National Institute for Health and Care Excellence

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Draft for consultation

Neonatal parenteral nutrition

[D9] Ratio of calcium to phosphate

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

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ISBN:

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IV minerals: Calcium and phosphate

Review question

What are the optimal target dosages for calcium and phosphate in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Introduction

The provision of both calcium and phosphate in optimal proportions is required in the formation of bone. As 80% of bone mineral is laid down in the third trimester in term infants, preterm infants have reduced stores of minerals at birth. In addition, it can be challenging to provide both term and preterm babies with enough calcium and phosphate for adequate bone mineralisation as the establishment of enteral nutrition may be delayed. It may also be difficult to supply sufficient minerals in the correct proportion using parenteral nutrition (PN). It is important to give babies receiving PN optimal intakes of calcium and phosphates to prevent electrolyte disturbances such as hyper or hypocalcaemia, and hyper and hypophosphataemia.

Summary of protocol

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

Table 1: Summary of the protocol (PICO table)

Population	• Babies born preterm, up to 28 days after their due birth date (preterm babies) • Babies born at term, up to 28 days after their birth (term babies)
Intervention	Any amount of calcium or phosphate
Comparison	Each other

Outcomes	**Critical**
	• Metabolic bone disease of prematurity
	• Fractures
	• Growth/Anthropometric measures
	  ○ Weight gain (g/kg/d)
	  ○ Linear growth
	  ○ Head circumference (mm)
	• Adverse effects of PN
	  ○ Hypercalcaemia
	  ○ Hypercalciuria
	  ○ Hyperphosphataemia (high blood level of phosphate)
	  ○ Hypophosphataemia
	Important
	• Mortality

PN: Parenteral nutrition

For full details see the review protocol in appendix A.

Clinical evidence

Included studies

Seven randomised controlled trials (RCTs) were identified for inclusion in this review(Aiken 1986; Koo 1987, Koo 1989, Macmahon 1989, Mazouri 2017, Prestridge 1993, and Vileisis 1997).

The included studies are summarised in Table 2.

Five studies compared high calcium and phosphorous levels to standard (low) calcium and phosphorous (Aiken 1986, Koo 1987, Koo 1989, Macmahon 1989, Prestridge 1993). One study compared high and moderate phosphorous levels to low phosphorous (Vileisis 1997), and one study compared phosphorous to no phosphorous (Mazouri 2017).

The doses of calcium and phosphate in the control arm of Prestige 1993 were similar to doses of calcium and phosphate in the high dose group in studies conducted by Koo (1987 and 1989) and therefore it would not appropriate to be combined these.

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

Excluded studies

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

Summary of clinical studies included in the evidence review

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

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Comments
Aiken 1986 RCT UK	N = 15 Mean BW (g) High Ca and PO: 1066 (SD 198) Standard: 1067 (SD 239) Mean GA (weeks) High Ca and PO: 27.9 (SD 1.2) Standard: 28.0 (SD 1.0)	High Calcium and Phosphate (n=10) 1.08 mmol/kg/d calcium 0.89 mmol/kg/d phosphate	Standard solution (n=5) 0.55 mmol/kg/d calcium 0.44 mmol/kg/d phosphate	• Weight gain • Fracture • Rickets	Duration of feeding varied from 26 to 75 days, infants studies only after 10 days

Study	Population	Intervention	Comparison	Outcomes	Comments
Koo 1987 RCT US	N = 18 Infants with surgical indications for PN Mean BW (g) High: 2717 (SD 672) Low: 2903 (SD 474) Mean GA (weeks) High: 37.0 (SD 2.4) Low: 37.9 (SD 2.4)	High Calcium and Phosphate (n=9) 15mM each: 1.5-2 mmol/kg/d calcium 1.5-2.0 mmol/kg/d phosphate	Standard solution (Low Calcium and Phosphate) (n-9) 5mM each: 0.5 mmol/kg/d calcium 0.5 mmol/kg/d phosphate	• Weight gain	Amounts of calcium and phosphate have been converted by calculation from mg P/dL into mmol/kg/day at an assumed PN intake of 100ml/kg/day (approximate intakes have been calculated to allow comparisons).
Koo 1989 RCT US	N=26 Preterm infants Mean BW (g) High: 1065 (SD 447) Low: 1115 (SD 485) Mean GA (weeks) High: 28.8 (SD 3.6) Low: 29.0 (SD 3.5)	High-dose Calcium and Phosphate (n=13) 15mM each: 1.5 mmol/kg/d calcium 1.5 mmol/kg/d phosphate	Standard solution (Low-dose Calcium and Phosphate) (n=12) 5mM each: 0.5 mmol/kg/d calcium and phosphate	• Fracture	Enteral feedings were attempted for all infants whenever possible, and any feedings tolerated were recorded Amounts of calcium and phosphorous have been converted by calculation from mg/dl into mmol/kg/day at a PN intake of 100ml/kg/day (approximate intakes have been calculated to allow approximate comparisons).
Macmahon 1989 RCT UK	N=27 Mean BW (g) Increased group: 830 (range 590-1495)	Increased mineral content (n=14) 1.25 mmol/kg/d calcium	Standard solution (n= 13) 0.68 mmol/kg/d calcium	• Rickets	≥ 75% of the volume of fluid was given intravenously When enteral feeding was possible the mother's own

Study	Population	Intervention	Comparison	Outcomes	Comments
	Standard group: 960 (range 580 -1760) Mean GA (weeks) Increased group: 26 (range 24-41) Standard group: 28 (range 25-33)	1.20 mmol/kg/d phosphorous	0.61 mmol/kg/d phosphorous		expressed milk was used in preference. If not, a proprietary preterm formula was used
Prestridge 1993 RCT US	N=24 Mean BW (g) High group: 875 (SD 180) Standard group: 921 (SD 171) Mean GA (weeks) High group: 27, (SD 2) Standard group: 27, (SD 2)	High Calcium and Phosphate (35% more) 1.8 mmol/kg/d calcium 2.5 mmol/kg/d phosphate	Standard PN 1.5 mmol/kg/d calcium 1.8 mmol/kg/d phosphate	• Bone mineral content	Parenteral nutrition initiated postnatal day 3 Enteral intake started at 19 ± 5 days (Standard PN) and 17 ± 2 days (High Ca P) Amounts of calcium and phosphate have been converted by calculation from mmol/dL into mmol/kg/day
Mazouri 2017 RCT Iran	N=50 Mean BW (kg) Phosphate: 1.31 (SD 0.14) No Phosphate: 1.27 (SD 0.16) Mean GA (weeks) Phosphate: 29.5 (SD 1) No phosphate: 29.7 (SD 1.2)	Phosphorous (n=25) PN plus 1.5 mmol/kg/day phosphorous sodium glycerol-phosphate	No phosphorous (n=25) PN without sodium glycerol-phosphate	• Bone mineral density	Neonates selected by convenience sampling

Study	Population	Intervention	Comparison	Outcomes	Comments
Vileisis 1987 RCT US	N=27 Mean BW (kg) Moderate: 1.09 (SD 2.86) Low: 0.88 (SD 0.22) Mean GA (weeks) Moderate: 28.2 (SD 3.11) Low: 27.2 (SD 1.26)	Moderate (n=8) 1.34 mmol/kg/d phosphate, 0.87 mmol/kg/d Calcium High 1.67 mmol/kg/d phosphate, 0.73 mmol/kg/day calcium	Low phosphorous (n=10) 1.01 mmol/kg/d Phosphate, 0.85 mmol/kg/d Calcium	• Hypercalciuria • Weight gain	Received study infusion for the first 14 days of life

BW: Birth weight; Ca: calcium; GA: gestational age; P: phosphate; PN: parenteral nutrition; RCT: randomised controlled trial; SD: standard deviation; VLBW: very low birth weight; UK: United Kingdom; 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, but no evidence was identified to provide data on 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

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Clinical Evidence statements

High calcium and phosphorous versus standard (low) calcium and phosphorous

Weight gain

- Very low quality evidence from 2 -RCT (n=33 showed no clinically important difference in weight gain in babies who received high calcium and phosphorous intakes compared to babies who received standard (low) calcium and phosphorous. However, there was uncertainty around the effect, Standard mean difference (SMD): 0.28 (95% CI -0.43, 0.99).

Fractures

- Very low quality evidence from 2 RCT (n=41) showed a clinically important difference in fractures between babies who received high calcium and phosphorous intakes compared to babies who received standard (low) calcium and phosphorous intakes, with fewer events in those receiving high calcium and phosphorous. However, there was uncertainty around the effect: Peto Odds ratio (OR) 0.08 (95% CI 0.00, 1.40).

Rickets

- Very low quality evidence from 2 RCT (n=42) showed a clinically important difference in rickets in babies who received high calcium and phosphorous intakes compared to babies who received standard (low) calcium and phosphorous intakes, with fewer events in those receiving high calcium and phosphorous. However, there was uncertainty around the effect, RR 0.29 (95%CI 0.07, 1.23).

Bone mineral content at 4 weeks after birth (BMC, measured in mg/cm)

- High quality evidence from 1 RCT (n=24) showed a clinically important difference in bone mineral content in babies who received high calcium and phosphorous intakes compared to babies who received standard (low) calcium and phosphorous intakes, with higher bone mineral content in babies who received high calcium and phosphorous., Mean difference (MD) 2.28 (95%CI 1.36, 3.20).

Bone mineral content at 8 weeks after birth (BMC, measured in mg/cm)

- Moderate quality evidence from 1 RCT (n=24) showed no clinically important difference in bone mineral content in babies who received high calcium and phosphorous intakes compared to babies who received standard (low) calcium and phosphorous intakes. However, there was uncertainty around the effect, MD 1.29 (95% CI -4.59, 7.17).

High and moderate phosphorous versus low phosphorous

Hypercalciuria

- Low quality evidence from 1 RCT (n=27) showed a clinically important difference in hypercalciuria in babies who received high and moderate phosphorous intakes compared to babies who received low phosphorous intakes, with lower events of hypercalciuria in those with high/moderate phosphorous intake. RR 0.08 (95% CI 0.01, 0.59).

Weight gain (g)

- Very low quality evidence from 1 RCT (n=27) showed no clinically important difference in weight gain in babies who received high and moderate phosphorous intakes compared to babies who received low phosphorous intakes. However, there was high uncertainty around the effect, MD 15 (95% CI -47.21, 77.21).

Phosphorous versus no phosphorous

Bone mineral density (BMD, measured in g/cm^2)

- Moderate quality evidence from 1 RCT (n=50) showed a clinically important difference in bone mineral density in babies who received TPN with sodium glycerophosphate compared to babies who received TPN without sodium glycerophosphate, with greater bone mineral density in babies who received phosphate, MD 0.03 (95%CI 0.02, 0.04).

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 outcomes as critical, specifically metabolic bone disease of prematurity, and the incidence of fractures. These outcomes were selected as critical, because while rare, they are clinically important, and may significantly add to the baby's discomfort or length of stay and bone development is directly related to the mineral content of PN. Biochemical disturbances such as hypercalcaemia and hyper and hypophosphataemia and hypokalaemia may be relatively more common but may also be clinically important if not treated promptly, and may in addition occur most frequently in babies when suboptimal amounts of calcium and phosphate are given in PN. Outcomes such as weight gain, linear growth and head circumference were also considered critical as adequate growth would indicate sufficient nutrition and provision of the substrates required for growth. Mortality was considered an important outcome.

The quality of the evidence

The quality of evidence for this review was assessed using GRADE methodology. The evidence presented was generally either very low or low quality, with the exception of one high quality piece of evidence for bone mineral density at 4 weeks in babies who received higher calcium/phosphate compared with lower calcium/phosphate, and some moderate quality evidence for bone mineral density in babies who received phosphate compared with no phosphate, indicating high uncertainty in the reliability of the data. This was due to serious and very serious risks of bias, and very serious and serious imprecision. Very serious and serious risk of bias were due to selection bias in one of the studies (Aiken 1986) where alternation occurred, and performance bias in two studies (Koo 1987 and Koo 1989) where the initial blinding of assessors was broken. Bias also occurred in one study (Aiken 86) where the standard regimen was stopped early due to "*biochemical and clinical problems seen in babies receiving this treatment*". Unclear methods of randomisation, unclear allocation concealment, unclear blinding of assessors, and unclear attrition were also apparent across studies. In addition, the studies had small sample sizes. Serious and very serious imprecision occurred whereby the 95% confidence intervals crossed the minimally important difference on one or both sides. The committee acknowledged that the evidence presented was old and did not accurately reflect the amounts of calcium and phosphate given via PN in current clinical practice. The committee also acknowledged that it was

difficult to make comparisons across the studies due to the overlap in doses administered to babies in the high and standard dose arms of the studies.

