National Institute for Health and Care Excellence

Final

Neonatal parenteral nutrition

[A2] Optimal timeframe to start 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

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Optimal timeframe to starting parenteral nutrition

Review question

For those neonates where parenteral nutrition is required, what is the optimal timeframe for doing this?

Introduction

Where provision of parenteral nutrition (PN) support has been agreed, the optimal timeframe for starting such support is important. Delaying provision of PN may lead to increased nutritional deficits, especially for the preterm infant, where body stores are low. However, provision of early PN exposes infants to the recognised risks of PN administration, such as electrolyte imbalance, metabolic disturbance or fluid overload.

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	Early start of PN*
Comparison	Late start of PN*
Outcomes	**Critical** • Neurodevelopmental outcomes (general cognitive abilities at two years corrected age as measured by a validated scale) • Growth: ○ Weight gain (g/kg/d) ○ Linear growth ○ Head circumference (mm) • Infection (including sepsis) • Body composition (measured as lean mass, fat-free mass, fat mass, adipose tissue) • Adverse effects of PN ○ Hyperglycaemia ○ Hypoglycaemia ○ Hypertriglyceridemia ○ Other PN associated liver disease **Important** • Mortality • Duration of hospital stay • Nutritional intake (prescribed PN actually received)

**The decision was made not to specifically define the timeframe of 'early' or 'late' in the protocol because it was recognised that this could be interpreted as the 'time from birth to starting PN' or as 'the time from birth to the*

decision to start PN', which could take into account an initial trial of enteral feeding. This could lead to very different timings and would mean what definitions of 'early' in one study may be 'late' in another. The timing would therefore be extracted directly as reported in the studies and the details of this taken into consideration in the discussion.
PN: Parenteral nutrition

For full details see the review protocol in appendix A.

Clinical evidence

Included studies

Four studies were identified for inclusion in this review (Brownlee 1993, Dongming 2016, Ibrahim 2004, and van Puffelen 2018).

Three randomised controlled trials (RCTs) compared early to late PN in preterm babies. One study (n=129) defined early PN as before 36 hours, and late as 6 days (Brownlee 1993). One study (n=80) defined early PN as before 24 hours and late as 3 days (Dongming 2016). One study (n=32) defined early PN as before 2 hours and late as 48 hours PN (Ibrahim 2004). Due to the similarity in definitions for early PN in the Brownlee study (1993) and late PN in the Ibrahim study (2004), 36 hours and 48 hours respectively, it was not appropriate to pool outcome data.

One RCT (n=209) compared early (within 24 hours of admission) to late (1 week) PN in term babies (van Puffelen 2018).

The included studies are summarised in Table 2.

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

Excluded studies

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

Summary of clinical studies included in the evidence review

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

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes
Brownlee 1993 RCT UK	N=129 <u>Median GA</u> (range): Early: 29 weeks (23-33) Late: 29 weeks (24 – 36) <u>Median BW</u> (range) Early: 1144g (539 – 1748)	Early PN (n= 63) Received PN within the first 36 hours. PN followed standard regimen - 20% intralipid, 0.5 g/kg/day glucose (increased daily to 3.5 g/kg/day)	Late PN (n=66) Received PN on the sixth complete day PN followed standard regimen - 20% intralipid, 0.5 g/kg/day glucose (increased daily to 3.5 g/kg/day)	• Weight gain • Mortality • Nutrient intake

Study	Population	Intervention	Comparison	Outcomes
	Late: 1147g (415 – 1647)	Fluid regimen – started on 75ml/kg/day (increased to 165-180 ml.kg/day) of 10% dextrose solution	Fluid regimen – started on 75ml/kg/day (increased to 165-180 ml.kg/day) of 10% dextrose solution	
Dongming 2016 RCT China	N=80 <u>Mean age</u> Early: 30.3 weeks (SD 2.4) Late: 30.4 weeks (SD 2.2) <u>Mean BW</u> Early: 1140g (SD 220) Late: 1148g (SD 216)	Early PN (n=40) Received PN within the first 24 hours after birth with 20% fat emulsion and 6% amino acid, initial dose 1.5 g/kg/day, daily increments of 0.5 g/kg/day up to 3 g/kg/day	Late PN (n=40) Received PN within 3 days with 5-10% glucose After day 3 received the same intravenous nutrition as the early group.	• Proportion of body weight loss (%) • Hyperglycaemia
Ibrahim 2004 RCT USA	N=32 <u>Mean GA</u> Early: 27 weeks (SD 1.6) Late: 26.8 weeks (SD 1.5) <u>Mean BW</u> Early: 846g (SD 261) Late: 968 (SD 244)	Early PN (n=16) Received PN within the first 2 hours after birth 3.5g/kg/day AA, 3g/kg/day of 20% lipid	Late PN (n=16) Received a solution containing 5 to 10% glucose during the first 48 hours of life After 48 hours PN included 2g/kg/day AA and 0.5g/kg/day lipid. These increased to a maximum of 3.5g/kg/day and 3g/kg/day respectively	• Calorie intake • Mortality • Sepsis
van Puffelen 2018 RCT Belgium, Canada & Netherlands	N=209 <u>Mean GA</u> Early: 38.4 weeks (SD 1.4) Late: 38.6 weeks (SD 1.6) <u>Mean BW</u>	Early PN (n=98) Received PN within 24 hours of admission	Late PN (n=111) Received PN after 1 week	• PICU acquired infections • Hypoglycaemia • Mortality

Study	Population	Intervention	Comparison	Outcomes
	Early: 3193g (SD 538) Late: 3238g (SD 510)			

AA: Amino acid; BW: Birth weight; GA: Gestational age; VLBW: Very low birth weight; PICU: Paediatric intensive care unit; PN: Parenteral nutrition; RCT: Randomised controlled trail; SD Standard deviation.

See appendix D for the full evidence tables.

Quality assessment of clinical outcomes included in the evidence review

GRADE was conducted to assess the quality of outcomes. Evidence was identified for critical and important outcomes. The clinical evidence profiles can be found in 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 medium priority for economic evaluation. However, the identified clinical data was insufficient to inform de-novo economic modelling in this area.

Evidence statements

Clinical evidence statements

Early versus late parenteral nutrition in preterm babies

Weight gain

- Very low quality evidence from 1 RCT (n=129) showed no clinically important difference in weight gain at 2 weeks in babies who had received early PN (36 hours) as compared to late PN (6 days). However, there was uncertainty around the effect: Mean difference (MD) 13g (95% CI -3.92 to 29.92).
- Very low quality evidence from 1 RCT (n=129) showed no clinically important difference in weight gain per day until discharge between babies who received early PN (36 hours) as compared to late PN (6 days). However, there was uncertainty around the effect: MD -2.4g (95% CI -5.3 to 0.5).

Hyperglycaemia

- Very low quality evidence from 1 RCT (n=80) showed a clinically important difference in the number of babies with hyperglycaemia between those who received early PN (24 hours) as compared to late PN (3 days), with fewer occurrences of hyperglycaemia in babies given early PN. However, there was high uncertainty around the effect: Relative risk (RR) 0.33 (95% CI 0.04 to 3.07)

Sepsis

- Very low quality evidence from 1 RCT (n=29) showed no clinically important difference in the number of babies with sepsis between those who received early PN (within 2 hours) as compared to late PN (within 48 hours). However, there was high uncertainty around the effect: RR 0.92 (95% CI 0.41 to 2.07).

Mortality

- Very low quality evidence from 1 RCT (n=129) showed no clinically important difference in mortality between those who received early PN (36 hours) as compared to late PN (6 days). However, there was high uncertainty around the effect: RR 0.82 (95% CI 0.4 to 1.67).
- Very low quality evidence from 1 RCT (n=29) showed a clinically important difference in mortality of babies between those who received early PN (within 2 hours) as compared to late PN (within 48 hours), with fewer occurrences of mortality in those given early PN. However, there was high uncertainty around the effect: RR 0.5 (95% CI 0.05 to 4.98).

Caloric intake

- Moderate quality evidence from 1 RCT (n=32) showed a clinically important difference in calorie intake between babies who received early PN (within 2 hours) as compared to those who received late PN (within 48 hours) with a greater intake associated with a later start of PN: MD 18.4kcal (95% CI 17.22 to 19.58)

Early versus late parenteral nutrition in critically ill, term babies

Paediatric intensive care unit (PICU) acquired infections

- Low quality evidence from 1 RCT (n=209) showed a clinically important difference in the number of babies with PICU acquired infections between those who received early PN (within 24 hours) as compared to late PN (after 1 week), with more occurrences of infection in those given early PN. However, there was uncertainty around the effect: RR 1.89 (95% CI 1.13 to 3.17).
- Low quality evidence from the same RCT (n=38) showed a clinically important difference in the number of babies with PICU acquired infections between those who received early PN (within 24 hours) as compared to late PN (after 1 week), with more occurrences of infection in those given early PN, in a subsample of babies who received no or minimal enteral nutrition. However, there was uncertainty around the effect: RR 1.49 (95% CI 0.81 to 2.73).

Hypoglycaemia during the first week

- Low quality evidence from 1 RCT (n=209) showed a clinically important difference in the number of babies with hypoglycaemia between those who received early PN (within 24 hours) as compared to late PN (after 1 week), with fewer occurrences of hypoglycaemia in those given early PN. However, there was uncertainty around the effect: RR 0.61 (95% CI 0.34 to 1.10).
- Low quality evidence from the same RCT (n=38) showed a clinically important difference in the number of babies with hypoglycaemia between those who received early PN (within 24 hours) as compared to late PN (after 1 week), with fewer occurrences of

hypoglycaemia in those given early PN, in a subsample of babies who received no or minimal enteral nutrition. However, there was uncertainty around the effect: RR 0.33 (95% CI 0.12 to 0.89).

