The Neonatal Parenteral Nutrition (PN)

QIPP Toolkit

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Neonatal PN QIPP Overview

Background

Very preterm infants have to adapt to be able to digest milk, this takes around 14 days but can be much longer. Other sick neonates are also unable to receive milk for a period. Neonatal parenteral nutrition (PN) allows complete nutrition of the infants while waiting for milk feeds to be established. Neonatal PN is a complex fluid mixture containing essential salts, the protein and energy for growth, vitamins and other "micronutrients" necessary to maintain health. It requires highly specialised licensed manufacture in aseptic pharmacy manufacturing units (either NHS or commercial suppliers).

Over the last decade, UK survey and audit data have repeatedly demonstrated massive variation in neonatal PN provision both within (ie between similar infants) and between UK neonatal services. While the reasons for this were multifactorial, a major factor was the belief that the fluid, biochemical and nutritional needs of the neonate were so complex that individualised (bespoke) PN was in the best interests of the patient. It is now recognised that standardised and concentrated neonatal PN regimens provide major benefits for safety, quality and cost:

Safety

1. Standardisation allows a range of quality assurance processes to be completed during manufacture
2. It reduces the risk of dispensing and prescribing error
3. It is more likely to ensure the actual PN intake matches the prescribed PN intake
4. It reduces variation between similar infants
5. It allows standardisation of local and regional protocols

Quality

1. Standardised PN can be provided immediately after birth
2. Standardised regimens allow protocols that consistently deliver the desired nutritional intake
3. Nutritional intakes can be improved by up to 25% using a nutritionally equivalent standardised concentrated formulation
4. Early growth outcomes (including head growth) are improved

Cost

1. Pharmacy aseptic unit capacity planning can be increased without additional resources
2. Unit costs of manufacture are much lower for standardised PN
3. Stock control is more efficient and wastage falls
4. Prescribing and dispensing time is reduced
5. Regional standardisation offers further economies of scale

Barriers to change

Despite the evidence and expert guidance, many neonatal PN services do not have the safety, quality and budget data to demonstrate a change in local practice is needed. Some local neonatal PN providers have particular challenges due to existing service configuration or geography. Many

clinicians are resistant to change because although national and international bodies make neonatal nutritional recommendations, the evidence base is limited. For example, while there is proof that early growth outcomes are improved with increased early PN there is no definitive study that demonstrates a benefit for clinically important long term outcomes such as neurodevelopment. Very limited safety data about different PN formulations has been published. Thus, clinicians can legitimately resist the implementation of one formulation over another. However, what is beyond dispute, is that standardisation of any given neonatal PN formulation has benefits for safety, quality and cost.

The CoMPaSS regimen (Concentrated Macronutrient in Parenteral Standardised Solutions)

The CoMPaSS regimen has been developed at Liverpool Women's Hospital in associations with an NHS Pharmacy Aseptic Manufacturing Unit at the Royal Liverpool Hospital. It is a latest version of a standardised, concentrated neonatal PN regimen providing published audit and RCT data. It is currently being implemented in two further level 3 NICUs in the NW ODN with associated evaluations of nutritional intake. The CoMPaSS regimen represents a concept rather than a rigid formulation (although it's the only UK formulation to have published outcomes associated with it).

Other standardised PN regimens

Other NICUs and ODNs have utilised the concept either independently or following the published evidence. For example, the East of England ODN (EOE) has implemented a single standardised PN formulation with a concentrated option. Although the process has been shared, the methodology did not allow evaluation of safety, quality and cost benefits. There is now a need to collate current experience with standardised and concentrated neonatal PN regimens to realise the benefits across the NHS. A pilot NW ODN QIPP project is to provide the regional methodology (utilising the CoMPaSS concept) required to achieve a national neonatal PN QIPP.

The UK PN QIPP Toolkit

The national QIPP scheme requires baseline assessment of current neonatal PN costs and an audit of actual PN nutritional intakes in the PN-dependent neonatal population within each ODN. This process is complex and the toolkit will include the following:

1. Background information about the CoMPaSS concept and other methods needed to improve neonatal PN provision
2. A summary of the principles of concentration (including presentation for educational package)
3. Nutritional audit tools for prescribing and administering PN
4. A PN costing tool
5. A "roadmap" for each neonatal ODN to follow
6. Options for neonatal PN provision: case examples and audit data (Version 2.0)

The audit and costing tools will be used to establish the case for change (including whether there is a case for local change)

1. Background to the Neonatal PN QIPP: the CoMPaSS concept

The Liverpool Women's Hospital and the Royal Liverpool Hospital Pharmacy Aseptic Manufacturing Service had a long standing relationship developing a novel neonatal PN formulation and regimen. The CoMPaSS concept is a system of neonatal PN delivery that has evolved following a series of audits and randomized controlled trials (1-4).

Clinical benefits of improving early neonatal nutrition

Preterm survivors are at risk of significant neurocognitive disabilities, particularly under 26 weeks gestation (5). Although many factors are associated with an increased risk of neurocognitive impairment, postnatal growth failure is now recognised as an important and potentially reversible risk. (6,7,8). Suboptimal growth is common (9,10) especially in those under 29 weeks (11) and results from the severe nutritional deficit that usually develops in preterm infants in the first few weeks of life (6,7). The deficit refers to the shortfall in energy and protein required to mimic fetal growth rates. Current recommendations (12) use estimates based on matching fetal growth in utero (13) but even these may be too low for infants with complications of prematurity (14,15).

Very preterm infants have a gut that is too immature to digest milk in sufficient quantity to meet nutritional requirements. Virtually all preterm infants <29 weeks gestation and <1200g require parenteral nutrition (PN) for a period that depends on gestation birthweight and other morbidities (9). Given these infants have the highest incidence of early and late growth failure and long term neurocognitive disability, effective PN delivery is essential to avoid major early nutritional deficits in these infants.

There is evidence that nutritional interventions in very preterm infants can improve growth (16-19) although evidence for effects on neurodevelopmental outcomes is still limited (20-22)

Variations and deficiencies in clinical practice

There are huge variations in neonatal nutritional practice (23-29) particularly in the UK (26-29). Some of this variability relates to the complexities of clinical practice and the need for a highly adaptable PN regimen. We have conducted a telephone survey (2012) of all level 3 neonatal services in the UK (ie those with primary responsibility for care of infants born <29 weeks gestation) which show large differences in the estimated daily macronutrient intake consistent with earlier surveys (27,28) with 22% units falling below the minimum recommendations. There were large variations in the approach maintaining nutrient intake during PN "intolerance" especially the management hyperglycaemia and the use of insulin (30). There are no surveys specific to level 2 units but the implications of the recent NCEPOD report (26) suggest similar concerns.

These wide variations in clinical nutritional (neonatal PN) practice reflect a combination of factors:

i) Limited evidence base for one nutritional strategy over another
ii) Local PN policy relying on local clinician(s) with nutritional expertise/enthusiasm
iii) Variations in the local pharmacy/dietetic expertise and availability
iv) PN policy driven by local service organisation (rather than the other way round)
v) Different policies to manage PN intolerance (eg insulin use, TG levels)

The role of standardising and concentrating neonatal PN in reducing variability

Deficiencies due to local PN policies are compounded by practical difficulties that create a difference between the PN prescribed and actual received by the infant. The conventional neonatal PN strategy has been based on individualised prescription and formulation to address the rapidly changing and variable fluid and electrolyte needs characteristic of the very preterm infant. This can subvert early nutritional strategy particularly with inexperienced neonatal PN prescribers (27-28). Computer aided prescribing can help (31) and improve protein and energy intake (32,33).