Benefits and harms

The committee considered the evidence presented, and used this alongside their knowledge and clinical experience to develop the recommendations by informal consensus. The committee agreed the evidence was old and the amounts of calcium and phosphate given to participating babies were lower than those currently given to babies in clinical practice in the United Kingdom, (apart from in one included study [Prestridge 1993]). Benefits were evident in critical outcomes in babies who received higher amounts of calcium and phosphate, specifically in the reduction in the incidence of rickets, fracture and hypercalciuria, and an increase in bone mineral density.

The committee considered what could be practically delivered when considering calcium and phosphate doses currently given to babies, including amounts delivered when using standardised bags.

The committee agreed that calcium may be given in variable amounts without altering other electrolytes and could be individualised when required to meet the needs of the baby. Even though the evidence was of low quality it showed a pattern that was consistent with the committee's knowledge that showed better bone health (fractures and rickets) associated with higher calcium intake particularly when the lower group received dosages below 0.8 mmol/kg/d. However, some caution should be applied, as there was a relationship between serum calcium and phosphate levels. The committee agreed there was a lack of evidence to support the preference for either 0.8 mmol/kg/d or 1.0 mmol/kg/d of calcium, compared to the other. Therefore calcium in the range of 0.8-1.0mmol/kg/d was recommended, based on informal consensus, which took in to consideration the restrictions on the amount of phosphate that could be given to babies in the first 48 hours of life. Increases in calcium after 48 hours to 1.5-2 mmol/kg/d were consistent with the recommended increases of phosphate during the same time period (see below) and adhered to the recommended calcium to phosphate ratio.

The committee considered the preference for higher amounts of phosphate in the early stages, specifically for soft tissue growth, and to reduce the likelihood of hypercalcaemia. However in practice, as phosphate is likely to be given in the form of sodium glycerophosphate, corresponding increases in sodium intake occur and there is a potential for electrolyte imbalance. It was agreed that babies aged less than 48 hours would be less able to tolerate increases in sodium, specifically when contraction of the extracellular fluid compartment and postnatal diuresis have not yet occurred. Therefore caution should be applied and lower amounts of phosphate was recommended by informal consensus for babies in the early stages. Phosphate at 1 mmol/kg/d was recommended by informal consensus, increasing after 48 hours to 2 mmol/kg/d, when sodium may be better tolerated by babies, and sodium restriction is no longer necessary. The committee acknowledged that phosphate may be needed in higher dosage as the baby grows, and therefore if indicated by low serum phosphate a higher dosage should be administered.

Given these dosages the committee agreed that the resulting ratio of 0.75:1 to 1:1 of calcium to phosphate intake would be appropriate.

Cost effectiveness and resource use

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

The committee explained that recommendations pertaining to the provision of calcium and phosphate components would not incur extra resource implications to the health care system.

The committee noted that optimising the relative amounts of calcium and phosphate for neonatal PN may result in avoiding additional costs associated with adverse effects to the NHS given that incorrect relative amounts of calcium and phosphate for neonatal PN can result in an increased risk of rickets, fracture and hypercalciuria, and a decrease in bone mineral density which may require resource-intensive management.

Although, the recommendations in this area reflect practice across many units and as such cost savings to the NHS, if any, are likely to be negligible.

References

Aiken 1986

Aiken, G., Lenney, W., Calcium and phosphate content of intravenous feeding regimens for very low birthweight infants, Archives of disease in childhood, 61, 495-501, 1986

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Koo, W. W., Tsang, R. C., Steichen, J. J., Succop, P., Babcock, D., Oestreich, A. E., Noseworthy, J., Horn, J., Farrell, M. K., Parenteral nutrition for infants: effect of high versus low calcium and phosphorus content, Journal of pediatric gastroenterology and nutrition, 6, 96-104, 1987

Koo 1989

Koo, W. W., Tsang, R. C., Succop, P., Krug-Wispe, S. K., Babcock, D., Oestreich, A. E., Minimal vitamin D and high calcium and phosphorus needs of preterm infants receiving parenteral nutrition, Journal of pediatric gastroenterology and nutrition, 8, 225-33, 1989

MacMahon 1989

MacMahon, P., Blair, M. E., Treweeke, P., Kovar, I. Z., Association of mineral composition of neonatal intravenous feeding solutions and metabolic bone disease of prematurity, Archives of Disease in Childhood, 64, 489-93, 1989

Mazouri 2017

Mazouri, A., Khosravi, N., Bordbar, A., Khalesi, N., Saboute, M., Taherifard, P., Mirababaee, M., Ebrahimi, M., Does adding intravenous phosphorus to parenteral nutrition has any effects on calcium and phosphorus metabolism and bone mineral content in preterm neonates? Acta Med Iran 55 (6): 395-398 2017

Prestige 1993

Prestridge, L. L., Schanler, R. J., Shulman, R. J., Burns, P. A., Laine, L. L., Effect of parenteral calcium and phosphorus therapy on mineral retention and bone mineral content in very low birth weight infants, Journal of Pediatrics, 122, 761-8, 1993

Vileisis 1987

Vileisis, R. A., Effect of phosphorus intake in total parenteral nutrition infusates in premature neonates, The Journal of pediatrics, 110, 586-90, 1987

Appendices

Appendix A – Review protocols

Review protocol for review question: What are the optimal target doses for calcium and phosphate in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Table 3: Evidence review protocol for calcium and phosphate

Field (based on PRISMA-P	Content
Review question	What are the optimal target dosages for calcium and phosphate in preterm and term babies who are receiving parenteral nutrition and neonatal care?
Type of review question	Intervention
Objective of the review	Inadequate amounts of calcium and phosphate delivered via PN may contribute to bone disease in preterm and term babies. Delivery of calcium and phosphate should be adequate to achieve retention of amounts which match those in utero, but at a concentration that does not result in adverse events. The aim of this review is to determine the optimal dosages for calcium and phosphate in preterm and term babies who are receiving PN
Eligibility criteria – population/disease/condition/issue/domain	• Babies born preterm, up to 28 days after their due birth date (preterm babies) • Babies born at term, up to 28 days after their birth (term babies).
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Any amount of calcium or phosphate (may be reported in a number of ways, for example (mmol/kg/day), (mmols/ml of PN per day))
Eligibility criteria – comparator(s)/control or reference (gold) standard	Each other

Outcomes and prioritisation	**Critical**
	• Metabolic bone disease of prematurity
	• Fractures
	• Growth/Anthropometric measures:
	  ○ Weight gain (g/kg/d)
	  ○ Linear growth
	  ○ Head circumference (mm)
	• Adverse effects of PN:
	  ○ Hypercalcaemia

Field (based on PRISMA-P	Content
	○ Hypercalciuria ○ Hyperphosphataemia (high blood level of phosphate) ○ Hypophosphataemia **Important** • Mortality
Eligibility criteria – study design	Only published full text papers: • Systematic reviews of RCTs • RCTs • Comparative cohort studies (only if RCTs unavailable or limited data to inform decision making) • Conference abstracts will only be considered if related to RCTs
Other inclusion exclusion criteria	No sample size restriction No date restriction
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroup analysis: Population subgroups: • Age of baby (first 2 weeks vs later) • Preterm (extremely preterm <28 weeks' GA; very preterm: 28-31 weeks' GA; moderately preterm: 32-36 weeks' GA) • Birthweight: Low birth weight (< 2500g); very low birth weight (< 1500g) and extremely low birth weight (< 1000g) • Critically ill babies or those requiring surgery (for example, inotropic support, therapeutic hypothermia or fluid restriction) • First week of life and after first week of life?
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. A random sample of the references identified in the search will be sifted by a second reviewer. This sample size will be 10% of the total, or 100 studies if the search identifies fewer than 1000 studies. All disagreements in study inclusion will be discussed and resolved between the two reviewers. The senior systematic reviewer or guideline lead will be involved if discrepancies cannot be resolved between the two reviewers.
Data management (software)	Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists (ROBIS (systematic reviews and meta-analyses); Cochrane risk of bias tool (RCTs or comparative cohort studies); Cochrane risk of bias tool (Non-randomised studies); Newcastle-Ottawa scale (Non-comparative studies)).

Field (based on PRISMA-P	Content
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. 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.

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

CDSR: Cochrane Database of Systematic Reviews; CCTR: Cochrane Controlled Trials Register; DARE: Database of Abstracts of Reviews of Effects; GA: gestational age; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; NGA: National Guideline Alliance; NIHR: National Institute for Health Research; NHS: National health service; NICE: National Institute for Health and Care Excellence; 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 are the optimal target dosages for calcium and phosphate in preterm and term babies who are receiving parenteral nutrition and neonatal care?

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

#	Searches
1	INFANT, NEWBORN/
2	(neonat$ or newborn$ or new-born$ or baby or babies).ti,ab.
3	PREMATURE BIRTH/
4	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 (birth? or born)).ab,ti.
5	exp INFANT, PREMATURE/
6	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 infan$).ti,ab.
7	(pre#mie? or premie or premies).ti,ab.
8	exp INFANT, LOW BIRTH WEIGHT/
9	(low adj3 birth adj3 weigh$ adj5 infan$).ti,ab.
10	((LBW or VLBW) adj5 infan$).ti,ab.
11	INTENSIVE CARE, NEONATAL/
12	INTENSIVE CARE UNITS, NEONATAL/
13	NICU?.ti,ab.
14	or/1-13
15	PARENTERAL NUTRITION/
16	PARENTERAL NUTRITION, TOTAL/
17	PARENTERAL NUTRITION SOLUTIONS/
18	ADMINISTRATION, INTRAVENOUS/
19	INFUSIONS, INTRAVENOUS/
20	CATHETERIZATION, CENTRAL VENOUS/
21	exp CATHETERIZATION, PERIPHERAL/
22	(parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?).ti,ab.
23	((peripheral$ or central$) adj3 (line? or catheter$)).ti,ab.
24	drip?.ti,ab.
25	or/15-24
26	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 calcium).mp.
27	((mmol? or ml) adj3 (d or day) adj5 calcium).mp.
28	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.
29	((mmol? or ml) adj3 (d or day) adj5 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.
30	CALCIUM/ad [Administration & Dosage]
31	CALCIUM, DIETARY/ad [Administration & Dosage]
32	exp PHOSPHATES/ad [Administration & Dosage]
33	PHOSPHORUS/ad [Administration & Dosage]
34	PHOSPHORUS, DIETARY/ad [Administration & Dosage]
35	or/26-34
36	exp AMINO ACIDS/ and ratio?.ti,ab.
37	(ratio? adj10 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-

#	Searches
	Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp.
38	exp PHOSPHATES/ and ratio?.ti,ab.
39	PHOSPHORUS/ and ratio?.ti,ab.
40	PHOSPHORUS, DIETARY/ and ratio?.ti,ab.
41	(ratio? adj10 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.
42	(percent$ adj10 (Phosph$ or amino acid?)).mp.
43	(percent$ adj5 feed$).ti,ab.
44	or/36-43
45	exp AMINO ACIDS/ and (exp PHOSPHATES/ or PHOSPHORUS/ or PHOSPHORUS, DIETARY/)
46	((amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid) adj5 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.
47	or/45-46
48	14 and 25 and 35
49	14 and 25 and 44
50	14 and 25 and 47
51	or/48-50
52	limit 51 to english language
53	LETTER/
54	EDITORIAL/
55	NEWS/
56	exp HISTORICAL ARTICLE/
57	ANECDOTES AS TOPIC/
58	COMMENT/
59	CASE REPORT/
60	(letter or comment*).ti.
61	or/53-60
62	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
63	61 not 62
64	ANIMALS/ not HUMANS/
65	exp ANIMALS, LABORATORY/
66	exp ANIMAL EXPERIMENTATION/
67	exp MODELS, ANIMAL/
68	exp RODENTIA/
69	(rat or rats or mouse or mice).ti.
70	or/63-69
71	52 not 70

