National Institute for Health and Care Excellence

Final

Neonatal parenteral nutrition

[G] Stopping parenteral nutrition

NICE guideline NG154

Evidence reviews

February 2020

Final

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

Disclaimer

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

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

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 All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-3673-1

Contents

Stopping parenteral nutrition in preterm and term babies

Review question

What amount of enteral feed (measured in terms of ml/kg/d, or kcal/kg/d, or ratios in relation to parenteral nutrition and enteral feeds) indicates that parenteral nutrition is no longer required?

Introduction

Determining when parenteral nutrition (PN) can be stopped is important; there is risk of malnutrition and associated complications to the baby if parenteral feeding is stopped too early. In contrast, the longer PN is continued, the greater the risk of line sepsis and PN associated liver disease. Guidance for clinicians on how to determine when it is safe to transition from combined parenteral and enteral nutrition to enteral nutrition (EN) alone is required.

Summary of the protocol

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

Table 1: Summary of the protocol (PICO table)

Population	• Babies born preterm, up to 28 days after their due birth date (preterm babies) • Babies born at term, up to 28 days after their birth (term babies)
Intervention	• Volume of PN (ml/kg/day or kcal/kg/day) plus EN (ml/kg/day or kcal/kg/day • Ratio of PN (ml/kg/day or kcal/kg/day) and EN (ml/kg/day or kcal/kg/day)
Comparison	• Comparison volume of PN (ml/kg/day or kcal/kg/day) plus EN (ml/kg/day or kcal/kg/day) • Different ratio of PN (ml/kg/day or kcal/kg/day) to EN (ml/kg/day or kcal/kg/day)

Outcomes	**Critical**
	• Total nutritional intake, protein/carbohydrate/lipid/energy (for example, kcal/kg/day as a total of the parental + enteral)
	• Growth/Anthropometric measures:
	  ○ Weight gain
	  ○ Linear growth
	  ○ Head circumference
	• Body composition (lean mass, fat-free mass, fat mass, adipose tissue, nitrogen accretion)
	Important
	• Mortality
	• Duration of hospital stay
	• Necrotising enterocolitis

	• Neurodevelopmental outcomes (general cognitive abilities at two years, measured using validated scales only) • Duration of PN • Sepsis (central line infections)

EN: enteral nutrition; PICO: population, intervention, comparison and outcome; PN: parenteral nutrition

For further details see the review protocol in appendix A.

Clinical evidence

Included studies

As limited RCT evidence was available, we also included observational studies. Three studies were identified for inclusion in this review (Choi 2016, Dinerstein 2006, and Perrem 2019).

One randomised controlled trial (RCT) (n=137) compared stopping PN when EN reached 100ml/kg/day to stopping PN when EN reached 140ml/kg/day (Perrem 2019).

One observational study (n=87) compared stopping PN when EN reached 100ml/kg/day to stopping PN when EN reached 120ml/kg/day (Choi 2016).

One observational study (n=182compared stopping PN when EN reached 60kcal/kg/day to stopping PN when EN reached 100kcal/kg/day (Dinerstein 2006).

The included studies are summarised in Table 2.

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

Excluded studies

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

Summary of clinical studies included in the evidence review

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

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Comments
Choi 2016 Observational study Korea	N=87* VLBW infants (<1500g) born before 34 weeks' gestation Mean GA: 29.4 weeks (SD 2.5)	100ml/kg/day (n=50) Nutrition supplements added and PN discontinued at 100ml/kg/day of EN Proteins started on day 1 at	120ml/kg/day (n=37) Nutrition supplements added and PN discontinued at 120ml/kg/day of EN Proteins started on day 1 at	• Weight gain • Length <10th centile at 36 and 40 weeks post conception • Head circumference <10th centile at 36 and 40 weeks post conception	Multiple differences between nutrition protocols apart from point at which PN was discontinued. Therefore, difficult to conclude if any differences are a result of

Study	Population	Intervention	Comparison	Outcomes	Comments
	Mean BW: 1126g (SD 235) *124 infants are included in the paper but 37 infants from period 3 were not included in this review question	3.0g/kg/day and advanced to 4.0g/kg/day Lipids were started on day 1 at 1.0/kg/day and advanced to 3.5g/kg/day	1.5g/kg/day and advanced to 3.5g/kg/day Lipids were started on day 2 at 0.5g/kg/day and advanced to 3.0g/kg/day	• Duration (days) of hospital stay • Necrotising enterocolitis • Duration (days) of PN • Sepsis	when PN was stopped
Dinerstein 2006 Observational study Argentina	N=182 Infants weighing between 750g and 1500g at birth GA range 24 to 36 weeks Median BW 1230g for 60kcal/kg/day cohort and 1245g for 100kcal/kg/day cohort	60kcal/kg/day (n=117) PN was discontinued when infants reached 60kcal/kg/day of EN Fluids started at 80ml/kg/day and advanced to 150ml/kg/day over 7 to 10 days AA started on day 3 at 0.5g/kg/day and advanced to 3g/kg/day Glucose started (day NR) at 5.6mg/kg/minute and advanced to 8 to 9mg/kg/minute Lipids started on day 3 or 4 at 0.5g/kg/day and advanced to 3g/kg/day	100kcal/kg/day (n=65) PN was discontinued when infants reached 100kcal/kg/day of EN Fluids started at 80ml/kg/day and advanced to 150 to 180ml/kg/day over 7 days AA started on day 1 at 1.5g/kg/day and advanced to 4g/kg/day Glucose started on day 1 at 5.6mg/kg/minute and advanced to 13mg/kg/minute Lipids started at 24 hours at 0.5g/kg/day and advanced to 3.5g/kg/day	• Weight gain • Length (cm) at 40 weeks postmenstrual age • Head circumference (cm) at 40 weeks postmenstrual age • Necrotising enterocolitis • Late onset sepsis	Multiple differences between nutrition protocols apart from point at which PN was discontinued. Therefore, difficult to conclude if any differences are a result of when PN was stopped
Perrem 2019 RCT Ireland	N=137 VLBW (<1500g), preterm infants with a peripherally inserted central venous catheter (PICC) and less than	100ml/kg/day (n=67) PICC was removed and PN discontinued when infants reached 100ml/kg/day of EN	140ml/kg/day (n=70) PICC was removed and PN discontinued when infants reached 140ml/kg/day of EN	• Weight gain • Linear growth • Head circumference • Mortality • Necrotising enterocolitis • Central venous catheter-	There were 12 protocol violations in both arms, where PICC was removed at a different time point than specified by the group allocation. Results of per-

Study	Population	Intervention	Comparison	Outcomes	Comments
	100ml/kg/day of EN Mean GA: 28.6 weeks (SD 2.4) Median BW 1060g for 100mll/kg/day group and 1070g for 140ml/kg/day group	Fluid started at 60-80ml/kg/day on day 1 using standard bag Standard bag content/100ml: amino acids 2.51g, glucose 10%, sodium 2.5mmol, potassium 2mmol, calcium 1mmol, magnesium 0.15mmol, phosphate 1.25mmol Fluids increased up to 150 to 160ml/kg/day	Fluid started at 60-80ml/kg/day on day 1 using standard bag Standard bag content/100ml: amino acids 2.51g, glucose 10%, sodium 2.5mmol, potassium 2mmol, calcium 1mmol, magnesium 0.15mmol, phosphate 1.25mmol Fluids increased up to 150 to 160ml/kg/day	associated late onset sepsis	protocol analysis were not significantly different from results of intention-to-treat analysis for primary outcome.

AA: amino acids; BW: Birth weight; EN: enteral nutrition; GA: gestational age; NR: not reported; PICC: peripherally inserted central venous catheter; PN: Parenteral nutrition; RCT: Randomised controlled trail; SD: standard deviation; VLBW: Very low birth weight

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. The clinical evidence profiles can be found in appendix F.

Economic evidence

Included studies

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

Excluded studies

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

Summary of studies included in the economic evidence review

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

Economic model

This question was a medium priority for economic evaluation. However, the identified clinical data was very limited and insufficient to inform useful economic modelling in this area.

Evidence statements

Clinical evidence statements

Stopping PN when EN reached 100ml/kg/day versus stopping PN when EN reached 140ml/kg/day

Weight gain

- Moderate quality evidence from 1 RCT (n=137) showed no clinically important difference in time to regain birth weight in VLBW and ELBW babies who had PN stopped at 100ml/kg/day of EN compared with 140ml/kg/day of EN. However, there was uncertainty around the effect: Mean difference (MD) 1.50 days (95% CI 0.31 to 2.69).
- Moderate quality evidence from 1 RCT (n=83) showed no clinically important difference in time to regain birth weight in VLBW babies who had PN stopped at 100ml/kg/day of EN compared with 140ml/kg/day of EN. However, there was uncertainty around the effect: MD 0.60 days (95% CI -0.80 to 2.00).
- Moderate quality evidence from 1 RCT (n=54) showed a clinically important difference in time to regain birth weight in ELBW babies who had PN stopped at 100ml/kg/day of EN compared with 140ml/kg/day of EN with longer time to regain birthweight associated with stopping at the lower EN. However, there was uncertainty around the effect: MD 2.80 days (95% CI 0.80 to 4.80).
- High quality evidence from 1 RCT (n=137) showed no clinically important difference in weight at discharge in babies who had PN stopped at 100ml/kg/day of EN compared with 140ml/kg/day of EN, MD 13.00g (95% CI -191.05 to 217.05).
- Low quality evidence from 1 RCT (n=137) showed no clinically important difference in the number of babies whose weight was less than the 10th centile at discharge between those who had PN stopped at 100ml/kg/day of EN compared with 140ml/kg/day of EN. However, there was high uncertainty around the effect: Relative risk (RR) 1.09 (95% CI 0.70 to 1.68).

Linear growth

- High quality evidence from 1 RCT (n=137) showed no clinically important difference in length at discharge in babies who had PN stopped at 100ml/kg/day of EN compared with 140ml/kg/day of EN, MD 0.90cm (95% CI -0.54 to 2.34).
- Low quality evidence from 1 RCT (n=137) showed no clinically important difference in the number of babies whose length was less than the 10th centile at discharge between those who had PN stopped at 100ml/kg/day of EN compared with 140ml/kg/day of EN. However, there was high uncertainty around the effect: RR 1.07 (95% CI 0.78 to 1.48).

Head circumference

- High quality evidence from 1 RCT (n=137) showed no clinically important difference in head circumference at discharge in babies who had PN stopped at 100ml/kg/day of EN compared with 140ml/kg/day of EN, MD 0.10cm (95% CI -0.87 to 0.67).

- Low quality evidence from 1 RCT (n=137) showed a clinically important difference in the number of babies whose head circumference was less than the 10th centile at discharge between those who had PN stopped at 100ml/kg/day of EN compared with 140ml/kg/day of EN with more babies below the 10th centile in the group of babies stopped at the lower EN. However, there was high uncertainty around the effect: RR 1.27 (95% CI 0.68 to 2.37).

Mortality

- Low quality evidence from 1 RCT (n=137) showed no clinically important difference in mortality in babies who had PN stopped at 100ml/kg/day of EN compared with 140ml/kg/day of EN. However, there was high uncertainty around the effect: RR 1.04 (95% CI 0.22 to 5.00).

Necrotising enterocolitis

- Low quality evidence from 1 RCT (n=137) showed a clinically important difference in the number of babies with necrotising enterocolitis between those who had PN stopped at 100ml/kg/day of EN compared with 140ml/kg/day of EN with more babies with necrotising enterocolitis associated with stopping at a higher EN. However, there was high uncertainty around the effect: RR 0.35 (95% CI 0.04 to 3.27).

Sepsis

- Low quality evidence from 1 RCT (n=137) showed a clinically important difference in the number of babies with central venous catheter-associated late onset sepsis between those who had PN stopped at 100ml/kg/day of EN compared with 140ml/kg/day of EN with more babies with central venous catheter-associated late onset sepsis associated with stopping at a higher EN. However, there was high uncertainty around the effect: RR 0.35 (95% CI 0.04 to 3.27).