Mortality at 90 days

- Low quality evidence from 1 RCT (n=209) showed a clinically important difference in mortality between those who received early PN (within 24 hours) as compare to late PN (after 1 week), with more occurrences of mortality in those given early PN. However, there was uncertainty around the effect: RR 2.83 (95% CI 1.14 to 7.01).
- Very low quality evidence from 1 RCT (n=38) showed a clinically important difference in mortality between those who received early PN (within 24 hours) as compare to late PN (after 1 week), with more occurrences of mortality in those given early PN, in a subsample of babies who received no or minimal enteral nutrition. However, there was high uncertainty around the effect: RR 2.28 (95% CI 0.55 to 9.54).

Economic evidence statements

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

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the critical outcomes were neurodevelopmental outcomes, growth and body composition. These were agreed as a delay in PN provision is likely to have direct effects on these anthropometric measures (i.e. growth and body composition) and also on the development of the brain. Infection and adverse events were also considered critical as these may occur as part of the practicalities of administration of PN. The committee agreed mortality, duration of hospital stay and nutrient intake should be considered as important outcomes; although influenced by PN other factors may impact on mortality and duration of hospital stay. The committee did not think the nutrient intake was as critical as the effect of intake on the individual baby (i.e. as long as the baby is growing, the detailed nutrient intake in itself is less important due to multiple influences on metabolism).

The quality of the evidence

The quality of evidence for this review was assessed using GRADE methodology. The evidence presented was mainly considered very low quality, indicating high uncertainty in the reliability of the data, with the exception of caloric intake which was considered moderate quality. Evidence was downgraded due to serious or very serious risk of bias associated with unclear methods of allocation, unclear concealment of allocation, and unclear blinding of assessors. In addition, the studies had small sample sizes leading to imprecision.

Another quality issue that the committee considered was the applicability or generalisability of the studies. The committee acknowledged that the evidence presented reflected how clinical practice has changed over time, as the earlier studies started PN later than what would now be considered good clinical practice.

Benefits and harms

The evidence on preterm babies presented in this review was heterogeneous regarding what was defined as early (ranged from 2 hours to 36 hours without very clear descriptions of the enteral feeding regimen). There was also no consistent pattern of findings. While none of the outcomes favoured late administration only a couple of them clearly indicated better outcomes associated with an earlier start of PN (fewer babies with hyperglycaemia and lower

mortality). Other outcomes suggested no clear difference (weight gain and sepsis) and there was a higher caloric intake associated with later start (which is difficult to interpret as favouring either early or late). The evidence for all outcomes, apart from caloric intake, was rated as very low quality, and there were also limitations in its applicability to current clinical practice (most studies were old and were not considered to provide PN formulations that would now be considered optimal). Due to these issues, the committee had low confidence in the evidence and therefore made the recommendations using informal consensus, based on their clinical experience and expertise.

There was one study comparing early (within 24 hours) and late (after 1 week) provision of PN in term babies. There was evidence of greater rates of infection and mortality when PN was provided early compared with late, but lower rates of hypoglycaemia. These differences were observed both in the whole group of babies, and a subgroup who received no or minimal enteral nutrition. However, evidence was all low or very low quality.

The committee noted that some of the included studies specified a timeframe of two hours. They discussed that these were randomised controlled trials, which would have clear protocols and service arrangements in place that would make it possible for the participating centres to adhere to this schedule. The committee agreed that PN should be given as soon as possible once the decision to start PN (see evidence review A1 for the predictors of enteral feeding success) has been made and the earlier the better which was supported by some of the evidence. However, they decided that two hours would be unrealistic and likely to have a large resource impact, and that out-of-hours services could make such a timeframe unachievable. They therefore balanced the benefits of early administration (better nutrition) with the logistic challenges of adhering to a specific timeframe and decided that within eight hours would be both safe and achievable. Based on their experience the committee agreed that eight hours would not detrimentally affect growth outcomes. They also agreed that in certain circumstances, for example when a preterm baby requires PN or a term baby is critically unwell, or a baby has surgical problems, there are several competing treatment priorities; it may be the case that resuscitative measures must take precedence over the provision of PN, and therefore, a recommendation to give PN in under two hours could adversely affect essential treatment prioritisation. The committee provided examples of achievable timeframes from different levels of neonatal units, ranging from three hours to 17 hours; therefore, they agreed that a “within timeframe” recommendation was the most appropriate recommendation, and that based on their clinical experience and expertise, eight hours is both achievable and safe.

The committee discussed the possibility of giving a longer timeframe to start PN, but they were concerned that in practice this would be exceeded. It was agreed that stating a shorter timeframe would highlight the importance of starting PN as soon as possible. However, they agreed that this can vary in different situations, for example a moderately term baby may be tried on enteral feeds for a while before the decision is made for them to get PN. This would therefore be a delay in starting PN. They therefore intentionally phrased this to include the wording of ‘when a baby meets the indications for parenteral nutrition” to indicate that the decision is not always clear cut (as in 8 hours after the baby is born).

The committee discussed whether different timeframes should be recommended for preterm and term babies. They discussed the evidence on critically ill term babies showing an increased risk of infection and mortality, but decreased hypoglycaemia, associated with the earlier start They noted that this evidence was from a pre-planned subgroup analysis (which was small), the parenteral nutrition regimens used were not consistent across the different study sites and the intervention may not have been appropriate because parenteral nutrition would not normally be started on day 1 for critically ill term babies due to restricted fluid volumes and strain on organ systems. They therefore agreed that there was too much uncertainty to suggest a longer time to start based on these findings.

They agreed that without PN preterm babies will develop a nutritional deficit more rapidly than term babies; therefore, the committee decided that it may take longer to come to a decision whether PN in term babies is needed. Reaching this conclusion may take longer because term babies have greater nutritional reserves. However, once the decision is made that PN is needed, it should be started within eight hours, regardless of whether babies are term or preterm.

Having identified the limitations of the evidence, the committee agreed that there is a need for further research in this area in clearly defined populations (i.e. critically ill term babies and surgical babies). Identifying the timeframe for starting PN administration is crucial to ensure optimum care is provided and to improve outcomes for babies. They therefore made a research recommendation, by informal consensus, to address this topic in clearly defined populations.

Cost effectiveness and resource use

There was no existing economic evidence on the cost-effectiveness of an earlier versus later start of PN. The committee acknowledged the inconclusive clinical evidence in this area. However, according to the committee's expertise alongside the limited clinical evidence presented it was concluded that early initiation of PN would have the benefit of adequate nutritional intake to support early development when compared to the late initiation of PN. In regards to costs, earlier initiation of PN is likely to reduce nutritional deficits arising which reduces the costs associated with dealing with those nutritional deficits. The total length of time PN is given for is closely tied to enteral feed tolerance and not just dependant on the time PN is started. Starting PN later would not necessarily result in a shorter duration of PN as the delayed nutritional delivery has the potential to reduce growth. Additionally, the recommendation to start PN earlier is likely to be most easily achieved through the use of standardised PN bags as opposed to bespoke PN bags. In general, standardised PN bags are cheaper than bespoke ones so this may lead to cost savings. Additionally, the committee felt the better outcomes for a baby initiated on earlier PN meant that this was the preferred strategy and therefore the benefits would outweigh the costs.

Other factors the committee took into account

The committee agreed that the use of standardised bags (which is recommended by the committee and discussed in evidence review E) would facilitate neonatal units to achieve this timeframe target because standardised bags would be readily available to administer when the decision has been made to start PN.

References

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Appendices

Appendix A – Review protocols

Review protocol for review question: For those neonates where parenteral nutrition is required, what is the optimal timeframe for doing this?

Table 3: Review protocol – optimal timeframe to starting PN

Field (based on PRISMA-P)	Content
Review question	For those neonates where parenteral nutrition is required, what is the optimal timeframe for doing this?
Type of review question	Intervention
Objective of the review	Where provision of parenteral nutrition (PN) support has been agreed, the optimal timeframe for starting such support is important.
Eligibility criteria – population/disease/condition/issue/domain	Where a decision has been made that PN is needed: 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)	Early start of PN The decision was made not to specifically define the timeframe of 'early' or 'late' in the protocol because it was recognised that this could be interpreted as the 'time from birth to starting PN' or as 'the time from birth to the decision to start PN', which could take into account an initial trial of enteral feeding. This could lead to very different timings and would mean what definitions of 'early' in one study may be 'late' in another. The timing would therefore be extracted directly as reported in the studies and the details of this taken into consideration in the discussion.
Eligibility criteria – comparator(s)/control or reference (gold) standard	Late start of PN

Outcomes and prioritisation	**Critical**
	• Neurodevelopmental outcomes (general cognitive abilities at two years corrected age as measured by a validated scale)
	• Growth:
	  ○ Weight gain (g/kg/d)
	  ○ Linear growth
	  ○ Head circumference (mm)

