Neonatal parenteral nutrition

[D4] Lipid emulsions

NICE guideline NG154

Evidence reviews

February 2020

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

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

© NICE 2020. All rights reserved. Subject to Notice of Rights.

ISBN: 978-1-4731-3673-1
Economic evidence study selection for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)? ................. 28
Appendix H – Economic evidence tables .................................................................................. 29
Economic evidence study selection for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)? ................. 29
Appendix I – Economic evidence profiles .................................................................................. 30
Economic evidence profiles for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)? .................................................. 30
Appendix J – Economic analysis ................................................................................................. 31
Economic analysis for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)? .................................................. 31
Appendix K – Excluded studies .................................................................................................. 32
Excluded studies for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)? .................................................. 32
Clinical studies ....................................................................................................................... 32
Economic studies ...................................................................................................................... 32
Appendix L – Research recommendations .................................................................................. 33
Research recommendations for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)? .................................................. 33
Safety and effectiveness of different lipid formulations in parenteral nutrition for preterm and term babies

Review question

What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)?

Introduction

Lipid emulsions are a vital part of neonatal parenteral nutrition (PN). However, soybean oil-based lipid emulsions (S-L), which have been used conventionally, contain a high amount of polyunsaturated fatty acid (PUFA) and phytosterols which may contribute to adverse events in neonates, including PN associated liver disease (PNALD). There are newer lipid emulsions available from other lipid sources that decrease fatty acid content. Guidance on the effectiveness and safety of different lipid emulsions is required.

Summary of the protocol

Please 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 | Any concentrations of:  
|              | • Soy based (Intralipid)  
|              | • Specific Multicomponent (Soy, MCT, olive oil, fish oil) SMOFlipid  
|              | • Olive oil +soy oil (clinoleic)  
|              | • Fish oil (omegaven) |
| Comparison | Each other |
| Outcomes | Critical  
|          | • Growth/anthropometric measures:  
|          | o Weight gain  
|          | o Linear growth  
|          | o Head circumference  
|          | • Neurodevelopmental outcomes (general cognitive abilities at two years corrected age as measured by a validated scale)  
|          | • Adverse effects of lipids:  
|          | o PN related liver disease (abnormal liver function, cholestasis, conjugated Hyperbilirubinaemia, Intrahepatocellular lipid)  
|          | Important  
|          | • Mortality  
|          | • Adverse effects of lipids:  
|          | o Infection including sepsis  
|          | o Hyperglycaemia (due to high rates of infusion) |
Safety and effectiveness of different lipid formulations in parenteral nutrition for preterm and term babies

Clinical evidence

Included studies

In a collaboration with Cochrane Neonatal two Cochrane reviews were conducted specifically to address this topic for the guideline to be included in this review (Kapoor 2018a and Kapoor 2018b). This was initially planned as an update review by Cochrane Neonatal, but adjustments were made to address the needs of the current guideline (such as additional comparisons and a separate review for late-preterm and term babies).

For methodological considerations related to this collaboration see supplementary material C.

One review compared the safety and efficacy of different lipid emulsions in preterm (before 27 weeks' gestation) babies (Kapoor 2018a).

One review compared the safety and efficacy of different lipid emulsions in term and late preterm (between 34 and 36+6 weeks’ gestation) babies (Kapoor 2018b).

Studies are summarised in Table 2 (with hyperlinks to the full reviews) and hyperlinks to study evidence tables are in appendix D.

See the Cochrane reviews for the literature search strategy, study selection flow chart, forest plots, and GRADE tables.

Excluded studies

See the Cochrane reviews for list of excluded studies with reasons for their exclusions.

Summary of clinical studies included in the evidence review

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparisons</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kapoor 2018a</td>
<td>Included in review N = 29 studies N = 2037 babies</td>
<td>• Fish oil lipid emulsion versus non-fish oil lipid emulsion • Fish oil lipid emulsion versus another fish oil lipid emulsion • Alternative lipid emulsion versus</td>
<td>• Weight gain • Linear growth • Head growth • Neurodevelopmental outcomes • Parenteral nutrition associated liver disease (PNALD)/cholestasis</td>
<td>Two of the 3 studies of babies with surgical conditions of cholestasis were stopped early which may have</td>
</tr>
</tbody>
</table>
Safety and effectiveness of different lipid formulations in parenteral nutrition for preterm and term babies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparisons</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kapoor 2018b</td>
<td><strong>Systematic review</strong>&lt;br&gt;N = 9 studies N = 273 babies&lt;br&gt;<strong>Included in meta-analysis</strong> N = 5 studies N = 150 babies&lt;br&gt;Term babies born at 37 weeks’ gestation or after; late preterm babies born between 34+0 and 36+6 weeks’ gestation&lt;br&gt;Subgroups: term or late preterm babies with surgical conditions; term or late preterm babies with cholestasis</td>
<td><strong>Fish oil lipid emulsion versus non-fish oil lipid emulsion</strong>&lt;br&gt;<strong>Evidence included in the evidence review</strong>&lt;br&gt;N = 9 studies N = 273 babies&lt;br&gt;<strong>Included in meta-analysis</strong> N = 5 studies N = 150 babies</td>
<td>• Death before discharge&lt;br&gt;• Sepsis&lt;br&gt;• Hyperglycaemia&lt;br&gt;• Hypertriglyceridemia&lt;br&gt;• Duration of hospital stay</td>
<td>Three of the 5 studies that contributed data to the review were stopped early which may have introduced bias.</td>
</tr>
</tbody>
</table>

