started at 4.2 to 5.5 mg/kg/min on day 1, increasing to a maximum of 10 to 12 mg/kg/min by day 7. Amino acids (AA) started at 1 g/kg/day on day 3 and increased by 0.5 g/kg/day to a maximum of 2.5 g/kg/day. AA stopped when enteral feeds comprised 67% of intake. Lipid emulsion introduced as 0.5 g/kg/day of 10% Intralipid on day 5 and increased by 0.5 g/kg/day to a maximum of 2 g/kg/day. Lipids	Categorical data were analysed using the chi-square test. Multivariate analysis was conducted using logistic regression, with results transformed to odds ratios and 95% confidence intervals (CIs) for adverse outcomes. Intention-to-treat (ITT) analysis Not reported.	Aggressive PN: 3 (5) Control: 2 (3) <u>Mortality - n/N</u> Aggressive PN: 15/64 Control: 15/61 <u>Hospital stay (days)* - median (IQR)</u> Aggressive PN: 61 (24 to 87) Control: 60 (36 to 86) <u>Hypertriglyceridemia (≥1 episode) - n (%)</u> Aggressive PN: 22 (43) Control: 18 (33)	Detection bias: The authors stated that it was not possible to blind treatment group assignment and clinical outcomes were therefore pre-defined; outcomes were objective (low risk of bias). Attrition bias: No loss to follow-up (other than deaths) was reported (low risk of bias). Reporting bias: Certain pre-specified outcomes were reported in surviving infants (i.e. babies who died were excluded from the analysis); data for some outcomes were not presented (unclear risk of bias). Other bias: It is unclear what effect the use of enteral feeds may have had on the outcomes; the authors stated that their sample size calculation may have been based on inaccurate estimates (unclear risk of bias).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		stopped when enteral feeds comprised 50% of intake. Lipids were infused for 20 hours a day. Parenteral minerals supplied from day 2 of life. Fat soluble vitamins given as an additive to the lipid emulsion. Water soluble vitamins and trace elements given from day 5 of life.			Other information *Defined as duration of time in days to death or hospital discharge.

AA: amino acids; AGA: appropriate for gestational age; ANOVA: analysis of variance; BSID-III: Bayley scales of infant development III: CI: confidence interval; CNLD: chronic neonatal lung disease; CNS: central nervous system; DB: direct bilirugin; DOL: day of life; EN: enteral nutrition; IQR: interquartile range; ITT: intention-to-treat; IV: intravenous; IVFE: invtravenous fat emulsions; IVL: intravenous lipids; LCT: long chain triglyceride; MCT: medium chain triglyceride; N: number; NICE: National Institute for Health and Care Excellence; NICU: neonatal intensive care unit; OR: odds ratio; PN: parenteral nutrition; RR: relative risk; SD: standard deviation; SEM: standard error of the mean; S-IFE: soybean-based intravenous fat emulsions; S-ILE: soybean;based intravenous lipid emulsion; TB: total bilirunin; TNA: total nutrient admixture; TPN: total parenteral nutrition; UK: United Kingdom; USA: United States of America; VLBW: very low birthweight.

Appendix E – Forest plots

Forest plots for review question: What is the optimal target for lipid dosage in preterm and term babies who are receiving parenteral nutrition and neonatal care? and What is the optimal way (starting dose and approach to increment, if employed) to achieve that?

Lipids versus no lipids for neonates

Figure 2: Days to regain birth weight

	Lipids			No lipids				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Gunn 1978	12.8	9	17	13.8	4.1	14	40.7%	-1.00 [-5.79, 3.79]
Hammerman 1988	19	7	20	17	6	22	59.3%	2.00 [-1.96, 5.96]
Total (95% CI)			**37**			**36**	**100.0%**	**0.78 [-2.27, 3.83]**

Heterogeneity: Chi² = 0.90, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)

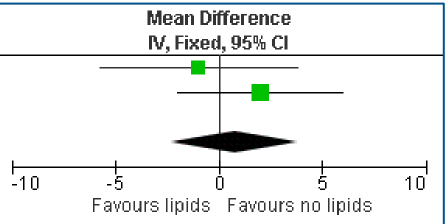
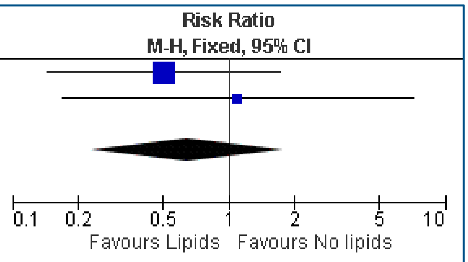


Figure 3: Mortality

	Lipids		No lipids			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Gunn 1978	3	20	6	20	75.9%	0.50 [0.14, 1.73]
Hammerman 1988	2	20	2	22	24.1%	1.10 [0.17, 7.09]
Total (95% CI)		**40**		**42**	**100.0%**	**0.64 [0.23, 1.78]**
Total events	5		8			

Heterogeneity: Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.40)



High versus low dose of lipids for neonates

Figure 4: Sepsis

	High		Low			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Calkins 2017	3	16	3	20	35.1%	1.25 [0.29, 5.38]
Levit 2016	3	67	5	69	64.9%	0.62 [0.15, 2.48]
Total (95% CI)		**83**		**89**	**100.0%**	**0.84 [0.31, 2.27]**
Total events	6		8			

Heterogeneity: Chi² = 0.47, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.34 (P = 0.73)

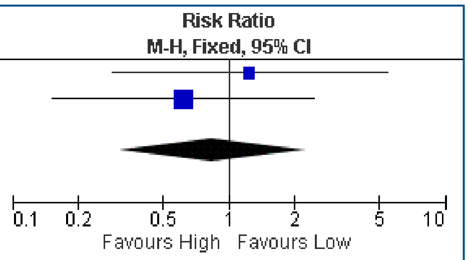


Figure 5: Cholestasis

	High		Low			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Calkins 2017	6	16	6	20	11.0%	1.25 [0.50, 3.14]
Levit 2016	39	63	45	69	89.0%	0.95 [0.73, 1.23]
Total (95% CI)		**79**		**89**	**100.0%**	**0.98 [0.76, 1.27]**
Total events	45		51			

Heterogeneity: Chi² = 0.33, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)

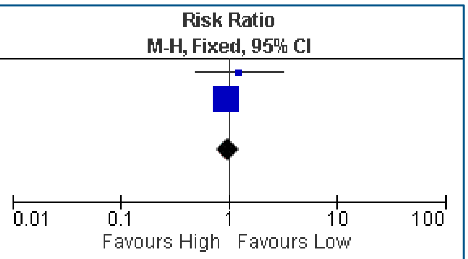


Figure 6: Mortality

Study or Subgroup	High Events	High Total	Low Events	Low Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Levit 2016	5	67	5	69	70.2%	1.03 [0.31, 3.40]
Shouman 2012	3	22	2	20	29.8%	1.36 [0.25, 7.34]
Total (95% CI)		**89**		**89**	**100.0%**	**1.13 [0.43, 2.98]**
Total events	8		7			

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.81)

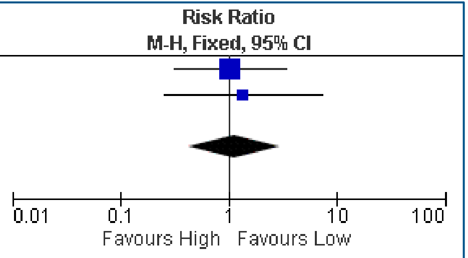
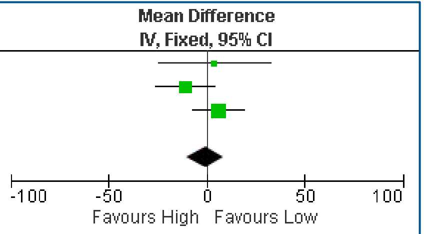


Figure 7: Length of hospital stay

Study or Subgroup	High Mean	High SD	High Total	Low Mean	Low SD	Low Total	Weight	Mean Difference IV, Fixed, 95% CI
Calkins 2017	58	47	16	54	38	20	10.5%	4.00 [-24.42, 32.42]
Levit 2016	84	35.69	67	94.77	51.31	69	38.6%	-10.77 [-25.59, 4.05]
Shouman 2012	37.3	22.5	22	31.4	20.2	20	50.9%	5.90 [-7.01, 18.81]
Total (95% CI)			**105**			**109**	**100.0%**	**-0.74 [-9.95, 8.47]**

Heterogeneity: Chi² = 2.88, df = 2 (P = 0.24); I² = 31%
Test for overall effect: Z = 0.16 (P = 0.88)



Early versus late delivery of lipids in neonates

Figure 8: Sepsis

Study or Subgroup	Early Events	Early Total	Late Events	Late Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gilbertson 1991	2	16	5	13	11.9%	0.33 [0.07, 1.41]
Wilson 1997	32	64	40	61	88.1%	0.76 [0.56, 1.03]
Total (95% CI)		**80**		**74**	**100.0%**	**0.71 [0.53, 0.96]**
Total events	34		45			

Heterogeneity: Chi² = 1.30, df = 1 (P = 0.25); I² = 23%
Test for overall effect: Z = 2.21 (P = 0.03)

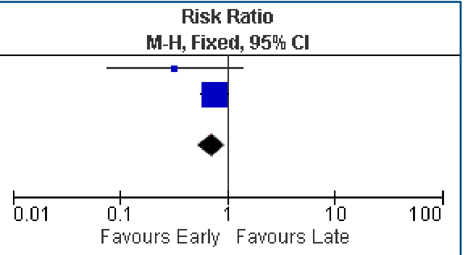


Figure 9: Mortality during first 28 days

Study or Subgroup	Early Events	Early Total	Late Events	Late Total	Weight	Risk Ratio M-H, Random, 95% CI
Gilbertson 1991	1	16	2	13	18.1%	0.41 [0.04, 4.00]
Sosenko 1993 600-800g	18	42	7	37	48.2%	2.27 [1.07, 4.81]
Sosenko 1993 801-1000g	3	28	5	26	33.7%	0.56 [0.15, 2.10]
Total (95% CI)		**86**		**76**	**100.0%**	**1.03 [0.32, 3.30]**
Total events	22		14			

Heterogeneity: Tau² = 0.58; Chi² = 4.55, df = 2 (P = 0.10); I² = 56%
Test for overall effect: Z = 0.06 (P = 0.95)

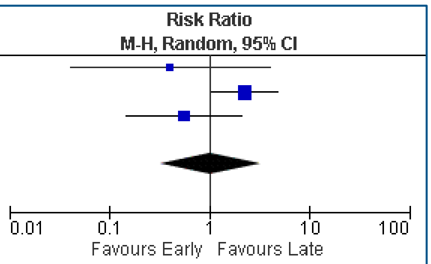
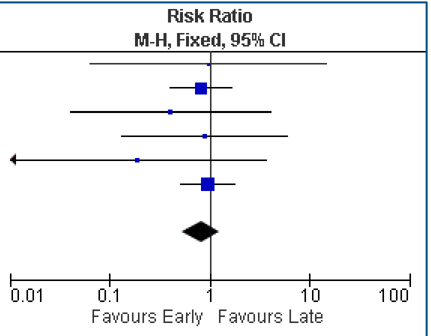


Figure 10: Mortality before discharge

Study or Subgroup	Early Events	Early Total	Late Events	Late Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alwaidh 1996	1	33	1	32	2.7%	0.97 [0.06, 14.85]
Brownlee 1993	11	63	14	66	37.0%	0.82 [0.40, 1.67]
Gilbertson 1991	1	16	2	13	6.0%	0.41 [0.04, 4.00]
Sosenko 1993 600-800g (1)	2	42	2	37	5.8%	0.88 [0.13, 5.95]
Sosenko 1993 801-1000g (2)	0	28	2	26	7.0%	0.19 [0.01, 3.71]
Wilson 1997	15	64	15	61	41.5%	0.95 [0.51, 1.78]
Total (95% CI)		**246**		**235**	**100.0%**	**0.81 [0.53, 1.26]**
Total events	30		36			

Heterogeneity: Chi² = 1.56, df = 5 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)



Footnotes
(1) Data reported are the number of babies who died >28 days
(2) Data reported are the number of babies who died >28 days

Figure 11: Hypertriglyceridemia

Study or Subgroup	Early Events	Early Total	Late Events	Late Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gilbertson 1991	3	16	1	13	5.6%	2.44 [0.29, 20.75]
Wilson 1997	22	64	18	61	94.4%	1.16 [0.70, 1.95]
Total (95% CI)		**80**		**74**	**100.0%**	**1.24 [0.75, 2.04]**
Total events	25		19			

Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.41)

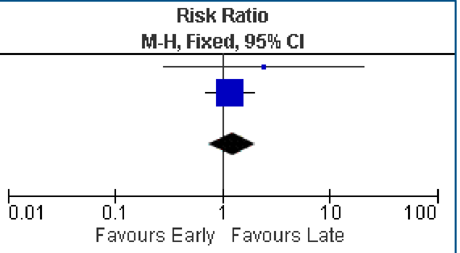
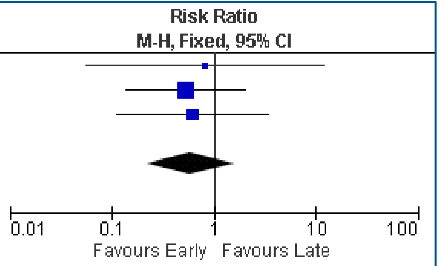


Figure 12: Necrotising enterocolitis

Study or Subgroup	Early Events	Early Total	Late Events	Late Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gilbertson 1991	1	16	1	13	11.6%	0.81 [0.06, 11.77]
Sosenko 1993 600-800g	3	42	5	37	55.8%	0.53 [0.14, 2.06]
Sosenko 1993 801-1000g	2	28	3	26	32.6%	0.62 [0.11, 3.41]
Total (95% CI)		**86**		**76**	**100.0%**	**0.59 [0.22, 1.58]**
Total events	6		9			

Heterogeneity: Chi² = 0.08, df = 2 (P = 0.96); I² = 0%
Test for overall effect: Z = 1.05 (P = 0.30)



Appendix F – GRADE tables

GRADE tables for review question: What is the optimal target for lipid dosage in preterm and term babies who are receiving parenteral nutrition and neonatal care? and What is the optimal way (starting dose and approach to increment, if employed) to achieve that?