Stopping PN when EN reached 100ml/kg/day versus stopping PN when EN reached 120ml/kg/day

Weight gain

- Very low quality evidence from 1 observational study (n=87) showed no clinically important difference in time to regain birth weight in babies who had PN stopped at 100ml/kg/day of EN compared with 120ml/kg/day of EN. However, there was uncertainty around the effect: MD -3.40 days (95% CI -6.45 to 0.35).
- Very low quality evidence from 1 observational study (n=87) showed a clinically important difference in the number of babies whose weight was less than the 10th centile at 36 weeks' post conception between those who had PN stopped at 100ml/kg/day of EN compared with 120ml/kg/day of EN, with more babies below the 10th centile in the group of babies stopped at the higher EN. However, there was uncertainty around the effect: RR 0.72 (95% CI 0.58 to 0.90).
- Very low quality evidence from 1 observational study (n=87) showed a clinically important difference in the number of babies whose weight was less than the 10th centile at 40 weeks' post conception between those who had PN stopped at 100ml/kg/day of EN compared with 120ml/kg/day of EN, with more babies below the 10th centile in the group of babies stopped at the higher EN. However, there was uncertainty around the effect: RR 0.56 (95% CI 0.39 to 0.80).

Linear growth

- Very low quality evidence from 1 observational study (n=87) showed a clinically important difference in the number of babies whose length was less than the 10th centile at 36 weeks' post conception between those who had PN stopped at 100ml/kg/day of EN compared with 120ml/kg/day of EN, with more babies below the 10th centile in the group of babies stopped at the higher EN. However, there is uncertainty around the effect: RR 0.76 (95% CI 0.59 to 1.00).
- Very low quality evidence from 1 observational study (n=87) showed a clinically important difference in the number of babies whose length was less than the 10th centile at 40 weeks' post conception between those who had PN stopped at 100ml/kg/day of EN compared with 120ml/kg/day of EN, with more babies below the 10th centile in the group of babies stopped at the higher EN. However, there is uncertainty around the effect: RR 0.79 (95% CI 0.63 to 0.99).

Head circumference

- Very low quality evidence from 1 observational study (n=87) showed a clinically important difference in the number of babies whose head circumference was less than the 10th centile at 36 weeks' post conception between those who had PN stopped at 100ml/kg/day of EN compared with 120ml/kg/day of EN, with more babies below the 10th centile in the group of babies stopped at the higher EN: RR 0.54 (95% CI 0.37 to 0.77).
- Very low quality evidence from 1 observational study (n=87) showed a clinically important difference in the number of babies whose head circumference was less than the 10th centile at 40 weeks' post conception between those who had PN stopped at 100ml/kg/day of EN compared with 120ml/kg/day of EN, with more babies below the 10th centile in the group of babies stopped at the higher EN. However, there is uncertainty around the effect: RR 0.60 (95% CI 0.41 to 0.88).

Duration of hospital stay

- Very low quality evidence from 1 observational study (n=87) showed no clinically important difference in duration of hospital stay in babies who had PN stopped at 100ml/kg/day of EN compared with 120ml/kg/day of EN. However, there is uncertainty around the effect: MD -7.90 days (95% CI -19.10 to 3.30).

Necrotising enterocolitis

- Very low quality evidence from 1 observational study (n=87) showed a clinically important difference in the number of babies with necrotising enterocolitis between those who had PN stopped at 100ml/kg/day of EN compared with 120ml/kg/day of EN, with more babies with necrotising enterocolitis associated with stopping at a lower EN. However, there is uncertainty around the effect: Peto odds ratio (POR) 5.82 (95% CI 0.35, 97.53).

Duration of PN

- Very low quality evidence from 1 observational study (n=87) showed no clinically important difference in duration of PN in babies who had PN stopped at 100ml/kg/day of EN compared with 120ml/kg/day of EN. However, there is uncertainty around the effect: MD -3.50 days (95% CI -9.88 to 2.88).

Sepsis

- Very low quality evidence from 1 observational study (n=87) showed a clinically important difference in the number of babies with sepsis between those who had PN stopped at 100ml/kg/day of EN compared with 120ml/kg/day of EN, with more babies with sepsis associated with stopping at a lower EN. However, there is high uncertainty around the effect: RR 0.79 (95% CI 0.46 to 1.34).

Stopping PN when EN reached 60kcal/kg/day versus stopping PN when EN reached 100kcal/kg/day

Weight gain

- Very low quality evidence from 1 observational study (n=182) showed a clinically important difference in the number of babies with postnatal growth failure at 40 weeks' postmenstrual age between those who had PN stopped at 60kcal/kg/day of EN compared with 100kcal/kg/day of EN, with more babies with growth failure in the group of babies stopped at the lower EN. However, there is uncertainty around the effect: RR 1.45 (95% CI 1.17 to 1.80).

Linear growth

- Very low quality evidence from 1 observational study (n=182) showed no clinically important difference in length at 40 weeks' postmenstrual age in babies who had PN stopped at 60kcal/kg/day of EN compared with 100kcal/kg/day of EN. However, there is uncertainty around the effect: MD -1.00cm (95% CI -1.81 to -0.19).

Head circumference

- Very low quality evidence from 1 observational study (n=182) showed a clinically important difference in head circumference at 40 weeks' postmenstrual age in babies who had PN stopped at 60kcal/kg/day of EN compared with 100kcal/kg/day of EN, with greater head circumference in the group of babies stopped at the higher EN: MD -0.90cm (95% CI -0.96 to -0.84).

Necrotising enterocolitis

- Very low quality evidence from 1 observational study (n=182) showed a clinically important difference in the number of babies with necrotising enterocolitis between those who had PN stopped at 60kcal/kg/day of EN compared with 100kcal/kg/day of EN, with more babies with necrotising enterocolitis associated with stopping at a lower EN. However, there is high uncertainty around the effect: RR 2.70 (95% CI 0.46 to 15.75).

Late onset sepsis

- Very low quality evidence from 1 observational study (n=182) showed no clinically important difference in the number of babies with late onset sepsis between those who had PN stopped at 60kcal/kg/day of EN compared with 100kcal/kg/day of EN. However, there is high uncertainty around the effect: RR 0.90 (95% CI 0.52 to 1.55).

Economic evidence statements

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

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

EN is less energy dense than PN, which is designed to provide an ideal energy composition. Additionally, EN must be digested in order to release energy, as opposed to PN which is delivered 'ready to use'. Therefore, the committee prioritised total nutritional intake, growth and body composition measures as critical outcomes, as nutritional intake has a direct impact on growth and body composition.

Mortality and neurodevelopmental outcomes were selected as important outcomes as these are also likely to be affected by differences in nutrition. Sepsis was selected as an important outcome as there is an increased risk of sepsis with longer duration of PN due to the presence of inserted lines. For this reason, duration of PN was also selected as an important outcome to help quantify the risk or benefit associated with stopping PN at different thresholds. Finally, duration of hospital stay and necrotising enterocolitis were selected as important outcomes as these may be affected by EN, nutritional intake and duration of PN.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE methodology. The observational evidence was very low quality due to risk of bias in the included studies and uncertainty around the effects. The RCT evidence ranged from low to high quality and was downgraded due to uncertainty around the effects.

The committee noted that the evidence from the observational studies was confounded due to differences in the PN regimens used between arms, which were in addition to the difference in the point at which PN was stopped. For example, in one study (Choi 2016), the nutritional intake from PN was higher in the arm that stopped PN at a smaller volume of EN compared with the arm that stopped at a higher volume of EN. It was therefore often difficult to interpretdifferences in the outcomes between groups. The committee were also concerned that the duration of PN in one of the observational studies (Choi 2016) was much longer than they would expect based on their knowledge, so may not be representative of practice. The committee also acknowledged that it was difficult to make comparisons across the studies due to the overlap in doses administered to babies in the low and high energy arms of the studies. Therefore, the committee agreed that it was not possible to draw firm conclusions about the point at which PN should be stopped from the observational evidence.

There was no RCT evidence available for nutritional intake, body composition or neurodevelopmental outcomes and duration of PN and hospital stay were not reported sufficiently for analysis.

Benefits and harms

The committee discussed that, based on their expertise, there are a number of factors that need to be considered when making the decision to stop PN, beyond the volume of EN that has been reached. How well enteral feeds are being tolerated should be considered as further PN may be required if babies stop tolerating enteral feeds. Further, the nutritional composition of different types of EN is not equivalent and consideration should therefore be given to the composition of EN before PN is stopped to avoid nutritional deficits. Consideration should also be given to the relative benefit of additional nutritional intake from maintaining PN and the risk of venous catheter sepsis, which may be dependent on the

gestational age and size of the baby. Finally, the committee discussed the need to consider the individual baby's circumstances as the decision to stop PN for babies with complex or surgical conditions is more complicated. The committee discussed that clinicians may want to wait until increasing volumes of EN have been tolerated for a longer period of time before stopping PN, and to consider how difficult it may have been to obtain venous access, and how many venous access sites are remaining before PN is stopped. However, there was no evidence for this group so the committee could not make specific recommendations.

The RCT evidence showed that it took longer for extremely low birth weight babies to regain their birthweight if PN was stopped at a smaller volume of EN (100ml/kg/day) compared with a larger volume of EN (140ml/kg/day). There were no clinically important differences based on the stopping point of PN for any of the growth outcomes in extremely low and very low birth weight babies combined, with the exception of head circumference which was more likely to be in the bottom 10th centile when PN was stopped at a smaller volume of EN. There were no clinically important differences in mortality rates between groups.

Low quality evidence showed an increased risk of sepsis and necrotising enterocolitis when PN was stopped at a larger volume of EN compared with a smaller volume of EN. The committee agreed this was consistent with their expectation of increased risk of sepsis with longer duration of PN and that the decision to stop PN requires a balance between optimising nutritional intake and minimising the risk of sepsis. However, the committee acknowledged that the study was powered to detect differences in time taken to regain birthweight, not adverse events.

The committee agreed that for extremely low birth weight babies, prioritising nutrition, and therefore growth, was most critical and that PN should be stopped at a larger volume of EN. Whilst the evidence related to extremely low birth weight the committee decided to make recommendations based on gestational age (extremely preterm babies <28^{+0} weeks' gestation) rather than birthweight to be consistent with other recommendations made in this guideline and because extremely preterm babies would be more likely to have extremely low birth weight than babies born at a later gestational age. The committee noted that EN was fortified at 140ml/kg/day in the RCT, which is not common in clinical practice so there was concern from the committee that nutrition may be inadequate if PN was stopped at 140ml/kg/day when EN was not fortified. Therefore, the committee recommended that clinicians consider stopping PN when EN reached 140-150ml/kg/day. The upper limit of 150ml/kg/day was recommended as the committee agreed that this was the threshold at which the potential benefits of continuing PN would not outweigh the risks and, therefore, the balance favoured discontinuing PN.

The committee discussed that it is important to maintain nutritional intake when transitioning from parenteral to enteral nutrition. However, the committee discussed that clinicians may consider stopping PN at a lower volume of enteral feeds for babies born from 28^{+0} weeks' gestation onwards than for extremely preterm babies, as the balance between the risk from nutritional shortfall and the risk of sepsis may be different in this population. The committee acknowledged that this balance may be different for growth restricted babies but did not have evidence to support a specific recommendation for this group. The committee discussed the lower threshold for stopping PN in babies born from 28^{+0} weeks' gestation at length. Whilst there was little evidence of growth deficits for very low birthweight babies in the RCT when PN was stopped at 100ml/kg/day, the committee were concerned that this threshold was too low and would result in stopping PN before adequate nutritional intake had been achieved. Therefore, the committee recommended by informal consensus that clinicians consider stopping PN when EN reached 120-140ml/kg/day for these babies.

The committee agreed that the thresholds specified in these recommendations should be the point at which PN is no longer prescribed, but that any existing PN which is still in place should be finished. In practical terms, the committee agreed this would mean stopping PN within 24 hours of EN volume reaching the specified volumes.

Cost effectiveness and resource use

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

The committee discussed that these recommendations would reduce variation in practice as the point at which parental nutrition is stopped is inconsistent across services. For some services, these recommendations will result in providing PN for a longer duration, which would have increased costs associated with additional PN and nurse time required to administer PN. However, for other services, these recommendations would result in providing PN for a shorter duration and may produce cost savings.

The volume of PN is decreased as the volume of EN is increased during the transition from PN to EN. Therefore, the committee were concerned that stopping PN at larger volumes of EN may result in very small volumes of PN being prescribed, which would not be practical or economically viable i.e. due to a high wastage of PN. As a result, the committee discussed whether there should be a minimum volume of parental nutrition that is prescribed, such as 30ml/kg/day. This could mean that PN is stopped at this point, or that this volume is maintained, rather than decreased further, until the threshold of EN is reached. However, the minimal volume of parental nutrition was outside the scope of this review question, so no evidence was reviewed to support a minimal volume.