Subgroups: preterm babies without surgical conditions of cholestasis; preterm babies with surgical conditions; preterm babies with cholestasis

PNALD: parenteral nutrition associated liver disease

See appendix D for the 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 the Cochrane reviews.
Economic evidence

Included studies
A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question. 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 this review question.

Economic evidence statements
No studies were identified which were applicable to this review question.

Summary of studies included in the economic evidence review
No economic evaluations were identified which were applicable to this review question.

Economic model
This question was medium priority for economic evaluation. However, the identified clinical data was insufficient to inform de-novo economic modelling in this area.

Evidence statements

Clinical evidence statements
Evidence statements were based on the GRADE analysis carried out by the authors of the Cochrane reviews.

Fish oil lipid emulsion (MOFS-LE) compared with non-fish oil lipid emulsion for preterm babies

Weight gain

Rate of weight gain
- Low quality evidence from 5 randomised controlled trials (RCTs) (n=347) showed no clinically important difference in rate of weight gain in babies who received MOFS-LE compared with S-LE. However, there was uncertainty around the effect: Mean difference (MD) 0.71g/kg/day (95% CI -0.17 to 1.60).

PNALD/cholestasis

Direct bilirubin ≥ 2mg/dl (equivalent to 34.2mmol/L)
- Low quality evidence from 4 RCTs (n=328) showed a clinically important difference in the rate of direct bilirubin ≥ 2mg/dl in babies who received fish oil lipid emulsions compared with non-fish oil lipid emulsions. Fewer babies receiving fish oil lipid emulsions had PNALD/cholestasis. However, there was high uncertainty around the effect: Relative risk (RR) 0.61 (95% CI 0.24 to 1.56).
Safety and effectiveness of different lipid formulations in parenteral nutrition for preterm and term babies

Any definition

- Very low quality evidence from 11 RCTs (n=1154) showed a clinically important difference in the rate of PNALD/cholestasis (using any definition) in babies who received fish oil lipid emulsions compared with non-fish oil lipid emulsions. Fewer babies receiving fish oil lipid emulsions had PNALD/cholestasis. However, there was uncertainty around the effect: RR 0.63 (95% CI 0.43 to 0.91).

Death before discharge

- Low quality evidence from 9 RCTs (n=855) showed no clinically important difference in rate of death before discharge in babies who received MOFS-LE compared with S-LE. However, there was uncertainty around the effect: RR 1.24 (95% CI 0.81 to 1.90).

Sepsis

Culture positive

- Low quality evidence from 7 RCT (n=774) showed no clinically important difference in the rate of cultures positive for sepsis in babies who received fish oil lipid emulsions compared with non-fish oil lipid emulsions. However, there was uncertainty around the effect: RR 1.16 (95% CI 0.91 to 1.48).

Fish oil lipid emulsion (MOFS-LE) compared with another fish oil lipid emulsion (MFS-LE) for preterm babies

Weight gain

- Low quality evidence from 1 RCT (n=55) showed no clinically important difference in rate of weight gain in babies who received MOFS-LE compared with MFS-LE. However, there was uncertainty around the effect: MD 4g/kg/day (95% CI -2.03 to 10.03).

PNALD/cholestasis

- Low quality evidence from 1 RCT (n=55) showed no clinically important difference in the rate of direct bilirubin \( \geq 2 \text{mg/dl} \) in babies who received MOFS-LE compared with MFS-LE. However, there was high uncertainty around the effect: RR 0.96 (95% CI 0.06 to 14.65).

Death before discharge

- Low quality evidence from 1 RCT (n=60) showed no clinically important difference in the rate of death before discharge in babies who received MOFS-LE compared with MFS-LE. However, there was high uncertainty around the effect: RR 1.00 (95% CI 0.15 to 6.64).

Sepsis

- Low quality evidence from 1 RCT (n=55) showed a clinically important difference in the rate of sepsis in babies who received MOFS-LE compared with MFS-LE. More babies receiving MOFS-LE had sepsis. However, there was high uncertainty around the effect: RR 1.69 (95% CI 0.56 to 5.11).
Alternative lipid emulsion compared with Soybean based emulsion (S-LE) for preterm babies

Weight gain

Rate of weight gain
- Low quality evidence from 1 RCT (n=60) showed no clinically important difference in rate of weight gain in babies who received MS-LE compared with S-LE. However, there was uncertainty around the effect: MD -2.67g/kg/day (95% CI -8.20 to 2.86).
- Low quality evidence from 2 RCTs (n=123) showed no clinically important difference in rate of weight gain in babies who received OS-LE compared with S-LE. However, there was uncertainty around the effect: MD -0.42 (95% CI -5.15 to 4.30).