Although individualised PN prescription is flexible, the manufactured individualised PN bag is not. It does not allow rapid responses to changes in fluid and electrolyte requirements after the PN bag had been prescribed. Tan (4) compared 2 indvidualised neonatal PN (iNPN) regimens with a 30% difference in macronutrient content but only achieved a 15% difference with >50% infants receiving <80% prescribed PN protein. PN delivery was impaired by co-administration of other drug infusions, fluid restriction and changing electrolyte requirements. Thus, maximising nutritional intake in very preterm infants cannot be guaranteed by simply increasing the macronutrients in the PN formulation.

Standardised versus individualised neonatal PN has been reviewed (34) but there is little guidance (12,35). While some evidence suggests iNPN may be beneficial (33,36,37) increasing evidence indicates that most infants can be managed on a standardised PN formulation (3,37-43) and indeed improve macronutrient intake when compared to iNPN regimens (1,44,45). One of the important ways in which standardisation helps improve nutrition is allowing PN to be started immediately after birth. The provision of early amino acids in particular is important for early nitrogen retention, reducing early nutritional deficits and improving growth (1, 19, 45-47). This also minimises interpatient variation in nutritional management resulting from lack of PN services over weekends. Patient safety concerns make the logistics of RCT comparing individualised and standardised PN regimens impossible. However, many before and after studies shown improved nutrient intake comparing standardised with individualised regimens. Standardisation also allows regional and national collaboration (48) with potential benefits for patient safety, reduced variation and cost.

Concentration of neonatal PN (ie reducing the volume) has the potential to maintain nutritional intake in the face of fluid restriction and multiple drug infusions. Conventionally, stability and osmolality concerns have limited this approach, but current guidelines have virtually no evidence base. The SCAMP nutrition study (see below) provides limited reassurance that increasing osmolality does not increase line complication rates (49). While use of individually prescribed concentrated neonatal PN is well recognised, this approach does not allow consistency of nutrient delivery or individualised quality assurance processes (stability testing). The standardised, concentrated approach has been subject to observational (50) and randomised controlled study (1), both showing consistent nutrient delivery and improved early head growth.

The scNPN prototype, the SCAMP nutrition study and the CoMPaSS concept

Using the standardisation and concentration concepts, the preterm infant's competing needs for extreme flexibility for fluid and electrolyte management versus consistent optimal nutritional delivery can be accommodated in a "two compartment" PN model. We developed a standardised concentrated neonatal PN (scNPN) regimen:

i) 85ml/kg/day aqueous PN with 3 nutritionally identical standard aqueous bags:
   a. Aqueous bag 1: no electrolytes
   b. Aqueous bag 2: maintenance electrolytes
   c. Aqueous bag 3: bag 2 with additional sodium
ii) 15ml/kg/day intravenous lipid
iii) 50ml/kg/day supplementary fluid compartment

The supplementary compartment is then reduced or increased as total fluid requirements demand thereby "protecting" the nutrition compartment. Standardised electrolyte and drug infusions replace part of the supplementary infusion and are then titrated against it (not the nutrition compartment) as required. This system allows maximum flexibility of fluid, electrolyte and drug infusion management with minimal impact on nutrient delivery. The choice of 3 standard bags meets the needs of most preterm infants while minimizing the use of supplementary electrolyte infusions.

Following its local implementation in 2006, we have shown the scNPN system of PN delivery is more effective at delivering protein, with >90% infants receiving >90% prescribed protein (3). This lead to a 20% increase in the first 14 day protein intake when compared to a nutritionally identical iNPN regimen (3). Significant cost reductions were also achieved (38%) similar to those reported for other standardised regimens (40). In 2009 the scNPN regimen was modified to start immediately after birth. The intended increase in protein intake (4g/kg) was closely matched by that actually achieved in clinical practice (2). Most recently, the benefits of the standardized, concentrated neonatal PN concept has recently been demonstrated in a non-randomised study by another independent group of workers in New Zealand (44,45).

There are no randomised controlled trials comparing standardised versus individualised neonatal PN, probably because logistics and patient safety considerations make this unfeasible in the complex very preterm population. However, given the potential benefits of the scNPN, a randomised controlled trial (the SCAMP nutrition study) comparing the existing scNPN regimen (control) with one where macronutrient content was maximised (SCAMP regimen). The study showed improved postnatal head growth at 28 days in the SCAMP group (1). This effect persisted at 36 weeks corrected gestational age even though the intervention ceased on day 28. This supports an evolving hypothesis that: early nutritional deficiencies can be corrected and have immediate implications for brain growth with long term implications for neurodevelopment. This has yet to be tested in a sufficiently powered RCT.

The SCAMP nutrition study has also provided some assurances about the safety of standardised NPN regimens when using higher concentrations of nutrients. This includes preterm mortality and morbidity (1), line complications (49), hyperglycaemia (30) and plasma electrolyte stability (51). However, it is also clear that amino acid formulations do not meet the needs of the PN-dependent preterm infant and this will not be addressed by standardising or concentrating current neonatal PN formulations currently licenced in the UK (52).

Following the outcomes of the SCAMP study the formulation was modified slighted and rolled out in a neighbouring regional level 3 NICU (July 2014). This implementation process was funded as part of the CoMPaSS project. The post implementation audit has just been completed. Both the implementation package and post implementation audit have supported the CoMPaSS concept as a framework to facilitate the optimisation of neonatal PN provision as part of a national QIPP.

The CoMPaSS concept and other improvement strategies for neonatal PN

The concept of standardising neonatal PN is not new. Nevertheless, both the work demonstrating the nutritional failings (unintentionally) of conventional neonatal PN strategies (4) and the subsequent study demonstrating this can be largely avoided by adopting the principles of standardisation and concentration (1) benefit from the rigour of an RCT setting. The evidence base has also been enhanced by other international observational studies that have demonstrated the benefits of standardisation (44) and concentration (45,49). In the UK, many neonatal PN providers have already explored the potential benefits of standardisation and commercial standardised neonatal PN formulations have been available for more than a decade. Regional PN strategies have been less evident but the East of England ODN and the East Midland networks (Trent and Central) have completed regional PN procurement exercises which have greatly contributed to the toolkit.

The Paediatric Chief Pharmacists Report from 2011: improving practice and reducing risk in the provision of parenteral nutrition for neonates and children published 59 recommendations covering all aspects of neonatal PN provision:

General Guidance

- Capacity Planning

Clinical Guidance

- Nutrition Support Teams
- Initiation of parenteral nutrition
- Pharmacy Provision of Parenteral Nutrition
- Parenteral Nutrition Content
- Standard Parenteral Nutrition Solutions
- Routes of Parenteral Nutrition Delivery
- Safety checks & Biochemical Monitoring
- Routine Biochemical Monitoring
- Administration of Vitamins
- Additions to PN Solutions
- Out of Hours Service

Technical Guidance

- Process and Quality Control
- Documentation
- Methods of Compounding
- Compounding Processes and Process Controls Workload
- Additions to Standard PN Solutions
- Stability Data
- Workforce Planning
- Quality Assurance
- Giving Sets and Filters .
- Error Reporting

The principles of standardisation and concentration in neonatal PN provision give a clear framework in which to meet these national recommendations.