Field (based on PRISMA-P)	Content
	○ Infection (including sepsis) ○ Body composition (measured as ○ lean mass, fat-free mass, fat mass, ○ adipose tissue) • Adverse effects of PN ○ Hyperglycaemia ○ Hypoglycaemia ○ Hypertriglyceridemia ○ Other PN associated liver disease **Important** • Mortality • Duration of hospital stay • Nutritional intake (prescribed PN actually received)
Eligibility criteria – study design	Systematic reviews of RCTs RCTs Comparative cohort studies (only if RCTs unavailable or limited data to inform decision making). The decision to include comparative cohort studies will be determined for each parameter according to available RCT data Conference abstracts of RCTs will only be considered if no evidence is available from full published RCTs (if no evidence from RCTs or comparative cohort studies available and are recent i.e., in the last 2 years- authors will be contacted for further information).
Other inclusion exclusion criteria	No sample size restriction No date restriction
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) Babies who are critically ill or need surgery Where evidence exists, consideration will be given to the specific needs of population subgroups: Age of baby (first 2 weeks vs. later)

Field (based on PRISMA-P)	Content
	Preterm (Extremely preterm <28 weeks GA; very preterm: 28-31 weeks GA; moderately preterm: 32-36 weeks GA) Birth weight: Low birth weight (< 2500g); very low birth weight (< 1500g) and extremely low birth weight (< 1000g) Possible equality considerations Mothers aged 17 or below Parents or carers whose first language is not English Parents or carers who have learning difficulties 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) Sex of baby Gestation Neurodevelopmental outcomes: Biological (sex, small for gestational age, ethnicity) Neonatal (PVL, IVH, infarct, sepsis, ROP, NEC, antenatal/postnatal steroids, BPD at 36 weeks) Social (SES, substance abuse, alcohol abuse, multiple pregnancy, chorioamnionitis, neglect, maternal age, maternal mental health disorder) Postnatal (epilepsy, age of establishing feeding) Secure venous access
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. A random sample of the references will be sifted by a second reviewer. This sample size will be 10% of the total, or 100 studies if the search identifies fewer than 1000 studies. All disagreements will be resolved by discussion between the two reviewers. The senior systematic reviewer or guideline lead will act as arbiter where necessary.
Data management (software)	Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5).

Field (based on PRISMA-P)	Content
	'GRADEpro' will be used to assess the quality of evidence for each outcome. Low income countries will be downgraded for indirectness. NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists (ROBIS (systematic reviews and meta-analyses); Cochrane risk of bias tool (RCTs or comparative cohort studies); Cochrane risk of bias tool (Non-randomised studies).
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase. Limits (e.g. date, study design): All study designs. Apply standard animal/non-English language filters. No date limit. Supplementary search techniques: No supplementary search techniques were used. See appendix B for full strategies.
Identify if an update	This is not an update
Author contacts	Developer: The National Guideline Alliance 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. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.

Field (based on PRISMA-P)	Content
	Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014.
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Joe Fawke (Consultant Neonatologist and Honorary Senior Lecturer, University Hospitals Leicester NHS Trust), in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from The National Guideline Alliance, undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details of the methods please see supplementary material C.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by The Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by The Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	This review is not registered with PROSPERO

BPD: bronchopulmonary dysplasia; CCTR: Cochrane controlled trials register; CDSR: Cochrane database of systematic reviews; DARE: database of abstracts of reviews of effects; GA: Gestational age; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: health technology assessment; IVH: intraventricular haemorrhage; NEC: necrotising enterocolitis; NGA: National Guidelines Alliance; NHS: National Health Service; NICE: National Institute of Clinical Excellence; NIHR: National Institute for Health Research; NGA: National Guideline Alliance; NHS: National Health Service; PN: Parenteral nutrition; PROSPERO: International prospective register of systematic reviews; PVL: periventricular leukomalacia; RCT: randomised controlled trial; ROBIS; risk of bias in systematic reviews; ROP: retinopathy of prematurity; SES: socioeconomic status.

Appendix B – Literature search strategies

Literature search strategy for review question: For those neonates where parenteral nutrition is required, what is the optimal timeframe for doing this?

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	((Initiat$ or Start$ or Introduc$ or begin$ or commenc$ or inaugurat$ or launch$ or instigat$ or establish$ or set$ up or timing or early or earlier or prompt$ or quick$ or speed$ or rapid$ or fast or delay$ or late? or wait$ or slow$ or postpon$ or put$ off or defer$ or push$ back or belated$) adj5 parenteral$).ti,ab.
16	((Initiat$ or Start$ or Introduc$ or begin$ or commenc$ or inaugurat$ or launch$ or instigat$ or establish$ or set$ up or timing or early or earlier or prompt$ or quick$ or speed$ or rapid$ or fast or delay$ or late? or wait$ or slow$ or postpon$ or put$ off or defer$ or push$ back or belated$) and parenteral$).ti.
17	((Initiat$ or Start$ or Introduc$ or begin$ or commenc$ or inaugurat$ or launch$ or instigat$ or establish$ or set$ up or timing or early or earlier or prompt$ or quick$ or speed$ or rapid$ or fast or delay$ or late? or wait$ or slow$ or postpon$ or put$ off or defer$ or push$ back or belated$) adj5 (PN or SPN or IPN or TPN or STD-PN or IND-PN)).ti,ab.
18	((Initiat$ or Start$ or Introduc$ or begin$ or commenc$ or inaugurat$ or launch$ or instigat$ or establish$ or set$ up or timing or early or earlier or prompt$ or quick$ or speed$ or rapid$ or fast or delay$ or late? or wait$ or slow$ or postpon$ or put$ off or defer$ or push$ back or belated$) adj5 (intravenous$ or intra-venous$ or IV or venous$ or infusion?) adj5 (nutrition$ or feed$ or fed$)).ti,ab.
19	((Initiat$ or Start$ or Introduc$ or begin$ or commenc$ or inaugurat$ or launch$ or instigat$ or establish$ or set$ up or timing or early or earlier or prompt$ or quick$ or speed$ or rapid$ or fast or delay$ or late? or wait$ or slow$ or postpon$ or put$ off or defer$ or push$ back or belated$) and (intravenous$ or intra-venous$ or IV or venous$ or infusion?) and (nutrition$ or feed$ or fed$)).ti.
20	((24 h$ or 24h$) adj5 parenteral$).ti,ab.
21	or/15-20
22	*PARENTERAL NUTRITION/
23	*PARENTERAL NUTRITION, TOTAL/
24	*PARENTERAL NUTRITION SOLUTIONS/
25	or/22-24
26	TIME FACTORS/
27	(Initiat$ or Start$ or Introduc$ or begin$ or commenc$ or inaugurat$ or launch$ or instigat$ or establish$ or set$ up or timing or early or earlier or prompt$ or quick$ or speed$ or rapid$ or fast or delay$ or late? or wait$ or slow$ or postpon$ or put$ off or defer$ or push$ back or belated$).ti.
28	14 and 21
29	14 and 25 and 26
30	14 and 25 and 27
31	or/28-30
32	limit 31 to english language
33	LETTER/
34	EDITORIAL/
35	NEWS/
36	exp HISTORICAL ARTICLE/
37	ANECDOTES AS TOPIC/
38	COMMENT/
39	CASE REPORT/
40	(letter or comment*).ti.
41	or/33-40
42	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
43	41 not 42
44	ANIMALS/ not HUMANS/
45	exp ANIMALS, LABORATORY/
46	exp ANIMAL EXPERIMENTATION/

#	Searches
47	exp MODELS, ANIMAL/
48	exp RODENTIA/
49	(rat or rats or mouse or mice).ti.
50	or/43-49
51	32 not 50

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	((Initiat$ or Start$ or Introduc$ or begin$ or commenc$ or inaugurat$ or launch$ or instigat$ or establish$ or set$ up or timing or early or earlier or prompt$ or quick$ or speed$ or rapid$ or fast or delay$ or late? or wait$ or slow$ or postpon$ or put$ off or defer$ or push$ back or belated$) adj5 parenteral$).ti,ab.
15	((Initiat$ or Start$ or Introduc$ or begin$ or commenc$ or inaugurat$ or launch$ or instigat$ or establish$ or set$ up or timing or early or earlier or prompt$ or quick$ or speed$ or rapid$ or fast or delay$ or late? or wait$ or slow$ or postpon$ or put$ off or defer$ or push$ back or belated$) and parenteral$).ti.
16	((Initiat$ or Start$ or Introduc$ or begin$ or commenc$ or inaugurat$ or launch$ or instigat$ or establish$ or set$ up or timing or early or earlier or prompt$ or quick$ or speed$ or rapid$ or fast or delay$ or late? or wait$ or slow$ or postpon$ or put$ off or defer$ or push$ back or belated$) adj5 (PN or SPN or IPN or TPN or STD-PN or IND-PN)).ti,ab.
17	((Initiat$ or Start$ or Introduc$ or begin$ or commenc$ or inaugurat$ or launch$ or instigat$ or establish$ or set$ up or timing or early or earlier or prompt$ or quick$ or speed$ or rapid$ or fast or delay$ or late? or wait$ or slow$ or postpon$ or put$ off or defer$ or push$ back or belated$) adj5 (intravenous$ or intra-venous$ or IV or venous$ or infusion?) adj5 (nutrition$ or feed$ or fed$)).ti,ab.
18	((Initiat$ or Start$ or Introduc$ or begin$ or commenc$ or inaugurat$ or launch$ or instigat$ or establish$ or set$ up or timing or early or earlier or prompt$ or quick$ or speed$ or rapid$ or fast or delay$ or late? or wait$ or slow$ or postpon$ or put$ off or defer$ or push$ back or belated$) and (intravenous$ or intra-venous$ or IV or venous$ or infusion?) and (nutrition$ or feed$ or fed$)).ti.
19	((24 h$ or 24h$) adj5 parenteral$).ti,ab.
20	or/14-19
21	*PARENTERAL NUTRITION/
22	*TOTAL PARENTERAL NUTRITION/
23	PERIPHERAL PARENTERAL NUTRITION/
24	PARENTERAL SOLUTIONS/
25	INTRAVENOUS FEEDING/
26	or/21-25
27	TIME FACTOR/
28	(Initiat$ or Start$ or Introduc$ or begin$ or commenc$ or inaugurat$ or launch$ or instigat$ or establish$ or set$ up or timing or early or earlier or prompt$ or quick$ or speed$ or rapid$ or fast or delay$ or late? or wait$ or slow$ or postpon$ or put$ off or defer$ or push$ back or belated$).ti.
29	13 and 20
30	13 and 26 and 27
31	13 and 26 and 28
32	or/29-31
33	limit 32 to english language
34	letter.pt. or LETTER/
35	note.pt.
36	editorial.pt.
37	CASE REPORT/ or CASE STUDY/
38	(letter or comment*).ti.
39	or/34-38
40	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
41	39 not 40
42	ANIMAL/ not HUMAN/
43	NONHUMAN/
44	exp ANIMAL EXPERIMENT/
45	exp EXPERIMENTAL ANIMAL/
46	ANIMAL MODEL/
47	exp RODENT/
48	(rat or rats or mouse or mice).ti.