1

2 **Databases: Embase; and Embase Classic**

#	Searches
1	NEWBORN/
2	(neonat$ or newborn$ or new-born$ or baby or babies).ti,ab.
3	PREMATURITY/

#	Searches
4	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 (birth? or born)).ab,ti.
5	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 infan$).ti,ab.
6	(pre#mie? or premie or premies).ti,ab.
7	exp LOW BIRTH WEIGHT/
8	(low adj3 birth adj3 weigh$ adj5 infan$).ti,ab.
9	((LBW or VLBW) adj5 infan$).ti,ab.
10	NEWBORN INTENSIVE CARE/
11	NEONATAL INTENSIVE CARE UNIT/
12	NICU?.ti,ab.
13	or/1-12
14	PARENTERAL NUTRITION/
15	TOTAL PARENTERAL NUTRITION/
16	PERIPHERAL PARENTERAL NUTRITION/
17	PARENTERAL SOLUTIONS/
18	INTRAVENOUS FEEDING/
19	INTRAVENOUS DRUG ADMINISTRATION/
20	exp INTRAVENOUS CATHETER/
21	(parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?).ti,ab.
22	((peripheral$ or central$) adj3 (line? or catheter$)).ti,ab.
23	drip?.ti,ab.
24	or/14-23
25	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 calcium).mp.
26	((mmol? or ml) adj3 (d or day) adj5 calcium).mp.
27	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.
28	((mmol? or ml) adj3 (d or day) adj5 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.
29	CALCIUM/ad, do [Drug Administration, Drug Dose]
30	CALCIUM INTAKE/
31	PHOSPHATE/ad, do [Drug Administration, Drug Dose]
32	PHOSPHORUS/ad, do [Drug Administration, Drug Dose]
33	PHOSPHATE INTAKE/
34	or/25-33
35	exp *AMINO ACIDS/ and ratio?.ti,ab.
36	(ratio? adj10 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp.
37	PHOSPHATE/ and ratio?.ti,ab.
38	PHOSPHORUS/ and ratio?.ti,ab.
39	PHOSPHATE INTAKE/ and ratio?.ti,ab.
40	(ratio? adj10 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.
41	(percent$ adj10 (Phosph$ or amino acid?)).mp.
42	(percent$ adj5 feed$).ti,ab.
43	or/35-42
44	exp AMINO ACIDS/ and (PHOSPHATE/ or PHOSPHORUS/ or PHOSPHATE INTAKE/)
45	((amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or

#	Searches
	Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid) adj5 (Phosph$ or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)).mp.
46	or/44-45
47	13 and 24 and 34
48	13 and 24 and 43
49	13 and 24 and 46
50	or/47-49
51	limit 50 to english language
52	letter.pt. or LETTER/
53	note.pt.
54	editorial.pt.
55	CASE REPORT/ or CASE STUDY/
56	(letter or comment*).ti.
57	or/52-56
58	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
59	57 not 58
60	ANIMAL/ not HUMAN/
61	NONHUMAN/
62	exp ANIMAL EXPERIMENT/
63	exp EXPERIMENTAL ANIMAL/
64	ANIMAL MODEL/
65	exp RODENT/
66	(rat or rats or mouse or mice).ti.
67	or/59-66
68	51 not 67

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: [PARENTERAL NUTRITION] this term only
16	MeSH descriptor: [PARENTERAL NUTRITION, TOTAL] this term only
17	MeSH descriptor: [PARENTERAL NUTRITION SOLUTIONS] this term only
18	MeSH descriptor: [ADMINISTRATION, INTRAVENOUS] this term only
19	MeSH descriptor: [INFUSIONS, INTRAVENOUS] this term only
20	MeSH descriptor: [CATHETERIZATION, CENTRAL VENOUS] this term only

#	Searches
21	MeSH descriptor: [CATHETERIZATION, PERIPHERAL] explode all trees
22	(parenteral* or intravenous* or intra-venous* or IV or venous* or infusion?):ti,ab
23	((peripheral* or central*) near/3 (line? or catheter*)):ti,ab
24	drip?:ti,ab
25	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26	((Dose? or Dosage? or Regimen? or Amount? or Optimal* or Optimis* or Requir* or Target? or Rate? or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/5 calcium):ti,ab
27	((mmol? or ml) near/3 (d or day) near/5 calcium):ti,ab
28	((Dose? or Dosage? or Regimen? or Amount? or Optimal* or Optimis* or Requir* or Target? or Rate? or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/5 (Phosph* or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)):ti,ab
29	((mmol? or ml) near/3 (d or day) near/5 (Phosph* or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)):ti,ab
30	MeSH descriptor: [CALCIUM] this term only and with qualifier(s): [Administration & dosage - AD]
31	MeSH descriptor: [CALCIUM, DIETARY] this term only and with qualifier(s): [Administration & dosage - AD]
32	MeSH descriptor: [PHOSPHATES] explode all trees and with qualifier(s): [Administration & dosage - AD]
33	MeSH descriptor: [PHOSPHORUS] this term only and with qualifier(s): [Administration & dosage - AD]
34	MeSH descriptor: [PHOSPHORUS, DIETARY] this term only and with qualifier(s): [Administration & dosage - AD]
35	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34
36	MeSH descriptor: [AMINO ACIDS] explode all trees
37	ratio?:ti,ab
38	#36 and #37
39	(ratio? near/10 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)):ti,ab
40	MeSH descriptor: [PHOSPHATES] explode all trees
41	MeSH descriptor: [PHOSPHORUS] this term only
42	MeSH descriptor: [PHOSPHORUS, DIETARY] this term only
43	#40 or #41 or #42
44	ratio?:ti,ab
45	#43 and #44
46	(ratio? near/10 (Phosph* or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)):ti,ab
47	(percent* near/10 (Phosph* or amino acid?)):ti,ab
48	(percent* near/5 feed*):ti,ab
49	#38 or #39 or #45 or #46 or #47 or #48
50	MeSH descriptor: [AMINO ACIDS] explode all trees
51	MeSH descriptor: [PHOSPHATES] explode all trees
52	MeSH descriptor: [PHOSPHORUS] this term only
53	MeSH descriptor: [PHOSPHORUS, DIETARY] this term only
54	#51 or #52 or #53
55	#50 and #54
56	((amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain?

#	Searches
	or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid) near/5 (Phosph* or Apatite? or Hydroxyapatite? or Durapatite or Calcium Pyrophosphate or Polyphosphate? or Diphosphate? or Calcium Pyrophosphate or Technetium Tc 99m Pyrophosphate or Tin Polyphosphate? or Struvite)):ti,ab
57	#55 or #56
58	#14 and #25 and #35
59	#14 and #25 and #49
60	#14 and #25 and #57
61	#58 or #59 or #60

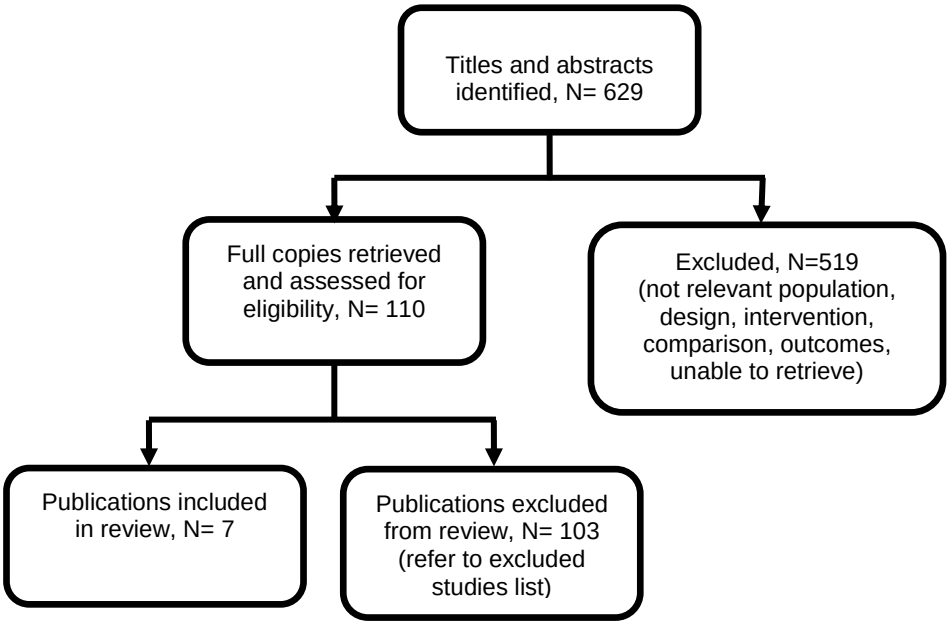
1

2

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What are the optimal target dosages for calcium and phosphate in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Figure 1: PRISMA flow chart of clinical article selection for review question on optimal target dosages for calcium and phosphate.



Appendix D – Clinical evidence tables

Clinical evidence table for review question: What are the optimal target dosages for calcium and phosphate in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Table 4: Clinical evidence table

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aiken, G., Lenney, W., Calcium and phosphate content of intravenous feeding regimens for very low birthweight infants, Archives of disease in childhood, 61, 495-501, 1986 Ref Id 606272 Country/ies where the study was carried out UK Study type RCT Aim of the study To test whether the increase of calcium and phosphate contained in IF decrease the likelihood for premature infants to	Sample size Regimen A: n=5 and Regimen B: n=10 Characteristics Infants' birth weight < 1500g when started the IF. Inclusion criteria Premature infants receiving IF exclusively. Exclusion criteria Premature infants who were not fed exclusively with IF.	Intravenous feeding (IF) consisted of 10% Vamin-dextrose solution beginning on day 3 at a rate of 120ml/kg/day and Intralipid 20% solution beginning on day 5 given at 10-15 ml/kg/day. The intralipid 20% solution was composed of 100 ml intralipid 20% and 10 ml vitlipid infant and provided a vitamin D2 intake of roughly 100U/kg/day. This was identical for the two arms except of the calcium and phosphate intakes. Regimen A: calcium: 0.55 mmol/kg/day and phosphate: 0.44 mmol/kg/day (n=5).	Regimen A was stopped after day 10 because biochemical and clinical problems were encountered. One infant developed frank radiological rickets while on IF and one developed mild radiological rickets after the period of IF. Two further babies had plasma phosphate concentration persistently below 1.2 mmol/l (3.7 mg/100ml) after the period of feeding and these required phosphate supplementation. The duration of IF varied from 26-75 days and 8 infants	(Regimen A vs Regimen B, results assessed between 11 and 30 days after starting the IF), Birth weight(g): Regimen A: 1067, SD 239 Regimen B: 1066, SD 198 Weight gain (g/kg/day): Regimen A: 11.3, SD 3 Regimen B: 13, SD 1.7 Fracture: Rib fracture developed in 1 infant given Regimen A Rickets: Rickets developed in 2 babies given Regimen A and 2	Limitations Risk of bias assessment: Random sequence allocation: Unclear Allocation concealment: High-risk Blinding of participants and personnel: Unclear Blinding of outcome assessment: Unclear Incomplete outcome data: Unclear Selective reporting: Unclear Anything else-ideally prespecified: High-risk Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
experience poor bone mineralisation and develop osteopenia and rickets. Study dates Not reported (definitely before 1986). Source of funding Royal Alexandra Hospital Centenary Fund.		Regimen B: calcium: 1.08 and 0.89 mmol/kg/day (n=10).	received it for more than 40 days.	babies given Regimen B.	Concentration of urine calcium and phosphate are reported and expressed as mmol/mmol creatinine.
Koo, W. W., Tsang, R. C., Steichen, J. J., Succop, P., Babcock, D., Oestreich, A. E., Noseworthy, J., Horn, J., Farrell, M. K., Parenteral nutrition for infants: effect of high versus low calcium and phosphorus content, Journal of pediatric gastroenterology and nutrition, 6, 96-104, 1987 Ref Id 606449 Country/ies where the study was carried out USA	Total n = 18. Characteristics All infants received 25 IU vitamin D2 (ergocalciferol)/dl of amino acid-dextrose solution. The contents of the nutrient infusate were the same, except for calcium and phosphorus. Infants with surgical indications for parenteral nutrition. No significant differences on key variables at baseline between the two arms (intervention and control). Inclusion criteria Not reported.	High Ca and P infusate: (15mM each; 80 mg Ca and 60 mg P/dl) (n =9). [1.5-1.9 mmol/kg/d Ca and 1.5- 2.0 mmol/kg/day Ph] Low Ca and P infusate (standard solution): (5mM each; 20 mg Ca and 15.5 mg P/dl) (n = 9). [0.5 mmol/kg/day Ca, and 0.3 mmol/kg/day Ph]	No significant differences regarding the differences of the two groups in the rate of change of body weight and head circumference are reported.	Weight gained/day (g): High: 19.0, SEM 5.0 [Calculated SD: 15] Low: 19.5, SEM 5.1 [Calculated SD: 15.3]	Limitations Risk of bias assessment: Random sequence allocation: Low-risk Allocation concealment: Unclear Blinding of participants and personnel: High-risk Blinding of outcome assessment: High-risk Incomplete outcome data: Unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT Aim of the study to test whether high concentrations of calcium and phosphorus in the infusate delivery quantities of calcium and phosphorus, in a combination at or above the reported calcium and phosphorus retention in human milk, would result in little metabolic stress for calcium and phosphorus haemostatic mechanisms. Study dates Not reported (before 1987). Source of funding Research grants (NIH IROI HD 18505-01A1, NIH RR 00123, and NIH RR 00068.	Exclusion criteria Not reported.				Selective reporting: Unclear Anything else-ideally pre-specified: High-risk Other information Number of dropouts are not reported. It is not explicitly reported that participants were not receiving oral intakes during this study (potentially this study could be excluded) Amounts of calcium and phosphorous have been converted by calculation into mmol/kg/day at a PN intake of 100ml/kg/day
Koo, W. W., Tsang, R. C., Succop, P., Krug-	N=26	Interventions	Details	Results Fracture:	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Wispe, S. K., Babcock, D., Oestreich, A. E., Minimal vitamin D and high calcium and phosphorus needs of preterm infants receiving parenteral nutrition, Journal of pediatric gastroenterology and nutrition, 8, 225-33, 1989 Ref Id 393852 Country/ies where the study was carried out USA Study type RCT Aim of the study To determine the adequacy of parenteral nutrition infusates given to small preterm infants with fixed, low dose Vitamin D and two combinations of calcium and phosphorous Study dates	(N=13; high dose: N=12; low dose) *two infants were changed to the high-dose calcium and phosphorous infusate at 22 and 68 days on request from their clinicians because of severe hypophosphataemia (serum phosphorous level <2.5 mg/dl) Characteristics Race (white/black)(b): [(b) cross tabular analysis, p>0.05] High dose: 11/2 Low dose: 11/1 Sex (male/female)(b): [(b) cross tabular analysis, p>0.05] High dose: 6/7 Low dose: 5/7 Gestation (wk)(c): [(c) student's t-test, p>0.05] High dose: 28.8, SEM 1.0 Low dose: 29, SEM 1.0 Birth weight (g)(d): [(d) Wilcoxon two-group rank test, p>0.05] High dose: 1,065, SEM 124 Low dose: 1,115, SEM 140 Age at entry (days)(d): [(d) Wilcoxon two-group rank test, p>0.05]	High Dose Ca and P: 15mM each (60mg/dl of Ca and 46.5 mg/dl of P) [1.5 mmol/kg/d Ca and 1.5 mmol/kg/d P] Low dose Ca and P: standard solution in use at CHMC: 5mM each (20mg/dl of Ca and 15 mg/dl of P) [0.5 mmol/kg/day Ca and P]	All infants received 25 IU of vitamin D2 The Ca and P content of the high dose solution was increased over 2 days, beginning at 80% Enteral feedings were attempted for all infants whenever possible, and these were recorded. Therefore 18 infants were enrolled after 9, SD 1.8 days of supplemental PN (when they could not tolerate adequate enteral feeds) Statistical Methods: Contingency tables were analysed to test for group differences in discrete variables. The Wilcoxon two-group rank sum test was used for comparing groups with non-normally distributed variables. The unpaired Student's t test was performed for normally distributed variables. A random coefficient regression (RCR) model was used for the replicated	1 infant on Low-dose Ca/P; Fractured distal left ulna noted on the forearm radiograph and additional fracture involving the shaft of the right humerus 1 week later when the infant was tolerating enteral feeding.	Risk of bias assessment: Random sequence allocation: Unclear Allocation concealment: Unclear Blinding of participants and personnel: High-risk Blinding of outcome assessment: Low-risk Incomplete outcome data: Unclear Selective reporting: Unclear Anything else-ideally pre-specified: High-risk Other information Amounts of calcium and phosphorous have been converted by calculation into mmol/kg/day at a PN intake of 100ml/kg/day

