National Institute for Health and Care Excellence

Draft for consultation

Neonatal parenteral nutrition

[B] Venous access

NICE guideline tbc

Evidence reviews

September 2019

Draft for Consultation

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.

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ISBN:

Contents

Venous access for parenteral nutrition in preterm and term babies

Review question

What overall osmolality (concentration of calcium and glucose/dextrose), in parenteral nutrition can determine whether to administer centrally or peripherally?

Introduction

Parenteral Nutrition (PN) is administered intravenously, and either peripheral or central venous lines can be used. Central lines are often inserted through the umbilical vessels in new-born infants; however, lines can also be inserted peripherally; they are used for drug infusions as well as PN.

Central lines are positioned in a large bore central vein. This allows infusion of more concentrated substances securely; and in general these lines are able to be left in situ for a longer period of time if carefully maintained. However, they require a greater degree of technical skill for insertion; and can be more prone to serious complications such as being a source of late onset sepsis. Peripheral lines are very commonly used for a number of indications on neonatal units and are generally easier to insert. They have a shorter life span. As the infusions are running into a smaller peripheral vein, there is greater risk of the infusion causing direct damage to the vein (thrombophlebitis) or leaking out into the surrounding tissues (extravasation). This is particularly true where there is a higher concentration (as measured by osmolality or osmolarity depending on the unit of measurement) of the PN infusion fluid, such as a formulation with a higher dextrose load.

Current practice varies with regards to the administration of PN centrally or peripherally, and this review aims to look at whether the osmolality or osmolarity of PN can help guide whether it is safe to administer peripherally or if PN should be administered centrally.

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	• Intervention 1: A specified level of osmolality or osmolarity, (or percentage of dextrose/glucose or calcium) given centrally • Intervention 2: A specified level of osmolality or osmolarity, (or percentage of dextrose/glucose or calcium) given peripherally
Comparison	• Comparison 1: The same specified level of osmolality or osmolarity, (or percentage of dextrose or calcium) given in the intervention arm, but given peripherally • Comparison 2: A different level of osmolality or osmolarity, (or percentage of dextrose or calcium) given in the intervention arm, given peripherally
Outcomes	**Critical**

	• Tissue damage • Extravasation (skin ulceration, limb swelling) • Bloodstream infections • Thrombophlebitis **Important** • None

1 For full details see the review protocol in appendix A.

2 Clinical evidence

3 Included studies

4 No randomised controlled trials (RCTs) were identified; therefore, observational studies were
5 included to inform decision making.

6 One observational study was identified for this review (Cies 2014).

7 This study compared a PN formulation with osmolarity > 900 mOsm/L to a PN formulation
8 with osmolarity ≤ 900 mOsm/L in babies receiving peripherally inserted catheters (Cies
9 2014).

10 The included study is summarised in Table 2.

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

13 Excluded studies

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

16 Summary of clinical studies included in the evidence review

17 A summary of the study included in this review is presented in Table 2.

18 **Table 2: Summary of included studies**

Study	Population	Intervention	Comparison	Outcomes	Comments
Cies 2014 Observational study US	N=236 NICU patients receiving PN Median GA (range): Exposed: 32 weeks (22-42) Non-exposed: 34 weeks (22-42)	Exposed group (n=77) Patients received PPN with Osm > 900 mOsm/L Group received PPN for a total of 204 days (Range: 1-11 days)	Non-exposed group (n=159) Patients received PPN Osm ≤ 900 mOsm/L Group received PPN for a total of 464 days (Range: 1-14 days) Median days of PPN per	• Line related event (defined as any episode of an infiltrate, extravasation, or thrombophlebitis) – these were classified as grades 1 to 4 according to severity from least severe to most severe (grades 1 and 2 of line-related events were grouped	Study included children aged from birth to 21 years with separate analysis conducted for NICU and non-NICU patients. Only data for the NICU group is included. Analysis was conducted according to events per number of patient days of PPN and rate per 100

Study	Population	Intervention	Comparison	Outcomes	Comments
		Median days of PPN per baby (range): 2(1-11)	baby (range): 2(1-14)	together in the analysis)	patient days of PPN.

GA: Gestational age; NICU: Neonatal intensive care unit; Osm: Osmolarity; PPN: Peripheral parenteral nutrition; PN: Parenteral nutrition; US: United States.

See appendix D for full evidence tables.

Quality assessment of clinical outcomes included in the evidence review

GRADE was conducted to assess the quality of outcomes. Evidence was identified for critical outcomes; no important outcomes were selected by the committee. 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 topic was prioritised for economic modelling. However, no economic modelling was undertaken for this review because the clinical data were insufficient to inform the economic analysis.

Evidence statements

Clinical Evidence statements

Line related events per number of patient days of PN (grade 1-2)

- Very low quality evidence from 1 observational study (n=236) showed no clinically important difference in babies receiving PN with osmolarity > 900 mOsm/L versus PN with osmolarity ≤ 900 mOsm/L: Relative risk (RR) 1.06 (95% CI 0.90, 1.24)

Line related events per number of patient days of PN (grade 3)

- Very low quality evidence from 1 observational study (n=236) showed no clinically important difference (there were no events in either arm) in babies receiving PN with osmolarity > 900 mOsm/L versus PN with osmolarity ≤ 900 mOsm/L: Risk difference (RD) 0.00 (-0.01 to 0.01, 0 events in both groups).

Line related events per number of patient days of PN (grade 4)

- Very low quality evidence from 1 observational study (n=236) showed a clinically important difference in the number of Grade 4 line related events in babies receiving PN with osmolarity > 900 mOsm/L as compared to those receiving PN with osmolarity ≤ 900 mOsm/L; with fewer events in those receiving PN with osmolality > 900 mOsm/L. However, there was high uncertainty around the effect: Peto odds ratio (POR) 0.24 (95% CI 0.00, 16.71)

Line related events per number of patient days of PN (all grades)

- Very low quality evidence from 1 observational study (n=236) showed no clinically important difference in babies receiving PN with osmolarity > 900 mOsm/L versus PN with osmolarity ≤ 900 mOsm/L. However, there was uncertainty around the effect: RR 1.06 (95% CI 0.90, 1.24)

Rate of line related events per 100 patient days of PN (<32 weeks' GA)

- Very low quality evidence from 1 observational study (n=236) showed no clinically important difference in babies receiving PN with osmolarity > 900 mOsm/L versus PN with osmolarity ≤ 900 mOsm/L. However, there was uncertainty around the effect: RR 1.07 (95% CI 0.80, 1.43)

Rate of line related events per 100 patient days of PN (32-37 weeks' GA)

- Very low quality evidence from 1 observational study (n=236) in NICU babies who received PN for a median of 2 days showed no clinically important difference in babies receiving PN with osmolarity > 900 mOsm/L versus PN with osmolarity ≤ 900 mOsm/L. However, there was uncertainty around the effect: RR 1.24 (95% CI 0.92, 1.67)

Rate of line related events per 100 patient days of PN (>37 weeks' GA)

- Very low quality evidence from 1 observational study (n=236) showed no clinically important difference in babies receiving PN with osmolarity > 900 mOsm/L versus PN with osmolarity ≤ 900 mOsm/L. However, there was uncertainty around the effect: RR 0.85 (95% CI 0.64, 1.13)

Economic evidence statements

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

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee prioritised a number of critical outcomes including extravasation, bloodstream infections and thrombophlebitis. These outcomes were selected because they are clinically relevant adverse events which are directly associated with the concentration of the fluid given through a centrally and peripherally inserted catheter for PN in babies. Extravasation (leakage of fluid into the body), bloodstream infections and thrombophlebitis can all occur when the vein is weakened either by multiple insertion or by higher concentration of the fluid. No important outcomes were selected by the committee.

The quality of the evidence

The quality of evidence for this review was assessed using GRADE methodology. The evidence presented was considered very low quality indicating high uncertainty in the reliability of the data. This was due to very serious risks of bias associated with the selection of participants, classification of the interventions and the measurement of outcomes. The study was retrospective, it was unclear whether the start and follow-up of the intervention was the same for all participants, and the measurement of outcomes may have been minimally influenced due to knowledge of the intervention. The evidence was also considered very low quality due to serious and very serious imprecision, whereby the 95% confidence intervals crossed either one or both default minimally important differences (MIDs).

Benefits and harms

The committee discussed the evidence and noted that the pattern of results suggested that PN with an osmolarity greater than 900 mOsm/L could be given peripherally for a short duration without adverse events. However, they were concerned that this was based on only one study and that the evidence for all outcomes was assessed as very low quality according to GRADE criteria. Given their limited confidence in the evidence, the committee made the recommendations by informal consensus and based on their experience and expertise.