#	Searches
49	or/41-48
50	33 not 49

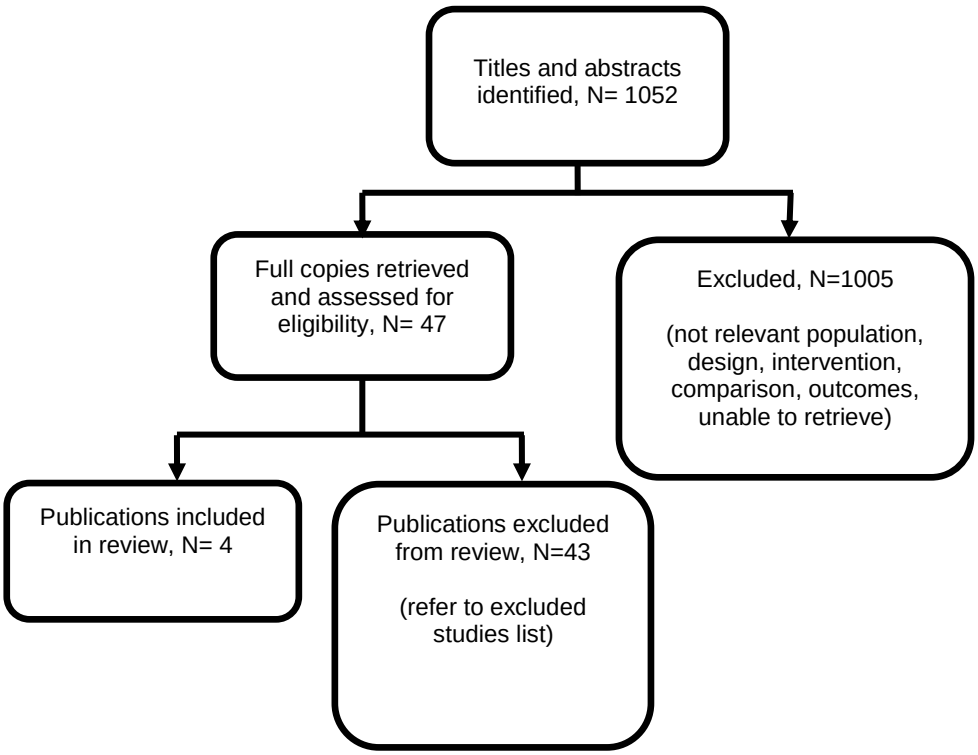
Databases: Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; and Health Technology Assessment

#	Searches
1	MeSH descriptor: [INFANT, NEWBORN] this term only
2	(neonat* or newborn* or new-born* or baby or babies):ti,ab
3	MeSH descriptor: [PREMATURE BIRTH] this term only
4	((preterm* or pre-term* or prematur* or pre-matur*) near/5 (birth? or born)).ab,ti.
5	MeSH descriptor: [INFANT, PREMATURE/
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/
9	(low near/3 birth near/3 weigh* near/5 infan*):ti,ab
10	((LBW or VLBW) near/5 infan*):ti,ab
11	MeSH descriptor: [INTENSIVE CARE, NEONATAL] this term only
12	MeSH descriptor: [INTENSIVE CARE UNITS, NEONATAL] this term only
13	NICU?:ti,ab
14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
15	((Initiat* or Start* or Introduc* or begin* or commenc* or inaugurat* or launch* or instigat* or establish* or set* up or timing or early or earlier or prompt* or quick* or speed* or rapid* or fast or delay* or late? or wait* or slow* or postpon* or put* off or defer* or push* back or belated*) near/5 parenteral*):ti,ab
16	((Initiat* or Start* or Introduc* or begin* or commenc* or inaugurat* or launch* or instigat* or establish* or set* up or timing or early or earlier or prompt* or quick* or speed* or rapid* or fast or delay* or late? or wait* or slow* or postpon* or put* off or defer* or push* back or belated*) near/10 parenteral*).ti.
17	((Initiat* or Start* or Introduc* or begin* or commenc* or inaugurat* or launch* or instigat* or establish* or set* up or timing or early or earlier or prompt* or quick* or speed* or rapid* or fast or delay* or late? or wait* or slow* or postpon* or put* off or defer* or push* back or belated*) near/5 (PN or SPN or IPN or TPN or STD-PN or IND-PN)):ti,ab
18	((Initiat* or Start* or Introduc* or begin* or commenc* or inaugurat* or launch* or instigat* or establish* or set* up or timing or early or earlier or prompt* or quick* or speed* or rapid* or fast or delay* or late? or wait* or slow* or postpon* or put* off or defer* or push* back or belated*) near/5 (intravenous* or intra-venous* or IV or venous* or infusion?) near/5 (nutrition* or feed* or fed*)):ti,ab
19	((Initiat* or Start* or Introduc* or begin* or commenc* or inaugurat* or launch* or instigat* or establish* or set* up or timing or early or earlier or prompt* or quick* or speed* or rapid* or fast or delay* or late? or wait* or slow* or postpon* or put* off or defer* or push* back or belated*) near/10 (intravenous* or intra-venous* or IV or venous* or infusion?) near/10 (nutrition* or feed* or fed*)).ti.
20	((24 h* or 24h*) near/5 parenteral*):ti,ab
21	#15 or #16 or #17 or #18 or #19 or #20
22	MeSH descriptor: [PARENTERAL NUTRITION] this term only
23	MeSH descriptor: [PARENTERAL NUTRITION, TOTAL] this term only
24	MeSH descriptor: [PARENTERAL NUTRITION SOLUTIONS] this term only
25	#22 or #23 or #24
26	MeSH descriptor: [TIME FACTORS] this term only
27	(Initiat* or Start* or Introduc* or begin* or commenc* or inaugurat* or launch* or instigat* or establish* or set* up or timing or early or earlier or prompt* or quick* or speed* or rapid* or fast or delay* or late? or wait* or slow* or postpon* or put* off or defer* or push* back or belated*).ti.
28	#14 and #21
29	#14 and #25 and #26
30	#14 and #25 and #27
31	#28 or #29 or #30

Appendix C – Clinical evidence study selection

Clinical study selection for review question: For those neonates where parenteral nutrition is required, what is the optimal timeframe for doing this?

Figure 1: PRISMA Flow chart of clinical article selection for review question, for those neonates where PN is required, what is the optimal timeframe?



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: For those neonates where parenteral nutrition is required, what is the optimal timeframe for doing this? In babies on parenteral nutrition, what is the optimal frequency of blood sampling and monitoring?

Table 4: Clinical evidence tables for included studies

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Brownlee, K. G., Kelly, E. J., Ng, P. C., Kendall-Smith, S. C., Dear, P. R., Early or late parenteral nutrition for the sick preterm infant?, Archives of disease in childhood, 69, 281-3, 1993 Ref Id 606318 Country/ies where the study was carried out United Kingdom (England) Study type RCT Aim of the study To compare the effect of early parenteral or late parental nutrition in preterm infants with lung disease Study dates January 1990 - November 1991	Sample size n = 129 randomised Early parenteral nutrition (EPN) n = 63 Late parenteral nutrition (LPN) n = 66 n = 104 available for analysis (EPN n = 52 vs LPN n = 52) Characteristics Preterm infants admitted to the Regional Neonatal Intensive Care Unit at St James's University Hospital, Leeds. Gestational age (weeks) - median (range) EPN: 29 (23 to 33) LPN: 29 (24 to 36) Birthweight (g) - median (range)	Interventions Infants allocated to early or late PN when they were between 12 and 24 hours of age. EPN infants receive PN within the first 36 hours. LPN infants received PN on the sixth complete day. PN followed standard regimen Intralipid 20% (KabiVitrum) and either Vamin 9 glucose or Vamin Infant (KabiVitrum) started at a dose of 0.5g/kg/day and increased daily by the same amount to a maximum of 3.5 g/kg/day. Lipid infusions were continuous over 24 hours. Fluid regimen same for both groups	Details Lipid intake reduced to 1.5 g/kg/day if serum bilirubin concentration increased to >200 µmol/l, if the infant had sepsis, or if the C reactive protein concentration was >20 mg/l. Statistical analyses Mann-Whitney U test used for non-normally distributed data and Student's t test for normally distributed data.	Results Weight gain at 2 weeks (g) - mean ±SD EPN (n=52): 88 (49) LPN (n=52): 75 (49) Weight gain/day to discharge - mean ±SD EPN (n=52): 18.6 (7.7) LPN (n=52): 21.0 (9.1) Mortality* (n) EPN: 22 LPN: 14 Nutrient intakes during the first 7 complete days of life EPN (n=63): lipid (10.89 g/kg); Vamin (11.1	Limitations Cochrane risk of bias tool Selection bias: Random sequence generation: Unclear risk. Infants were randomly allocated when they were between 12 and 24 hours, stratified according to gestation and the severity of lung disease (determined by the pressure/shunt product at 12 hours of age) Allocation concealment: High risk. Allocation based on gestation and severity of lung disease, therefore unlikely to be adequately concealed Performance bias Blinding of participants and personnel: Unclear risk. Infants would be unaware of their assignment and it would be likely those responsible for nursing and clinical procedures would not be blinded for safety reasons