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported Source of funding Supported by grants from the National Institutes of Health.	High dose: 20, SEM 5.5 Low dose: 18, SEM 4.1 Weight at entry (g)(c): [(c) student's t-test, p>0.05] High dose: 1,173, SEM 147 Low dose: 1,082, SEM 115 Maximum infusate volume (ml/kg/day)(c): [(c) student's t-test, p>0.05] High dose: 124, SEM 4.6 Low dose: 123, SEM 5.3 Maximum vitamin D infused (IU/kg/day)(c): [(c) student's t-test, p>0.05] High dose: 31, SEM 1.2 Low dose: 31, SEM 1.3 Enteral intake during study (kcal/kg/day) (e): [(e) enteral intake was the infant's own mother's milk (n=4) or standard 20-kcal/oz. cow's milk formula (n=12). Six infants received protein hydrolysate and another received a preterm infant formula. ten infants also received a glucose/electrolyte solution as a supplement to milk feedings] High dose: 12, SEM 3.4 Low dose: 12, SEM 2.9 [LD] Enteral vitamin D intake during study (IU/day):		serum and urine measured. Values are reported as mean, SEM.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	High dose: 8, SEM 2.3 Low dose: 10, SEM 2.8 Inclusion criteria preterm infants requiring PN (major indications for PN included prematurity with respiratory dysfunction and/or inadequate gut function, necrotising enterocolitis, omphalocoele, and congenital small bowel obstruction) Exclusion criteria Not reported				
MacMahon, P., Blair, M. E., Treweeke, P., Kovar, I. Z., Association of mineral composition of neonatal intravenous feeding solutions and metabolic bone disease of prematurity, Archives of Disease in Childhood, 64, 489-93, 1989 Ref Id 701163 Country/ies where the study was carried out	N= 27 (N=13; group 1. N=14; group 2) Characteristics Group 1 (standard) VS Group 2 (increased mineral content) The following are expressed as Median (range): Birthweight: Standard: 960 (580-1760) Increased min: 830 (590-1495)	Standard solution (group 1): 0.68 mmol/kg/day of calcium and 0.61 mmol/kg/day of phosphorus Increased mineral content (group 2): 1.25 mmol/kg/day of calcium and 1-20 mmol/kg/day of phosphorus	PN solution included Calcium as 10% calcium gluconate (2-2 mmol/ 10 ml) and Phosphorus as 8-7% potassium phosphate (5 mmol/10 ml). The sequence of additions was coordinated to avoid precipitation whereby phosphorus salt was the first additive to the amino acid/dextrose mixture, and any calcium salts were added last. The solutions were refrigerated until required. The amount	Rickets: The only three infants to develop classical radiographic changes of rickets (grade 2) received standard solution	Cochrane risk of bias tool: Selection bias Random sequence allocation: Unclear risk. No details provided on the method of randomisation. Allocation concealment: Unclear risk. Participants were sequentially allocated however it is not described if they are numbered etc.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
UK Study type RCT Aim of the study To assess the effects of PN with increased mineral content on biochemical and radiological indicators of metabolic bone disease of prematurity Study dates July 1985 - October 1986 Source of funding Not reported	Gestational age: Standard: 28 (25-33) Increased min: 26 (24-41) Male: female ratio: Standard: 7:6 Increased mineral: 8:6 Duration of Parenteral nutrition: (days) Standard: 48 (14-199) Increased mineral: 56 (14-77) Intermittent positive pressure ventilation: (days) Standard: 48 (0-102) Increased min: 40 (2-83) Supplementary oxygen: Standard: 18 (0-51) Increased min: 16 (0-75) Parenteral intake: Energy (MJ/kg/day) Standard: 0-360 (0.176-0-594) Increased min: 0.360 (0.142-0.523) Protein (g/kg/day) Standard: 3-43 (105-4 2) Increased: 3.49 (0.2-4.2)		of each solution infused was recorded and from this, the delivered amount of calcium and phosphorus actually was calculated Statistical analysis Student's t test was used to assess significance of differences for parametric data, and the Mann-Whitney U test for non-parametric data		Performance bias Blinding of participants and personnel: Unclear risk. Infants would be unaware of their assignment however it is unclear whether personnel were blinded. Detection bias: Blinding of outcome assessment: Low-risk. Outcomes are objective. Attrition bias: Incomplete outcome data: Unclear risk. The study does not comment on withdrawals or exclusions Reporting bias: Selective reporting: Unclear risk. The study protocol is not available and it is not clear that the published reports include all expected outcomes. Other sources of bias: Unclear risk.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Fat (g/kg/day) Standard: 2-2 (0-4) Increased: 2.1 (0-4.1) Dextrose: (g/kg/day) Standard: 13-5 (6-8-23) Increased: 13.2 (3.1-20.1) Enteral intake Energy (MJ/kg/day) Standard: 0.004 (0-0.146) Increased: 0.008 (0.-0.155) Calcium (mmol/kg/day) Standard: 0 (0-0.2) Increased: 0.02 (0-0.4) Phosphorus (mmol/kg/day) Standard: 0 (0-0.4) Increased: 0.02 (0-0.81) Total mineral intake: Calcium (mmol/kg/day) Standard: 0.68 (0.32-1.05) Increased min: 1.25 (0.29-1.84) Phosphorus (mmol/kg/day) Standard: 0.61 (0-16-0.98) Increased: 1.20 (0.39-1.74) Inclusion criteria				Other information When enteral feeding was possible the mother's own expressed breast milk was used in preference; if not, a proprietary preterm formula was used. The mineral content of expressed breast milk was assumed to be 7.0 mmol/l of calcium and 4.8 mmol/l of phosphorus with an average absorption rate of 34 and 86% respectively. The mineral content of any proprietary milk used was calculated from the manufacturer's data sheet and the percentage absorption of calcium and phosphorus was assumed to be 42 and 82.5, respectively. From these data the amount of calcium and phosphorus absorbed from any enteral feeds was calculated.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Neonatal infants who required parenteral nutrition for ≥ 14 days with ≥ 75% of the volume of fluid given intravenously Exclusion criteria Not reported				
Prestridge, L. L., Schanler, R. J., Shulman, R. J., Burns, P. A., Laine, L. L., Effect of parenteral calcium and phosphorus therapy on mineral retention and bone mineral content in very low birth weight infants, Journal of Pediatrics, 122, 761-8, 1993 Ref Id 393295 Country/ies where the study was carried out USA Study type RCT Aim of the study To determine whether greater quantities of Ca and P in parenteral	N=24 (N=12, standard PN Vs N=12 High Ca-P PN) Characteristics Standard PN Vs High Ca-P PN Birth weight (gm): Standard: 921, SD 171 High: 875, SD 180 Gestational age (wk): Standard: 27, SD 2 High: 27, SD 2 Gender (M/F): Standard: 6/6 High: 4/8 PN start (days): Standard: 3.6, SD 1.2 High: 3.2, SD 0.6 PN duration (days): Standard: 24, SD 7 High: 22, SD 0.6 Average fluid intake (ml/kg/day): Standard: 153, SD 10 High: 152, SD 8	Standard PN solution (group STAND): 1.25 mmol calcium and 1.5 mmol phosphorus per decilitre [1.5 mmol/kg/day Ca, and 1.8 mmol/kg/day P] 35% more Ca and P (group HIGH):1.7 mmol calcium and 2.0 mmol phosphorus per decilitre [1.8 mmol/kg/day Ca, and 2.5 mmol/kg/day P]	Infants were enrolled the day after their birth. PN was initiated on postnatal day 3. The volume was adjusted by protocol on the basis of birth weight: 80, 100, 120, and 130 ml /kg/day on successive days 3 to 6. Thereafter, fluid volumes were adjusted daily on the basis of body weight to maintain a PN intake of 130 ml/kg. Intravenous administration of lipid emulsion started day 5, and quantities were increased daily from 1 to 4 g/kg, as indicated on the basis of serial serum triglyceride concentrations. Additional fluid needs, as indicated clinically were met with	BMC The rate of change in bone mineral content (BMC) was greater in group HIGH than in group STAND Between 1 and 4 weeks [p = 0.005] HIGH: 2.33 ± 0.99 mg/cm/wk STAND: 0.05 ± 1.3 mg/cm/wk Between 1 and 8 weeks [p <0.001] HIGH: 1.97 ± 0.63 mg/cm/wk STAND: 0.71 ± 0.68 mg/cm/wk Time-point: Week 4 HIGH: 27.5(13.86) STAND: 31(3.46) Time-point: week 8 HIGH: 34(10.39) STAND: 32(10.39)	Limitations Enteral intake was started at 19 ± 5 and 17 ± 2 days in group STAND and group HIGH Cochrane risk of bias tool Selection bias Random sequence generation: Low risk. Randomisation was conducted by Pharmacy personnel, using random number cards stratified by birth weight. Allocation concealment: Low risk. Central allocation. Randomisation was conducted by Pharmacy personnel. Performance bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
nutrition will promote increased apparent retention of Ca and P, and improve bone mineral content in VLBW infants Study dates Not reported Source of funding Supported by the General Clinical Research Centre, Baylor College of Medicine/Texas Children's Hospital Clinical Research Centre and by the U.S. Department of Agriculture, Agricultural Research Service	Average energy intake (kcal/kg/day): Standard: 94, SD 9 High: 92, SD 7 Regain birth weight (days): Standard: 14, SD 4 High: 18, SD 6 Weight change during PN (gm/kg/day): Standard: 14, SD 6 High: 14, SD 9 Inclusion criteria birth weight <1.2 kg, no major congenital malformations, and the expectation that PN would be required for approximately 3 weeks Exclusion criteria Not reported		parenteral solutions not containing Ca and P. Statistical Analysis Subject characteristics were analysed with a Student t test or chi-square analysis. Baseline measurements of intravenous nutrient intake, urinary excretion, and serum indexes of mineral status were compared with a Student t test for normally distributed data or the Mann-Whitney test for non-normal data. Linear regression analyses were used to determine changes with time in measurements obtained serially during the PN interval. Average value of the serial determinations was used in the analyses. The comparison of baseline with the average value		Blinding of participants and personnel: Low risk. Infants would be unaware of their assignment and Investigators and care givers were unaware of group assignment. Detection bias Blinding of outcome assessment: Low risk. Outcomes are objective. Attrition bias Incomplete outcome data: Low risk. No missing outcome data. Reporting bias Selective reporting: Unclear risk. The study protocol is not available and it is not clear that the published reports include all expected outcomes. Other bias Other sources of bias: Unclear risk. Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			during the PN interval was made by using a paired t test. Analysis of variance for repeated measures and analysis of covariance, with BMC at 1 week as the covariate, were used to analyse BMC data. Unless otherwise noted, data are expressed as the mean + SD.		Amounts of calcium and phosphorous have been converted by calculation into mmol/kg/day at a PN intake of 100ml/kg/day
Vileisis, R. A., Effect of phosphorus intake in total parenteral nutrition infusates in premature neonates, The Journal of pediatrics, 110, 586-90, 1987 Ref Id 606630 Country/ies where the study was carried out USA Study type RCT Aim of the study	N=27 (N=10 Low, N=8 Moderate, N=9 High) Characteristics Low VS Moderate Vs High Gestational age (wk) Low: 27.2, SEM 0.4 Moderate: 28.2, SEM 1.1 High: 29.8, SEM 0.5* [(*)Low versus high P intake difference, P <0.002; no differences in any other parameters] Birth weight (kg) Low: 0.88, SEM 0.07 Moderate: 1.09, SEM 0.12 High: 1.18, SEM 0.09	Low: 1.01, SEM 0.04 mmol phosphorus/kg/d Moderate: 1.34, SEM 0.03 phosphorus mmol/kg/d High: 1.67, SEM 0.05 phosphorus mmol/kg/d All babies received a low calcium intake, 0.25 mmol/l/day	After randomisation, infants received one of the infusates for the next 14 days of life. Doses of phosphorus were within recommended guidelines and P intake was calculated to include both the contribution from lipids and the potassium phosphate in the TPN infusate. Each infant received 1 vial of multivitamin solution per day (providing 400 IU vitamin D and 30 to 35 mg/kg/d elemental calcium as the	Hypercalciuria *Defined as urinary calcium excretion ≥4 mg/ kg/d Low: incidence was 70% (seven of 10 infants) Moderate: incidence of 12.5% High: incidence of 0% Weight gain over study period (g): Low: 25.0, SEM 27 [Calculated SD: 85.38] Moderate: 40.0, SEM 32	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Unclear risk. No details provided on the method of randomisation. Allocation concealment: Unclear risk. No information provided on the method of allocation. Performance bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To evaluate the influence of three alternate total parenteral nutrition regimens differing in phosphorus amount on Ca and P homeostasis in premature, critically ill infants Study dates Not reported Source of funding Supported by the Walker P. lnman Fund and Perry Como Children's Classic Fund	Age prior to initiation of TPN (d) Low: 6.3, SEM 1.4 Moderate: 11.4, SEM 5.2 High: 10.1, SEM 3.7 Study TPN prior to urine collection (d) Low: 6.1, SEM 1.1 Moderate: 6.8, SEM 1.2 High: 7.2, SEM 1.0 Patients with bowel disease Low: 1 Moderate: 1 High: 2 Weight gain over study period (g) Low: 25.0, SEM 27 Moderate: 40.0, SEM 32 High: 40.0, SEM 6 Inclusion criteria birth weight <1500g who required TPN Exclusion criteria Not reported		gluconate salt). Crystalline amino acid infusion was 2.5 g/kg/d. Glucose, lipid, and electrolyte intakes were dictated by the patient's clinical status and fluid requirements. All but three infants were nourished exclusively with glucose-electrolyte solutions until the initiation of TPN. Three infants (one in each P intake group) had received small feedings orally prior to onset of necrotising enterocolitis. Average daily caloric intake was approximately 60 kcal/kg. Caloric intake was limited by the infants' intolerance of larger fluid, dextrose, or lipid infusion rates. Statistical Analysis Unpaired t test used for comparison of urinary chemical results. Significance was assigned to P <0.005 as an adjustment for	High: 40.0, SEM 16 [Calculated combined SD for Moderate and High: 68.82]	Blinding of participants and personnel: Unclear risk. Infants would be unaware of their assignment however it is unclear whether personnel were blinded. Detection bias Blinding of outcome assessment: Low risk. Outcomes are objective. Attrition bias Incomplete outcome data: Unclear risk. The study does not comment on withdrawals or exclusions. Reporting bias Selective reporting: Unclear risk. The study protocol is not available and it is not clear that the published reports include all expected outcomes. Other bias Other sources of bias: Unclear risk.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			multiple comparisons. Chi-square analysis used for comparison of incidence of abnormal urinary excretion between groups. Analysis of variance for repeated measures with the Bonferroni t test was made for comparison of serum chemical concentrations over time and between groups. Values represented as mean ± SEM.		
Mazouri, Ali, Khosravi, Nastaran, Bordbar, Arash, Khalesi, Nasrin, Saboute, Maryam, Taherifard, Pegah, Mirzababaee, Marjan, Ebrahimi, Mehran, Does Adding Intravenous Phosphorus to Parenteral Nutrition Has Any Effects on Calcium and Phosphorus Metabolism and Bone Mineral Content in Preterm Neonates?, Acta medica Iranica, 55, 395-398, 2017	Sample size N=50 Intervention: TPN with intravenous Glycophos (n=25) Control: TPN without Glycophos (n=25) Characteristics male gender Control: 68% Int: 60.0% P=0.556 mean birth weight Case: 1.31, SD 0.14 kg	Intervention: TPN with intravenous sodium glycerophosphate or Glycophos (1.5 mmol/kg/day) Control: TPN without sodium glycerophosphate	At baseline as well as every week during treatment, the Serum levels of calcium, phosphorus, and alkaline phosphatase and urine levels of calcium, phosphorus, and creatinine were measured for the diagnosis and treatment of osteopenia (at baseline and every week during treatment) At the end of the fourth week of treatment, the presence of osteopenia	BMD (g/cm2) Glyco: 0.13, SD 0.01 No Glyco: 0.10, SD 0.02 p=<0.001 Those who received TPN with intravenous Glycophos experienced more increase in bone mineral density than those in control group (0.13, SD 0.01 versus 0.10, SD 0.02, P<0.001).	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Unclear risk. No details provided on the randomisation. Described only as block randomisation. Allocation concealment: Unclear risk. No information provided on allocation. Performance bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 743224 Country/ies where the study was carried out Iran Study type RCT Aim of the study To assess the effect of additional intravenous phosphorus to total parenteral nutrition (TPN) on calcium and phosphorus metabolism and bone mineral content in preterm neonates Study dates 2014 Source of funding Not reported	Control: 1.27, SD 0.16 kg P=0.352 mean gestational age Case: 29.5, SD 1.1 weeks Control: 29.7, SD 1.2 weeks P=0.542 mean duration of TPN regimen Case: 9.8, SD 3.0 days Control: 10.0, SD 2.7 days P=0.805 Inclusion criteria preterm neonates with a gestational age < 32 weeks and neonatal weight <1500 grams Exclusion criteria neonates with a history of maternal hyperparathyroidism or maternal vitamin D deficiency		was examined using DEXA Scan. Drug side effects resulting from intervention were also assessed. Statistical analysis Results are presented as mean ± standard deviation (SD) for quantitative variables and were summarised by absolute frequencies and percentages for categorical variables. Categorical variables were compared using chi-square test. Quantitative variables were also compared using t test or Mann-Whitney U test. The correlations were tested using Pearson's or Spearman’s Rank order correlation tests. P ≤ 0.05 considered statistically significant.		Blinding of participants and personnel: Low risk. Infants would be unaware of their assignment and personnel for DEXA scanning and statistical analyser were blinded to study protocol. Detection bias Blinding of outcome assessment: Low risk. Outcomes are objective. Attrition bias Incomplete outcome data: Unclear risk. The study does not comment on withdrawals or exclusions. Reporting bias Selective reporting: Unclear risk. The study protocol is not available and it is not clear that the published reports include all expected outcomes. Other bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Other sources of bias: Unclear risk.