The committee noted that there is a need to balance the risk and benefits of PN including optimising nutritional intake and minimising the risk of sepsis and necrotising enterocolitis i.e. there was evidence of an increased risk of sepsis and necrotising enterocolitis when PN is stopped at a larger volume of EN compared with a smaller volume of EN. However, the committee questioned the finding for necrotising enterocolitis due to the studies being underpowered to detect a difference in this outcome. The recommendations in this area will mean that PN is stopped at an optimal time and will potentially result in fewer cases of sepsis. Sepsis incurs substantial costs to the NHS. According to the Hospital Episode Statistics 2016/17 the mean duration of stay at NICU was 8 days for babies with sepsis. The mean cost of stay at NICU is £1,445 per day. Any strategy that reduces the risk of sepsis is likely to represent a cost effective use of NHS resources.

Other factors the committee took into account

Whilst the focus of this review question was the point at which PN should be stopped, the committee agreed that it was also important to ensure that adequate nutritional intake has been reached before weaning from PN is started. However, they could not make recommendations in this area as it was outside the scope of the review question.

References

Choi 2016

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

Dinerstein 2006

Dinerstein, A., Nieto, R. M., Solana, C. L., Perez, G. P., Otheguy, L. E., Larguia, A. M., Early and aggressive nutritional strategy (parenteral and enteral) decreases postnatal growth failure in very low birth weight infants, Journal of Perinatology, 26, 436-42, 2006

Perrem 2019

Perrem, L., Semberova, J., O'Sullivan, A., Kieran, E. A., O'Donnel, C. P. F., White, M. J., Miletin, J., Effect of early parenteral nutrition discontinuation on time to regain birth weight in very low birth weight infants: a randomized controlled trial, Journal of Parenteral and Enteral Nutrition, 2019

Appendices

Appendix A – Review protocols

Review protocol for review question: What amount of enteral feed (measured in terms of ml/kg/d, or kcal/kg/d, or ratios in relation to PN and enteral feeds) indicates that parenteral nutrition is no longer required?

Table 3: Review protocol – stopping parenteral nutrition in preterm and term babies

Field (based on PRISMA-P	Content
Review question RQ 1.2	What amount of enteral feed (measured in terms of ml/kg/d, or kcal/kg/d, or ratios in relation to PN and enteral feeds) indicates that parenteral nutrition is no longer required?
Type of review question	Intervention
Objective of the review	Determining when parenteral nutrition can be stopped is important; there is risk of malnutrition and associated complications to the baby if parenteral feeding is stopped too early. In contrast, the longer parenteral feeding is continued, the greater the risk of line sepsis. Guidance for clinicians on how to determine when it is safe to transition from combined parenteral and enteral nutrition to enteral nutrition alone is required.
Eligibility criteria – population/disease/condition/issue/domain	• Babies born preterm, up to 28 days after their due birth date (preterm babies) • Babies born at term, up to 28 days after their birth (term babies)
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Volume of PN (ml/kg/day or kcal/kg/day) plus EN (ml/kg/day or kcal/kg/day Ratio of PN (ml/kg/day or kcal/kg/day) and EN (ml/kg/day or kcal/kg/day)
Eligibility criteria – comparator(s)/control or reference (gold) standard	Comparison volume of PN (ml/kg/day or kcal/kg/day) plus EN (ml/kg/day or kcal/kg/day) Different ratio of PN (ml/kg/day or kcal/kg/day) to EN (ml/kg/day or kcal/kg/day)
Outcomes and prioritisation	**Critical** • Total nutritional intake, protein/carbohydrate/lipid/energy (for example, kcal/kg/day as a total of the parental + enteral) • Growth/Anthropometric measures: ○ Weight gain ○ Linear growth ○ Head circumference (mm) ○ Body composition (lean mass, fat-free mass, fat mass, adipose tissue, nitrogen accretion) **Important**

Field (based on PRISMA-P	Content
	• Mortality • Duration of hospital stay • Necrotising enterocolitis • Neurodevelopmental outcomes (general cognitive abilities at two years, measured using validated scales only) • Duration of PN • Sepsis (central line infections)
Eligibility criteria – study design	Systematic reviews of RCTs RCTs Comparative cohort studies (only if RCTs unavailable or limited data to inform decision making), retrospective or prospective
Other inclusion exclusion criteria	No sample size restriction No date restriction Studies conducted in the community, residential, primary and secondary care will be included
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analysis Babies born preterm, up to 28 days after their due birth date (preterm babies) Babies born at term, up to 28 days after their birth (term babies) Where evidence exists, consideration will be given to the specific needs of population subgroups: Age of baby (first 2 weeks vs. later) Preterm (Extremely preterm <28 weeks' GA; very preterm: 28-31 weeks' GA; moderately preterm: 32-36 weeks' GA) Birth weight: Low birth weight (< 2500g); very low birth weight (< 1500g) and extremely low birth weight (< 1000g) Critically ill babies or those requiring surgery (for example, inotropic support, therapeutic hypothermia or fluid restriction) Important confounders (when comparative observational studies are included for interventional reviews): Age of baby (first 2 weeks vs. later) Preterm (Very early <28 weeks' GA; 28-31 weeks' GA; 32-36 weeks' GA) Birth weight: Low birth weight (< 2500g); very low birth weight (< 1500g) and extremely low birth weight (< 1000g)
Selection process – duplicate screening/selection/analysis	Study Selection Studies will be imported to the NGA STAR database for screening by one reviewer. Dual sifting will not be performed for this review question. All full texts identified will be screened for inclusion by two reviewers. All

Field (based on PRISMA-P	Content
	disagreements will be resolved by discussion between the two reviewers. The senior systematic reviewer or guideline lead will act as arbiter where necessary.
Data management (software)	Data Analysis Where data is available, pair-wise meta-analysis using a fixed effects model, will be used to combine results from similar studies, this will be performed using Cochrane Review Manager (RevMan5). Heterogeneity will be considered, and if a random-effects model is considered more appropriate, it will be conducted. Quality Assessment Appraisal of methodological quality will be conducted using the appropriate tool: ROBIS (systematic reviews and meta-analyses), Cochrane risk of bias tool for RCTs (RCT or comparative cohort studies). Cochrane risk of bias tool, ROBINS-I (Non-randomised studies) The quality of evidence for each outcome will be assessed using GRADEpro: Outcomes will be downgraded if the randomisation and/or concealment methods are unclear or inadequate. Outcomes will also be downgraded if there is considerable missing data (if there is a dropout of more than 20%, or if there is a difference of >20% between groups. Heterogeneity will be assessed using the I2, outcomes will be downgraded once if I2 >50%, twice if I2 >80%. Imprecision: Outcomes will be downgraded if the 95% CI is imprecise (i.e. crosses 0.8 or 1.25, (dichotomous) or -0.5 or 0.5 (continuous)). Outcomes will be downgraded two levels depending on how many lines of imprecision are crossed. If the clinical decision threshold is NOT crossed, we will consider whether the criterion for Optimal Information Size is met, if not we will downgrade one level for dichotomous outcomes with less than 300 events, and downgrade one level for continuous outcomes when less than 400 participants are included. Clinical effectiveness For dichotomous outcomes, minimal important differences will be considered using thresholds of RR >0.80 and <1.25. For continuous outcomes, minimal important differences will be considered 0.5 times the SD of the control group
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase. Limits (e.g. date, study design): All study designs. Apply standard animal/non-English language filters. No date limit. Supplementary search techniques: No supplementary search techniques were used. See appendix B for full strategies.
Identify if an update	This is not an update

Field (based on PRISMA-P	Content
Author contacts	Developer: The National Guideline Alliance 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. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual 2014.
Methods for analysis – combining studies and exploring (in)consistency	For details of the methods please see supplementary material C.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014.
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Joe Fawke (Consultant Neonatologist and Honorary Senior Lecturer, University Hospitals Leicester NHS Trust) in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details of the methods please see supplementary material C.
Sources of funding/support	The 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

Field (based on PRISMA-P	Content
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	The review is not registered with PROSPERO

CDSR: Cochrane Database of Systematic Reviews; CCTR: Cochrane controlled trials register; DARE: Database of Abstracts of Reviews of Effects; EN: enteral nutrition; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; ICF: International Classification of Functioning, Disability and Health; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; PN: parenteral nutrition; PROSPERO: International prospective register of systematic reviews; RCT: randomised controlled trial; RoB: risk of bias; ROBINS-I: risk of bias in non-randomised studies of interventions; ROBIS; risk of bias in systematic reviews; RR: risk ratio; SD: standard deviation

Appendix B – Literature search strategies

Literature search strategies for review question: What amount of enteral feed (measured in terms of ml/kg/d, or kcal/kg/d, or ratios in relation to PN and enteral feeds) indicates that parenteral nutrition is no longer required?

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

#	Searches
1	INFANT, NEWBORN/
2	(neonat$ or newborn$ or new-born$ or baby or babies).ti,ab.
3	PREMATURE BIRTH/
4	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 (birth? or born)).ab,ti.
5	exp INFANT, PREMATURE/
6	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 infan$).ti,ab.
7	(pre#mie? or premie or premies).ti,ab.
8	exp INFANT, LOW BIRTH WEIGHT/
9	(low adj3 birth adj3 weigh$ adj5 infan$).ti,ab.
10	((LBW or VLBW) adj5 infan$).ti,ab.
11	INTENSIVE CARE, NEONATAL/
12	INTENSIVE CARE UNITS, NEONATAL/
13	NICU?.ti,ab.
14	or/1-13
15	PARENTERAL NUTRITION/
16	PARENTERAL NUTRITION, TOTAL/
17	PARENTERAL NUTRITION SOLUTIONS/
18	ADMINISTRATION, INTRAVENOUS/ and (nutrition$ or feed$ or fed$).ti,ab.
19	INFUSIONS, INTRAVENOUS/ and (nutrition$ or feed$ or fed$).ti,ab.
20	CATHETERIZATION, CENTRAL VENOUS/ and (nutrition$ or feed$ or fed$).ti,ab.
21	exp CATHETERIZATION, PERIPHERAL/ and (nutrition$ or feed$ or fed$).ti,ab.
22	((parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?) adj3 (nutrition$ or feed$ or fed$)).ti,ab.
23	((peripheral$ or central$) adj3 line? adj3 (nutrition$ or feed$ or fed$)).ti,ab.
24	(catheter$ adj3 (nutrition$ or feed$ or fed$)).ti,ab.
25	(drip? adj3 (nutrition$ or feed$ or fed$)).ti,ab.
26	or/15-25
27	ENTERAL NUTRITION/
28	INTUBATION, GASTROINTESTINAL/
29	GASTROSTOMY/
30	JEJUNOSTOMY/
31	((enteral$ or tube? or oral$ or sip) adj3 (nutrition$ or feed$ or fed$)).ti,ab.
32	((Nasogastric$ or gastrointestinal$) adj3 (tube? or intubate$ or nutrition$ or feed$ or fed$)).ti,ab.
33	Gastrostom$.ti,ab.
34	Jejunostom$.ti,ab.
35	or/27-34
36	((wean$ or decreas$ or de-creas$ or halt$ or ceas$ or cessat$ or suspen$ or stop$ or end$ or discontinu$ or dis-continu$ or finish$ or transition$) adj5 (parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?) adj3 (nutrition$ or feed$ or fed$)).ti,ab.
37	((wean$ or decreas$ or de-creas$ or halt$ or ceas$ or cessat$ or suspen$ or stop$ or end$ or discontinu$ or dis-continu$ or finish$ or transition$) adj5 (PN or SPN or IPN or TPN or STD-PN or IND-PN)).ti,ab.
38	or/36-37
39	((Advanc$ or Achiev$ or Establish$ or Tolera$ or Success$ or Full$) adj3 (enteral$ or tube? or oral$ or sip) adj3 (nutrition$ or feed$ or fed$)).ti,ab.
40	((amount? or volume? or ratio?) adj10 (parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?) adj10 (enteral$ or tube? or oral$ or sip) adj10 (nutrition$ or feed$ or fed$)).ti,ab.
41	((ml? or milliliter? or kcal? or kilocalor$) adj3 (kg? or kilogram?) adj3 (d or day)).ti,ab.
42	ENERGY INTAKE/
43	NUTRITIONAL STATUS/
44	((energy or volume? or kcal or kilocalorie? or nutrition$) adj3 (goal? or target$)).ti,ab.
45	((optimi$ or success$) adj3 (nutrition$ or feed$ or fed$)).ti,ab.
46	or/42-45