Table 5: Evidence profile for outcomes related to the comparison of lipids versus no lipids

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lipids	No lipids	Relative (95% CI)	Absolute	Quality	Importance
Days to regain birth weight (Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	37	36	-	MD 0.78 higher (2.27 lower to 3.83 higher)	⊕OOO VERY LOW	CRITICAL
Mortality												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/40 (12.5%)	8/42 (19%)	RR 0.64 (0.23 to 1.78)	69 fewer per 1000 (from 147 fewer to 149 more)	⊕OOO VERY LOW	IMPORTANT
Hypoglycaemia requiring glucose - Glucose 10% + AA + lipid vs Glucose 10%												
1	randomised trials	very serious[4]	no serious inconsistency	serious[5]	very serious[3]	none	2/8 (25%)	6/10 (60%)	RR 0.42 (0.11 to 1.53)	348 fewer per 1000 (from 534 fewer to 318 more)	⊕OOO VERY LOW	IMPORTANT
Hypoglycaemia requiring glucose - Glucose 10% + AA + lipid vs Glucose 10% + AA												
1	randomised trials	very serious[4]	no serious inconsistency[5]	serious[5]	serious[6]	none	2/8 (25%)	9/11 (81.8%)	RR 0.31 (0.09 to 1.05)	565 fewer more per 1000 (from 745 fewer to 41 more)	⊕OOO VERY LOW	IMPORTANT
Necrotising enterocolitis												
1	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[8]	none	2/20 (10%)	0/22 (0%)	Peto OR 8.61 (0.52 to 142.87)	--	⊕OOO VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lipids**	**No lipids**	**Relative (95% CI)**	**Absolute**		
Retinopathy of prematurity												
1	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[6]	none	8/11 (72.7%)	4/17 (23.5%)	RR 3.09 (1.22 to 7.84)	492 more per 1000 (from 52 more to 1000 more)	⊕OOO VERY LOW	IMPORTANT

AA: amino acids; CI: confidence interval; MD: mean difference; RR: risk ratio.
[1] Evidence downgraded by 2 due to high risk in blinding of personnel in 1 study and unclear risk for blinding of outcome assessors, attrition, reporting of outcomes, and other risk of bias.
[2] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses both default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-2.52, 2.52).
[3] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses both default MID for dichotomous outcomes (0.8 and 1.25).
[4] Evidence downgraded by 2 due to high risk in attrition rates and unclear risk for selection of participants, blinding and other bias.
[5] Evidence downgraded by 1 due to use of proxy measure for number of infants with hypoglycaemia (i.e. outcome measured as days on which an increase in glucose initiated).
[6] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for dichotomous outcomes (0.80 or 1.25).
[7] Evidence was downgraded by 2 due to high risk of bias for blinding of personnel, and unclear risk for blinding of outcome assessors, outcome reporting and other bias.
[8] Evidence was downgraded for risk of imprecision due to low event rate

Table 6: Evidence profile for outcomes related to the comparison of high dose and low dose lipids

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**High dose**	**Low dose**	**Relative (95% CI)**	**Absolute**		
Cognitive skills (2 years) FU - N <1 SD of norm (follow-up 2 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/15 (13.3%)	3/15 (20%)	RR 0.67 (0.13 to 3.44)	66 fewer per 1000 (from 174 fewer to 488 more)	⊕OOO VERY LOW	CRITICAL
Language skills (2 years) FU - N <1 SD of norm (follow-up 2 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	4/15 (26.7%)	2/15 (13.3%)	RR 2 (0.43 to 9.32)	133 more per 1000 (from 76 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Motor skills (2 years) FU - N <1 SD of norm (follow-up 2 years)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**High dose**	**Low dose**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/15 (6.7%)	2/15 (13.3%)	RR 0.5 (0.05 to 4.94)	67 fewer per 1000 (from 127 fewer to 525 more)	⊕OOO VERY LOW	CRITICAL
Growth weight first 28 days (g/day) (follow-up 28 days; Better indicated by lower values)												
1	randomised trials	very serious[4]	no serious inconsistency	serious[2]	serious[5]	none	16	20	-	MD 6 higher (2.59 lower to 14.59 higher)	⊕OOO VERY LOW	CRITICAL
Growth weight first 28 days (g/week) (follow-up 28 days; Better indicated by lower values)												
1	randomised trials	serious[6]	no serious inconsistency	serious[2]	no serious imprecision	none	61	67	-	MD 3 higher (9.65 lower to 15.65 higher)	⊕⊕OO LOW	CRITICAL
Discharge weight (g) (Better indicated by lower values)												
1	randomised trials	very serious[4]	no serious inconsistency	serious[2]	serious[7]	none	16	20	-	MD 0.1 higher (0.42 lower to 0.62 higher)	⊕OOO VERY LOW	CRITICAL
Discharge weight (g/week) (Better indicated by lower values)												
1	randomised trials	serious[6]	no serious inconsistency	serious[2]	no serious imprecision	none	61	62	-	MD 0 higher (10.26 lower to 10.26 higher)	⊕⊕OO LOW	CRITICAL
Length gain first 28 days (cm/week) (follow-up 28 days; Better indicated by lower values)												
1	randomised trials	serious[6]	no serious inconsistency	serious[2]	serious[8]	none	61	61	-	MD 0.1 lower (0.28 lower to 0.08 higher)	⊕OOO VERY LOW	CRITICAL
Discharge length (cm) (Better indicated by lower values)												
1	randomised trials	very serious[4]	no serious inconsistency	serious[2]	serious[9]	none	16	20	-	MD 1 lower (3.63 lower to 1.63 higher)	⊕OOO VERY LOW	CRITICAL
Discharge length (cm/week) (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**High dose**	**Low dose**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious[6]	no serious inconsistency	serious[2]	serious[10]	none	61	63	-	MD 0.2 lower (0.39 to 0.01 lower)	⊕OOO VERY LOW	CRITICAL
Head circumference gain cm/week (Better indicated by lower values)												
1	randomised trials	serious[6]	no serious inconsistency	serious[2]	serious[11]	none	61	61	-	MD 0.1 lower (0.21 lower to 0.01 higher)	⊕OOO VERY LOW	CRITICAL
Discharge head circumference (cm) (Better indicated by lower values)												
1	randomised trials	very serious[4]	no serious inconsistency	serious[2]	very serious[12]	none	16	20	-	MD 1 higher (1.15 lower to 3.15 higher)	⊕OOO VERY LOW	CRITICAL
Discharge head circumference (cm/week) (Better indicated by lower values)												
1	randomised trials	serious[6]	no serious inconsistency	serious[2]	serious[13]	none	61	61	-	MD 0.1 lower (0.21 lower to 0.01 higher)	⊕OOO VERY LOW	CRITICAL
Sepsis												
2	randomised trials	very serious[4,6]	no serious inconsistency	serious[2]	very serious[14]	none	6/83 (7.2%)	8/89 (9%)	RR 0.84 (0.31 to 2.27)	14 fewer per 1000 (from 62 fewer to 114 more)	⊕OOO VERY LOW	CRITICAL
Cholestasis												
2	randomised trials	very serious[4,6]	no serious inconsistency	serious[2]	very serious[14]	none	45/79 (57%)	51/89 (57.3%)	RR 0.98 (0.76 to 1.27)	11 fewer per 1000 (from 138 fewer to 155 more)	⊕OOO VERY LOW	CRITICAL
Direct bilirubin >1 mg/dL												
1	randomised trials	very serious[4]	no serious inconsistency	serious[2]	very serious[14]	none	9/16 (56.3%)	10/20 (50%)	RR 1.12 (0.61 to 2.08)	60 more per 1000 (from 195 fewer to 540 more)	⊕OOO VERY LOW	CRITICAL
Mortality												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose	Low dose	Relative (95% CI)	Absolute		
2	randomised trials	serious[15]	no serious inconsistency	serious[2,16]	very serious[14]	none	8/89 (9%)	7/89 (7.9%)	RR 1.13 (0.43 to 2.98)	10 more per 1000 (from 45 fewer to 156 more)	⊕OOO VERY LOW	IMPORTANT
Length of hospital stay, days (Better indicated by lower values)												
3	randomised trials	very serious[4,6]	no serious inconsistency	serious[2,16]	no serious imprecision	none	105	109	-	MD 0.74 lower (9.95 lower to 8.47 higher)	⊕OOO VERY LOW	IMPORTANT
Necrotising enterocolitis												
1	randomised trials	serious[6]	no serious inconsistency	serious[2]	very serious[14]	none	8/67 (11.9%)	11/69 (15.9%)	RR 0.75 (0.32 to 1.75)	40 fewer per 1000 (from 108 fewer to 120 more)	⊕OOO VERY LOW	IMPORTANT
Retinopathy of prematurity												
1	randomised trials	serious[6]	no serious inconsistency	serious[2]	very serious[14]	none	7/67 (10.4%)	9/69 (13%)	RR 0.8 (0.32 to 2.03)	26 fewer per 1000 (from 89 fewer to 134 more)	⊕OOO VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio; SD: standard deviation.
[1] Evidence was downgraded by 2 due to high risk for attrition rates and unclear risk for blinding.
[2] It is unclear what effect the use of enteral feeds may have had on the outcomes.
[3] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MID for dichotomous outcomes (0.80 and 1.25).
[4] Evidence was downgraded by 2 due to high risk for blinding of personnel and study being underpowered, and unclear risk for blinding of outcome assessors.
[5] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (4.00).
[6] Evidence downgraded by 1 due to unclear risk for blinding of personnel and outcome assessors, and reporting of outcomes.
[7] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.45).
[8] Evidence was downgraded by 1 due to serious imprecision, 95 confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.25).
[9] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-2.00).
[10] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.35).
[11] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.15).
[12] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses both default MID for continuous outcomes, calculated as 0.5 x SD control at

baseline (-1.00 and 1.00).
[13] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.2).
[14] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence intervals crosses two default MID for dichotomous outcomes (0.8 and 1.25).
[15] Evidence downgraded by 1 due to unclear risk of blinding of outcome assessors, and other bias
[16] It is unclear what effect the use of different antibiotic treatments may have had on the outcomes.

Table 7: Evidence profile for outcomes related to the comparison of early versus late delivery of lipids

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early lipids**	**Late lipids**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
BSID-III motor score <70 (follow-up 2 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/45 (2.2%)	2/44 (4.5%)	RR 0.49 (0.05 to 5.2)	23 fewer per 1000 (from 43 fewer to 191 more)	⊕OOO VERY LOW	CRITICAL
BSID-III psychomotor score <70 (follow-up 2 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/45 (2.2%)	2/44 (4.5%)	RR 0.49 (0.05 to 5.2)	23 fewer per 1000 (from 43 fewer to 191 more)	⊕OOO VERY LOW	CRITICAL
Mean weight gain/day to discharge (g) - Early (36 hrs) vs late (day 6) PN (Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	serious[2]	serious[5]	none	63	66	-	MD 2.4 lower (5.3 lower to 0.5 higher)	⊕OOO VERY LOW	CRITICAL
Mean weight gain/day to discharge (g) - Early (Glucose + AA) vs late (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	49	48	-	MD 0.8 lower (3.51 lower to 1.91 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mean weight gain/day to discharge (g) - Early (Glucose + high dose AA) vs late (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[6]	none	47	48	-	MD 1.2 higher (1.9 lower to 4.3 higher)	⊕⊕OO LOW	CRITICAL
Days to regain birth weight (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early lipids**	**Late lipids**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[8]	none	16	13	-	MD 1.3 lower (5.88 lower to 3.28 higher)	⊕⊕OO LOW	CRITICAL
Mean final weight (g) (Better indicated by lower values)												
1	randomised trials	serious[9]	no serious inconsistency	serious[2]	no serious imprecision	none	64	61	-	MD 31 higher (269.45 lower to 331.45 higher)	⊕⊕OO LOW	CRITICAL
Growth in length (cm/wk) (Better indicated by lower values)												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[10]	none	16	13	-	MD 0.1 higher (0.18 lower to 0.38 higher)	⊕⊕OO LOW	CRITICAL
Mean final length (cm) (Better indicated by lower values)												
1	randomised trials	serious[9]	no serious inconsistency	serious[2]	no serious imprecision	none	64	61	-	MD 0.2 higher (1.94 lower to 2.34 higher)	⊕⊕OO LOW	CRITICAL
Rate of head circumference growth (cm/week) - Early (first day) vs late (day 8) (Better indicated by lower values)												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[11]	none	16	13	-	MD 0 higher (0.28 lower to 0.28 higher)	⊕OOO VERY LOW	CRITICAL
Rate of head circumference growth (cm/week) - Early (Glucose + AA) vs late (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[12]	none	49	48	-	MD 0.02 lower (0.08 lower to 0.04 higher)	⊕⊕OO LOW	CRITICAL
Rate of head circumference growth (cm/week) - Early (Glucose + high dose AA) vs late (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	47	48	-	MD 0.01 higher (0.04 lower to 0.06 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mean final head circumference (cm) (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early lipids**	**Late lipids**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious[9]	no serious inconsistency	serious[2]	no serious imprecision	none	64	61	-	MD 0.1 lower (1.77 lower to 1.57 higher)	⊕⊕OO LOW	CRITICAL
Sepsis - Pooled data												
2	randomised trials	serious[7,9]	no serious inconsistency	serious[2]	serious[13]	none	34/80 (42.5%)	45/74 (60.8%)	RR 0.71 (0.53 to 0.96)	176 fewer per 1000 (from 24 fewer to 286 fewer)	⊕OOO VERY LOW	CRITICAL
Sepsis - Non-pooled data - Early (Glucose + high dose AA) vs late												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[14]	none	17/47 (36.2%)	8/48 (16.7%)	RR 2.17 (1.04 to 4.54)	195 more per 1000 (from 7 more to 590 more)	⊕⊕OO LOW	CRITICAL
Sepsis - Non-pooled data - Early (Glucose + AA) vs control												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[14]	none	16/49 (32.7%)	8/48 (16.7%)	RR 1.96 (0.93 to 4.15)	160 more per 1000 (from 12 fewer to 525 more)	⊕⊕OO LOW	CRITICAL
Cholestasis												
1	randomised trials	serious[9]	no serious inconsistency	serious[2]	very serious[15]	none	3/64 (4.7%)	2/61 (3.3%)	RR 1.43 (0.25 to 8.26)	14 more per 1000 (from 25 fewer to 238 more)	⊕OOO VERY LOW	CRITICAL
Jaundice												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[15]	none	7/16 (43.8%)	5/13 (38.5%)	RR 1.14 (0.47 to 2.75)	54 more per 1000 (from 204 fewer to 673 more)	⊕OOO VERY LOW	CRITICAL
Mortality during first 28 days												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early lipids	Late lipids	Relative (95% CI)	Absolute		
2	randomised trials	very serious[7,16]	serious[17]	no serious indirectness	very serious[15]	none	22/86 (25.6%)	14/76 (18.4%)	RR 1.03 (0.32 to 3.3)	6 more per 1000 (from 125 fewer to 424 more)	⊕OOO VERY LOW	IMPORTANT
Mortality before discharge - pooled data												
5	randomised trials	very serious[4,7,9,16,18]	no serious inconsistency	serious[2,19]	very serious[15]	none	30/246 (12.2%)	36/235 (15.3%)	RR 0.81 (0.53 to 1.26)	29 fewer per 1000 (from 72 fewer to 40 more)	⊕OOO VERY LOW	IMPORTANT
Mortality before discharge - non-pooled data - Early (Glucose + high dose AA) vs late												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[15]	none	10/47 (21.3%)	5/48 (10.4%)	RR 2.04 (0.75 to 5.53)	108 more per 1000 (from 26 fewer to 472 more)	⊕OOO VERY LOW	IMPORTANT
Mortality before discharge - non-pooled data - Early (Glucose + AA) vs late												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[15]	none	7/49 (14.3%)	5/48 (10.4%)	RR 1.37 (0.47 to 4.02)	39 more per 1000 (from 55 fewer to 315 more)	⊕OOO VERY LOW	IMPORTANT
Hospital stay - Early (Glucose + AA) vs late (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	49	48	-	MD 3.3 higher (10.99 lower to 17.59 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Hospital stay - Early (Glucose + high dose AA) vs late (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	47	48	-	MD 4.5 lower (18.52 lower to 9.52 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Hospital stay - Aggressive vs control (Better indicated by lower values)												
1	randomised trials	serious[9]	no serious inconsistency	serious[2]	no serious imprecision	none	64	61	-	MD 1 higher (3.97 lower to 5.97 higher)	⊕⊕OO LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early lipids**	**Late lipids**	**Relative (95% CI)**	**Absolute**		
Hypertriglyceridemia												
2	randomised trials	serious[7,9]	no serious inconsistency	serious[2]	very serious[15]	none	25/80 (31.3%)	19/74 (25.7%)	RR 1.24 (0.75 to 2.04)	62 more per 1000 (from 64 fewer to 267 more)	⊕OOO VERY LOW	IMPORTANT
Hypoglycaemia												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[15]	none	7/16 (43.8%)	5/13 (38.5%)	RR 1.14 (0.47 to 2.75)	54 more per 1000 (from 204 fewer to 673 more)	⊕OOO VERY LOW	IMPORTANT
Necrotising enterocolitis - pooled data												
2	randomised trials	very serious[7,16]	no serious inconsistency	no serious indirectness	very serious[15]	none	6/86 (7%)	9/76 (11.8%)	RR 0.59 (0.22 to 1.58)	49 fewer per 1000 (from 92 fewer to 69 more)	⊕OOO VERY LOW	IMPORTANT
Necrotising enterocolitis - non-pooled data - Early (Glucose + high dose AA) vs late												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[15]	none	4/47 (8.5%)	2/48 (4.2%)	RR 2.04 (0.39 to 10.63)	43 more per 1000 (from 25 fewer to 401 more)	⊕OOO VERY LOW	IMPORTANT
Necrotising enterocolitis - non-pooled data - Early (Glucose + AA) vs late)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[15]	none	1/49 (2%)	2/48 (4.2%)	RR 0.49 (0.05 to 5.23)	21 fewer per 1000 (from 40 fewer to 176 more)	⊕OOO VERY LOW	IMPORTANT
Retinopathy of prematurity												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[20]	none	0/16 (0%)	1/13 (7.7%)	Peto OR 0.11 (0.00 to 5.53)	68 fewer per 1000 (from 77 fewer to 348 more)	⊕OOO VERY LOW	IMPORTANT

