# National Institute for Health and Care Excellence

Draft for consultation

# Neonatal parenteral nutrition

## [E] Standardised neonatal parenteral nutrition formulations

*NICE guideline tbc*

*Evidence reviews*

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*Draft for Consultation*

*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

# Standardised neonatal parenteral nutrition formulations ('standardised bags')

## Review question

What is the effectiveness, efficacy and safety of standardised parenteral nutrition bags compared with individualised bags?

### Introduction

Parenteral nutrition (PN) can be delivered using formulations that are wholly or partly made up to meet the needs of each individual. Standardised parenteral nutrition (SPN) refers to approaches in which the PN solutions are manufactured according to a pre-specified standard formulation. Both techniques have been employed for PN.

In the past, individualised (also referred to as bespoke) PN regimens (IPN) were considered to be the best way to provide for the complex individual needs of the PN-dependent baby. Such needs might also be met using SPN and with possible practical and safety advantages. There is a need to compare outcomes in babies receiving IPN and babies receiving SPN regimens. The aim of this review is to compare the effectiveness of standardised bags versus individualised bags in neonatal PN.

### 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)<br>• Babies born at term, up to 28 days after their birth (term babies) |
| **Intervention** | • Any standardised approach to providing parenteral nutrition |
| **Comparison** | • Any individualised parenteral nutrition solutions (bespoke prescriptions) |
| **Outcomes** | **Critical**<br>• Growth/anthropometric measures<br>• Neurodevelopmental outcomes<br>• Adverse events<br>• Nutritional intake<br>**Important**<br>• Mortality<br>• Prescribing error<br>• Duration of hospital stay |

For further details see the review protocol in appendix A.

# Clinical evidence

## Included studies

As limited randomised controlled trial (RCT) evidence was available, we also included observational studies. Seven studies were identified for inclusion in this review. One of these was an RCT (Dice 1981) and 6 were observational studies (Iacobelli 2010, Evering 2017, Lenclen 2006, Morgan 2009, Smolkin 2010, Yeung 2003). Despite differences in the formulations of SPN used across studies, where outcomes allowed the data were combined.

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 that were included in this review are presented in Table 2.

**Table 2: Summary of included studies**

| Study | Population | Intervention | Comparison | Outcomes | Comments |
|---|---|---|---|---|---|
| Dice 1981<br><br>RCT<br>US | N=28<br><br>Mean BW: 1109g (SD 211.37)<br><br>Mean GA: 31 weeks (SD 1.52) | SPN (n=14)<br>Solutions prepared in the pharmacy, physicians were allowed to make essential glucose and electrolyte manipulations.<br><br>Standard solutions were available as either 10% or 13% dextrose. | IPN (n=14)<br>Individual requirements were determined by the physician and pharmacist. | • Weight gain<br>• Protein intake<br>• Non-protein calorie intake | Babies assigned to SPN or IPN alternately |
| Evering 2017<br><br>Observational study<br><br>The Netherlands | N = 198<br><br>Mean GA: 205 days (SD 26.5) | SPN (n=104)<br>NEOmix – contained: 66kcal with osmolarity of 805mOsmol/L, 2.6g protein, 2.0 | IPN (n= 94)<br>Variable amounts energy, protein, triglycerides, glucose, sodium, | • Weight gain/loss<br>• TPN duration<br>• Days in NICU<br>• Mortality<br>• Sepsis | 101 additional babies received partially standardised bags, these are not |

| Study | Population | Intervention | Comparison | Outcomes | Comments |
|---|---|---|---|---|---|
| | | triglycerides, 8.9g glucose, 2.1mmol sodium, 0.66mmol potassium, 0.1mmol magnesium, 0.7mmol calcium, 0.93mmol phosphate and 1.39mmol chloride | potassium, magnesium, calcium, phosphate, chloride and variable osmolarity. | | included in this data |
| Iacobelli 2010<br><br>Observational study<br><br>France | N = 107<br><br>Mean BW: 1175g (SD 333.48)<br><br>Mean GA: 29 weeks (SD 1.77) | SPN (n=67)<br>Designed to provide identical initial dosage and proportional increase as indicated by the written protocol of the unit.<br><br>Solutions were commercially batch-produced following criteria of Fasonut Laboratories (Montpellier, France) | IPN (n= 40)<br>Prescriptions were developed using a computer system which calculated nutrient volumes according to data entered by the physician | • Weight loss<br>• Sepsis<br>• NEC<br>• Amino acid intake<br>• Glucose intake<br>• Lipid intake<br>• Energy intake | Study conducted over 2 time periods |
| Lenclen 2006<br><br>Observational study<br><br>France | N = 40<br><br>Mean GA: 28 weeks (SD 2.42)<br><br>Mean BW: 886g (SD 203.60) | SPN (n=20)<br>Prescription of PN was based on 3 solutions of predefined composition designed with reference to published evidence.<br><br>Solutions were prepared in the hospital pharmacy. | IPN (n=20)<br>Individualised following recommendations of the unit, using a standard prescribing protocol.<br><br>Solutions were prepared by the nurses in the department. | • Weight gain<br>• Duration of PN<br>• Non-protein energy intake<br>• Amino acid intake<br>• Glucose intake | |

| Study | Population | Intervention | Comparison | Outcomes | Comments |
|---|---|---|---|---|---|
| Morgan 2009<br><br>Observational study<br><br>UK | N = 118<br><br>Mean BW: birth weight: 930g (SD 222.85)<br><br>Mean GA: 27 weeks (SD 1.51)<br>D | SPN (n=38)<br>The macronutrient content did not differ to the IPN.<br>The aqueous content was concentrated and the remaining fluid provided by dextrose. The aqueous solution had a standard electrolyte content with three different options: no electrolytes, maintenance electrolytes, and additional sodium. | IPN (n= 59)<br>The protocol aimed to start PN within 24 hours, starting at 1g/kg/day protein/lipid, increasing to 2g/kg/day for another 48 hours, with a maximum 3g/kg/day protein/lipid).<br><br>Electrolyte content was individually prescribed, if deficiencies were identified the IPN was changed. | • Calorie intake<br>• Protein intake | |
| Smolkin 2010<br><br>Observational study<br><br>Israel | N = 140<br><br>Mean BW: 1285g (SD 298.58)<br><br>Mean GA: 29 weeks (SD 1.83) | SPN (n=70)<br>Five pre-set formulations were available with various glucose concentrations (2.5, 5, 7.5, 10 and 11%) and AA concentrations ranging from 1.5 to 2g/100ml of PN. | IPN (n=70)<br>A standard formula was started until tailored IPN became available (glucose 7.5-11%), which could be up to 48hours.<br><br>IPN was adjusted daily for water, glucose, AA, lipids, electrolytes, vitamins and trace elements. | • Weight gain<br>• Weight at discharge<br>• Head circumference<br>• Duration of stay<br>• Sepsis<br>• Energy intake<br>• Protein intake<br>• Fat intake<br>• Glucose intake | |
| Yeung 2003<br><br>Observational study | N = 58<br><br>Mean BW:1101g (SD 293.47) | SPN (n=27)<br>Formulations were batch produced as two solutions: | IPN (n=31)<br>Formulations were determined according to the | • Glucose intake<br>• Amino acid intake | |

| Study | Population | Intervention | Comparison | Outcomes | Comments |
|---|---|---|---|---|---|
| Australia | Mean GA:28 weeks (SD 1.93) | Solution A: Glucose 125g/L, AA 24.5g/L, Sodium 8.0mmol/L<br><br>Solution B: Glucose 100g/L, AA 24.5g/L, Sodium 25mmol/L, | neonatologist's discretion, based on morning serum biochemical data. | | |

*AA: Amino acid; BW: Birth weight, GA: Gestational age; IPN: Individualised parenteral nutrition; N: Number; NEC: Necrotising enterocolitis; NICU: Neonatal intensive care unit; PN: parenteral nutrition; RCT: Randomised controlled trial; SD: standard deviation; SPN: Standardised parenteral nutrition; TPN: Total parenteral nutrition; US: United States.*

See the full evidence tables in appendix D and the forest plots in appendix E.

## 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. Clinical evidence profiles can be found in appendix F.

## Economic evidence

### Included studies

Three cost-effectiveness studies were identified for inclusion in this review (Kreissl 2016, Smolkin 2010, Yeung 2003).

See appendix D for the economic evidence study selection, appendix H for Economic evidence tables and appendix J for Economic evidence profiles.

### Excluded studies

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

## Summary of studies included in the economic evidence review

Kreissl (2016) reported the costs associated with SPN compared with IPN in preterm infants with a birth weight of ≤1500 g and a gestational age (GA) less than 37 weeks. The Numeta brand of SPN bags was used. It is a triple-chamber bag, including amino acids plus electrolytes, glucose, and lipids. This was a prospective observational study (374 prescriptions in 34 infants) conducted in Austria. Even though the authors have not combined the costs and outcomes, the potential cost effectiveness could be derived since both costs and outcomes were reported for the study participants.

The analysis was conducted from a narrow healthcare payer perspective and considered only costs associated with the parenteral solution, consumables, and preparation time. The

actual consumables included were not reported. The resource use estimates were based on the observational study participants. The source of unit costs was unclear. The cost year was not reported and all costs were assumed to refer to 2015 prices.

The observational study reported a number of outcomes. The primary outcome measure was protein intake. The time horizon was not explicitly reported with only the mean cost per solution bag reported and the primary outcome at day 1 of life, days 2-6 of life, and also days 7-35 of life reported.

SPN resulted in lower protein intake at day 1 of life compared with IPN (1.6 versus 2.1 g/kg/day) respectively, implying a difference of 0.5, p<0.001. SPN resulted in lower protein intake at days 2-6 of life compared with IPN (3.1 versus 3.6 g/kg/day) respectively, implying a difference of 0.5, p<0.001. SPN also resulted in lower protein intake at days 7-35 of life compared with SPN (3.2 versus 3.8 g/kg/day) respectively; difference 0.5, p<0.001.

The mean cost per solution bag was €55 (SD €15) and €37 (SD €4) for SPN and IPN, respectively, implying a difference of €18 (in favour of IPN).

The mean preparation time was 4.06 minutes and 6.31 minutes, for SPN and IPN, respectively, implying a difference of 2.25 minutes (in favour of SPN). It was unclear how the preparation time was valued in the study. However, assuming that PN will be prepared by a pharmacist (Band 7 at £44 per working hour, PSSRU 2018) and assuming 1:1.14 exchange rate for GBP to Euro exchange rate the cost of preparation was approximately €3 and €5 for SPN and IPN, respectively; the difference of €2 (in favour of SPN).

Taking into account the cost per solution bag and preparation time the total daily cost was €58 and €42 for SPN and IPN, respectively, implying a difference of €16 (in favour of IPN).

Based on the above costs and outcomes IPN was dominant when using protein intake as the outcome measure (that is, IPN resulted in a lower cost per bag and also greater protein intake).

Smolkin (2010) reported the costs associated with SPN compared with IPN in preterm infants with a birth weight of ≤1500 g and a GA less than 32 weeks. This was a retrospective observational study (n=160) conducted in the USA. Even though the authors have not combined the costs and outcomes, the potential cost effectiveness could be derived since both costs and outcomes were reported for the study participants.

The analysis was conducted from a very narrow healthcare payer perspective and considered only costs associated with the parenteral solution and consumables including intravenous set, syringe, stockpot, lipid bag, nurse time, and physician/dietitian costs. The resource use estimates were based on the observational study participants. The source of unit costs was unclear. The cost year was not reported and all costs were assumed to refer to 2009 prices. The observational study reported a number of outcomes. However, the primary outcome measure was growth during the NICU defined as the change in weight standard deviation score. The time horizon was not explicitly reported with only the mean extra cost per solution bag reported. It was unclear to what comparator the extra cost was reported. However, since the extra cost to the common comparator was reported for both SPN and IPN the incremental cost of one type of parenteral nutrition over the other could be derived. The longest available follow up for the primary outcome was 1 month.

SPN resulted in lower weight gain standard deviation score at 1 month compared with IPN (-1.23 versus -0.88 for SPN and IPN, respectively), implying a difference of 0.35 (in favour of IPN), $p<0.05$.

The mean extra cost per infant per day was \$7.5 and \$9 for SPN and IPN, respectively. It was unclear what SPN and IPN were compared to. However, the mean difference between IPN and SPN was \$1.5 per infant per day (in favour of SPN). This is equivalent to the cost savings of \$45 associated with the SPN (versus IPN) per infant per month. Based on the above costs and outcomes the incremental cost-effectiveness ratio of SPN (versus IPN) is \$128 savings per weight SD score lost. It has to be noted that \$7.5 and \$9 for SPN and IPN, respectively, do not represent the unit cost of each solution bag but the 'mean extra cost' of each PN. For IPN the mean extra cost was accounted for by a more expensive solution bag and extra work time of the clinician prescribing IPN. For SPN the mean extra cost was accounted for by an extra intravenous set, syringe and stockpot, extra lipid bag, and extra nursing time when administering intravenous lipids separately).

Yeung (2003) reported the costs associated with SPN compared with IPN in preterm infants with a gestational age of less than 33 weeks. This was a retrospective observational study (272 prescriptions in 58 infants) conducted in Australia. Even though the authors have not combined the costs and outcomes, the potential cost effectiveness could be derived since both costs and outcomes were reported for the study participants. The analysis was conducted from a very narrow healthcare payer perspective and considered only intervention costs. The actual cost categories included are not reported. The resource use estimates were based on the observational study participants. The source of unit costs was unclear. . The cost year was not reported and were assumed to refer to 2002 prices. The observational study reported a number of outcomes. However, the primary outcome measure was protein intake. The time horizon was not explicitly reported with only the cost per solution bag reported and the primary outcome reported at the first week of life.

SPN resulted in the greater cumulative protein intake compared with IPN (13.6 versus 9.6 g/kg) respectively, implying a difference of 4.0, $p<0.05$.

The mean cost per solution bag was \$88 and \$130 for SPN and IPN, respectively, implying a difference of \$42 (in favour of SPN).

Based on the above costs and outcomes SPN (versus IPN) was dominant when using protein intake as the outcome measure (that is, SPN resulted in a lower cost per bag and also greater protein intake).

## Economic model

A decision-analytical model was developed to assess the costs of SPN and IPN for babies who require PN. The rationale for economic modelling, the methodology adopted, the results and the conclusions from this economic analysis are described in detail in appendix J. This section provides a summary of the methods employed and the results of the economic analysis.

### Overview of methods

A decision-analytic model in the form of a decision-tree was constructed to evaluate the costs of PN over the duration of an initial hospital stay (<2 weeks). The PN assessed were SPN and IPN. The study population comprised of preterm and term babies requiring PN. The

evidence pertaining to clinical outcomes was insufficient to inform the economic analysis. Consequently, the economic analysis only considered the duration of the initial hospital length of stay.

The perspective of the analysis was that of NHS. Resource use was based on the published literature and the committee expert opinion and included PN bag costs and setting costs including costs associated with the stay at neonatal intensive care unit (NICU) and high dependency unit (HDU). National UK unit costs were used. The cost year was 2016/17. Two methods were employed for the analysis of input parameter data and presentation of the results. First, a deterministic analysis was undertaken, where data were analysed as point estimates. A probabilistic analysis was subsequently performed in which most of the model input parameters were assigned probability distributions. Subsequently, 10,000 iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. Mean costs for each alternative were calculated by averaging across the 10,000 iterations. This approach allowed more comprehensive consideration of the uncertainty characterising the input parameters and also enabled the estimation of confidence intervals around the cost estimates.

### Findings of the base-case economic analysis

According to the deterministic analysis, SPN resulted in lower costs when compared with IPN. The expected costs were £15,966 and £16,265 for SPN and IPN, respectively; savings of £299. The cost savings were sensitive to the assumption pertaining to the duration of an initial hospital stay for SPN and IPN. Conclusions of probabilistic analysis were similar to those of deterministic analysis. The expected costs were £15,961 (95%CI: £13,677; £18,571) and £16,267 (95%CI: £13,703; £19,158) for SPN and IPN, respectively; savings of £306 (95%CI: -£1,725; £2,324). According to what-if analysis quality-adjusted life year (QALY) gain associated with IPN would need to be 0.015 for IPN to be the preferred option i.e. for the incremental cost-effectiveness ratio (ICER) of IPN (versus SPN) to be below the threshold of £20,000 per QALY.

### Strengths and limitations

The clinical data was insufficient to inform full economic evaluation. Consequently, the analysis only considered costs associated with PN. Although, a what-if analysis was undertaken to estimate what a QALY gain would need to be for IPN (versus SPN) to be cost-effective at threshold of £20,000 per QALY. Some of the model inputs were informed by the committee expert opinion. Also, the findings were sensitive to the assumption pertaining to the initial hospital stay for IPN and SPN. Although, the committee advised that they do not expect there to be differences in the duration of an initial hospital stay in babies receiving IPN and SPN.

## Evidence statements

### Clinical evidence statements

#### Weight

- Very low quality evidence from 1 RCT (N=28) showed a clinically important difference in daily weight gain of babies receiving SPN as compared to IPN; babies receiving SPN

gained less weight per day than those on IPN. However there was uncertainty around the effect: Mean difference (MD) -6.9g/day (95% CI -11.9 to -1.9).

- Very low quality evidence from 1 observational study (N = 140) showed no clinically important difference in weight at 1 week in babies receiving SPN as compared to IPN, MD 24.8g (95% CI -70.51to 120.11).
- Very low quality evidence from 1 observational study (N = 140) showed no clinically important difference in weight at 1 month in babies receiving SPN as compared to IPN, MD -21.2g (95% CI -163.43to121.03).
- Very low quality evidence from 1 observational study (N = 140) showed a clinically important difference in weight at discharge in babies receiving SPN as compared to IPN, with those receiving SPN having a smaller weight. However, there was uncertainty around the effect: MD -192.3g (95% CI -301.05to-83.55).

**Weight loss**

- Very low quality evidence from 1 observational study (N=107) showed no clinically important difference in peak percentage weight loss of babies receiving SPN as compared to IPN over seven days. However, there was uncertainty around the effect, MD 1% (95% CI -0.64to 2.64).

**Head circumference**

- Very low quality evidence from 1 observational study (N = 140) showed a clinically important difference in babies' daily increase of head circumference, those receiving SPN had smaller increases as compared to those on IPN. However, there was uncertainty around the effect: MD -0.02cm (95% CI -0.02 to -0.01).
- Very low quality evidence from 1 observational study (N = 140) showed a clinically important difference in head circumference at discharge in babies receiving SPN as compared to IPN, those receiving SPN had a smaller head circumference than those on IPN. However, there was uncertainty around the effect: MD -0.85cm (95% CI -1.26to -0.44).

**Sepsis**

- Very low quality evidence from 1 observational study (N=107) showed no clinically important difference in the number of babies with early onset sepsis in those receiving SPN as compared to IPN. However, there was high uncertainty around the effect, Relative risk (RR) 1.0 (95% CI 0.25 to 3.94).
- Very low quality evidence from 2 observational studies (N = 338) showed no clinically important difference in the number of babies with sepsis in those receiving SPN as compared to those on IPN. However, there was uncertainty around the effect, RR 1.11 (95% CI 0.83 to 1.50).

**Necrotising enterocolitis**

- Very low quality evidence from 1 observational study (N=107) showed a clinically important difference in the number of babies with necrotising enterocolitis, with more events in those receiving SPN as compared to IPN. However there was uncertainty around the effect: Peto odds ratio (POR) 5.01 (95% CI 0.28, 89.15).
- Very low quality evidence from 2 observational studies (N = 237) showed a clinically important difference in the number of babies with necrotising enterocolitis, with more

events in those receiving SPN as compared to those on IPN. However, there was high uncertainty around the effect: RR 1.30 (95% CI 0.49 to 3.43).

**Energy intake**

- Very low quality evidence from 1 observational study (N=107) showed a clinically important difference in the energy intake of babies receiving SPN as compared to IPN, those on SPN had a higher overall energy intake over seven days: MD 9kcal/kg/day (95% CI 6.79to 11.21).
- Very low quality evidence from 1 observational study (n=97) showed no clinically important difference in cumulative energy intake over 7 days in babies receiving SPN as compared to IPN. However, there was uncertainty around the effect, MD -17kcal/kg/7days (95% CI -38.09to 4.09).
- Very low quality evidence from 1 observational study (n=97) showed a clinically important difference in cumulative energy intake over 14 days in babies receiving SPN as compared to IPN, with those on SPN receiving a higher intake. However, there was uncertainty around the effect: MD 49kcal/kg/14days (95% CI 2.31 to 95.69).
- Very low quality evidence from 1 observational study (n=140) showed a clinically important difference in overall energy intake in babies receiving SPN as compared to IPN, with those babies on SPN receiving a lower intake: MD -21.97kcal/kg/day (95% CI -24.82 to -19.12).