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding None reported	EPN: 1144 (539 to 1748) LPN: 1147 (415 to 1647) Inclusion criteria Preterm babies born with birthweight ≤1750g requiring intermittent positive pressure ventilation (IPPV) at 12 hours of age with radiographic features of respiratory distress syndrome Exclusion criteria Preterm infants with severe congenital abnormalities Preterm infants with pulmonary hypoplasia	with 75 ml/kg/day of 10% dextrose solution, increased daily in increments to 165-180 ml/kg/day.		g/kg); energy (1.79 kcal/kg) LPN (n=66): lipid (1.35 g/kg); Vamin (1.4 g/kg); energy (1.29 kcal/kg)	Detection bias Blinding of outcome assessment: Unclear risk. Not clear whether outcome assessors were blinded, however, outcome measures were objective Attrition bias Incomplete outcome data: Low risk. There were no study withdrawals (apart from deaths) Reporting bias Selective reporting: Low risk. All outcomes reported Other bias Other sources of bias: Low risk. None Other information No significant benefit from early PN in terms of weight gain, however at 2 weeks the trend was in favour of the early PN group. *Deaths as a direct result of chronic lung disease: EPN (4); LPN (3). Other deaths due to severe respiratory distress syndrome or pulmonary interstitial emphysema, sepsis, congenital abnormalities.
Full citation	Sample size	Interventions	Details	Results	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Dongming, Lang, Fengran, Zhou, Zhaojun, Zhang, The study of early intravenous nutrition therapy in very low birth weight infants, Pakistan journal of pharmaceutical sciences, 29, 2293-2295, 2016 Ref Id 701728 Country/ies where the study was carried out China Study type RCT Aim of the study To analyse the clinical effect of early intravenous nutrition therapy for very low birth weight infants Study dates June 2013 - June 2015 Source of funding None stated	n = 80 randomised Early parenteral nutrition (EPN): n=40 Late parenteral nutrition (LPN): n=40 Characteristics Infants admitted to the paediatric centre of Linyi People's Hospital. Sex (male) - n EPN: 24 LPN: 25 Gestational age (weeks) range EPN: 28 to 34 LPN: 28 to 34 Age (weeks) - mean ±SD EPN: 30.2 (2.4) LPN: 30.4 (2.2) Birth weight (g) - range EPN: 995 to 1500 LPN: 990 to 1500 Weight (g) - mean ±SD EPN: 1140 (220) LPN: 1148 (216) Inclusion criteria	EPN infants receive PN within the first 24 hours after birth with 20% fat emulsion and 6% paediatric amino acid, initial dose 1.5g/kg/day and daily increment was 0.5g/kg/day up to 3.0g/kg/day LPN infants received PN within 3 days after birth, with 5 to 10% glucose and same intravenous nutrition as the EPN group	Infants without infection and severe asphyxia were on minimal feeds within 24 hours after birth. The amount of intravenous nutrition was reduced gradually with increased mi intake. Once oral milk calorie was up to 292.6 KJ/kg/day, intravenous nutrition provision was stopped and infants given full enteral nutrition Statistical analyses Where data were presented as means and standard deviations (SDs), comparisons were made using the t test. If data were presented as a percentage (%), the chi-squared test was used.	Proportion of body weight loss (%) - mean ±SD EPN (n=40): 7.7 (1.5) LPN (n=40): 10.6 (3.3); p<0.05 Hyperglycaemia - n/N EPN: 1/40 LPN: 3/40	Cochrane risk of bias tool Selection bias: Random sequence generation: Unclear risk. Infants were randomly allocated immediately after birth, however no details provided on the randomisation Allocation concealment Unclear risk. Infants were randomly divided between both groups, however no details provided on the randomisation Performance bias Blinding of participants and personnel: Unclear risk. Infants would be unaware of their assignment and it would be likely those responsible for nursing and clinical procedures would not be blinded for safety reasons Detection bias Blinding of outcome assessment: Unclear risk. Unclear whether outcome assessors were blinded, however, outcomes were measured objectively Attrition bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Very low birthweight infants Oral and written consent obtained from the parents prior to treatment. Exclusion criteria Digestive system malformations Cyanotic congenital heart disease Congenital metabolic disease				Incomplete outcome data: Low risk. There were no study withdrawals Reporting bias Selective reporting: Low risk. All outcomes reported Other bias Other sources of bias: Low risk. None. Other information Early intravenous nutrition therapy in VLBW infants positively associated with a reduction in malnutrition and reducing the proportion of body weight loss.
Full citation Ibrahim, Hassan M., Jeroudi, Majied A., Baier, R. J., Dhanireddy, Ramasubbareddy, Krouskop, Richard W., Aggressive early total parental nutrition in low-birth-weight infants, Journal of perinatology : official journal of the California Perinatal Association, 24, 482-6, 2004 Ref Id 606418	Sample size n = 32 randomised Early parenteral nutrition (EPN) = 16 versus Late parenteral nutrition (LPN) = 16 29 analysed (EPN n = 14 vs LPN n = 15) Characteristics Preterm infants admitted to the regional neonatal intensive care unit at the regional	Interventions Infants allocated to early or late PN at 1 hour of age. All infants received IVH prophylaxis indomethacin. The EPN group started within the first 2 hours after birth, received 3.5 g/kg/day amino acids and 3/g/kg/day of 20% intralipid. The LPN group started on a solution containing	Details Water intake, glucose, and electrolytes were ordered by the attending physician and were not dictated by a protocol. Glucose intake was adjusted according to chemical estimates. Power analysis Sample size of 16 per treatment group to detect a difference of 30% in the mean	Results Caloric intake (kcal/kg/day) in the first 5 days of life - mean ±SEM EPN (n=15): 78.2 (0.42) LPN (n=14): 59.8 (0.43) Mortality - n EPN: 1 LPN: 2 Sepsis EPN: 6	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Unclear risk. Infants were randomly allocated immediately after birth, however no details provided on the randomisation Allocation concealment: Low risk. Infants were randomised to groups by numbers placed in sealed envelopes.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out US Study type RCT Aim of the study To compare nitrogen balance and biochemical tolerance of early aggressive versus late total parenteral nutrition in very low birth weight infants over the first week of life Study dates July 2001 to April 2002 Source of funding None stated	neonatal intensive care unit at Louisiana State University Health Sciences Centre. Gestational age (weeks) - mean ±SD EPN: 27 (1.6) LPN: 26.8 (1.5) Birthweight (g) - mean ±SD EPN: 846 (261) LPN: 968 (244) 5-minute Apgar score - median (range) EPN: 7 (3 to 8) LPN: 6 (3 to 8) Sex (male) - n/N EPN: 10/16 LPN: 9/16 Inclusion criteria Preterm infants with a birth weight between 501 to 1250g with a gestational age of 24 to 32 weeks who required mechanical ventilation for respiratory disease syndrome. Infants enrolled at 1 hour of age whose	5 to 10% glucose during the first 48 hours of life, then 2g/kg/day amino acid and 0.5g/kg/day intralipid to a maximum of 3.5g/kg/day and 3g/kg/day, respectively.	nitrogen balance, with 80% power. Statistical analyses Student's t-test for two independent samples was used to compare means for parametric data. Non-parametric categorical data were assessed using Fisher's exact test. The Wilcoxon sum-of-rank test was used for non-normally distributed data, and a two-way ANOVA was used for repeated measures.	LPN: 7	Performance bias Blinding of participants and personnel: Unclear risk. Infants would be unaware of their assignment and it would be likely those responsible for nursing and clinical procedures would not be blinded for safety reasons Detection bias Blinding of outcome assessment: Unclear risk. Unclear whether outcome assessors were blinded, however, outcomes were measured objectively Attrition bias Incomplete outcome data: Low risk. There were no study withdrawals (apart from deaths) Reporting bias Selective reporting: Low risk. All outcomes reported Other bias Other sources of bias: Low risk. None. Other information Intake of 3.5g/k/d AA and 3g/k/d IL immediately after birth can be tolerated without