#	Searches
47	PARENTERAL NUTRITION/mt [Methods]
48	ENTERAL NUTRITION/mt [Methods]
49	14 and 35 and 38
50	14 and 26 and 39
51	14 and 40
52	14 and 26 and 35 and 41
53	14 and 26 and 35 and 46
54	14 and 47 and 48
55	or/49-54
56	limit 55 to english language
57	LETTER/
58	EDITORIAL/
59	NEWS/
60	exp HISTORICAL ARTICLE/
61	ANECDOTES AS TOPIC/
62	COMMENT/
63	CASE REPORT/
64	(letter or comment*).ti.
65	or/57-64
66	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
67	65 not 66
68	ANIMALS/ not HUMANS/
69	exp ANIMALS, LABORATORY/
70	exp ANIMAL EXPERIMENTATION/
71	exp MODELS, ANIMAL/
72	exp RODENTIA/
73	(rat or rats or mouse or mice).ti.
74	or/67-73
75	56 not 74

Databases: Embase; and Embase Classic

#	Searches
1	NEWBORN/
2	(neonat$ or newborn$ or new-born$ or baby or babies).ti,ab.
3	PREMATURITY/
4	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 (birth? or born)).ab,ti.
5	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 infan$).ti,ab.
6	(pre#mie? or premie or premies).ti,ab.
7	exp LOW BIRTH WEIGHT/
8	(low adj3 birth adj3 weigh$ adj5 infan$).ti,ab.
9	((LBW or VLBW) adj5 infan$).ti,ab.
10	NEWBORN INTENSIVE CARE/
11	NEONATAL INTENSIVE CARE UNIT/
12	NICU?.ti,ab.
13	or/1-12
14	PARENTERAL NUTRITION/
15	TOTAL PARENTERAL NUTRITION/
16	PERIPHERAL PARENTERAL NUTRITION/
17	PARENTERAL SOLUTIONS/
18	INTRAVENOUS FEEDING/
19	INTRAVENOUS DRUG ADMINISTRATION/ and (nutrition$ or feed$ or fed$).ti,ab.
20	exp INTRAVENOUS CATHETER/ and (nutrition$ or feed$ or fed$).ti,ab.
21	((parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?) adj3 (nutrition$ or feed$ or fed$)).ti,ab.
22	((peripheral$ or central$) adj3 line? adj3 (nutrition$ or feed$ or fed$)).ti,ab.
23	(catheter$ adj3 (nutrition$ or feed$ or fed$)).ti,ab.
24	(drip? adj3 (nutrition$ or feed$ or fed$)).ti,ab.
25	or/14-24
26	ENTERIC FEEDING/
27	exp DIGESTIVE TRACT INTUBATION/
28	GASTROSTOMY/
29	JEJUNOSTOMY/
30	((enteral$ or tube? or oral$ or sip) adj3 (nutrition$ or feed$ or fed$)).ti,ab.
31	((Nasogastric$ or gastrointestinal$) adj3 (tube? or intubate$ or nutrition$ or feed$ or fed$)).ti,ab.

#	Searches
32	Gastrostom$.ti,ab.
33	Jejunostom$.ti,ab.
34	or/26-33
35	((wean$ or decreas$ or de-creas$ or halt$ or ceas$ or cessat$ or suspen$ or stop$ or end$ or discontinu$ or dis-continu$ or finish$ or transition$) adj5 (parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?) adj3 (nutrition$ or feed$ or fed$)).ti,ab.
36	((wean$ or decreas$ or de-creas$ or halt$ or ceas$ or cessat$ or suspen$ or stop$ or end$ or discontinu$ or dis-continu$ or finish$ or transition$) adj5 (PN or SPN or IPN or TPN or STD-PN or IND-PN)).ti,ab.
37	or/35-36
38	((Advanc$ or Achiev$ or Establish$ or Tolera$ or Success$ or Full$) adj3 (enteral$ or tube? or oral$ or sip) adj3 (nutrition$ or feed$ or fed$)).ti,ab.
39	((amount? or volume? or ratio?) adj10 (parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?) adj10 (enteral$ or tube? or oral$ or sip) adj10 (nutrition$ or feed$ or fed$)).ti,ab.
40	((ml? or milliliter? or kcal? or kilocalor$) adj3 (kg? or kilogram?) adj3 (d or day)).ti,ab.
41	CALORIC INTAKE/
42	NUTRITIONAL STATUS/
43	((energy or volume? or kcal or kilocalorie? or nutrition$) adj3 (goal? or target$)).ti,ab.
44	((optimi$ or success$) adj3 (nutrition$ or feed$ or fed$)).ti,ab.
45	or/41-44
46	13 and 34 and 37
47	13 and 25 and 38
48	13 and 39
49	13 and 25 and 34 and 40
50	13 and 25 and 34 and 45
51	or/46-50
52	limit 51 to english language
53	letter.pt. or LETTER/
54	note.pt.
55	editorial.pt.
56	CASE REPORT/ or CASE STUDY/
57	(letter or comment*).ti.
58	or/53-57
59	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
60	58 not 59
61	ANIMAL/ not HUMAN/
62	NONHUMAN/
63	exp ANIMAL EXPERIMENT/
64	exp EXPERIMENTAL ANIMAL/
65	ANIMAL MODEL/
66	exp RODENT/
67	(rat or rats or mouse or mice).ti.
68	or/60-67
69	52 not 68

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

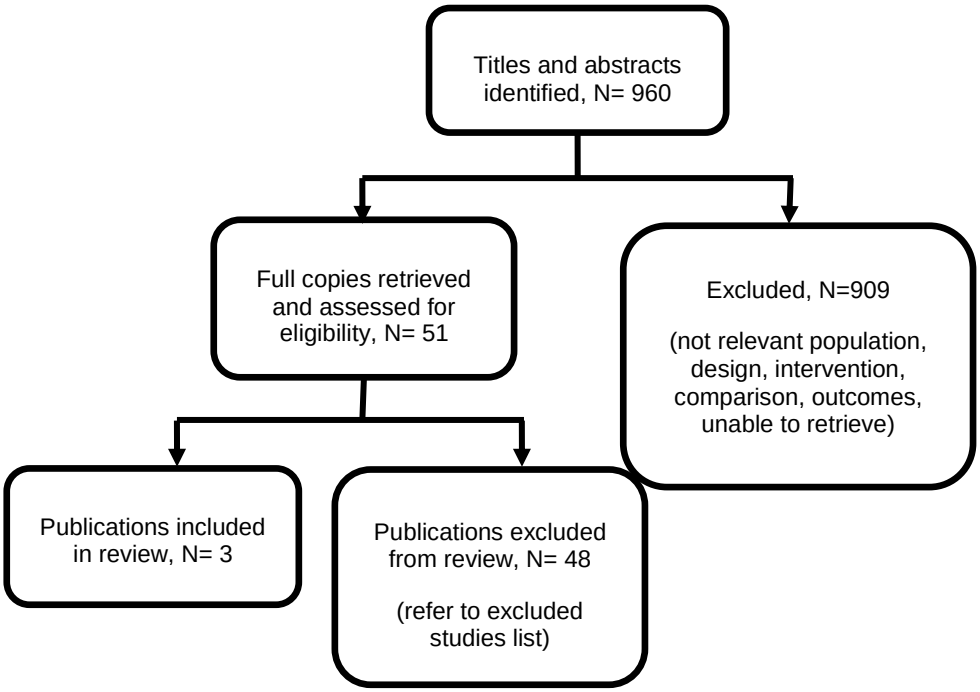
#	Searches
#1	MeSH descriptor: [INFANT, NEWBORN] this term only
#2	(neonat* or newborn* or new-born* or baby or babies):ti,ab
#3	MeSH descriptor: [PREMATURE BIRTH] this term only
#4	((preterm* or pre-term* or prematur* or pre-matur*) near/5 (birth* or born)):ti,ab
#5	MeSH descriptor: [INFANT, PREMATURE] explode all trees
#6	((preterm* or pre-term* or prematur* or pre-matur*) near/5 infan*):ti,ab
#7	(pre?mie? or premie or premies):ti,ab
#8	MeSH descriptor: [INFANT, LOW BIRTH WEIGHT] explode all trees
#9	(low near/3 birth near/3 weigh* near/5 infan*):ti,ab
#10	((LBW or VLBW) near/5 infan*):ti,ab
#11	MeSH descriptor: [INTENSIVE CARE, NEONATAL] this term only
#12	MeSH descriptor: [INTENSIVE CARE UNITS, NEONATAL] this term only
#13	NICU?:ti,ab
#14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#	Searches
#15	MeSH descriptor: [PARENTERAL NUTRITION] this term only
#16	MeSH descriptor: [PARENTERAL NUTRITION, TOTAL] this term only
#17	MeSH descriptor: [PARENTERAL NUTRITION SOLUTIONS] this term only
#18	MeSH descriptor: [ADMINISTRATION, INTRAVENOUS] this term only
#19	MeSH descriptor: [INFUSIONS, INTRAVENOUS] this term only
#20	MeSH descriptor: [CATHETERIZATION, CENTRAL VENOUS] this term only
#21	MeSH descriptor: [CATHETERIZATION, PERIPHERAL] explode all trees
#22	#18 or #19 or #20 or #21
#23	(nutrition* or feed* or fed*) :ti,ab
#24	#22 and #23
#25	((parenteral* or intravenous* or intra-venous* or IV or venous* or infusion?) near/3 (nutrition* or feed* or fed*)) :ti,ab
#26	((peripheral* or central*) near/3 line? near/3 (nutrition* or feed* or fed*)) :ti,ab
#27	(catheter* near/3 (nutrition* or feed* or fed*)) :ti,ab
#28	(drip? near/3 (nutrition* or feed* or fed*)) :ti,ab
#29	#15 or #16 or #17 or #24 or #25 or #26 or #27 or #28
#30	MeSH descriptor: [ENTERAL NUTRITION] this term only
#31	MeSH descriptor: [INTUBATION, GASTROINTESTINAL] this term only
#32	MeSH descriptor: [GASTROSTOMY] this term only
#33	MeSH descriptor: [JEJUNOSTOMY] this term only
#34	((enteral* or tube? or oral* or sip) near/3 (nutrition* or feed* or fed*)) :ti,ab
#35	((Nasogastric* or gastrointestinal*) near/3 (tube? or intubate* or nutrition* or feed* or fed*)) :ti,ab
#36	Gastrostom*:ti,ab
#37	Jejunostom*:ti,ab
#38	#30 or #31 or #32 or #33 or #34 or #35 or #36 or #37
#39	((wean* or decreas* or de-creas* or halt* or ceas* or cessat* or suspen* or stop* or end* or discontinu* or dis-continu* or finish* or transition*) near/5 (parenteral* or intravenous* or intra-venous* or IV or venous* or infusion*) near/3 (nutrition* or feed* or fed*)):ti,ab
#40	((wean* or decreas* or de-creas* or halt* or ceas* or cessat* or suspen* or stop* or end* or discontinu* or dis-continu* or finish* or transition*) near/5 (PN or SPN or IPN or TPN or STD-PN or IND-PN)):ti,ab
#41	#39 or #40
#42	((Advanc* or Achiev* or Establish* or Tolera* or Success* or Full*) near/3 (enteral* or tube* or oral* or sip) near/3 (nutrition* or feed* or fed*)):ti,ab
#43	((amount* or volume* or ratio*) near/10 (parenteral* or intravenous* or intra-venous* or IV or venous* or infusion*) near/10 (enteral* or tube* or oral* or sip) near/10 (nutrition* or feed* or fed*)):ti,ab
#44	((ml* or milliliter* or kcal* or kilocalor*) near/3 (kg* or kilogram*) near/3 (d or day)):ti,ab
#45	MeSH descriptor: [ENERGY INTAKE] this term only
#46	MeSH descriptor: [NUTRITIONAL STATUS] this term only
#47	((energy or volume* or kcal or kilocalorie* or nutrition*) near/3 (goal* or target*)):ti,ab
#48	((optimi* or success*) near/3 (nutrition* or feed* or fed*)):ti,ab
#49	#45 or #46 or #47 or #48
#50	MeSH descriptor: [PARENTERAL NUTRITION] this term only and with qualifier(s): [methods - MT]
#51	MeSH descriptor: [ENTERAL NUTRITION] this term only and with qualifier(s): [methods - MT]
#52	#14 and #38 and #41
#53	#14 and #29 and #42
#54	#14 and #43
#55	#14 and #29 and #38 and #44
#56	#14 and #29 and #38 and #49
#57	#14 and #50 and #51
#58	#52 or #53 or #54 or #55 or #56 or #57

Appendix C – Clinical evidence study selection

Clinical study selection for: What amount of enteral feed (measured in terms of ml/kg/d, or kcal/kg/d, or ratios in relation to PN and enteral feeds) indicates that parenteral nutrition is no longer required?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What amount of enteral feed (measured in terms of ml/kg/d, or kcal/kg/d, or ratios in relation to PN and enteral feeds) indicates that parenteral nutrition is no longer required?