**Glucose intake**

- Very low quality evidence from 1 observational study (N=107) showed no clinically important difference in glucose intake of babies receiving SPN as compared to IPN. However, there was uncertainty around the effect, MD 0.6g/kg/day (95% CI 0.15 to 1.05).
- Very low quality evidence from 2 observational studies (n = 98) showed no clinically important difference in glucose intake over 3 days in babies receiving SPN as compared to those receiving IPN. However, there was uncertainty around the effect, MD 0.56g/kg (95% CI -0.78 to 1.90).
- Very low quality evidence from 2 observational studies (n = 98) showed no clinically important difference in glucose intake over 8 days in babies receiving SPN as compared to those receiving IPN. However, there was high uncertainty around the effect, MD 0.41g/kg (95% CI -2.13 to 2.96).
- Very low quality evidence from 1 observational study (n= 140) showed a clinically important difference in daily glucose intake in babies receiving SPN as compared to IPN; those babies on SPN received a lower daily glucose intake as compared to those on IPN: MD -1.04mg/kg/min (95% CI -1.41 to -0.67).

**Protein intake**

- Low quality evidence from 1 RCT (N=28) showed a clinically important difference in protein intake in babies receiving SPN as compared to IPN, with lower intake in those on SPN as compared to IPN: MD -0.3g/kg/day (95% CI -0.49 to -0.11).
- Very low quality evidence from 1 observational study (N=107) showed a clinically important difference in amino acid intake of babies receiving SPN as compared to IPN, those on SPN had a greater intake over seven days: MD 0.4g/kg/day (95% CI 0.27 to 0.53).

- Very low quality evidence from 1 observational study (n = 97) showed no clinically important difference in cumulative protein intake over 7 days in babies receiving SPN as compared to those receiving SPN. However, there was uncertainty around the effect, MD 0.1g/kg/day (95% CI -0.59 to 0.79).
- Very low quality evidence from 1 observational study (n = 97) showed a clinically important difference in cumulative protein intake over 14 days in babies receiving SPN as compared to those receiving IPN, with those on SPN receiving a higher protein intake: MD 6.3g/kg/day (95% CI 5.02 to 7.58).
- Very low quality evidence from 2 observational studies (n = 55) showed a clinically important difference in mean protein intake on day 3 day in babies receiving SPN as compared to those receiving IPN, those on SPN received a higher protein intake: MD 0.67g/kg/day (95% CI 0.48 to 0.87).
- Very low quality evidence from 2 observational studies (n = 55) showed no clinically important difference in mean protein intake on day 8 in babies receiving SPN as compared to those receiving IPN. However, there was uncertainty around the effect, MD 0.21g/kg/day (95% CI -0.18 to 0.60).
- Very low quality evidence from 1 observational study (n = 140) showed a clinically important difference in mean protein intake over 31 days in babies receiving SPN as compared to those receiving IPN, those on SPN received a lower protein intake: MD -0.89g/kg/day (95% CI -1.00 to -0.78).

**Non-protein calorie intake**

- Low quality evidence from 1 RCT (N=28) showed a clinically important lower intake of non-protein energy in babies receiving SPN as compared to IPN: MD -10kcal/kg/day (95% CI -14.83 to 5.17).

**Lipid intake**

- Very low quality evidence from 1 RCT (N=28) showed a clinically important lower intake of lipids in babies receiving SPN as compared to IPN: MD -0.5g/kg/day (95% CI -0.74 to -0.26).
- Very low quality evidence from 1 observational study (N=107) showed a clinically important difference in lipid intake of babies receiving SPN as compared to IPN, those on SPN had a greater intake over seven days: MD 0.4g/kg/day (95% CI 0.24 to 0.56).
- Very low quality evidence from 1 observational study (n = 40) showed no clinically important difference in mean lipid intake on day 8 in babies receiving SPN as compared to those receiving IPN. However, there was uncertainty around the effect, MD 2.5g/kg/day (95% CI -2.56 to 7.56).
- Very low quality evidence from 1 observational study (n = 140) showed a clinically important difference in mean lipid intake over 31 days in babies receiving SPN as compared to those receiving IPN, those on SPN received a lower intake: MD -1.31g/kg/day (95% CI -1.43 to -1.19)

**Duration of Total parenteral nutrition (TPN)**

- Very low quality evidence from 1 RCT (N=28) showed no clinically important difference in the duration of TPN in babies receiving SPN as compared to IPN. However, there was uncertainty around the effect, MD -1.6 days (95% CI -6.92 to 3.72).

- Very low quality evidence from 3 observational studies (n= 378) showed no clinically important difference in the duration of days that babies received total parenteral nutrition when receiving SPN as compared to IPN. However, there was uncertainty around the effect, MD 0.53 (95% CI -2.04 to 3.10).

**Length of stay**

- Very low quality evidence from 2 observational studies (n= 338) showed no clinically important difference in the length of stay of babies receiving SPN as compared to IPN, MD 0.47(95% CI -4.32 to 5.26).

**Mortality**

- Very low quality evidence from 1 observational study (n = 198) showed a clinically important difference in mortality of babies receiving SPN as compared to those receiving IPN, more occurrences of mortality were observed in those on SPN; however there was high uncertainty around the effect: RR 1.36 (95% CI 0.39 to 4.66).

## Economic evidence statements

- There was evidence from one cost-effectiveness analysis based on an observational study (n=374 prescriptions) conducted in Austria. SPN was dominated when compared with IPN (that is, SPN resulted in higher costs per PN bag and also lower protein intake at day 1 of life, days 2-6 of life, and days 7-35 of life). This study was partially applicable to the NICE decision making context and had potentially serious methodological limitations.
- There was evidence from one cost-effectiveness analysis based on an observational study (n=160) conducted in the USA. The ICER of SPN (versus IPN) was $128 savings per weight standard deviation score lost. This study was partially applicable to the NICE decision making context and had potentially serious methodological limitations.
- There was evidence from one cost-effectiveness analysis based on an observational study (n=272 prescriptions) conducted in Australia. SPN was dominant when compared with IPN (that is, SPN resulted in lower costs per PN bag and also greater protein intake). This study was partially applicable to the NICE decision making context and had potentially serious methodological limitations.
- There was evidence from an original cost analysis conducted for the guideline which showed that SPN resulted in the cost savings of £306 when compared with IPN. However, the cost difference was not significant. The cost savings were sensitive to assumptions pertaining to the duration of initial hospital stay for SPN and IPN. This evidence was directly applicable to the NICE decision making context and was characterised by minor methodological limitations.

## The committee's discussion of the evidence

### Interpreting the evidence

#### *The outcomes that matter most*

The committee agreed that the critical outcomes were growth (including weight and head circumference), adverse events, nutrient intake, and neurodevelopmental outcomes. These outcomes were considered the most likely to be influenced by differences in SPN or IPN formulations. None of the included studies provided data on neurodevelopmental outcomes.

For all of these outcomes the committee acknowledged that a favourable result for standardised formulations would only be possible if the content of the bag would provide optimal nutrition.

Important outcomes were duration of PN, prescribing error, and length of hospital stay; however, the committee considered that these outcomes are influenced by many complex factors in addition to the nutrition regimen chosen.

***The quality of the evidence***

The included outcomes were assessed using GRADE methodology. The quality of all the evidence was considered to be very low or low. All studies were considered to have serious or very serious risk of bias. Overall, this was due to the risk of bias with one of the included studies which not truly randomised, as allocation was by alternation (Dice 1981) and study design because the other included studies were all observational which in GRADE means that they start as low quality. The quality was also downgraded due to imprecision. In addition some of the evidence may not be considered a true reflection of current practice and the committee discussed its validity in this context, for example, one study (Smolkin 2010) provided PN formulations in the standardised group with dosages of constituents which would not be considered adequate in today's practice; therefore, this evidence is not a reflection of current practice, nor an example of good standardisation. Therefore, differences between the groups might have resulted from the sub-optimal composition of the standardised bag and so were not informative with regard to the use of appropriately formulated standard bags. The evidence presented was highly heterogeneous; however, the committee and the technical team did not feel it was necessary to conduct formal sensitivity analysis, as the differences were considered obvious. Overall the committee were not confident that the data represented a true reflection of the potential differences between individualised and standardised PN.

The committee therefore reflected mainly on their current practice, their knowledge and experience and costs to draft recommendations by informal consensus.

***Benefits and harms***

The committee agreed that the evidence identified did not provide data on some of the key factors which are important when considering SPN. For example, none of the included studies provided data on prescribing errors, nor on facilitation of PN delivery. The committee agreed that one of the key benefits of standardised bags is that they allow PN to be commenced without delay. Standardised bags can be stored for immediate use as soon as the decision is made that the baby requires PN. Despite the lack of information on these key factors the committee believed strong recommendations were required particularly because reliance on IPN formulation can result in delays in initiating PN.

Based on their experience, the committee agreed that it is important that standard formulations should be made up in a relatively concentrated solution so as to allow administration of the required amounts of nutrients within the fluid allowances appropriate for the neonate. Therefore according to varying fluid requirements, a range of set standards are needed, one bag will not fit all situations The committee do not anticipate that neonatal units themselves will make up these standardised bags, they are formulated by appropriate manufactures, whether this is within hospital pharmacies or external commercial producers

The committee also agreed IPN can increase risks to patient safety (for example, errors in prescribing, manufacturing and administering). All SPN is quality assured, in line with the

Royal Pharmaceutical Society and NHS Pharmaceutical Quality Assurance Processes. This ensures the stability of SPN formulations, this process does not occur for individualised formulations. Overall it was the committee's opinion that SPN is likely to result in fewer prescribing errors, increase compliance and increase speed of delivery of PN and the committee agreed by informal consensus a strong recommendation for standardised PN formulations was justified. They took into account the benefits of easy access and cost, and their clinical experience indicating that this was a safe and effective way to provide PN.

The committee discussed how the SPN given to babies within the included studies provided low levels of macronutrients as compared to the IPN, explaining that if a baby receives a dilute form of PN then growth will inevitably be reduced, and as such the comparisons were not a true reflection of good SPN.

The committee discussed how in certain circumstances individualised PN would be the preferred option (for example in the situation of renal failure or complex gastrointestinal conditions), and this was also included in the recommendations.

The committee discussed how individualised PN and standardised PN may influence length of hospital stay; however, other factors which have not been accounted for in these studies are more likely influential. The committee could not determine any biological or clinical argument for either individualised or standardised PN to directly influence length of stay and therefore did not think it was appropriate to make recommendations on this.

The committee agreed that IPN drives variation across practice, and they believe that not only should standardised bags be recommended, but that units should have standard protocols for PN delivery. A standard system would likely lead to consistency within and across units, ensuring all babies receive optimum care.

**Cost effectiveness and resource use**

The committee acknowledged the existing economic evidence from non-UK settings. However, the results were conflicting and the committee could not draw any firm conclusions from this evidence.

The committee explained that in the existing economic evaluations the nutrients in the SPN bags were on the lower end of the dosages suggested by the committee and not representative of clinical practice. The clinical effectiveness data used in the economic evaluations were derived from small, underpowered studies. Also, the acquisition costs of PN bags are likely to be different in the UK NHS and so the results are of limited applicability, that is, the committee were aware of the cost of SPN bags used in some regional networks in the UK and that these were generally cheaper than IPN solutions.

The committee were shown the guideline economic model based on a simple decision tree comparing the total costs of an episode of PN which showed that IPN resulted in higher costs when compared with SPN. However, the committee acknowledged that the cost difference between the two was not significant.

The committee discussed potential differences in quality of life between IPN and SPN. While there was evidence of fewer side-effects (on average) with SPN, these differences did not reach statistical significance overall and were not pursued in the economic analysis. The committee agreed that it was a plausible finding that there was very little difference between the two in respect of the QALYs, and therefore it was appropriate to pick PN that would generate the lowest opportunity cost to the NHS. The committee also noted that based on

the modelling the required QALY gain for IPN to be cost effective was large (that is, 0.015 QALYs over approximately two weeks).

The committee were shown two studies with health economic relevance; Smolkin (2010) and Dice (1981) with contradictory data on whether there was difference in length of stay between SPN and IPN. The committee explained that neither of the PN regimens studied represented acceptable current nutritional practice, and it was difficult to extrapolate anything from either paper given these limitations. The committee further explained that there was no biological mechanism by which SPN would be expected to increase length of stay. Therefore, the committee agreed that the conservative approach should be taken of assuming no difference in length of stay between the two PN regimens in the base-case analysis.

The committee explained that it was sufficient to show that SPN and IPN have equivalent costs and outcomes in order to recommend SPN. SPN comes as ready-made bags and would result in other benefits such as fewer prescribing errors, preventing delay in PN and eliminating gaps in the PN provision, sub-optimal nutrition delivery and not meeting nutritional requirements and eliminating variation in practice. The committee explained that PN prescribing errors, inappropriate PN delivery and suboptimal nutrition are associated with increased neonatal mortality and morbidity.

Also, it was noted that SPN would already have been quality assured by the manufacturer whereas IPN needs to be supervised by a pharmacist or another senior clinician (that is, checking scripts) which makes the whole process much more costly.

The committee discussed potentially higher wastage with SPN. However, it was highlighted that IPN also results in wastage. It was explained that wastage associated with SPN is becoming less of an issue with the shelf life on the newer SPN bags becoming longer. The committee explained that wastage could be substantially reduced by effective planning of stock, that is, stock rotation.

All of the above are important considerations. However, the identified data was insufficient to allow these to be captured in the formal economic analysis that was undertaken for the guideline.

Overall, the committee was of a view that given the above considerations SPN is likely to represent a cost effective use of NHS resources with IPN reserved only for babies whose condition is complicated and unstable.

**Other factors the committee took into account**

The committee discussed how RCTs are unlikely to be conducted to compare SPN and IPN in current practice (as safely conducting such a study is logistically very difficult) and therefore the evidence base is unlikely to change. Similarly, potential benefits relating to patient safety (for example, improved quality control) cannot realistically be investigated as a primary outcome measure in RCTs.

The committee also discussed that it is important that their recommendations related to the dosages of individual constituents (see section 1.4 of the guideline) can provide the nutritional requirement in a standard formulation (standardised bag). They therefore provided illustrations of the ways that standardised bags could be provided based on the recommendations within this guideline (see appendix M). The examples are not intended as specific recommendations for PN formulations or as strategies for administration, they

illustrate ways in which the guideline recommendations on nutrient requirements, energy, and ratios of non-nitrogen energy to nitrogen energy and carbohydrate to lipids, could be fulfilled with a standardised bag. Three examples are provided, minimum, mid-range and maximum ratios.

## References

**Briggs 2006**

Briggs, A., Sculpher, M. and Claxton, K., 2006. Decision modelling for health economic evaluation. OUP Oxford.

**Dice 1981**

Dice, J. E., Burckart, G. J., Woo, J. T., Helms, R. A., Standardized versus pharmacist-monitored individualized parenteral nutrition in low-birth-weight infants, American journal of hospital pharmacy, 38, 1487-9, 1981

**Evering 2017**

Evering, Vincent H. M., Andriessen, Peter, Duijsters, Carola E. P. M., Brogtrop, Jeroen, Derijks, Luc J. J., The Effect of Individualized Versus Standardized Parenteral Nutrition on Body Weight in Very Preterm Infants, Journal of clinical medicine research, 9, 339-344, 2017

**Iacobelli 2010**

Iacobelli, Silvia, Bonsante, Francesco, Vintejoux, Amelie, Gouyon, Jean-Bernard, Standardized parenteral nutrition in preterm infants: early impact on fluid and electrolyte balance, Neonatology, 98, 84-90, 2010

**Kreissl 2016**

Kreissl, A., Repa, A., Binder, C., Thanhaeuser, M., Jilma, B., Berger, A., Haiden, N. Clinical experience with numeta in preterm infants: impact on nutrient intake and costs, Journal of Parenteral and Enteral Nutrition, 40, 536-542**,** 2016

**Lenclen 2006**

Lenclen, R., Crauste-Manciet, S., Narcy, P., Boukhouna, S., Geffray, A., Guerrault, M. N., Bordet, F., Brossard, D., Assessment of implementation of a standardized parenteral formulation for early nutritional support of very preterm infants, European Journal of Pediatrics, 165, 512-518, 2006

**Morgan 2009**

Morgan, C., Badhawi, I., Grime, C., Herwitker, S., Improving early protein intake for very preterm infants using a standardised concentrated parenteral nutrition formulation, e-SPEN, 4, e324-e328, 2009

**Smolkin 2010**

Smolkin, Tatiana, Diab, Giselle, Shohat, Irit, Jubran, Huda, Blazer, Shraga, Rozen, Geila S., Makhoul, Imad R., Standardized versus individualized parenteral nutrition in very low birth weight infants: a comparative study, Neonatology, 98, 170-8, 2010

**Yeung 2003**

Yeung, M. Y., Smyth, J. P., Maheshwari, R., Shah, S., Evaluation of standardized versus individualized total parenteral nutrition regime for neonates less than 33 weeks gestation, Journal of paediatrics and child health, 39, 613-7, 2003

# Appendices

## Appendix A – Review protocols

### Review protocol for review question: What is the effectiveness, efficacy and safety of standardised parenteral nutrition bags compared with individualised bags?

**Table 3: Review protocol for standardised versus individualised nutrition formulations**

| Field (based on PRISMA-P) | Content |
|---|---|
| Review question | What is the effectiveness, efficacy and safety of standardised parenteral nutrition bags compared with individualised bags? |
| Type of review question | Intervention |
| Objective of the review | There is a need to compare target nutrient attainment between individualised and standardised neonatal PN regimens. |
| Eligibility criteria – population/disease/condition/issue/domain | • Babies born preterm, up to 28 days after their due birth date (preterm babies)<br>• Babies born at term, up to 28 days after their birth (term babies) |
| Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s) | • Any standardised approach to providing PN |
| Eligibility criteria – comparator(s)/control or reference (gold) standard | • Any individualised PN solutions (bespoke prescriptions) |
| Outcomes and prioritisation | **Critical**<br>• Growth/anthropometric measures<br>  ○ Head circumference<br>  ○ Weight gain<br>  ○ Height gain<br>• Neurodevelopmental outcomes (general cognitive abilities at two years corrected age as measured by a validated scale)<br>• Adverse effects of PN:<br>  ○ Infection including sepsis<br>  ○ Hyperglycaemia |

| Field (based on PRISMA-P) | Content |
|---|---|
| | ○ PN related liver disease (abnormal liver function, cholestasis, conjugated hyperbilirubinaemia, intrahepatocellular lipid)<br>○ Hypophosphataemia/hypercalcaemia<br>• Nutritional intake (g/kg/day) (proportion of macronutrient received)<br><br>**Important**<br>• Mortality<br>• Duration of hospital stay<br>• Prescribing error |
| Eligibility criteria – study design | Only published full text papers<br>• Systematic reviews of RCTs<br>• RCTs<br>• Comparative cohort studies (only if RCTs unavailable or limited data to inform decision making)<br><br>No date restriction applied.<br><br>Conference abstracts of RCTs will only be considered if no evidence is available from full published RCT (if no evidence from RCTs or comparative cohort studies available and are recent (that is, last 2 years)authors will be contacted for further information). |
| Other inclusion exclusion criteria | Clinical settings that provide neonatal care or specialist paediatric care.<br>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 | **Stratified analysis:**<br>• Babies born preterm, up to 28 days after their due birth date (preterm babies)<br>• Babies born at term, up to 28 days after their birth (term babies)<br><br>**Subgroup analysis:**<br>The following groups will be considered for subgroup analysis:<br><br>• Population subgroups:<br>○ Age of baby (first 2 weeks versus later) |

| Field (based on PRISMA-P) | Content |
|---|---|
| | ○ Preterm (extremely preterm <28 weeks' GA; very preterm: 28-31 weeks' GA; moderately preterm: 32-36 weeks' GA)<br>○ Birthweight: low birthweight (<2500g); very low birthweight (<1500g) and extremely low birthweight (<1000g)<br>○ Critically ill babies<br><br>• Setting subgroups:<br>○ Specialist versus standard neonatal care<br><br>**Confounders:**<br>Important confounders (when comparative observational studies are included for interventional reviews)<br>• Age of baby (first 2 weeks versus later)<br>• Birthweight: low birthweight (<2500g); very low birthweight (<1500g) and extremely low birthweight (<1000g)<br>• Actual dose received<br>• Time to initiation of PN<br>• Other underlying conditions (e.g., chronic lung disease)<br>• Sex of baby<br>• Gestation (preterm vs. term)<br>• For neurodevelopmental outcomes:<br>○ Biological (sex, small for gestational age, ethnicity)<br>○ Neonatal (PVL, IVH, infarct, sepsis, ROP, NEC, antenatal/postnatal steroids, BPD at 36 weeks)<br>○ 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.<br>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).<br>'GRADEpro' will be used to assess the quality of evidence for each outcome. Low income countries will be downgraded for indirectness. |

| Field (based on PRISMA-P) | Content |
|---|---|
| | 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, CENTRAL, CDSR, DARE, HTA, Embase.<br>Limits (e.g. date, study design): All study designs. Apply standard animal/non-English language filters. No date limit.<br>Supplementary search techniques: No supplementary search techniques were used.<br>See appendix B for full strategies. |
| Identify if an update | This is not an update. |
| Author contacts | Developer: The National Guideline Alliance<br>https://www.nice.org.uk/guidance/indevelopment/gid-ng10037 |
| 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.<br>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.<br>If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots. |

| Field (based on PRISMA-P) | Content |
|---|---|
| | 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.<br>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 | Not registered with PROSPERO. |

*BPD: Bronchopulmonary dysplasia; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GA: Gestational age; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; IVH: Intraventricular haemorrhage of the newborn; NEC: Necrotising enterocolitis; NGA: National Guidelines Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; PN: Parenteral nutrition; PROSPERO: International prospective register of systematic reviews; PVL: Periventricular leukomalacia; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: risk of bias in systematic reviews; ROP: Retinopathy of prematurity SD: standard deviation; SES: Social economic status; UK: United Kingdom; WHO: World Health Organisation.*

# Appendix B – Literature search strategies

## Literature search strategies for review question: What is the effectiveness, efficacy and safety of standardised parenteral nutrition bags compared with individualised bags?