Death before discharge
- Low quality evidence from 3 RCTs (n=224) showed no clinically important difference in the rate of death before discharge in babies who received OS-LE compared with S-LE. However, there was high uncertainty around the effect: RR 1.00 (95% CI 0.21 to 4.82).

Sepsis

Culture positive
- Low quality evidence from 2 RCTs (n=164) showed no clinically important difference in the rate of cultures positive for sepsis in babies who received OS-LE compared with S-LE. However, there was high uncertainty around the effect: RR 1.22 (95% CI 0.54 to 2.78).

Alternative lipid emulsion compared with another alternative lipid emulsion for preterm babies

Weight gain

Rate of weight gain
- Low quality evidence from 1 RCT (n=59) showed no clinically important difference in rate of weight gain in babies who received MS-LE compared with OS-LE. However, there was uncertainty around the effect: MD -1.33g/kg/day (95% CI -7.36 to 4.70).

PNALD/cholestasis
- Low quality evidence from 1 RCT (n=59) showed a clinically important difference in the rate of direct bilirubin ≥ 2mg/dl in babies who received MS-LE compared with OS-LE. More babies receiving MS-LE had PNALD/cholestasis. However, there was high uncertainty around the effect: RR 2.90 (95% CI 0.12 to 68.5).

Sepsis
- Low quality evidence from 1 RCT (n=59) showed a clinically important difference in the rate of sepsis in babies who received MS-LE compared with OS-LE. More babies receiving MS-LE had sepsis. However, there was high uncertainty around the effect: RR 1.93 (95% CI 0.65 to 5.73).

Fish oil lipid emulsion compared with non-fish oil lipid emulsion for preterm babies with surgical conditions

PNALD/cholestasis
- Very low quality evidence from 1 RCT (n=19) showed no clinically important difference in the rate of direct bilirubin ≥ 2mg/dl in babies who received pure fish oil compared with S-
LE. However, there was high uncertainty around the effect: RR 1.11 (95% CI 0.08 to 15.28).

**Sepsis**
- Very low quality evidence from 1 RCT (n=19) showed no clinically important difference in the rate of cultures positive for sepsis in babies who received pure fish oil compared with S-LE. However, there was high uncertainty around the effect: RR 1.11 (95% CI 0.39 to 3.19).

**Fish oil lipid emulsion compared with non-fish oil lipid emulsion for preterm babies with cholestasis**

**Weight gain**
- Very low quality evidence from 1 RCT (n=16) showed a clinically important difference in rate of weight gain in babies who received pure fish oil compared with S-LE. Weight gain was greater in babies who received pure fish oil. However, there was uncertainty around the effect: MD 45g/week (95% CI 15 to 75).

**Head growth**
- Very low quality evidence from 1 RCT (n=16) showed a clinically important difference in rate of head growth in babies who received pure fish oil compared with S-LE. Head growth was greater in babies who received pure fish oil. However, there was uncertainty around the effect: MD 0.16cm/week (95% CI -0.01 to 0.33).

**PNALD/cholestasis**
- Very low quality evidence from 2 RCTs (n=40) showed a clinically important difference in the rate of PNALD/cholestasis (using any definition) in babies who received fish oil lipid emulsions compared with non-fish oil lipid emulsions. Fewer babies receiving fish oil had PNALD/cholestasis. However, there was uncertainty around the effect: RR 0.54 (95% CI 0.32 to 0.91).
- Very low quality evidence from 1 RCT (n=16) showed a clinically important difference in the rate of resolution of PNALD/cholestasis (direct bilirubin < 2 mg/dl) in babies who received pure fish oil compared with Intralipid. More babies receiving pure-fish oil had resolution of PNALD/cholestasis. However, there was high uncertainty around the effect: RR 5.60 (95% CI 0.34 to 93.35).

**Death before discharge**
- Very low quality evidence from 2 RCTs (n=40) showed a clinically important difference in the rate of death before discharge in babies who received fish oil lipid emulsions compared with non-fish oil lipid emulsions. Fewer babies receiving fish oil died before discharge. However, there was high uncertainty around the effect: RR 0.24 (95% CI 0.03 to 1.87).

**Sepsis**
- Very low quality evidence from 2 RCTs (n=40) showed no clinically important difference in the rate of sepsis in babies who received fish oil lipid emulsions compared with non-fish oil lipid emulsions. However, there was high uncertainty around the effect: RR 1.21 (95% CI 0.50 to 2.92).
Fish oil lipid emulsion compared with non-fish oil lipid emulsion for term and late preterm babies with surgical conditions

**PNALD/cholestasis**
- Very low quality evidence from 1 RCT (n=19) showed no clinically important difference in the rate of direct bilirubin ≥ 2mg/dl in babies who received pure fish oil compared with S-LE. However, there was high uncertainty around the effect: RR 1.11 (95% CI 0.08 to 15.28).
- Low quality evidence from 2 RCTs (n=68) showed no clinically important difference in the rate of PNALD/cholestasis (using any definition) in babies who received fish oil lipid emulsions compared with non-fish oil lipid emulsions. However, there was high uncertainty around the effect: RR 1.20 (95% CI 0.38 to 3.76).