BMC: bone mineral content; CA: calcium; IF: intravenous feed; NIH: National Institutes of Health; P: phosphate; PN: parenteral nutrition; RCT: randomised controlled trial; SD: standard deviation; SEM: standard error of the mean; STAND: standard; TPN: total parenteral nutrition; UK: United Kingdom; USA: United States of America; WK: week.

Appendix E – Forest plots

Forest plots for review question: What are the optimal target doses for calcium and phosphate in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Figure 2: Forest plot for comparison of high calcium and high phosphorous versus standard (low) calcium and phosphorous: Weight gain

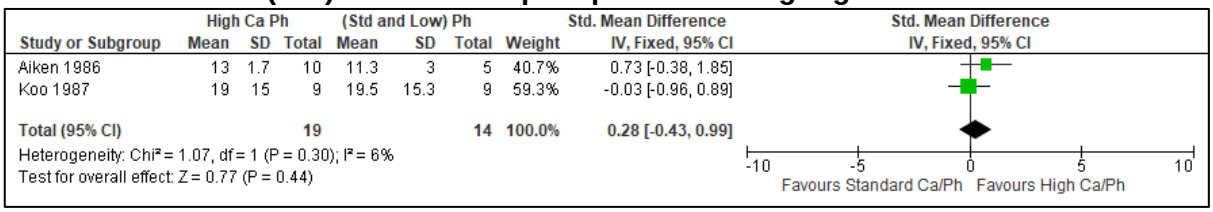


Figure 3: Forest plot for comparison of high calcium and high phosphorous versus standard (low) calcium and standard (low) phosphorous: Fracture

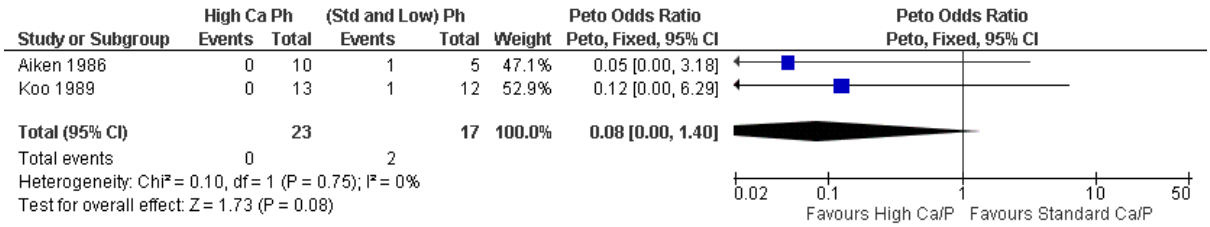
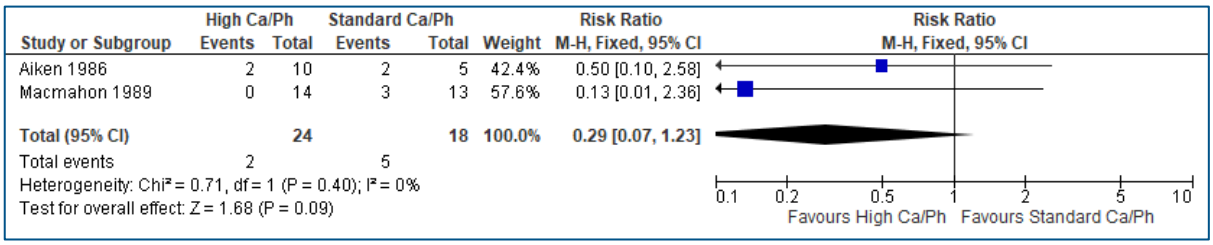


Figure 4: Forest plot for comparison of high calcium and high phosphorous versus standard (low) calcium and standard (low phosphorous): Rickets



Appendix F – GRADE tables

GRADE tables for review question: What are the optimal target doses for calcium and phosphate in preterm and term babies who are receiving parenteral nutrition and neonatal care?