Potential for improving quality outcomes for patients

1. **Preterm neonatal nutrient intake:** Up to 25% of protein and calorie intake can be "lost" with convention neonatal parenteral nutrition (PN) regimens. Evaluation of the CoMPaSS cencept indicates a 20% increase in protein intake compared to conventional regimens. Moreover, when changes are made to the nutrient composition of the CoMPaSS concept, the change in actual nutrient intake is effectively achieved in clinical practice. Not only does this have benefits for patient care but this provides a robust methodology for studying future nutritional interventions in clinical trials.
2. **Consistent PN delivery:** Improving the consistency of nutrient delivery reduces variation and increases nutrient target attainment. Target attainment measures the patients actual nutrient intake against the prescribed nutrient intake. Consistency is improved within and between centres. Consistent PN delivery is critical to ensuring safe administration.
3. **Patient safety:** Standardising neonatal PN reduces the risk of medication error. Ensuring the all prescribed PN is actually received by the infant (see above) also reduces clinical risk. The potential toxicity of neonatal PN nutrition components (eg individual amino acid levels) is poorly understood, especially for the very preterm infant, but consistent nutrient delivery is likely to reduce this risk. Consistent nutrient delivery will also enhance the feasibility and quality of studies investigating potential toxicity.
4. **Postnatal metabolic adaptation.** We have shown how the CoMPaSS concept can and consequently reduce the risk of early metabolic complications (eg hyperglycaemia) by optimise nutrient intake and reducing variability in very preterm infants. This has the potential to reduce long term complications of prematurity. Nutritional modulation of postnatal metabolic adaptation is a key area of research interest and requires consistent nutrient delivery to conduct the multicentre RCT required.
5. **Short term growth outcomes.** Early postnatal growth failure is a major problem for very preterm infants and optimal early nutrient intake is a key factor in prevention.
6. **Long term neurodevelopmental outcome.** Poor nutritional intake in the early neonatal period is associated with poorer neurodevelopmental outcome at 18 months in a number of studies. The CoMPaSS concept provides an important methodological advance the future multicentre randomised controlled trials required to show improved nutrient intake causes improved neurodevelopmental outcomes.

Potential for minimising costs of neonatal PN provision

1. **Reduced manufacturing costs**. Standardising neonatal PN has major benefits for the cost of PN manufacture and capacity planning pharmacy aseptic manufacturing services. This translates into a 30% reduction in the cost of neonatal PN provision (original single centre evaluation).
2. **Improved efficiency**. If the reduced cost of manufacturing is combined with the improved nutrient delivery described above then efficiency (ie cost per gram of macronutrient actually received by the infant) is greatly increased (>40%).
3. **Cost effectiveness**. There are realistic surrogate measures for neurodevelopmental outcomes that would allow cost effectiveness to be measured.

References

1. Morgan C, McGowan P, Herwitker S et al. Preventing early postnatal head growth failure in very preterm infants: the randomised controlled SCAMP nutrition study *Pediatrics* 2014:133:e120-8.

2. Mahaveer A, Grime C, Morgan C. Increasing early protein intake is associated with a decrease in insulin-treated hyperglycaemia in preterm infants receiving parenteral nutrition. *Nutr Clin Pract* 2012;

3. Morgan C, Badhawi I, Grime C, Herwitker S. Improving early protein intake in very preterm infants using a standardised concentrated neonatal parenteral nutrition formulation. *European e-Journal Clinical Nutrition and Metabolism* 2009;**4**:e324-e328.

4. Tan MJ, Cooke RWI. Improving head growth in very preterm infants – a randomized controlled trial I: neonatal outcomes. *Arch Dis Child Fetal Neonatal Ed* 2008;**93**:F337-41.

5. Wood NS, Marlow N Costeloe K et al. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group *N Engl J Med* 2000;**343**: 378-84.

6. Clarke RH, Wagner CL, Merritt RJ *et al*. Nutrition in the intensive care unit: how do we reduce the incidence of extrauterine growth restriction? *J Perinatol* 2003;**23**: 337-344.

7. Dusick AM, Poindexter BB, Ehrenkranz RA *et al*. Growth failure in the preterm infant: can we catch up? *Sem Perinatol* 2003;**27**: 302-10.

8. Ehrenkranz RA, Dusick AM, Vohr BR et al. Growth in the neonatal intensive care unit influences neurodevelopment and growth outcomes of extremely low birth weight infants. *Pediatrics* 2006;**117**: 1253-61.

9. Ehrenkranz RA, Younes N, Lemons JA *et al*. Longitudinal growth of hospitalized very low birthweight infants. *Pediatrics* 1999: **104**: 280-9.

10. Clark RH, Thomas P, Peabody J. Extrauterine growth restriction remains a serious problem in prematurely born neonates. *Pediatrics* 2003:**111**:986-90.

11. Wood NS, Costeloe K, Gibson AT et al The EPICure study: growth and associated problems in children born at 25 weeks of gestational age or less. *Arch Dis Child Fetal Neonatal Ed* 2003;**88**: F492-500.

12. Koletzko B, Goulet O, Hunt J et al. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society for Paediatric Research (ESPR). *J Paediatr Gastroentrol Nutr* 2005;**41(Suppl 2)**:S1-87.

13. Cooke RJ. Postnatal growth in preterm infants. In: Neonatal Nutrition and Metabolism. Thureen PJ, Hay WW (Eds). Cambridge University Press, Cambridge 2006:pp47-57.

14. Berry MA, Abrahamowicz M, Usher RH. Factors associated with growth of extremely premature infants during initial hospitalisation *Pediatrics* 1997:**100**:640-6.

15. Embelton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? *Pediatrics* 2001;**107**:270-3.

16. Wilson DC, Cairns P, Halliday HL et al. Randomised controlled trial of an aggressive nutrition regimen in sick very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 1997;**77**:F4-F11.

17. Dinerstein A, Nieto RM Solana CL et al. Early and aggressive nutritional strategy (parenteral and enteral) decreases postnatal growth failure in very low birth-weight infants. *J Perinatol* 2006;**26**:436-42.

18. Poindexter BB, Langer JC, Dusick AM et al. Early provision of parenteral amino acids in extremely low birth weight infants: relation to growth and neurodevelopmental outcome. *J Pediatr* 2006;**148**: 300-5

19. Senterre T, Rigo J. Reduction in postnatal cumulative nutritional deficit and improvement of growth in extremely preterm infants. *Acta Paediatr*. 2012;**101**:e64-70.

20. Tan MJ, Cooke RWI, Abernethy L Improving head growth in very preterm infants – a randomized controlled trial II: MRI and developmental outcomes in the first year. *Arch Dis Child Fetal Neonatal Ed* 2008;**93**:F342-6.

21. Stephens BE, Walden RV, Gargus RA et al. First week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. *Pediatrics* 2009;**123**:1377-43.

22: Cester EA, Bloomfield FH, Taylor J, Smith S, Cormack BE. Do recommended protein intakes improve neurodevelopment in extremely preterm babies? Arch Dis Child Fetal Neonatal Ed. 2015;100:F243-7.

23. Donovan R, Puppala B Angst D. Outcome of early nutrition support in extremely low birth weight infants. *Nutr Clin Pract* 2006;**21**:395-400.

24. Olsen IE, Richardson DK, Schmid CH et al Intersite differences in weight growth velocity of extremely premature infants. *Pediatrics* 2002;**110**:1125-1132.