**Sepsis**

**Culture positive**
- Very low quality evidence from 2 RCTs (n=51) showed no clinically important difference in the rate of cultures positive for sepsis in babies who received fish oil lipid emulsions compared with non-fish oil lipid emulsions. However, there was high uncertainty around the effect: RR 1.05 (95% CI 0.47 to 2.34).

Fish oil lipid emulsion compared with non-fish oil lipid emulsion for term and late preterm babies with cholestasis

**Weight gain**
- Very low quality evidence from 1 RCT (n=16) showed a clinically important difference in rate of weight gain in babies who received pure fish oil compared with S-LE. Weight gain was greater in babies who received pure fish oil. However, there was uncertainty around the effect: MD 45g/week (95% CI 15 to 75).

**PNALD/cholestasis**
- Very low quality evidence from 2 RCTs (n=40) showed a clinically important difference in the rate of PNALD/cholestasis (using any definition) in babies who received fish oil lipid emulsions compared with non-fish oil lipid emulsions. Fewer babies receiving fish oil had PNALD/cholestasis. However, there was uncertainty around the effect: RR 0.54 (95% CI 0.32 to 0.91).
- Very low quality evidence from 1 RCT (n=16) showed a clinically important difference in the rate of resolution of PNALD/cholestasis (direct bilirubin < 2 mg/dl) in babies who received pure fish oil compared with Intralipid. More babies receiving pure-fish oil had resolution of PNALD/cholestasis. However, there was high uncertainty around the effect: RR 5.60 (95% CI 0.34 to 93.35).

**Death before discharge**
- Very low quality evidence from 2 RCTs (n=40) showed a clinically important difference in the rate of death before discharge in babies who received fish oil lipid emulsions compared with non-fish oil lipid emulsions. Fewer babies receiving fish oil died before discharge. However, there was high uncertainty around the effect: RR 0.24 (95% CI 0.03 to 1.87).

**Sepsis**
- Very low quality evidence from 2 RCTs (n=40) showed no clinically important difference in the rate of sepsis in babies who received fish oil lipid emulsions compared with non-fish oil lipid emulsions. However, there was high uncertainty around the effect: RR 1.21 (95% CI 0.50 to 2.92).
Safety and effectiveness of different lipid formulations in parenteral nutrition for preterm and term babies

Hypertriglyceridemia

- Very low quality evidence from 1 RCT (n=24) showed a clinically important difference in the rate of hypertriglyceridemia in babies who received MOFS-LE compared with S-LE. Fewer babies receiving MOFS-LE had hypertriglyceridemia. However, there was high uncertainty around the effect: RR 0.79 (95% CI 0.30 to 2.09).

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

Lipids are an essential part of PN; therefore, growth and neurodevelopmental outcomes were prioritised as critical outcomes by the committee. PN associated liver disease (PNALD) was also selected as a critical outcome as different lipid emulsions contain varying amounts of polyunsaturated fatty acid and phytosterols which may contribute to PNALD.

Other adverse effects of intravenous lipid emulsions (infection including sepsis, hyperglycaemia, hypertriglyceridemia and hyperlipidaemia) were selected as important outcomes as they may vary according to the type of lipid emulsion used. Duration of hospital stay and mortality were selected as important outcomes as they may be affected by both the type of lipid emulsion used and the overall clinical condition of the baby. Nutritional intake was also selected as an important outcome as nutritional composition varies across different lipid emulsions.

The quality of the evidence

The quality of the Cochrane systematic reviews was assessed using the ROBIS tool. Both reviews were rated as having a low risk of bias. The Cochrane authors performed a GRADE analysis of the outcomes. The evidence was all very low and low quality and was downgraded due to risk of bias in included studies, small sample sizes, small number of events, and uncertainty around effects.

There was no evidence for neurodevelopmental outcomes, hyperglycaemia, hyperlipidaemia, duration of hospital stay or nutritional intake.

There was no evidence for late preterm or term babies that did not have pre-existing PNALD or surgical conditions.

Benefits and harms

There was limited evidence of greater weight gain and head growth, greater resolution of PNALD and less mortality and hypertriglyceridemia when babies with PNALD were given composite lipid emulsions, for example those containing fish oil, compared with pure soybean lipid emulsions. However, there was no evidence comparing different composite lipid emulsions to each other, or composite lipid emulsions not containing fish oil with pure soybean lipid emulsions, in babies with PNALD. Therefore, the committee could not conclude what composite lipid emulsions provided the most benefit over pure soybean lipid emulsions. The evidence was from preterm and late preterm babies; however, the committee agreed that late preterm and term babies are often treated the same in clinical practice and that term babies with PNALD would be likely to also benefit from using a composite lipid emulsion. Therefore, the committee recommended, that therapeutic use of composite lipid emulsions,
rather than a pure soybean lipid emulsion, should be considered for preterm and term babies with PNALD.