Table 4: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation 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 Ref Id 688689 Country/ies where the study was carried out Korea Study type Observational study Aim of the study The aim of the study was to: 1) modify parenteral and enteral	Sample size N=124; only n=87 of interest for the purpose of this review question (n=50 100ml/kg/day; n=37 120ml/kg/day) n=37 infants from period 3 were not included as differences between nutritional protocols in period 2 and 3 are changes to enteral practices, not PN Characteristics Gestational age (weeks) - mean (SD) 100ml/kg/day: 29+1 (2+2) 120ml/kg/day: 29+5 (2+5) Birth weight (g) - mean (SD) 100ml/kg/day: 1120 (222)	Interventions Infants admitted between October 2010 and September 2011 formed the first cohort. Infants admitted between October 2011 and December 2012 formed the second cohort (after modifications to PN protocol, and minimal modifications to EN protocol). Period 1 - 120ml/kg/day: Nutritional supplements were added and PN discontinued when infants reached 100ml/kg/day of enteral feeds Period 2 - 100ml/kg/day:	Details PN regimen prior to stopping: On day 1 of life, 60ml of fluid was started with glucose infusion rate of 4 to 6mg/kg/minute and increased to 10 to 15mg/kg/minute based on blood glucose level. Proteins were supplied using a 10% amino acid 100ml solution and lipids were supplied using a 20% lipid 250ml solution. During period 1, proteins were started on the first day of life at 1.5g/kg/day and advanced to 3.5g/kg/day; lipids were started on the second day of life at 0.5g/kg/day and advanced to 3.0g/kg/day. During period 2, proteins was started on the first day of life at 3.0g/kg/day and advanced to 4.0g/kg/day; lipids were	Results Weight gain - time (days) to regain birth weight - mean (SD): 100ml/kg/day (n=50): 14.3 (5.3) 120ml/kg/day (n=37): 17.7 (8.3) Weight gain - weight <10th centile at 36 weeks post conception - n/N: 100ml/kg/day: 33/50 120ml/kg/day: 34/37 Weight gain - weight <10th centile at 40 weeks post conception - n/N: 100ml/kg/day: 22/50 120ml/kg/day: 29/37 Linear growth - length <10th centile at 36	Limitations Quality of study assessed using ROBINS-I Confounding bias: Low risk. Selection of participants' bias: Moderate risk. Retrospective study; start and follow-up of the two cohorts differ. Classification of interventions bias: Low risk. Intervention groups clearly defined. Deviations from intended interventions bias: Unclear risk. Protocol violations, if any occurred, are not reported. Missing data bias: Low risk. No missing data. Measurement of outcomes bias: Low risk.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
nutrition protocols based on recent literature, and 2) evaluate the impact of modified protocols on growth of very low birth weight infants Study dates October 2010 to April 2014 (only interested in October 2010 to December 2012 for the purpose of this review question) Source of funding No sources of funding reported	120ml/kg/day: 1135 (252) Length (cm) at birth - mean (SD) 100ml/kg/day: 36.3 (3.0) 120ml/kg/day: 37.2 (3.0) Head circumference (cm) at birth - mean (SD) 100ml/kg/day: 26.2 (1.8) 120ml/kg/day: 26.5 (1.9) Inclusion criteria Very low birth weight infants (<1,500g) born before 34 weeks' gestation who were admitted to 1 NICU between October 2010 and April 2014. Exclusion criteria Died during hospitalisation; transferred to other hospitals; serious congenital malformation that needed surgical treatment	Nutritional supplements were added and PN discontinued when infants reached 120ml/kg/day of enteral feeds	started on the first day of life at 1.0/kg/day and advanced to 3.5g/kg/day. Enteral regimen: Minimal enteral feeding was started as soon as possible at 10 to 15ml/kg/day and increased by 10 to 30ml/kg/day. Human milk was preferred but preterm formula was used if milk was unavailable. Milk was fortified and supplemented with protein when full enteral feeds were reached. During period 1, the goal for enteral feeding was 3.0 to 3.5g/kg/day of protein and 120kcal/kg/day; protein goals were the same in period 2 but calorie goal was 130kcal/kg/day. Power analysis: Not stated Statistical analysis: Analysis was conducted using SPSS version 22.0. Chi-squared tests and Fisher exact tests were used for categorical variables, Kruskal-Wallis	weeks post conception - n/N: 100ml/kg/day: 31/50 120ml/kg/day: 30/37 Linear growth - length <10th centile at 40 weeks' post conception - n/N: 100ml/kg/day: 34/50 120ml/kg/day: 32/37 Head circumference <10th centile at 36 ' post conception - n/N: 100ml/kg/day: 21/50 120ml/kg/day: 29/37 Head circumference <10th centile at 40 weeks' post conception - n/N: 100ml/kg/day: 21/50 120ml/kg/day: 26/37 Duration (days) of hospital stay - mean (SD): 100ml/kg/day (n=50): 68.9 (21.4) 120mlkg/day (n=37): 76.8 (29.5)	Unlikely that outcome assessors were blind to intervention for safety reasons but all outcomes are objective. Selection of the reported results bias: Moderate risk. Insufficient reporting of growth rates and measurements at 40 weeks' post conceptional age for weight, height and head circumference. Other information There are multiple differences between the nutrition protocols followed during the different time periods apart from the point at which PN was discontinued. Therefore, it is difficult to conclude whether any differences observed between groups are a result of when PN was stopped.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			test was used for serial variants and Pearson coefficient was used for correlations.	Necrotising enterocolitis - n/N: 100ml/kg/day: 2/50 120ml/kg/day: 0/37 Duration (days) of PN - mean (SD): 100ml/kg/day (n=50): 25.5 (14.3) 120mlkg/day (n=37): 29.0 (15.5) Sepsis - n/N: 100ml/kg/day: 17/50 120ml/kg/day: 16/37	
Full citation Dinerstein, A., Nieto, R. M., Solana, C. L., Perez, G. P., Otheguy, L. E., Larguia, A. M., Early and aggressive nutritional strategy (parenteral and enteral) decreases postnatal growth failure in very low birth weight infants, Journal of Perinatology, 26, 436-42, 2006 Ref Id 378253	Sample size N=200 (n=128 100kcal/kg/day; n=72 60kcal/kg/day) N=182 analysed (n=117 100kcal/kg/day [n=6 died; n=5 transferred before 40 weeks postmenstrual age]; n=65 60kcal/kg/day [n=3 died; n=4 transferred before 40 weeks postmenstrual age]) Characteristics Gestational age (weeks) - median (range) 60kcal/kg/day: 30 (24-36)	Interventions Infants born between August 2001 and July 2003 were treated according to the aggressive nutritional regimen and infants born during the preceding year were treated according to the conservative nutritional regimen. Aggressive regimen - 100kcal/kg/day: PN was discontinued when infants reached 100kcal/kg/day of enteral feeds	Details Aggressive nutritional regimen: Fluids were begun at 80ml/kg/day and advanced to 150 to 180ml/kg/day over 7 days. Amino acids were delivered from day 1 in a 10% solution starting at 1.5g/kg/day and advanced by 0.5g/kg/day to 4g/kg/day, unless there was renal failure or metabolic acidosis. Glucose infusion began on day 1 at a rate of 5.6mg/kg/minute and advanced by 1mg/kg/minute every day	Results Nutritional intake (kcal/kg/week)* - median (min/max): Week 1 100kcal/kg/day: 497 (331/731) 60kcal/kg/day: 351 (195/605) Week 2 100kcal/kg/day: 770 (411/1120) 60kcal/kg/day: 679 (348/917) Week 3 100kcal/kg/day: 875 (333/1371) 60kcal/kg/day: 802 (288/935)	Limitations Quality of study assessed using ROBINS-I Confounding bias: Low risk. Selection of participants' bias: Moderate risk. Start and follow-up of the two cohorts differ. Classification of interventions bias: Low risk. Intervention groups clearly defined. Deviations from intended interventions bias: Unclear risk. Protocol violations, if any