25. Bloom BT, Mulligan J, Arnold C Improving growth of very low birth weight infants in the first 28 days. *Pediatrics* 2003;**112**:8-14.

26. Stewart JAD, Mason, DG, Smith N et al. A Mixed Bag: An enquiry into the care of hospital patients receiving parenteral nutrition. A Report by the National Confidential Enquiry into Patient Outcome and Death 2010.

27. Ahmed M, Irwin S, Tuthill DP. Education and evidence are needed to improve neonatal parenteral nutrition practice *J Parenter Enteral Nutr* 2004;**28**:176-9.

28. Grover A, Khashu M, MukherjeeA et al. Iatrogenic malnutrition in neonatal intensive care units: urgent need to modify practice *J Parenter Enteral Nutr* 2008;**32**:140-4.

29. Lapillonne A, Carnielli VP, Embleton ND Mihatsch W. Quality of newborn care: adherence to guidelines for parenteral nutrition in preterm infants in 4 European countries. *BMJ Open* 2013;3:e003478.

30. Morgan C. What is the evidence base for using insulin treatment to prevent or treat neonatal hyperglycaemia? *Early Hum Dev* 2015;**91**:655-9

31. Puago MA, Nguyen HL, Sheridan MJ. Computerized PN ordering optimizes timely nutrition therapy in a neonatal intensive care unit. *J Am Diet Assoc*. 1997;**97**: 258-261

32. Eleni-dit-Trolli S, Kermorvant-Duchemin E, Huon C Early individualized parenteral nutrition for preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2009; 94: F152-3

33. Riskin A, Shiff Y, Shamir R. Parenteral nutrition in neonatology - to standardize or individualize? *IMAJ* 2006;**8**:641-5.

34. Fusch C, Bauer K, Bohles HJ, Jochum F, Koletzko B, Krawinkel M, Krohn K, Muhlebach S. Neonatology/paediatrics – guidelines on parenteral nutrition, Chapter 13 *German Medical Science* 2009;**7**:1-23.

35. Hans DM, Pylipow M, Long JD, Thureen PJ, Georgieff MK. Nutritional practices in the neonatal intensive care unit: analysis of a 2006 neonatal nutrition survey. *Pediatrics* 2009;**123**:51-57.

36. Smolkin T, Diab G, Shohat I et al Standardized versus individualized parenteral nutrition in very low birth weight infants: a comparative study *Neonatology* 2010;**98**:170-8.

37. Hartwig SC Gardner DK. Use of standardized Total Parenteral Nutrition solutions for preterm neonates *Am J Hosp Pharm* 1989;**46**:993-5.

38. Beecroft C, Martin H, Puntis JWL. How often do parenteral nutrition prescription for the newborn need to be individualised? *Clin Nutr* 1999;**18**:83-5.

39. Keady S, Morgan C, Ozzard A, Chauhan B. Effect of a standard neonatal aqueous parenteral nutrition formulation on aseptic unit capacity planning. *European e-Journal Clinical Nutrition and Metabolism* 2010;**5**:e14-e17.

40. Yeung MY, Smyth JP, Maheshwari R et al. Evaluation of standardized versus individualized total parenteral nutrition regime for neonates less than 33 weeks gestation. *J Paediatr Child Health* 2003;**39**:613-7.

41. Lenclen R Crauste-Manciet S Narcy P et al. Assessment of implementation of a standardized parenteral nutrition formulation for early nutritional support of very preterm infants. *Eur J Pediatr* 2006;**165**:512-8.

42. Skouroliakou M, Koutri K, Stathopoulou M, Vourvouhaki E, Giannopoulou I, Gounaris A. Comparison of two types of TPN prescription methods in preterm neonates *Pharm World Sci* 2009;**31**:202-8.

43. Iacobelli S, Bonsante F, Vintejoux A, Gouyon J-B. Standardised parenteral nutrition in preterm infants: early impact on fluid and electrolyte balance. *Neonatology* 2010;**98**:84-90.

44: Rigo J, Senterre T. Intrauterine-like growth rates can be achieved with premixed parenteral nutrition solution in preterm infants. J Nutr. 2013;143(12 Suppl):2066S-2070S.

45. Cormack BE, Bloomfield FH, Dezoete A, Kuschel CA. Does more protein in the first week of life change outcomes for very low birthweight babies? *J Paediatr Child Health* 2011;**47**:898-903.

46. Moyses HE, Johnson MJ, Leaf AA, Cornelius VR. Early parenteral nutrition and growth outcomes in preterm infants: a systematic review and meta-analysis. Am J Clin Nutr 2013;97:816-26.

47. Trevidi A, Sinn JKH. Early versus late administration of amino acids in preterm infants receiving parenteral nutrition (review).*Cochrane Database of Systematic Reviews* 2013: CD008771.

48 Bolisetty, Osborn D, Sinn J, Lui K. Standardised neonatal parenteral nutrition formulations – an Australasian group consensus 2012. *BMC Pediatr* 2014;**14**:48-58.

49. Whitby T, McGowan P, Turner MA, Morgan C. Concentrated parenteral nutrition solutions and central venous catheter complications in preterm infants *Arch Dis Child Fetal Neonatal Ed* 2015**;100:**F250-2.

50. Cormack BE, Bloomfield FH. Increased protein intake decreases postnatal growth faltering in ELBW babies *Arch Dis Child Fetal Neonatal Ed* 2013;98:F399-404.

51. Green J, McGowan P, Morgan C. Hyperalimentation and electrolyte requirements in very preterm infants: a randomised controlled parenteral nutrition study *Arch Dis Child Neonatal Ed* 2014;**99(Suppl1)**:A6.

52. Morgan C, Burgess L. High protein intake does not prevent low plasma levels of conditionally essential amino acids in very preterm infants receiving parenteral nutrition. *JPEN* 2015 pii: 0148607115594009. [Epub ahead of print]

2. The Principle of Concentrating Neonatal PN

Concerns about the stability and osmolality of neonatal PN mean that the conventional approach to PN prescription has been to prescribe aqueous components in the largest fluid volume possible. This usually means to total fluid volume (minus the intravenous lipid volume). Unfortunately, this means if there are other demands on the fluid volume (eg drug infusions) then aqueous nutrients (protein, glucose, minerals, trace elements, vitamins) are reduced. With individualised prescription, this is sometimes offset by calculating the total volume of fluid available after taking into account other infusions. However, in preterm infants the total fluid intake and rates of drug infusions change frequently and often will have changed in the time between PN prescription and administration (usually at least 8 hours), never mind for the duration of the bag (24 hours). This approach also has implications for quality assurance given the stability of this individual solution cannot be pretested for stability or tested after manufacture.

Concentrating the PN for all infants (and therefore standardising) provides aqueous PN in a volume that is considerably less than the usual fluid intake volume. This approach means stability can be definitively established for the formulation and quality testing can be incorporated in the manufacturing process. The difference between the PN fluid volume (85ml/kg/d in the example below) and the total fluid volume (150ml/kg/d in the example below) is made up by the intravenous lipid and a supplementary glucose infusion.

Although a standardised bag, more than one formulation can be made available. This is particularly useful for varying electrolyte requirements. In the example below (Figure 1) there are 3 nutritionally identical options with electrolyte variations that cover the needs of most preterm infants. Further variation can be managed with supplementary electrolyte infusions (see below).