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	clinical conditions seemed to preclude oral feedings for a period of at least 5 to 7 days. Exclusion criteria Infants with major congenital anomalies, twin-to-twin transfusions, maternal diabetes treated with insulin, placenta previa, placenta abruption, or maternal history of drug abuse were not eligible.				metabolic or respiratory complications. SD calculated from SEM provided
Full citation van Puffelen, E., Vanhorebeek, I., Joosten, K. F. M., Wouters, P. J., Van den Berghe, G., Verbruggen, Scat, Early versus late parenteral nutrition in critically ill, term neonates: a preplanned secondary subgroup analysis of the PEPaNIC multicentre, randomised controlled trial, The lancet child and adolescent health, 2, 505-515, 2018 Ref Id 1009152 Country/ies where the study was carried out	Sample size n = 209 Early parenteral nutrition (EPN): n=98 Late parenteral nutrition (LPN): n=111 Characteristics Sex (male) - n/N EPN: 58/98 LPN: 62/11 Gestational age (weeks) - mean (SD) EPN: 38.4 (1.35) LPN: 38.6 (1.55) Age at randomisation (days) - median (IQR) EPN: 2 (0-8)	Interventions Parenteral nutrition was given if less than 80% of local age and weight-specific calorie targets were being received from enteral nutrition. Dose and composition of parenteral nutrition was based on local protocols. The EPN group started parenteral nutrition within 24 hours of admission. The LPN group started parenteral nutrition 1 week after admission. This group received a	Details No or minimal enteral nutrition was defined as unable to receive enteral nutrition or only receiving trophic feeding (<40ml per day and 80ml per week). Power analyses Whole trial was powered to detect differences in new infections. Retrospective power calculation was done for the planned subgroup analysis based on observed differences in new infections (one-tailed test, α 0.05 = 79.6%)	Results All critically ill, term neonates PICU-acquired infections - n/N EPN: 30/98 LPN: 18/111 Hypoglycaemia during first week - n/N EPN: 14/98 LPN: 26/111 Mortality at 90 days - n/N EPN: 15/98 LPN: 6/111	Limitations Cochrane risk of bias tool Selection bias: Random sequence generation: Low risk. Central computerised randomisation. Permuted blocks of 10 according to age and diagnosis on admission. (taken from Fivez 2016) Allocation concealment: Unclear risk. Block size unknown to medical and research teams but does not report concealment method (e.g., sealed, opaque envelopes) (taken from Fivez 2016) Performance bias: Blinding of participants and personnel: Unclear risk.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Beligum, Canada & Netherlands Study type RCT (preplanned subgroup analysis) Aim of the study Whole trial: To investigate the effect of giving parenteral nutrition within 24 hours of admission to paediatric intensive care compared with delaying parenteral nutrition for a week. Preplanned subgroup analysis: To investigate the above in critically ill, term neonates (≤28 days old). Study dates June 2012 - July 2015 Source of funding Flemish Agency for Innovation through Science and Technology; Methusalem-Programme Flemish Government; European Research Council; Fonds NutsOhra; Stichting Agis-Zorginnovatie; the Sophia Research Foundation	LPN: 3 (1-13) Birthweight (g) - mean (SD) EPN: 3193 (538) LPN: 3238 (510) Inclusion criteria Whole trial: Critically ill children aged from term newborn (gestational age ≥37 weeks) to 17 years who had a medium or high risk of malnutrition and were admitted to one of three paediatric intensive care units (and expected to have a length of stay >24 hours; taken from Fivez 2016). Preplanned subgroup analysis: Critically ill term neonates (gestational age ≥37 weeks and ≤28 days old) who had a medium or high risk of malnutrition and were admitted to one of three paediatric intensive care units (and expected to have a length of stay >24 hours; taken from Fivez 2016). Exclusion criteria	dextrose (5%) and saline solution during the first week to match fluid administration of the early group and received trace elements, minerals and vitamins to prevent refeeding syndrome.	Statistical analyses Two-sided p values of less than 0.05 were considered as statistically significant for all analyses and there were no corrections for multiple testing. Results were reported as odds ratios, hazard ratios, or β, with corresponding 95% confidence intervals. Methods for univariate analyses are not reported.	Critically ill, term neonates receiving no or minimal enteral nutrition PICU-acquired infections - n/N EPN: 16/23 LPN: 7/15 Hypoglycaemia during first week - n/N EPN: 4/23 LPN: 8/15 Mortality at 90 days - n/N EPN: 7/23 LPN: 2/15	Infants would be unaware of their assignment and it would be likely those responsible for nursing and clinical procedures would not be blinded for safety reasons Detection bias: Blinding of outcome assessment: Low risk. Outcome assessors and investigators not directly involved in the paediatric ICU were not informed of treatment allocation Attrition bias: Incomplete outcome data: Low risk. There were no study withdrawals (apart from deaths) or missing data Reporting bias: Selective reporting: Low risk. All outcomes reported in protocol are reported in paper. Other bias: Other sources of bias: Low risk. None Other information Baseline characteristics differed between groups (late group slightly older at admission, had lower PIM2 scores and lower risk of mortality). This was corrected for in multivariate analyses,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Not critically ill enough to need nutritional support; STRONGkids score <2 on admission; 'do not resuscitate' instructions at admission; ketoacidotic or hyperosmolar coma; inborn metabolic disease requiring specific diet; previously needed parenteral nutrition for more than 7 days before admission; transfer from another unit after a stay >7 days; readmitted after previous enrolment; enrolment in another trial (taken from Fivez 2016).				which show largely the same pattern of results.

ANOVA: analysis of variance; EPN: early parenteral nutrition; IPPV: intermittent positive pressure ventilation; IVH: intraventricular haemorrhage; LPN: late parenteral nutrition; PICU: Paediatric intensive care unit; PN: parenteral nutrition; RCT: randomised controlled trial; SD: standard deviation; SEM: standard error of the mean; US: United States; VLBW: very low birth weight.

Appendix E – Forest plots

Forest plots for review question: For those neonates where parenteral nutrition is required, what is the optimal timeframe for doing this?

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

Appendix F – GRADE tables

GRADE tables for review question: For those neonates where parenteral nutrition is required, what is the optimal timeframe for doing this?

Table 5: Clinical evidence profile for early versus late delivery of parenteral nutrition in preterm babies

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early PN	Late PN	Relative (95% CI)	Absolute		
Weight gain at 2 weeks (g) (follow-up mean 2 weeks; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	63	66	-	MD 13 higher (3.92 lower to 29.92 higher)	⊕OOO VERY LOW	CRITICAL
Weight gain per day to discharge (Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	63	66	-	MD 2.4 lower (5.3 lower to 0.5 higher)	⊕OOO VERY LOW	CRITICAL
Hyperglycaemia												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/40 (2.5%)	3/40 (7.5%)	RR 0.33 (0.04 to 3.07)	50 fewer per 1000 (from 72 fewer to 155 more)	⊕OOO VERY LOW	CRITICAL
Sepsis												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/14 (42.9%)	7/15 (46.7%)	RR 0.92 (0.41 to 2.07)	37 fewer per 1000 (from 275 fewer to 499 more)	⊕OOO VERY LOW	CRITICAL
Mortality - 36 hours versus 6 days (follow-up median 8 days)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early PN**	**Late PN**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	11/63 (17.5%)	14/66 (21.2%)	RR 0.82 (0.4 to 1.67)	38 fewer per 1000 (from 127 fewer to 142 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Mortality - 2 hours versus 48 hours												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/16 (6.3%)	2/16 (12.5%)	RR 0.5 (0.05 to 4.98)	62 fewer per 1000 (from 119 fewer to 498 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Caloric intake in first five days of life (kcal/kg/day) (follow-up mean 5 days; Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16	16	-	MD 18.4 higher (17.22 to 19.58 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: confidence interval; PN: parenteral nutrition; RR: risk ratio.
[1] Very serious risk of bias, evidence downgraded due to unclear risk of allocation and selection bias. No details provided regarding methods of allocation or randomisation. Unclear risk of performance and detection bias, unclear if care personnel or assessors were blinded to treatment.
[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 (24)
[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 (4.6)
[4] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MID for dichotomous outcomes, (0.8 and 1.25).
[5] Serious risk of bias, evidence downgraded due to unclear risk of selection bias, no details provided regarding methods of randomisation. Unclear risk of performance and detection bias, unclear if care personnel or assessors were blinded to treatment.

Table 6: Clinical evidence profile for early versus late parenteral nutrition in critically ill, term babies

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early PN**	**Late PN**	**Relative (95% CI)**	**Absolute**		
PICU acquired infection - whole sample												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early PN	Late PN	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30/98 (30.6%)	18/111 (16.2%)	RR 1.89 (1.13 to 3.17)	144 more per 1000 (from 21 more to 352 more)	⊕⊕OO LOW	CRITICAL
PICU acquired infection - no/minimal EN												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16/23 (69.6%)	7/15 (46.7%)	RR 1.49 (0.81 to 2.73)	229 more per 1000 (from 89 fewer to 807 more)	⊕⊕OO LOW	CRITICAL
Hypoglycaemia in first week - whole sample												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/98 (14.3%)	26/111 (23.4%)	RR 0.61 (0.34 to 1.1)	91 fewer per 1000 (from 155 fewer to 23 more)	⊕⊕OO LOW	CRITICAL
Hypoglycaemia in first week - no/minimal EN												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/23 (17.4%)	8/15 (53.3%)	RR 0.33 (0.12 to 0.89)	357 fewer per 1000 (from 59 fewer to 469 fewer)	⊕⊕OO LOW	CRITICAL
Mortality at 90 days - whole sample												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/98 (15.3%)	6/111 (5.4%)	RR 2.83 (1.14 to 7.01)	99 more per 1000 (from 8 more to 325 more)	⊕⊕OO LOW	IMPORTANT
Mortality at 90 days - no/minimal EN												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/23 (30.4%)	2/15 (13.3%)	RR 2.28 (0.55 to 9.54)	171 more per 1000 (from 60 fewer to 1000 more)	⊕OOO VERY LOW	IMPORTANT

CI: confidence interval; EN: enteral nutrition; PICU: paediatric intensive care unit; PN: parenteral nutrition; RR: risk ratio.

[1] Serious risk of bias, evidence downgraded due to unclear risk of allocation concealment and performance bias.