### 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 | or/15-17 |
| 19 | standard$.ti. |
| 20 | (standard$ adj10 (nutrition$ or feed$ or fed$ or regimen? or prescription? or preparation? or formulat$ or solution? or bag?)).ab. |
| 21 | individual$.ti. |
| 22 | (individual$ adj10 (nutrition$ or feed$ or fed$ or regimen? or prescription? or preparation? or formulat$ or solution? or bag?)).ab. |
| 23 | or/19-22 |
| 24 | (standard$ adj10 parenteral$).ti,ab. |
| 25 | ((premixed$ or pre-mixed$) adj10 parenteral$).ti,ab. |
| 26 | (standard$ adj10 (PN or TPN)).ti,ab. |
| 27 | STD-PN.ti,ab. |
| 28 | (individual$ adj10 parenteral$).ti,ab. |
| 29 | ((bespoke$ or be-spoke$) adj10 parenteral$).ti,ab. |
| 30 | (tailor$ adj10 parenteral$).ti,ab. |
| 31 | (modif$ adj10 parenteral$).ti,ab. |
| 32 | (enhanc$ adj10 parenteral$).ti,ab. |
| 33 | (individual$ adj10 (PN or TPN)).ti,ab. |
| 34 | IND-PN.ti,ab. |
| 35 | ((standard$ or individual$) adj10 (intravenous$ or intra-venous$ or IV or venous$ or infusion?) adj10 (nutrition$ or feed$ or fed$)).ti,ab. |
| 36 | or/24-35 |
| 37 | PARENTERAL NUTRITION/st [Standards] |
| 38 | PARENTERAL NUTRITION, TOTAL/st [Standards] |
| 39 | PARENTERAL NUTRITION SOLUTIONS/st [Standards] |
| 40 | or/37-39 |
| 41 | 14 and 18 and 23 |
| 42 | 14 and 36 |
| 43 | 14 and 40 |
| 44 | or/41-43 |
| 45 | limit 44 to english language |
| 46 | LETTER/ |
| 47 | EDITORIAL/ |

| # | Searches |
|---|---|
| 48 | NEWS/ |
| 49 | exp HISTORICAL ARTICLE/ |
| 50 | ANECDOTES AS TOPIC/ |
| 51 | COMMENT/ |
| 52 | CASE REPORT/ |
| 53 | (letter or comment*).ti. |
| 54 | or/46-53 |
| 55 | RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab. |
| 56 | 54 not 55 |
| 57 | ANIMALS/ not HUMANS/ |
| 58 | exp ANIMALS, LABORATORY/ |
| 59 | exp ANIMAL EXPERIMENTATION/ |
| 60 | exp MODELS, ANIMAL/ |
| 61 | exp RODENTIA/ |
| 62 | (rat or rats or mouse or mice).ti. |
| 63 | or/56-62 |
| 64 | 45 not 63 |

## 1 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 | or/14-18 |
| 20 | standard$.ti. |
| 21 | (standard$ adj10 (nutrition$ or feed$ or fed$ or regimen? or prescription? or preparation? or formulat$ or solution? or bag?)).ab. |
| 22 | individual$.ti. |
| 23 | (individual$ adj10 (nutrition$ or feed$ or fed$ or regimen? or prescription? or preparation? or formulat$ or solution? or bag?)).ab. |
| 24 | or/20-23 |
| 25 | (standard$ adj10 parenteral$).ti,ab. |
| 26 | ((premixed$ or pre-mixed$) adj10 parenteral$).ti,ab. |
| 27 | (standard$ adj10 (PN or TPN)).ti,ab. |
| 28 | STD-PN.ti,ab. |
| 29 | (individual$ adj10 parenteral$).ti,ab. |
| 30 | ((bespoke$ or be-spoke$) adj10 parenteral$).ti,ab. |
| 31 | (tailor$ adj10 parenteral$).ti,ab. |
| 32 | (modif$ adj10 parenteral$).ti,ab. |
| 33 | (enhanc$ adj10 parenteral$).ti,ab. |
| 34 | (individual$ adj10 (PN or TPN)).ti,ab. |
| 35 | IND-PN.ti,ab. |
| 36 | ((standard$ or individual$) adj10 (intravenous$ or intra-venous$ or IV or venous$ or infusion?) adj10 (nutrition$ or feed$ or fed$)).ti,ab. |
| 37 | or/25-36 |
| 38 | 13 and 19 and 24 |
| 39 | 13 and 37 |
| 40 | or/38-39 |

| # | Searches |
|---|---|
| 41 | limit 40 to english language |
| 42 | letter.pt. or LETTER/ |
| 43 | note.pt. |
| 44 | editorial.pt. |
| 45 | CASE REPORT/ or CASE STUDY/ |
| 46 | (letter or comment*).ti. |
| 47 | or/42-46 |
| 48 | RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab. |
| 49 | 47 not 48 |
| 50 | ANIMAL/ not HUMAN/ |
| 51 | NONHUMAN/ |
| 52 | exp ANIMAL EXPERIMENT/ |
| 53 | exp EXPERIMENTAL ANIMAL/ |
| 54 | ANIMAL MODEL/ |
| 55 | exp RODENT/ |
| 56 | (rat or rats or mouse or mice).ti. |
| 57 | or/49-56 |
| 58 | 41 not 57 |

**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)).ab,ti. |
| 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 | #15 or #16 or #17 |
| 19 | standard*.ti. |
| 20 | (standard* near/10 (nutrition* or feed* or fed* or regimen? or prescription? or preparation? or formulat* or solution? or bag?)).ab. |
| 21 | individual*.ti. |
| 22 | (individual* near/10 (nutrition* or feed* or fed* or regimen? or prescription? or preparation? or formulat* or solution? or bag?)).ab. |
| 23 | #19 or #20 or #21 or #22 |
| 24 | (standard* near/10 parenteral*):ti,ab |
| 25 | ((premixed* or pre-mixed*) near/10 parenteral*):ti,ab |
| 26 | (standard* near/10 (PN or TPN)):ti,ab |
| 27 | STD-PN:ti,ab |
| 28 | (individual* near/10 parenteral*):ti,ab |
| 29 | ((bespoke* or be-spoke*) near/10 parenteral*):ti,ab |
| 30 | (tailor* near/10 parenteral*):ti,ab |
| 31 | (modif* near/10 parenteral*):ti,ab |
| 32 | (enhanc* near/10 parenteral*):ti,ab |
| 33 | (individual* near/10 (PN or TPN)):ti,ab |
| 34 | IND-PN:ti,ab |
| 35 | ((standard* or individual*) near/10 (intravenous* or intra-venous* or IV or venous* or infusion?) near/10 (nutrition* or feed* or fed*)):ti,ab |
| 36 | #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 |

| # | Searches |
|---|---|
| 37 | MeSH descriptor: [PARENTERAL NUTRITION] this term only and with qualifier(s): [Standards - ST] |
| 38 | MeSH descriptor: [PARENTERAL NUTRITION, TOTAL] this term only and with qualifier(s): [Standards - ST] |
| 39 | MeSH descriptor: [PARENTERAL NUTRITION SOLUTIONS] this term only and with qualifier(s): [Standards - ST] |
| 40 | #37 or #38 or #39 |
| 41 | #14 and #18 and #23 |
| 42 | #14 and #36 |
| 43 | #14 and #40 |
| 44 | #41 or #42 or #43 |

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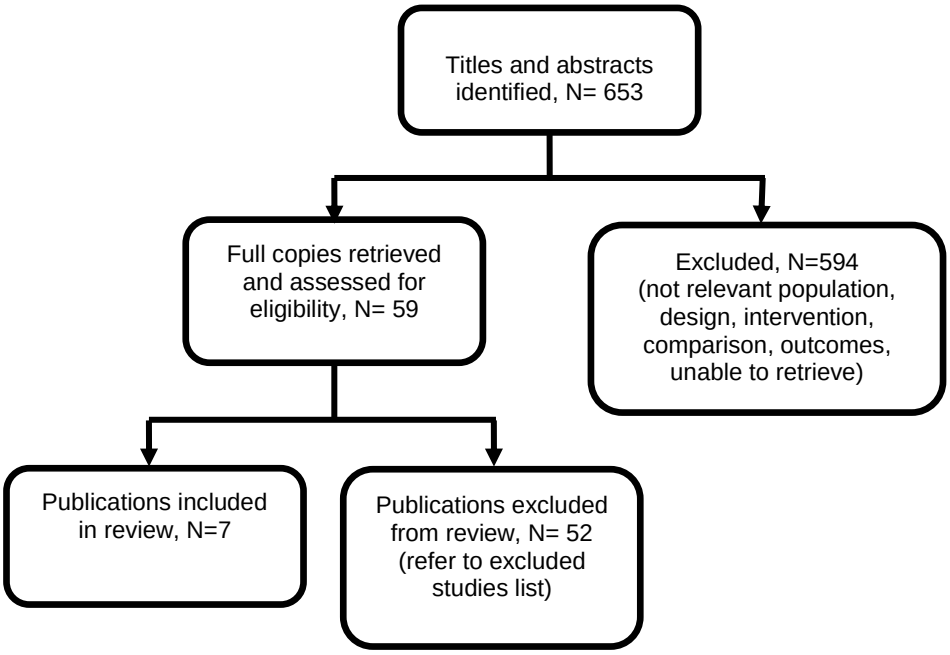
# Appendix C – Clinical evidence study selection

## Clinical study selection for: What is the effectiveness, efficacy and safety of standardised parenteral nutrition bags compared with individualised bags?

**Figure 1: PRISMA flow chart for clinical article selection for review question, standardised versus individualised PN**



# Appendix D – Clinical evidence tables

## Clinical evidence tables for review question: What is the effectiveness, efficacy and safety of standardised parenteral nutrition bags compared with individualised bags?