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Argentina Study type Observational study (intervention group was observed and compared to a historical cohort) Aim of the study To determine the effect of an early and aggressive nutrition protocol on postnatal growth of very low birth weight infants. A secondary objective of the study was to determine nutritional deficits during the first 4 weeks of life. Study dates August 2000 to July 2003 (Intervention group recruited August 2001 to July 2003, but control group was from the 'immediate preceding year') Source of funding	100kcal/kg/day: 30 (26-35) Birth weight (g) - median (range) 60kcal/kg/day: 1230 (720-1500) 100kcal/kg/day: 1245 (730-1500) Length (cm) at birth - mean (SD) 60kcal/kg/day: 37.0 (0.2) 100kcal/kg/day: 37.1 (2.3) Head circumference (cm) at birth - mean (SD) 60kcal/kg/day: 26.5 (1.9) 100kcal/kg/day: 26.3 (1.9) Inclusion criteria Infants weighing more than 750g and less than 1500g at birth. Exclusion criteria Major congenital anomalies; died or transferred within 7 days of birth	Conservative regimen - 60kcal/kg/day: PN was discontinued when infants reached 60kcal/kg/day of enteral feeds	to a maximum of 13mg/kg/minute. Lipids were introduced in a 20% solution at 24 hours of age at a rate of 0.5g/kg/day and increased by 0.5g/kg/day up to 3.5g/kg/day. Enteral feeds (either breast milk or 24kcal/oz preterm formula) were introduced on day 1 at a rate of 10ml/kg/day and advanced by 10ml/kg/day for the first 7 days and by 15 to 20ml/kg/day after this until feeds of 180ml/kg/day were reached. Infants receiving breast milk were switched to 50% and 66% preterm formula when enteral feeds reached 100ml/kg/day and 150ml/kg/day, respectively, as human milk fortifier was not available. Conservative nutritional regimens: Fluids were begun at 80ml/kg/day and advanced to 150ml/kg/day over 7 to 10 days; PN was introduced. Infants were started on	Week 4 100kcal/kg/day: 934 (331/1159) 60kcal/kg/day: 828 (477/932) Weight gain - time (days) to regain birth weight* - median (range): 100kcal/kg/day: 10 (1-21) 60kcal/kg/day: 16 (1-29) Weight gain - postnatal growth failure at 40 weeks' postmenstrual age - n/N: 100kcal/kg/day: 62/117 60kcal/kg/day: 50/65 Linear growth - length (cm) at 40 weeks' postmenstrual age - mean (SD): 100kcal/kg/day (n=117): 46.6 (2.6) 60kcal/kg/day (n=65): 45.6 (2.7) Head circumference (cm) at 40 weeks'	occurred, are not reported. Missing data bias: Low risk. The amount of, and reason for, loss to follow-up are similar between groups. Measurement of outcomes bias: Low risk. Unlikely that outcome assessors were blind to intervention for safety reasons but all outcomes are objective. Selection of the reported results bias: Low risk. All outcomes reported in sufficient detail. Other information There are multiple differences between the nutrition protocols followed during the different time periods apart from the point at which PN was discontinued. Therefore, it is difficult to conclude whether any differences observed between groups are a result of when PN was stopped.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
No sources of funding reported			amino acids using a 10% solution at the discretion of neonatal staff on day 3 of life at a rate of 0.5g/kg/day; this was advanced by 0.5g/kg/day up to 3g/kg/day. Glucose was started (day not reported) at a rate of 5.6mg/kg/minute and advanced by 1mg/kg/minute every day to a maximum of 8 to 9mg/kg/minute. Lipids were introduced in a 20% solution at day 3 or 4 of life at a rate of 0.5g/kg/day and increased by 0.5g/kg/day up to 3g/kg/day. Enteral feeds were introduced when the attending physician thought the infant was clinically stable. Power analysis: Not stated Statistical analysis: Analysis was conducted using Stata version 7. Categorical variables were analysed using chi-squared tests. Student's t tests were used for	postmenstrual age - mean (SD): 100kcal/kg/day (n=117): 35.2 (0.17) 60kcal/kg/day (n=65): 34.3 (0.21) Necrotising enterocolitis - n/N: 100kcal/kg/day: 2/117 60kcal/kg/day: 3/65 Duration (days) of PN* - median (range): 100kcal/kg/day: 10 (5-36) 60kcal/kg/day: 4 (0-37) Sepsis - late onset sepsis - n/N: 100kcal/kg/day: 30/117 60kcal/kg/day: 15/65 *Not analysed as data is reported as medians	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			normally distributed continuous variables and Mann-Whitney U-tests were used when data was not normally distributed.		
Full citation Perrem, L., Semberova, J., O'Sullivan, A., Kieran, E. A., O'Donnel, C. P. F., White, M. J., Miletin, J., Effect of early parenteral nutrition discontinuation on time to regain birth weight in very low birth weight infants: a randomized controlled trial, Journal of Parenteral and Enteral Nutrition, 2019 Ref Id 1009143 Country/ies where the study was carried out Ireland Study type Randomised controlled trial Aim of the study	Sample size N=317 assessed for eligibility (n=104 did not meet inclusion criteria; n=54 reached 100 mL/kg/day of enteral feeds before study enrolment; n=20 declined participation) N=139 randomised (n=69 100ml/kg/day; n=70 140ml/kg/day) N=137 analysed (n=67 100ml/kg/day [n=1 withdrew consent; n=1 died prior to primary outcome]; n=70 140ml/kg/day) Characteristics Gestational age (weeks) - mean (SD) 100ml/kg/day: 28.7 (2.6) 140ml/kg/day: 28.5 (2.1) Birth weight Weight (g) - median (IQR) 100ml/kg/day: 1060 (800-1300)	Interventions Infants were randomised to the below groups when they were clinically stable and had a PICC inserted, but before they reached 100m;/kg/day of enteral feeds. 100ml/kg/day: PICC was removed and PN discontinued when infants reached 100ml/kg/day of enteral feeds 140ml/kg/day: PICC was removed and PN discontinued when infants reached 140ml/kg/day of enteral feeds	Details PN regimen prior to stopping: All infants received 60-80ml/kg/day PN within the first 24 hours of life using a standard bag of preterm PN (content/100 mL: amino acids 2.51g, glucose 10%, sodium 2.5mmol, potassium 2mmol, calcium 1mmol, magnesium 0.15mmol, phosphate 1.25mmol). This was increased by 10-20ml/kg/day up to a target volume of 150-160ml/kg/day. Enteral regimen: If infants were stable, 10-20ml/kg/day of enteral feeds were started on the first day of life. Expressed breast milk (EBM), either maternal or donor, was the preferred choice of enteral feeds and was received by all infants ≤1250g and growth-restricted infants >1250g at higher risk of	Results Weight gain - time (days) to regain birth weight - mean (SD): All infants (VLBW & ELBW) 100ml/kg/day (n=67): 10.8 (3.6) 140ml/kg/day (n=70): 9.3 (3.5) VLBW infants 100ml/kg/day (n=41): 10.7 (3.5) 140ml/kg/day (n=42): 10.1 (3.0) ELBW infants 100ml/kg/day (n=26): 10.9 (3.7) 140ml/kg/day (n=28): 8.1 (3.8) Weight gain - weight (g) at discharge - mean (SD): 100ml/kg/day (n=67): 2391 (660) 140ml/kg/day (n=70): 2378 (551)	Limitations Quality of study assessed using Cochrane risk of bias tool Selection bias Random sequence generation: Low risk. Computer-generated in blocks of 4 and 8, stratified by birth weight (<1000g or 1000-1499g) and centre. Allocation concealment: Low risk. Randomisation list prepared by research assistant who had no involvement in the trial and placed in sealed, opaque, sequentially numbered envelopes. Performance bias Blinding of participants and personnel: Low risk. Infants would be unaware of their assignment. Caregivers were not blinded, likely due to safety reasons.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To compare the effect of stopping parenteral nutrition at 2 different volumes of enteral feeding on the time taken for very low birth weight infants to regain birth weight Study dates July 2013 to April 2016 Source of funding No sources of funding reported	140ml/kg/day: 1070 (860-1280) <100g - n (%) 100ml/kg/day: 26 (39) 140ml/kg/day: 28 (40) <2nd centile - n (%) 100ml/kg/day: 9 (13) 140l/kg/day: 7 (10) <10th centile - n (%) 100ml/kg/day: 21 (31) 140ml/kg/day: 19 (27) Head circumference (cm) at birth - mean (SD) 100ml/kg/day: 25.7 (2.4) 140ml/kg/day: 25.6 (3.8) Length (cm) at birth - mean (SD) 100ml/kg/day: 36.0 (10.9) 140ml/kg/day: 37.4 (12.4) Inclusion criteria VLBW (<1500g), preterm infants who had a peripherally inserted central venous catheter (PICC) and were receiving less than 100ml/kg/day of enteral feeds		necrotising enterocolitis (NEC). Preterm formula (80kcal/100ml) was given to appropriately grown infants >1250g if maternal EBM was not available by day 2 of life. If there were no contraindications, enteral feeds were advanced at 20-30ml/kg/day, as tolerated, and fortified when they reached 140ml/kg/day. Enteral feeds were discontinued if NEC was suspected and resumed at the same volume once NEC and infection were excluded. Power analysis: 140 patients (allowing for 10% mortality and 10% withdrawal from the trial) would be needed to detect a 2-day difference (defined as a clinically significant difference by the authors) in time taken to regain birth weight between groups. Statistical analysis: Conducted based on intention-to-treat. Normally distributed	Weight gain - weight <10th centile at discharge - n/N: 100ml/kg/day: 26/67 140ml/kg/day: 25/70 Linear growth - length (cm) at discharge - mean (SD): 100ml/kg/day (n=67): 44.7 (3.9) 140ml/kg/day (n=70): 43.8 (4.7) Linear growth - length <10th centile at discharge - n/N: 100ml/kg/day: 36/67 140ml/kg/day: 35/70 Head circumference (cm) at discharge - mean (SD): 100ml/kg/day (n=67): 32.0 (2.5) 140ml/kg/day (n=70): 32.1 (2.1) Head circumference <10th centile at discharge - n/N: 100ml/kg/day: 17/67 140ml/kg/day: 14/70	Blinding of outcome assessment: Low risk. Outcome assessors were not blind to treatment allocation but all outcomes are objective. Attrition bias Incomplete outcome data: Low risk. Only 2 infants in the intervention arm were withdrawn from the study; no infants in the intervention arm were withdrawn. Reporting bias Selective reporting: Low risk. All outcomes reported Other bias Other sources of bias: Low risk. None. Other information In both arms, there were 12 protocol violations where PICC was removed at a different time point than specified by the group allocation (median delay of 9.5 hours in intervention group [100ml/kg/day] and median 6.5 hours early in

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Major congenital anomaly; likely to need prolonged PN or intravenous antibiotics after achieving 100ml/kg/day of enteral feeds; death or transfer out of NICU likely to occur before birth weight could be regained		continuous variables were analysed using t-tests and dichotomous and categorical variables were analysed with chi-squared tests, Mann-Whitney U tests and Fisher's exact tests.	Mortality - n/N: 100ml/kg/day: 3/67 140ml/kg/day: 3/70 Duration (days) of hospital stay* - median (IQR): 100ml/kg/day: 49.6 (38.2-69.2) 140ml/kg/day: 53.9 (38.9-71.3) p=0.86 Necrotising enterocolitis - n/N: 100ml/kg/day: 1/67 140ml/kg/day: 3/70 Duration (days) of PN* - median (IQR): 100ml/kg/day: 5.6 (4.5-6.9) 140ml/kg/day: 6.1 (5.2-8.1) p=0.04 Sepsis - central venous catheter-associated late onset sepsis - n/N: 100ml/kg/day: 1/67 140ml/kg/day: 3/70	control group [140ml/kg/day]); results of per-protocol analysis were not significantly different from results of intention-to-treat analysis for primary outcome (time in days to regain birth weight).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				*Not analysed as data is reported as medians	

EBM: expressed breast milk; EN: enteral nutrition; IQR: interquartile range; NEC: necrotising enterocolitis; NICU: neonatal intensive care unit; N: number; PICC: peripherally inserted central venous catheter; PN: parenteral nutrition; ROBINS-I: risk of bias in non-randomised studies of interventions; SD: standard deviation; VLBW: very low brithweight.

Appendix E – Forest plots

Forest plots for review question: What amount of enteral feed (measured in terms of ml/kg/d, or kcal/kg/d, or ratios in relation to PN and enteral feeds) indicates that parenteral nutrition is no longer required?

No meta-analysis was conducted for this review; therefore there are no forest plots.

Appendix F – GRADE tables

GRADE tables for review question: What amount of enteral feed (measured in terms of ml/kg/d, or kcal/kg/d, or ratios in relation to PN and enteral feeds) indicates that parenteral nutrition is no longer required?

Table 5: Clinical evidence profile for stopping PN when EN reached 100ml/kg/day versus stopping PN when EN reached 140ml/kg/day

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	100ml/kg/day	140ml/kg/day	Relative (95% CI)	Absolute	Quality	Importance
Weight gain - time (days) to regain birth weight - All infants (VLBW & ELBW) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	67	70	-	MD 1.5 higher (0.31 to 2.69 higher)	⊕⊕⊕O MODERATE	CRITICAL
Weight gain - time (days) to regain birth weight - VLBW infants (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	41	42	-	MD 0.6 higher (0.8 lower to 2 higher)	⊕⊕⊕O MODERATE	CRITICAL
Weight gain - time (days) to regain birth weight - ELBW infants (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	26	28	-	MD 2.8 higher (0.8 to 4.8 higher)	⊕⊕⊕O MODERATE	CRITICAL
Weight gain - weight (g) at discharge (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	67	70	-	MD 13 higher (191.05 lower to 217.05 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Weight gain - weight <10th centile at discharge												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	100ml/kg/day	140ml/kg/day	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	26/67 (38.8%)	25/70 (35.7%)	RR 1.09 (0.7 to 1.68)	32 more per 1000 (from 107 fewer to 243 more)	⊕⊕OO LOW	CRITICAL
Linear growth - length (cm) at discharge (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	67	70	-	MD 0.9 higher (0.54 lower to 2.34 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Linear growth - length <10th centile at discharge												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	36/67 (53.7%)	35/70 (50%)	RR 1.07 (0.78 to 1.48)	35 more per 1000 (from 110 fewer to 240 more)	⊕⊕OO LOW	CRITICAL
Head circumference (cm) at discharge (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	67	70	-	MD 0.1 lower (0.87 lower to 0.67 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Head circumference <10th centile at discharge												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	17/67 (25.4%)	14/70 (20%)	RR 1.27 (0.68 to 2.37)	54 more per 1000 (from 64 fewer to 274 more)	⊕⊕OO LOW	CRITICAL
Mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	3/67 (4.5%)	3/70 (4.3%)	RR 1.04 (0.22 to 5)	2 more per 1000 (from 33 fewer to 171 more)	⊕⊕OO LOW	IMPORTANT
Necrotising enterocolitis												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	100ml/kg/day	140ml/kg/day	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	1/67 (1.5%)	3/70 (4.3%)	RR 0.35 (0.04 to 3.27)	28 fewer per 1000 (from 41 fewer to 97 more)	⊕⊕OO LOW	IMPORTANT
Central venous catheter-associated late onset sepsis												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	1/67 (1.5%)	3/70 (4.3%)	RR 0.35 (0.04 to 3.27)	28 fewer per 1000 (from 41 fewer to 97 more)	⊕⊕OO LOW	IMPORTANT

CI: confidence interval; ELBW: extremely low birthweight; MD: mean difference; RR: risk ratio; VLBW: very low birthweight.
[1] 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 (3.5).
[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 (3.0).
[3] 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 (3.8).
[4] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MID for dichotomous outcomes (0.8 and 1.25).