Figure 1

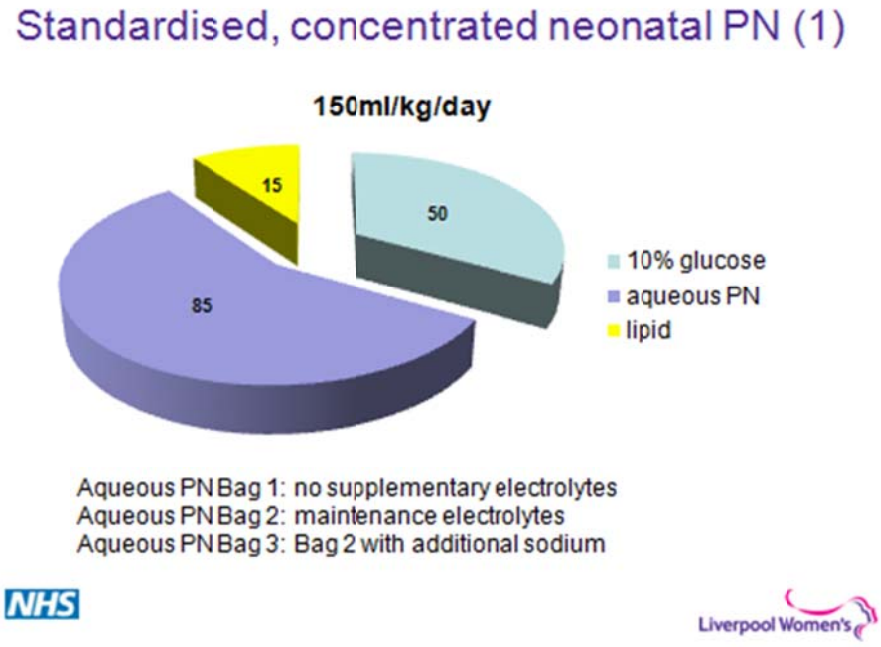
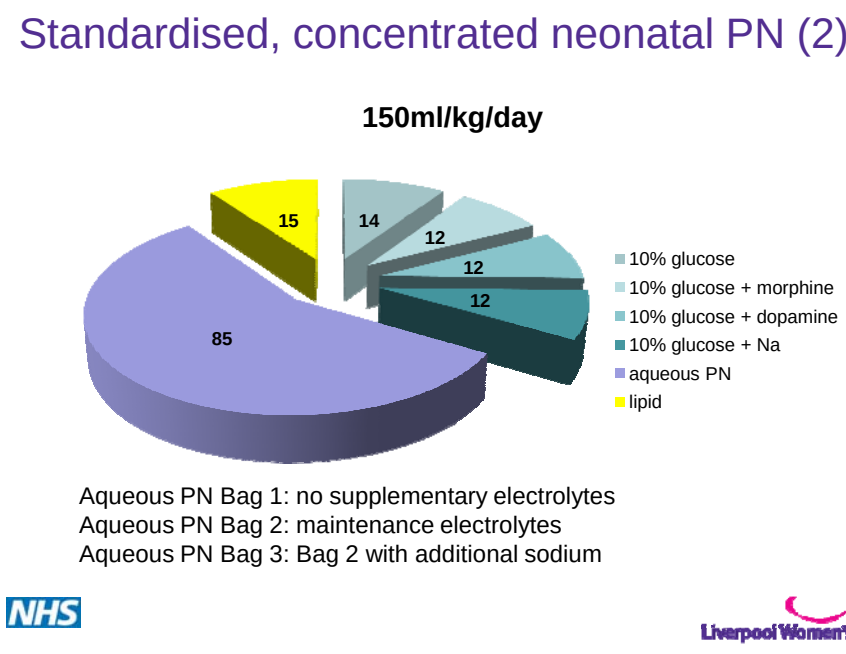


Figure 2 illustrates how the fluid compartment containing amino acids and other aqueous nutrients (85ml/kg/day) is protected in the face of multiple drug infusions. Without concentration, the reduction in aqueous PN volume results in reduced nutrient intake. Electrolyte deficiency (sodium in the example shown) can be corrected using a standardised electrolyte infusion as soon as the trend (or treatment threshold) is identified. This does not require further PN prescription and can be started at any time of day. The aqueous PN compartment is also protected in the event of fluid restriction (down to 100ml/kg/day including lipid assuming no other drug infusions).

Figure 2

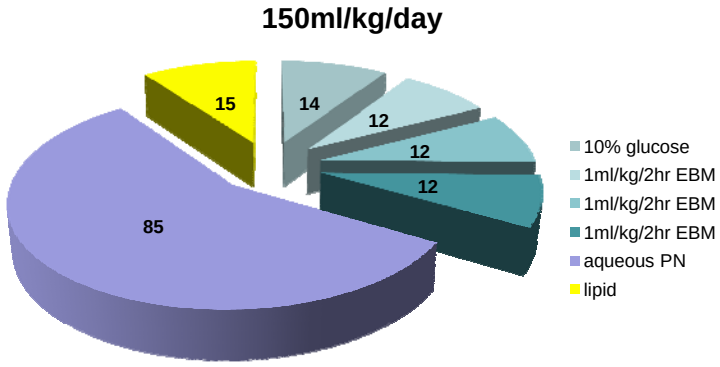


Nutrient intake is also compromised during the transition phase between parenteral and enteral nutrition. While small quantities of milk (minimal eneteral nutrition) are commonly excluded from the fluid intake as they rise the PN is often weaned simultaneously. This milk is often unfortified EBM (relatively low protein and calorie intake) and stopped and started. The concentrated aqueous PN allows the enteral feed to be increased to 50ml/kg/day before weaning the PN (see Figure 3) while maintaining the same daily fluid intake (150ml/kg/day).

Auditing two nutritionally identical PN regimens, one individualised and not concentrated and the other standardised and concentrated showed the latter increased mean protein intake by 20% (Figure 4). See also section on target attainment.

Figure 3

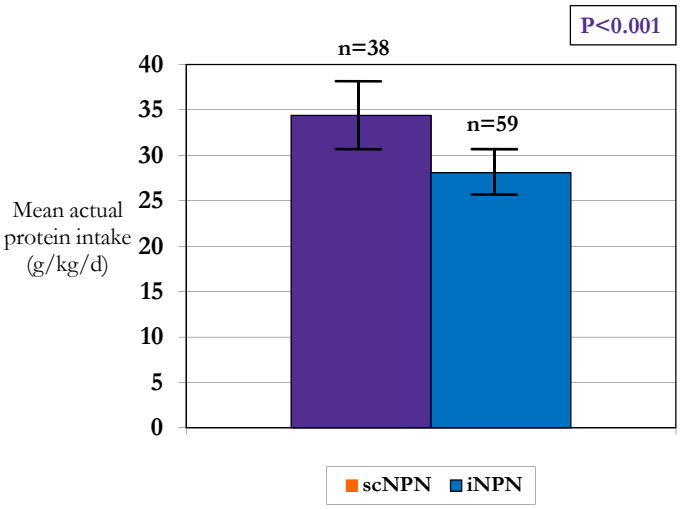
Standardised, concentrated neonatal PN (3)



Aqueous PN Bag 1: no supplementary electrolytes
Aqueous PN Bag 2: maintenance electrolytes
Aqueous PN Bag 3: Bag 2 with additional sodium

Figure 4

Protein intake in the first 14 days of life:
Individualised, non-concentrated vs standardised, concentrated PN



The principle of concentration can seem abstract without given specific examples of PN solutions. Table 1 provides a "league table" of existing neonatal aqueous PN solutions in current clinical practice in the UK. Amino acids (AA) are the key macronutrient in PN and so the table demonstrates the volume of the aqueous bag required to deliver recommended minimum (3g/kg/day) and maximum (4g/kg/day) amino acid intakes. The closer that volume is to the total daily fluid requirement, the more likely that drug infusions or unpredicted fluid restriction will impact on the actual AA intake achieved by the infant. This is more likely in the first few days of life when total fluid intakes are most restrictive. This principle applies to all other nutrients (including minerals and electrolytes) contained within the aqueous bag.