**Table 4: Clinical evidence tables**

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| Full citation<br>Dice, J. E., Burckart, G. J., Woo, J. T., Helms, R. A., Standardized versus pharmacist-monitored individualized parenteral nutrition in low-birth-weight infants, American journal of hospital pharmacy, 38, 1487-9, 1981<br>Ref Id<br>606693<br><br>Country/ies where the study was carried out<br>US<br><br>Study type<br>Randomised controlled trial<br><br>Aim of the study | Sample size<br>N = 28<br><br>SPN =14<br>IPN =14<br>Characteristics<br>Mean birth weight (g)<br>IPN: 1054 (SD 190)<br>SPN: 1164 (SD 224)<br><br>Mean gestational age (weeks)<br>IPN: 31.0 (SD 1.5)<br>SPN: 31.0 (SD 1.8)<br><br>Small for gestational age (n/N)<br>IPN: 9/14<br>SPN: 8/14 | Interventions<br>IPN<br>Individual requirements were determined by the physician and pharmacist, with pharmacist daily monitoring.<br><br>Amount per day: Protein = 2.0-2.5g/kg, Sodium = 3.0-5.0meq/kg, Potassium = 3.0-5.0meq/kg, Calcium = 1.0-1.5meq/kg, Magnesium = 0.3--0.5meq/kg, Phosphorous = 1.0-1.5mM/kg, Multivitamins = 2.0ml, Lipid = 1.0-3.0g/kg<br><br>SPN<br>Solutions were prepared in the pharmacy; however, physicians could make essential glucose and electrolyte manipulations. Solutions were available | Details<br>The amounts of nutrients in all formulations were based on recommendations for neonates on TPN.<br>Glucose was administered as a 10% solution unless the infant had hyperglycaemia or glycosuria.<br>Intravenous lipids were not given if total serum bilirubin was greater than 6mg/dl<br><br>Statistical analyses<br>Student's t test for independent samples was used to compare differences between the two intervention groups. | Results<br>Mean weight gain (g/day)<br>IPN: 11.8 (SD 5.2)<br>SPN: 4.9 (SD 8.0); p<0.02<br><br>Mean non-protein calories (kcal/kg/day)<br>IPN: 63.0 (SD 7.0)<br>SPN: 53.0 (SD 6.0); p<0.001<br><br>Mean protein (g/kg/day)<br>IPN: 2.2 (SD 0.2)<br>SPN: 1.9 (SD 0.3); p<0.01<br><br>Mean lipid (g/kg/day)<br>IPN 2.0 (SD 0.2)<br>SPN 1.5 (SD 0.3); p<0.001 | Limitations<br>Cochrane risk of bias for randomised trials: High risk of bias<br>Selection bias: High risk, Unclear if participants were randomised, allocation was by alternation of babies.<br><br>Performance bias: Unclear risk: Poor allocation concealment (babies assigned to SPN or IPN alternately). Blinding of assessors unlikely to influence outcomes<br><br>Attrition bias: Unclear risk, no data on missing outcomes<br><br>Reporting bias: Unclear risk, protocol |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| To compare the use of standardised total parenteral nutrition formulation with a pharmacist-assisted individualised programme of total parenteral nutrition<br><br>Study dates<br>May 1980<br><br>Source of funding<br>Not stated | Inclusion criteria<br>Infants who required TPN<br>Parents provided informed consent<br><br>Exclusion criteria<br>If the infant had received TPN for less than five days<br>Had received oral feeding<br>If they were fluid restricted (less than 75ml/kg/day) | with either 10% or 13% dextrose.<br><br>Amount administered per day: Protein = 2.3g/kg, Sodium = 2.8meq/kg, Potassium = 1.8meq/kg, Calcium = 0.6meq/kg, Magnesium = 0.23meq/kg, Phosphorous = 1.8mM/kg, Multivitamins = 1.8ml, lipid = when ordered by the physician. | | Mean duration on PN (days)<br>IPN: 11.4 (SD 9.2)<br>SPN: 9.8 (SD 4.3) | not available, no time-points specified<br><br>Other bias: low risk<br>Other information<br>Standardised PN but with additional electrolyte and glucose where required.<br><br>Nurses made 46 electrolyte additions to 6 infants in the SPN group and 4 electrolyte additions for 1 patient in the IPN group.<br><br>Glucose concentration was adjusted 95 times in all 14 SPN infants, and no manipulations were made for IPN infants.<br><br>Length of time for follow up not stated. |
| Full citation<br>Evering, Vincent H. M., Andriessen, Peter, Duijsters, Carola E. P. M., Brogtrop, Jeroen, Derijks, Luc J. J., The | Sample size<br>N=299<br><br>ITPN = 94<br>STPN = 104 | Interventions<br>ITPN<br>(BAXA compounder): Variable quantities of potassium sodium phosphate 2 mmol/mL, | Details<br>Statistical analysis<br>Based on statistical power of 80%, 192 infants were required (64 infants in each treatment group). | Results<br>Maximum weight loss (g/kg) after birth<br>ITPN: -120<br>STPN: -75 | Limitations<br>Cochrane risk of bias tool for non-randomised trials (ROBINS-I): Serious risk of bias |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| Effect of Individualized Versus Standardized Parenteral Nutrition on Body Weight in Very Preterm Infants, Journal of clinical medicine research, 9, 339-344, 2017<br>Ref Id<br>701097<br><br>Country/ies where the study was carried out<br>The Netherlands<br><br>Study type<br>Observational study<br><br>Aim of the study<br>To assess whether standardised total parenteral nutrition (STPN) is at least non-inferior to individualised total parenteral nutrition (ITPN) in preterm infants with a gestational age <32 weeks<br><br>Study dates<br>ITPN administered in 2011 | Characteristics<br>Gestational age (days)<br>ITPN: 210<br>STPN: 207<br><br>Mean birth weight (g)<br>ITPN: 1243 (SD 347)<br>STPN: 1213 (SD 382)<br><br>Gender (male) - n (%)<br>ITPN: 39 (41)<br>STPN: 56 (54)<br><br>TPN duration (days)<br>ITPN: 6<br>STPN: 5; p=0.01<br><br>Singleton births - n (%)<br>ITPN: 53 (56)<br>STPN: 66 (63)<br><br>Inclusion criteria<br>Preterm infants with a gestational age <32 weeks | sodium chloride 10%, potassium chloride 1 mmol/mL, glucose 50%, trace elements, calcium glubionate 137.5 mg/mL, magnesium chloride, vitamins, lipid emulsion (ClinOleic® 20%), and water injections.<br><br>STPN<br>(NEOmix): Energy (66 kcal), protein (2.6g), triglycerides (2.0), glucose (8.9 g), sodium (2.1 mmol), potassium (0.66 mmol), magnesium (0.1 mmol), calcium (0.7 mmol), phosphate (0.93 mmol), chloride (1.39 mmol) | However, the total sample size was increased to 300 (100 infants in each treatment group).<br><br>Normal data were presented as means ± standard deviations (SDs) or median (interquartile range; IQR). One-way ANOVA (with Bonferroni correction or Tanane post hoc analysis) was used to test for differences between treatment groups on parametric continuous data. Non-parametric continuous data were tested using Kruskal-Wallis and Mann-Whitney U.<br><br>Multivariate analysis was used to study patient characteristics. Categorical data were assessed using Chi-square and Fisher exact tests. | Culture proven sepsis - n (%)<br>ITPN: 35 (37)<br>STPN: 40 (38); p<0.01<br><br>Hyperbilirubinaemia - n (%)<br>ITPN: 77 (82)<br>STPN: 66 (63); p=0.01<br><br>Mortality - n (%)<br>ITPN: 4 (4)<br>STPN: 6 (6)<br><br>Hospitalisation time NICU (days)<br>ITPN: 13<br>STPN: 14 (24) | Confounding bias: Low risk of bias<br><br>Selection of participant's bias: High risk of bias (retrospective analysis for ITPN group 2011, matched to STPN group 2014)<br><br>Classification of interventions bias: Moderate risk of bias<br><br>Deviations from intended interventions bias: Low risk of bias (no deviations reported)<br><br>Missing data bias: Low risk of bias (all infants evaluable)<br><br>Measurement of outcomes bias: NI (unclear whether outcome assessors were blinded, but unlikely due to safety reasons) |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| STPN administered in 2014<br><br>Source of funding<br>None stated | Exclusion criteria<br>Preterm infants who died within <72 hours. | | | | Selection of the reported results bias: Moderate risk of bias - data not clearly presented, no protocol specifying outcomes.<br><br>Other information<br>STPN described as an all-in-one completely standardised composition (NEOmix), but not specifically stated as pre-manufactured.<br><br>There was a third treatment arm using a partially standardised composition (Numeta® G13%E), but not discussed in the evidence report as it is not applicable to the protocol (and withdrawn from the market because of a reported higher risk on developing hypermagnesaemia). |
| Full citation<br>Iacobelli, Silvia, Bonsante, Francesco, Vintejoux, Amelie, | Sample size<br>N= 107<br><br>IPN = 40 | Interventions<br>IPN<br>Nutrient volumes calculated by a computer system | Details<br><br>Statistical analyses | Results<br>There was no difference in the percentage of | Limitations<br>Cochrane risk of bias tool for non-randomised trials |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| Gouyon, Jean-Bernard, Standardized parenteral nutrition in preterm infants: early impact on fluid and electrolyte balance, Neonatology, 98, 84-90, 2010<br>Ref Id<br>701134<br><br>Country/ies where the study was carried out<br>France<br><br>Study type<br>Observational study<br><br>Aim of the study<br>To compare fluid and electrolyte balance in very preterm infants receiving individualised parenteral nutrition (IPN) to standardised parenteral nutrition (SPN)<br><br>Study dates<br>June 2006 to October 2006 (IPN period)<br><br>November 2006 to July 2007 (SPN period) | SPN = 67<br>Characteristics<br>Mean gestational age (weeks)<br>IPN: 29.0 (SD 1.9)<br>SPN: 29.1 (SD 1.7)<br><br>Small for gestational age - %<br>IPN: 30<br>SPN: 21<br><br>Mean birth weight (g)<br>IPN: 1216 (SD 341)<br>SPN: 1150 (SD 329)<br><br>Apgar score <7 at 5 minutes of life - %<br>IPN: 18<br>SPN: 14<br><br>Antenatal steroids - %<br>IPN: 85<br>SPN: 78<br><br>Singleton births - %<br>IPN: 57<br>SPN: 75 | according to the input chosen by the prescribing physician.<br><br>SPN<br>8 different solutions for day 1 to day 7 of life. To avoid fluid overload, the volume delivered via SPN was lower than the daily volume intake recommended by the guidelines (i.e. starting fluid intake at 80 ml/kg/day, then giving fluid and electrolyte input to allow a daily weight loss of 2 to 4% and to maintain serum sodium and potassium concentrations within 135 to 145 and 4 to 6 mEq/L, respectively.<br><br>Starting sodium and potassium intakes at day 3. Prescribing amino acid and energy supply according to published recommended dietary intakes for preterm infants). 10% dextrose or sterile water for injection at choice could be added to SPN to achieve required water supply. | Categorical data analysed using chi-square test or Fisher's exact test for small samples.<br><br>Continuous data expressed as means ± SD and differences between groups analysed using Student's t-test or Mann-Whitney U test for non-normally distributed data.<br>Univariate analyses, using one-factor analysis of variance), were conducted to explore the relationship between water and electrolyte balance (where statistically significant between IPN and SPN groups) and perinatal variables and water, electrolyte, energy and amino acid intakes. | nutrients given between feeds.<br><br>Mean percentage weight loss<br>IPN: 9.6% (SD 4.2%)<br>SPN: 10.6% (SD 4.2%)<br><br>Mean daily sodium during the first week (mmol/kg/day)<br>IPN: = 0.93 (SD 0.47)<br>SPN: 1.48 (SD 0.48); p<0.001<br><br>Mean daily potassium during the first week (mmol/kg/day)<br>IPN: 1.03 (SD 0.38)<br>SPN: 1.11 (SD 0.19); p=NS<br><br>Mean daily energy during the first week (kcal/kg/day)<br>IPN: 55 (SD 6)<br>SPN: 64 (SD 5); p<0.001 | (ROBINS-I): moderate risk of bias<br><br>Confounding bias: Low risk of bias<br><br>Selection of participant's bias: Moderate risk of bias, cohorts were not homogeneous and intervention periods do not coincide for all babies<br><br>Classification of interventions bias: Low risk of bias<br><br>Deviations from intended interventions bias: Low risk of bias (no deviations reported)<br><br>Missing data bias: Low risk of bias (all infants evaluable)<br><br>Measurement of outcomes bias: Low risk of bias (methods of outcome assessment |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| Source of funding<br>Not stated | Caesarean section - %<br>IPN: 80<br>SPN: 82<br><br>Parenteral nutrition prescriptions - n<br>IPN: 278<br>SPN: 466<br><br>Inclusion criteria<br>Infants born below 33 weeks of gestational age<br>Hospitalised within 6 hours after birth<br>Had a central venous line<br><br>Exclusion criteria<br>Major congenital abnormalities<br><br>Secondary exclusion<br>Death within the first week<br>Central venous line in place for less than five days over the first week | Minimal enteral feeding by donor human milk at 20 ml/kg/day was initiated in all infants within the first 24 hours of life whenever possible and maintained over 2 to 4 days, oral intake was increased if tolerated by 20 ml/kg/day. | | Mean daily glucose during the first week (g/kg/day)<br>IPN: 9.8 (SD 1.3)<br>SPN: 10.4 (SD 0.8); p<0.01<br><br>Mean daily amino acids during the first week (g/kg/day)<br>IPN: 1.8 (SD 0.4)<br>SPN: 2.2 (SD 0.2); p<0.001<br><br>Mean daily lipids during the first week (g/kg/day)<br>IPN: 1.3 (SD 0.4)<br>SPN: 1.7 (SD 0.4); p<0.001 | comparable across groups. Outcomes unlikely to be influence by lack of blinding)<br><br>Selection of the reported results bias: Moderate risk of bias, outcomes were not predefined; however, anticipated nutritional outcomes are presented<br><br>Other information<br>Composition of SPN bags committed to the commercial manufacturer and designed to provide identical initial dosage, day for initiation and proportional increase of nutrient (commercially batch-produced). |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| Full citation<br>Lenclen, R., Crauste-Manciet, S., Narcy, P., Boukhouna, S., Geffray, A., Guerrault, M. N., Bordet, F., Brossard, D., Assessment of implementation of a standardized parenteral formulation for early nutritional support of very preterm infants, European Journal of Pediatrics, 165, 512-518, 2006<br>Ref Id<br>689352<br><br>Country/ies where the study was carried out<br>France<br><br>Study type<br>Observational study<br><br>Aim of the study<br>To evaluate the implementation of a standardised parenteral nutrition regime, and to compare nutrient supplies between | Sample size<br>N = 40<br><br>IND = 20<br>STD = 20<br>Characteristics<br>Mean gestational age (weeks)<br>IND = 28 (SD 2.4)<br>STD = 28 (SD 2.5); p = 0.98<br><br>Mean birth weight (g)<br>IND = 883 (SD 216)<br>STD = 889 (SD 196); p = 0.93<br><br>Small for gestational age<br>IND = 20%<br>STD = 25%; p = >0.99<br><br>Mean Clinical Risk Index for babies<br>IND =3.75 (SD 2.5)<br>STD = 3.4 (SD 2.5); p = 0.62<br><br>Mean duration of PN (days) | Interventions<br>IND<br>PN for premature infants less than 32 weeks gestation were individualised following recommendations, using a standard prescribing protocol. Composition individualised in compliance with instructions for volume and the amino acid pattern of increase.<br>Solutions were prepared by the nurses in the department.<br><br>STD<br>Prescription of PN was based on three solutions of predefined composition designed with reference to published evidence. Solutions were prepared in the hospital pharmacy.<br><br>Solution 1 (days 1 and 2): Per 100ml - glucose = 10g, AA = 1.1g, non-protein energy = 40kcal, nitrogen = 160mg, sodium = 1.8mmol, potassium = 0mmol, calcium = 0.64mmol, phosphate = 0.67mmol, magnesium = 0.26mmol. | Details<br>The same support protocol was used across time periods. Administration of donor human milk (10ml/kg/d) was started in the first week after birth, volume was increased after 3 to 5 days, progression was consistent across time periods.<br>The same protocol was followed for insulin intravenous therapy to control for persistent hyperglycaemia.<br><br>Statistical analyses<br><br>20 infants per treatment group were required to reveal a difference of 20% relative to the mean usual cumulated figure for amino acids during the first week, with a power of 80%.<br><br>Continuous data were analysed using t-test and Mann Whitney test for non-normal distribution. Quality variables were | Results<br>Mean weight gain (g)<br>Day 14<br>IND: 37 (95%CI: -5 to 79)<br>STD = 52 (95%CI: 25 to 79)<br><br>Day 28<br>IND: 222 (95%CI: 170 to 250)<br>STD = 262 (95%CI: 170 to 375)<br><br>Mean parenteral intake<br>Day 3<br>IND: Total volume 108.1ml (104.2-112.1), glucose 9.6g (9-10.1),* AA 0.9g (0.7-1.2),* non-protein energy 38.4kcal (36-40.4)<br>STD: Total volume 109.8ml (103.3-116.4), glucose 10.7g (10.3-11.1), AA 1.5g (1.4-1.6), non-protein energy 42.8kcal (41.12-44.4)<br>Glucose (p = 0.002) and AA (p=0.0001) | Limitations<br><br>Cochrane risk of bias tool for non-randomised trials (ROBINS-I): Serious risk of bias<br><br>Confounding bias: Low risk of bias<br><br>Selection of participant's bias: High risk of bias (retrospective analysis for IPN group 2001, matched to SPN group 2003)<br><br>Classification of interventions bias: Low risk of bias<br><br>Deviations from intended interventions bias: High risk of bias (as enteral feed increased, parenteral nutrition decreased, but no further details provided; insulin intake greater in IPN infants; authors mention lower level of deviation from protocol for SPN) |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| individualised (IND) and standardised (STD) prescription of PN<br><br>Study dates<br>2001 IND period<br><br>2003 STD period<br><br>Source of funding<br>Not stated | IND = 25.7 (SD 8.9)<br>STD = 26.2 (SD 9.9); p = 0.88<br><br>Mean duration of mechanical ventilation (days)<br>IND = 14.1 (SD 16.4)<br>STD = 8.6 (SD 11.2); p = 0.23<br><br>Inclusion criteria<br>Premature infants of less than 32 weeks gestation<br>Received PN for at least 10 days<br>Remained in hospital of at least 28 days postpartum<br><br>Exclusion criteria<br>None stated | Solution 2 (days 3 and 4): Per 100ml - glucose = 10.1g, AA = 1.6g, non-protein energy = 40.4kcal, nitrogen = 230mg, sodium = 2.5mmol, potassium = 1.4mmol, calcium = 0.63mmol, phosphate = 0.69mmol, magnesium = 0.22mmol.<br><br>Solution 3 (>day 4): Per 100ml - glucose = 10.3g, AA = 2.1g, non-protein energy = 41.2g, nitrogen = 300mg, sodium = 2.4mmol, potassium = 1.3mmol, calcium = 0.62mmol, phosphate = 0.71mmol, magnesium = 0.27mmol. Trace elements, zinc, and L-carnitine added; hydrosoluble vitamins were mixed into the lipid emulsion. | analysed using chi-square test. Nutritional and biological data were presented as means and 95% confidence intervals (CIs). | significantly different between groups<br><br>Day 8<br>IND: Total volume 138.8ml (126.3-151.4), glucose 14.4g (13.3-15.5), AA 2.8g (2.4-3.1), carbohydrate energy 57.6kcal (53.2-62), fat energy 12.4kcal (8.6-16.2)<br>STD: Total volume 141.5ml (128.2-154.8), glucose 13.5g (12.2-14.7), AA 2.8g (2.6-3.1), carbohydrate energy 54kcal (48.8-58.8), fat energy 14.9kcal (11-18.7)<br>No significant differences between the groups<br><br>Cumulative intakes during the first week (/kg/week) - mean (95% CI)<br>IND: Total volume 818ml (788-849), glucose 77.8g (74.1- | Missing data bias: Low risk of bias (all infants evaluable)<br><br>Measurement of outcomes bias: NI (unclear whether outcome assessors were blinded, but unlikely due to safety reasons)<br><br>Selection of the reported results bias: Moderate risk of bias, outcomes were not predefined; however, anticipated nutritional outcomes are presented<br><br>Other information<br>STD prepared in the hospital pharmacy, available in the neonatal intensive care unit on a permanent basis and tailored to the nutritional needs of premature infants <32 weeks gestation |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| | | | | 81.4), AA 11.1g (9.9-12.2), carbohydrate energy 311kcal (296-325), fat energy 23.7kcal (13.4-34)<br>STD = Total volume 831ml (795-868), glucose 81.8g (78.6-85), AA 13.6g* (12.9-14.2), carbohydrate energy 327kcal (314-340), fat energy 21.5kcal (13-30)<br>AA intake was significantly greater in the STD group (p=0.0003) | Babies from the two time periods were matched for gestational age and for birth weight |
| Full citation<br>Morgan, C., Badhawi, I., Grime, C., Herwitker, S., Improving early protein intake for very preterm infants using a standardised concentrated parenteral nutrition formulation, e-SPEN, 4, e324-e328, 2009<br>Ref Id<br>414047 | Sample size<br>N = 97<br><br>iNPN = 59<br>scNPN = 38<br>Characteristics<br>Mean birth weight (g)<br>iNPN: 950 (SD 219)<br>scNPN: 898 (SD 228); p=0.27<br><br>Mean gestation (weeks) | Interventions<br>iNPN<br>The protocol aimed to start PN within 24 hours, starting at 1g/kg/day protein/lipid for 48 hours, increasing to 2g/kg/day for another 48 hours, with a maximum 3g/kg/day protein/lipid).<br>Electrolyte content was individually prescribed each day, if deficiencies were identified the iNPN was changed. | Details<br>The study was conducted at Liverpool Women's Hospital Neonatal Intensive Care Unit<br>All data was collected retrospectively from electronic records.<br><br>iNPN: Enteral feeds were managed using the NICU enteral feeding policy for infants <1500 g and were introduced within 48 hours where possible. | Results<br>Mean protein intake (g/kg/days)<br>7 days<br>iNPN: 11.9 (SD 1.3)<br>scNPN: 12 (SD 1.9); p=0.78<br><br>14 days<br>iNPN: 28.1 (SD 2.5)<br>scNPN: 34.4 (SD 3.5); p<0.001 | Limitations<br>Cochrane risk of bias tool for non-randomised trials (ROBINS-I): Serious risk of bias<br><br>Confounding bias: Low risk of bias<br><br>Selection of participant's bias: High risk of bias (retrospective analysis for iNPN group pre- |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| Country/ies where the study was carried out<br>UK<br><br>Study type<br>Obervational study<br>iNPN was part of an RCT, scNPN was the comparative group<br><br>Aim of the study<br>To determine whether a standardised parenteral nutrition (scNPN) regimen can improve protein intake as compared to individualised parenteral nutrition (iNPN)<br><br>Study dates<br>Individualised period - pre June 2006<br><br>Standardised period - post June 2006<br><br>Source of funding<br>The study has no funding | iNPN: 26.9 (SD 1.5)<br>scNPN: 26.5 (SD 1.5); p=0.20<br><br>Median time on ventilator (days)<br>iNPN: 4 (IQR: 3-8)<br>scNPN: 10 (IQR: 5 to 25); p<0.01<br><br>Inclusion criteria<br>All infants receiving scNPN and born in the 6 months following the introduction of scNPN in June 2006<br>Infants <29 weeks gestation<br>Receiving > 12 days of PN<br>Ex-utero transfers from other hospitals were included if the transfer occurred within 48 hours of birth<br><br>Exclusion criteria<br>Not stated | iNPN content: Aqueous PN volume 135ml, supplementary dextrose volume 0ml, lipid volume 15ml, non-protein calories 89kcal, protein 3g, glucose 13.5g, lipid 3g.<br><br>scNPN<br>The macronutrient content did not differ to the iNPN. The aqueous content was concentrated and the remaining fluid provided by supplementary dextrose. The aqueous solution had a standard electrolyte, content with three different options: no electrolytes, preterm maintenance electrolytes, and additional sodium. scNPN was prescribed every 24 hours but changed every 48 hours. Where deficiencies after a scNPN change were identified, then standardised supplementary electrolyte infusions were administered according to the PN protocol.<br><br>scNPN content: Aqueous PN volume 85ml, supplementary dextrose volume 50ml, lipid volume | Sequential reductions in aqueous parenteral nutrition volume were made as feeds were increased. The intravenous lipid infusion rate was halved once enteral feeds exceeded 75 ml/kg/day and all iNPN stopped once enteral feeds exceeded 100 to 120 ml/kg/day.<br><br>scNPN: Enteral feeds were introduced in the same way as for iNPN, but once enteral feeds were included in the fluid total, aqueous scNPN was only reduced once the supplementary dextrose infusion rate had been reduced to zero.<br><br>Statistical analyses<br>Protein and calorie intake were compared using the unpaired student t-test. Other major neonatal outcomes were compared using the student t-test, chi-squared test and Mann-Whitney U test, as appropriate. | Mean calorie intake (kcal/kg/days)<br>7 days<br>iNPN: 505 (SD 48)<br>scNPN: 488 (SD 54); p=0.12<br><br>14 days<br>iNPN: 1159 (SD 96)<br>scNPN = 1208 (SD 125); p=0.04 | June 2006, matched to scNPN group post-June 2006)<br><br>Classification of interventions bias: Moderate risk of bias (intervention status defined, yet retrospective design has the potential to influence outcomes)<br><br>Deviations from intended interventions bias: Moderate risk of bias (3 infants received <90% of the target scNPN volume; 8 infants received <95% scNPN)<br><br>Missing data bias: Low risk of bias (all infants evaluable)<br><br>Measurement of outcomes bias: NI (unclear whether outcome assessors were blinded, but unlikely due to safety reasons) |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| | | 15ml, non-protein calories 89kcal, protein 3g, glucose 13.5g, lipid 3g. | | | Selection of the reported results bias: Moderate risk of bias (unclear if all outcomes reported, data not presented per day but per week, may indicate selection of reporting)<br><br>Other information<br>Standardised PN with supplementary electrolyte and dextrose, where required. |
| Full citation<br>Smolkin, Tatiana, Diab, Giselle, Shohat, Irit, Jubran, Huda, Blazer, Shraga, Rozen, Geila S., Makhoul, Imad R., Standardized versus individualized parenteral nutrition in very low birth weight infants: a comparative study, Neonatology, 98, 170-8, 2010<br>Ref Id<br>606787 | Sample size<br>N = 140<br><br>IND-PN = 70<br>STD-PN = 70<br>Characteristics<br>Mean gestational age (weeks)<br>IND: 29.24 (SD 1.86)<br>STD: 29.25 (SD 1.81); p=0.8 | Interventions<br>IND-PN<br>A standard formula was started until tailored IND-PN became available (glucose 7.5-11%), this could be up to 48hours<br>IND was adjusted daily for water, glucose, AA, lipids, electrolytes, vitamins and trace elements. The aim was to supply glucose 10-12mg/kg/min, AA 3-4g/kg/day, lipids 3-4g/kg/day. | Details<br>The study was carried out at Meyer Children's Hospital, Rambam Health Care Campus, Haifa, Israel.<br><br>The protocol for daily PN fluid volumes was the same in both interventions: Day 1 = 80-100ml/kg/day, day 2 = 110-150ml/kg/day, day 3 140-200ml/kg/day, days 4-5 150-250ml/kg/day, days 6-7 150-220ml/kg/day. | Results<br>Mean daily weight gain (g)<br>IND: 23.76 (SD 4.24)<br>STD: 20.27 (SD 4.52); p<0.00001<br><br>Mean weight at 1 week (g)<br>IND: 1151.5 (SD 289.3)<br>STD: 1176.3 (SD 286.1); p=0.32 | Limitations<br>Cochrane risk of bias tool for non-randomised trials (ROBINS-I): Serious risk of bias<br><br>Confounding bias: Low risk of bias<br><br>Selection of participant's bias: High risk of bias (retrospective analysis for IND group 2000 to |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| Country/ies where the study was carried out<br>Israel<br><br>Study type<br>Observational study<br><br>Aim of the study<br>To compare individualised (IND-PN) to standard (STD-PN) parenteral nutrition on nutrition parameters, growth, complications in very low birth weight babies<br><br>Study dates<br>Standardised period: January 2000 to December 2001<br><br>Individualised period: January 2006 to December 2007<br><br>Source of funding<br>Not stated | Mean birth weight (g)<br>IND: 1246.8 (SD 291.4)<br>STD: 1322.8 (SD 302.9); p=0.005<br><br>Gender (male) - n (%)<br>IND: 44 (62.9)<br>STD: 37 (52.9); p=0.09<br><br>Resuscitation at birth - n (%)<br>IND: 62 (88.6)<br>STD: 46 (65.7); p=0.004<br><br>Antenatal medications - n (%)<br>IND: steroids 38 (54.3); indomethacin 5 (7.1); pressolat 5 (7.1)<br>STD: steroids 31 (44.3); indomethacin 7 (10); pressolat 1 (1.4)<br><br>Inclusion criteria<br>very low birth weight babies, 1500g | STD-PN<br>Five pre-set formulations were available with various glucose concentrations (2.5, 5, 7.5, 10 and 11%) and AA concentrations ranging from 1.5 to 2g/100ml of PN. The aim was to supply glucose 10-12mg/kg/min, AA 3-4g/kg/day, and lipids 3/4g/kg/day. Lipids were supplied separately for 24 hours. | PN was delivered via umbilical vein catheters until day 7 of aged, and then via percutaneous intravascular central catheter.<br>IND: Enteral nutrition was provided by mother's milk supplemented with human milk fortifier and/or Similac Special Care.<br>STD: Enteral nutrition was provided through mother's milk supplemented with Nutriprem human milk fortifier.<br><br>Enteral nutrition was started on day 3 in both groups in infants weighing 1000 to 1500 g and on day 5 in infants <1000 g. Increments of 2 to 3 ml every 3 hours were allowed daily.<br><br>Statistical analyses<br>70 infants required for each treatment group based on the following assumptions: paired study, type I (alpha) error = 0.05, power = 80% and a 20% difference between | Mean weight at 1 month (g)<br>IND: 1679.7 (SD 412.8)<br>STD: 1658.5 (SD 445.2); p=0.54<br><br>Mean discharge weight (g)<br>IND: 2626.6 (SD 368.7)<br>STD: 2434.3 (SD 282.1); p=0.001<br><br>Mean daily head circumference gain (cm)<br>IND: 0.12 (SD 0.02)<br>STD: 0.104 (SD 0.02); p=0.0001<br><br>Mean head circumference at discharge (cm)<br>IND: 33.9 (SD 1.17)<br>STD: 33.05 (SD 1.3); p=0.0002<br><br>Nutrition composition during the first month of life<br>Days on PN<br>IND: 5.63 (SD 5.42) | 2001, matched to STD group 2006 to 2007)<br><br>Classification of interventions bias: Moderate risk of bias (intervention status defined, yet retrospective design has the potential to influence outcomes)<br><br>Deviations from intended interventions bias: Low risk of bias<br><br>Missing data bias: Low risk of bias (all infants evaluable)<br><br>Measurement of outcomes bias: NI (unclear whether outcome assessors were blinded, but unlikely due to safety reasons)<br><br>Selection of the reported results bias: Low risk of bias (all outcomes reported)<br><br>Other information |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| | Appropriate for gestational age status (birth weight between 10th and 90th percentiles)<br>need for partial or total PN during the first week of life or longer<br>Survival to discharge from the NICU<br><br>Exclusion criteria<br>Significant congenital malformation | | the 2 treatment groups, as to the mean change in weight SDS during the first month of life.<br><br>Outcomes for the two treatment groups were compared using a paired t-test for continuous data, a rank-signed Wilcoxon test for ordinal data, and the McNemar test for dichotomous data. | STD: 7.9 (SD 7.01); p=0.007<br><br>Mean kcal/kg/day whilst on PN<br>IND: 74.9 (SD 8.67)<br>STD: 52.93 (SD 8.53); p<0.00001<br><br>Mean daily glucose whilst on PN (mg/kg/min)<br>IND: 7.46 (SD 1.18)<br>STD: 6.42 (SD 1.03); p<0.00001<br><br>Mean protein on PN (g/kg/day)<br>IND: 2.81 (SD 0.28)<br>STD: 1.92 (SD 0.36); p<0.00001<br><br>Mean fat on PN (g/kg/day)<br>IND: 2.68 (SD 0.32)<br>STD: 1.37 (SD 0.4); p<0.00001<br><br>Mean length of stay (days)<br>IND: 58.64 (SD 18.56) | Unclear STD-PN - stated as 5 parenteral pre-set formulas<br><br>Neonates in the IND arm were matched to a similar neonate who received STD-PN, matched at a similar gestational age (+/- 4 days) |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| | | | | STD: 58.50 (SD 23.51)<br><br>The rates of infants with hyperglycaemia (serum glucose >120 mg/dl in at least one of the measurements) were similar between treatment groups. | |
| Full citation<br>Yeung, M. Y., Smyth, J. P., Maheshwari, R., Shah, S., Evaluation of standardized versus individualized total parenteral nutrition regime for neonates less than 33 weeks gestation, Journal of paediatrics and child health, 39, 613-7, 2003<br>Ref Id<br>606812<br>Country/ies where the study was carried out<br>Australia<br><br>Study type<br>Observational study<br><br>Aim of the study | Sample size<br>N = 58<br><br>IPN = 31<br>SPN = 27<br>Characteristics<br>Mean gestation (weeks)<br>IPN = 28.3 (SD 1.7)<br>SPN = 28.6 (SD 2.6); p = 0.76<br><br>Mean birth weight (g)<br>IPN = 1117 (SD 236)<br>SPN = 1083 (SD 352); p = 0.56<br><br>Median Clinical Risk Index for Babies | Interventions<br>IPN<br>Formulations were determined according to the neonatologists discretion, based on morning serum biochemical data. Prescribing guidelines for protein were daily increments from 0.5 to 1g/kg/day up to 3g/kg/day. Protein adjustments were made according to serum urea concentrations.<br><br>Glucose intake was 5 to 8mg/kg per min for a target of blood glucose concentration of 6 to 8mmol/.<br><br>Total fluid intake was started at 80mL/kg per day, | Details<br>The study was carried out in the NICU of the Nepean Hospital, affiliated with the University of Sydney.<br>Fluid management was the same across time periods.<br><br>Fat emulsion, which incorporated vitamins was given separately and in the same stepwise dose increments in both time periods.<br><br>Statistical analyses<br>Unpaired two-tailed t-test with Welch correction for two samples of unequal variance were used to analyse normally | Results<br>Mean parenteral nutrition intakes (SEM)<br>Aged 2 days<br>IPN: Glucose = 9.0g/kg (0.45), AA = 0.8g/kg (0.09),* Total volume = 62mL/kg (4.82)<br>SPN: Glucose = 8.7g/kg (0.59), AA = 1.6 g/kg (0.14), Total volume = 67mL/kg (6.01)<br>AA intake was significantly greater in the SPN infants, p=0.0001<br><br>Aged 7 days | Limitations<br>Cochrane risk of bias tool for non-randomised trials (ROBINS-I): Serious risk of bias<br><br>Confounding bias: Low risk of bias<br><br>Selection of participant's bias: High risk of bias (retrospective analysis for IPN group 1999 to 2000, matched to SPN group 2000 to 2001)<br><br>Classification of interventions bias: moderate risk of bias (intervention |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| To compare the nutrient intakes in newborn infants (<33 weeks gestation) who received either standardised (SPN) or individualised (IPN) parenteral nutrition<br><br>Study dates<br>Individualised period was September 1999 to July 2000<br><br>Standardised period was August 2000 to February 2001<br><br>Source of funding<br>Not stated | IPN = 2.0<br>SPN = 2.0; (p = 0.71)<br><br>Inclusion criteria<br>Newborn infants < 33 weeks gestation<br>Received ≥5 days of PN<br><br>Exclusion criteria<br>None reported | increased by 20mL/kg/day increments to a maximum of 160 to 180mL/kg/day. Sodium (usually 2 to 3 mmol/kg/day) and potassium (usually 1.5 to 2 mmol/kg/day) were prescribed after 48 hours postnatal age when diuresis was established.<br><br>SPN<br>Formulations were batch produced as two solutions:<br>Solution A: Glucose 125g/L, AA 24.5g/L, Sodium 8.0mmol/L, Potassium 0mmol/L, Calcium 10mmol/L, Magnesium 2.0mmol/L, Chloride 24mmol/L, Phosphate 0mmol/L, Acetate 8mmol/L, Heparin 1000units/L<br><br>Solution B: Glucose 100g/L, AA 24.5g/L, Sodium 25mmol/L, Potassium 17mmol/L, Calcium 12.5mmol/L, Magnesium 2.0mmol/L, Chloride 29mmol/L, Phosphate 12.5mmol/L, Acetate 17mmol/L, Heparin 1000units/L | distributed data and the Mann-Whitney U-test was used to analyse non-normally distributed data. | IPN: Glucose = 8.5g/kg (0.51), * AA = 2.1g/kg (0.14),* Total volume = 96mL/kg (5.85)<br>SPN: Glucose = 10.2g/kg (0.51), AA = 2.5g/kg (0.13), Total volume = 100.5mL/kg (5.27)<br>Glucose and AA intake were significantly greater in SPN infants, p=0.02 and 0.03 | status defined, yet retrospective design has the potential to influence outcomes)<br><br>Deviations from intended interventions bias: Low risk of bias<br>Missing data bias: Low risk of bias (All babies included)<br><br>Measurement of outcomes bias: NI (unclear whether outcome assessors were blinded, but unlikely due to safety reasons)<br><br>Selection of the reported results bias: Moderate risk of bias, outcomes were not predefined; however, anticipated nutritional outcomes are presented.<br><br>Other information<br>SPN commercially batch produced.<br><br>No growth outcomes |