The committee agreed, based on their experience and expertise, that in general a central venous catheter should be used when giving PN. The committee discussed the risks and benefits associated with centrally and peripherally inserted catheters in clinical practice. They noted how the use of a centrally inserted catheter can reduce the number of peripheral cannulae inserted and hence the number of procedures the baby is exposed to and the number of skin punctures required. Serious potential complications such as central venous thrombosis and extravasation (including into the thoracic cavity and pericardium) are rare but must be considered with centrally inserted catheters, as they are not associated with peripheral catheters. Even though babies with central venous catheters are thought to be at greater risk of sepsis the committee agreed, based on their knowledge, that this risk would be outweighed by the greater risk of localised thrombosis and extravasation for peripheral administration. The committee also discussed the perspective of parents and acknowledged the possible increased distress due the potential to require multiple insertions of peripheral cannulae. The committee agreed, based on expertise that on balance the use of centrally inserted catheters would be the preferred option for clinical practice. Deviation from this would be on an individual risk/benefit basis which could be discussed with the baby's parents.

The committee discussed the evidence presented which indicated that PN with an osmolarity greater than 900 mOsm/L could be given peripherally for a short duration without adverse events, and specifically up to 1425 mOsm/L (Cies 2014). Therefore, the use of peripherally inserted catheters could be considered for use with PN of higher osmolality or osmolarity. Despite this the committee acknowledged that although severe extravasation injuries are rare with peripherally inserted catheters, the likelihood of these may be increased, depending on the osmolality and type of fluid infused. As a result, PN is not usually given peripherally in clinical practice when the osmolality or osmolarity is high and they decided to only recommend peripheral insertion in particular circumstances. Based on their knowledge of clinical practice, the committee noted that the insertion of central catheters requires more skill and starting PN may be delayed if the necessary expertise required for insertion is unavailable. Peripherally inserted catheters do not require the same level of expertise for insertion and can generally be inserted quicker than a central line, and so can be used for more immediate PN administration; therefore, if the use of a central venous catheter is likely to delay administration of PN, then peripheral venous access should be used. To avoid repeated insertion of peripheral lines (due to their shorter life span) the committee also noted that it could be used for short term administration of PN or for a short time to avoid

interruption (for instance if the expertise for a more complicated insertion is not immediately available) in the provision of PN.

Only if neither of the above options are possible, or there is a prolonged need for PN (for example in babies with a critical illness), then surgically inserted central catheters could be recommended, the committee agreed this by informal consensus and based on their clinical experience. . This would be because only a small proportion of babies would require this, it would need to be carried out by a surgeon (which would cause delay) and being a more invasive procedure than non-surgically placed central catheters it would also be a riskier procedure for the baby.

Having identified the limitations of the evidence, the committee agreed that there is a need for further research in this area because of the risks associated with administering PN in babies through a centrally or peripherally inserted catheter. It is important to identify whether osmolality or osmolarity of PN can help guide whether it is safe to administer PN peripherally or centrally to avoid adverse events and to provide babies with optimum care. The committee therefore made a research recommendation by informal consensus to address this topic.

Cost effectiveness and resource use

No economic studies were identified which were applicable to this review question. This review was prioritised for economic modelling. However, clinical data was insufficient to inform the economic analysis.

The committee agreed that peripheral venous line insertion is cheap, quick and has a relatively low risk of sepsis when compared to central venous lines. However, the risk of localised thrombosis and extravasation are greater for peripheral administration which may require expensive management and result in detrimental impact on health related quality of life and a quality-adjusted life year (QALY) loss.

The committee further explained that a central venous catheter to administer PN is a relatively expensive procedure, requires expertise for insertion; and although rare can be associated with significant adverse events. However, the committee noted that in most babies the overall intervention costs are likely to be similar between a one-off central venous catheter insertion and multiple daily peripheral line placements since PN is generally given over a number of days. The committee further explained that since a baby may require peripheral venous reinsertion each day for PN and multiple extravasation injuries, which although mostly minor add to the handling and distress of the baby and family. This method creates multiple opportunities for infections that may require expensive NHS care. The committee also pointed out that peripheral line placement is painful and requires more frequent handling of babies which may have a detrimental impact on babies' health-related quality of life and a QALY loss. Moreover, the committee also discussed the perspective of parents who would likely experience more distress due to the multiple insertion points associated with peripherally inserted catheters. Consequently the use of a central venous catheter may lead to the improvements not only in babies' but also in parents' health related quality of life and a QALY gain. Overall, given the above considerations and that the benefits outweighed the harms, the committee was of a view that generally a central venous catheter was potentially a more cost-effective approach for PN when compared with a peripheral venous administration for PN.

The committee further explained that in some instances the use of peripheral venous administration of PN is likely to represent a cost-effective use of NHS resources. Mainly, this is expected to be when the duration of PN is likely to be short or in cases where central venous access is unavailable and there is a potential for delays in starting PN. The committee explained that where the duration of PN is short the high cost associated with a central venous catheter insertion could be avoided. Also, the delays in PN can exacerbate problems which may require expensive NHS care.

Similarly, the committee agreed based on experience that surgically inserted central catheters could be considered to ensure positive outcomes for babies in whom central access is required but is not accessible through other means; or where long-term PN is anticipated. In this small proportion of babies a surgically inserted central catheter for PN would be deemed a cost effective approach.

The committee further explained that the recommendations in this area reflect practice across many units and as such the resource impact to the NHS, if any, is likely to be negligible.

References

Cies 2014

Cies, Jeffrey J., Moore, Wayne S., 2nd, Neonatal and pediatric peripheral parenteral nutrition: what is a safe osmolarity? Nutrition in clinical practice: official publication of the American Society for Parenteral and Enteral Nutrition, 29, 118-24, 2014

Appendices

Appendix A – Review protocols

Review protocol for review question: What overall osmolality (concentration of calcium and glucose/dextrose), in parenteral nutrition can determine whether to administer centrally or peripherally?

Field (based on PRISMA-P	Content
Review question	What overall osmolality (concentration of calcium and glucose/dextrose), in parenteral nutrition can determine whether to administer centrally or peripherally?
Type of review question	Intervention
Objective of the review	Peripherally inserted catheters are an alternative option to central catheters, and are considered easier to insert and less expensive. However, administration of PN peripherally can result in complications such as thrombophlebitis due to high osmotic content of the formula. The aim of this review is to determine what osmolality, dextrose/glucose or calcium levels in PN determine whether to administer centrally of peripherally
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)	Intervention 1 A specified level of osmolality or osmolarity, (or percentage of dextrose/glucose or calcium) given centrally Intervention 2 A specified level of osmolality or osmolarity, (or percentage of dextrose/glucose or calcium) given peripherally
Eligibility criteria – comparator(s)/control or reference (gold) standard	Comparison 1 The same specified level of osmolality or osmolarity, (or percentage of dextrose or calcium) given in the intervention arm, but given peripherally Comparison 2 A different level of osmolality or osmolarity (or percentage of dextrose or calcium) given peripherally
Outcomes and prioritisation	**Critical** • Tissue damage

Field (based on PRISMA-P	Content
	• Extravasation (skin ulceration, limb swelling) • Bloodstream infections • Thrombophlebitis **Important** None
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 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 is available and are recent i.e., published 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) 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	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.

Field (based on PRISMA-P	Content
Data management (software)	Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. Low income countries will be downgraded for indirectness. NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists (ROBIS (systematic reviews and meta-analyses); Cochrane risk of bias tool (RCTs or comparative cohort studies); Cochrane risk of bias tool (Non-randomised studies).
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.

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

CDSR: Cochrane Database of Systematic Reviews; CCTR: Cochrane Controlled Trials Register; DARE: Database of Abstracts of Reviews of Effects; GA: gestational age; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; NIHR: National Institute for Health Research; NHS: National health service; PN: Parenteral nutrition; PRISMA-P: preferred reporting items for systematic review and meta-analysis protocols; PROSPERO: International prospective register of systematic reviews; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: risk of bias in systematic reviews; SD: standard deviation

Appendix B – Literature search strategies

Literature search strategy for review question: What overall osmolality (concentration of calcium and glucose/dextrose), in parenteral nutrition can determine whether to administer centrally or peripherally?