It should be noted that many standardised PN formulations have a "standard" and "concentrated" form indicating the need for concentration is an accepted principle. The degree to which this is predictable determines whether the most concentrated formulation could be used routinely for all infants (as currently with the SCAMP intervention regimen) or whether this should be used only when the daily fluid regimen requires it. The disadvantage of the latter is that if 3 variants of the "standard" bag are required to manage electrolyte variations then this would imply 6 variations of the "standard" and "concentrated" formulations. Some PN providers chose to overcome this by individualising electrolyte content in a single aqueous bag (in a PAMU) but this then undermines some of the benefits of standardisation.

Table 1: Nutritional content of standardised aqueous PN bags in ascending order of protein (amino acid; AA) concentration.

Standardised PN bag (adapted from published data)	Protein (AA) g/100ml	Glucose g/100ml	Calories* kcal/100ml	PN volume (ml/kg) required for	
				3gAA/kg/day	4gAA/kg/day
10% glucose	-	10	40	-	-
NEON (control)	2.0 (2.3)	7.2	29	133	178
Babiven	2.3 (2.6)	11.1	44	116	155
NEON (intervention)	2.7 (3.0)	7.2	29	100	133
Numeta (3CB)	3.1 (3.3)	13.3	53	91	121
East of England (standard)	3.1 (3.3)	11	44	91	121
SCAMP (control)	3.3 (3.7)	10	40	81	108
Babiven (concentrated)	3.4 (3.9)	16.7	67	77	103
Numeta (2CB)	3.7 (3.9)	16.7	67	77	103
SCAMP (intervention)**	3.8 (4.3)	12	48	70	93
East of England (concentrated)	3.8 (4.3)	14.5	58	70	93

*non-protein calories excluding any supplementary glucose and lipid infusions

**now slightly modified and called the CoMPaSS regimen

3. Neonatal PN QIPP Audit Tools

The primary aim of the neonatal PN QIPP is to improve the actual nutrient intake of each preterm infant and reduce the avoidable variation in nutrient intake between infants and between neonatal services providing PN. The audit tools are designed to establish the case for change. Where there is a case for change is will provide the local benchmark for post-implementation audit. Where no case for change it made it will reaffirm the current PN provision is of consistently high quality when benchmarking against other providers. Nutritional audit tools are potentially complex and time consuming to complete. The audit tools provided have been designed to collect the minimum dataset required to measure the quality of parenteral nutrient provision.

The PN prescribing audit tool (see Appendix 3.1)

The aim of the PN prescribing audit tool is twofold

i) To describe how much variation there is between sequential prescriptions in infants receiving individually prescribed PN
ii) To match prescribing practice with policy and identify how much protein/AA was prescribed in each day of life.

The audit tool is simple and can be customised to match the recorded information on the PN prescription (eg protein or AA or nitrogen can be recorded) including the selection of units measuring the content of other aqueous PN bag components . The variation in prescription will define whether standardised bags are feasible and what form would suit the local PN policy. The daily prescribed protein/AA intake will provide the target intake with which to compare the actual protein/AA intake (see below).

The PN nutritional audit tool (see Appendix 3.2)

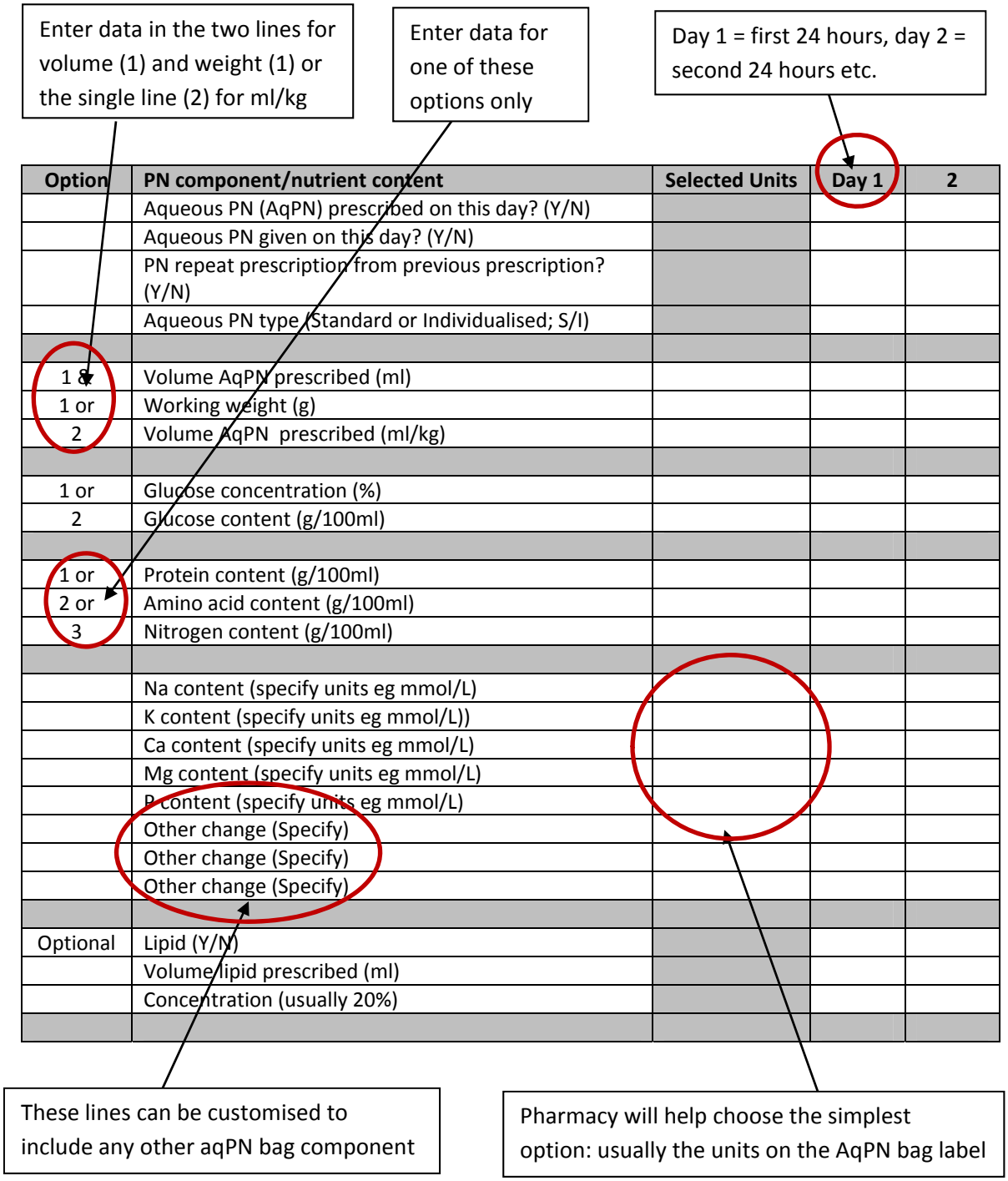
This audit tool is simplified but involves more complex data collection than above. This is because actual protein (AA) intake cannot be obtained from national neonatal datasets and needs to be obtained manually from the patient record. The data entry can still be customised to match local documentation (see above). The total fluid and enteral intakes are also required to interpret the data. This is why the audit is restricted to the first 14 days in 10 consecutive patients (who are PN dependent for a minimum of 7 days). The data is best corrected prospectively (although best started when the infant is > 7 days old). The daily parenteral and total protein (AA) intakes can be calculated and compared to the PN prescription and the targets identified from the local PN policy.