High calcium and phosphorous versus standard (low) calcium and phosphorous

Table 5: Evidence profile for outcomes related to the comparison of high calcium and phosphorous versus standard (low) calcium and phosphorous.

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High Ca/Ph	Std/ Low Ca/ Ph	Relative (95% CI)	Absolute	Quality	Importance
Weight gain (g/kg/day) (Better indicated by higher values)												
2	rando mised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19	14	-	SMD 0.28 higher (0.43 lower to 0.99 higher)	⊕OOO VERY LOW	CRITICAL
Incidence of Fracture (Better indicated by lower values)												
2	rando mised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	0/23 (0%)	2/17 (11.8 %)	Peto OR 0.08 (0.00 to 1.40)	108 fewer per 1000 (from 118 fewer to 47 more)	⊕OOO VERY LOW	CRITICAL
Incidence of rickets (Better indicated by lower values)												
2	rando mised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	2/24 (8.3%)	5/18 (27.8 %)	RR 0.29 (0.07 to 1.23)	197 fewer per 1000 (from 258	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High Ca/Ph	Std/ Low Ca/ Ph	Relative (95% CI)	Absolute		
										fewer to 64 more)		
Bone mineral content (mg/cm)(week 4) (Better indicated by higher values)												
1	rando mised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	12	-	MD 2.28 higher (1.36 higher to 3.20 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Bone mineral content (mg/cm) (week 8) (Better indicated by higher values)												
1	rando mised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	12	12	-	MD 1.29 higher (4.59 lower to 7.17 higher)	⊕⊕⊕O MODE RATE	CRITICAL

Ca: calcium; CI: confidence interval; OR: odds ratio; Ph: phosphorous; RCT: randomised controlled trial; RR: risk ratio; SMD: standardised mean difference.

[1] *Evidence downgraded due to non-specified randomisation, inadequate method of allocation concealment and deviation from the protocol.*

[2] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for SMD (0.5).*

[3] *Evidence downgraded due to non-specified randomisation, inadequate method of allocation concealment, broken blinding and early termination of treatment.*

[4] *Evidence* was downgraded for risk of imprecision due to low event rate

[5] *Very serious risk of bias due to lack of allocation concealment and stopping the control group early for benefit.*

[6] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for dichotomous outcomes (0.8 or 1.25).*

[7] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-5.20 and 5.20).*

High/moderate phosphorous versus low phosphorous

Table 6: Evidence profile for outcomes related to the comparison of high and moderate phosphorous versus low phosphorous.

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High/ Mod Ph	Low Ph	Relative (95% CI)	Absolute	Quality	Importance
Hypercalciuria (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/17 (5.9 %)	7/10 (70 %)	RR 0.08 (0.01 to 0.59)	644 fewer per 1000 (from 287 fewer to 693 fewer)	⨁⨁◯◯ LOW	CRITICAL
Weight gain (g) (Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17	10	-	MD 15 higher (47.21 lower to 77.21 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; MD: mean difference; Ph: phosphorous; RR: risk ratio.

[1] *Evidence downgraded due to unclear randomisation method and allocation concealment, unclear blinding and unclear attrition.*

[2] *Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses both default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-42.69 and 42.69).*

Phosphorous versus no phosphorous

Table 7: Evidence profile for outcomes related to the comparison of phosphorous versus no phosphorous.

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	+Ph	-Ph	Relative (95% CI)	Absolute	Quality	Importance
Bone mineral density (g/cm2) (Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	+Ph	-Ph	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25	25	-	MD 0.03 higher (0.02 to 0.04 higher)	⊕⊕⊕O MODERATE	CRITICAL

CI: confidence interval; MD: mean difference; Ph: phosphorous.
[1] *Serious risk of bias due to non-random sequence generation.*

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What are the optimal target dosages for calcium and phosphate in preterm and term babies who are receiving parenteral nutrition and neonatal care?

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 are the optimal target dosages for calcium and phosphate in preterm and term babies who are receiving parenteral nutrition and neonatal care?

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

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What are the optimal target dosages for calcium and phosphate in preterm and term babies who are receiving parenteral nutrition and neonatal care?

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

Appendix J – Economic analysis

Economic evidence tables for review question: What are the optimal target dosages for calcium and phosphate in preterm and term babies who are receiving parenteral nutrition and neonatal care?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: What are the optimal target dosages for calcium and phosphate in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Clinical studies

Study	Reason for Exclusion
Aiken, C. G., Sherwood, R. A., Kenney, I. J., Furnell, M., Lenney, W., Mineral balance studies in sick preterm intravenously fed infants during the first week after birth. A guide to fluid therapy, Acta paediatrica Scandinavica. Supplement, 355, 1-59, 1989	Study does not provide adequate data for analysis.
Aiken, C. G., Sherwood, R. A., Lenney, W., Role of plasma phosphate measurements in detecting rickets of prematurity and in monitoring treatment, Annals of clinical biochemistry, 30 (Pt 5), 469-75, 1993	Intervention does not meet review protocol eligibility criteria - Participants also received enteral feeding.
Aladangady, N., Coen, P. G., White, M. P., Rae, M. D., Beattie, T. J., Urinary excretion of calcium and phosphate in preterm infants, Pediatric Nephrology, 19, 1225-1231, 2004	Intervention does not meet review protocol eligibility criteria - participants also received enteral nutrition.
Allwood, M. C., The compatibility of calcium phosphate in paediatric TPN infusions, Journal of Clinical Pharmacy and Therapeutics, 12, 293-301, 1987	Intervention does not meet review protocol eligibility criteria - objectives of the review are not relevant to the protocol (solubility).
Andronikou, S., Rothberg, A. D., Pettifor, J. M., Thomson, P. D., Early introduction of parenteral nutrition in premature infants and its effect on calcium and phosphate homeostasis, South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde, 64, 349-51, 1983	Study design and outcomes do not meet review protocol eligibility criteria - prospective comparative study but the allocation was made arbitrarily. Compared AA against Ca-dextrose.
Ardicli, B., Karnak, I., Ciftci, A. O., Ozen, H., Tanyel, F. C., Senocak, M. E., Composition of parenteral nutrition solution affects the time of occurrence but not the incidence of cholestasis in surgical infants, Turkish Journal of Pediatrics, 56, 500-506, 2014	Study design does not meet review protocol eligibility criteria - retrospective case control design.
Atkinson, S. A., Calcium and phosphorus requirements of low birth weight infants: a nutritional and endocrinological perspective, Nutrition reviews, 41, 69-78, 1983	Study design does not meet review protocol eligibility criteria - not a systematic review of RCTs.
Awad, H. A., Fand, T. M., Khafagy, S. M., Nofal, R. I., Bone mineral content measured by DEXA scan in preterm neonates receiving total parentral nutrition with and without phosphorus supplementation, Pakistan Journal of Biological Sciences, 13, 891-895, 2010	Study design and outcomes do not meet review protocol eligibility criteria - case-control design - compares phosphorous to non-phosphorous control; unable to assess optimal dosage.
Bentur, L., Alon, U., Berant, M., Bone and mineral homeostasis in the preterm infant: A review, Pediatric Reviews and Communications, 1, 291-310, 1987	Study design does not meet review protocol eligibility criteria - not a systematic review of RCTs.
Berg, G., Recommendations for parenteral nutrition, Zeitschrift fur Ernahrungswissenschaft.	Study design does not meet review protocol eligibility criteria - recommendations of practice.

Study	Reason for Exclusion
Journal of nutritional sciences. Supplementa, 9, 1-40, 1970	
Berry, M. A., Conrod, H., Usher, R. H., Growth of very premature infants fed intravenous hyperalimentation and calcium-supplemented formula, Pediatrics, 100, 647-653, 1997	Study design does not meet review protocol eligibility criteria - not an RCT or comparative cohort study.
Bloomfield, F. H., Crowther, C. A., Harding, J. E., Conlon, C. A., Jiang, Y., Cormack, B. E., The ProVIDe study: The impact of protein intravenous nutrition on development in extremely low birthweight babies, BMC Pediatrics, 15, 2015	Study design and outcomes do not meet review protocol eligibility criteria - protocol of RCT - the arms of the RCT do not accommodate the objectives of the review (AA vs placebo).
Bolisetty, S., Osborn, D., Sinn, J., Lui, K., Kent, A., Trivedi, A., Yaacou, D., Morris, S., Marshall, P., Birch, P., Corban, J., Natthondan, V., Ching, S. K., Wake, C., Vaidya, U., Tobiansky, R., Pazanin, N., Tan, K., Downe, L., Deshpande, G., Paoli, T. D., Colvin, J., Ravindranathan, H., Gupta, N., Gibney, D., Luig, M., Ng, K., Pham, T., McPhee, A., Standardised neonatal parenteral nutrition formulations - an Australasian group consensus 2012, BMC Pediatrics, 14, 48, 2014	Study design and outcomes do not meet review protocol eligibility criteria - literature review - consensus group - refers to optimal dosages of Ca and P.
Bonsante, F., Iacobelli, S., Latorre, G., Rigo, J., de Felice, C., Robillard, P. Y., Gouyon, J. B., Initial Amino Acid Intake Influences Phosphorus and Calcium Homeostasis in Preterm Infants - It Is Time to Change the Composition of the Early Parenteral Nutrition, PLoS ONE, 8, e72880, 2013	Study design and intervention do not meet review protocol eligibility criteria - non-comparative observational study that includes enteral and parenteral nutrition).
Boubred, F., Herlenius, E., Bartocci, M., Jonsson, B., Vanpee, M., Extremely preterm infants who are small for gestational age have a high risk of early hypophosphatemia and hypokalemia, Acta Paediatrica, International Journal of Paediatrics, 104, 1077-1083, 2015	Study design does not meet review protocol eligibility criteria - observational cohort design not a RCT.
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	Study design does not meet review protocol eligibility criteria - clinical guidelines.
Brener Dik, P. H., Galletti, M. F., Bacigalupo, L. T., Jonusas, S. F., Mariani, G. L., Hypercalcemia and hypophosphatemia among preterm infants receiving aggressive parenteral nutrition, Archivos Argentinos de Pediatria, 116, e371-e377, 2018	Study design does not meet review protocol eligibility criteria - non-randomised comparative study.
Brown, D. R., Salsburey, D. J., Short-term biochemical effects of parenteral calcium treatment of early-onset neonatal hypocalcemia, The Journal of pediatrics, 100, 777-81, 1982	Study design does not meet review protocol eligibility criteria - cross-sectional study.
Brown, D. R., Steranka, B. H., Taylor, F. H., Treatment of early-onset neonatal hypocalcemia. Effects on serum calcium and	Does not address any of the outcomes specified in the protocol.

Study	Reason for Exclusion
ionized calcium, American journal of diseases of children (1960), 135, 24-8, 1981	
Bustos Lozano, Gerardo, Soriano-Ramos, Maria, Pinilla Martin, Maria Teresa, Chumillas Calzada, Silvia, Garcia Soria, Carmen Elia, Pallas-Alonso, Carmen Rosa, Early Hypophosphatemia in High-Risk Preterm Infants: Efficacy and Safety of Sodium Glycerophosphate From First Day on Parenteral Nutrition, JPEN. Journal of parenteral and enteral nutrition, 43, 419-425, 2019	Study design does not meet review protocol eligibility criteria - non-randomised comparative study.
Castillo, Salinas F, Clinical efficacy of organic phosphorus in newborns who require parenteral nutrition, Revista espanola de pediatria, 69, 312-318, 2013	Non-English publication (full text in Spanish).
Changaris, D. G., Purohit, D. M., Balentine, J. D., Levkoff, A. H., Holden, A. E., Dean, D. L., Jr., Biggs, P. J., Brain calcification in severely stressed neonates receiving parenteral calcium, The Journal of pediatrics, 104, 941-6, 1984	Study does not meet review protocol eligibility criteria.
Chessex, P., Pineault, M., Brisson, G., Delvin, E. E., Glorieux, F. H., Role of the source of phosphate salt in improving the mineral balance of parenterally fed low birth weight infants, The Journal of pediatrics, 116, 765-72, 1990	Study outcomes do not meet review protocol eligibility criteria - testing solubility of plasma for Ca and P.
Chessex, P., Pineault, M., Zebiche, H., Ayotte, R. A., Calciuria in parenterally fed preterm infants: role of phosphorus intake, The Journal of pediatrics, 107, 794-6, 1985	Study design does not meet review protocol eligibility criteria - Non-comparative prospective cohort.
Chetta, K. E., Hair, A. B., Hawthorne, K. M., Abrams, S. A., Serum phosphorus levels in premature infants receiving a donor human milk derived fortifier, Nutrients, 7, 2562-2573, 2015	Study design does not meet review protocol eligibility criteria - observational cohort study - does not directly compare Ca and P.
Christmann, V., De Grauw, A. M., Visser, R., Matthijsse, R. P., Van Goudoever, J. B., Van Heijst, A. F. J., Early postnatal calcium and phosphorus metabolism in preterm infants, Journal of Pediatric Gastroenterology and Nutrition, 58, 398-403, 2014	Study design does not meet review protocol eligibility criteria -non-comparative prospective cohort study.
Christmann, V., Gradussen, C. J. W., Kornmann, M. N., Roeleveld, N., van Goudoever, J. B., van Heijst, A. F. J., Changes in biochemical parameters of the calcium-phosphorus homeostasis in relation to nutritional intake in very-low-birth-weight infants, Nutrients, 8 (12) (no pagination), 2016	Intervention does not meet review protocol eligibility criteria - participants receive both enteral and parenteral nutrition.
Christmann, V., van der Putten, M. E., Rodwell, L., Steiner, K., Gotthardt, M., van Goudoever, J. B., van Heijst, A. F. J., Effect of early nutritional intake on long-term growth and bone mineralization of former very low birth weight infants, Bone, 108, 89-97, 2018	Study design does not meet review protocol eligibility criteria - not RCT (observational cohort study).
Colonna, F., Candusso, M., De Vonderweid, U., Marinoni, S., Gazzola, A. M., Calcium and phosphorus balance in very low birth weight babies on total parenteral nutrition, Clinical Nutrition, 9, 89-95, 1990	Study outcomes do not meet review protocol eligibility criteria - assesses maturation/tolerability/ and retention of Ca and P in PN patients.