[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 2 due to very serious imprecision, 95% confidence interval crosses two default MID for dichotomous outcomes, (0.8 and 1.25).

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: For those neonates where parenteral nutrition is required, what is the optimal timeframe for doing this?

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: For those neonates where parenteral nutrition is required, what is the optimal timeframe for doing this?

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

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: For those neonates where parenteral nutrition is required, what is the optimal timeframe for doing this?

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

Appendix J – Economic analysis

Economic analysis for review question: For those neonates where parenteral nutrition is required, what is the optimal timeframe for doing this?

No economic analysis was undertaken for this review question.

Appendix K – Excluded studies

Excluded studies for review question: For those neonates where PN is required what is the optimal timeframe for doing this?

Clinical studies

Table 7: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Abdou, R. M., Weheiba, H. M. I., The effect of early versus late lipid infusion in parenteral nutrition on the biochemical and cortical auditory evoked potential parameters in preterm neonates, Egyptian Pediatric Association Gazette, 2018	Study intervention does not meet protocol eligibility criteria - early vs late lipids; infants receive glucose and dextrose from birth and amino acids from day 2.
Aroor, Amitha R., Krishnan, Lalitha, Reyes, Zenaida, Fazallulah, Muhammed, Ahmed, Masood, Khan, Ashfaq A., Al-Farsi, Yahya, Early versus Late Parenteral Nutrition in Very Low Birthweight Neonates: A retrospective study from Oman, Sultan Qaboos University medical journal, 12, 33-40, 2012	Study design does not meet the inclusion criteria, this is a retrospective cohort study. Additionally, only AA are started early compared to late, all other constituents are given at the same time point.
Bishay, M., Lakshminarayanan, B., Arnaud, A., Garriboli, M., Cross, K. M., Curry, J. I., Drake, D., Kiely, E. M., De Coppi, P., Pierro, A., Eaton, S., The role of parenteral nutrition following surgery for duodenal atresia or stenosis, Pediatric Surgery International, 29, 191-5, 2013	Population does not meet the inclusion criteria.
Blanco, Cynthia Liudmilla, Falck, Alison, Green, Belinda Kay, Cornell, John E., Gong, Alice Kim, Metabolic responses to early and high protein supplementation in a randomized trial evaluating the prevention of hyperkalemia in extremely low birth weight infants, The Journal of pediatrics, 153, 535-40, 2008	Intervention does not meet the inclusion criteria; study focus is on amino acid dose and starting time.
Blanco, Cynthia Liudmilla, Gong, Alice Kim, Green, Belinda Kay, Falck, Alison, Schoolfield, John, Liechty, Edward A., Early changes in plasma amino acid concentrations during aggressive nutritional therapy in extremely low birth weight infants, The Journal of pediatrics, 158, 543-548.e1, 2011	Intervention does not meet the inclusion criteria; study focus is on amino acid dose and starting time.
Bulbul, Ali, Okan, Fusun, Bulbul, Lida, Nuhoglu, Asiye, Effect of low versus high early parenteral nutrition on plasma amino acid profiles in 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, 25, 770-6, 2012	Intervention does not meet the inclusion criteria; both groups received early PN.
Can, E., Bulbul, A., Uslu, S., Comert, S., Bolat, F., Nuhoglu, A., Evaluation of two different types of parenteral nutrition on early growth of preterm infants, Early Human Development, 86, S85, 2010	Conference abstract.

Study	Reason for Exclusion
Can, Emrah, Bulbul, Ali, Uslu, Sinan, Bolat, Fatih, Comert, Serdar, Nuhoglu, Asiye, Early Aggressive Parenteral Nutrition Induced High Insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP3) Levels Can Prevent Risk of Retinopathy of Prematurity, Iranian journal of pediatrics, 23, 403-10, 2013	Intervention does not meet the inclusion criteria; both groups started PN at the same time.
Chan, S. H. T., Johnson, M. J., Vollmer, B., Early nutrition and neurodevelopmental outcomes in very preterm infants: A systematic review and meta-analysis, Developmental Medicine and Child Neurology, 56, 42-43, 2014	Conference abstract.
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	Intervention does not meet the inclusion criteria; the nutrition strategy includes EN.
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	Study design does not meet inclusion criteria; retrospective chart review.
Elstgeest, Liset E., Martens, Shirley E., Lopriore, Enrico, Walther, Frans J., te Pas, Arjan B., Does parenteral nutrition influence electrolyte and fluid balance in preterm infants in the first days after birth?, PLoS ONE, 5, e9033, 2010	Outcomes do not meet the inclusion criteria: Serum sodium, potassium levels and fluid balance.
Fivez, T, Kerklaan, D, Verbruggen, S, Vanhorebeek, I, Verstraete, S, Tibboel, D, Guerra, Gg, Wouters, Pj, Joffe, A, Joosten, K, Mesotten, D, Berghe, G, Impact of withholding early parenteral nutrition completing enteral nutrition in pediatric critically ill patients (PEPaNIC trial): study protocol for a randomized controlled trial, Trials, 16, 202, 2015	Protocol paper.
Geary, C. A., Fonseca, R. A., Caskey, M. A., Malloy, M. H., Improved growth and decreased morbidities in <1000 g neonates after early management changes, Journal of perinatology : official journal of the California Perinatal Association, 28, 347-53, 2008	Intervention does not meet the inclusion criteria; both groups received early PN at the same time.
Genoni, G., Binotti, M., Monzani, A., Bernascone, E., Stasi, I., Bona, G., Ferrero, F., Nonrandomised interventional study showed that early aggressive nutrition was effective in reducing postnatal growth restriction in preterm infants, Acta Paediatrica, International Journal of Paediatrics, 106, 1589-1595, 2017	Intervention does not meet the inclusion criteria; both intervention and comparative historical cohorts started PN on day 1 of life.
Haghedooren, R., Jenniskens, M., Guiza, F., Verbruggen, S., Guerra, G., Joosten, K., Langouche, L., Van Den Berghe, G., Prevalence and prognostic value of abnormal liver test	Study design does not meet protocol eligibility criteria - conference abstract.

Study	Reason for Exclusion
results in critically ill children and the impact of nutrition hereon, Critical Care, 22, 2018	
Heimler, Ruth, Bamberger, Janine M., Sasidharan, Ponthenkandath, The effects of early parenteral amino acids on sick premature infants, Indian journal of pediatrics, 77, 1395-9, 2010	Intervention does not meet the inclusion criteria; study focus is on Amino Acids.
Ho, Man-Yau, Yen, Y. u-Hsuan, Hsieh, Mao-Chih, Chen, Hsiang-Yin, Chien, Shu-Chen, Hus-Lee, Shing-Mei, Early versus late nutrition support in premature neonates with respiratory distress syndrome, Nutrition (Burbank, Los Angeles County, Calif.), 19, 257-60, 2003	Intervention does not meet the inclusion criteria; study focus is on Amino Acids.
Jimenez, Lissette, Mehta, Nilesh M., Duggan, Christopher P., Timing of the initiation of parenteral nutrition in critically ill children, Current Opinion in Clinical Nutrition and Metabolic Care, 20, 227-231, 2017	Study design does not meet protocol eligibility criteria - not a systematic review.
Joffe, Ari, Anton, Natalie, Lequier, Laurance, Vandermeer, Ben, Tjosvold, Lisa, Larsen, Bodil, Hartling, Lisa, Nutritional support for critically ill children, Cochrane Database of Systematic Reviews, 2016	Participants do not meet the inclusion criteria; children aged 1 to 18 years.
Kennedy, K. A., Tyson, J. E., Chamnanvanikij, S., Early versus delayed initiation of progressive enteral feedings for parenterally fed low birth weight or preterm infants, The Cochrane database of systematic reviews, CD001970, 2000	Intervention does not fit the inclusion criteria; timing of EN feeding.
Kotsopoulos, K., Benadiba-Torch, A., Cuddy, A., Shah, P. S., Safety and efficacy of early amino acids in preterm <28 weeks' gestation: Prospective observational comparison, Journal of Perinatology, 26, 749-754, 2006	Intervention does not meet the inclusion criteria; study focus is on Amino Acids.
Leenders, Erika K. S. M., de Waard, Marita, van Goudoever, Johannes B., Low- versus High-Dose and Early versus Late Parenteral Amino-Acid Administration in Very-Low-Birth-Weight Infants: A Systematic Review and Meta-Analysis, Neonatology, 113, 187-205, 2018	Systematic review - references cross-checked.
Loys, C. M., Maucort-Boulch, D., Guy, B., Putet, G., Picaud, J. C., Hays, S., Extremely low birthweight infants: how neonatal intensive care unit teams can reduce postnatal malnutrition and prevent growth retardation, Acta Paediatrica, 102, 242-8, 2013	Intervention does not meet the inclusion criteria; comparison includes earlier introduction of lipids and protein and EN.
Mamunes,P., Baden,M., Bass,J.W., Nelson,J., Early intravenous feeding of the low birth weight neonate, Pediatrics, 43, 241-250, 1969	Interventions does not meet the inclusion criteria; early intravenous (IV group) versus delayed oral feedings (fasted group).
Morgan, Jessie, Young, Lauren, McGuire, William, Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants, Cochrane Database of Systematic Reviews, 2014	Intervention does not meet the inclusion criteria; timing of EN feeding.
Moyses, H. E., Johnson, M. J., Cornelius, V., Leaf, A. A., Is there any benefit to starting total parenteral nutrition early in very low birth weight	Conference abstract.