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	OSMOLAR CONCENTRATION/
16	osmolalit$.ti,ab.
17	osmolarit$.ti,ab.
18	(osmolar adj3 concentrat$).ti,ab.
19	(ionic adj3 strength?).ti,ab.
20	or/15-19
21	CALCIUM/
22	CALCIUM, DIETARY/
23	calcium.mp.
24	or/21-23
25	GLUCOSE/
26	glucose.mp.
27	dextrose.mp.
28	or/25-27
29	CATHETERIZATION, CENTRAL VENOUS/
30	CENTRAL VENOUS CATHETERS/
31	(central$ adj3 (line? or catheter$ or access$ or route? or administ$)).ti,ab.
32	(central$ adj3 (nutrition$ or feed$ or fed$)).ti,ab.
33	(central$ adj3 (vein? or venous$ or intravenous$ or intra-venous$ or IV or infusion?)).ti,ab.
34	CVC?.ti,ab.
35	or/29-34
36	exp CATHETERIZATION, PERIPHERAL/
37	(peripheral$ adj3 (line? or catheter$ or access$ or route? or administ$)).ti,ab.
38	(peripheral$ adj3 (nutrition$ or feed$ or fed$)).ti,ab.
39	(peripheral$ adj3 (vein? or venous$ or intravenous$ or intra-venous$ or IV or infusion?)).ti,ab.
40	PICC?.ti,ab.
41	or/36-40
42	PARENTERAL NUTRITION/
43	PARENTERAL NUTRITION, TOTAL/
44	PARENTERAL NUTRITION SOLUTIONS/
45	(parenteral$ adj3 (nutrition$ or feed$ or fed$)).ti,ab.
46	or/42-45
47	PARENTERAL NUTRITION/ae [Adverse Effects]
48	CATHETERIZATION, CENTRAL VENOUS/ae [Adverse Effects]
49	CENTRAL VENOUS CATHETERS/ae [Adverse Effects]
50	exp CATHETERIZATION, PERIPHERAL/ae [Adverse Effects]
51	14 and 20 and (35 or 41)
52	14 and 24 and (35 or 41)
53	14 and 28 and (35 or 41)
54	14 and 35 and 41 and 46
55	14 and (35 or 41) and 47
56	14 and 46 and (48 or 49 or 50)
57	or/51-56

#	Searches
58	limit 57 to english language
59	LETTER/
60	EDITORIAL/
61	NEWS/
62	exp HISTORICAL ARTICLE/
63	ANECDOTES AS TOPIC/
64	COMMENT/
65	CASE REPORT/
66	(letter or comment*).ti.
67	or/59-66
68	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
69	67 not 68
70	ANIMALS/ not HUMANS/
71	exp ANIMALS, LABORATORY/
72	exp ANIMAL EXPERIMENTATION/
73	exp MODELS, ANIMAL/
74	exp RODENTIA/
75	(rat or rats or mouse or mice).ti.
76	or/69-75
77	58 not 76

1 Databases: Embase; and Embase Classic

#	Searches
1	NEWBORN/
2	(neonat$ or newborn$ or new-born$ or baby or babies).ti,ab.
3	PREMATURITY/
4	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 (birth? or born)).ab,ti.
5	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 infan$).ti,ab.
6	(pre#mie? or premie or premies).ti,ab.
7	exp LOW BIRTH WEIGHT/
8	(low adj3 birth adj3 weigh$ adj5 infan$).ti,ab.
9	((LBW or VLBW) adj5 infan$).ti,ab.
10	NEWBORN INTENSIVE CARE/
11	NEONATAL INTENSIVE CARE UNIT/
12	NICU?.ti,ab.
13	or/1-12
14	"OSMOLARITY AND OSMOLALITY"/
15	exp OSMOLALITY/
16	exp OSMOLARITY/
17	osmolalit$.ti,ab.
18	osmolarit$.ti,ab.
19	(osmolar adj3 concentrat$).ti,ab.
20	(ionic adj3 strength?).ti,ab.
21	or/14-20
22	CALCIUM/
23	CALCIUM INTAKE/
24	calcium.mp.
25	or/22-24
26	GLUCOSE/
27	glucose.mp.
28	dextrose.mp.
29	or/26-28
30	CENTRAL VENOUS CATHETERIZATION/
31	exp CENTRAL VENOUS CATHETER/
32	(central$ adj3 (line? or catheter$ or access$ or route? or administ$)).ti,ab.
33	(central$ adj3 (nutrition$ or feed$ or fed$)).ti,ab.
34	(central$ adj3 (vein? or venous$ or intravenous$ or intra-venous$ or IV or infusion?)).ti,ab.
35	CVC?.ti,ab.
36	or/30-35
37	exp PERIPHERAL VENOUS CATHETER/
38	(peripheral$ adj3 (line? or catheter$ or access$ or route? or administ$)).ti,ab.
39	(peripheral$ adj3 (nutrition$ or feed$ or fed$)).ti,ab.
40	(peripheral$ adj3 (vein? or venous$ or intravenous$ or intra-venous$ or IV or infusion?)).ti,ab.
41	PICC?.ti,ab.
42	or/37-41
43	PARENTERAL NUTRITION/
44	TOTAL PARENTERAL NUTRITION/
45	PARENTERAL SOLUTIONS/
46	(parenteral$ adj3 (nutrition$ or feed$ or fed$)).ti,ab.

#	Searches
47	or/43-46
48	PERIPHERAL PARENTERAL NUTRITION/
49	PARENTERAL NUTRITION/ae [Adverse Drug Reaction]
50	CENTRAL VENOUS CATHETERIZATION/ae [Adverse Drug Reaction]
51	exp CENTRAL VENOUS CATHETER/ae [Adverse Drug Reaction]
52	exp CENTRAL VENOUS CATHETER/am [Adverse Device Effect]
53	exp CENTRAL VENOUS CATHETER/dc [Device Comparison]
54	exp PERIPHERAL VENOUS CATHETER/am [Adverse Device Effect]
55	exp PERIPHERAL VENOUS CATHETER/dc [Device Comparison]
56	13 and 21 and (36 or 42)
57	13 and 25 and (36 or 42)
58	13 and 29 and (36 or 42)
59	13 and 36 and 42 and 47
60	13 and 48
61	13 and (36 or 42) and 49
62	13 and 47 and (50 or 51 or 52 or 53 or 54 or 55)
63	or/56-62
64	limit 63 to english language
65	letter.pt. or LETTER/
66	note.pt.
67	editorial.pt.
68	CASE REPORT/ or CASE STUDY/
69	(letter or comment*).ti.
70	or/65-69
71	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
72	70 not 71
73	ANIMAL/ not HUMAN/
74	NONHUMAN/
75	exp ANIMAL EXPERIMENT/
76	exp EXPERIMENTAL ANIMAL/
77	ANIMAL MODEL/
78	exp RODENT/
79	(rat or rats or mouse or mice).ti.
80	or/72-79
81	64 not 80

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

#	Searches
1	MeSH descriptor: [INFANT, NEWBORN] this term only
2	(neonat* or newborn* or new-born* or baby or babies):ti,ab
3	MeSH descriptor: [PREMATURE BIRTH] this term only
4	((preterm* or pre-term* or prematur* or pre-matur*) near/5 (birth* or born)):ti,ab
5	MeSH descriptor: [INFANT, PREMATURE] explode all trees
6	((preterm* or pre-term* or prematur* or pre-matur*) near/5 infan*):ti,ab
7	(pre?mie? or premie or premies):ti,ab
8	MeSH descriptor: [INFANT, LOW BIRTH WEIGHT] explode all trees
9	(low near/3 birth near/3 weigh* near/5 infan*):ti,ab
10	((LBW or VLBW) near/5 infan*):ti,ab
11	MeSH descriptor: [INTENSIVE CARE, NEONATAL] this term only
12	MeSH descriptor: [INTENSIVE CARE UNITS, NEONATAL] this term only
13	NICU?:ti,ab
14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
15	MeSH descriptor: [OSMOLAR CONCENTRATION] this term only
16	osmolalit*:ti,ab
17	osmolarit*:ti,ab
18	(osmolar near/3 concentrat*):ti,ab
19	(ionic near/3 strength*):ti,ab
20	#15 or #16 or #17 or #18 or #19
21	MeSH descriptor: [CALCIUM] this term only
22	MeSH descriptor: [CALCIUM, DIETARY] this term only
23	calcium:ti,ab
24	#21 or #22 or #23
25	MeSH descriptor: [GLUCOSE] this term only
26	glucose:ti,ab
27	dextrose:ti,ab
28	#25 or #26 or #27
29	MeSH descriptor: [CATHERTIZATION, CENTRAL VENOUS] this term only