AA: amino acids; CI: confidence interval; MD: mean difference; OR: odds ratio; PN: parenteral nutrition; RR: risk ratio.

[1] *Evidence downgraded by 1 due to high risk in blinding of personnel and unclear risk for other bias.*
[2] *It is unclear what effect the use of enteral feeds may have had on the outcomes.*
[3] *Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MID for dichotomous outcomes (0.80 and 1.25).*
[4] *Evidence downgraded by 1 due to unclear risk in selection of participants, blinding, and other bias.*
[5] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-4.55).*
[6] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (4.05).*
[7] *Evidence downgraded by 1 due to unclear risk for selection of participants, blinding, and other bias.*
[8] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-3.46).*
[9] *Evidence downgraded by 1 due to unclear risk for selection of participants, blinding, and other risk of bias.*
[10] *Evidence downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.18).*
[11] *Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses both default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.18 and 0.18).*
[12] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.065).*
[13] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for dichotomous outcomes (0.80 or 1.25).*
[14] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for dichotomous outcomes (0.80 or 1.25).*
[15] *Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MID for dichotomous outcomes (0.80 and 1.25).*
[16] *Evidence downgraded by 2 due to high risk of bias for blinding of personnel and outcome reporting, and unclear risk for other bias.*
[17] *Evidence was downgraded by 1 due to statistical heterogeneity between studies (I2=56%).*
[18] *Evidence downgraded by 1 due to unclear risk for selection of participants, blinding and other risk of bias.*
[19] *13 infants in the late lipid group in 1 RCT received no IV lipid because PN had already been discontinued by day 14.*
[20] *Evidence was downgraded for risk of imprecision due to low event rate*

Table 8: Evidence profile for outcomes related to the comparison of different infusion rates

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Higher or continuous infusion**	**Lower or intermittent infusion rate**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Time to regain birth weight (days) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	52	-	MD 0.36 lower (1.82 lower to 1.1 higher)	⊕⊕⊕O MODERATE	CRITICAL
Weight at discharge (g) (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher or continuous infusion	Lower or intermittent infusion rate	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	52	-	MD 52.17 lower (289.29 lower to 184.95 higher)	⊕⊕⊕O MODERATE	CRITICAL
Infants in ≥10th percentile for weight												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/48 (41.7%)	9/52 (17.3%)	RR 2.41 (1.22 to 4.76)	244 more per 1000 (from 38 more to 651 more)	⊕⊕OO LOW	CRITICAL
Length at discharge (cm) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	52	-	MD 0.54 lower (2 lower to 0.92 higher)	⊕⊕⊕O MODERATE	CRITICAL
Head circumference at discharge (cm) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	52	-	MD 0.25 lower (1.17 lower to 0.67 higher)	⊕⊕⊕O MODERATE	CRITICAL
Sepsis												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/19 (5.3%)	4/24 (16.7%)	RR 0.32 (0.04 to 2.60)	113 fewer per 1000 (from 160 fewer to 267 more)	⊕OOO VERY LOW	CRITICAL
Mortality - Higher versus lower infusion rate												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[8]	none	0/48 (0%)	3/52 (5.8%)	Peto OR 0.14 (0.01 to 1.38)	50 fewer per 1000 (from 57 fewer to 22 more)	⊕⊕OO LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Higher or continuous infusion**	**Lower or intermittent infusion rate**	**Relative (95% CI)**	**Absolute**		
Mortality - Higher (at 24 hrs) versus lower (at 24 hrs) infusion rate												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	v serious[8]	none	0/11 (0%)	1/14 (7.1%)	Peto OR 0.17 (0.00 to 8.69)	59 fewer per 1000 (from 71 fewer to 549 more)	⊕⊕OO LOW	IMPORTANT
Mortality - Higher (at 24 hrs) versus lower (at 16 hrs) infusion rate												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[8]	none	0/11 (0%)	1/13 (7.7%)	Peto OR 0.16 (0.00 to 8.06)	65 fewer per 1000 (from 77 fewer to 543 more)	⊕⊕OO LOW	IMPORTANT
Mortality - Intermittent versus continuous infusion rate												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[8]	none	0/19 (0%)	1/24 (4.2%)	Peto OR 0.17 (0.00 to 8.63)	35 fewer per 1000 (from 42 fewer to 318 more)	⊕⊕OO LOW	IMPORTANT
Duration of hospital stay (days) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	48	52	-	MD 6.93 lower (17.39 lower to 3.53 higher)	⊕⊕OO LOW	IMPORTANT
Hypertriglyceridemia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/48 (14.6%)	2/52 (3.8%)	RR 3.79 (0.83 to 17.37)	107 more per 1000 (from 7 fewer to 630 more)	⊕⊕OO LOW	IMPORTANT
Necrotising enterocolitis												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/48 (0%)	7/52 (13.5%)	Peto OR 7.75 (1.68 to 35.77)	909 more per 1000 (from 92 more to 1000 more)	⊕⊕⊕O MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Higher or continuous infusion**	**Lower or intermittent infusion rate**	**Relative (95% CI)**	**Absolute**		
Retinopathy of prematurity												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	3/48 (6.3%)	12/52 (23.1%)	RR 0.27 (0.08 to 0.9)	168 fewer per 1000 (from 23 fewer to 212 fewer)	⊕⊕OO LOW	IMPORTANT

CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio.
[1] Evidence downgraded by 1 due to unclear risk for selection of participants, and blinding of personnel and outcome assessors.
[2] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for dichotomous outcomes (0.80 or 1.25).
[3] Evidence downgraded by 1 due to unclear risk for all risk of bias domains.
[4] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MID for dichotomous outcomes (0.8 and 1.25).
[5] Evidence downgraded by 1 due to unclear risk for selection of participants and blinding.
[6] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-16.5).
[7] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for dichotomous outcomes (0.8 or 1.25)
[5] Evidence was downgraded for risk of imprecision due to low event rate
.

Appendix G – Economic evidence study selection

Economic evidence study selection for review questions: What is the optimal target for lipid dosage in preterm and term babies who are receiving parenteral nutrition and neonatal care? and What is the optimal way (starting dose and approach to increment, if employed) to achieve that?

One global search was conducted for all review questions. See supplementary material D for further information.

Appendix H – Economic evidence tables

Economic evidence tables for review questions: What is the optimal target for lipid dosage in preterm and term babies who are receiving parenteral nutrition and neonatal care? and What is the optimal way (starting dose and approach to increment, if employed) to achieve that?

No evidence was identified which was applicable to these review questions.

Appendix I – Health economic evidence profiles

Economic evidence study selection for review questions: What is the optimal target for lipid dosage in preterm and term babies who are receiving parenteral nutrition and neonatal care? and What is the optimal way (starting dose and approach to increment, if employed) to achieve that?

No evidence was identified which was applicable to these review questions.

Appendix J – Health economic analysis

Economic analysis for review questions: What is the optimal target for lipid dosage in preterm and term babies who are receiving parenteral nutrition and neonatal care? and What is the optimal way (starting dose and approach to increment, if employed) to achieve that?

No economic analyse were conducted for these review questions.

Appendix K – Excluded studies

Excluded studies for review question: What is the optimal target for lipid dosage in preterm and term babies who are receiving parenteral nutrition and neonatal care? and What is the optimal way (starting dose and approach to increment, if employed) to achieve that?

Clinical studies

Table 9: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
A. S. P. E. N. Intravenous Fat Emulsion National Shortage Task Force, Vanek, Vincent W., Allen, Penny, Harvey Banchik, Lillian P., Bistrian, Bruce, Collier, Sharon, Driscoll, David F., Gura, Kathleen, Houston, Deborah R., Miles, John, Mirtallo, Jay, Mogensen, Kris M., Seidner, Doug, Parenteral nutrition intravenous fat emulsions product shortage considerations, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 28, 528-9, 2013	Study design and topic does not meet protocol eligibility criteria - Guideline for dealing with product shortages.
Abdou, R. M., Weheiba, H. M. I., The effect of early versus late lipid infusion in parenteral nutrition on the biochemical and cortical auditory evoked potential parameters in preterm neonates, Egyptian Pediatric Association Gazette, 2018	Study design does not meet protocol eligibility criteria - Not an RCT.
Abrams, S. A., Impact of new-generation parenteral lipid emulsions in pediatric nutrition, Advances in nutrition (Bethesda, Md.), 4, 518-520, 2013	Study design does not meet protocol eligibility criteria - Summary of symposium.
Adamkin, D. H., Gelke, K. N., Andrews, B. F., Fat emulsions and hypertriglyceridemia, Journal of Parenteral and Enteral Nutrition, 8, 563-567, 1984	Study design does not meet protocol eligibility criteria - Narrative review.
Adamkin, D. H., Gelke, K. N., Wilkerson, S. A., Influence of intravenous fat therapy on tracheal effluent phospholipids and oxygenation in severe respiratory distress syndrome, The Journal of pediatrics, 106, 122-4, 1985	Outcomes do not meet protocol eligibility criteria - lung phospholipids and oxygenation.
Adamkin, D. H., Radmacher, P. G., Klingbeil, R. L., Use of intravenous lipid and hyperbilirubinemia in the first week, Journal of Pediatric Gastroenterology and Nutrition, 14, 135-139, 1992	Study design does not meet protocol eligibility criteria - Cohort study.
Agrawal, A., Shrivastava, J., Dwivedi, R., Siddiqui, M., Assessment of serum apolipoprotein B and apolipoprotein A-1 and their ratio in healthy full term small	Not relevant topic - analysis of cord blood.

Study	Reason for Exclusion
for gestational age newborns, Journal of Neonatal-Perinatal Medicine, 10, 49-53, 2017	
Amin, S. B., Effect of free fatty acids on bilirubin-albumin binding affinity and unbound bilirubin in premature infants, Journal of Parenteral and Enteral Nutrition, 34, 414-420, 2010	Outcomes do not meet protocol eligibility criteria - bilirubin-albumin binding affinity.
Amin, S. B., Harte, T., Scholer, L., Wang, H., Intravenous lipid and bilirubin-albumin binding variables in premature infants, Pediatrics, 124, 211-217, 2009	Outcomes do not meet protocol eligibility criteria - bilirubin-albumin binding.
Andersen, G. E., Christensen, N. C., Johansen, K. B., Fatty acid changes in plasma lipids and lymphocyte phospholipids after infusion of intralipid to newborn infants, JPEN. Journal of parenteral and enteral nutrition, 9, 691-4, 1985	Outcomes do not meet protocol eligibility criteria - plasma lipids and lymphocyte phospholipids.
Andrew, G., Chan, G., Schiff, D., Lipid metabolism in the neonate. II. The effect of Intralipid on bilirubin binding in vitro and in vivo, The Journal of pediatrics, 88, 279-84, 1976	Outcomes do not meet protocol eligibility criteria - bilirubin binding.
Andrew, G., Chan, G., Schiff, D., Lipid metabolism in the neonate. I. The effects of Intralipid infusion on plasma triglyceride and free fatty acid concentrations in the neonate, The Journal of pediatrics, 88, 273-8, 1976	Outcomes do not meet protocol eligibility criteria - plasma triglyceride and free fatty acid concentrations.
Angsten, G., Boberg, M., Cederblad, G., Meurling, S., Stiernstrom, H., Metabolic effects in neonates receiving intravenous medium-chain triglycerides, Acta paediatrica (Oslo, Norway : 1992), 91, 188-97, 2002	Outcomes do not meet protocol eligibility criteria - lipid and carnitine metabolism and respiratory quotient.
Anonymous,, Boxed warning on I.V. fat emulsions, FDA drug bulletin, 11, 6, 1981	Study design does not meet protocol eligibility criteria - Not an RCT.
Anonymous,, Pulmonary fat accumulation after parenteral fat emulsion--real or artifactual?, Nutrition reviews, 43, 15-7, 1985	Study design does not meet protocol eligibility criteria - Review.
Anonymous,, Unpredictability and variability of parenteral fat emulsion tolerance in neonates, Nutrition reviews, 42, 155-6, 1984	Study design does not meet protocol eligibility criteria - Review.
Anonymous,, Pulmonary arterial lipid deposits after intravenous lipid infusions in neonates, Nutrition reviews, 39, 271-3, 1981	Study design does not meet protocol eligibility criteria - case series review.
Anonymous,, Clinical conference on pediatric nutrition. The role of Neopham and Intralipid in TPN, Acta chirurgica	Conference paper.