Study	Reason for Exclusion
Cooper, L. J., Anast, C. S., Circulating immunoreactive parathyroid hormone levels in premature infants and the response to calcium therapy, Acta Paediatrica Scandinavica, 74, 669-673, 1985	There is no randomisation. prospective comparative study - does not address the outcomes reported to the protocol.
De Schepper, J., Cools, F., Vandenplas, Y., Louis, O., Whole body bone mineral content is similar at discharge from the hospital in premature infants receiving fortified breast milk or preterm formula, Journal of Pediatric Gastroenterology and Nutrition, 41, 230-234, 2005	Study intervention does not meet review protocol eligibility criteria - oral feeding.
Dear, P. R. F., Total parenteral nutrition of the newborn, Care of the Critically Ill, 8, 252-257, 1992	Study design does not meet review protocol eligibility criteria - not a systematic review of RCTs.
Dilena, B. A., White, G. H., The responses of plasma ionised calcium and intact parathyrin to calcium supplementation in preterm infants, Acta Paediatrica Scandinavica, 80, 1098-1100, 1991	Study outcomes do not meet review protocol eligibility criteria - assesses whole blood ionised.
Dreyfus, Lelia, Fischer Fumeaux, Celine Julie, Remontet, Laurent, Essomo Megnier Mbo Owono, Murielle Christine, Laborie, Sophie, Maucort-Boulch, Delphine, Claris, Olivier, Low phosphatemia in extremely low birth weight neonates: A risk factor for hyperglycemia?, Clinical nutrition (Edinburgh, Scotland), 35, 1059-65, 2016	Study design and intervention do not meet review protocol eligibility criteria -retrospective cohort - EN and PN.
Enomoto, M., Minami, H., Takano, T., Katayama, Y., Lee, Y. K., High-dose calcium reduces early-onset hyperkalemia in extremely preterm neonates, Pediatrics International, 54, 918-922, 2012	Study design does not meet review protocol eligibility criteria - retrospective cohort not an RCT.
Forsythe, R. M., Wessel, C. B., Billiar, T. R., Angus, D. C., Rosengart, M. R., Parenteral calcium for intensive care unit patients, Cochrane Database of Systematic Reviews, (4) (no pagination), 2008	Study design does not meet review protocol eligibility criteria - narrative review.
Gaio, P., Fantinato, M., Daverio, M., Nardo, D., Favero, V., Meneghelli, M., De Terlizzi, F., Verlato, G., Bone status in preterm infants: Influences of maternal factors and nutritional regimens, Journal of Pediatric Gastroenterology and Nutrition, 62, 707, 2016	Study design and objectives do not meet review protocol eligibility criteria - not an RCT (prospective, experimental study) - other than reviews' objectives.
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	Study design and intervention do not meet review protocol eligibility criteria - prospective, non-randomised study - PN and EN.
Giapros, V., Vantziou, S., Cholevas, V., Challa, A., Andronikou, S., Effect of intravenous phosphate on the red cell phosphate metabolites of the preterm infant, Nutrition Research, 21, 71-79, 2001	Study comparator does not meet review protocol eligibility criteria -Control group was enterally fed.
Glenn, S. R., Finch, C., DellaValle, D. M., Taylor, S., Parenteral nutrition in extremely low	Abstract only.

Study	Reason for Exclusion
birth weight infants: Increased phosphorus and early potassium delivery, Journal of Investigative Medicine, 67, 518-519, 2019	
Green, J., Burgess, L., Morgan, C., Insulin treated hyperglycaemia, hyperalimentation and metabolic changes associated with growth in very preterm infants receiving parenteral nutrition, Archives of Disease in Childhood, 99, A208, 2014	Study does not meet review protocol eligibility criteria - other than the objectives of the review.
Green, J., McGowan, P., Hyperalimentation and electrolyte requirements in very preterm infants: A randomised controlled parenteral nutrition study, Archives of Disease in Childhood: Fetal and Neonatal Edition, 99, A6, 2014	Abstract only. Did not assess outcomes of interest.
Green, J., McGowan, P., Morgan, C., Hyperalimentation and electrolyte requirements in very preterm infants: The randomised controlled scamp nutrition study, Archives of Disease in Childhood, 99, A58, 2014	Study does not meet review protocol eligibility criteria - other than the objectives of the review.
Guellec, I., Gascoin, G., Beuchee, A., Boubred, F., Tourneux, P., Ramful, D., Zana-Taieb, E., Baud, O., Biological Impact of Recent Guidelines on Parenteral Nutrition in Preterm Infants, Journal of Pediatric Gastroenterology & Nutrition, 61, 605-9, 2015	Study design does not meet review protocol eligibility criteria -not a systematic review of RCTs.
Hair, A. B., Chetta, K. E., Bruno, A. M., Hawthorne, K. M., Abrams, S. A., Delayed introduction of parenteral phosphorus is associated with hypercalcemia in extremely preterm infants, Journal of Nutrition, 146, 1212-1216, 2016	Study design does not meet review protocol eligibility criteria - not an RCT; addresses some of the outcomes of interest and the different ratios between Ca and P, however, this is not a comparison/balanced study.
Hanning, R. M., Atkinson, S. A., Whyte, R. K., Efficacy of calcium glycerophosphate vs conventional mineral salts for total parenteral nutrition in low-birth-weight infants: a randomized clinical trial, The American journal of clinical nutrition, 54, 903-8, 1991	Study outcomes do not meet review protocol eligibility criteria - does not compare directly Ca and phosphate.
Hay Jr, W. W., Intravenous nutrition of the very preterm neonate, Acta Paediatrica, International Journal of Paediatrics, 94, 47-56, 2005	Study design does not meet review protocol eligibility criteria - expert/narrative/guidance review.
Heird, W. C., Winters, R. W., Total intravenous alimentation, American journal of diseases of children (1960), 126, 287-9, 1973	Study design does not meet review protocol eligibility criteria - practice report.
Hicks, W., Hardy, G., Phosphate supplementation for hypophosphataemia and parenteral nutrition, Current opinion in clinical nutrition and metabolic care, 4, 227-233, 2001	Study design does not meet review protocol eligibility criteria -expert/narrative/guidance review.
Hoehn, G. J., Carey, D. E., Rowe, J. C., Horak, E., Raye, J. R., Alternate day infusion of calcium and phosphate in very low birth weight infants: wasting of the infused mineral, Journal of pediatric gastroenterology and nutrition, 6, 752-7, 1987	Study outcomes do not meet review protocol eligibility criteria - assessed sequence not different dosages.
Iacobelli, S., Bonsante, F., Vintejoux, A., Gouyon, J. B., Standardized parenteral nutrition in preterm infants: early impact on fluid and	Study design does not meet review protocol eligibility criteria - not an RCT (prospective

Study	Reason for Exclusion
electrolyte balance, Neonatology, 98, 84-90, 2010	comparative but does not meet the eligibility criteria).
Ichikawa, G., Watabe, Y., Suzumura, H., Sairenchi, T., Muto, T., Arisaka, O., Hypophosphatemia in small for gestational age extremely low birth weight infants receiving parenteral nutrition in the first week after birth, Journal of Pediatric Endocrinology and Metabolism, 25, 317-321, 2012	Study design does not meet review protocol eligibility criteria - retrospective review; not an RCT.
Jain, Ashish, Agarwal, Ramesh, Sankar, M. Jeeva, Deorari, Ashok K., Paul, Vinod K., Hypocalcemia in the newborn, Indian Journal of Pediatrics, 75, 165-9, 2008	Study design does not meet review protocol eligibility criteria - not a systematic review of RCTs.
Johnston, I. D., Management of prolonged intravenous feeding, Proceedings of the Royal Society of Medicine, 66, 770-1, 1973	Study design does not meet review protocol eligibility criteria - expert/opinion review.
Kamali, K., Pishva, N., Deireh, E., The effects of low and high dose oral calcium and phosphor supplementation on nephrocalcinosis diagnosed by sonography in premature and low birth weight neonates, Iranian Journal of Medical Sciences, 39, 559-64, 2014	Study outcomes do not meet review protocol eligibility criteria.
Kashyap, Sudha, Is the early and aggressive administration of protein to very low birth weight infants safe and efficacious?, Current opinion in pediatrics, 20, 132-6, 2008	Study design does not meet review protocol eligibility criteria - narrative review.
Khan,M.A.G., Upadhyay,A., Chikanna,S., Jaiswal,V., Efficacy of prophylactic intravenous calcium administration in first 5 days of life in high risk neonates to prevent early onset neonatal hypocalcaemia: A randomised controlled trial, Archives of Disease in Childhood: Fetal and Neonatal Edition, 95, F462-F463, 2010	Study outcomes do not meet review protocol eligibility criteria - hypocalcaemia measured.
Knight, P., Heer, D., Abdenour, G., CaxP and Ca/P in the parenteral feeding of preterm infants, Journal of Parenteral and Enteral Nutrition, 7, 110-114, 1983	Study does not meet review protocol eligibility criteria.
Koo, W. W., Parenteral nutrition-related bone disease, JPEN. Journal of parenteral and enteral nutrition, 16, 386-94, 1992	Study does not meet review protocol eligibility criteria.
Koo, W. W., Calcium, phosphorus, and vitamin D requirements of infants receiving parenteral nutrition, Journal of perinatology : official journal of the California Perinatal Association, 8, 263-268, 1988	Study design does not meet review protocol eligibility criteria - narrative/expert review.
Koo, W. W., Tsang, R. C., Mineral requirements of low-birth-weight infants, Journal of the American College of Nutrition, 10, 474-86, 1991	Study design does not meet review protocol eligibility criteria - not a systematic review of RCTs.
Koo, W. W., Tsang, R. C., Poser, J. W., Laskarzewski, P., Buckley, D., Johnson, R., Steichen, J. J., Elevated serum calcium and osteocalcin levels from calcitriol in preterm infants. A prospective randomized study, American journal of diseases of children (1960), 140, 1152-8, 1986	Study outcomes do not meet review protocol eligibility criteria - assesses calcitriol only.