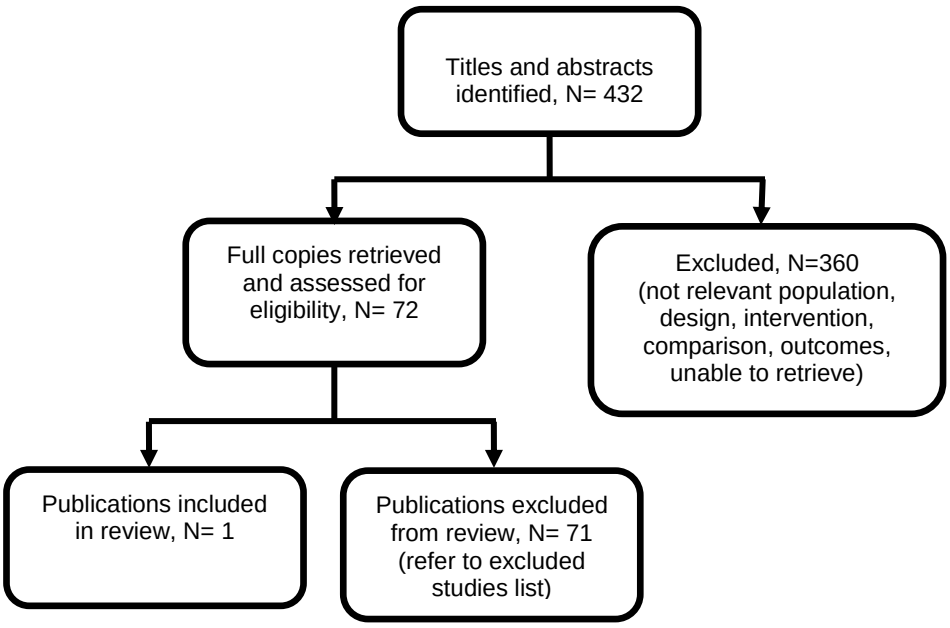
#	Searches
30	MeSH descriptor: [CENTRAL VENOUS CATHETERS] this term only
31	(central* near/3 (line* or catheter* or access* or route* or administ*)):ti,ab
32	(central* near/3 (nutrition* or feed* or fed*)):ti,ab
33	(central* near/3 (vein* or venous* or intravenous* or intra-venous* or IV or infusion*)):ti,ab
34	CVC*:ti,ab
35	#29 or #30 or #31 or #32 or #33 or #34
36	MeSH descriptor: [CATHETERIZATION, PERIPHERAL] explode all trees
37	(peripheral* near/3 (line* or catheter* or access* or route* or administ*)):ti,ab
38	(peripheral* near/3 (nutrition* or feed* or fed*)):ti,ab
39	(peripheral* near/3 (vein* or venous* or intravenous* or intra-venous* or IV or infusion*)):ti,ab
40	PICC*:ti,ab
41	#36 or #37 or #38 or #39 or #40
42	MeSH descriptor: [PARENTERAL NUTRITION] this term only
43	MeSH descriptor: [PARENTERAL NUTRITION, TOTAL] this term only
44	MeSH descriptor: [PARENTERAL NUTRITION SOLUTIONS] this term only
45	(parenteral* near/3 (nutrition* or feed* or fed*)):ti,ab
46	#42 or #43 or #44 or #45
47	MeSH descriptor: [PARENTERAL NUTRITION] this term only and with qualifier(s): [Adverse effects - AE]
48	MeSH descriptor: [CATHETERIZATION, CENTRAL VENOUS] this term only and with qualifier(s): [Adverse effects - AE]
49	MeSH descriptor: [CENTRAL VENOUS CATHETERS] this term only and with qualifier(s): [Adverse effects - AE]
50	MeSH descriptor: [CATHETERIZATION, PERIPHERAL] explode all trees and with qualifier(s): [Adverse effects - AE]
51	#14 and #20 and (#35 or #41)
52	#14 and #24 and (#35 or #41)
53	#14 and #28 and (#35 or #41)
54	#14 and #35 and #41 and #46
55	#14 and (#35 or #41) and #47
56	#14 and #46 and (#48 or #49 or #50)
57	#51 or #52 or #53 or #54 or #55 or #56

1

Appendix C – Clinical evidence study selection

Clinical study selection for review question: What overall osmolality (concentration of calcium and glucose/dextrose), in parenteral nutrition can determine whether to administer centrally or peripherally?

Figure 1: PRISMA Flow chart of clinical article selection for review question on venous access for PN in preterm and term babies.



Appendix D – Clinical evidence tables

Clinical evidence table for review question: What overall osmolality (concentration of calcium and glucose/dextrose), in parenteral nutrition can determine whether to administer centrally or peripherally?

Table 3: Clinical evidence table for included studies

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Cies, Jeffrey J., Moore, Wayne S., 2nd, Neonatal and pediatric peripheral parenteral nutrition: what is a safe osmolarity?, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 29, 118-24, 2014 Ref Id 888614 Country/ies where the study was carried out US Study type Observational study Aim of the study To determine the incidence of line-related events when	Sample size N=236 patients receiving PPN in the neonatal intensive care unit (NICU) N=77 in group Exposed (>900 mOsm/L) N=159 in group Non-Exposed (≤900 mOsm/L) Characteristics Median GA (weeks), range Group Non-Exposed: 34 (22-42) Group Exposed: 32 (22-42) Mean weight (kg), range	Interventions Exposed (E) group versus Non-exposed (NE) group. Patients receiving PPN with osmolarities > 900 mOsm/L via a peripheral line were defined as Exposed. Patients receiving PPN with osmolarities ≤ 900 mOsm/L via a peripheral line were defined as Non-Exposed.	Details A line-related event was defined as any episode of an infiltrate, extravasation, or thrombophlebitis. Grades 1 and 2 line-related events were grouped together for analysis. Statistical Analysis A sub-analysis was conducted with patients receiving PPN while residing in the neonatal intensive care unit (NICU) compared to patients receiving PPN outside of the NICU. Line-related events were stratified by gestational age (GA) and peripheral access site to remove any potential confounding that could be introduced by either of these variables A student's t test for continuous variables was conducted. For non-continuous variables a chi-square, Fisher's exact test or Mann–Whitney U test was conducted. A 2-sided significance level of α = .05 was used to determine statistical significance.	Results Intravenous Line-Related Events by Grade for the NICU Cohort Only Grade 1/2: Group NE: 230; Group E: 107 Grade 3: Group NE: 0; Group E: 0 Grade 4: Group NE: 1 (812 mOsm/L); Group E: 0 Rate of IV Line-Related Events per 100 Patient Days Stratified by GA for the NICU Cohort Only Group NE: ≤900 mOsm/L (n = 159), Group E: >900 mOsm/L (n = 77) GA < 32 weeks: NE: 45.8; E: 48.5; P=0.71; RR = 1.06, 95% CI 0.82-1.37 32-37 weeks: NE: 41.9; E: 51.5; P=0.19; RR = 1.23, 95% CI 0.91-1.65	Limitations ROBINS-I Bias due to confounding: Low risk of bias Bias in selection of participants into study: Moderate risk of bias - Retrospective study, unclear whether the start and follow-up of the intervention is the same for all participants, outcomes are adjusted (analysed per 100 days) Bias in classification of interventions: Moderate risk of bias - Intervention status is well designed, retrospective analysis Bias due to deviations from intended intervention: No information - No

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
administering peripheral parenteral nutrition (PPN) with an osmolarity > 900 mOsm/L compared to osmolarity > 900 mOsm/L Study dates 1st January 2005 to 31st December 2007 Source of funding Not reported	Group Non-Exposed: 3 (0.71-7) Group Exposed: 3 (0.89-7) Mean age (days), range Group Non-Exposed: 26 (0-185) Group Exposed: 37 (0-186) Female (%) Group Non-Exposed: 49 Group Exposed: 51.8 Median days of PPN, range Group Non-Exposed: 2 (1-14) Group Exposed: 2 (1-11) Events by IV site (%) Arm: Non-Exposed: 121 (26.2); Exposed: 53 (25.9) Foot: Non-Exposed: 144 (31.2); Exposed: 52 (25.5)		A power of 80%, and a 10% confidence interval range, 200 days of PPN per group are needed to detect a 10% difference in the rate of line-related events.	>37 weeks: NE: 53.3; E: 44.9; P=0.33; RR = 0.84, 95% CI 0.6-1.19 There was a statistically significant difference in the mean osmolarity between the NE and E groups, 804 (range 400-899) *vs*. 981 (range 900-1425) mOsm/L, P < .001. NE group: N=159 patients accounted for 464 days of PPN; Overall incidence of line-related events: 50 per 100 patient days E group: N= 77 patients accounted for 204 days of PPN; Overall incidence of line-related events was 52 per 100 patient days Comparing the NE group to the E group, there was no difference in the overall incidence of line-related events ($\chi 2$ = 0.07, P = 0.79). The relative risk (RR) for developing a line-related event was 1.02 (95% CI: interval, 0.88-1.18)	deviations reported, unclear whether deviations occurred Bias due to missing data: No information - No missing data reported, potential for missing data Bias in measurement of outcomes: Moderate risk of bias - Methods of outcome assessment were comparable, outcome could be minimally influenced by knowledge of the intervention Bias in selection of the reported result: Moderate risk of bias - Analyses are reported as specified, no indication of selective reporting of analysis. Overall risk of bias: Moderate risk Other information A line-related event was defined as any episode of an infiltrate, extravasation, or thrombophlebitis