Study	Reason for Exclusion
Scandinavica. Supplementum, 517, 1-203, 1983	
Anonymous,, Effect of parenteral linoleate on fatty acid composition of infant brain and liver, Nutrition reviews, 45, 232-4, 1987	Study design does not meet protocol eligibility criteria - Review.
Anonymous,, Development of essential fatty acid deficiency in the premature infant given fat-free TPN, Nutrition reviews, 43, 14-5, 1985	Study design does not meet protocol eligibility criteria - Review.
Ariyawangso, U., Puttilerpong, C., Ratanachuek, S., Anuntkosol, M., Short-term safety and efficacy of fish-oil emulsions on the prevention of parenteral nutrition-associated liver disease in surgical neonates: a randomized controlled trial, Thai Journal of Pharmaceutical Sciences, 38, 202-209, 2014	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Avila-Figueroa, C., Goldmann, D. A., Richardson, D. K., Gray, J. E., Ferrari, A., Freeman, J., Intravenous lipid emulsions are the major determinant of coagulase-negative staphylococcal bacteremia in very low birth weight newborns, The Pediatric infectious disease journal, 17, 10-7, 1998	Study design does not meet protocol eligibility criteria - Case-control study.
Baack, Michelle L., Puumala, Susan E., Messier, Stephen E., Pritchett, Deborah K., Harris, William S., Daily Enteral DHA Supplementation Alleviates Deficiency in Premature Infants, Lipids, 51, 423-33, 2016	Intervention does not meet protocol eligibility criteria - Enteral feeding.
Baack, Michelle L., Puumala, Susan E., Messier, Stephen E., Pritchett, Deborah K., Harris, William S., What is the relationship between gestational age and docosahexaenoic acid (DHA) and arachidonic acid (ARA) levels?, Prostaglandins, leukotrienes, and essential fatty acids, 100, 5-11, 2015	Intervention does not meet protocol eligibility criteria - No PN intervention.
Baeckert,P.A., Greene,H.L., Fritz,I., Oelberg,D.G., Adcock,E.W., Vitamin concentrations in very low birth weight infants given vitamins intravenously in a lipid emulsion: measurement of vitamins A, D, and E and riboflavin, Journal of Pediatrics, 113, 1057-1065, 1988	Outcomes do not meet protocol eligibility criteria - change in plasma vitamins in response to lipid emulsion.
Baird, L. L., Protecting TPN and lipid infusions from light: reducing hydroperoxides in NICU patients, Neonatal network : NN, 20, 17-22, 2001	Outcomes do not meet protocol eligibility criteria - storage and protection of PN.
Bargen-Lockner, C., Hahn, P., Pendray, M., Riddell, G., Effect of intralipid on total and high-density lipoprotein cholesterol	Outcomes do not meet protocol eligibility criteria - lipoprotein cholesterol levels.

Study	Reason for Exclusion
levels in newborns and infants, Biology of the Neonate, 44, 272-7, 1983	
Beghin, Laurent, Storme, Laurent, Coopman, Stephanie, Rakza, Thameur, Gottrand, Frederic, Parenteral nutrition with fish oil supplements is safe and seems to be effective in severe preterm neonates with respiratory distress syndrome, Acta paediatrica (Oslo, Norway : 1992), 104, e534-6, 2015	Study design does not meet protocol eligibility criteria - Review.
Beken, S., Dilli, D., Fettah, N. D., Kabatas, E. U., Zenciroglu, A., Okumus, N., The influence of fish-oil lipid emulsions on retinopathy of prematurity in very low birth weight infants: A randomized controlled trial, Early Human Development, 90, 27-31, 2014	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Bell, L. M., Alpert, G., Slight, P. H., Campos, J. M., Malassezia furfur skin colonization in infancy, Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America, 9, 151-153, 1988	Study design does not meet protocol eligibility criteria - Cohort study.
Bendapudi, P., Battersby, C., Hind, J., Hickey, A., The change from a soybean based to a mixed source lipid as first line parenteral lipid in infants born with gastroschisis improves bilirubin and enteral feeding outcomes, Journal of Pediatric Gastroenterology and Nutrition, 62, 874-875, 2016	Abstract only.
Biagetti, C., Vedovelli, L., Savini, S., Simonato, M., D'Ascenzo, R., Pompilio, A., Cogo, P. E., Carnielli, V. P., Double blind exploratory study on de novo lipogenesis in preterm infants on parenteral nutrition with a lipid emulsion containing 10% fish oil, Clinical Nutrition, 35, 337-343, 2016	Outcomes do not meet protocol eligibility criteria - lipogenesis.
Bialecka-Pikul, M., Lauterbach, R., Pawlik, D., May the supplementation of lipid emulsion containing DHA in VLBW infants influence their psychological development evaluated at three years of age? Preliminary study, Developmental period medicine, 18, 432-438, 2014	Study design does not meet protocol eligibility criteria - Cohort study.
Bientz, J., Frey, A., Schirardin, H., Bach, A. C., Medium-chain triglycerides in parenteral nutrition in the newborn: a short-term clinical trial, Infusionstherapie (Basel, Switzerland), 15, 96-9, 1988	Intervention does not meet protocol eligibility criteria - Different types of lipid emulsions.
Blackmer, Allison B., Warschausky, Seth, Siddiqui, Sabina, Welch, Kathleen B., Horn, Karolyn, Wester, Ashley, Warschausky, Micah, Teitelbaum, Daniel	Study design does not meet protocol eligibility criteria - Cohort study.

Study	Reason for Exclusion
H., Preliminary findings of long-term neurodevelopmental outcomes of infants treated with intravenous fat emulsion reduction for the management of parenteral nutrition-associated cholestasis, JPEN. Journal of parenteral and enteral nutrition, 39, 34-46, 2015	
Blackmer, Allison Beck, Partipilo, M. Luisa, Three-in-one parenteral nutrition in neonates and pediatric patients: risks and benefits, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 30, 337-43, 2015	Study design does not meet protocol eligibility criteria - Narrative review.
Booth, G., Havranek, T., Armbrecht, E., Revenis, M., Klein, C., Scavo, L., Safety and efficacy of omegaven in preterm neonates with parenteral nutrition associated liver disease, Archives of Disease in Childhood, 97, A205, 2012	Abstract only.
Brans, Y. W., Andrew, D. S., Carrillo, D. W., Dutton, E. B., Menchaca, E. M., Puelo-Scheppke, B. A., Tolerance of fat emulsions in very low birthweight neonates: effect of birthweight on plasma lipid concentrations, American Journal of Perinatology, 7, 114-7, 1990	Study design does not meet protocol eligibility criteria - Tolerance study.
Brans, Y. W., Andrew, D. S., Carrillo, D. W., Dutton, E. B., Menchaca, E. M., Puleo-Scheppke, B. A., Tolerance of fat emulsions in very-low-birthweight neonates. Monitoring of plasma lipid concentrations, American Journal of Perinatology, 5, 8-12, 1988	Study does not meet protocol eligibility criteria - Tolerance study.
Brans,Y.W., Dutton,E.B., Andrew,D.S., Menchaca,E.M., West,D.L., Fat emulsion tolerance in very low birth weight neonates: effect on diffusion of oxygen in the lungs and on blood pH, Pediatrics, 78, 79-84, 1986	Outcomes do not meet protocol eligibility criteria - Diffusion of oxygen and blood pH.
Bridges, Kayla M., Pereira-da-Silva, Luis, Tou, Janet C., Ziegler, Jane, Brunetti, Luigi, Bone metabolism in very preterm infants receiving total parenteral nutrition: do intravenous fat emulsions have an impact?, Nutrition reviews, 73, 823-36, 2015	Study design does not meet protocol eligibility criteria - Narrative review on effects of lipids on bone.
Bryan, H., Shennan, A., Griffin, E., Angel, A., Intralipid: Its rational use in parenteral nutrition of the newborn, Pediatrics, 58, 787-790, 1976	Study design does not meet protocol eligibility criteria - Commentary.
Buck, M. L., Wooldridge, P., Ksenich, R. A., Comparison of methods for intravenous infusion of fat emulsion during extracorporeal membrane	Comparison does not meet protocol eligibility criteria - Method of delivery.

Study	Reason for Exclusion
oxygenation, Pharmacotherapy, 25, 1536-1540, 2005	
Burch, P. T., Spigarelli, M. G., Lambert, L. M., Loftus, P. D., Sherwin, C. M., Linakis, M. W., Sheng, X., LuAnn Minich, L., Williams, R. V., Use of Oxandrolone to Promote Growth in Neonates following Surgery for Complex Congenital Heart Disease: An Open-Label Pilot Trial, Congenital Heart Disease, 11, 693-699, 2016	Intervention does not meet protocol eligibility criteria - Oxandrolone therapy.
Burckart, G. J., Whitington, P. F., Halbrehder, D. K., Helms, R. A., Triglyceride and fatty acid clearance in neonates following safflower oil emulsion infusion, Journal of Parenteral and Enteral Nutrition, 7, 251-253, 1983	Study design does not meet protocol eligibility criteria - Cohort study.
Burrin, D. G., Ng, K., Stoll, B., Saenz De Pipaon, M., Impact of new-generation lipid emulsions on cellular mechanisms of parenteral nutrition-associated liver disease, Advances in nutrition (Bethesda, Md.), 5, 82-91, 2014	Study design does not meet protocol eligibility criteria - Narrative review.
Cairns, P. A., Wilson, D. C., Jenkins, J., McMaster, D., McClure, B. G., Tolerance of mixed lipid emulsion in neonates: effect of concentration, Archives of disease in childhood. Fetal and neonatal edition, 75, F113-6, 1996	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Caldwell, M. D., Jonsson, H. T., Othersen, H. B., Jr., Essential fatty acid deficiency in an infant receiving prolonged parenteral alimentation, The Journal of pediatrics, 81, 894-8, 1972	Study does not meet protocol eligibility criteria - Case study.
Calkins, K. L., Dunn, J. C. Y., Shew, S. B., Reyen, L., Farmer, D. G., Devaskar, S. U., Venick, R. S., Pediatric intestinal failure-associated liver disease is reversed with 6 months of intravenous fish oil, Journal of Parenteral and Enteral Nutrition, 38, 682-692, 2014	Population does not meet protocol eligibility criteria - Paediatric.
Calkins, K. L., Havranek, T., Kelley-Quon, L., Gibson, L., Venick, R., Shew, S., Low dose soybean oil for the prevention of parenteral nutrition associated cholestasis in neonates with congenital gastrointestinal disorders, Journal of Investigative Medicine, 61, 157-158, 2013	Included 2017 paper with full data set.
Carnielli, V. P., Rossi, K., Badon, T., Gregori, B., Verlato, G., Orzali, A., Zacchello, F., Medium-chain triacylglycerols in formulas for preterm infants: Effect on plasma lipids, circulating concentrations of medium-chain fatty acids, and essential fatty	Study does not meet protocol eligibility criteria - Cohort study.

Study	Reason for Exclusion
acids, American Journal of Clinical Nutrition, 64, 152-158, 1996	
Carnielli, V. P., Sulkers, E. J., Moretti, C., Wattimena, J. L., van Goudoever, J. B., Degenhart, H. J., Zacchello, F., Sauer, P. J., Conversion of octanoic acid into long-chain saturated fatty acids in premature infants fed a formula containing medium-chain triglycerides, Metabolism: Clinical and Experimental, 43, 1287-92, 1994	Study does not meet protocol eligibility criteria - Cohort study.
Cashore, W. J., Growth and transcutaneous oxygen transport in very low birthweight infants receiving intravenous fat emulsion, Acta Chirurgica Scandinavica, 149, 123-134, 1983	Study does not meet protocol eligibility criteria - Not an RCT.
Chaieb, S. D., Chaumeil, J. C., Jebnoun, S., Khrouf, N., Hedhili, A., Sfar, S., Effect of high calcium and phosphate concentrations on the physicochemical properties of two lipid emulsions used as total parenteral nutrition for neonates, PDA Journal of Pharmaceutical Science and Technology, 63, 27-41, 2009	Intervention does not meet protocol eligibility criteria - Storage.
Chan, S., McCowen, K. C., Bistrian, B., Medium-chain triglyceride and n-3 polyunsaturated fatty acid-containing emulsions in intravenous nutrition, Current Opinion in Clinical Nutrition and Metabolic Care, 1, 163-169, 1998	Study does not meet protocol eligibility criteria - Narrative review.
Chang, M., Kang, H., The effect of a fish-oil-based lipid emulsion on the parenteral nutrition-associated liver disease in very low birth weight infants, Archives of Disease in Childhood, 97, A207-A208, 2012	Abstract only.
Cheung, H. M., Lam, H. S., Tam, Y. H., Lee, K. H., Ng, P. C., Rescue treatment of infants with intestinal failure and parenteral nutrition-associated cholestasis (PNAC) using a parenteral fish-oil-based lipid, Clinical Nutrition, 28, 209-12, 2009	Study does not meet protocol eligibility criteria - Not an RCT.
Chirinian, N., Shah, V., Does decreasing the frequency of changing intravenous administration sets (>24 h) increase the incidence of sepsis in neonates receiving total parenteral nutrition?, Paediatrics and Child Health (Canada), 17, 501-504, 2012	Intervention does not meet protocol eligibility criteria - Timing of changing PN administration sets.
Choi, A., Fusch, G., Abed, H., Rochow, N., Fusch, C., Profiling fatty acid concentrations in hypertriglyceridemic plasma from preterm infants,	Outcomes do not meet protocol eligibility criteria - Fatty acid concentrations.

Study	Reason for Exclusion
Monatsschrift fur Kinderheilkunde, 164, S277, 2016	
Christensen, M. L., Helms, R. A., Mauer, E. C., Storm, M. C., Plasma carnitine concentration and lipid metabolism in infants receiving parenteral nutrition, The Journal of pediatrics, 115, 794-8, 1989	Outcomes do not meet protocol eligibility criteria - Plasma carnitine, triglycerides, free fatty acids, acetoacetate, and beta-hydroxybutyrate.
Chung, P. H. Y., Wong, K. K. Y., Wong, R. M. S., Tsoi, N. S., Chan, K. L., Tam, P. K. H., Clinical experience in managing pediatric patients with ultra-short bowel syndrome using omega-3 fatty acid, European journal of pediatric surgery : official journal of Austrian Association of Pediatric Surgery ... [et al] = Zeitschrift fur Kinderchirurgie, 20, 139-42, 2010	Study design does not meet protocol eligibility criteria - Not an RCT.
Cober, M. P., Killu, G., Brattain, A., Welch, K. B., Kunisaki, S. M., Teitelbaum, D. H., Intravenous fat emulsions reduction for patients with parenteral nutrition-associated liver disease, Journal of Pediatrics, 160, 421-427, 2012	Study design does not meet protocol eligibility criteria - Cohort study.
Cober, M. P., Teitelbaum, D. H., Prevention of parenteral nutrition-associated liver disease: Lipid minimization, Current Opinion in Organ Transplantation, 15, 330-333, 2010	Study design does not meet protocol eligibility criteria - Review.
Cohen,I.T., Dahms,B., Hays,D.M., Peripheral total parenteral nutrition employing a lipid emulsion (Intralipid): complications encountered in pediatric patients, Journal of Pediatric Surgery, 12, 837-845, 1977	Study design does not meet protocol eligibility criteria - Non comparative study.
Cole, C., Robertson, S., Nine cases of unintentional rapid infusion of lipid emulsion in children: Root cause analysis and changes to practice, Archives of Disease in Childhood, 99, e3, 2014	Population does not meet protocol eligibility criteria - Paediatric.
Cooke, R. J., Buis, M., Zee, P., Yeh, Y. Y., Safflower oil emulsion administration during parenteral nutrition in the preterm infant. 2. Effect on triglyceride and free fatty acid levels, Journal of Pediatric Gastroenterology and Nutrition, 4, 804-7, 1985	Outcomes do not meet protocol eligibility criteria - Plasma triglycerides and free fatty acids.
Cooke, R. J., Burckhart, G. J., Hypertriglyceridemia during the intravenous infusion of a safflower oil-based fat emulsion, Journal of Pediatrics, 103, 959-961, 1983	Comparison not relevant - different types of lipid emulsions.
Cooke, R. J., Yeh, Y. Y., Gibson, D., Debo, D., Bell, G. L., Soybean oil	No relevant outcomes reported in sufficient detail.