For babies with surgical conditions, there was no evidence of advantage of any specific lipid formulation. Therefore, the committee agreed they could not make a recommendation for this population. They discussed that for babies with surgical conditions who are likely to be on long term PN, such as those with little or no remaining bowel, the duration of parental nutrition will be much longer than is covered by the scope of this guideline and these babies may require management by a multidisciplinary team, including a gastroenterologist.

There was some evidence of a benefit of fish oil containing lipid emulsions at reducing the rate of PNALD in preterm babies without surgical conditions or pre-existing PNALD. The committee discussed whether or not fish oil containing lipid emulsions should be considered in these babies and could not reach agreement as it was felt that there was no conclusive evidence of benefit, particularly as benefits of fish oil containing lipid emulsions were not seen for outcomes beyond PNALD. The committee also discussed that there is a risk of essential fatty acid deficiency with pure fish oil.

There was also no evidence comparing different lipid emulsions in late preterm or term babies without surgical conditions or pre-existing PNALD. The committee discussed that it might be more beneficial to use fish-oil containing lipid emulsions in babies that are likely to be on PN for a longer duration, as there will be a greater risk of developing PNALD; however, the committee did not think there was sufficient evidence to support this as a recommendation. Further, in the absence of surgical conditions, it might not always be possible to know how long babies are likely to need PN.

Cost effectiveness and resource use

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

The committee note that in preterm and term babies with PNALD the use of fish oil containing lipid emulsions may result in avoiding the costs associated with poorer growth, worsening of PNALD and increased risk of hypertriglyceridemia. These are severe long-lasting complications which result in substantial costs to the NHS and also have a detrimental impact on the health-related quality of life of babies and also their parents or carers. Combined with an increased risk of mortality the use of lipid emulsions that do not contain fish oil would result in substantial losses in quality adjusted life years (QALYs). The committee explained that the use of fish oil containing lipid emulsions will have negligible, if any, impact on the unit cost of PN. As a result, the committee was of a view that the use of fish oil containing lipid emulsions would represent a cost effective use of NHS resources in pre-term and term babies with PNALD.

References

Kapoor 2018a

Kapoor 2018b
Appendices

Appendix A – Review protocols

Review protocol for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)?

The protocol drafted by the committee is displayed below and formed the basis of discussion with Cochrane Neonatal. The two Cochrane protocols were then adapted in line with this protocol.

See Cochrane reviews for the review protocols:


Table 3: Original review protocol presented to the committee and discussed with Cochrane to develop the Cochrane protocols—

<table>
<thead>
<tr>
<th>Field (based on PRISMA-P)</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review question</td>
<td>What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)?</td>
</tr>
<tr>
<td>Type of review question</td>
<td>Intervention</td>
</tr>
<tr>
<td>Objective of the review</td>
<td>Inadequate amounts of calcium and phosphate delivered via PN may contribute to bone disease in preterm and term babies. Delivery of calcium and phosphate should be adequate to achieve retention of amounts which match those in utero, but at a concentration that does not result in adverse events. The aim of this review is to determine the optimal ratio of phosphate to amino acids in preterm and term babies who are receiving PN</td>
</tr>
</tbody>
</table>
| 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 (term babies). |
| Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s) | Any concentrations of:  
• Soy based (Intralipid)  
• Specific Multicomponent (Soy, MCT, olive oil, fish oil) SMOFlipid  
• Olive oil +soy oil (clinoleic)  
• Fish oil (omegaven) |
| Eligibility criteria – comparator(s)/control or reference (gold) standard | • Each other |
### Field (based on PRISMA-P) | Content
--- | ---
**Outcomes and prioritisation** | **Critical**
- Growth/Anthropometric measures:
  - Weight gain (g/kg/d)
  - Linear growth
  - Head circumference (mm)
- Neurodevelopmental outcomes
- Adverse events of lipids (PN related liver disease, abnormal liver function, cholestasis, conjugated hyperbilirubinaemia, intrahepatocellular lipid)

**Important**
- Mortality
- Adverse events (including sepsis, hyperglycaemia, hypertriglyceridemia, hyperlipidaemia)
- Duration of hospital stay
- Nutritional intake (g/kg/day – proportion of lipid received or essential fatty acids at 2 days)

**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)
- Conference abstracts will only be considered if related to RCTs