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Hand: Non-Exposed: 179 (38.3); Exposed: 81 (39.7) Scalp: Non-Exposed: 17 (3.6); Exposed: 18 (8.8) Inclusion criteria Children from birth to 21 years of age receiving PN via a peripheral line Exclusion criteria Patients receiving PN through a central access site			Osmolarity was not found to increase the incidence of line-related events (OR=0.96, 95% CI, 0.89-1.04, P = 0.79). According to univariate analysis, regressed on the outcomes of interest: Other outcomes effect on the incidence of a line-related event: site of peripheral line placement (OR = 1.01, 95% CI 0.99-1.04, P =0.86); Gender (OR = 0.96, 95% CI 0.89-1.04, P =0.36); Gestational Age (OR = 1.02, 95% CI 0.97-1.06, P =0.51); Postnatal age (OR = 0.99, 95% CI 0.95-1.04, P =0.81); Postmenstrual age (OR = 1.02, 95% CI 0.97-1.07, P = 051). According to multivariable logistic regression, influences on the incidence of a line-related event: Osmolarity (OR = 1.06, 95% CI 0.76-1.49, P =0.73); Site of peripheral line placement (OR = 1, 95% CI 0.87-1.17, P =0.95); Gender (OR = 0.85, 95% CI 0.63-1.17, P =0.32); Gestational Age (OR =	Analysis conducted separately for neonates and children - only extracted data on neonates for this review

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				1, 95% CI 0.66-1.5, P = 1); Postnatal age (OR = 0.97, 95% CI 0.7-1.34, P =0.83); Postmenstrual age (OR = 1.1, 95% CI 0.72-1.7, P =0.65).	

CI: confidence interval; E: exposed; NE: non-exposed; GA: gestational age; NICU: neonatal intensive care unit; OR: odds ratio; OSM: osmolality; PN: parenteral nutrition; PPN: peripheral parenteral nutrition; ROBINS-I: risk of bias in non-randomised studies of interventions; RR: relative risk.

Appendix E – Forest plots

Forest plots for review question: What overall osmolality (concentration of calcium and glucose/dextrose), in parenteral nutrition can determine whether to administer centrally or peripherally?

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

Appendix F – GRADE tables

GRADE tables for review question: What overall osmolality (concentration of calcium and glucose/dextrose), in parenteral nutrition can determine whether to administer centrally or peripherally?

Table 4: Evidence profile for outcomes related to the comparison of PN with osmolarity > 900 mOsm/L versus PN with osmolarity ≤ 900 mOsm/L in babies receiving peripherally inserted catheters

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Osm > 900 mOsm/L via peripheral line	Osm ≤ 900 mOsm/L via peripheral line	Relative (95% CI)	Absolute	Quality	Importance
Line related events: All grades (Events per number of patient days of PN)												
1	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	107/612 (17.5%)	231/1392 (16.6%)	RR 1.06 (0.9 to 1.24)	18 more per 1000 (from 33 fewer to 90 more)	⊕OOO VERY LOW	CRITICAL
Line related events: Grade 1-2 (Events per number of patient days of PN)												
1	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	107/204 (52.5%)	230/464 (49.6%)	RR 1.06 (0.9 to 1.24)	30 more per 1000 (from 50 fewer to 119 more)	⊕OOO VERY LOW	CRITICAL
Line related events: Grade 3 (Events per number of patient days of PN)												
1	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/204 (0%)	0/464 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Line related events: Grade 4 (Events per number of patient days of PN)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Osm > 900 mOsm/L via peripheral line	Osm ≤ 900 mOsm/L via peripheral line	Relative (95% CI)	Absolute	Quality	Importance
1	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/204 (0%)	1/464 (0.22%)	Peto OR 0.24 (0.00 to 16.71)	2 fewer per 1000 (from 2 fewer to 34 more)	⊕OOO VERY LOW	CRITICAL
Rate of line related events: <32 weeks' GA (Rate per 100 patient days of PN)												
1	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	49/100 (49%)	46/100 (46%)	RR 1.07 (0.8 to 1.43)	32 more per 1000 (from 92 fewer to 198 more)	⊕OOO VERY LOW	CRITICAL
Rate of line related events: 32-37 weeks' GA (Rate per 100 patient days of PN)												
1	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	52/100 (52%)	42/100 (42%)	RR 1.24 (0.92 to 1.67)	101 more per 1000 (from 34 fewer to 281 more)	⊕OOO VERY LOW	CRITICAL
Rate of line related events: > 37 weeks' GA (Rate per 100 patient days of PN)												
1	observational studies	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	45/100 (45%)	53/100 (53%)	RR 0.85 (0.64 to 1.13)	79 fewer per 1000 (from 191 fewer to 69 more)	⊕OOO VERY LOW	CRITICAL

CI: confidence interval; GA: gestational age; Osm: Osmolarity; PN: parenteral nutrition; RR: risk ratio.

[1]Evidence downgraded by 2 due to moderate risks in selection of participants, classification of interventions, and the measurement and reporting of outcomes, and unclear attrition.

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

[3]Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MID for dichotomous outcomes (0.80 and 1.25).

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What overall osmolality (concentration of calcium and glucose/dextrose), in parenteral nutrition can determine whether to administer centrally or peripherally?

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 overall osmolality (concentration of calcium and glucose/dextrose), in parenteral nutrition can determine whether to administer centrally or peripherally?

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

Appendix I – Health economic evidence profiles

Economic evidence profiles for review question: What overall osmolality (concentration of calcium and glucose/dextrose) in parenteral nutrition can determine whether to administer centrally or peripherally?

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

Appendix J – Health economic analysis

Economic analysis for review question: What overall osmolality (concentration of calcium and glucose/dextrose) in parenteral nutrition can determine whether to administer centrally or peripherally?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: What overall osmolality (concentration of calcium and glucose/dextrose), in parenteral nutrition can determine whether to administer centrally or peripherally?

Clinical studies

Table 5: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Abdulla, F., Dietrich, K. A., Pramanik, A. K., Percutaneous femoral venous catheterization in preterm neonates, The Journal of pediatrics, 117, 788-91, 1990	Study intervention does not meet protocol eligibility criteria - percutaneous femoral vs non-femoral catheterisation.
Aggarwal, R., Downe, L., Use of percutaneous silastic central venous catheters in the management of newborn infants, Indian pediatrics, 38, 889-92, 2001	Study design does not meet protocol eligibility criteria - non-comparative, CVC used for all infants.
Ainsworth, S. B., Furness, J., Fenton, A. C., Randomized comparative trial between percutaneous longlines and peripheral cannulae in the delivery of neonatal parenteral nutrition, Acta paediatrica (Oslo, Norway : 1992), 90, 1016-20, 2001	Study does not match eligibility criteria. It does not report on osmolality/osmolarity, glucose/dextrose or calcium.
Ainsworth, S. B., McGuire, W., Peripherally inserted central catheters vs peripheral cannulas for delivering parenteral nutrition in neonates, JAMA - Journal of the American Medical Association, 315, 2612-2613, 2016	Narrative review.
Ainsworth, Sean, McGuire, William, Percutaneous central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates, Cochrane Database of Systematic Reviews, 2015	Study does not match eligibility criteria. It does not report on osmolality/osmolarity, glucose/dextrose or calcium.
Aldakauskiene, Ilona, Tameliene, Rasa, Marmiene, Vitalija, Rimdeikiene, Inesa, Smigelskas, Kastytis, Kevalas, Rimantas, Influence of Parenteral Nutrition Delivery Techniques on Growth and Neurodevelopment of Very Low Birth Weight Newborns: A Randomized Trial, Medicina (Kaunas, Lithuania), 55, 2019	Study does not match eligibility criteria. It does not report osmolality/osmolarity.
Banister, A., Matin-Siddiqi, S. A., Hatcher, G. W., Hendrickse, R. G., Intravenous feeding of young infants with persistent diarrhoea, Acta Paediatrica Scandinavica, 64, 732-40, 1975	Non-comparative observational study. Does not match eligibility criteria.
Barria, R. M., Lorca, P., Munoz, S., Randomized controlled trial of vascular access in newborns in the neonatal intensive care unit, 36, 450-6, 2007	Study does not match eligibility criteria. Study does not report on osmolality/osmolarity, glucose/dextrose or calcium.
Benda, G. I., Babson, S. G., Peripheral intravenous alimentation of the small premature infant, The Journal of pediatrics, 79, 494-8, 1971	Study design does not meet protocol eligibility criteria - non-comparative study.
Blotte, Carolina, Styers, Jennifer, Zhu, Hong, Channabasappa, Nandini, Piper, Hannah G., A comparison of Broviac and peripherally inserted central catheters in children with intestinal	Study does not match eligibility criteria. Study does not report on osmolality/osmolarity, glucose/dextrose or calcium.