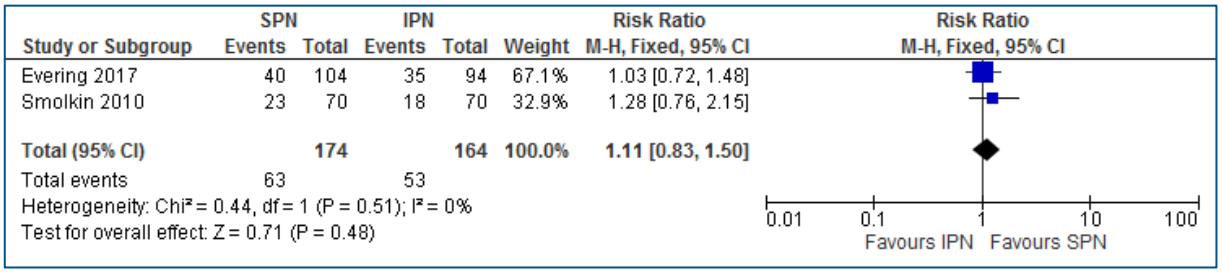
| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| | | Solution A was for infants aged <48hours and Solution B was for those aged 48 hours or greater | | | |

*AA: amino acids; ANOVA: analysis of variance; CI: confidence interval; IND: individualised; IND-PN/iNPN/IPN: individualised parenteral nutrition; IQR: interquartile range; ITPN: individualised total parenteral nutrition; NICU: neonatal intensive care unit; PN: parenteral nutrition; ROBINS-I: risk of bias in non-randomised studies of interventions; ScNPN/SPN/STD-PN/ STPN: standardised parenteral nutrition; SD: standard deviation; SDS: standard deviation score; TPN: total parenteral nutrition.*

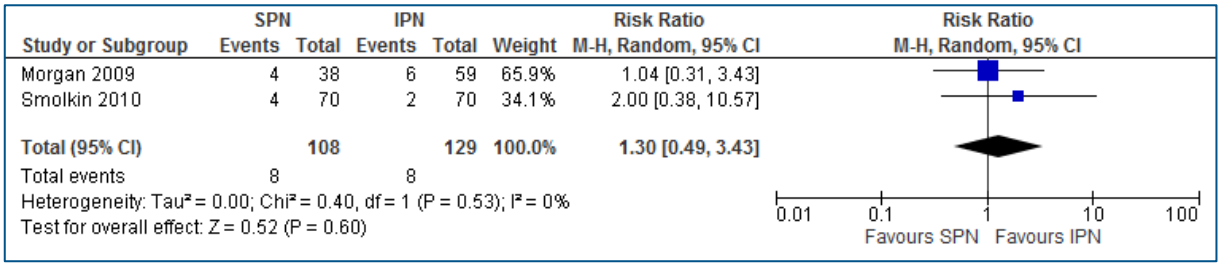
# Appendix E – Forest plots

## Forest plots for review question: What is the effectiveness, efficacy and safety of standardised parenteral nutrition bags compared with individualised bags?

### Figure 2: Forest plot to show number of babies with sepsis




### Figure 3: Forest plot to show number of babies with necrotising enterocolitis




### Figure 4: Forest plot to show glucose intake of babies on standardised and individualised PN

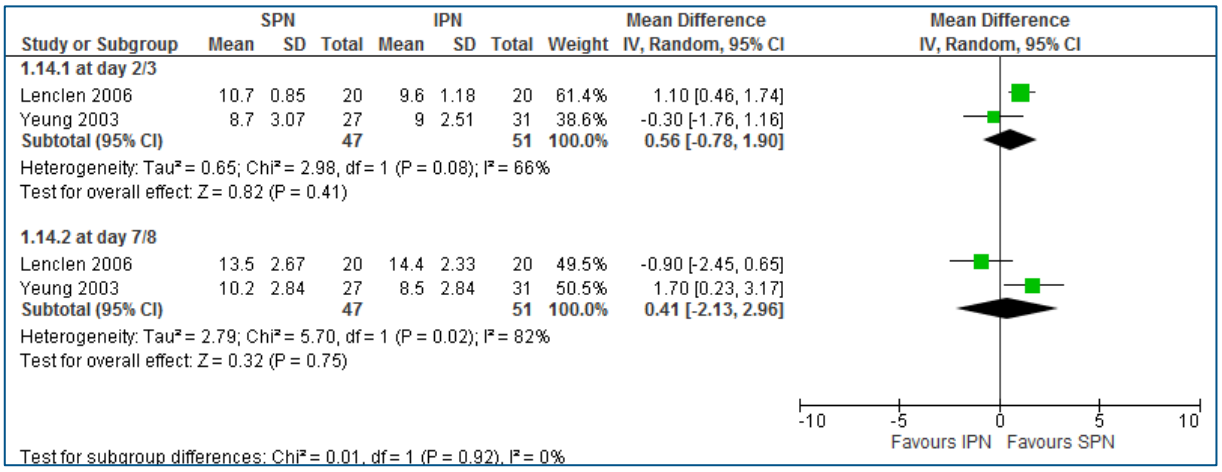


**Figure 5: Forest plot to show mean protein intake of babies on standardised and individualised PN**

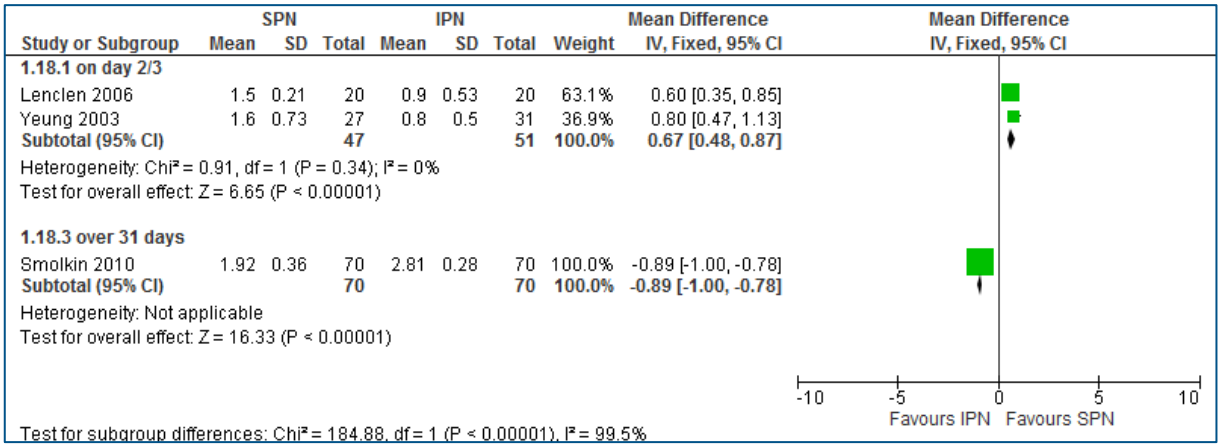
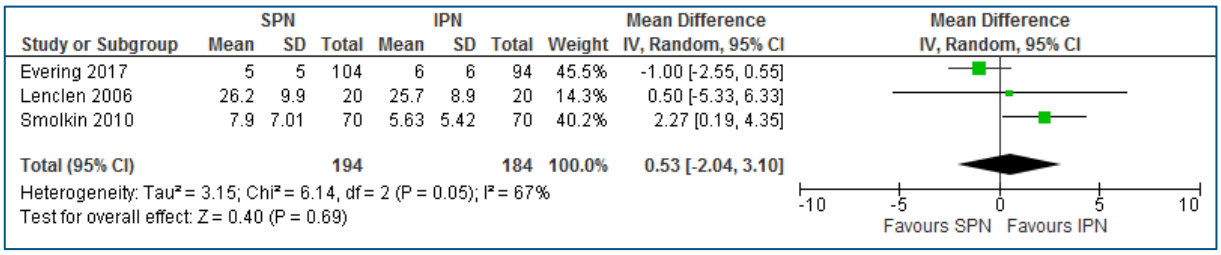



**Figure 6: Forest plot to show duration of PN**



# Appendix F – GRADE tables

## GRADE tables for review question: What is the effectiveness, efficacy and safety of standardised parenteral nutrition bags compared with individualised bags?

**Table 5: Clinical evidence profile for comparison standardised versus individualised PN**

| Quality assessment | | | | | | | No of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | SPN versus IPN | Control | Relative (95% CI) | Absolute | Quality | Importance |
| **Weight gain (g/day) (Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | RCT | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 14 | 14 | - | MD 6.9 lower (11.9 to 1.9 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Weight (g) - 1 week (follow-up mean 1 weeks; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 70 | 70 | - | MD 24.8 higher (70.51 lower to 120.11 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Weight (g) - 1 month (follow-up mean 1 months; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 70 | 70 | - | MD 21.2 lower (163.43 lower to 121.03 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Weight (g) - At discharge (Better indicated by higher values)** | | | | | | | | | | | | |

| Quality assessment | | | | | | | No of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **SPN versus IPN** | **Control** | **Relative (95% CI)** | **Absolute** | **Quality** | **Importance** |
| 1 | observational studies | serious[3] | no serious inconsistency | no serious indirectness | serious[4] | none | 70 | 70 | - | MD 192.3 lower (301.05 to 83.55 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Weight loss (% peak loss) (Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[5] | no serious inconsistency | no serious indirectness | serious[6] | none | 67 | 40 | - | MD 1 higher (0.64 lower to 2.64 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Head circumference-daily increase (Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[3] | no serious inconsistency | no serious indirectness | serious[7] | none | 70 | 70 | - | MD 0.02 lower (0.02 to 0.01 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Head circumference at discharge (cm) (Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[3] | no serious inconsistency | no serious indirectness | serious[8] | none | 70 | 70 | - | MD 0.85 lower (1.26 to 0.44 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Early onset sepsis (follow-up mean 7 days)** | | | | | | | | | | | | |
| 1 | observational studies | serious[5] | no serious inconsistency | no serious indirectness | very serious[9] | none | 5/67 (7.5%) | 3/40 (7.5%) | RR 1 (0.25 to 3.94) | 0 fewer per 1000 (from 56 fewer to 221 more) | ⊕OOO VERY LOW | CRITICAL |
| **Sepsis** | | | | | | | | | | | | |

| Quality assessment | | | | | | | No of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **SPN versus IPN** | **Control** | **Relative (95% CI)** | **Absolute** | **Quality** | **Importance** |
| 2 | observational studies | serious[3] | no serious inconsistency | no serious indirectness | serious[10] | none | 63/174 (36.2%) | 53/164 (32.3%) | RR 1.11 (0.83 to 1.5) | 36 more per 1000 (from 55 fewer to 162 more) | ⊕OOO VERY LOW | CRITICAL |
| **Necrotising enterocolitis (follow-up mean 7 days)** | | | | | | | | | | | | |
| 1 | observational studies | serious[5] | no serious inconsistency | no serious indirectness | serious[11] | none | 2/67 (3%) | 0/40 (0%) | RD 0.03 (-0.03 to 0.09) | - | ⊕OOO VERY LOW | CRITICAL |
| **Necrotising enterocolitis** | | | | | | | | | | | | |
| 2 | observational studies | serious[12] | serious[13] | no serious indirectness | serious[26] | none | 8/108 (7.4%) | 8/129 (6.2%) | Peto OR 5.01 (0.28 to 89.15) | - | ⊕OOO VERY LOW | CRITICAL |
| **Energy intake (kcal/g/day) in the first week (follow-up mean 7 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[5] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 67 | 40 | - | MD 9 higher (6.79 to 11.21 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Cumulative energy intake (kcal/kg/day) - kcal/kg/7days (follow-up mean 7 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[12] | no serious inconsistency | no serious indirectness | serious[14] | none | 38 | 59 | - | MD 17 lower (38.09 lower to 4.09 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Cumulative energy intake (kcal/kg/day) - kcal/kg/14days (follow-up mean 14 days; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[12] | no serious inconsistency | no serious indirectness | serious[15] | none | 38 | 59 | - | MD 49 higher (2.31 | ⊕OOO VERY LOW | CRITICAL |