Study	Reason for Exclusion
emulsion administration during parenteral nutrition in the preterm infant: effect on essential fatty acid, lipid, and glucose metabolism, The Journal of pediatrics, 111, 767-73, 1987	
Cooke, R. J., Zee, P., Yeh, Y. Y., Safflower oil emulsion administration during parenteral nutrition in the preterm infant. 1. Effect on essential fatty acid status, Journal of pediatric gastroenterology and nutrition, 4, 799-803, 1985	No relevant outcomes reported in sufficient detail.
Coran, A. G., Drongowski, R., Sarahan, T. M., Wesley, J. R., Studies on the efficacy of a new 20% fat emulsion in pediatric parenteral nutrition, JPEN. Journal of parenteral and enteral nutrition, 6, 222-225, 1982	Study design does not meet protocol eligibility criteria - Cohort study.
Coran, A. G., Drongowski, R., Sarahan, T. M., Wesley, J. R., Comparison of a new 10% and 20% safflower oil fat emulsion in pediatric parenteral nutrition, JPEN. Journal of parenteral and enteral nutrition, 5, 236-9, 1981	Study design does not meet protocol eligibility criteria - Cohort study.
Cowan, Eileen, Nandivada, Prathima, Puder, Mark, Fish oil-based lipid emulsion in the treatment of parenteral nutrition-associated liver disease, Current Opinion in Pediatrics, 25, 193-200, 2013	Study design does not meet protocol eligibility criteria - Review.
Crill, Catherine M., Hak, Emily B., Robinson, Lawrence A., Helms, Richard A., Evaluation of microbial contamination associated with different preparation methods for neonatal intravenous fat emulsion infusion, American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists, 67, 914-8, 2010	Intervention does not meet protocol eligibility criteria - Methods of delivery.
Curran, J. S., Williams, P. R., Kanarek, K. S., Novak, M., Monkus, E. F., An evaluation of orally supplemented L-carnitine in premature infants receiving Intralipid 20%, Acta chirurgica Scandinavica. Supplementum, 517, 157-64, 1983	Intervention does not meet protocol eligibility criteria - L-carnitine supplementation.
Dahl, G. B., Svensson, L., Kinnander, N. J., Zander, M., Bergstrom, U. K., Stability of vitamins in soybean oil fat emulsion under conditions simulating intravenous feeding of neonates and children, JPEN. Journal of parenteral and enteral nutrition, 18, 234-9, 1994	Outcomes do not meet protocol eligibility criteria - Vitamin concentrations.
D'Ascenzo, R., D'Egidio, S., Angelini, L., Bellagamba, M. P., Manna, M., Pompilio,	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsion.

Study	Reason for Exclusion
A., Cogo, P. E., Carnielli, V. P., Parenteral nutrition of preterm infants with a lipid emulsion containing 10% fish oil: Effect on plasma lipids and long-chain polyunsaturated fatty acids, Journal of Pediatrics, 159, 33, 2011	
D'Ascenzo, R., Savini, S., Biagetti, C., Bellagamba, M. P., Marchionni, P., Pompilio, A., Cogo, P. E., Carnielli, V. P., Higher Docosahexaenoic acid, lower Arachidonic acid and reduced lipid tolerance with high doses of a lipid emulsion containing 15% fish oil: A randomized clinical trial, Clinical Nutrition, 33, 1002-1009, 2014	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsion.
Davidson, G. P., Phelan, P. D., Townley, R. R., A controlled trial using intravenous infusion of soya oil emulsion in the treatment of children with cystic fibrosis, Australian Paediatric Journal, 14, 80-2, 1978	Study design does not meet protocol eligibility criteria - Cohort study.
De Leeuw, R., Kok, K., De Vries, I. J., Beganovic, N., Tolerance of intravenously administered lipid in newborns, Acta Paediatrica Scandinavica, 74, 52-56, 1985	Study design does not meet protocol eligibility criteria - Non-comparative study.
de Meijer, Vincent E., Le, Hau D., Meisel, Jonathan A., Gura, Kathleen M., Puder, Mark, Parenteral fish oil as monotherapy prevents essential fatty acid deficiency in parenteral nutrition-dependent patients, Journal of pediatric gastroenterology and nutrition, 50, 212-8, 2010	Study design does not meet protocol eligibility criteria - Cohort study.
DeLuca, F. G., Study of Intralipid 20% intravenous fat emulsion in post-surgical neonates, Acta chirurgica Scandinavica. Supplementum, 517, 165-8, 1983	Comparison does not meet protocol eligibility criteria - Different lines of infusion.
Demirel, G, Oguz, Ss, Celik, Ih, Erdeve, O, Uras, N, Dilmen, U, The metabolic effects of two different lipid emulsions used in parenterally fed premature infants--a randomized comparative study, Early Human Development, 88, 499-501, 2012	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsion.
Deshpande, G, Simmer, K, Deshmukh, M, Mori, Ta, Croft, Kd, Kristensen, J, Fish Oil (SMOFlipid) and olive oil lipid (Clinoleic) in very preterm neonates, Journal of Pediatric Gastroenterology and Nutrition, 58, 177-182, 2014	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Deshpande, G. C., Simmer, K., Mori, T., Croft, K., Parenteral lipid emulsions based on olive oil compared with soybean oil in preterm (<28 weeks' Gestation) neonates: A randomised	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsion.

Study	Reason for Exclusion
controlled trial, Journal of Pediatric Gastroenterology and Nutrition, 49, 619-625, 2009	
Deshpande, Girish, Simmer, Karen, Lipids for parenteral nutrition in neonates, Current Opinion in Clinical Nutrition and Metabolic Care, 14, 145-50, 2011	Study design does not meet protocol eligibility criteria - Review.
D'Harlingue, A., Hopper, A. O., Stevenson, D. K., Shahin, S. M., Kerner, J. A., Jr., Limited value of nephelometry in monitoring the administration of intravenous fat in neonates, JPEN. Journal of parenteral and enteral nutrition, 7, 55-8, 1983	Outcomes do not meet protocol eligibility criteria - serum IVF level, triglyceride, cholesterol, and free fatty acid/albumin molar ratio.
Diamond, Ivan R., Pencharz, Paul B., Wales, Paul W., Omega-3 lipids for intestinal failure associated liver disease, Seminars in pediatric surgery, 18, 239-45, 2009	Study design does not meet protocol eligibility criteria - Review.
Driscoll, David F., Bistrian, Bruce R., Demmelmair, Hans, Koletzko, Berthold, Pharmaceutical and clinical aspects of parenteral lipid emulsions in neonatology, Clinical nutrition (Edinburgh, Scotland), 27, 497-503, 2008	Study design does not meet protocol eligibility criteria - Review.
Ernst, K. D., Essential fatty acid deficiency during parenteral soybean oil lipid minimization, Journal of Perinatology, 37, 695-697, 2017	Study design does not meet protocol eligibility criteria - Cohort study.
Filler, R. M., Takada, Y., Carreras, T., Heim, T., Serum Intralipid levels in neonates during parenteral nutrition: The relation to gestational age, Journal of Pediatric Surgery, 15, 405-410, 1980	Study design does not meet protocol eligibility criteria - Cohort study.
Foote, K. D., MacKinnon, M. J., Innis, S. M., Effect of early introduction of formula vs fat-free parenteral nutrition on essential fatty acid status of preterm infants, American Journal of Clinical Nutrition, 54, 93-97, 1991	Study design does not meet protocol eligibility criteria - Cohort study.
Forte, T. M., Genzel-Boroviczeny, O., Austin, M. A., Kao, L. C., Scott, C., Albers, J. J., D'Harlingue, A. E., Effect of total parenteral nutrition with intravenous fat on lipids and high density lipoprotein heterogeneity in neonates, JPEN. Journal of parenteral and enteral nutrition, 13, 490-500, 1989	Study design does not meet protocol eligibility criteria - Cohort study.
Fox, M., Molesky, M., Van Aerde, J. E., Muttitt, S., Changing parenteral nutrition administration sets every 24 h versus every 48 h in newborn infants, Journal canadien de gastroenterologie	Intervention does not meet protocol eligibility criteria - Timing of changing PN administration sets.

Study	Reason for Exclusion
[Canadian journal of gastroenterology], 13, 147-51, 1999	
Friedman, Z., Essential fatty acid consideration at birth in the premature neonate and the specific requirement for preformed prostaglandin precursors in the infant, Progress in lipid research, 25, 355-364, 1986	Study design does not meet protocol eligibility criteria - Review.
Garrido Alejos, G., Riera Armengol, P., Cardenete Ornaque, J., Prenafeta Torres, J., Estelrich Latras, J., Mangues Bafalluy, M. A., Cardona Pera, D., Physicochemical stability and sterility of all-in-one parenteral emulsions for neonates, Clinical Nutrition, 35, S127, 2016	Intervention does not meet protocol eligibility criteria - Stability testing.
Gawecka, A, Kornacka, Mk, uckiewicz, B, Rudzi?ska, I, Tolerance of two lipid emulsions used in parenterally-fed premature infants - a comparative study, Medycyna wieku rozwojowego, 12, 782-788, 2008	Full text not in English.
Gawecka, A, Michalkiewicz, J, Kornacka, Mk, Luckiewicz, B, Kubiszewska, I, Immunologic properties differ in preterm infants fed olive oil vs soy-based lipid emulsions during parenteral nutrition, JPEN. Journal of parenteral and enteral nutrition, 32, 448-453, 2008	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsion.
Genzel-Boroviczeny, O., D'Harlingue, A., Forte, T., Low density lipoproteins (LDL) heterogeneity and intravenous fat in neonates, European journal of medical research, 1, 315-20, 1996	Study design does not meet protocol eligibility criteria - Cohort study.
Georgieva, R. W., Muskiet, F. A. J., Schaafsma, A., ESPGHAN recommendations for DHA in preterm formulae do not seem to be sufficient for healthy late preterm infants to reach optimal DHA status within 8 postnatal weeks, Journal of Pediatric Gastroenterology and Nutrition, 62, 841-842, 2016	Abstract only.
Gever, L. N., Pharmacist on call: intravenous lipids, Nursing, 11, 160-1, 1981	Study design does not meet protocol eligibility criteria - Not an RCT.
Giordano, V., Klebermass-Schrehof, K., Haiden, N., Binder, C., Thanhauser, M., Kreissl, A., Tardelli, M., Berger, A., Repa, A., Parenteral nutrition using a lipid emulsion containing fish oil improves neuronal conduction in preterm infants born between the 29th-31st gestational week, European Journal of Pediatrics, 175, 1441, 2016	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.

Study	Reason for Exclusion
Gobel, Y., Koletzko, B., Bohles, H. J., Engelsberger, I., Forget, D., Le Brun, A., Peters, J., Zimmermann, A., Parenteral fat emulsions based on olive and soybean oils: A randomized clinical trial in preterm infants, Journal of Pediatric Gastroenterology and Nutrition, 37, 161-167, 2003	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Goel, R., Hamosh, M., Stahl, G. E., Henderson, T. R., Spear, M. L., Hamosh, P., Plasma lecithin: cholesterol acyltransferase and plasma lipolytic activity in preterm infants given total parenteral nutrition with 10% or 20% Intralipid, Acta paediatrica (Oslo, Norway :, 1992) 84, 1060-4, 1995	Study design does not meet protocol eligibility criteria - Cohort study.
Gohlke, B. C., Fahnenstich, H., Kowalewski, S., Serum lipids during parenteral nutrition with a 10% lipid emulsion with reduced phospholipid emulsifier content in premature infants, Journal of Pediatric Endocrinology and Metabolism, 10, 505-509, 1997	Study design does not meet protocol eligibility criteria - Cohort study.
Goulet, Olivier, Joly, Francisca, Corriol, Odile, Colomb-Jung, Virginie, Some new insights in intestinal failure-associated liver disease, Current Opinion in Organ Transplantation, 14, 256-61, 2009	Study design does not meet protocol eligibility criteria - Review.
Greene, H. L., Phillips, B. L., Franck, L., Fillmore, C. M., Said, H. M., Murrell, J. E., Moore, M. E., Briggs, R., Persistently low blood retinol levels during and after parenteral feeding of very low birth weight infants: examination of losses into intravenous administration sets and a method of prevention by addition to a lipid emulsion, Pediatrics, 79, 894-900, 1987	Outcomes do not meet protocol eligibility criteria - Serum retinol levels.
Griffin, E. A., Bryan, M. H., Angel, A., Variations in intralipid tolerance in newborn infants, Pediatric Research, 17, 478-481, 1983	Outcomes do not meet protocol eligibility criteria - Plasma intralipid concentration.
Griffin, E., Breckenridge, W. C., Kuksis, A., Bryan, M. H., Angel, A., Appearance and characterization of lipoprotein X during continuous intralipid infusions in the neonate, Journal of Clinical Investigation, 64, 1703-1712, 1979	Outcomes do not meet protocol eligibility criteria - hyperphospholipidaemia and hypercholesterolaemia.
Gura, Kathleen M., Lee, Sang, Valim, Clarissa, Zhou, Jing, Kim, Sendia, Modi, Biren P., Arsenault, Danielle A., Strijbosch, Robbert A. M., Lopes, Suzanne, Duggan, Christopher, Puder, Mark, Safety and efficacy of a fish-oil-based fat emulsion in the treatment of	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.