Study	Reason for Exclusion
failure, Journal of Pediatric Surgery, 52, 768-771, 2017	
Boullata, J. I., Gilbert, K., Sacks, G., Labossiere, R. J., Crill, C., Goday, P., Kumpf, V. J., Mattox, T. W., Plogsted, S., Holcombe, B., Compher, C., A.S.P.E.N. Clinical guidelines: Parenteral nutrition ordering, order review, compounding, labeling, and dispensing, Journal of Parenteral and Enteral Nutrition, 38, 334-377, 2014	A.S.P.E.N. Clinical guidelines. All relevant references were checked however the studies refer to an adult population (not neonates).
Cairns,P.A., Wilson,D.C., McClure,B.G., Halliday,H.L., McReid,M., Percutaneous central venous catheter use in the very low birth weight neonate, European Journal of Pediatrics, 154, 145-147, 1995	Retrospective non-comparative study. Study does not match eligibility criteria. Study does not report on osmolality/osmolarity, glucose/dextrose or calcium.
Can, E., Salihotlu, O., Ozturk, A., Gungor, A., Guler, E., Hatipotlu, S., Complication profiles of central and non-central 1 Fr PICCs in neonates weighing <1500 g, Journal of Maternal-Fetal and Neonatal Medicine, 27, 1522-1525, 2014	Descriptive observational study examining peripherally inserted central venous catheters (PICCs) only. Alternate insertions of distal tips were compared (e.g. superior or inferior vena cava were defined as central, versus common iliac or external iliac vein, defined as non-central).
Chathas, M. K., Paton, J. B., Sepsis outcomes in infants and children with central venous catheters: percutaneous versus surgical insertion, Journal of obstetric, gynecologic, and neonatal nursing : JOGNN, 25, 500-6, 1996	Systematic Review - it does not report on osmolality/osmolarity, glucose/dextrose or calcium.
Cheong, S. M., Totsu, S., Nakanishi, H., Uchiyama, A., Kusuda, S., Outcomes of peripherally inserted double lumen central catheter in very low birth weight infants, Journal of Neonatal-Perinatal Medicine, 9, 99-105, 2016	Study design does not meet protocol eligibility criteria - non-comparative study.
Childs, A. M., Murdoch Eaton, D. G., Standring, P., Puntis, J. W., A prospective comparison of central and peripheral vein access for parenteral nutrition in the newborn, Clinical nutrition (Edinburgh, Scotland), 14, 303-5, 1995	Study does not match eligibility criteria. It does not report on osmolality/osmolarity, glucose/dextrose or calcium.
Chung, C. M., Li, N. H., Peripheral intravenous alimentation of preterm infants, Modern medicine of Asia, 14, 59-63, 1978	Study does not match eligibility criteria. Study includes enteral feeding and does not report on intervention or outcomes of interest.
Collinge, J. M., Aranda, J. V., Nonmetabolic complications of neonatal intravenous therapy: Epidemiologic considerations, American Journal of Perinatology, 1, 185-189, 1983	Study design does not meet protocol eligibility criteria - non-comparative study.
Coran, A. G., Total intravenous feeding of infants and children without use of a central venous catheter, Annals of Surgery, 179, 445-9, 1974	Study design does not meet protocol eligibility criteria - non-comparative; case series.
Coran, A. G., Weintraub, W. H., Peripheral intravenous nutrition without fat in neonatal surgery, Journal of Pediatric Surgery, 12, 195-199, 1977	Non-comparative observational study. Does not match eligibility criteria.
Dugan, Shannon, Le, Jennifer, Jew, Rita K., Maximum tolerated osmolarity for peripheral administration of parenteral nutrition in pediatric patients, JPEN. Journal of parenteral and enteral nutrition, 38, 847-51, 2014	Retrospective, matched-cohort study. Population does not match eligibility criteria. (patients <=18 years and no separate data on neonates). Reports on peripheral PN only (no comparison to central PN).

Study	Reason for Exclusion
Fonzo-Christe, C., Parron, A., Combescure, C., Pfister, R., Rimensberger, P., Bonnabry, P., Peripheral infusions in neonatal and paediatric intensive care: Extravasation rate and risk factors, European Journal of Hospital Pharmacy, 22, A146, 2015	Conference abstract.
Fox, H. A., Krasna, I. H., Total intravenous nutrition by peripheral vein in neonatal surgical patients, Pediatrics, 52, 14-20, 1973	Study design does not meet protocol eligibility criteria - non-comparative study.
Frantz, S., Guidance issued on feeding of sick newborn babies, BMJ (Clinical research ed.), 322, 1562, 2001	Commentary. Does not match eligibility criteria.
Gulcan, H., Hanta, D., Torer, B., Ozdemir, Z., Our clinical experience of central venous catheterization in very low birth weight infants, Early Human Development, 86, S105, 2010	Conference abstract.
Haworth, J. C., Ford, J. D., Robinson, T. J., Peripheral and portal vein blood sugar after lactose and galactose feedings, Clinical science, 29, 83-92, 1965	Study does not match eligibility criteria - case study reporting on blood sugar levels.
Holmes, A., Dore, C. J., Saraswatula, A., Bamford, K. B., Richards, M. S., Coello, R., Modi, N., Risk factors and recommendations for rate stratification for surveillance of neonatal healthcare-associated bloodstream infection, The Journal of hospital infection, 68, 66-72, 2008	Observational study. Does not match eligibility criteria.
Hosseini, Mohammad Bagher, Jodeiri, Behzad, Mahallei, Majid, Abdoli-Oskooi, Shahram, Safari, Ahmad, Salimi, Zakieh, Early outcome of peripherally inserted central catheter versus peripheral IV line in very low birth weight neonates, Feyz Journal of Kashan University of Medical Sciences, 17, 561-567, 2014	Full text not written in English.
Ikeda, K., Suita, S., Total parenteral nutrition using peripheral veins in surgical neonates, Archives of Surgery, 112, 1045-1049, 1977	Study design does not meet protocol eligibility criteria - non-comparative study.
Jacob, J., Davis, R. F., Differences in serum glucose determinations in infants with umbilical artery catheters, Journal of perinatology : official journal of the California Perinatal Association, 8, 40-42, 1988	The study does not match the eligibility criteria - Study does not report any of the outcomes of interest.
Janes, M., Kalyn, A., Pinelli, J., Paes, B., A randomized trial comparing peripherally inserted central venous catheters and peripheral intravenous catheters in infants with very low birth weight, 35, 1040-4, 2000	Study does not match eligibility criteria. Study does not report on osmolality/osmolarity, glucose/dextrose or calcium.
Kakzanov, Vered, Monagle, Paul, Chan, Anthony K. C., Thromboembolism in infants and children with gastrointestinal failure receiving long-term parenteral nutrition, JPEN. Journal of parenteral and enteral nutrition, 32, 88-93, 2008	Narrative review.
Kanarek, K. S., Kuznicki, M. B., Blair, R. C., Infusion of total parenteral nutrition via the umbilical artery, Jpen, Journal of parenteral and enteral nutrition. 15, 71-4, 1991	Retrospective study. Does not match eligibility criteria. Study does not report on osmolality/osmolarity, glucose/dextrose or calcium.