Table 6: Clinical evidence profile for stopping PN when EN reached 100ml/kg/day versus stopping PN when EN reached 120ml/kg/day

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	100ml/kg/day	120ml/kg/day	Relative (95% CI)	Absolute	Quality	Importance
Weight gain - time (days) to regain birth weight (Better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50	37	-	MD 3.4 lower (6.45 to 0.35 lower)	⊕OOO VERY LOW	CRITICAL
Weight gain - weight <10th centile - At 36 weeks' post conception												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	33/50 (66%)	34/37 (91.9%)	RR 0.72 (0.58 to 0.9)	257 fewer per 1000 (from 92	⊕OOO VERY LOW	CRITICAL

										fewer to 386 fewer)		
Weight gain - weight <10th centile - At 40 weeks' post conception												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	22/50 (44%)	29/37 (78.4%)	RR 0.56 (0.39 to 0.8)	345 fewer per 1000 (from 157 fewer to 478 fewer)	⊕OOO VERY LOW	CRITICAL
Linear growth - length <10th centile - At 36 weeks' post conception												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	31/50 (62%)	30/37 (81.1%)	RR 0.76 (0.59 to 1)	195 fewer per 1000 (from 332 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
Linear growth - length <10th centile - At 40 weeks' post conception												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	34/50 (68%)	32/37 (86.5%)	RR 0.79 (0.63 to 0.99)	182 fewer per 1000 (from 9 fewer to 320 fewer)	⊕OOO VERY LOW	CRITICAL
Head circumference <10th centile - At 36 weeks' post conception												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/50 (42%)	29/37 (78.4%)	RR 0.54 (0.37 to 0.77)	361 fewer per 1000 (from 180 fewer to 494 fewer)	⊕OOO VERY LOW	CRITICAL
Head circumference <10th centile - At 40 weeks' post conception												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	21/50 (42%)	26/37 (70.3%)	RR 0.6 (0.41 to 0.88)	281 fewer per 1000 (from 84 fewer to 415 fewer)	⊕OOO VERY LOW	CRITICAL
Duration (days) of hospital stay (Better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	50	37	-	MD 7.9 lower (19.1 lower to 3.3 higher)	⊕OOO VERY LOW	IMPORTANT
Necrotising enterocolitis												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	2/50 (4%)	0/37 (0%)	Peto OR 5.82 (0.35 to 97.53)	-	⊕OOO VERY LOW	IMPORTANT
Duration (days) of PN (Better indicated by lower values)												

1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	50	37	-	MD 3.5 lower (9.88 lower to 2.88 higher)	⊕OOO VERY LOW	IMPORTANT
Sepsis												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	17/50 (34%)	16/37 (43.2%)	RR 0.79 (0.46 to 1.34)	91 fewer per 1000 (from 234 fewer to 147 more)	⊕OOO VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio.

[1] Evidence downgraded by 1 due to moderate risk of selection bias (as timeframe for the 2 cohorts differs) and moderate risk of reporting bias as some outcomes are not reported sufficiently to be included in analysis.
[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 (8.3).
[3] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for dichotomous outcomes (0.8 or 1.25).
[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 (29.5).
[5] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MID for dichotomous outcomes (0.8 and 1.25).[6] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses 1 default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (15.5).
[6] Evidence was downgraded for risk of imprecision due to low event rate

Table 7: Clinical evidence profile for stopping PN when EN reached 60kcal/kg/day versus stopping PN when EN reached 100kcal/kg/day

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**60kcal/kg/day**	**100kcal/kg/day**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Weight gain - postnatal growth failure at 40 weeks' postmenstrual age												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50/65 (76.9%)	62/117 (53%)	RR 1.45 (1.17 to 1.8)	238 more per 1000 (from 90 more to 424 more)	⊕OOO VERY LOW	CRITICAL
Linear growth - length (cm) at 40 weeks' postmenstrual age (Better indicated by higher values)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	65	117	-	MD 1 lower (1.81 to 0.19 lower)	⊕OOO VERY LOW	CRITICAL
Head circumference (cm) at 40 weeks' postmenstrual age (Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	60kcal/kg/day	100kcal/kg/day	Relative (95% CI)	Absolute		
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	65	117	-	MD 0.9 lower (0.96 to 0.84 lower)	⊕OOO VERY LOW	CRITICAL
Necrotizing enterocolitis												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	3/65 (4.6%)	2/117 (1.7%)	RR 2.7 (0.46 to 15.75)	29 more per 1000 (from 9 fewer to 252 more)	⊕OOO VERY LOW	IMPORTANT
Late onset sepsis												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	15/65 (23.1%)	30/117 (25.6%)	RR 0.9 (0.52 to 1.55)	26 fewer per 1000 (from 123 fewer to 141 more)	⊕OOO VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio.
[1] Evidence downgraded by 1 due to moderate risk of selection bias (as timeframe for the 2 cohorts differs).
[2] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for dichotomous outcomes (0.8 or 1.25).
[3] 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 (1.3).
[4] 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).

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What amount of enteral feed (measured in terms of ml/kg/d, or kcal/kg/d, or ratios in relation to PN and enteral feeds) indicates that parenteral nutrition is no longer required?

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

Appendix H – Economic evidence tables

Economic evidence tables for review question: What amount of enteral feed (measured in terms of ml/kg/d, or kcal/kg/d, or ratios in relation to PN and enteral feeds) indicates that parenteral nutrition is no longer required?

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

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What amount of enteral feed (measured in terms of ml/kg/d, or kcal/kg/d, or ratios in relation to PN and enteral feeds) indicates that parenteral nutrition is no longer required?

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

Appendix J – Economic analysis

Economic evidence analysis for review question: What amount of enteral feed (measured in terms of ml/kg/d, or kcal/kg/d, or ratios in relation to PN and enteral feeds) indicates that parenteral nutrition is no longer required?

No economic analysis was undertaken for this review question.

Appendix K – Excluded studies

Excluded clinical and economic studies for review question: What amount of enteral feed (measured in terms of ml/kg/d, or kcal/kg/d, or ratios in relation to PN and enteral feeds) indicates that parenteral nutrition is no longer required?

Clinical studies

Table 8: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Als, Heidelise, Gilkerson, Linda, Duffy, Frank H., McAnulty, Gloria B., Buehler, Deborah M., Vandenberg, Kathleen, Sweet, Nancy, Sell, Elsa, Parad, Richard B., Ringer, Steven A., Butler, Samantha C., Blickman, Johan G., Jones, Kenneth J., A three-center, randomized, controlled trial of individualized developmental care for very low birth weight preterm infants: medical, neurodevelopmental, parenting, and caregiving effects, Journal of developmental and behavioral pediatrics : JDBP, 24, 399-408, 2003	Intervention does not meet inclusion criteria - observing and classifying neonate behaviour
Bergsten, G., Aziz, K., Lau, G., Brown, K., Brunet, K., Larsen, B., Energy and protein intakes during the transition of parenteral to enteral nutrition, Paediatrics and Child Health, 16, 40A-41A, 2011	Conference abstract - insufficient information reported
Braudis, Nancy J., Curley, Martha A. Q., Beaupre, Karen, Thomas, Kristi C., Hardiman, Gina, Laussen, Peter, Gauvreau, Kimberlee, Thiagarajan, Ravi R., Enteral feeding algorithm for infants with hypoplastic left heart syndrome poststage I palliation, Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies, 10, 460-6, 2009	Intervention does not meet inclusion criteria - feeding algorithm does not specify the volume or ratio of enteral feeds at which PN should be stopped
Brennan, A. M., Fenton, S., Murphy, B. P., Kiely, M. E., Transition Phase Nutrition Recommendations: A Missing Link in the Nutrition Management of Preterm Infants, Journal of Parenteral and Enteral Nutrition, 42, 343-351, 2018	Intervention does not meet inclusion criteria - classification of nutritional requirements according to the nutritional phase of the neonate compared with chronological age
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	Comparison does not meet inclusion criteria - stopping point for PN was at the discretion of neonatologist (and is not reported)
Camacho, J. E., Santos Oren, M., DuPont, T., Stefanescu, A., Stefanescu, B., Evaluation of a nutrition protocol on infectious and growth	Conference abstract - insufficient information reported

Study	Reason for Exclusion
outcomes, Journal of Investigative Medicine, 66, 176-177, 2018	
Chetry, S., Kler, N., Saluja, S., Soni, A., Feasibilty of early total enteral feeds in very low birthweight infants, Journal of Paediatrics and Child Health, 48, 48, 2012	Conference abstract - insufficient information reported
Christmann, V., Visser, R., Engelkes, M., De Grauw, A. M., Van Goudoever, J. B., Van Heijst, A. F. J., The enigma to achieve normal postnatal growth in preterm infants - Using parenteral or enteral nutrition?, Acta Paediatrica, International Journal of Paediatrics, 102, 471-479, 2013	Intervention does not meet inclusion criteria - nutrition protocol does not specify the volume or ratio of enteral feeds at which PN should be stopped
Collins, Carmel T., Chua, Mei Chien, Rajadurai, Victor S., McPhee, Andrew J., Miller, Lisa N., Gibson, Robert A., Makrides, Maria, Higher protein and energy intake is associated with increased weight gain in pre-term infants, Journal of Paediatrics and Child Health, 46, 96-102, 2010	Intervention does not meet inclusion criteria - feeding approach does not specify the volume or ratio of enteral feeds at which PN should be stopped
Cordero Gonzalez, G., Maynez Gonzalez, C. G., Echaniz-Aviles, M. O., Carrera Muinos, S., Yllescas Medrano, E., Corral Kassian, E., Fernandez Carrocera, L. A., Aggressive parenteral nutrition and mean growth rate in newborns less than 1500 g in a 3rd level hospital in Mexico City, Perinatologia y Reproduccion Humana, 32, 54-59, 2018	Full text not written in English
Culpepper, Christine, Hendrickson, Kendra, Marshall, Susan, Benes, Jessica, Grover, Theresa R., Implementation of Feeding Guidelines Hastens the Time to Initiation of Enteral Feeds and Improves Growth Velocity in Very Low Birth-Weight Infants, Advances in neonatal care : official journal of the National Association of Neonatal Nurses, 17, 139-145, 2017	Intervention does not meet inclusion criteria - feeding guideline does not specify the volume or ratio of enteral feeds at which PN should be stopped
Donovan, Ramona, Puppala, Bhagya, Angst, Denise, Coyle, Bryan W., Outcomes of early nutrition support in extremely low-birth-weight infants, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 21, 395-400, 2006	Comparison does not meet inclusion criteria - does not specify the volume or ratio of enteral feeds at which PN should be stopped
Flidel-Rimon, O., Raz, M., Balla, U., Hofi, L., Juster-Reicher, A., Shinwell, E. S., Early, rapidly progressive enteral nutrition promotes growth of very low birth weight (VLBW) infants, Journal of Maternal-Fetal and Neonatal Medicine, 30, 1227-1231, 2017	Intervention does not meet inclusion criteria - quality improvement project does not specify the volume or ratio of enteral feeds at which PN should be stopped
Garratt, J., Norman, S., Wong, H. L., Goh, S. H., Lam, A., Simmer, K., Nathan, L., McLeod, G., An audit to assess the efficacy of changes to nutritional practice on nutrition and growth	Conference abstract - insufficient information reported