**Other inclusion exclusion criteria**
- No sample size restriction
- No date restriction

**Proposed sensitivity/sub-group analysis, or meta-regression**
Subgroup analysis:
- Population subgroups:
  - Age of baby (first 2 weeks vs later)
  - Preterm (extremely preterm <28 weeks’ GA; very preterm: 28-31 weeks’ GA; moderately preterm: 32-36 weeks’ GA)
  - Birthweight: Low birth weight (< 2500g); very low birth weight (< 1500g) and extremely low birth weight (< 1000g)
  - Critically ill babies or those requiring surgery (for example, inotropic support, therapeutic hypothermia or fluid restriction)
### Field (based on PRISMA-P) | Content
---|---
First week of life and after first week of life? |  

#### 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 identified in the search will be sifted by a second reviewer. This sample size will be 10% of the total, or 100 studies if the search identifies fewer than 1000 studies. All disagreements in study inclusion will be discussed and resolved between the two reviewers. The senior systematic reviewer or guideline lead will be involved if discrepancies cannot be resolved between the two reviewers.

#### 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. 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
Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase. Limits (e.g. date, study design): All study designs. Apply standard animal/non-English language filters. No date limit. Supplementary search techniques: No supplementary search techniques were used. See appendix B for full strategies.

#### Identify if an update
This is not an update

#### Author contacts
Developer: The National Guideline Alliance

#### Search strategy – for one database
For details please see section 4.5 of [Developing NICE guidelines: the manual](https://www.nice.org.uk/media/6487/developingniceguidelinesmanual.pdf) 2014.

#### 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](https://www.nice.org.uk/media/6487/developingniceguidelinesmanual.pdf) 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/](http://www.gradeworkinggroup.org/).
### Safety and effectiveness of different lipid formulations in parenteral nutrition for preterm and term babies

<table>
<thead>
<tr>
<th>Field (based on PRISMA-P)</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria for quantitative synthesis (where suitable)</td>
<td>For details please see section 6.4 of Developing NICE guidelines: the manual 2014.</td>
</tr>
<tr>
<td>Methods for analysis – combining studies and exploring (in)consistency</td>
<td>For details of the methods please see supplementary material C.</td>
</tr>
</tbody>
</table>
| Meta-bias assessment – publication bias, selective reporting bias | For details please see section 6.2 of Developing NICE guidelines: the manual 2014.  
If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.  
Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway. |
| 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 guideline. The committee was convened by The National Guideline Alliance and chaired by Joe Fawke (Consultant Neonatologist and Honorary Senior Lecturer, University Hospitals Leicester NHS Trust), in line with section 3 of Developing NICE guidelines: the manual 2014.  
Staff from The National Guideline Alliance, 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 National Guideline Alliance is funded by NICE and hosted by The Royal College of Obstetricians and Gynaecologists.                  |
| Name of sponsor                                               | The National Guideline Alliance is funded by NICE and hosted by The Royal College of Obstetricians and Gynaecologists.                  |
| Roles of sponsor                                              | NICE funds the National Guideline Alliance 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.                                                                                         |

CDSR: Cochrane Database of Systematic Reviews; CCTR: Cochrane Controlled Trials Register; DARE: Database of Abstracts of Reviews of Effects; GA: gestational age; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; ICF: International Classification of Functioning, Disability and Health; MID: minimally important difference; NGA: National Guideline Alliance; NIHR: National Institute for Health Research; NHS: National health service; NICE: National Institute for Health and Care Excellence; PRISMA-P: preferred reporting items for systematic review and meta-analysis protocols; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: risk of bias in systematic reviews; SD: standard deviation
Appendix B – Literature search strategies

Literature search strategy for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)?

See the Cochrane reviews for the literature search strategy:

https://www.cochrane.org/CD013163/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-preterm-infants

https://www.cochrane.org/CD013171/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-term-and-late-preterm-infants
Appendix C – Clinical evidence study selection

Clinical study selection for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)?

See the Cochrane reviews for the study selection flow charts:

https://www.cochrane.org/CD013163/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-preterm-infants

https://www.cochrane.org/CD013171/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-term-and-late-preterm-infants
Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)?