Study	Reason for Exclusion
parenteral nutrition-associated liver disease, Pediatrics, 121, e678-86, 2008	
Gutcher, G. R., Farrell, P. M., Intravenous infusion of lipid for the prevention of essential fatty acid deficiency in premature infants, American Journal of Clinical Nutrition, 54, 1024-1028, 1991	Study design does not meet protocol eligibility criteria - Non-comparative study.
Guthrie, G., Premkumar, M., Burrin, D. G., Emerging clinical benefits of new-generation fat emulsions in preterm neonates, Nutrition in Clinical Practice, 32, 326-336, 2017	Study design does not meet protocol eligibility criteria - Review.
Hamilton, J. J., Phang, M., Innis, S. M., Elevation of plasma lathosterol, as an indicator of increased cholesterol synthesis, in preterm (23-32 weeks gestation) infants given intralipid, Pediatric Research, 31, 186-192, 1992	Outcomes do not meet protocol eligibility criteria - Plasma lathosterol.
Hanssler, L, Schlotzer, E, Blenkers, B, Roll, C, Zhou, C, Kordass, U, Elimination of fat emulsions of various concentrations from the blood. Observational study in the intravenous administration of Lipovenös 10% and 20% in premature infants with very low birth weight, Klinische padiatrie, 204, 27-33, 1992	Study design does not meet protocol eligibility criteria - Observational study.
Hardy, Gil, Puzovic, Marko, Formulation, stability, and administration of parenteral nutrition with new lipid emulsions, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 24, 616-25, 2009	Study design does not meet protocol eligibility criteria - Review.
Hartman, C., Shamir, R., Intravenous lipid emulsions in term infants: impact on laboratory and clinical outcomes and long-term consequences, World review of nutrition and dietetics, 112, 81-89, 2015	Study design does not meet protocol eligibility criteria - Review.
Haumont, D., Deckelbaum, R. J., Richelle, M., Dahlan, W., Coussaert, E., Bihain, B. E., Carpentier, Y. A., Plasma lipid and plasma lipoprotein concentrations in low birth weight infants given parenteral nutrition with twenty or ten percent lipid emulsion, The Journal of pediatrics, 115, 787-93, 1989	No relevant outcomes reported sufficiently for extraction.
Haumont, D., Richelle, M., Deckelbaum, R. J., Coussaert, E., Carpentier, Y. A., Effect of liposomal content of lipid emulsions on plasma lipid concentrations in low birth weight infants receiving parenteral nutrition, Journal of Pediatrics, 121, 759-763, 1992	Outcomes do not meet protocol eligibility criteria - Triglyceride, cholesterol, and phospholipid concentrations.

Study	Reason for Exclusion
Haumont, D., Rossle, C., Clercx, A., Spehl, L., Biver, A., Richelle, M., Carpentier, Y. A., Modifications of surfactant phospholipid pattern in premature infants treated with Curosurf: Clinical and dietary correlations, Biology of the Neonate, 61, 37-43, 1992	Outcomes do not meet protocol eligibility criteria - Surfactant phospholipids.
Haumont, Dominique, Lipid infusion and intravenous access in newborn infants, Chinese medical journal, 123, 2766-8, 2010	Study does not meet protocol eligibility criteria - Review.
Hegyi, T., Kleinfeld, A., Huber, A., Weinberger, B., Memon, N., Shih, W. J., Carayannopoulos, M., Oh, W., Effects of Soybean Lipid Infusion on Unbound Free Fatty Acids and Unbound Bilirubin in Preterm Infants, Journal of Pediatrics, 184, 45, 2017	Outcomes do not meet protocol eligibility criteria - Bilirubin and free fatty acids.
Hegyi, Thomas, Kleinfeld, Alan, Huber, Andrew, Weinberger, Barry, Memon, Naureen, Joe Shih, Weichung, Carayannopoulos, Mary, Oh, William, Effects of soybean lipid infusion on triglyceride and unbound free fatty acid levels in preterm infants, The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 1-6, 2018	Study does not meet protocol eligibility criteria - Not an RCT.
Hegyi, Thomas, Kleinfeld, Alan, Huber, Andrew, Weinberger, Barry, Memon, Naureen, Shih, Weichung Joe, Carayannopoulos, Mary, Oh, William, Effects of Soybean Lipid Infusion on Unbound Free Fatty Acids and Unbound Bilirubin in Preterm Infants, The Journal of pediatrics, 184, 45-50.e1, 2017	Study does not meet protocol eligibility criteria - Not an RCT.
Heird, W. C., Biochemical homeostasis and body growth are reliable end points in clinical nutrition trials, Proceedings of the Nutrition Society, 64, 297-303, 2005	Study design does not meet protocol eligibility criteria - Narrative review.
Heird, W. C., Driscoll, J. M., Jr., Use of intravenously administered lipid in neonates, Pediatrics, 56, 5-7, 1975	Study design does not meet protocol eligibility criteria - Review.
Helms, R. A., Herrod, H. G., Burckart, G. J., Christensen, M. L., E-rosette formation, total T-cells, and lymphocyte transformation in infants receiving intravenous safflower oil emulsion, JPEN. Journal of parenteral and enteral nutrition, 7, 541-5, 1983	Outcomes do not meet protocol eligibility criteria - Immunological outcomes.
Herson, V. C., Block, C., Eisenfeld, L., Maderazo, E. G., Krause, P. J., Effects	Outcomes do not meet protocol eligibility criteria - Immunological outcomes.

Study	Reason for Exclusion
of intravenous fat infusion on neonatal neutrophil and platelet function, Journal of Parenteral and Enteral Nutrition, 13, 620-622, 1989	
Hertel, J., Tygstrup, I., Andersen, G. E., Intravascular fat accumulation after Intralipid infusion in the very low-birth-weight infant, The Journal of pediatrics, 100, 975-6, 1982	Outcomes do not meet protocol eligibility criteria - Intravascular fat accumulation.
Hicks, R. W., Becker, S. C., Chuo, J., A summary of NICU fat emulsion medication errors and nursing services: data from MEDMARX, Advances in neonatal care : official journal of the National Association of Neonatal Nurses, 7, 2007	Outcomes do not meet protocol eligibility criteria - Medication errors.
Hilliard, J. L., Shannon, D. L., Hunter, M. A., Brans, Y. W., Plasma lipid levels in preterm neonates receiving parenteral fat emulsions, Archives of Disease in Childhood, 58, 29-33, 1983	Outcomes do not meet protocol eligibility criteria - Plasma lipid levels.
Hirai, Y., Sanada, Y., Hasegawa, S., Fujiwara, T., Iwakiri, K., Total parenteral nutrition in low-birth-weight neonates with complicated surgical disorders; effects and difficulties, The Japanese journal of surgery, 11, 175-83, 1981	Study design does not meet protocol eligibility criteria - Not an RCT.
Ho, M. Y., Yen, Y. H., Trend of Nutritional Support in Preterm Infants, Pediatrics and Neonatology, 57, 365-370, 2016	Study design does not meet protocol eligibility criteria - Review.
Holtrop, P., Swails, T., Riggs, T., Hypertriglyceridemia in extremely low birth weight infants receiving lipid emulsions, Journal of Neonatal-Perinatal Medicine, 8, 133-136, 2015	Study design does not meet protocol eligibility criteria - Not an RCT.
Hunt, C. E., Engel, R. R., Modler, S., Hamilton, W., Bissen, S., Holman, R. T., Essential fatty acid deficiency in neonates: inability to reverse deficiency by topical applications of EFA-rich oil, The Journal of pediatrics, 92, 603-7, 1978	Outcomes do not meet protocol eligibility criteria - Serum essential fatty acid levels.
Ichikawa, J., Ichikawa, G., Tsuboi, Y., Kuribayashi, R., Watabe, Y., Sairenchi, T., Suzumura, H., Arisaka, O., Safety of lipid emulsion in very low-birthweight infants according to cytokine level, Pediatrics International, 2016	Outcomes do not meet protocol eligibility criteria - Cytokine levels.
Inder, T. E., Darlow, B. A., Sluis, K. B., Winterbourn, C. C., Graham, P., Sanderson, K. J., Taylor, B. J., The correlation of elevated levels of an index of lipid peroxidation (MDA-TBA) with adverse outcome in the very low birthweight infant, Acta paediatrica	Study design does not meet protocol eligibility criteria - Not an RCT.

Study	Reason for Exclusion
(Oslo, Norway : 1992), 85, 1116-22, 1996	
Innis, S. M., Essential fatty acid transfer and fetal development, Placenta, 26 Suppl A, S70-5, 2005	Study design does not meet protocol eligibility criteria - Not an RCT.
Innis, S. M., n-3 Fatty acid requirements of the newborn, Lipids, 27, 879-885, 1992	Study design does not meet protocol eligibility criteria - Review.
Jalabert, A., Grand, A., Steghens, J. P., Barbotte, E., Pigue, C., Picaud, J. C., Lipid peroxidation in all-in-one admixtures for preterm neonates: Impact of amount of lipid, type of lipid emulsion and delivery condition, Acta Paediatrica, International Journal of Paediatrics, 100, 1200-1205, 2011	Topic not relevant - Storage study.
Janvier, A., Beaumier, L., Barrington, K. J., Intestinal Absorption of Lipid Emulsion in Premature Infants: A Pilot Study, Neonatology, 100, 248-252, 2011	Intervention does not meet protocol eligibility criteria - Enteral nutrition.
Jarvis,W.R., Highsmith,A.K., Allen,J.R., Haley,R.W., Polymicrobial bacteremia associated with lipid emulsion in a neonatal intensive care unit, Pediatric Infectious Disease, 2, 203-208, 1983	Outcomes do not meet protocol eligibility criteria - Polymicrobial bacteraemia.
Joffe, Ari, Anton, Natalie, Lequier, Laurance, Vandermeer, Ben, Tjosvold, Lisa, Larsen, Bodil, Hartling, Lisa, Nutritional support for critically ill children, Cochrane Database of Systematic Reviews, 2016	Comparisons do not meet protocol eligibility criteria - Different combinations of parenteral and/or enteral nutrition.
Johnson, P. J., Review of macronutrients in parenteral nutrition for neonatal intensive care population, Neonatal network : NN, 33, 29-34, 2014	Study design does not meet protocol eligibility criteria - Review.
Josephson, J. K., Wales, P. W., Nation, P. N., Wizzard, P., Mager, D., Field, C. J., Ball, R. O., Pencharz, P. B., Turner, J. M., Parenteral lipid minimization versus composition for intestinal failure associated liver disease, FASEB Journal, 27, 2013	Population does not meet protocol eligibility criteria - Animal study.
Kanarek, K. S., Santeiro, M. L., Malone, J. I., Continuous infusion of insulin in hyperglycemic low-birth weight infants receiving parenteral nutrition with and without lipid emulsion, Jpen: Journal of Parenteral & Enteral NutritionJPEN J Parenter Enteral Nutr, 15, 417-20, 1991	Study design does not meet protocol eligibility criteria - Not an RCT.
Kapoor, V., Glover, R., Malviya, M. N., Alternative lipid emulsions versus pure soy oil based lipid emulsions for parenterally fed preterm infants, The Cochrane database of systematic reviews, 12, CD009172, 2015	Comparisons do not meet protocol eligibility criteria - Different types of lipid emulsions.

Study	Reason for Exclusion
Karagiozoglou-Lampoudi, T., Skouroliakou, M., Konstantinou, D., Agakidis, C., Delikou, N., Koutri, K., Antoniadi, M., Omega-3-polyunsaturated fatty acid-enriched parenteral lipid emulsion and prevention of cholestasis in preterm infants. Comparison with soybean-based lipid emulsion, European Journal of Hospital Pharmacy: Science and Practice, 19 (2), 221-222, 2012	Abstract only.
Kelly, Deirdre A., Preventing parenteral nutrition liver disease, Early Human Development, 86, 683-7, 2010	Study design does not meet protocol eligibility criteria - Review.
Kerner, John A., Jr., Poole, Robert L., The use of IV fat in neonates, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 21, 374-80, 2006	Study design does not meet protocol eligibility criteria - Review.
Kerner,J.A.,Jr., Cassani,C., Hurwitz,R., Berde,C.B., Monitoring intravenous fat emulsions in neonates with the fatty acid/serum albumin molar ratio, Jpen: Journal of Parenteral and Enteral Nutrition, 5, 517-518, 1981	Outcomes do not meet protocol eligibility criteria - Fatty acid/serum albumin molar ratios.
Kerzner, B., Sloan, H. R., Lubin, A. H., Rainey, L., McClung, H. J., McClead, R., Anderson, C., Gregoire, R., The use of Intralipid 10% and 20% in very low birthweight premature infants, Acta chirurgica Scandinavica. Supplementum, 517, 135-48, 1983	Outcomes do not meet protocol eligibility criteria.
Kesiak, M., Nowiczewski, M., Talar, T., Gulczynska, E., Early use of intravenous lipids in two different doses in the group of very low birth weight newborns - RCT, Early Human Development, 86, S86, 2010	Abstract only.
Kessler, U., Poeschl, J., Raz, D., Linderkamp, O., Bauer, J., Effects of intralipid infusion on blood viscosity and other haemorheological parameters in neonates and children, Acta Paediatrica, International Journal of Paediatrics, 93, 1058-1062, 2004	Outcomes do not meet protocol eligibility criteria - Haemorrheological parameters.
Kessler, Ulf, Zachariou, Zacharias, Raz, Dorothea, Poeschl, Johannes, Linderkamp, Otwin, Effects of Intralipid infusion on hemorheology and peripheral resistance in neonates and children, Pediatric surgery international, 21, 197-202, 2005	Outcomes do not meet protocol eligibility criteria - Haemorrheological outcomes.
Khanam, S., Khan, J., Sharma, D., Chawla, D., Murki, S., Nutritional bundle to improve growth outcomes among very low birth weight infants, Journal of	Study design does not meet protocol eligibility criteria - Not an RCT.

Study	Reason for Exclusion
Maternal-Fetal & Neonatal Medicine, 28, 1851-5, 2015	
Klein, C. J., Havranek, T. G., Revenis, M. E., Hassanali, Z., Scavo, L. M., Plasma fatty acids in premature infants with hyperbilirubinemia: Before-and-after nutrition support with fish oil emulsion, Nutrition in Clinical Practice, 28, 87-94, 2013	Study design does not meet protocol eligibility criteria - Not an RCT.
Köksal, N, Kavurt, Av, Cetinkaya, M, Ozarda, Y, Ozkan, H, Comparison of lipid emulsions on antioxidant capacity in preterm infants receiving parenteral nutrition, Pediatrics international : official journal of the Japan Pediatric Society, 53, 562-6, 2011	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Koletzko, B., Parenteral lipid infusion in infancy: Physiological basis and clinical relevance, Clinical Nutrition, 21, 53-65, 2002	Study design does not meet protocol eligibility criteria - Review.
Koletzko, B., Lipid supply and metabolism in infancy, Current Opinion in Clinical Nutrition and Metabolic Care, 1, 171-177, 1998	Study design does not meet protocol eligibility criteria - Review.
Koletzko, B., Demmelmair, H., Socha, P., Nutritional support of infants and children: supply and metabolism of lipids, Bailliere's clinical gastroenterology, 12, 671-96, 1998	Study design does not meet protocol eligibility criteria - Review.
Koletzko, B., Filler, R. M., Heim, T., Immaturity alters plasma lipoprotein composition of intravenously alimented newborn infants, European journal of medical research, 3, 89-94, 1998	Intervention does not meet protocol eligibility criteria - PN did not contain lipids.
Komura, J., Yano, H., Tanaka, Y., Tsuru, T., Increased incidence of cholestasis during total parenteral nutrition in children--factors affecting stone formation, The Kurume medical journal, 40, 7-11, 1993	Study design does not meet protocol eligibility criteria - Review.
Kotiya, P., Zhao, X., Cheng, P., Zhu, X., Xiao, Z., Wang, J., Fish oil- and soy oil-based lipid emulsions in neonatal parenteral nutrition: a systematic review and meta-analysis, European journal of clinical nutrition, 70, 1106-1115, 2016	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Krohn, Kathrin, Koletzko, Berthold, Parenteral lipid emulsions in paediatrics, Current opinion in clinical nutrition and metabolic care, 9, 319-23, 2006	Study design does not meet protocol eligibility criteria - Review.
Lajoinie, A., Gelas, P., Salmon, D., Bergoin, C., Roussel, L., Falson, F., Chambrier, C., Souquet, J. C., Pivot, C., Haftek, M., Pirot, F., Impact of intravenous lipid emulsion infusion on	Outcomes do not meet protocol eligibility criteria - Stratum corneum barrier function.