Study	Reason for Exclusion
Ladefoged, K., Efsen, F., Krogh Christoffersen, J., Jarnum, S., Long-term parenteral nutrition. II. Catheter-related complications, Scandinavian journal of gastroenterology, 16, 913-9, 1981	Study does not match eligibility criteria - patients were aged between 6-69 years.
Lapillonne, A., Berleur, M. P., Brasseur, Y., Calvez, S., Safety of parenteral nutrition in newborns: Results from a nationwide prospective cohort study, Clinical Nutrition, 37, 624-629, 2018	Prospective cohort study comparing two different PN solutions with data collected in case report form. Does not compare osmolality, percentage of dextrose/glucose or calcium given centrally or peripherally.
Leibovitz,E., Iuster-Reicher,A., Amitai,M., Mogilner,B., Systemic candidal infections associated with use of peripheral venous catheters in neonates: a 9-year experience, Clinical Infectious Diseases, 14, 485-491, 1992	Study design does not meet protocol eligibility criteria - non-comparative study.
Lindblad, B. S., Settergren, G., Feychting, H., Persson, B., Total parenteral nutrition in infants. Blood levels of glucose, lactate, pyruvate, free fatty acids, glycerol, d-beta-hydroxybutyrate, triglycerides, free amino acids and insulin, Acta paediatrica Scandinavica, 66, 409-19, 1977	Study design and population do not meet protocol eligibility criteria - case control; includes children aged 2 to 12 months.
Liossis,G., Bardin,C., Papageorgiou,A., Comparison of risks from percutaneous central venous catheters and peripheral lines in infants of extremely low birth weight: a cohort controlled study of infants < 1000 g, Journal of Maternal-Fetal and Neonatal Medicine, 13, 171-174, 2003	Observational cohort study. Does not match eligibility criteria. Both catheters inserted peripherally; does not report on osmolality, percentage of dextrose/glucose or calcium given.
Mactier, H., Alroomi, L. G., Young, D. G., Raine, P. A., Central venous catheterisation in very low birthweight infants, Archives of Disease in Childhood, 61, 449-53, 1986	Non-comparative observational study. Does not match eligibility criteria.
Mahieu,L.M., De Muynck,A.O., Ieven,M.M., De Dooy,J.J., Goossens,H.J., Van Reempts,P.J., Risk factors for central vascular catheter-associated bloodstream infections among patients in a neonatal intensive care unit, Journal of Hospital Infection, 48, 108-116, 2001	Study does not match eligibility criteria. It does not report on osmolality/osmolarity, glucose/dextrose or calcium.
McCay, A. S., Elliott, E. C., Walden, M., PICC placement in the neonate, New England Journal of Medicine, 370, e17-5, 2014	Summary document. Does not match eligibility criteria.
Meng, H. C., Stahlman, M. T., Otten, A., Dolanski, E. A., Caldwell, M. D., O'Neill, J. A., The use of a crystalline amino acid mixture for parenteral nutrition in low-birth-weight infants, Pediatrics, 59, 699-709, 1977	Study does not match eligibility criteria; does not compare osmolality, percentage of dextrose/glucose or calcium given centrally or peripherally.
Nahirya, Patricia, Byarugaba, Justus, Kiguli, Sarah, Kaddu-Mulindwa, Deogratias, Intravascular catheter related infections in children admitted on the paediatric wards of Mulago Hospital, Uganda, African health sciences, 8, 206-16, 2008	Study does not meet protocol eligibility criteria - Cross-sectional study including non-eligible population.
Njere, Ike, Islam, Saidul, Parish, Deborah, Kuna, Jauro, Keshtgar, Alireza S., Outcome of peripherally inserted central venous catheters in surgical and medical neonates, Journal of Pediatric Surgery, 46, 946-50, 2011	Study does not match eligibility criteria. It does not report on osmolality/osmolarity, glucose/dextrose or calcium.

Study	Reason for Exclusion
Ozkiraz, S., Gokmen, Z., Ince, D. A., Akcan, A. B., Kilicdag, H., Ozel, D., Ecevit, A., Peripherally inserted central venous catheters in critically ill premature neonates, Journal of Vascular Access, 14, 320-324, 2013	Retrospective study. All patients received PN via peripherally inserted central venous catheters. Study does not report on osmolality/osmolarity, glucose/dextrose or calcium.
Pereira, G. R., Lim, B. K., Ing, C., Medeiros, H. F., Umbilical vs peripheral vein catheterization for parenteral nutrition in sick premature neonates, Yonsei medical journal, 33, 224-31, 1992	Retrospective study. Patients received enteral feeding.
Pettit, Janet, Assessment of infants with peripherally inserted central catheters: Part 1. Detecting the most frequently occurring complications, Advances in neonatal care : official journal of the National Association of Neonatal Nurses, 2, 304-15, 2002	Narrative review
Piper, Hannah G., de Silva, Nicole T., Amaral, Joao G., Avitzur, Yaron, Wales, Paul W., Peripherally inserted central catheters for long-term parenteral nutrition in infants with intestinal failure, Journal of Pediatric Gastroenterology and Nutrition, 56, 578-81, 2013	Study design does not meet protocol eligibility criteria - non-comparative study.
Ragavan, M., Gazula, S., Yadav, D. K., Agarwala, S., Srinivas, M., Bajpai, M., Bhatnagar, V., Gupta, D. K., Peripherally inserted central venous lines versus central lines in surgical newborns - A comparison, Indian Journal of Pediatrics, 77, 171-174, 2010	Study does not match eligibility criteria. Study does not report on osmolality/osmolarity, glucose/dextrose or calcium.
Rais-Bahrami, K., Karna, P., Dolanski, E. A., Effect of fluids on life span of peripheral arterial lines, American Journal of Perinatology, 7, 122-4, 1990	Study intervention does not meet protocol eligibility criteria - different saline to maintain peripheral arterial line patency.
Rosado, V., Camargos, P. A. M., Anchieta, L. M., Bouzada, M. C. F., Oliveira, G. M. D., Clemente, W. T., Romanelli, R. M. D. C., Risk factors for central venous catheter-related infections in a neonatal population - systematic review, Jornal de Pediatria, 94, 3-14, 2018	Systematic review.
Sierra Colomina, M., Zamora Flores, E., Arriaga Redondo, M., Sanchez Luna, M., Incidence and risk factors for catheter-related bloodstream infection in very low weight neonates, Journal of Perinatal Medicine, 43, 2015	Study design does not meet protocol eligibility criteria - retrospective descriptive observational study.
Singh, Amit, Bajpai, Minu, Panda, Shasanka Shekhar, Jana, Manisha, Complications of peripherally inserted central venous catheters in neonates: Lesson learned over 2 years in a tertiary care centre in India, African journal of paediatric surgery : AJPS, 11, 242-7, 2014	Study design does not meet protocol eligibility criteria - non-comparative study.
Soares, Beatriz Nicolau, Pissarra, Susana, Rouxinol-Dias, Ana Lidia, Costa, Sandra, Guimaraes, Hercilia, Complications of central lines in neonates admitted to a level III Neonatal Intensive Care Unit, The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal	Study design does not meet protocol eligibility criteria - non-comparative study.