Study	Reason for Exclusion
infants? A systematic review, Proceedings of the Nutrition Society, 70, E259, 2011	
Moyses, Helen E., Johnson, Mark J., Leaf, Alison A., Cornelius, Victoria R., Early parenteral nutrition and growth outcomes in preterm infants: a systematic review and meta-analysis, The American journal of clinical nutrition, 97, 816-26, 2013	Systematic review, references checked for inclusion. Article is in Chinese.
Radmacher, P. G., Lewis, S. L., Adamkin, D. H., Early amino acids and the metabolic response of ELBW infants (< or = 1000 g) in three time periods, Journal of perinatology : official journal of the California Perinatal Association, 29, 433-7, 2009	Intervention does not meet the inclusion criteria; the study focus is on Amino Acids.
Rao, S., Rao, U., Jape, G., Early versus late parnteral nutrition in critically ill full term neonates: A systematic review, Journal of Paediatrics and Child Health, 53, 49, 2017	Conference abstract.
Ribed Sanchez, A., Romero Jimenez, R. M., Sanchez De Orgaz, M. C., De Juan, A., Tovar Pozo, M., Diaz Garzon, J., Sanjurjo Saez, M., Early aggressive parenteral nutrition in preterm infants, International Journal of Clinical Pharmacy, 35, 983, 2013	Conference abstract.
Stensvold, Hans Jorgen, Strommen, Kenneth, Lang, Astri M., Abrahamsen, Tore G., Steen, Eline Kjorsvik, Pripp, Are H., Ronnestad, Arild E., Early Enhanced Parenteral Nutrition, Hyperglycemia, and Death Among Extremely Low-Birth-Weight Infants, JAMA pediatrics, 169, 1003-10, 2015	Study design does not meet the inclusion criteria; observational cohort study.
te Braake, F. W. J., van den Akker, C. H. P., Riedijk, M. A., van Goudoever, J. B., Parenteral amino acid and energy administration to premature infants in early life, Seminars in Fetal and Neonatal Medicine, 12, 11-18, 2007	Non-systematic review.
Tewari, Vishal Vishnu, Dubey, Sachin Kumar, Kumar, Reema, Vardhan, Shakti, Sreedhar, C. M., Gupta, Girish, Early versus Late Enteral Feeding in Preterm Intrauterine Growth Restricted Neonates with Antenatal Doppler Abnormalities: An Open-Label Randomized Trial, Journal of tropical pediatrics, 2017	Intervention does not meet the inclusion criteria; babies receive breast milk.
Tim-Aroon, Thipwimol, Harmon, Heidi M., Nock, Mary L., Viswanathan, Sreekanth K., McCandless, Shawn E., Stopping Parenteral Nutrition for 3 Hours Reduces False Positives in Newborn Screening, The Journal of pediatrics, 167, 312-6, 2015	Intervention does not meet the inclusion criteria; study focus is on Amino Acids.
Trintis,J., Donohue,P., Aucott,S., Outcomes of early parenteral nutrition for premature infants, Journal of Perinatology, 30, 403-407, 2010	Intervention does not meet the inclusion criteria; study focus is on Amino Acids.
Trivedi,A., Sinn,J.K., Early versus late administration of amino acids in preterm infants receiving parenteral nutrition, Cochrane Database of Systematic Reviews, -, 2013	Intervention does not meet the inclusion criteria; study focus is on Amino Acids.

Study	Reason for Exclusion
Valentine, C. J., Fernandez, S., Rogers, L. K., Gulati, P., Hayes, J., Lore, P., Puthoff, T., Dumm, M., Jones, A., Collins, K., Curtiss, J., Hutson, K., Clark, K., Welty, S. E., Early amino-acid administration improves preterm infant weight, Journal of Perinatology, 29, 428-432, 2009	Intervention does not meet the inclusion criteria; study focus is on Amino Acids.
van Puffelen, Esther, Hulst, Jessie M., Vanhorebeek, Ilse, Dulfer, Karolijn, Van den Berghe, Greet, Verbruggen, Sascha C. A. T., Joosten, Koen F. M., Outcomes of Delaying Parenteral Nutrition for 1 Week vs Initiation Within 24 Hours Among Undernourished Children in Pediatric Intensive Care: A Subanalysis of the PEPaNIC Randomized Clinical Trial, JAMA network open, 1, e182668, 2018	Results not presented separately for neonates.
Vanhorebeek, Ilse, Verbruggen, Sascha, Casaer, Michael P., Gunst, Jan, Wouters, Pieter J., Hanot, Jan, Guerra, Gonzalo Garcia, Vlasselaers, Dirk, Joosten, Koen, Van den Berghe, Greet, Effect of early supplemental parenteral nutrition in the paediatric ICU: a preplanned observational study of post-randomisation treatments in the PEPaNIC trial, The Lancet. Respiratory medicine, 5, 475-483, 2017	Study design does not meet inclusion criteria; observational study (follow up study of PEPaNIC trial - PN in critically ill children).
Verstraete, Soren, Verbruggen, Sascha C., Hordijk, Jose A., Vanhorebeek, Ilse, Dulfer, Karolijn, Guiza, Fabian, van Puffelen, Esther, Jacobs, An, Leys, Sandra, Durt, Astrid, Van Cleemput, Hanna, Eveleens, Renate D., Garcia Guerra, Gonzalo, Wouters, Pieter J., Joosten, Koen F., Van den Berghe, Greet, Long-term developmental effects of withholding parenteral nutrition for 1 week in the paediatric intensive care unit: a 2-year follow-up of the PEPaNIC international, randomised, controlled trial, The Lancet. Respiratory medicine, 7, 141-153, 2019	Study intervention does not meet protocol eligibility criteria - PN administered as supplement to EN.
Weiler, Hope A., Fitzpatrick-Wong, Shirley C., Schellenberg, Jeannine M., Fair, Denise E., McCloy, Ursula R., Veitch, Rebecca R., Kovacs, Heather R., Seshia, Mary M., Minimal enteral feeding within 3 d of birth in prematurely born infants with birth weight < or = 1200 g improves bone mass by term age, The American journal of clinical nutrition, 83, 155-62, 2006	Intervention does not meet inclusion criteria; study focus is on Amino Acids.
Whitfield, M. F., Spitz, L., Milner, R. D., Clinical and metabolic consequences of two regimens of total parenteral nutrition in the newborn, Archives of Disease in Childhood, 58, 168-75, 1983	Interventions do not meet inclusion criteria; study compares sequential versus continuous regimens.

Economic studies

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

Appendix L – Research recommendations

Research recommendations for review question: For those neonates where PN is required what is the optimal timeframe for doing this?

Research recommendation

What is the optimal timeframe for starting parenteral nutrition in term babies who are critically ill or who require surgery?

Why this is important

Where provision of parenteral nutrition (PN) has been agreed, the optimal timeframe for starting such support is important. Delaying the provision of PN may lead to increased nutritional deficits, and this is especially important in preterm babies who lack nutritional stores and for babies who are critically ill or babies who require surgery. Some evidence was identified for preterm babies; however, there was little evidence for term babies who are critically ill or babies requiring surgery.

Table 8: Research recommendation rationale

Research question	For neonates where parenteral nutrition is required, what is the optimal timeframe for doing this?
Why is this needed	
Importance to 'patients' or the population	High: The timing of starting PN administration is crucial in order to avoid nutritional deficits and exposure to risks associated with PN administration.
Relevance to NICE guidance	High: Only four, randomised studies were identified for inclusion in this review. The evidence that was identified was limited in quality and did not reflect current good clinical practice. Findings from the included studies were inconsistent and the studies did not provide data to determine the optimal timing of starting PN administration in clearly defined populations (particularly in term babies who are critically ill or require surgery).
Relevance to the NHS	High: Identifying the timeframe for starting PN in clearly defined populations (i.e. critically ill term babies and surgical babies) is critical for the provision of optimum care and to ensure optimal growth, development and survival.
National priorities	The NHS Long term plan (launched in January 2019) for the next 10 years highlights 'enabling everyone to get the best start in life' as one of the main areas to improve the quality of patient care and health outcomes.
Current evidence base	The guideline identified that there is a gap in the evidence base. The four studies had small sample sizes (450 babies included across four studies), and were considered to be very low quality, with a high risk of bias. Furthermore, the studies were heterogeneous with regard to definitions for early PN and were not considered to provide PN formulations that would now be considered optimal.

Research question	For neonates where parenteral nutrition is required, what is the optimal timeframe for doing this?
Equality	Some parents and carers may need information in different languages and there may be cultural sensitivities around PN. Those with learning disabilities may need additional support.
Feasibility	This would require NHS ethical approval but would be feasible and safe to conduct.
Other comments	

NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PN: Parenteral nutrition

Table 9: Research recommendation modified PICO table

Criterion	Explanation
Population	• Critically ill babies born > 37 weeks of gestational age, up to 28 days after their due date (term babies) including those requiring surgery.
Intervention	Early start of PN (defined as within 48 hours)
Comparator	Late start of PN (later than 2 days)
Outcomes	Survival to discharge Rates of nosocomial infections Incidence of hypoglycaemia Neurodevelopment Growth Infection Body composition Adverse effects of PN
Study design	Randomised controlled trial
Timeframe	From birth to discharge
Additional information	The decision was made not to specifically defined the timeframe of 'early' or 'late' in the protocol because it was recognised that this could be interpreted as the 'time from birth to starting PN' or as 'the time from birth to the decision to start PN', which could take into account an initial trial of enteral feeding. This could lead to very different timings and would mean what definitions of 'early' in one study may be 'late' in another. The timing would therefore be extracted directly as reported in the studies and the details of this taken into consideration in the discussion.

PN: Parenteral nutrition