Study	Reason for Exclusion
the stratum corneum barrier function in patients receiving parenteral nutrition, European journal of dermatology : EJD, 2013	
Lam, H. S., Tam, Y. H., Poon, T. C. W., Cheung, H. M., Yu, X., Chan, B. P. L., Lee, K. H., Lee, B. S. C., Ng, P. C., A double-blind randomised controlled trial of fish oil-based versus soy-based lipid preparations in the treatment of infants with parenteral nutrition-associated cholestasis, Neonatology, 105, 290-296, 2014	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Lapillonne, A., Enteral and parenteral lipid requirements of preterm infants, World review of nutrition and dietetics, 110, 82-98, 2014	Study does not meet protocol eligibility criteria - Review.
Larsen, Bm, Field, Cj, Leong, Ay, Goonewardene, La, Aerde, Je, Joffe, Ar, Clandinin, Mt, Pretreatment with an intravenous lipid emulsion increases plasma eicosapentanoic acid and downregulates leukotriene b4, procalcitonin, and lymphocyte concentrations after open heart surgery in infants, JPEN. Journal of parenteral and enteral nutrition, 39, 171-9, 2015	Outcomes do not meet protocol eligibility criteria - Plasma phospholipids and immunological outcomes.
Larsen, Bm, Goonewardene, La, Joffe, Ar, Aerde, Je, Field, Cj, Olstad, Dl, Clandinin, Mt, Pre-treatment with an intravenous lipid emulsion containing fish oil (eicosapentaenoic and docosahexaenoic acid) decreases inflammatory markers after open-heart surgery in infants: a randomized, controlled trial, Clinical nutrition (Edinburgh, Scotland), 31, 322-9, 2012	Outcomes do not meet protocol eligibility criteria - Inflammatory markers.
Lavoie, P. M., Lavoie, J. C., Watson, C., Rouleau, T., Chang, B. A., Chessex, P., Inflammatory response in preterm infants is induced early in life by oxygen and modulated by total parenteral nutrition, Pediatric Research, 68, 248-251, 2010	Study does not meet protocol eligibility criteria - Not an RCT.
Lee, S. I., Valim, C., Johnston, P., Le, H. D., Meisel, J., Arsenault, D. A., Gura, K. M., Puder, M., Impact of fish oil-based lipid emulsion on serum triglyceride, bilirubin, and albumin levels in children with parenteral nutrition-associated liver disease, Pediatric Research, 66, 698-703, 2009	Comparisons do not meet protocol eligibility criteria - Different types of lipid emulsions.
Lehner, F, Demmelmair, H, Röschinger, W, Decsi, T, Szász, M, Adamovich, K, Arnecke, R, Koletzko, B, Metabolic effects of intravenous LCT or MCT/LCT	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.

Study	Reason for Exclusion
lipid emulsions in preterm infants, Journal of Lipid Research, 47, 404-411, 2006	
Levene, M. I., Batisti, O., Wigglesworth, J. S., Desai, R., Meek, J. H., Bulusu, S., Hughes, E., A prospective study of intrapulmonary fat accumulation in the newborn lung following intralipid infusion, Acta paediatrica Scandinavica, 73, 454-60, 1984	Outcomes do not meet protocol eligibility criteria - Intrapulmonary fat accumulation.
Liet, J. M., Piloquet, H., Marchini, J. S., Maugere, P., Bobin, C., Roze, J. C., Darmaun, D., Leucine metabolism in preterm infants receiving parenteral nutrition with medium-chain compared with long-chain triacylglycerol emulsions, The American journal of clinical nutrition, 69, 539-43, 1999	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Lilja, Helene Engstrand, Finkel, Yigael, Paulsson, Mattias, Lucas, Steven, Prevention and reversal of intestinal failure-associated liver disease in premature infants with short bowel syndrome using intravenous fish oil in combination with omega-6/9 lipid emulsions, Journal of Pediatric Surgery, 46, 1361-7, 2011	Study design does not meet protocol eligibility criteria - Non-comparative study.
Lopez-Alarcon, M., Bernabe-Garcia, M., Valle, O. d, Gonzalez-Moreno, G., Martinez-Basilea, A., Villegas, R., Oral administration of docosahexaenoic acid attenuates interleukin-1beta response and clinical course of septic neonates, Nutrition	Intervention does not meet protocol eligibility criteria - Docosahexaenoic acid.
Magnusson, G., Boberg, M., Cederblad, G., Meurling, S., Plasma and tissue levels of lipids, fatty acids and plasma carnitine in neonates receiving a new fat emulsion, Acta paediatrica (Oslo, Norway : 1992), 86, 638-44, 1997	Study does not meet protocol eligibility criteria - Not an RCT.
Mandyla, H., Hatjidemitriou, A., Tsingoglou, S., Xanthou, M., Parental nutrition in sick low-birth-weight neonates, Padiatrie und Padologie, 17, 201-9, 1982	Study does not meet protocol eligibility criteria - Not an RCT.
Martinez, M., Ballabriga, A., Effects of parenteral nutrition with high doses of linoleate on the developing human liver and brain, Lipids, 22, 133-8, 1987	Study does not meet protocol eligibility criteria - Cohort study.
McClead, R. E., Jr., Lentz, M. E., Coniglio, J. G., Meng, H. C., Gozs, S., The effect of three intravenous fat emulsions containing different concentrations of linoleic and alpha-linolenic acids on the plasma total fatty acid profile of neonates, Journal of	Study does not meet protocol eligibility criteria - Cohort study.

Study	Reason for Exclusion
pediatric gastroenterology and nutrition, 12, 89-95, 1991	
McClead, R. E., Jr., Meng, H. C., Gregory, S. A., Budde, C., Sloan, H. R., Comparison of the clinical and biochemical effect of increased alpha-linolenic acid in a safflower oil intravenous fat emulsion, Journal of pediatric gastroenterology and nutrition, 4, 234-9, 1985	Comparison does not meet protocol eligibility criteria - Different content of alpha-linolenic acid.
Meng, H. C., Significance of eicosapentaenoic acid (EPA) in nutritional support, Infusionstherapie und Klinische Ernahrung - Forschung und Praxis, 14, 51-56, 1987	Study does not meet protocol eligibility criteria - Not an RCT.
Meng, H. C., Stahlman, M. T., Otten, A., Dolanski, E. A., Caldwell, M. D., O'Neill, J. A., The use of a crystalline amino acid mixture for parenteral nutrition in low-birth-weight infants, Pediatrics, 59, 699-709, 1977	Study does not meet protocol eligibility criteria - Not an RCT.
Mirtallo, Jay M., Dasta, Joseph F., Kleinschmidt, Kurt C., Varon, Joseph, State of the art review: Intravenous fat emulsions: Current applications, safety profile, and clinical implications, The Annals of pharmacotherapy, 44, 688-700, 2010	Study does not meet protocol eligibility criteria - Review.
Mohammadzadeh, A., Farhat, A. S., Esmaeli, H., Amiri, R., Effect of clofibrate on serum triglyceride and cholesterol after intravenous lipid in very low birth weight neonates, Iranian Journal of Neonatology, 4, 20-25, 2013	Intervention does not meet protocol eligibility criteria - Clofibrate.
Morgan, C., Parry, S., Tan, M., Neurodevelopmental outcome in very preterm infants randomized to receive two different parenteral nutrition regimens: The scamp nutrition study, Journal of Neonatal-Perinatal Medicine, 10, 220-221, 2017	Abstract only.
Nasr, Ahmed, Diamond, Ivan R., de Silva, Nicole T., Wales, Paul W., Is the use of parenteral omega-3 lipid emulsions justified in surgical neonates with mild parenteral nutrition-associated liver dysfunction?, Journal of pediatric surgery, 45, 980-6, 2010	Study does not meet protocol eligibility criteria - Cohort study.
Nehra, D., Fallon, E. M., Carlson, S. J., Potemkin, A. K., Hevelone, N. D., Mitchell, P. D., Gura, K. M., Puder, M., Provision of a soy-based intravenous lipid emulsion at 1 g/kg/d does not prevent cholestasis in neonates, Journal of Parenteral and Enteral Nutrition, 37, 498-505, 2013	Study does not meet protocol eligibility criteria - Cohort study.

Study	Reason for Exclusion
Nehra, D., Fallon, E. M., Potemkin, A. K., Voss, S. D., Mitchell, P. D., Valim, C., Belfort, M. B., Bellinger, D. C., Duggan, C., Gura, K. M., Puder, M., A comparison of 2 intravenous lipid emulsions: Interim analysis of a randomized controlled trial, Journal of Parenteral and Enteral Nutrition, 38, 693-701, 2014	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsion.
O'Meara, M., Hall, N. J., Hickey, A., Garvie, D., Kader, M., Observational study of an omega 3 based lipid emulsion in surgical infants with parenteral nutrition associated liver disease, Archives of Disease in Childhood, 94, e2, 2009	Study does not meet protocol eligibility criteria - Not an RCT.
Ong, M. L., Purdy, I., Molchan, L., Grogan, T., Elashoff, D., Calkins, K. L., Intravenous low dose soybean oil in preterm infants: Long-term follow-up on growth and neurodevelopment, Journal of Investigative Medicine, 62, 234, 2014	Abstract only.
Palchevska-Kocevska,S., Kojik,L., Associative tolerance of intravenously administered lipid and gestational age in preterm infants receiving total parenteral nutrition, Macedonian Journal of Medical Sciences, 2, 63-68, 2009	Study does not meet protocol eligibility criteria - Cohort study.
Park, Hye Won, Lee, Na Mi, Kim, Ji Hee, Kim, Kyo Sun, Kim, Soo-Nyung, Parenteral fish oil-containing lipid emulsions may reverse parenteral nutrition-associated cholestasis in neonates: a systematic review and meta-analysis, The Journal of nutrition, 145, 277-83, 2015	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Park, W., Paust, H., Brosicke, H., Knoblach, G., Helge, H., Impaired fat utilization in parenterally fed low-birth-weight infants suffering from sepsis, JPEN. Journal of parenteral and enteral nutrition, 10, 627-630, 1986	Study does not meet protocol eligibility criteria - Cohort study.
Park, W., Paust, H., Schroder, H., Lipid infusion in premature infants suffering from sepsis, Journal of Parenteral and Enteral Nutrition, 8, 290-292, 1984	Study does not meet protocol eligibility criteria - Cohort study.
Paust, H., Schroder, H., Park, W., Jakobs, C., Frauendienst, G., Fat elimination in parenterally fed low birth weight infants during the first two weeks of life, JPEN. Journal of parenteral and enteral nutrition, 7, 557-9, 1983	Study does not meet protocol eligibility criteria - Cohort study.
Pawlik, D., Lauterbach, R., Hurkala, J., The efficacy of fish-oil based fat emulsion administered from the first day of life in very low birth weight newborns,	Study does not meet protocol eligibility criteria - Not an RCT.

Study	Reason for Exclusion
Medycyna wieku rozwojowego, 15, 306-311, 2011	
Pawlik, D., Lauterbach, R., Turyk, E., Fish-oil fat emulsion supplementation may reduce the risk of severe retinopathy in VLBW infants, Pediatrics, 127, 223-228, 2011	Study does not meet protocol eligibility criteria - Not an RCT.
Pawlik, D., Lauterbach, R., Walczak, M., Hurkala, J., Sherman, M. P., Fish-oil fat emulsion supplementation reduces the risk of retinopathy in very low birth weight infants: A prospective, randomized study, Jpen, Journal of parenteral and enteral nutrition. 38, 711-6, 2014	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Pawlik,D., Lauterbach,R., Walczak,M., Hurkala,J., Docosahexaenoic acid (DHA) concentration in very low birth weight newborns receiving a fish-oil based fat emulsion from the first day of life. Preliminary clinical observation, Medycyna Wieku Rozwojowego, 15, 312-317, 2011	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Pencharz, P., Beesley, J., Sauer, P., Van Aerde, J., Canagarayar, U., Renner, J., McVey, M., Wesson, D., Swyer, P., Total-body protein turnover in parenterally fed neonates: Effects of energy source studied by using [15N]glycine and [1-13C]leucine, American Journal of Clinical Nutrition, 50, 1395-1400, 1989	Outcomes do not meet protocol eligibility criteria - Nitrogen retention and total-body protein turnover.
Phelps, S. J., Cochran, E. B., Effect of the continuous administration of fat emulsion on the infiltration of intravenous lines in infants receiving peripheral parenteral nutrition solutions, JPEN. Journal of parenteral and enteral nutrition, 13, 628-32, 1989	Population does not meet protocol eligibility criteria - Includes older infants.
Phelps, S., Dykes, E., Pierro, A., Bolus intravenous infusion of amino acids or lipids does not stimulate gallbladder contraction in neonates on total parenteral nutrition, Journal of Pediatric Surgery, 33, 817-20, 1998	Outcomes do not meet protocol eligibility criteria - Gallbladder contraction.
Pichler, J., Simchowitz, V., Macdonald, S., Hill, S., Comparison of liver function with two new/mixed intravenous lipid emulsions in children with intestinal failure, European Journal of Clinical Nutrition, 68, 1161-1167, 2014	Population does not meet protocol eligibility criteria - Included older children.
Piedboeuf, B., Chessex, P., Hazan, J., Pineault, M., Lavoie, J. C., Total parenteral nutrition in the newborn infant: Energy substrates and respiratory	Study does not meet protocol eligibility criteria - Cross-over study.