Study	Reason for Exclusion
Societies, the International Society of Perinatal Obstetricians, 31, 2770-2776, 2018	
Sol, J. J., van de Loo, M., Boerma, M., Bergman, K. A., Donker, A. E., van der Hoeven, M. A. H. B. M., Hulzebos, C. V., Knol, R., Djien Liem, K., van Lingen, R. A., Lopriore, E., Suijker, M. H., Vijlbrief, D. C., Visser, R., Veening, M. A., van Weissenbruch, M. M., van Ommen, C. H., NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): Evaluation of a national guideline on management of neonatal catheter-related thrombosis, BMC Pediatrics, 18, 84, 2018	Review protocol.
Stok, D., Wieringa, J. W., Continuous infusion versus intermittent flushing: Maintaining peripheral intravenous access in newborn infants, Journal of Perinatology, 36, 870-873, 2016	Study intervention does not meet protocol eligibility criteria - catheter placed to administer antibiotics; not for PN.
Suita, Sachiyo, Yamanouchi, Takeshi, Masumoto, Koji, Ogita, Keiko, Nakamura, Masatoshi, Taguchi, Shohei, Changing profile of parenteral nutrition in pediatric surgery: a 30-year experience at one institute, Surgery, 131, S275-82, 2002	Study intervention does not meet protocol eligibility criteria - does not report osmolality, percentage of dextrose/glucose or calcium.
Thornburg, Courtney D., Smith, P. Brian, Smithwick, Mary Laura, Cotten, C. Michael, Benjamin, Daniel K., Jr., Association between thrombosis and bloodstream infection in neonates with peripherally inserted catheters, Thrombosis research, 122, 782-5, 2008	Study design does not meet protocol eligibility criteria - non-comparative study.
Van Den Berg, J., Loofstrom, J., Olofsson, J., Fridlund, M., Farooqi, A., Peripherally inserted central catheter in extremely preterm infants: Characteristics and influencing factors, Journal of Neonatal-Perinatal Medicine, 10, 63-70, 2017	Study design does not meet protocol eligibility criteria - outcomes not reported by PICCs inserted centrally and non-centrally.
Vanhatalo, T, Tammela, Okt, 20 % or 15 % Glucose Infusion into Peripheral Veins for the Treatment of Neonatal Hypoglycemia, Pediatric academic societies annual meeting; 2005 May 14-17; washington DC, united states, 2005	Study intervention does not meet protocol eligibility criteria - catheter not to administer PN; infants received mother's or banked breast milk.
Vanhatalo, T., Tammela, O., Glucose infusions into peripheral veins in the management of neonatal hypoglycemia - 20% instead of 15%?, Acta Paediatrica, International Journal of Paediatrics, 99, 350-353, 2010	Study does not match eligibility criteria. Study includes enteral feeding and does not report on intervention or outcomes of interest.
Veralaine, J., Masriniwati, M., Salbiah, M., Maria, L., Fong, S. M., Surveillance of central venous catheter (CVC) infection in Nicu in Swach, Journal of Microbiology, Immunology and Infection, 48, S179, 2015	Conference abstract.
Warner, B. W., Gorgone, P., Schilling, S., Farrell, M., Ghory, M. J., Multiple purpose central venous access in infants less than 1,000 grams, Journal of Pediatric Surgery, 22, 820-2, 1987	Study design does not meet protocol eligibility criteria - non-comparative study.
Whitby, T., McGowan, P., Turner, M. A., Morgan, C., Concentrated parenteral nutrition	RCT reporting only central venous catheter for PN (no comparison to peripheral PN).

Study	Reason for Exclusion
solutions and central venous catheter complications in preterm infants, Archives of disease in childhood. Fetal and neonatal edition, 100, F250-2, 2015	
Whitby, T., Morgan, C., McGowan, P., Turner, M., Concentrated parenteral nutrition solutions and central venous catheter complications in preterm infants, Archives of Disease in Childhood: Fetal and Neonatal Edition, 99, A54, 2014	Conference abstract.
Wojkowska-Mach, Jadwiga, Gulczynska, Ewa, Nowiczewski, Marek, Borszewska-Kornacka, Maria, Domanska, Joanna, Merritt, T. Allen, Helwich, Ewa, Kordek, Agnieszka, Pawlik, Dorota, Gadzinowski, Janusz, Szczapa, Jerzy, Adamski, Pawel, Sulik, Malgorzata, Klamka, Jerzy, Brzychczy-Wloch, Monika, Heczko, Piotr B., Late-onset bloodstream infections of Very-Low-Birth-Weight infants: data from the Polish Neonatology Surveillance Network in 2009-2011, BMC infectious diseases, 14, 339, 2014	Study design does not meet protocol eligibility criteria.
Yamaguchi, Ricardo Silveira, Noritomi, Danilo Teixeira, Degaspare, Natalia Viu, Munoz, Gabriela Ortega Cisternas, Porto, Ana Paula Matos, Costa, Silvia Figueiredo, Ranzani, Otavio T., Peripherally inserted central catheters are associated with lower risk of bloodstream infection compared with central venous catheters in paediatric intensive care patients: a propensity-adjusted analysis, Intensive Care Medicine, 43, 1097-1104, 2017	Does not match eligibility criteria. Patients under the age of 30 days were excluded.
Yang, Janet Yk, Williams, Suzan, Brandao, Leonardo R., Chan, Anthony Kc, Neonatal and childhood right atrial thrombosis: recognition and a risk-stratified treatment approach, Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis, 21, 301-7, 2010	Review.
Yeung,C.Y., Lee,H.C., Huang,F.Y., Wang,C.S., Sepsis during total parenteral nutrition: exploration of risk factors and determination of the effectiveness of peripherally inserted central venous catheters, Pediatric Infectious Disease Journal, 17, 135-142, 1998	Study does not match eligibility criteria. Case study and does not report on relevant outcomes.
Yumani, Dana F. J., van den Dungen, Frank A. M., van Weissenbruch, Mirjam M., Incidence and risk factors for catheter-associated bloodstream infections in neonatal intensive care, Acta paediatrica (Oslo, Norway : 1992), 102, e293-8, 2013	Retrospective study. Study does not match eligibility criteria. Study does not report on osmolality/osmolarity, glucose/dextrose or calcium.
Ziegler, M., Jakobowski, D., Hoelzer, D., Eichelberger, M., Koop, C. E., Route of pediatric parenteral nutrition: proposed criteria revision, Journal of Pediatric Surgery, 15, 472-6, 1980	Study design does not meet protocol eligibility criteria - case series. Population is also unclear - described as children.

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 overall osmolality (concentration of calcium and glucose/dextrose) in parenteral nutrition can determine whether to administer centrally or peripherally?

Research recommendation

What overall osmolality (or concentration of calcium and glucose/dextrose) in parenteral nutrition can determine whether to administer centrally or peripherally?

Why this is important

Parenteral Nutrition (PN) is administered intravenously, and either peripheral or central venous lines can be used. Central lines are often inserted through the umbilical vessels in new-born infants, but can also be inserted peripherally; they are used for drug infusions as well as PN.

Central lines are positioned in a large bore central vein. This allows infusion of more concentrated substances securely; and in general these lines are able to be left in situ for a longer period of time if carefully maintained. However, they require a greater degree of technical skill for insertion; and can be more prone to serious complications such as being a source of late onset sepsis. Peripheral lines are very commonly used for a number of indications on neonatal units and are generally easier to insert. They have a shorter life span. As the infusions are running into a smaller peripheral vein, there is greater risk of the infusion causing direct damage to the vein (thrombophlebitis) or leaking out into the surrounding tissues (extravasation). This is particularly true where there is a higher concentration (as measured by osmolality or osmolarity depending on the unit of measurement) of the PN infusion fluid, such as a formulation with a higher dextrose load. It is therefore important to determine whether to administer PN centrally or peripherally.

Table 6: Research recommendation rationale

Research question	**What overall osmolality (concentration of calcium and glucose/dextrose), in parenteral nutrition can determine whether to administer centrally or peripherally?**
Why is this needed	
Importance to 'patients' or the population	High: It is crucial to determine whether to administer PN in babies through a centrally or peripherally inserted catheter in order to avoid adverse events such as extravasation (leakage of fluid into the body), bloodstream infections and thrombophlebitis, which can all occur when the vein is weakened either by multiple insertion or by higher concentration of the fluid.
Relevance to NICE guidance	High: Only one retrospective cohort study was identified for inclusion in this review. The study that was identified was very limited in quality and did not provide data to determine whether to administer PN centrally or peripherally as no evidence was presented on central catheters.
Relevance to the NHS	High: Current practice varies with regards to the administration of PN centrally or peripherally and it is important to identify whether osmolality or osmolarity of PN can help guide whether it is safe

Research question	What overall osmolality (concentration of calcium and glucose/dextrose), in parenteral nutrition can determine whether to administer centrally or peripherally?
	to administer peripherally or if PN should be administered centrally.
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 single study was retrospective and was considered to be very low quality, with a high risk of bias and serious imprecision. The study provided data only for osmolality >900 mOsm/L versus ≤900 mOsm/L given peripherally.
Equality	The research aims to ensure all babies are provided with optimum care.
Feasibility	This would require NHS ethical approval but would be feasible and safe to conduct.
Other comments	Not applicable

NHS: National Health Service; PN: Parenteral nutrition

Table 7: Research recommendation modified PICO table

Criterion	Explanation
Population	• Babies born preterm, up to 28 days after their due date (preterm babies) • Babies born at term, up to 28 days after their due data (term babies)
Intervention	• Intervention 1: A specified level of osmolality or osmolarity, (or percentage of dextrose/glucose or calcium) given centrally • Intervention 2: A specified level of osmolality or osmolarity, (or percentage of dextrose/glucose or calcium) given peripherally
Comparator	• Comparison 1: The same specified level of osmolality or osmolarity, (or percentage of dextrose or calcium) given in the intervention arm, but given peripherally • Comparison 2: A different level of osmolality or osmolarity, (or percentage of dextrose or calcium) given in the intervention arm, given peripherally
Outcomes	Tissue damage Extravasation Bloodstream infections Thrombophlebitis
Study design	Randomised controlled trial or comparative cohort studies
Timeframe	From birth to discharge
Additional information	Not applicable

PN: Parenteral nutrition