| Quality assessment | | | | | | | No of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | SPN versus IPN | Control | Relative (95% CI) | Absolute | Quality | Importance |
| | | | | | | | | | | to 95.69 higher) | | |
| **Energy intake (kcal/kg/day) (Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 70 | 70 | - | MD 21.97 lower (24.82 to 19.12 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Macronutrient intake (g/kg/day) in the first week - Glucose (follow-up mean 7 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[5] | no serious inconsistency | no serious indirectness | serious[16] | none | 67 | 40 | - | MD 0.6 higher (0.15 to 1.05 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Glucose intake (g/kg) - at day 2/3 (follow-up 2-3 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 2 | observational studies | serious[17] | serious[18] | no serious indirectness | serious[19] | none | 47 | 51 | - | MD 0.56 higher (0.78 lower to 1.9 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Glucose intake (g/kg) - at day 7/8 (follow-up 7-8 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 2 | observational studies | serious[17] | very serious[13] | no serious indirectness | very serious[20] | none | 47 | 51 | - | MD 0.41 higher (2.13 lower to 2.96 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Mean daily glucose (mg/kg/min) (Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 70 | 70 | - | MD 1.04 lower (1.41 | ⊕OOO VERY LOW | CRITICAL |

| Quality assessment | | | | | | | No of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | SPN versus IPN | Control | Relative (95% CI) | Absolute | Quality | Importance |
| | | | | | | | | | | to 0.67 lower) | | |
| **Protein intake (g/kg/day) (Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | RCT | very serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 14 | 14 | - | MD 0.3 lower (0.49 to 0.11 lower) | ⊕OOO LOW | CRITICAL |
| **Macronutrient intake (g/kg/day) in the first week - Amino acids (follow-up mean 7 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[5] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 67 | 40 | - | MD 0.4 higher (0.27 to 0.53 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Cumulative protein (g/kg/day) - at 7 days (follow-up mean 7 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[12] | no serious inconsistency | no serious indirectness | serious[21] | none | 38 | 59 | - | MD 0.1 higher (0.59 lower to 0.79 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Cumulative protein (g/kg/day) - at 14 days (follow-up mean 14 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[12] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 38 | 59 | - | MD 6.3 higher (5.02 to 7.58 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Mean protein intake (g/kg/d) - on day 2/3 (follow-up 2-3 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 2 | observational studies | serious[17] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 47 | 51 | - | MD 0.67 higher (0.48 | ⊕OOO VERY LOW | CRITICAL |

| Quality assessment | | | | | | | No of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | SPN versus IPN | Control | Relative (95% CI) | Absolute | Quality | Importance |
| | | | | | | | | | | to 0.87 higher) | | |
| **Mean protein intake (g/kg/d) - On day 7/8 (follow-up 7-8 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 2 | observational studies | serious[17] | serious[18] | no serious indirectness | serious[22] | none | 47 | 51 | - | MD 0.21 higher (0.18 lower to 0.6 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Mean protein intake (g/kg/d) - over 31 days (follow-up mean 31 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 70 | 70 | - | MD 0.89 lower (1 to 0.78 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Non-protein intake (kcal/kg/day) (Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | RCT | very serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 14 | 14 | - | MD 10 lower (14.83 to 5.17 lower) | ⊕OOO LOW | CRITICAL |
| **Lipid intake (g/kg/day) (follow-up mean 7 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 8 | 11 | - | MD 0.5 lower (0.74 to 0.26 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Macronutrient intake (g/kg/day) in the first week - Lipids (follow-up mean 7 days; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[5] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 67 | 40 | - | MD 0.4 higher (0.24 to 0.56 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Mean fat intake (g/kg/day) - on day 8 (follow-up mean 8 days; Better indicated by higher values)** | | | | | | | | | | | | |

| Quality assessment | | | | | | | No of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **SPN versus IPN** | **Control** | **Relative (95% CI)** | **Absolute** | **Quality** | **Importance** |
| 1 | observational studies | serious[17] | no serious inconsistency | no serious indirectness | serious[23] | none | 20 | 20 | - | MD 2.5 higher (2.56 lower to 7.56 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Mean fat intake (g/kg/day) - over 31 days (follow-up mean 31 days; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | observational studies | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 70 | 70 | - | MD 1.31 lower (1.43 to 1.19 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Duration on TPN (days) (Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | RCT | very serious[1] | no serious inconsistency | no serious indirectness | serious[24] | none | 14 | 14 | - | MD 1.6 lower (6.92 lower to 3.72 higher) | ⊕OOO VERY LOW | IMPORTANT |
| **Duration of TPN (days) (Better indicated by lower values)** | | | | | | | | | | | | |
| 3 | observational studies | serious[17] | serious[18] | no serious indirectness | serious[25] | none | 194 | 184 | - | MD 0.53 higher (2.04 lower to 3.1 higher) | ⊕OOO VERY LOW | IMPORTANT |
| **Length of stay (Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | observational studies | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 174 | 164 | - | MD 0.47 higher (4.32 lower to 5.26 higher) | ⊕OOO VERY LOW | IMPORTANT |
| **Mortality** | | | | | | | | | | | | |

| Quality assessment | | | | | | | No of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | SPN versus IPN | Control | Relative (95% CI) | Absolute | Quality | Importance |
| 1 | observational studies | serious[3] | no serious inconsistency | no serious indirectness | very serious[9] | none | 6/104 (5.8%) | 4/94 (4.3%) | RR 1.36 (0.39 to 4.66) | 15 more per 1000 (from 26 fewer to 156 more) | ⊕OOO VERY LOW | IMPORTANT |

*CI: confidence interval; IPN: individualised parenteral nutrition; MD: mean difference; OR: odds ratio; RR: risk ratio; SPN: standardised parenteral nutrition.*

*[1] Evidence downgraded for very serious risk of bias as unclear risk of reporting bias, poor allocation concealment, no timeframe is provided, it is therefore unclear if data was collected as initially planned. It is also unclear if care staff and/or assessors were blind to allocation. Allocation by alternation - not truly randomised.*

*[2] 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 (-2.6).*

*[3] Evidence downgraded due to high risk of selection bias, the two cohorts were selected.*

*[4] 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 (-184.4).*

*[5] Evidence downgraded by 1 due to serious risk of bias, the two cohorts were not homogenous.*

*[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 (2.1).*

*[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 (-0.012).*

*[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 (-0.59).*

*[9] 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).*

*[10] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for dichotomous outcomes (0.80 or 1.25).*

*[11] Evidence was downgraded by 1 due to serious imprecision, risk difference calculated due to low event rate.*

*[12] Evidence downgraded by 1 due to high risk of selection bias, cohorts were selected. Moderate risk of bias from deviations from the intended protocol (in Morgan 2009 3 infants received <90% of the target scNPN volume; 8 infants received <95% scNPN).*

*[13] Evidence was downgraded by 2 due to high inconsistency.*

*[14] 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 (-24).*

*[15] 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 (48).*

*[16] 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 (0.65).*

*[17] Evidence downgraded to serious risk of selection bias, the two cohorts were selected. High risk of bias due to deviation from the intended protocol, Lenclen 2006 state fewer deviations during the SPN period.*

*[18] Evidence was downgraded by 1 due to moderate inconsistency.*

[19] *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 (1.00).*

[20] *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 (-1.32, 1.32).*

[21] *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 (0.65).*

[22] *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 (0.37).*

[23] *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 (4.06).*

[24] *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 (4.6).*

[25] *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 (3.04)*

[26]*. Evidence was downgraded for risk of imprecision due to low event ra*

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# Appendix G – Economic evidence study selection

## Economic evidence study selection for review question: What is the effectiveness, efficacy and safety of standardised parenteral nutrition bags compared with individualised bags?

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

# 1 Appendix H – Economic evidence tables

## 2 Economic evidence tables for review question: What is the effectiveness, efficacy and safety of standardised parenteral 3 nutrition bags compared with individualised bags?

4 **Table 6: Economic evidence tables**

| **Study**<br>**Country**<br>**Study type** | **Intervention & comparator** | **Study population**<br>**Study design**<br>**Data sources** | **Costs: description and values**<br>**Outcomes: description and values** | **Results** | **Comments** |
|---|---|---|---|---|---|
| Kreissl, A., Repa, A., Binder, C., Thanhaeuser, M., Jilma, B., Berger, A., Haiden, N., Clinical experience with numeta in preterm infants: impact on nutrient intake and costs, Journal of Parenteral and Enteral Nutrition, 40, 536-542, 2016<br><br>Austria<br><br>Cost-effectiveness analysis<br><br>Conflict of interest: NR | Interventions:<br>SPN (Numeta) vs. IPN<br><br>Numeta is a triple-chamber bag, including amino acids plus electrolytes, glucose, and lipids. | Preterm infants with a birth weight ≤ 1500g and a gestational age <37 weeks<br><br>Prospective observational cohort study<br><br>Source of clinical effectiveness data: observational study (n= 34, 374 prescriptions)<br><br>Source of resource use data: observational study participants (n= 34, 374 prescriptions) | Costs: parenteral solution, consumables, and preparation time<br><br>Mean cost per solution bag[1]:<br>SPN: €58<br>IPN: €42<br>Difference: €16<br><br>Primary outcome measure: protein intake<br><br>Day 1 of life (mean g/kg/day and range):<br>SPN: 1.6 (1-2.2)<br>IPN: 2.1 (1.1-2.3)<br>Difference: -0.5, p< 0.001 | SPN is dominated using protein intake as an outcome measure<br><br>Sensitivity analyses: none undertaken | Perspective: narrow healthcare payer<br>Currency: Euros<br>Cost year: likely 2015<br>Time horizon: up to 35 days of life<br>Discounting: NA<br>Applicability: partially applicable<br>Quality: potentially serious limitations |

| Study<br>Country<br>Study type | Intervention & comparator | Study population<br>Study design<br>Data sources | Costs: description and values<br>Outcomes: description and values | Results | Comments |
|---|---|---|---|---|---|
| Funding: NR | | Source of unit costs: unclear | Days 2-6 of life (mean g/kg/day and range):<br>SPN: 3.1 (1.6-4.1)<br>IPN: 3.6 (1.7-5)<br>Difference: -0.5, p< 0.001<br><br>Days 7-35 of life (mean g/kg/day and range):<br>SPN: 3.2 (2.0-4.9)<br>IPN: 3.8 (2.4-5.4)<br>Difference: -0.5, p< 0.001 | | |
| Smolkin, T., Diab, G., Shobat, I., Jubran, H., Blazer, S., Rozen G. S., Makhoul, I. R., Standardised versus individualised parenteral nutrition in very low birth weight infants: a comparative study, Neonatology, 98, 170-178, 2010<br><br>Israel | Interventions:<br>SPN vs. IPN | Preterm infants with a birth weight ≤ 1500g, the mean gestational age was <32 weeks<br><br>Retrospective observational cohort study (n= 160)<br><br>Source of clinical effectiveness data: observational study (n= 160) | Costs: parenteral solution and consumables including i.v. set, syringe, stockpot, lipid bag, nurse time, physician/dietitian<br><br>Mean extra cost per solution bag (infant/day):<br>SPN: $7.5<br>IPN: $9 | The ICER of SPN (vs. IPN): $128 savings per weight SDS lost<br><br>Sensitivity analyses: none undertaken | Perspective: narrow healthcare<br>Currency: USD<br>Cost year: likely 2009<br>Time horizon: up to 1 month<br>Discounting: NA<br>Applicability: partially applicable<br>Quality: potentially serious limitations |

| Study<br>Country<br>Study type | Intervention & comparator | Study population<br>Study design<br>Data sources | Costs: description and values<br>Outcomes: description and values | Results | Comments |
|---|---|---|---|---|---|
| Cost-effectiveness analysis<br><br>Conflict of interest: NR<br><br>Funding: NR | | Source of resource use data: observational study participants (n= 160)<br><br>Source of unit costs: unclear | Difference: -$1.5 (-$45 per month)<br><br>Primary outcome measure: growth during NICU (change in weight SDS during 1st month of life)<br><br>Mean change in weight SDS during 1st month of life:<br>SPN: -1.23 (SD 0.68)<br>IPN: -0.88 (SD 0.52)<br>Difference: 0.35 (in favour of IPN), p< 0.05 | | |
| Yeung, M. Y., Smyth, J. P., Maheshwari, R., Shah, S., Evaluation of standardised versus individualized total parenteral nutrition regime for neonates less than 33 weeks gestation, J. Paediatr. Child Health, 39, 613-617, 2003<br><br>Australia | Interventions:<br>IPN vs. SPN | Preterm infants <33 weeks' gestation<br><br>Retrospective observational cohort study (n= 58, 272 prescriptions)<br><br>Source of clinical effectiveness data: retrospective observational cohort | Costs: unclear<br><br>Mean cost per solution bag:<br>SPN: $88<br>IPN: $130<br>Difference: -$42<br><br>Primary outcome measure: protein intake | SPN dominant using protein intake as the outcome measure<br><br>Sensitivity analyses: none undertaken | Perspective: narrow healthcare (intervention)<br>Currency: AUD<br>Cost year: likely 2002<br>Time horizon: up to 1 week<br>Discounting: NA<br>Applicability: partially applicable<br>Quality: potentially serious limitations |

| Study<br>Country<br>Study type | Intervention & comparator | Study population<br>Study design<br>Data sources | Costs: description and values<br>Outcomes: description and values | Results | Comments |
|---|---|---|---|---|---|
| Cost-effectiveness analysis<br><br>Conflict of interest: NR<br><br>Funding: NR | | study (n= 58, 272 prescriptions)<br><br>Source of resource use data: retrospective observational cohort study participants (n= 58, 272 prescriptions)<br><br>Source of unit costs: unclear | Cumulative protein intake during the first week of life (g/kg):<br>SPN 13.6<br>IPN: 9.6<br>Difference: 4.0, p< 0.05 | | |

*AUD: Australian Dollar; ICER: Incremental cost-effectiveness ratio; IPN: Individualised parenteral nutrition; NA: Not applicable; NICU: Neonatal intensive care unit; NR: Not reported; SDS: Standard deviation score; SPN: Standardised parenteral nutrition; USD United States Dollar*

*1. The valuation of the preparation time of PN was unclear in the study. As a result the value of time to prepare PN was valued assuming that PN will be prepared by a pharmacist (Band 6 worker at £44 per hour, PSSRU 2018), the exchange rate of GBP to Euro was assumed to be 1:1.14.*

# 1 Appendix I – Economic evidence profiles

## 2 Economic evidence profiles for review question: What is the effectiveness, efficacy and safety of standardised parenteral 3 nutrition bags compared with individualised bags?

4 **Table 7: Economic evidence profiles for**

| Study and country | Limitations | Applicability | Other comments | Incremental costs | Incremental effects | ICER | Uncertainty |
|---|---|---|---|---|---|---|---|
| Kreissl 2016<br><br>Austria | Potentially serious limitations[1] | Partially applicable[2] | Type of economic analysis: cost-effectiveness analysis<br>Time horizon: up to 35 days of life<br>Primary measure of outcome: protein intake (g/kg/day) | €16/bag[3] | -0.5 (days 1-35 of life) | SPN dominated | The difference in protein intake was statistically significant at day 1, days 2-6, and days 7-35 of life; p<0.001 |
| Smolkin 2010<br><br>USA | Potentially serious limitations[4] | Partially applicable[5] | Type of economic analysis: cost-effectiveness analysis<br>Time horizon: up to 1 month<br>Primary measure of outcome: growth during NICU (change in weight standard deviation score during 1st month of life) | -$1.5/day (-$45/month) | 0.35 (in favour of IPN) | $128 savings per weight standard deviation score lost | The difference in outcome was statistically significant; p < 0.05 |

| Study and country | Limitations | Applicability | Other comments | Incremental costs | Incremental effects | ICER | Uncertainty |
|---|---|---|---|---|---|---|---|
| Yeung 2003<br><br>Australia | Potentially serious limitations[6] | Partially applicable[7] | Type of economic analysis: cost-effectiveness analysis<br>Time horizon: up to 1 week<br>Primary measure of outcome: cumulative protein intake during the first week of life (g/kg) | -$42 | 4.0 | SPN dominant | The difference in outcome was statistically significant; p < 0.05 |
| Guideline economic analysis<br><br>UK | Minor limitations[8] | Directly applicable[9] | Type of economic analysis: cost analysis<br>Time horizon: up to 2 weeks | -£306 | NA | SPN cost saving | The cost difference was not statistically significant (95%CI: -£1,725; £2,324).<br><br>The cost savings were sensitive to the assumption pertaining to the initial hospital duration associated with IPN and SPN.<br><br>The cost savings were robust to changes in the proportion of babies initiated |

| Study and country | Limitations | Applicability | Other comments | Incremental costs | Incremental effects | ICER | Uncertainty |
|---|---|---|---|---|---|---|---|
| | | | | | | | on SPN who require IPN. |

*AUD: Australian Dollar; ICER: Incremental cost-effectiveness ratio; IPN: Individualised parenteral nutrition; NA: Not applicable; NICU: Neonatal intensive care unit; NR: Not reported; SDS: Standard deviation score; SPN: Standardised parenteral nutrition; USD United States Dollar*

1. *Consumables included not reported, source of unit cost data unclear*
2. *Non-UK study, no QALYs*
3. *Resource use data from a small observational cohort study, source of unit cost data unclear, the reporting of cost data unclear*
4. *The valuation of the preparation time of PN was unclear in the study. As a result the value of time to prepare PN was valued assuming that PN will be prepared by a pharmacist (Band 6 worker at £44 per hour, PSSRU 2018), the exchange rate of GBP to Euro was assumed to be 1:1.14*
5. *Non-UK study, no QALYs*
6. *Source of unit cost data unclear, reporting unclear*
7. *Non-UK study, no QALYs*
8. *Some model inputs based on Guideline committee expert opinion*
9. *UK study*

# Appendix J – Health economic analysis

## Economic analysis for review question: What is the effectiveness, efficacy and safety of standardised parenteral nutrition bags compared with individualised bags?

### Economic model

The choice of parenteral nutrition (PN) bags in preterm and term babies was identified by the committee and the guideline health economist as an area with potentially major resource implications. Existing economic evidence in this area was limited to non-UK studies. Clinical evidence was very limited but adequate to inform exploratory primary economic modelling. Based on the above considerations, a simple economic model was developed to assess the relative costs of PN bags in preterm and term babies. The economic analysis did not consider quality-adjusted life years (QALYs) since the systematic review did not identify any significant differences between the interventions in terms of adverse events and neurodevelopmental outcomes. There was some evidence which showed that mean daily weight gain and energy intake was statistically greater in babies receiving individualised PN IPN (as compared to standardised PN (SPN)). However, this evidence came from low-quality studies.

### Methods

#### *Population*

The study population of the economic model comprised babies requiring PN.

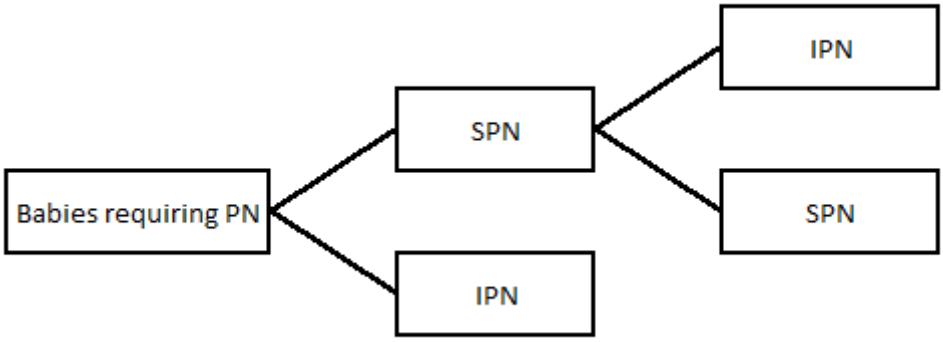
#### *Interventions assessed*

The economic analysis compared SPN with IPN.