Table 4: Clinical evidence tables for included studies

<table>
<thead>
<tr>
<th>Study details</th>
<th>Participants</th>
<th>Interventions</th>
<th>Methods</th>
<th>Outcomes and Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full citation Kapoor, V., Malviya, M. N., Soll, R., Lipid emulsions for parenterally fed preterm infants. Cochrane Database of Systematic Reviews 2018a, Issue 11</td>
<td>Preterm babies born before 37 weeks’ gestation</td>
<td>• Fish oil lipid emulsion versus non-fish oil lipid emulsion&lt;br&gt;• Fish oil lipid emulsion versus another fish oil lipid emulsion&lt;br&gt;• Alternative lipid emulsion versus soybean oil-based lipid emulsion&lt;br&gt;• Alternative lipid emulsion versus another alternative lipid emulsion</td>
<td>See Cochrane review for details. &lt;br&gt;<a href="https://www.cochrane.org/CD013163/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-preterm-infants">https://www.cochrane.org/CD013163/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-preterm-infants</a></td>
<td>See Cochrane review for details. &lt;br&gt;<a href="https://www.cochrane.org/CD013163/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-preterm-infants">https://www.cochrane.org/CD013163/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-preterm-infants</a></td>
<td>Limitations&lt;br&gt;Methodological quality was assessed using the ROBIS tool:&lt;br&gt;Study eligibility criteria - Low concern&lt;br&gt;Did the review adhere to pre-defined objectives and eligibility criteria? Yes&lt;br&gt;Were the eligibility criteria appropriate for the review question? Yes&lt;br&gt;Were eligibility criteria unambiguous? Yes&lt;br&gt;Were all restrictions in eligibility criteria based on study characteristics appropriate? Yes&lt;br&gt;Were any restrictions in eligibility criteria based on sources of information appropriate? Yes&lt;br&gt;Identification and selection of studies - Low concern&lt;br&gt;Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? Yes&lt;br&gt;Were methods additional to database searching used to identify relevant reports? Yes&lt;br&gt;Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? Yes&lt;br&gt;Were restrictions based on date, publication format, or language appropriate? Yes&lt;br&gt;Were efforts made to minimise errors in selection of studies? Yes&lt;br&gt;Data collection and study appraisal - Low concern&lt;br&gt;Were efforts made to minimise error in data collection? Yes</td>
</tr>
<tr>
<td>Ref Id N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country/ies where the study was carried out</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia, Oman, USA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type Systematic review of randomised or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Safety and effectiveness of different lipid formulations in parenteral nutrition for preterm and term babies

<table>
<thead>
<tr>
<th>Study details</th>
<th>Participants</th>
<th>Interventions</th>
<th>Methods</th>
<th>Outcomes and Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>quasi-randomised controlled studies</td>
<td>See Cochrane review for full details.</td>
<td></td>
<td></td>
<td></td>
<td>Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? Yes</td>
</tr>
<tr>
<td>Aim of the study</td>
<td>To compare the safety and effectiveness of different lipid emulsions for parenteral nutrition in preterm infants.</td>
<td></td>
<td></td>
<td></td>
<td>Were all relevant study results collected for use in the synthesis? Yes</td>
</tr>
<tr>
<td>Study dates</td>
<td>Articles published up to 18th July 2018</td>
<td></td>
<td></td>
<td></td>
<td>Was risk of bias (or methodological quality) formally assessed using appropriate criteria? Yes</td>
</tr>
<tr>
<td>Source of funding</td>
<td>NIHR Cochrane Programme Grant (16/114/03); Vermont Oxford Network; Cochrane Review Incentive Scheme, reference</td>
<td></td>
<td></td>
<td></td>
<td>Were efforts made to minimise errors in risk or bias assessment? Yes</td>
</tr>
</tbody>
</table>

**Synthesis and findings - High concern**

- Did the synthesises include all studies that it should? Unclear – The majority of included studies were rated as unclear risk of selection bias as protocols were not available. Therefore, it is unclear if all results were available to the reviewers.
- Were all predefined analyses followed or departures explained? Yes
- Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? Yes
- Was between-studies variation (heterogeneity) minimal or addressed in the synthesis? Yes
- Were the findings robust, e.g., as demonstrated through funnel plot or sensitivity analyses? Probably No – Funnel plots were used where possible to examine publication bias, which was not found. However, for one outcome exclusion of a high risk study reduced the magnitude of the effect and introduced more uncertainty around the estimate. For a number of comparisons and outcomes, only single small studies were available.
- Were biases in primary studies minimal or addressed in the synthesis? Yes

**Overall risk of bias - Low risk of bias**

- Did the interpretation of findings address all of the concerns identified in the phase 2 assessment? Probably Yes – The authors discuss the paucity of large randomised trials and make tentative conclusions based on the results.
### Study details

<table>
<thead>
<tr>
<th>Participants</th>
<th>Interventions</th>
<th>Methods</th>
<th>Outcomes and Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term babies born at 37 weeks’ gestation or after; late preterm babies born between 34-6 and 36-6 weeks’ gestation</td>
<td>Fish oil lipid emulsion versus non-fish oil lipid emulsion</td>
<td>See Cochrane review for details. <a href="https://www.cochrane.org/CD013171/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-term-and-late-preterm-infants">https://www.cochrane.org/CD013171/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-term-and-late-preterm-infants</a></td>
<td>See Cochrane review for details. <a href="https://www.cochrane.org/CD013171/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-term-and-late-preterm-infants">https://www.cochrane.org/CD013171/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-term-and-late-preterm-infants</a></td>
<td>Limitations Methodological quality was assessed using the ROBIS tool: Study eligibility criteria - Low concern Did the review adhere to pre-defined objectives and eligibility criteria? Yes Were the eligibility criteria appropriate for the review question? Yes Were eligibility criteria unambiguous? Yes Were all restrictions in eligibility criteria based on study characteristics appropriate? Yes Were any restrictions in eligibility criteria based on sources of information appropriate? Yes Identification and selection of studies - Low concern Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? Yes Were methods additional to database searching used to identify relevant reports? Yes Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? Yes Were restrictions based on date, publication format, or language appropriate? Yes Were efforts made to minimise errors in selection of studies? Probably Yes – It is unclear whether both title and abstracts and full texts were independently assessed but authors report that two authors independently search the database. More information is needed.</td>
</tr>
</tbody>
</table>