Study	Reason for Exclusion
Koren,G., Zarfin,Y., Maresky,D., Spiro,T.E., MacLeod,S.M., Pharmacokinetics of intravenous clindamycin in newborn infants, Pediatric Pharmacology, 5, 287-292, 1986	Study design and outcomes do not meet review protocol eligibility criteria.
Kreuder, J, Otten, A, Reiter, Hl, Klingmüller, V, Wolf, H, Efficacy and side effects of differential calcium and phosphate administration in prevention of osteopenia in premature infants, Monatsschrift Kinderheilkunde, 138, 775-779, 1990	Non-English publication (full text in German).
Lenclen, R., Crauste-Manciet, S., Narcy, P., Boukhouna, S., Geffray, A., Guerrault, M. N., Bordet, F., Brossard, D., Assessment of implementation of a standardized parenteral formulation for early nutritional support of very preterm infants, European Journal of Pediatrics, 165, 512-518, 2006	Study interventions do not meet review protocol eligibility criteria - compares Standard PN with individualised PN.
MacMahon, P., Mayne, P. D., Blair, M., Pope, C., Kovar, I. Z., Acid-base state of the preterm infant and the formulation of intravenous feeding solutions, Archives of Disease in Childhood, 65, 354-6, 1990	Study interventions do not meet review protocol eligibility criteria - not different dosages of Ca and P.
Marks, K. E., Crill, C. M., Calcium and phosphorous in pediatric parenteral nutrition, Journal of Pharmacy Practice, 17, 432-446, 2004	Study design does not meet review protocol eligibility criteria - not a systematic review of RCTs.
McCarthy, R., Segurado, R., Crealey, M., Twomey, A., Standardised versus individualised parenteral nutrition. Further food for thought, Irish Medical Journal, 109, 388, 2016	Study design does not meet review protocol eligibility criteria - non RCT - prospective comparative but it does not assess the objectives of the review.
McNelis, K., Viswanathan, S., Effects of parenteral phosphorus dose restriction in preterm infants, Journal of Neonatal-Perinatal Medicine, 9, 153-158, 2016	Study design does not meet review protocol eligibility criteria - retrospective case control.
Mimouni, F. B., Mandel, D., Lubetzky, R., Senterre, T., Calcium, phosphorus, magnesium and vitamin D requirements of the preterm infant, World review of nutrition and dietetics, 110, 140-151, 2014	Study design does not meet review protocol eligibility criteria - literature review (book chapter).
Moe, K., Beck-Nielsen, S. S., Lando, A., Greisen, G., Zachariassen, G., Administering different levels of parenteral phosphate and amino acids did not influence growth in extremely preterm infants, Acta Paediatrica, International Journal of Paediatrics, 104, 894-899, 2015	Retrospective study.
Morgan, C., Green, J., Hyperalimentation and electrolyte requirements in very preterm infants: A randomised controlled parenteral nutrition study, Clinical Nutrition, 33, S7, 2014	Study design does not meet review protocol eligibility criteria - conference abstract and does not accommodate reviews objectives.
Mulla, S., Stirling, S., Cowey, S., Close, R., Pullan, S., Howe, R., Radbone, L., Clarke, P., Severe hypercalcaemia and hypophosphataemia with an optimised preterm parenteral nutrition formulation in two epochs of differing phosphate supplementation, Archives of Disease in Childhood, 2017	Study design does not meet review protocol eligibility criteria - retrospective cohort study.

Study	Reason for Exclusion
Narendra, A., White, M. P., Rolton, H. A., Alloub, Z. I., Wilkinson, G., McColl, J. H., Beattie, J., Nephrocalcinosis in preterm babies, Archives of Disease in Childhood, Fetal and neonatal edition. 85, F207-213, 2001	Study design and outcomes do not meet review protocol eligibility criteria - non RCT (prospective observational cohort). Outcome measured is nephrocalcinosis.
Nehra,D., Carlson,S.J., Fallon,E.M., Kalish,B., Potemkin,A.K., Gura,K.M., Simpser,E., Compher,C., Puder,M., A.S.P.E.N. clinical guidelines: Nutrition support of neonatal patients at risk for metabolic bone disease, Journal of Parenteral and Enteral Nutrition, 37, 570-578, 2013	Study design does not meet review protocol eligibility criteria - clinical guidelines.
Orimadegun, Adebola Emmanuel, Akingbola, Titilola Stella, Routine administration of intravenous calcium during exchange blood transfusion for treatment of severe neonatal hyperbilirubinaemia: a systematic review of quantitative evidence protocol, JBI database of systematic reviews and implementation reports, 13, 134-45, 2015	Study design does not meet review protocol eligibility criteria - study protocol.
O'Shea, T. M., Kothadia, J. M., Klinepeter, K. L., Goldstein, D. J., Jackson, B., Dillard, R. G., Follow-up of preterm infants treated with dexamethasone for chronic lung disease, American Journal of Diseases of Children, 147, 658-61, 1993	Study design does not meet review protocol eligibility criteria - not an RCT (Longitudinal follow-up using historic controls).
Pajak, A., Krolak-Olejnik, B., Szafranska, A., Early hypophosphatemia in very low birth weight preterm infants, Advances in Clinical and Experimental Medicine, 27, 841-847, 2018	Study design does not meet review protocol eligibility criteria - non-randomised study.
Pelegano, J. F., Rowe, J. C., Carey, D. E., LaBarre, D. J., Edgren, K. W., Lazar, A. M., Horak, E., Effect of calcium/phosphorus ratio on mineral retention in parenterally fed premature infants, Journal of pediatric gastroenterology and nutrition, 12, 351-5, 1991	Does not assess any of the outcomes reported in the protocol.
Pelegano, J. F., Rowe, J. C., Carey, D. E., LaBarre, D. J., Raye, J. R., Edgren, K. W., Horak, E., Simultaneous infusion of calcium and phosphorus in parenteral nutrition for premature infants: use of physiologic calcium/phosphorus ratio, The Journal of pediatrics, 114, 115-9, 1989	Study does not meet review protocol eligibility criteria.
Pereira-Da-Silva, L, Costa, Ab, Pereira, L, Filipe, Af, Vierella, D, Moreira, Ac, Rosa, Ml, Mendes, L, Serelha, M, Short-Term Effect Of Two Different Parenteral Calcium And Phosphorus Regimens On Bone Strength In Preterm Infants, 50th annual meeting of the European society for paediatric research; 2009 October 9-12; Hamburg, Germany, 2009	Study outcomes do not meet review protocol eligibility criteria.
Pereira-Da-Silva, L., Costa, A. B., Pereira, L., Filipe, A. F., Virella, D., Leal, E., Moreira, A. C., Rosa, M. L., Mendes, L., Serelha, M., Early high calcium and phosphorus intake by parenteral nutrition prevents short-term bone strength decline in preterm infants, Journal of Pediatric	Study outcomes do not meet review protocol eligibility criteria - plasma concentrations, solubility, Precipitation.

Study	Reason for Exclusion
Gastroenterology and Nutrition, 52, 203-209, 2011	
Pereira-da-Silva, Luis, Nurmamodo, Abdurrachid, Amaral, Joao M. Videira, Rosa, Maria L., Almeida, Maria C., Ribeiro, Maria L., Compatibility of calcium and phosphate in four parenteral nutrition solutions for preterm neonates, American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists, 60, 1041-4, 2003	Study intervention does not meet review protocol eligibility criteria - composition.
Pohlandt, F., Prevention of postnatal bone demineralization in very low-birth-weight infants by individually monitored supplementation with calcium and phosphorus, Pediatric Research, 35, 125-9, 1994	Study intervention does not meet review protocol eligibility criteria - includes enteral feeding.
Porcelli, P. J., Jr., Oh, W., Effects of single dose calcium gluconate infusion in hypocalcemic preterm infants, American Journal of Perinatology, 12, 18-21, 1995	Does not assess any of the outcomes reported to the protocol
Prince, A., Groh-Wargo, S., Nutrition management for the promotion of growth in very low birth weight premature infants, Nutrition in Clinical Practice, 28, 659-68, 2013	Study design does not meet review protocol eligibility criteria - not a systematic review of RCTs.
Ronchera-oms, C. L., Allwood, M. C., Hardy, G., Organic phosphates in parenteral nutrition: pouring fresh water into an old bucket, Nutrition (Burbank, Los Angeles County, Calif.), 12, 388-9, 1996	Study design does not meet review protocol eligibility criteria - expert review.
Salle, B. L., David, L., Chopard, J. P., Grafmeyer, D. C., Renaud, H., Prevention of early neonatal hypocalcemia in low birth weight infants with continuous calcium infusion: Effect on serum calcium, phosphorus, magnesium, and circulating immunoreactive parathyroid hormone and calcitonin, Pediatric Research, 11, 1180-1185, 1977	Study design does not meet review protocol eligibility criteria - non-randomised comparative study.
Salsburey, D. J., Brown, D. R., Effect of parenteral calcium treatment on blood pressure and heart rate in neonatal hypocalcemia, Pediatrics, 69, 605-9, 1982	Study outcomes do not meet review protocol eligibility criteria.
Schanler, R. J., Shulman, R. J., Prestridge, L. L., Parenteral nutrient needs of very low birth weight infants, Journal of Pediatrics, 125, 961-8, 1994	Study outcomes do not meet review protocol eligibility criteria.
Scott, S. M., Ladenson, J. H., Aguanna, J. J., Walgate, J., Hillman, L. S., Effect of calcium therapy in the sick premature infant with early neonatal hypocalcemia, Journal of Pediatrics, 104, 747-751, 1984	Study outcomes do not meet review protocol eligibility criteria - reports only ionised and total calcium and comparisons are for bolus vs drip.
Senterre, T., Zahirah, I. A., Pieltain, C., De Halleux, V., Rigo, J., Electrolyte and mineral homeostasis after optimizing early macronutrient intakes in VLBW infants on parenteral nutrition, Journal of Pediatric Gastroenterology and Nutrition, 61, 491-498, 2015	Study design does not meet review protocol eligibility criteria - not an RCT (prospective cohort).

Study	Reason for Exclusion
Stein, J., Boehles, H. J., Blumenstein, I., Goeters, C., Schulz, R., Amino acids - Guidelines on Parenteral Nutrition, Chapter 4, German medical science : GMS e-journal, 7, 2009	Study design does not meet review protocol eligibility criteria - not an RCT (practice review).
Thowladda, N., Siritientong, T., Compatibility of calcium and sodium glycerophosphate in parenteral nutrition solutions, Thai Journal of Pharmaceutical Sciences, 40, 176-179, 2016	Study does not meet review protocol eligibility criteria.
Trindade, C. E. P., Minerals in the nutrition of extremely low birth weight infants, Journal de Pediatria, 81, S43-S51, 2005	Study design does not meet review protocol eligibility criteria - literature review.
Trotter, A., Pohlandt, F., Calcium and phosphorus retention in extremely preterm infants supplemented individually, Acta paediatrica (Oslo, Norway : 1992), 91, 680-3, 2002	Study intervention does not meet review protocol eligibility criteria - includes enteral feeding.
Tsang, R. C., Demarini, S., Rickets and calcium and phosphorus requirements in very low birth weight infants, Monatsschrift fur Kinderheilkunde, 143, S125-S129, 1995	Study design does not meet review protocol eligibility criteria - not an RCT (practice-literature review).
Uthaya, S., Liu, X., Babalis, D., Dore, C. J., Warwick, J., Bell, J., Thomas, L., Ashby, D., Durighel, G., Ederies, A., Yanez-Lopez, M., Modi, N., Nutritional Evaluation and Optimisation in Neonates: A randomized, double-blind controlled trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition, American Journal of Clinical Nutrition, 103, 1443-1452, 2016	Study interventions do not meet review protocol eligibility criteria - does not compare dosages of AA and phosphate.
van den Akker, Chris H. P., te Braake, Frans W. J., Weisglas-Kuperus, Nynke, van Goudoever, Johannes B., Observational outcome results following a randomized controlled trial of early amino acid administration in preterm infants, Journal of pediatric gastroenterology and nutrition, 59, 714-9, 2014	Study does not meet review protocol eligibility criteria.
Vileisis, R. A., Furosemide effect on mineral status of parenterally nourished premature neonates with chronic lung disease, Pediatrics, 85, 316-22, 1990	Study outcomes do not meet review protocol eligibility criteria.
Virella, D., Pereira-Da-Silva, L., Papoila, A. L., Parenteral phosphate and amino acids supply effect on the growth of extremely preterm infants: Accurate measurements and optimized statistical analysis are important, Acta Paediatrica, International Journal of Paediatrics, 104, e537, 2015	Study design does not meet review protocol eligibility criteria - letter to editor.
Watts, S., Mactier, H., Grant, J., Cameron Nicol, E., Mullen, A. B., Is additional oral phosphate supplementation for preterm infants necessary: An assessment of clinical audit, European Journal of Pediatrics, 172, 1313-1319, 2013	Study intervention does not meet review protocol eligibility criteria -oral feeding.
Yeung, M. Y., Smyth, J. P., Maheshwari, R., Shah, S., Evaluation of standardized versus individualized total parenteral nutrition regime for	Study design and interventions do not meet review protocol eligibility criteria - non RCT. Assesses standard vs total PN.

Study	Reason for Exclusion
neonates less than 33 weeks gestation, Journal of paediatrics and child health, 39, 613-7, 2003	

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2 **Economic studies**

3 No economic evidence was identified for this review question. See supplementary document
4 D for further information.

5

Appendix L – Research recommendations

Research recommendations for review question: What are the optimal target dosages for calcium and phosphate in preterm and term babies who are receiving parenteral nutrition and neonatal care?

No research recommendation was made for this review question.