Study	Reason for Exclusion
outcomes in an Australian tertiary neonatal unit, Journal of Paediatrics and Child Health, 51, 15, 2015	
Hanson, Corrine, Sundermeier, Julie, Dugick, Laura, Lyden, Elizabeth, Anderson-Berry, Ann L., Implementation, process, and outcomes of nutrition best practices for infants <1500 g, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 26, 614-24, 2011	Intervention does not meet inclusion criteria - nutrition regimen does not specify the volume or ratio of enteral feeds at which PN should be stopped (differences between arms are rate of advancement of PN and initiation and fortification of enteral feeds)
Hwang, J. Y., Shastry, P., Cayabyab, R., Ramanathan, R., Bhopal, N. S., Morley, E., Dang, T., Chang, M., Mihalek, A., Lin, E., Chavez, T., Luu, M., Garingo, A., Nair, S., Chin, S., Lin, T., Evaluation of a standardised feeding advancement guideline in preterm neonates less than 32 weeks' gestation, Journal of Investigative Medicine, 66 (1), 177, 2018	Conference abstract - insufficient information
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	Intervention does not meet inclusion criteria - nutrition protocol does not specify the volume or ratio of enteral feeds at which PN should be stopped
Johnson, Mark J., Leaf, Alison A., Pearson, Freya, Clark, Howard W., Dimitrov, Borislav D., Pope, Catherine, May, Carl R., Successfully implementing and embedding guidelines to improve the nutrition and growth of preterm infants in neonatal intensive care: a prospective interventional study, BMJ open, 7, e017727, 2017	Comparison does not meet inclusion criteria - does not specify the volume or ratio of enteral feeds at which PN should be stopped
Khanam, Siraj, Khan, Jafar, Sharma, Deepak, Chawla, Deepak, Murki, Srinivas, Nutritional bundle to improve growth outcomes among very low birth weight infants, The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 28, 1851-5, 2015	Intervention does not meet inclusion criteria - PN was stopped at the same volume of enteral feeds in both the intervention and control arms (differences between arms are initiation of PN, quantity of amino acids and lipids, and fortification of enteral feeds)
Kuzma-O'Reilly, Barbara, Duenas, Maria L., Greecher, Coleen, Kimberlin, Lois, Mujsce, Dennis, Miller, Debra, Walker, Donna Jean, Evaluation, development, and implementation of potentially better practices in neonatal intensive care nutrition, Pediatrics, 111, e461-70, 2003	Intervention does not meet inclusion criteria - does not specify the volume or ratio of enteral feeds at which PN should be stopped. Further, description of baseline nutrition practices is insufficient
Kwok, T. C., Dorling, Jon, Ojha, Shalini, Multicentre prospective observational study of	Study design does not meet inclusion criteria - non-comparative

Study	Reason for Exclusion
feeding practices in 30-33 weeks preterm infants, BMJ paediatrics open, 1, e000040, 2017	
Kwok, T. C., Ojha, S., Dorling, J., Early enteral feeding practice in 29+0 to 32+6 weeks preterm infants in two tertiary neonatal units in United Kingdom, European Journal of Pediatrics, 175, 1642, 2016	Conference abstract - full text identified
Lapointe, M., Barrington, K. J., Savaria, M., Janvier, A., Preventing postnatal growth restriction in infants with birthweight less than 1300 g, Acta Paediatrica, 105, e54-9, 2016	Intervention does not meet inclusion criteria - protocol does not specify the volume or ratio of enteral feeds at which PN should be stopped
Low, C. S., Ho, J. J., Nallusamy, R., Impact on growth of a nutrition policy to improve early oral and parenteral nutrition for preterm infants, Journal of Paediatrics and Child Health, 50, 88, 2014	Conference abstract - full text identified
Low, Chuen Siang, Ho, Jacqueline J., Nallusamy, Revathy, Impact of a new aggressive nutrition policy incorporating early introduction of parenteral nutrition and mother's own milk on growth of preterm infants, World journal of pediatrics : WJP, 12, 450-454, 2016	Intervention does not meet inclusion criteria - policy does not specify the volume or ratio of enteral feeds at which PN should be stopped
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	Intervention does not meet inclusion criteria - protocol does not specify the volume or ratio of enteral feeds at which PN should be stopped
Miller, Malki, Donda, Keyur, Bhutada, Alok, Rastogi, Deepa, Rastogi, Shantanu, Transitioning Preterm Infants from Parenteral Nutrition: A Comparison of 2 Protocols, JPEN. Journal of parenteral and enteral nutrition, 41, 1371-1379, 2017	Intervention does not meet inclusion criteria - PN was stopped at the same volume of enteral feeds in both the intervention and control arms. Although the nutritional intake differs between arms as the PN is concentrated in the intervention arm, this is not clearly expressed in terms of a stopping point(differences between arms are volume of PN used during transition, use of dextrose solutions and calorie content of formula if breast milk was unavailable)
Nangia, S., Bishnoi, A., Goel, A., Manda, P., Tiwari, S., Saili, A., Early total enteral feeding in stable very low birth weight infants: A before and after study, Journal of Tropical Pediatrics, 64, 24-30, 2018	Intervention does not meet inclusion criteria - no PN was given in the intervention arm (total enteral feeding started on day 1 of life with no PN)
Narogan, M., Ryumina, I., Grosheva, E., Feeding of very preterm infants: The results application of modern standardized approaches in the practices, Journal of Pediatric Gastroenterology and Nutrition, 62, 859-860, 2016	Conference abstract - insufficient information reported
Olsen, Irene E., Richardson, Douglas K., Schmid, Christopher H., Ausman, Lynne M., Dwyer, Johanna T., Intersite differences in	Insufficient information reported about when PN was stopped at different study sites

Study	Reason for Exclusion
weight growth velocity of extremely premature infants, Pediatrics, 110, 1125-32, 2002	
Olsen, Steven L., Park, Nesha D., Tracy, Kelly, Younger, Darian, Anderson, Betsi, Implementing Standardized Feeding Guidelines, Challenges, and Results, Neonatal network : NN, 37, 218-223, 2018	Comparison does not meet inclusion criteria - stopping point for PN before the standardised guideline was introduced is not specified
Passaro, R. Colby, Savoie, Kate B., Huang, Eunice Y., Use of a Gastroschisis Feeding Guideline to Improve Standardization of Care and Patient Outcomes at an Urban Children's Hospital, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 33, 545-552, 2018	Intervention does not meet inclusion criteria- guideline does not specify stopping point for PN
Perrem, L. M., Semberova, J., O'Sullivan, A., Kieran, E. A., O'Donnell, C. P. F., White, M. J., Miletin, J., Randomised controlled trial comparing PICC removal and parenteral nutrition discontinuation at 100mls/kg/day versus 140mls/kg/day enteral feeding in preterm infants less than 1500g, European Journal of Pediatrics, 175, 1517, 2016	Abstract only - full text has been included
Robinson, J., Gupta, R., Surcouf, J., Knecht, M., Improving preterm infant clinical outcomes through implementation of a feeding protocol, Journal of Investigative Medicine, 67, 529-530, 2019	Abstract only - insufficient information available about feeding protocol.
Rochow, Niels, Fusch, Gerhard, Muhlinghaus, Alexandra, Niesytto, Christian, Straube, Sebastian, Utzig, Norbert, Fusch, Christoph, A nutritional program to improve outcome of very low birth weight infants, Clinical nutrition (Edinburgh, Scotland), 31, 124-31, 2012	Intervention does not meet inclusion criteria - nutrition program does not specify the volume or ratio of enteral feeds at which PN should be stopped
Savoie, Kate B., Bachier-Rodriguez, Marielena, Jones, Tamekia L., Jeffreys, Kristen, Papraniku, Dita, Sevilla, Wednesday Marie A., Tillman, Emma, Huang, Eunice Y., Standardization of Feeding Advancement After Neonatal Gastrointestinal Surgery: Does It Improve Outcomes?, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 31, 810-818, 2016	Intervention does not meet inclusion criteria - feeding advancement strategy does not specify the volume or ratio of enteral feeds at which PN should be stopped
Shim, S. Y., Ahn, H. M., Cho, S. J., Park, E. A., Early aggressive nutrition enhances language development in very low-birthweight infants, Pediatrics International, 56, 845-850, 2014	Intervention does not meet inclusion criteria - PN was stopped at same volume of enteral feeds in both the intervention and control arms
Shinnick, Julia K., Wang, Elizabeth, Hulbert, Cheryl, McCracken, Courtney, Sarson, Gail Yvonne, Piazza, Anthony, Karpen, Heidi, Durham, Megan M., Effects of a Breast Milk Diet on Enteral Feeding Outcomes of Neonates with	Intervention does not meet inclusion criteria - comparison between babies who received 100% of diet from breast milk, between 50 and 100% of diet from breast milk and less than 50% of diet from breast milk. It is unclear if the

Study	Reason for Exclusion
Gastrointestinal Disorders, Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine, 2016	remaining percentage only refers to enteral feeds (e.g., formula) or includes parental nutrition
Shores, D. R., Bullard, J. E., Aucott, S. W., Stewart, F. D., Haney, C., Tymann, H., Miller, M. R., Nonyane, B. A. S., Schwarz, K. B., Implementation of feeding guidelines in infants at risk of intestinal failure, Journal of perinatology : official journal of the California Perinatal Association, 35, 941-8, 2015	Intervention does not meet inclusion criteria - feeding guideline does not specify the volume or ratio of enteral feeds at which PN should be stopped
Snyder, R., Allykas, S., Mennonna, A., Rogido, M. R., Nutrition of the extremely low birth weight (ELBW) infants: Are we making a difference?, Archives of Disease in Childhood, 97, A398, 2012	Conference abstract - insufficient information reported
Stefanescu, Beatrice M., Gillam-Krakauer, Maria, Stefanescu, Andrei R., Markham, Melinda, Kosinski, Jennifer L., Very low birth weight infant care: adherence to a new nutrition protocol improves growth outcomes and reduces infectious risk, Early Human Development, 94, 25-30, 2016	Comparison does not meet inclusion criteria - does not specify the volume or ratio of enteral feeds at which PN should be stopped
Stevens, Timothy P., Shields, Eileen, Campbell, Deborah, Combs, Adriann, Horgan, Michael, La Gamma, Edmund F., Xiong, KuangNan, Kacica, Marilyn, Variation in Enteral Feeding Practices and Growth Outcomes among Very Premature Infants: A Report from the New York State Perinatal Quality Collaborative, American Journal of Perinatology, 33, 9-19, 2016	Insufficient presentation of results - not reported separately based on stopping PN at different volumes or ratios of enteral feeds
Street, Jennifer L., Montgomery, Dianne, Alder, Stephen C., Lambert, Diane K., Gerstmann, Dale R., Christensen, Robert D., Implementing feeding guidelines for NICU patients<2000 g results in less variability in nutrition outcomes, JPEN. Journal of parenteral and enteral nutrition, 30, 515-8, 2006	Intervention does not meet inclusion criteria - feeding guideline does not specify the volume or ratio of enteral feeds at which PN should be stopped
Thoene, Melissa K., Lyden, Elizabeth, Anderson-Berry, Ann, Improving Nutrition Outcomes for Infants < 1500 Grams with a Progressive, Evidenced-Based Enteral Feeding Protocol, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 2018	Intervention does not meet inclusion criteria - feeding protocol does not specify the volume or ratio of enteral feeds at which PN should be stopped
Tillman, Emma M., Norman, Johanna L., Huang, Eunice Y., Lazar, Linda F., Crill, Catherine M., Evaluation of parenteral nutrition-associated liver disease in infants with necrotizing enterocolitis before and after the implementation of feeding guidelines, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 29, 234-7, 2014	Intervention does not meet inclusion criteria - feeding guideline does not specify the volume or ratio of enteral feeds at which PN should be stopped

Study	Reason for Exclusion
Tottman, A. C., Bloomfield, F. H., Cormack, B. E., Harding, J. E., Mohd Slim, M. A., Weston, A. F., Alsweiler, J. M., Relationships between Early Nutrition and Blood Glucose Concentrations in Very Preterm Infants, Journal of Pediatric Gastroenterology and Nutrition, 66, 960-966, 2018	Intervention does not meet inclusion criteria - nutrition protocol does not specify the volume or ratio of enteral feeds at which PN should be stopped
Westin, Vera, Klevebro, Susanna, Domellof, Magnus, Vanpee, Mireille, Hallberg, Boubou, Stoltz Sjostrom, Elisabeth, Improved nutrition for extremely preterm infants - A population based observational study, Clinical nutrition ESPEN, 23, 245-251, 2018	Intervention does not meet inclusion criteria - specifies the ratio of enteral feeds to parental nutrition at which lipid infusion should be stopped, but does not specify the volume or ratio of enteral feeds at which all PN should be stopped
Wilson, D. C., Cairns, P., Halliday, H. L., Reid, M., McClure, G., Dodge, J. A., Randomised controlled trial of an aggressive nutritional regimen in sick very low birthweight infants, Archives of disease in childhood. Fetal and neonatal edition, 77, F4-11, 1997	Intervention does not meet inclusion criteria - does not specify the volume or ratio of enteral feeds at which PN should be stopped. The control arm specifies the ratio of enteral feeds to parental nutrition at which PN amino acids and lipids should be stopped, but not when all PN should be stopped

Economic studies

No economic evidence was identified for this review. See supplementary material D for further information.

Appendix L – Research recommendations

Research recommendations for review question: What amount of enteral feed (measured in terms of ml/kg/d, or kcal/kg/d, or ratios in relation to PN and enteral feeds) indicates that parenteral nutrition is no longer required?

No research recommendations were made for this review question.