The PN nutritional target attainment tool (see Appendix 3.3)

This is an optional extra to allow greater interpretation of the audit tools above. Will be in version 2.0 of Toolkit

Appendix 3.1

Neonatal PN prescribing audit tool (provided as excel spreadsheet)



Option	PN component/nutrient content	Selected Units	Day 1	2
	Aqueous PN (AqPN) prescribed on this day? (Y/N)			
	Aqueous PN given on this day? (Y/N)			
	PN repeat prescription from previous prescription? (Y/N)			
	Aqueous PN type (Standard or Individualised; S/I)			
1 or	Volume AqPN prescribed (ml)			
1 or	Working weight (g)			
2	Volume AqPN prescribed (ml/kg)			
1 or	Glucose concentration (%)			
2	Glucose content (g/100ml)			
1 or	Protein content (g/100ml)			
2 or	Amino acid content (g/100ml)			
3	Nitrogen content (g/100ml)			
	Na content (specify units eg mmol/L)			
	K content (specify units eg mmol/L))			
	Ca content (specify units eg mmol/L)			
	Mg content (specify units eg mmol/L)			
	P content (specify units eg mmol/L)			
	Other change (Specify)			
	Other change (Specify)			
	Other change (Specify)			
Optional	Lipid (Y/N)			
	Volume lipid prescribed (ml)			
	Concentration (usually 20%)			

Appendix 3.2

Neonatal PN nutrition audit tool (provided as excel spreadsheet)

Enter data for one of these lines only

Enter time first PN given on day of birth (leave blank if none)

The 24 hour fluid intake data should start at 00:00

PN bags normally changed at fixed time point (enter time). The 24 hour fluid intake data is split between the two bags.

		Day 0	Day 1 (starts 00:00)		Day 2 (starts 00:00)	
Start time	**Selected**		**00:00**		**00:00**	
Aqueous Parenteral Nutritition	**Units**	**PN1**	**PN1**	**PN2**	**PN1**	**PN2**
Standardised bag (Y/N)						
Local/commercial name						
Individualised bag (Y/N)						
Protein content (g/100ml)						
Amino acid content (g/100ml)						
Nitrogen content (g/100ml)						
Volume actually given (ml)						
Working weight (g)						
Lipid (name)						
Volume actually given (ml)						
Milk (name)						
Fortifier (Y/N)						
Name						
Specify dose (eg 1 sachet/50ml)						
Volume actually given (ml)						
PN infusion rate reduced/weaned? (Y/N)						

There are many policies for weaning PN with increasing milk feeds. Answer "yes" if the volume of PN is less than "full PN" <u>because of enteral feed intake</u>

4. Neonatal PN QIPP Costing Tool

The aim of this document is to categorise all parenteral nutrition (PN) providers according to their PN supply chain. Twelve different categories of supply chain have been identified (Table 1). Each provider will have at least one aqueous aqNPN category and at least one lipid category. The methodology to calculate costs has been provided in Table for each category identified in Table 1. These individual category tables will allow providers to determine which supply chain most closely resembles their own PN provision and use this to calculate costs and the number of units produced. There may be more than one supply chain (especially for aqNPN) in which case the costs and usage should be calculated separately for each category.

A RAG rating has been provided for the difficulty of measuring costs. For example, purchasing a set number of units at a fixed price from an external manufacturer should be a straightforward calculation (rated green). Whereas local PAMU manufacture from multiple PN components contributing to paediatric and adult PN manufacture may be very difficult to cost (rated red). Where precise costings are not possible then these should be estimated locally. Where no local data are available then a national estimate will be applied (only to be used as a last resort).

Table 1: categories of PN provision and cost/usage data required

Table	PN component	Manufacturing cost	Dispensing cost	Wastage cost	Total cost	Total units used
i1aq	iAqNPN					
i2aq	iAqNPN					
i3aq	iAqNPN					
s1aq	sAqNPN					
s2aq	sAqNPN					
s3aq	sAqNPN					
s1lip	lipid					
s2lip	lipid					
s3lip	lipid					
s1supp	supplement					
s2supp	supplement					
s3supp	supplement					

Categorising the PN supply chain and calculating the cost of the total number of manufactured units will provide the unit cost of PN component manufacture but further data is required to calculate the cost of each PN day. Total PN days will be calculated for each neonatal Operational Delivery Network (ODN) and each PN provider within an ODN as described in Section 2 and Appendix A. Using both data sets will allow hidden wastage to be calculated (eg two PN units manufactured for one day, or a 48 hour bag only used for one day). Ultimately this will allow the cost of each PN day to be calculated for each provider taking into account all manufacturing, dispensing and wastage costs.

Individualised parenteral nutrition: aqueous component

Individualised neonatal parenteral nutrition (iNPN) is defined in this document as: same day manufacture of an aqueous neonatal PN (AqNPN) bag with one or more PN components prescribed for a named patient in an individualised PN concentration. This is usually driven by daily laboratory testing and involves mineral and electrolyte content together with local PN guidelines and nutritional policy. The tables below describe the steps involved in the individual manufacture of neonatal AqPN bags and provides the framework for annual costs to be calculated.

Table i1aq is the framework for AqNPN bags manufactured from scratch in a NHS Pharmacy Aseptic Manufacturing Unit (PAMU). Table i2aq is the framework for AqNPN bags (either standard or individualised) purchased from a commercial supplier and further manipulated based on named patient prescription in a (local) PAMU. Table i3aq is the framework for AqNPN purchased from a commercial supplier and dispensed locally without further manipulation. One costing framework should be used for each AqNPN bag (iNPN or sNPN) supplier.