#### *Model structure*

A decision analytic model was constructed using Microsoft Office Excel 2013 (Figure 7). The model estimated the total costs associated with the provision of each type of PN in babies. The structure of the model, which aimed to simulate clinical practice in the UK was driven by the availability of data. According to the model structure, a hypothetical cohort of babies was initiated on either SPN or IPN. It was modelled that all babies initiated on IPN will be successfully managed using bespoke PN. However, a proportion of babies initiated on SPN also require IPN. The time horizon of the analysis was determined by the availability of data and was limited to the duration of the parenteral nutrition during an initial hospital admission.

**Figure 7: Schematic diagram of the economic model constructed to assess the costs of SPN and IPN**




*IPN: individualised parenteral nutrition, SPN: standardised parenteral nutrition, PN: parenteral nutrition*

### *Costs considered in the analysis*

The economic analysis adopted the perspective of the NHS, as recommended by NICE (Developing NICE guidelines: the manual 2014). Costs consisted of intervention costs (SPN and IPN bags), as well as the costs associated with the setting where PN is administered. The cost year was 2017.

### *Model input parameters*

The main input parameter used in the economic analysis was the duration of PN in babies on IPN as compared to SPN. Three studies provided data on duration of PN (Dice 1981, Lenclen 2006, Smolkin 2010). The duration of PN in Lenclen 2006 was substantially higher than in the other studies and the committee advised that the duration reported in this study was not representative of clinical practice in the UK NHS. The data from Lenclen 2006 was not considered in the economic analysis. Moreover, the committee explained that overall they did not expect there to be a difference in the duration of PN between SPN and IPN. As a result, the base-case analysis assumed that there was no difference in the duration of PN between SPN and IPN groups.

Based on the committee expert opinion it was modelled that approximately 23.30% of babies initiated on SPN will require IPN and the remainder (76.70%) will be successfully managed using SPN. The committee further advised that of those receiving SPN approximately 9% would receive SPN starter bags and the remainder (91%) will receive SPN maintenance bags.

### *Cost data*

Intervention costs included the costs of IPN bags, SPN starter bags, and SPN maintenance bags. The costs associated with PN bags were estimated by combining the unit cost of PN bag with the time on PN. The unit costs of PN bags were based on committee expert opinion as £92.73 per day for IPN, £45.00 per day for an SPN starter bag, and £58.00 per day for an SPN maintenance bag.

In the base-case analysis, the duration on PN was modelled to be the same for SPN and IPN group and was obtained from Smolkin 2010. Smolkin 2010 compared SPN with IPN in very

low birth weight infants (n=140). This was a retrospective observational cohort study conducted in Israel. In this study, the mean duration of exclusive PN was 5.63 days (SD: 5.42) and 7.9 days (SD: 7.01) for the IPN and SPN groups, respectively. In this study, the mean days on combined PN and enteral nutrition were 8.54 days (SD: 3.68) and 9.53 days (SD: 4.49) for the IPN and SPN groups, respectively. To estimate the total days on PN days on exclusive PN and days on combined PN and enteral feeds were summed. The resulting days for the IPN group were also applied for the SPN group (that is, 5.63 days on exclusive PN and 8.54 days on combined PN and enteral feeds).

It was further modelled that the exclusive PN would be administered in a neonatal intensive care unit (NICU) and that the combined PN and enteral nutrition would be administered in a high dependency unit (HDU). The daily unit costs of a stay in NICU and HDU were obtained from NHS reference costs 2016/17 (HRG XA01Z and XA202Z for NICU and HDU, respectively).

Cost data used in the economic analysis are presented in Table 8 which also reports the mean (deterministic) values of all input parameters used in the economic model and provides information on the distributions assigned to specific parameters in probabilistic sensitivity analysis.

**Table 8: Input parameters utilised in the economic model of IPN and SPN for babies requiring PN**

| Input parameter | Mean value | Probabilistic distribution | Source of data - comments |
|---|---|---|---|
| **Intervention costs per day:**<br>IPN<br>SPN starter<br>SPN maintenance | <br>£93<br>£45<br>£58 | No distribution assigned | Committee audit data from their respective units |
| **Proportion on SPN and require:**<br>IPN<br>SPN starter<br>SPN maintenance | <br>23.3%<br>6.7%<br>70% | Normal distribution assuming SD 20% of the mean value | Committee expert opinion |
| **Setting costs per day:**<br>NICU<br>HDU | <br>£1,218<br>£872 | Normal distribution assuming SD 20% of the mean value | NHS reference costs 2016/17, XA01Z, XA02Z, XA05Z<br><br>The assumption is that exclusive PN is given in NICU only, combined enteral and PN is given in HDU ward. |
| **Time inputs:**<br>Days on exclusive PN<br>Days on combined PN and enteral feeding | <br>5.63<br>8.54 | Gamma distribution<br>Alpha: 75.53, beta: 0.07<br>Alpha: 376.98, beta: 0.02 | Smolkin 2010<br><br>The assumption is that the days of PN are the same for IPN and SPN groups |

*HDU: high dependency unit, IPN: individualised parenteral nutrition, NICU: neonatal intensive care unit, PN: parenteral nutrition, SD: standard deviation, SPN: standardised parenteral nutrition*

## Data analysis and presentation of results

Deterministic and probabilistic analyses were employed to analyse the input parameter data and present the results of the economic analysis.

A deterministic analysis was undertaken, where data were analysed as point estimates; results are presented as mean total costs associated with each option assessed. The cost difference between SPN and IPN was estimated. In addition to deterministic analysis, a probabilistic analysis was also conducted. In this case, all model input parameters were assigned probability distributions (rather than being expressed as point estimates), to reflect the uncertainty characterising the cost data. Subsequently, 10,000 iterations were performed, each drawing random values from the distributions fitted to the model input parameters. This exercise provides more accurate estimates of mean costs for each option assessed (averaging results from the 10,000 iterations) by capturing the non-linearity characterising the economic model structure (Briggs 2006). The distributions assigned to specific parameters in probabilistic sensitivity analysis are summarised in Table 8.

One-way sensitivity analyses explored the impact of varying the:

- duration of PN, that is, using data from Dice 1981 and Smolkin 2010
- proportion of babies who are on SPN and require IPN
- unit cost of an SPN maintenance bag.

A what-if analysis was also undertaken to estimate what QALY gain would be needed for IPN to be considered a cost-effective option at NICE's lower cost-effectiveness threshold of £20,000 per QALY gained.

## Economic modelling results

### *Results of the deterministic analysis*

According to the deterministic analysis, SPN resulted in lower costs when compared with IPN (Table 9). The costs were £15,966 and £16,265 for SPN and IPN, respectively, implying savings of £299.

The what-if analysis indicated that for IPN to be cost-effective at the £20,000 threshold the QALY gain for IPN (versus SPN) would need to be 0.015. A QALY gain of 0.015 is equivalent to 5 additional days in full health. Given the relatively short duration of PN, the required QALY gain of 0.015 for IPN to be cost-effective (versus SPN) is large.

In the base-case analysis, no difference in length of stay between IPN and SPN was assumed (that is, the length of stay as reported for IPN was also used for SPN). In the sensitivity analysis where data for both IPN and SPN from Smolkin 2010 was utilised (that is, 5.6 and 7.9 days on PN only for IPN and SPN, respectively; and 8.5 and 9.5 days on combined parenteral and enteral nutrition for IPN and SPN, respectively) SPN resulted in an increase of £2,800 in NHS costs (due to the longer overall length of stay). Using data from Dice 1981 (that is, 11.4 and 9.8 days on PN only for IPN and SPN, respectively), SPN resulted in a decrease of £1,910 in NHS costs.

In a further sensitivity analysis (Figure 8), where the proportion of babies initiated on SPN who subsequently require IPN was varied from 0% to 50% the cost difference between IPN and SPN varied from £504 to £129 (in favour of SPN).

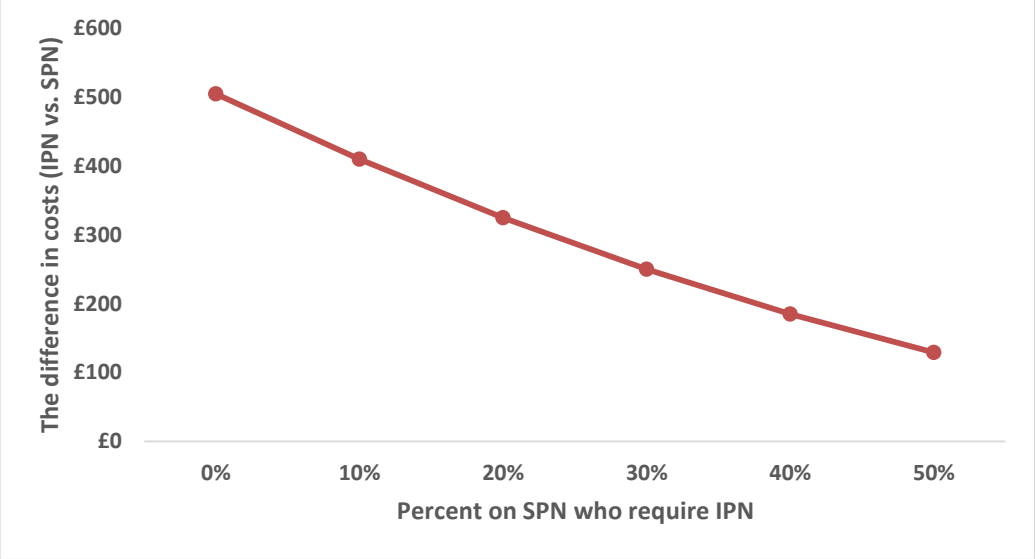
The committee discussed potentially higher wastage associated with SPN bags. However, the guideline systematic review did not identify data on PN wastage. The impact of wastage would be to increase the unit cost of an SPN maintenance bag. Consequently, an additional sensitivity analysis was undertaken where the unit cost of an SPN maintenance bag was varied. According to the sensitivity analysis (Figure 9) the unit cost of an SPN maintenance bag could increase by as much as 67% (from £58/bag to £97/bag) for the costs of SPN and IPN strategies to break-even (that is, the cost savings associated with SPN to be reduced to £0). The committee noted that IPN could also be associated with wastage but this problem is more pertinent to SPN bags. This analysis is only a very crude approximation of the issue but indicates that the wastage associated with SPN would need to be relatively high for the cost savings associated with SPN to be eliminated.

**Table 9: The mean expected costs for IPN and SPN for babies requiring parenteral nutrition - results per baby.**

| Parenteral nutrition type | Expected mean NHS costs |
|---|---|
| SPN | £15,966 |
| IPN | £16,265 |
| Difference (SPN versus IPN) | -£299 |

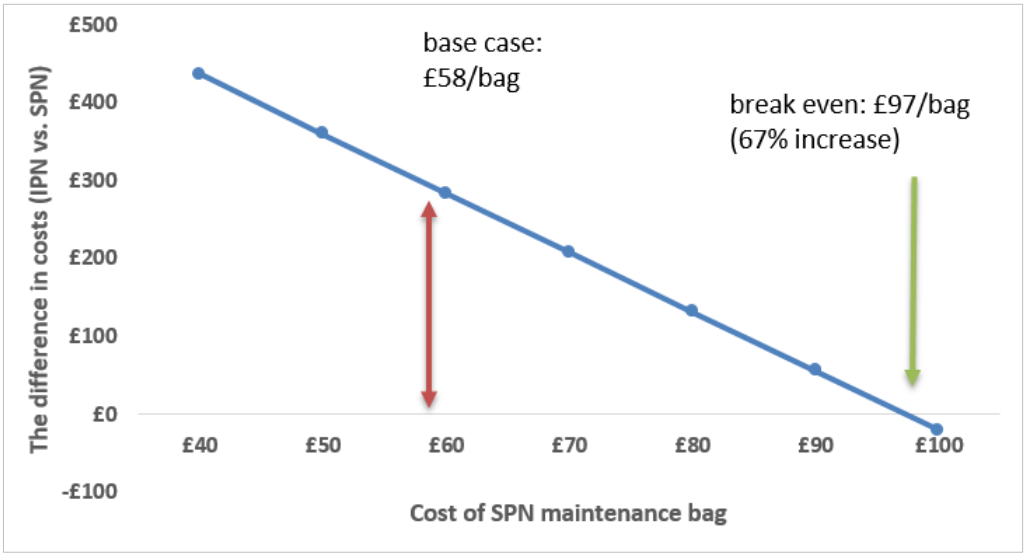
*IPN: individualised parenteral nutrition, SPN: standardised parenteral nutrition*

**Figure 8: Deterministic sensitivity analysis (varying the percent of babies on SPN who require IPN).**




*IPN: individualised parenteral nutrition, SPN: standardised parenteral nutrition*

**Figure 9: Deterministic sensitivity analysis (varying the unit cost of SPN maintenance bag).**




*IPN: individualised parenteral nutrition, SPN: standardised parenteral nutrition*

***Results of the probabilistic analysis***

Conclusions of probabilistic analysis derived from 10,000 iterations of the model were the same as those of deterministic analysis (Table 10). SPN resulted in lower costs when compared with IPN. The costs were £15,961 (95%CI: £13,677; £18,571) and £16,808 (95%CI: £13,703; £19,158) for SPN and IPN, respectively; the savings of £306 (95%CI: -£1,725; £2,324).

**Table 10: The mean expected costs for IPN and SPN in babies requiring parenteral nutrition - results per baby.**

| Parenteral nutrition type | Expected mean NHS costs and 95% CI |
|---|---|
| SPN | £15,961 (95%CI: £13,677; £18,571) |
| IPN | £16,808 (95%CI: £13,703; £19,158) |
| The difference (SPN vs. IPN) | -£306 (95%CI: -£1,725; £2,324) |

*CI: confidence interval, IPN: individualised parenteral nutrition, SPN: standardised parenteral nutrition*

The what-if analysis indicated that for IPN to be cost-effective at the £20,000 threshold the QALY gain for IPN (versus SPN) would need to be 0.015. A QALY gain of 0.015 is equivalent to 5 additional days in full health. Given the relatively short duration of PN, the required QALY gain of 0.015 for IPN (versus SPN) for IPN to be cost effective is large.

**Discussion – limitations of the analysis**

The economic analysis suggested that SPN is likely to be a cost saving option when compared with IPN. The conclusions were driven by higher bag costs associated with IPN. However, the cost difference was not significant and the conclusions varied depending on the assumption pertaining to the length of stay associated SPN and IPN. The length of stay varied across the studies and using data from Dice 1981 resulted in IPN being cost saving. Although, the committee explained that they would not expect the length of stay to differ

between SPN and IPN, and the costs analysis which assumes no difference in the length of stay should provide a reasonable approximation as to the costs associated with different PN bags.

The clinical review did not identify any important differences between IPN and SPN. There was evidence that the mean daily weight gain was statistically greater in babies receiving IPN as compared to SPN. IPN had clinically meaningful and significantly greater mean daily non-protein intake as compared to SPN. Also, at 1 week and at discharge those who received IPN had significantly greater mean weight as compared to those on SPN; this difference was considered clinically important. However, this effect was not sustained and the mean weight of babies was not significantly different at 1 month. The evidence on nutrient intake was conflicting. There was no difference between IPN and SPN in terms of adverse events. Generally, the clinical evidence was of low quality and each relevant outcomes was reported by a single study, and as a result it was insufficient to inform a full economic analysis.

Some of the model inputs were informed by committee expert opinion, including the proportion of babies on SPN who require IPN. However, the costings were robust to this model input.

# Appendix K – Excluded studies

## Excluded clinical and economic studies for review question: What is the effectiveness, efficacy and safety of standardised parenteral nutrition bags compared with individualised bags?

## Clinical studies

**Table 11: Excluded studies and reasons for their exclusion**

| Study | Reason for Exclusion |
|---|---|
| Badhawi, I., Morgan, C., Grimes, C., Improving neonatal nutritional delivery using a standard concentrated formulation of neonatal parenteral nutrition, Archives of Disease in Childhood, 94 (7), e2, 2009 | Conference abstract |
| Bethune, K., The use of standard parenteral nutrition solutions in pediatrics: a UK perspective, Nutrition (Burbank, Los Angeles County, Calif.), 17, 357-9, 2001 | Non-systematic review |
| Bolisetty, S., Pharande, P., Nirthanakumaran, L., Quy-Phong Do, T., Osborn, D., Smyth, J., Sinn, J., Lui, K., Improved nutrient intake following implementation of the consensus standardised parenteral nutrition formulations in preterm neonates a before-after intervention study, BMC Pediatrics, 14, 309, 2014 | Comparison does not meet the inclusion criteria. There are no individualised bags; the study compares pre- and post-consensus regimens |
| Butler, T. J., Szekely, L. J., Grow, J. L., A standardized nutrition approach for very low birth weight neonates improves outcomes, reduces cost and is not associated with increased rates of necrotizing enterocolitis, sepsis or mortality, Journal of Perinatology, 33, 851-7, 2013 | Study Intervention does not meet the inclusion criteria; the study evaluates a standard nutritional practice (which only partly included PN) |
| Cade, A., Thorp, H., Puntis, J. W. L., Does the computer improve the nutritional support of the newborn?, Clinical Nutrition, 16, 19-23, 1997 | Intervention does not meet the inclusion criteria; the study compares computer calculation to manual calculation of PN |
| Callaghan, F., Morgan, C., Target parenteral protein attainment in parenterally fed preterm infants following the implementation of the concentrated macronutrients in parenteral standardised solutions (CoMPaSS) programme, Journal of Pediatric Gastroenterology and Nutrition, 64, 805, 2017 | Conference abstract |
| Choi, A. Y., Lee, Y. W., Chang, M. Y., Modification of nutrition strategy for improvement of postnatal growth in very low birth weight infants, Korean Journal of Pediatrics, 59, 165-173, 2016 | Comparison does not meet the inclusion criteria; the study compares pre- and post-modification of PN regimen |
| Cleminson, Jemma S., Zalewski, Stefan P., Embleton, Nicholas D., Nutrition in the preterm | Non-systematic review |

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|---|---|
| infant: what's new?, Current opinion in clinical nutrition and metabolic care, 19, 220-5, 2016 | |
| Devlieger, H., De Pourcq, L., Casneuf, A., Vanhole, C., de Zegher, F., Jaeken, J., Eggermont, E., Standard two-compartment formulation for total parenteral nutrition in the neonatal intensive care unit: A fluid tolerance based system, Clinical nutrition (Edinburgh, Scotland), 12, 282-6, 1993 | Study design does not meet inclusion criteria; there is no comparison data or outcomes of interest |
| Doublet, J., Vialet, R., Nicaise, C., Loundou, A., Martin, C., Michel, F., Achieving parenteral nutrition goals in the critically ill newborns: standardized better than individualized formulations?, Minerva pediatrica, 65, 497-504, 2013 | No data presented in format to extract |
| Hartwig, S. C., Gardner, D. K., Use of standardized total parenteral nutrient solutions for premature neonates, American journal of hospital pharmacy, 46, 993-5, 1989 | No relevant outcomes reported |
| Huston, Robert K., Markell, Andrea M., McCulley, Elizabeth A., Marcus, Matthew J., Cohen, Howard S., Computer programming: quality and safety for neonatal parenteral nutrition orders, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 28, 515-21, 2013 | The intervention does not meet the inclusion criteria; the study compares pre- and post-computerised ordering systems for parenteral nutrition |
| Izquierdo, Montserrat, Martinez-Monseny, Antonio Federico, Pociello, Neus, Gonzalez, Paloma, Del Rio, Ruth, Iriondo, Martin, Iglesias-Platas, Isabel, Changes in Parenteral Nutrition During the First Week of Life Influence Early but Not Late Postnatal Growth in Very Low-Birth-Weight Infants, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 31, 666-72, 2016 | Study design does not meet the inclusion criteria; no individualised bag |
| Kreissl, Alexandra, Repa, Andreas, Binder, Christoph, Thanhaeuser, Margarita, Jilma, Bernd, Berger, Angelika, Haiden, Nadja, Clinical Experience with Numeta in Preterm Infants: Impact on Nutrient Intake and Costs, JPEN. Journal of parenteral and enteral nutrition, 40, 536-42, 2016 | No relevant outcomes reported |
| Krohn, Kathrin, Babl, Jurgen, Reiter, Karl, Koletzko, Berthold, Parenteral nutrition with standard solutions in paediatric intensive care patients, Clinical nutrition (Edinburgh, Scotland), 24, 274-80, 2005 | Study population does not meet the inclusion criteria |
| Lapillonne, A., Berleur, M. P., Brasseur, Y., Calvez, S., Safety of parenteral nutrition in newborns: Results from a nationwide prospective cohort study, Clinical Nutrition, 2017 | Study design does not meet the inclusion criteria; the study compares two standard PN solutions |