Page dimensions: 841.9x595.3

**Safety and effectiveness of different lipid formulations in parenteral nutrition for preterm and term babies**

Parenteral nutrition in neonates: Evidence reviews for different lipid formulations in parenteral nutrition for preterm and term babies (February 2020)
### Safety and effectiveness of different lipid formulations in parenteral nutrition for preterm and term babies

**Final**

Parenteral nutrition in neonates: Evidence reviews for different lipid formulations in parenteral nutrition for preterm and term babies (February 2020)

<table>
<thead>
<tr>
<th>Study details</th>
<th>Participants</th>
<th>Interventions</th>
<th>Methods</th>
<th>Outcomes and Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>randomised or quasi-randomised controlled studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>provided in Kapoor 2018a and it is likely the same methods were used for this review.</td>
</tr>
<tr>
<td>Aim of the study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Data collection and study appraisal - Low concern</td>
</tr>
<tr>
<td>To compare the safety and effectiveness of different lipid emulsions for parenteral nutrition in term and late preterm infants.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Were efforts made to minimise error in data collection? Yes</td>
</tr>
<tr>
<td>Study dates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? Yes</td>
</tr>
<tr>
<td>Articles published up to 18th June 2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Were all relevant study results collected for use in the synthesis? Yes</td>
</tr>
<tr>
<td>Source of funding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Was risk of bias (or methodological quality) formally assessed using appropriate criteria? Yes</td>
</tr>
<tr>
<td>NIHR Cochrane Programme Grant (16/114/03); Vermont Oxford Network; Cochrane Review Incentive Scheme,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Were efforts made to minimise errors in risk or bias assessment? Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Synthesis and findings - High concern</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Did the syntheses include all studies that it should? Unclear – A number of included studies were rated as unclear risk of selection bias as protocols were not available. Therefore, it is unclear if all results were available to the reviewers.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Were all predefined analyses followed or departures explained? Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Was between-studies variation (heterogeneity) minimal or addressed in the synthesis? Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Were the findings robust, e.g., as demonstrated through funnel plot or sensitivity analyses? Probably No – Authors were unable to use funnel plots due to the number of studies for each outcome. For a number of comparisons and outcomes, only one or two small studies were available.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Were biases in primary studies minimal or addressed in the synthesis? Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Overall risk of bias - Low risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Did the interpretation of findings address all of the concerns identified in the phase 2 assessment? Probably Yes – The</td>
</tr>
</tbody>
</table>
Safety and effectiveness of different lipid formulations in parenteral nutrition for preterm and term babies

<table>
<thead>
<tr>
<th>Study details</th>
<th>Participants</th>
<th>Interventions</th>
<th>Methods</th>
<th>Outcomes and Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>reference number 17/62/30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>authors discuss the paucity of large randomised trials and make tentative conclusions based on the results. Was the relevance of identified studies to the review's research question appropriately considered? Yes Did the reviewers avoid emphasising results on the basis of their statistical significance? Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other information: Three of the 5 studies that contributed data to the review were stopped early which may have introduced bias.</td>
<td></td>
</tr>
</tbody>
</table>

NIHR: National Institute of Health Research; ROBIS: risk of bias in systematic reviews; USA: United States of America.
Appendix E – Forest plots

Forest plots for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)?

See the Cochrane reviews for forest plots:

https://www.cochrane.org/CD013163/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-preterm-infants

https://www.cochrane.org/CD013171/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-term-and-late-preterm-infants

Appendix F – GRADE tables

GRADE tables for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)?

See the Cochrane reviews for GRADE tables:

https://www.cochrane.org/CD013163/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-preterm-infants

https://www.cochrane.org/CD013171/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-term-and-late-preterm-infants
Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)?

One global search was conducted for all review questions. See supplementary material D for further information.
Appendix H – Economic evidence tables

Economic evidence study selection for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)?

No economic studies were identified which were applicable to this review question.
Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)?

No economic studies were identified which were applicable to this review question.
Appendix J – Economic analysis

Economic analysis for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)?

No economic analysis was undertaken for this review question.
Appendix K – Excluded studies

Excluded studies for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)?

Clinical studies

See the Cochrane reviews for excluded studies:

https://www.cochrane.org/CD013163/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-preterm-infants

https://www.cochrane.org/CD013171/NEONATAL_systematic-review-lipid-emulsions-intravenous-nutrition-term-and-late-preterm-infants

Economic studies

No economic evidence was identified for this review question. See supplementary material D for further information.
Appendix L – Research recommendations

Research recommendations for review question: What is the clinical effectiveness, efficacy and safety of lipid formulations from different sources (for example, soya, fish oil, or mixed sources)?

No research recommendations were made for this review question.