Study	Reason for Exclusion
gas exchange, Journal of Pediatrics, 118, 97-102, 1991	
Pierro, A., Carnielli, V., Filler, R. M., Smith, J., Heim, T., Characteristics of protein sparing effect of total parenteral nutrition in the surgical infant, Journal of pediatric surgery, 23, 538-42, 1988	Outcomes do not meet protocol eligibility criteria - Oxygen consumption, carbon dioxide production, and energy expenditure.
Pietka, M., Stepska-Bodzon, D., Kryjak, M., Przybylo, A., Kowalik, A., Brniak, W., Klek, S., What is the right dosage of refined fish oil-based emulsion in neonates?, Clinical Nutrition, 35, S233, 2016	Outcomes do not meet protocol eligibility criteria - Use of fish-oil lipid emulsions.
Pineault, M., Chessex, P., Piedboeuf, B., Bisaillon, S., Beneficial effect of coinfusing a lipid emulsion on venous patency, Journal of Parenteral and Enteral Nutrition, 13, 637-640, 1989	Outcomes do not meet protocol eligibility criteria - Patency times.
Pineault, M., Lepage, G., Bisaillon, S., Roy, C. C., Chessex, P., Total parenteral nutrition in the newborn: Energy substrates and plasma total fatty acids, Pediatric Research, 26, 290-293, 1989	Outcomes do not meet protocol eligibility criteria - Plasma fatty acid levels.
Pitkanen, O. M., Luukkainen, P., Andersson, S., Attenuated lipid peroxidation in preterm infants during subsequent doses of intravenous lipids, Biology of the Neonate, 85, 184-187, 2004	Outcomes do not meet protocol eligibility criteria - Lipid peroxidation.
Rayyan, M., Devlieger, H., Jochum, F., Allegaert, K., Short-term use of parenteral nutrition with a lipid emulsion containing a mixture of soybean oil, olive oil, medium-chain triglycerides, and fish oil: A randomized double-blind study in preterm infants, Journal of Parenteral and Enteral Nutrition, 36, 81S-94S, 2012	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Rochow, N., Moller, S., Fusch, G., Drogies, T., Fusch, C., Levels of lipids in preterm infants fed breast milk, Clinical Nutrition, 29, 94-99, 2010	Intervention does not meet protocol eligibility criteria - Breast milk.
Roggero, P., Mosca, F., Gianni, M. L., Orsi, A., Amato, O., Migliorisi, E., Longini, M., Buonocore, G., F2-isoprostanes and total radical-trapping antioxidant potential in preterm infants receiving parenteral lipid emulsions, Nutrition, 26, 551-555, 2010	Outcomes do not meet protocol eligibility criteria - Lipid peroxidation.
Rollins, M. D., Ward, R. M., Jackson, W. D., Mulroy, C. W., Spencer, C. P., Ying, J., Greene, T., Book, L. S., Effect of decreased parenteral soybean lipid emulsion on hepatic function in infants at risk for parenteral nutrition-associated liver disease: A pilot study, Journal of Pediatric Surgery, 48, 1348-1356, 2013	No relevant outcomes reported sufficiently for extraction.

Study	Reason for Exclusion
Rollins, Michael D., Scaife, Eric R., Jackson, W. Daniel, Meyers, Rebecka L., Mulroy, Cecilia W., Book, Linda S., Elimination of soybean lipid emulsion in parenteral nutrition and supplementation with enteral fish oil improve cholestasis in infants with short bowel syndrome, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 25, 199-204, 2010	Study design does not meet protocol eligibility criteria - Cohort study.
Ruben, S., Kleinfeld, A. M., Richeiri, G. V., Hiatt, M., Hegyi, T., Serum levels of unbound free fatty acids II: The effect of Intralipid administration in premature infants, Journal of the American College of Nutrition, 16, 85-87, 1997	Study design does not meet protocol eligibility criteria - Not an RCT.
Rubin, M., Harell, D., Naor, N., Moser, A., Wielunsky, E., Merlob, P., Lichtenberg, D., Lipid infusion with different triglyceride cores (long-chain vs medium-chain/long-chain triglycerides): effect on plasma lipids and bilirubin binding in premature infants, JPEN. Journal of parenteral and enteral nutrition, 15, 642-6, 1991	Outcomes do not meet protocol eligibility criteria - Plasma lipids and bilirubin binding.
Rubin, M., Moser, A., Naor, N., Merlob, P., Pakula, R., Sirota, L., Effect of three intravenously administered fat emulsions containing different concentrations of fatty acids on the plasma fatty acid composition of premature infants, The Journal of pediatrics, 125, 596-602, 1994	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Sandstrom, K., Nilsson, K., Andreasson, S., Olegard, R., Larsson, L. E., Early postoperative lipid administration after neonatal surgery, Acta Paediatrica, International Journal of Paediatrics, 83, 249-254, 1994	Study design does not meet protocol eligibility criteria - Not an RCT.
Sann, L., Mathieu, M., Lasne, Y., Ruitton, A., Effect of oral administration of lipids with 67% medium chain Triglycerides on glucose homeostasis in preterm neonates, Metabolism: Clinical and Experimental, 30, 712-716, 1981	Study design does not meet protocol eligibility criteria - Not an RCT.
Savini, S., D'Ascenzo, R., Biagetti, C., Serpentini, G., Pompilio, A., Bartoli, A., Cogo, P. E., Carnielli, V. P., The effect of 5 intravenous lipid emulsions on plasma phytosterols in preterm infants receiving parenteral nutrition: A randomized clinical trial, American Journal of Clinical Nutrition, 98, 312-318, 2013	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsion.
Seida, Jennifer C., Mager, Diana R., Hartling, Lisa, Vandermeer, Ben, Turner,	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.

Study	Reason for Exclusion
Justine M., Parenteral omega-3 fatty acid lipid emulsions for children with intestinal failure and other conditions: a systematic review, JPEN. Journal of parenteral and enteral nutrition, 37, 44-55, 2013	
Simmer, K., Deshpande, G., Choice of parenteral lipid emulsion to maintain DHA status in very preterm infants- evidence from RCTS, Journal of Paediatrics and Child Health, 50, 9, 2014	Abstract only.
Skouroliakou, M., Konstantinou, D., Agakidis, C., Delikou, N., Koutri, K., Antoniadi, M., Karagiozoglou-Lampoudi, T., Cholestasis, bronchopulmonary dysplasia, and lipid profile in preterm infants receiving MCT/omega-3-PUFA-containing or soybean-based lipid emulsions, Nutrition in Clinical Practice, 27, 817-824, 2012	Study design does not meet protocol eligibility criteria - Cohort study.
Skouroliakou, M., Konstantinou, D., Agakidis, C., Kaliora, A., Kalogeropoulos, N., Massara, P., Antoniadi, M., Panagiotakos, D., Karagiozoglou-Lampoudi, T., Parenteral MCT/omega-3 Polyunsaturated Fatty Acid-Enriched Intravenous Fat Emulsion is Associated with Cytokine and Fatty Acid Profiles Consistent with Attenuated Inflammatory Response in Preterm Neonates: A Randomized, Double-Blind Clinical Trial, Nutrition in Clinical Practice, 31, 235-244, 2016	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsion.
Skouroliakou, M., Konstantinou, D., Koutri, K., Kakavelaki, C., Stathopoulou, M., Antoniadi, M., Xemelidis, N., Kona, V., Markantonis, S., A double-blind, randomized clinical trial of the effect of omega-3 fatty acids on the oxidative stress of preterm neonates fed through parenteral nutrition, European Journal of Clinical Nutrition, 64, 940-7, 2010	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsion.
Smuts, C. M., Tichelaar, H. Y., Kirsten, G. F., Dhansay, M. A., Faber, M., Van Jaarsveld, P. J., Benade, A. J. S., The effect of parenteral nutrition with lipovenous or intralipid on the fatty acid composition of plasma and erythrocyte membrane lipids in very-low-birthweight infants, South African medical journal, 89, 687-94, 1999	Outcomes do not meet protocol eligibility criteria - Fatty acid response.
Spear, M. L., Stahl, G. E., Paul, M. H., Egler, J. M., Pereira, G. R., Polin, R. A., The effect of 15-hour fat infusions of varying dosage on bilirubin binding to	Study design does not meet protocol eligibility criteria - Not an RCT.

Study	Reason for Exclusion
albumin, JPEN. Journal of parenteral and enteral nutrition, 9, 144-7, 1985	
Suganuma, Hiroki, Ikeda, Naho, Ohkawa, Natuki, Nagata, Satoru, Shoji, Hiromichi, Shimizu, Toshiaki, Fat emulsion given to very low-birthweight infants increases urinary L-FABP, Pediatrics international : official journal of the Japan Pediatric Society, 56, 207-10, 2014	Study design does not meet protocol eligibility criteria - Not an RCT.
Sunehag, A. L., The role of parenteral lipids in supporting gluconeogenesis in very premature infants, Pediatric Research, 54, 480-486, 2003	Study design does not meet protocol eligibility criteria - Not an RCT.
Techasatid, W., Sapsaprang, S., Tantiyavarong, P., Luvira, A., Effectiveness of multicomponent lipid emulsion in preterm infants requiring parenteral nutrition: A two-center, double-blind randomized clinical trial, Journal of the Medical Association of Thailand, 100, 972-979, 2017	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Thakur, A., Kansal, B. K., Saini, A., Kler, N., Garg, P., Modi, M., Soni, A., Saluja, S., Effect of aggressive versus standard nutritional regime on growth of extremely low birth weight infants-A randomized controlled trial, Journal of Pediatric Gastroenterology and Nutrition, 66, 1089, 2018	Abstract only.
Tomsits, E., Pataki, M., Tqlgyesi, A., Fekete, G., Rischak, K., Szollar, L., Safety and efficacy of a lipid emulsion containing a mixture of soybean oil, medium-chain triglycerides, olive oil, and fish oil: A randomised, double-blind clinical trial in premature infants requiring parenteral nutrition, Journal of Pediatric Gastroenterology and Nutrition, 51, 514-521, 2010	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsion.
Uauy, Ricardo, Mena, Patricia, Long-chain polyunsaturated fatty acids supplementation in preterm infants, Current Opinion in Pediatrics, 27, 165-71, 2015	Study design does not meet protocol eligibility criteria - Narrative review.
Van Aerde, J. E., Sauer, P. J., Pencharz, P. B., Smith, J. M., Heim, T., Swyer, P. R., Metabolic consequences of increasing energy intake by adding lipid to parenteral nutrition in full-term infants, The American journal of clinical nutrition, 59, 659-62, 1994	Conference abstract.
Van Aerde, J. E., Sauer, P. J., Pencharz, P. B., Smith, J. M., Swyer, P. R., Effect of replacing glucose with lipid on the energy metabolism of newborn	Outcomes do not meet protocol eligibility criteria - Energy metabolism.

Study	Reason for Exclusion
infants, Clinical science (London, England : 1979), 76, 581-8, 1989	
Vandenplas, Y., Leyssens, L., Bougatef, A., Sacre, L., Francois, B., Fatty acid patterns in parenterally fed premature and term infants: changes induced by intralipid and sunflower seed oil, American journal of perinatology, 6, 393-6, 1989	Comparison does not meet protocol eligibility criteria - Intralipid vs. sunflower seed oil rubbed on skin.
Vileisis, R. A., Cowett, R. M., Oh, W., Glycemic response to lipid infusion in the premature neonate, Journal of Pediatrics, 100, 108-112, 1982	Study design does not meet protocol eligibility criteria - Not an RCT.
Vina Romero, M., Gutierrez Nicolas, F., Fraile Clemente, C., Gonzalez Carretero, P., Plasencia Garcia, I., Merino Alonso, J., Martin Conde, J. A., Lipids in total parenteral nutrition for premature infants, European Journal of Hospital Pharmacy: Science and Practice, 19, 252, 2012	Conference abstract.
Vlaardingerbroek, H, Veldhorst, Ma, Spronk, S, Akker, Ch, Goudoever, Jb, Parenteral lipid administration to very-low-birth-weight infants: early introduction of lipids and use of new lipid emulsions - a systematic review and meta-analysis (Provisional abstract), American Journal of Clinical Nutrition, 96, 255-268, 2012	Conference abstract.
Vlaardingerbroek, H., Roelants, J. A., Dorst, K., Schierbeek, H., Van Den Akker, C. H., Vermeulen, M. J., Van Goudoever, J. B., Can early lipid administration increase protein synthesis in premature infants?, Journal of Pediatric Gastroenterology and Nutrition, 52, E205, 2011	Abstract only.
Vlaardingerbroek, H., Van Den Akker, C. H. P., Dorst, K. Y., Schierbeek, H., Van Goudoever, J. B., Early lipid and high dose amino acid administration increases anabolism in VLBW infants, Archives of Disease in Childhood, 97, A37, 2012	Conference abstract.
Vlaardingerbroek, H., van Goudoever, J. B., Intravenous lipids in preterm infants: impact on laboratory and clinical outcomes and long-term consequences, World Review of Nutrition & Dietetics, 112, 71-80, 2015	Study design does not meet protocol eligibility criteria - Review.
Vlaardingerbroek, H., Veldhorst, M. A. B., Spronk, S., Van Den Akker, C. H. P., Van Goudoever, J. B., Parenteral lipid administration to very-low-birth-weight infants - Early introduction of lipids and	Study design does not meet protocol eligibility criteria - Review.

Study	Reason for Exclusion
use of new lipid emulsions: A systematic review and meta-analysis, American Journal of Clinical Nutrition, 96, 255-268, 2012	
Vlaardingerbroek, H., Vermeulen, M. J., Carnielli, V. P., Vaz, F. M., Van Den Akker, C. H. P., Van Goudoever, J. B., Growth and fatty acid profiles of VLBW infants receiving a multicomponent lipid emulsion from birth, Journal of Pediatric Gastroenterology and Nutrition, 58, 417-427, 2014	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Wang, Y., Feng, Y., Lu, L. N., Wang, W. P., He, Z. J., Xie, L. J., Hong, L., Tang, Q. Y., Cai, W., The effects of different lipid emulsions on the lipid profile, fatty acid composition, and antioxidant capacity of preterm infants: A double-blind, randomized clinical trial, Clinical Nutrition, 35, 1023-31, 2016	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Webb, A. N., Hardy, P., Peterkin, M., Lee, O., Shalley, H., Croft, K. D., Mori, T. A., Heine, R. G., Bines, J. E., Tolerability and safety of olive oil-based lipid emulsion in critically ill neonates: A blinded randomized trial, Nutrition, 24, 1057-1064, 2008	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.
Wells, D. H., Ferlauto, J. J., Forbes, D. J., Graham, T. R., Newell, R. W., Wareham, J. A., Wilson, C. A., Lipid tolerance in the very low birth weight infant on intravenous and enteral feedings, Journal of Parenteral and Enteral Nutrition, 13, 623-627, 1989	Study design does not meet protocol eligibility criteria - Not an RCT.
Yang, Q., Ayers, K., Chen, Y., Helderman, J., Welch, C. D., O'Shea, T. M., Early enteral fat supplement and fish oil increases fat absorption in the premature infant with an enterostomy, Journal of Pediatrics, 163, 429-434, 2013	Intervention does not meet protocol eligibility criteria - Enteral nutrition.
Yang, Q., Ayers, K., Welch, C. D., O'Shea, T. M., Randomized controlled trial of early enteral fat supplement and fish oil to promote intestinal adaptation in premature infants with an enterostomy, Journal of Pediatrics, 165, 274, 2014	Intervention does not meet protocol eligibility criteria - Enteral nutrition.
Yoon, J., Park, H., In, Y., Lee, Y., Seo, J., The efficacy and safety of high dose intravenous lipid administration to extremely low birth weight infants in the early neonatal period, Clinical Nutrition, 35, S41-S42, 2016	Study design does not meet protocol eligibility criteria - Cohort study.
Zhao, Y., Wu, Y., Pei, J., Chen, Z., Wang, Q., Xiang, B., Safety and efficacy	Comparison does not meet protocol eligibility criteria - Different types of lipid emulsions.

Study	Reason for Exclusion
of parenteral fish oil-containing lipid emulsions in premature neonates, Journal of Pediatric Gastroenterology and Nutrition, 60, 708-716, 2015	

Economic studies

No economic evidence was identified for these reviews. See supplementary material D for further information.

Appendix L – Research recommendations

Research recommendations for review question: What is the optimal target for lipid dosage in preterm and term babies who are receiving parenteral nutrition and neonatal care? and What is the optimal way (starting dose and approach to increment, if employed) to achieve that?

No research recommendations were made for this review question.