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|---|---|
| Leow, L. Y. C., Oh, C. C., Neo, S. L., Chua, M. C., Role of standardized parenteral nutrition bags for neonates, Journal of Perinatal Medicine, 41, 2013 | Conference abstract |
| Marianczak, J. E., Tomlin, S., Review of standard & individualised parenteral nutrition (PN) prescribing in neonates, Archives of Disease in Childhood, 96, 2011 | Conference abstract |
| Martin, C., Bouchoud, L., Fonzo-Christe, C., Combescure, C., Pfister, R., Bonnabry, P., Standard parenteral nutrition for preterm infants: Impact on amino acid intake and growth, International Journal of Clinical Pharmacy, 33, 389, 2011 | Conference abstract |
| Mayes, Kelly, Tan, Maw, Morgan, Colin, Effect of hyperalimentation and insulin-treated hyperglycemia on tyrosine levels in very preterm infants receiving parenteral nutrition, JPEN. Journal of parenteral and enteral nutrition, 38, 92-8, 2014 | Comparison does not meet the inclusion criteria; the study compares increased levels of amino acids to a standard regimen |
| McCallie, K. R., Lee, H. C., Mayer, O., Cohen, R. S., Hintz, S. R., Rhine, W. D., Improved outcomes with a standardized feeding protocol for very low birth weight infants, Journal of perinatology : official journal of the California Perinatal Association, 31 Suppl 1, S61-7, 2011 | Comparison does not meet the inclusion criteria; the study compares pre- and post- standardised enteral feeding protocol |
| McCarthy, R., Segurado, R., Crealey, M., Twomey, A., Standardised versus individualised parenteral nutrition. Further food for thought, Irish Medical Journal, 109, 388, 2016 | No relevant outcomes reported |
| Meyer, R., Meike, T., Hegi, L., Ettel, E., Furlano, R., Schulzke, S., Developing and implementing standard parenteral nutrition solutions for a neonatal unit, Intensive Care Medicine, 37, S394, 2011 | Conference abstract |
| Morgan, C., Burgess, L., Grosdenier, M., Green, J., McGowan, P., Turner, M. A., Hyperalimentation and blood glucose control in very preterm infants: A randomised controlled parenteral nutrition study, Archives of Disease in Childhood: Fetal and Neonatal Edition, 99, A2-A3, 2014 | Conference abstract |
| Morgan, C., Burgess, L., Grosdenier, M., McGowan, P., Turner, M. A., Hyperalimentation and blood glucose control in very preterm infants: The randomised controlled scamp nutrition study, Archives of Disease in Childhood, 99, A208, 2014 | Conference abstract |
| Morgan, C., Mahaveer, A., Grime, C., Increasing early protein intake is associated with a reduction in the incidence of insulin-treated hyperglycaemia in very preterm infants, Journal | Intervention does not meet the inclusion criteria; the study compares two different standard regimens |

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|---|---|
| of Pediatric Gastroenterology and Nutrition, 52, E12-E13, 2011 | |
| Morgan, C., McGowan, P., Herwitker, S., Hart, A. E., Turner, M. A., Preventing early postnatal head growth failure in very preterm infants: The randomised controlled scamp nutrition study, Archives of Disease in Childhood: Education and Practice Edition, 98, 2013 | Conference abstract |
| Morgan, C., McGowan, P., Herwitker, S., Hart, A. E., Turner, M. A., Early postnatal head growth in very preterm infants: The randomised controlled scamp nutrition study, Journal of Neonatal-Perinatal Medicine, 6, 197, 2013 | Conference abstract |
| Morgan, C., Parry, S., Tan, M., Neurodevelopmental outcome in very preterm infants randomised to receive two different parenteral nutrition regimens: The scamp nutrition study, European Journal of Pediatrics, 175, 1516-1517, 2016 | Conference abstract |
| 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 | Study design does not meet protocol eligibility criteria - conference abstract |
| Morgan, C., Tan, M., Attainment targets for protein intake using standardised, concentrated and individualised neonatal parenteral nutrition regimens, European Journal of Pediatrics, 175, 1541, 2016 | Conference abstract |
| Morgan, Colin, Burgess, Laura, High Protein Intake Does Not Prevent Low Plasma Levels of Conditionally Essential Amino Acids in Very Preterm Infants Receiving Parenteral Nutrition, JPEN. Journal of parenteral and enteral nutrition, 41, 455-462, 2017 | Intervention does not meet the inclusion criteria; the study compares AA regimens |
| Morgan, Colin, Herwitker, Shakeel, Badhawi, Isam, Hart, Anna, Tan, Maw, Mayes, Kelly, Newland, Paul, Turner, Mark A., SCAMP: standardised, concentrated, additional macronutrients, parenteral nutrition in very preterm infants: a phase IV randomised, controlled exploratory study of macronutrient intake, growth and other aspects of neonatal care, BMC pediatrics, 11, 53, 2011 | Protocol paper |
| Morgan, Colin, McGowan, Patrick, Herwitker, Shakeel, Hart, Anna E., Turner, Mark A., Postnatal head growth in preterm infants: a randomized controlled parenteral nutrition study, Pediatrics, 133, e120-8, 2014 | Intervention does not meet the inclusion criteria; the study compares two standard regimens |
| Mutchie, K. D., Smith, K. A., MacKay, M. W., Marsh, C., Juluson, D., Pharmacist monitoring of | Population does not meet the inclusion criteria |

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|---|---|
| parenteral nutrition: clinical and cost effectiveness, American journal of hospital pharmacy, 36, 785-7, 1979 | |
| Natthondan, V., Bolisetty, S., Osborn, D. A., Sinn, J., Lui, K., Consensus for tpn formulation for NSW and ACT - Work in progress, Journal of Paediatrics and Child Health, 47, 98, 2011 | Conference abstract |
| Ohnishi, S., Ichiba, H., Tanaka, Y., Harada, S., Matsumura, H., Kan, A., Asada, Y., Shintaku, H., Early and intensive nutritional strategy combining parenteral and enteral feeding promotes neurodevelopment and growth at 18 months of corrected age and 3 years of age in extremely low birth weight infants, Early Human Development, 100, 35-41, 2016 | Intervention does not meet the inclusion criteria; the study compares AA regimen and includes both parenteral and enteral nutrition |
| Pharande, P., Nirthanakumaran, L., Do, T., Smyth, J., Lui, K., Sinn, J., Bolisetty, S., Implementation of consensus neonatal parenteral nutrition formulations and improved nutrient intakes in preterm neonates, Journal of Paediatrics and Child Health, 50, 56, 2014 | Conference abstract |
| Picaud, J. C., Braegger, C., Bronsky, J., Cai, W., Campoy, C., Carnielli, V., Darmaun, D., Decsi, T., Domellof, M., Embleton, N., Fewtrell, M., Fidler Mis, N., Franz, A., Goulet, O., Hartman, C., Hill, S., Hojsak, I., Iacobelli, S., Jochum, F., Joosten, K., Kolacek, S., Koletzko, B., Ksiazyk, J., Lapillonne, A., Lohner, S., Mesotten, D., Mihalyi, K., Mihatsch, W. A., Mimouni, F., Molgaard, C., Moltu, S. J., Nomayo, A., Picaud, J. C., Prell, C., Puntis, J., Riskin, A., Saenz De Pipaon, M., Senterre, T., Shamir, R., Simchowitz, V., Szitanyi, P., Tabbers, M. M., Van Den Akker, C. H. B., Van Goudoever, J. B., Van Kempen, A., Verbruggen, S., Wu, J., Yan, W., ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Standard versus individualized parenteral nutrition, Clinical Nutrition, 37, 2409-2417, 2018 | Study does not meet protocol eligibility criteria - review of individualised PN, standard PN, computer assisted prescribing; focus not on effective amounts of nutrients |
| Raimondi, Francesco, Spera, Anna Maria, Sellitto, Maria, Landolfo, Francesca, Capasso, Letizia, Amino acid-based formula as a rescue strategy in feeding very-low-birth-weight infants with intrauterine growth restriction, Journal of Pediatric Gastroenterology and Nutrition, 54, 608-12, 2012 | Population does not meet the inclusion criteria; babies are enterally fed |
| Rigo, J., Marlowe, M., Bonnot, D., Lapillonne, A., Biological tolerance of the first ready to use multi-chamber parenteral nutrition (PN) system specially designed for administration to preterm infants, Intensive Care Medicine, 37, S396-S397, 2011 | Conference abstract |

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|---|---|
| Riskin, A., Shiff, Y., Shamir, R., Parenteral nutrition in neonatology - To standardize or individualize?, Israel Medical Association Journal, 8, 641-645, 2006 | Non-systematic review |
| Roggero, P., Gianni, M. L., Orsi, A., Amato, O., Piemontese, P., Liotto, N., Morlacchi, L., Taroni, F., Garavaglia, E., Bracco, B., Agosti, M., Mosca, F., Implementation of Nutritional Strategies Decreases Postnatal Growth Restriction in Preterm Infants, PloS one, 7, 2012 | Intervention does not meet the inclusion criteria; there is no individualised component |
| Senterre, T., Habibi,, Rigo, F. J., Postnatal growth restriction may be limited in very-low-birthweight infants, Journal of Maternal-Fetal and Neonatal Medicine, 23, 325-326, 2010 | Conference abstract |
| Senterre, T., Rigo, J., Optimizing nutrition after birth with a unique standardized parenteral solution may reduce electrolytes anomalies in < 1250g infants, Archives of Disease in Childhood, 97, A394, 2012 | Conference abstract |
| Simmer, Karen, Rakshasbhuvankar, Abhijeet, Deshpande, Girish, Standardised parenteral nutrition, Nutrients, 5, 1058-70, 2013 | Non-systematic review |
| Skouroliakou, Maria, Koutri, Katerina, Stathopoulou, Maria, Vourvouhaki, Ekaterini, Giannopoulou, Ifigenia, Gounaris, Antonios, Comparison of two types of TPN prescription methods in preterm neonates, Pharmacy world & science : PWS, 31, 202-8, 2009 | Intervention does not meet the inclusion criteria; the study compares computer calculation to manual calculation of PN |
| Snyder, R., Crowley, K., Sawtell, C., Rogido, M., Impact of a standardized nutrition protocol in lean mass growth in VLBW infants, European Journal of Pediatrics, 175, 1729-1730, 2016 | Conference abstract |
| Sofia, B., Evolution of the paediatric parenteral nutrition bag prescriptions further to numetah (three chamber bag) marketing, European Journal of Hospital Pharmacy, 24, A227, 2017 | Conference abstract |
| Tagare, Amit, Walawalkar, Meenal, Vaidya, Umesh, Aggressive parenteral nutrition in sick very low birth weight babies: a randomized controlled trial, Indian pediatrics, 50, 954-6, 2013 | Comparison does not meet the inclusion criteria; the study compares standardised prescriptions |
| Tan, M. J., Cooke, R. W., Improving head growth in very preterm infants - A randomised controlled trial I: Neonatal outcomes, Archives of Disease in Childhood: Fetal and Neonatal Edition, 93, f337-f341, 2008 | Comparison does not meet the inclusion criteria; the study compares standardised prescriptions |
| Whitby, T., Morgan, C., McGowan, P., Turner, M., Concentrated parenteral nutrition solutions and central venous catheter complications in preterm infants, Archives of Disease in Childhood: Fetal and Neonatal Edition, 99, A54, 2014 | No relevant outcomes reported |

## Economic studies

All economic studies were excluded at the initial title and abstract screening stage and so there is no list of excluded studies. See supplementary material D for further information.

# Appendix L – Research recommendations

## Research recommendations for review question: What is the effectiveness, efficacy and safety of standardised parenteral nutrition bags compared with individualised bags?

No research recommendations were made for this review question.

# Appendix M – Example standardised bags

The following tables provide illustrations of the ways that standardised bags could be provided based on the recommendations within this guideline. The examples are not intended as specific recommendations for PN formulations or as strategies for administration, they illustrate ways in which the guideline recommendations on nutrient requirements, energy, and ratios of non-nitrogen energy to nitrogen energy and carbohydrate to lipids, could be fulfilled with a standardised bag. Three examples are provided, minimum, mid-range and maximum ratios.

**Table 12: Standardised bag example at the minimum ratio recommended in this guideline**

| PN solution ml / kg | Lipid ml /kg* | 12% Glucose 60g in 500ml bag g/kg/d | Amino Acids 15g in 500ml g/kg/d | Lipid emulsion 20% g/kg/d | Energy Kcal /kg/d | Non-nitrogen to nitrogen energy Kcal / g amino acid | CHO to lipids |
|---|---|---|---|---|---|---|---|
| 50 | 5 | 6 | 1.5 | 1 | 40 | 23 | 70:30 |
| 60 | 7 | 7.2 | 1.8 | 1.4 | 50 | 24 | 67:33 |
| 70 | 9 | 8.4 | 2.1 | 1.8 | 60 | 25 | 65:35 |
| 80 | 11 | 9.6 | 2.4 | 2.2 | 70 | 25 | 63:37 |
| 90 | 12 | 10.8 | 2.7 | 2.4 | 78 | 25 | 64:36 |
| 95 | 13 | 11.4 | 3 | 2.6 | 88 | 25 | 63:37 |
| 100 | 15 | 12 | 3 | 3 | 90 | 26 | 61:39 |

**This example assumes that vitamins have not been added to the lipid emulsion. When they are added the volume of lipid administered will be slightly different as the lipid concentration is altered.*

**Table 13 Standardised bag example at the mid-range ratios recommended in this guideline**

| PN solution ml / kg | Lipid ml /kg* | Glucose 70g in 500ml bag =14% g/kg/d | Protein 18g in 500ml g/kg/d | Lipid emulsion 20% g/kg/d | Energy Kcal /kg/d | Non-nitrogen to nitrogen energy Kcal / g protein | CHO to lipids |
|---|---|---|---|---|---|---|---|
| 50 | 7.5 | 7 | 1.8 | 1.5 | 49 | 23 | 67:37 |
| 60 | 10 | 8.4 | 2.2 | 2 | 60 | 23 | 65:35 |

| PN solution ml / kg | Lipid ml /kg* | Glucose 70g in 500ml bag =14% g/kg/d | Protein 18g in 500ml g/kg/d | Lipid emulsion 20% g/kg/d | Energy Kcal /kg/d | Non-nitrogen to nitrogen energy Kcal / g protein | CHO to lipids |
|---|---|---|---|---|---|---|---|
| 70 | 12.5 | 9.8 | 2.5 | 2.5 | 72 | 25 | 64:36 |
| 80 | 15 | 11.2 | 2.9 | 3 | 83 | 25 | 62:38 |
| 90 | 20 | 12.6 | 3.2 | 3.5 | 95 | 26 | 62:38 |
| 95 | 25 | 13.3 | 3.4 | 4 | 103 | 26 | 60:40 |
| 100 | 20 | 14 | 3.6 | 3.5 | 102 | 24 | 64:36 |

**This example assumes that vitamins have not been added to the lipid emulsion. When they are added the volume of lipid administered will be slightly different as the lipid concentration is altered.*

**Table 14 Standardised bag example at the maximum ratio recommended in this guideline**

| PN solution ml / kg | Lipid ml /kg* | 16% Glucose 80g in 500ml bag g/kg/d | Amino Acids 20g in 500ml g/kg/d | Lipid emulsion 20% g/kg/d | Energy Kcal /kg/d | Non-nitrogen to nitrogen energy Kcal / g amino acid | CHO to lipids |
|---|---|---|---|---|---|---|---|
| 50 | 10 | 8 | 2 | 2 | 60 | 26 | 61:39 |
| 60 | 12.5 | 9.6 | 2.4 | 2.5 | 73 | 26 | 61:39 |
| 70 | 15 | 11.2 | 2.8 | 3 | 86 | 27 | 60:40 |
| 80 | 17 | 12.8 | 3.2 | 3.4 | 98 | 29 | 61:39 |
| 90 | 19 | 14.4 | 3.6 | 3.8 | 110 | 27 | 60:40 |
| 95 | 20 | 15.2 | 3.8 | 4 | 116 | 27 | 60:40 |
| 100 | 20 | 16 | 4 | 4 | 120 | 26 | 62:38 |

**This example assumes that vitamins have not been added to the lipid emulsion. When they are added the volume of lipid administered will be slightly different as the lipid concentration is altered.*

**Table 15 Appropriate calcium, phosphate and sodium for minimum and maximum ratios**

| PN solution<br>ml / kg | Calcium<br>mmol/kg/d<br>10% Ca Gluconate<br>35 ml in 500 ml | Phosphate<br>mmol/kg/d<br>21.6% Sodium glycerophosphate<br>10 ml in 500 ml<br>(Ca:PO4 ratio) | Sodium |
|---|---|---|---|
| 50 | 0.8 | 1 | 2 |
| 60 | 1 | 1.2 (0.8) | 2.4 |
| 70 | 1.1 | 1.4 (0.8) | 2.8 |
| 80 | 1.3 | 1.6 (0.8) | 3.2 |
| 90 | 1.4 | 1.8 (0.8) | 3.6 |
| 95 | 1.5 | 1.9 (0.8) | 3.8 |
| 100 | 1.6 | 2 (0.8) | 4 |

**Table 16 Appropriate calcium, phosphate and sodium for mid-range ratios**

| PN solution | Lipid | 14% Glucose | Amino Acids | 20% Lipid emulsion | Calcium<br>mmol/kg/d | Phosphate<br>mmol/kg/d | Sodium |
|---|---|---|---|---|---|---|---|
| ml / kg | ml /kg* | 70g in 500ml<br>g/kg/d | 18g in 500ml<br>g/kg/d | g/kg/d | 10% Ca Gluconate<br>D1-2: Bag 1<br>(35 mls in 500 ml)<br>D3+: Bag 1 or 2<br>(50 mls in 500 ml)** | 21.6% Sodium glycerophosphate<br>D1-2: Bag 1<br>(10 mls in 500 ml)<br>D3+: Bag 1 or 2<br>(13 mls in 500 ml)** | |
| 50 | 7.5 | 7 | 1.8 | 1.5 | 0.8 | 1 | 2 |
| 60 | 10 | 8.4 | 2.2 | 2 | 1 | 1.2<br>(0.8) | 2.4 |
| 70 | 12.5 | 9.8 | 2.5 | 2.5 | 1.1 | 1.4 (0.8) | 2.8 |
| | | | | | 1.6 | 1.8 (0.9) | 3.6 |

| PN solution | Lipid | 14% Glucose | Amino Acids | 20% Lipid emulsion | Calcium mmol/kg/d | Phosphate mmol/kg/d | Sodium |
|---|---|---|---|---|---|---|---|
| 80 | 15 | 11.2 | 2.9 | 3 | 1.3 | 1.6 (0.8) | 3.2 |
| | | | | | 1.9 | 2.1 (0.9) | 4.2 |
| 90 | 20 | 12.6 | 3.2 | 3.5 | 1.4 | 1.8 (0.8) | 3.6 |
| | | | | | 2 | 2.3 (0.9) | 4.6 |
| 95 | 25 | 13.3 | 3.4 | 4 | 1.5 | 1.9 (0.8) | 3.8 |
| | | | | | 2.1 | 2.5 (0.8) | 5 |
| 100 | 20 | 14 | 3.6 | 3.5 | 1.6 | 2 (0.8) | 4 |
| | | | | | 2.3 | 2.6 (0.9) | 5.2 |

**This example assumes that vitamins have not been added to the lipid emulsion. When they are added the volume of lipid administered will be slightly different as the lipid concentration is altered.*

***Whenever there are two rows associated with one row of PN solution in this column this would indicate two types of bags being used (for example, in a PN solution of 70 ml/kg one bag would include 1.1 mmol/kg/d of calcium and the other 1.6 mmol/kg/d of calcium*

**Notes:**

Maintenance Na and K should be included in PN

Sodium column indicates Na derived from Sodium Glycerophosphate

10% Ca Gluconate =0.225 mmol/ml of calcium

21.6% Na glycerophosphate = 1 mmol phosphate & 2 mmol Na / ml

**PN Energy calculations**

1g glucose = 4 kcal

1g Amino acid = 4 kcal

1 g Lipid emulsion = 10kcal