Table i1aq	Prescribing process	Aqueous NPN Bag manufacture	RAG	Total Cost	Total Units
Commercial Supplier		PN components: Glucose AA Trace elements Vitamins Electrolytes Minerals Other			
Pharmacy Aseptic Manufacturing Unit (PAMU)	Individual bag manufactured according to named patient prescription	Manufacturing process: On costs: - Fully automated (compounder) - Partially automated - Manual preparation Consumables			
		Quality assurance: Microbiological testing Quality control Consumables			
Pharmacy Dispensing Service	Named patient prescription submitted	Dispensing process: Coordinates prescription, manufacture and dispensing			
Neonatal Service	Patient prescription checked against bag	Total waste cost: <u>all</u> unused individualised AqPN bags			

Table i2aq	Prescribing process	Aqueous NPN Bag manufacture	RAG	Total Cost	Total Units
Commercial Supplier (includes NHS PAMU not locally dispensing AqNPN)		Standard or individualised AqPN bag, PN components: Glucose AA ±Trace elements ±Vitamins ±Electrolytes ±Minerals ±Other			
Pharmacy Aseptic Manufacturing Unit (PAMU)	Individual bag manipulated according to named patient prescription	Manufacturing process: On costs Partially automated and/or manual addition of: - ±Trace elements - ±Vitamins - ±Electrolytes - ±Minerals Consumables			
		Quality assurance: Microbiological testing Quality control Consumables			
Pharmacy Dispensing Service	Named patient prescription submitted	Dispensing process: Coordinates prescription, manufacture and dispensing			
Neonatal Service	Patient prescription checked against bag	Total waste cost: all unused individualised AqPN bags			

Table i3aq	Prescribing process	Aqueous NPN Bag manufacture	RAG	Total Cost	Total Units
Commercial Supplier(includes NHS PAMU not locally dispensing AqNPN)	Individual bag manufactured according to named patient prescription	Complete individualised AqPN bag ordered from commercial supplier			
Pharmacy Aseptic Manufacturing Unit (PAMU)		No further manipulation of AqNPN Bag required			
Pharmacy Dispensing Service	Named patient prescription submitted	Dispensing process: Coordinates prescription, manufacturing order and dispensing			
Neonatal Service	Patient prescription checked against bag	Total waste cost: all unused individualised AqNPN bags			

Standardised parenteral nutrition: aqueous component

Standardised neonatal parenteral nutrition (sNPN) is defined in this document as: bulk manufacture of an aqueous PN (AqNPN) bag with all PN components in a predetermined PN concentration. There is usually more than one AqNPN bag formulation available. The selection of the standardised AqPN bag is usually driven by daily laboratory testing and involves mineral and electrolyte content together with local PN guidelines and nutritional policy. The tables below describe the steps involved in the manufacture of standardised neonatal AqNPN bags and provide the framework for annual costs to be calculated.

Table s1aq is the framework for AqPN bags manufactured from scratch in a NHS Pharmacy Aseptic Manufacturing Unit (PAMU). Table i2aq is the framework for AqPN bags purchased from a commercial supplier and further manipulated in a (local) PAMU to produce a modified standard bag (eg addition of vitamins or trace elements). Table s3aq is the framework for AqPN purchased from a commercial supplier and dispensed locally without further manipulation. One costing framework should be used for each AqPN bag (iNPN or sNPN) supplier.

Table s1aq	Prescribing process	Aqueous NPN Bag manufacture	RAG	Total Cost	Total Units
Commercial Supplier		PN components: Glucose AA Trace elements Vitamins Electrolytes Minerals Other			
Pharmacy Aseptic Manufacturing Unit (PAMU)	Standard bags bulk manufactured but selected according to named patient prescription	Manufacturing process: On costs: - Fully automated (compounder) - Partially automated - Manual preparation Consumables			
		Quality assurance: Microbiological testing Quality control Consumables			
Pharmacy Dispensing Service	Named patient prescription submitted	Dispensing process: Coordinates prescription, manufacture and dispensing			
Neonatal Service	Patient prescription checked against bag	Total waste cost: <u>all</u> unused standardised AqNPN bags			

Table s2aq	Prescribing process	Aqueous NPN Bag manufacture	RAG	Total Cost	Total Units
Commercial Supplier (includes NHS PAMU not locally dispensing AqNPN)		Standard or individualised AqPN bag, PN components: Glucose AA ±Trace elements ±Vitamins ±Electrolytes ±Minerals ±Other			
Pharmacy Aseptic Manufacturing Unit (PAMU)	Standard bags bulk manufactured and then further manipulated (in bulk) locally to complete standard bag formulation Selected according to named patient prescription	Manufacturing process: On costs Partially automated and/or manual addition of: - ±Trace elements - ±Vitamins - ±Electrolytes - ±Minerals - ±Other Consumables			
		Quality assurance: Microbiological testing Quality control Consumables			
Pharmacy Dispensing Service	Named patient prescription submitted	Dispensing process: Coordinates prescription, manufacture and dispensing			
Neonatal Service	Patient prescription checked against bag	Total waste cost: all unused standardised AqNPN bags			

Table s3aq	Prescribing process	Aqueous NPN Bag manufacture	RAG	Total Cost	Total Units
Commercial Supplier(includes NHS PAMU not locally dispensing AqNPN)	Standard bags bulk manufactured but selected according to named patient prescription	Complete standardised AqNPN bag ordered from commercial supplier			
Pharmacy Aseptic Manufacturing Unit (PAMU)		No further manipulation of AqPN Bag required			
Pharmacy Dispensing Service	Named patient prescription submitted	Dispensing process: Coordinates prescription, manufacturing order and dispensing			
Neonatal Service	Patient prescription checked against bag	Total waste cost: all unused standardised AqNPN bags			

Standardised parenteral nutrition: lipid component

Standardised neonatal parenteral nutrition (sNPN) is defined in this document as: bulk manufacture of an intravenous lipid infusion with all PN components in a predetermined PN concentration. There may be more than one lipid formulation available. Lipid formulations do not require individualised prescription because although laboratory testing may modify the prescribed dose, this is achieved by altering the rate of infusion not manipulating the PN components. The tables below describe the steps involved in the manufacture of standardised neonatal lipid infusions and provide the framework for annual costs to be calculated.

Table s1aq is the framework for lipid infusions manufactured from scratch in a NHS Pharmacy Aseptic Manufacturing Unit (PAMU). Table i2aq is the framework for lipid infusionss purchased from a commercial supplier and further manipulated in a (local) PAMU to produce a modified standard lipid infusion (eg addition of vitamins). Table s3aq is the framework for lipid infusions purchased from a commercial supplier and dispensed locally without further manipulation. One costing framework should be used for each lipid infusion supplier (usually one).

Table s1lip	Prescribing process	Lipid infusion manufacture	RAG	Total Cost	Total Units
Commercial Supplier		Standardised PN components: Lipid Vitamins Other			
Pharmacy Aseptic Manufacturing Unit (PAMU)	Standard lipid infusions bulk manufactured but selected according to named patient prescription	Manufacturing process: On costs: - Fully automated (compounder) - Partially automated - Manual preparation Consumables			
		Quality assurance: Microbiological testing Quality control Consumables			
Pharmacy Dispensing Service	Named patient prescription submitted	Dispensing process: Coordinates prescription, manufacture and dispensing			
Neonatal Service	Patient prescription checked against infusion	Total waste cost: <u>all</u> unused standardised lipid infusions			

Table s2lip	Prescribing process	Lipid infusion manufacture	RAG	Total Cost	Total Units
Commercial Supplier (includes NHS PAMU not locally dispensing iv lipid)		Standardised PN components: Lipid +Vitamins +Other			
Pharmacy Aseptic Manufacturing Unit (PAMU)	Standard lipid infusions bulk manufactured and then further manipulated (in bulk) locally to complete standard lipid formulation Selected according to named patient prescription	Manufacturing process: On costs Partially automated and/or manual addition of: - +Vitamins - +Other Consumables			
		Quality assurance: Microbiological testing Quality control Consumables			
Pharmacy Dispensing Service	Named patient prescription submitted	Dispensing process: Coordinates prescription, manufacture and dispensing			
Neonatal Service	Patient prescription checked against lipid infusion	Total waste cost: all unused standardised lipid infusions			

Table s3lip	Prescribing process	Lipid infusion manufacture	RAG	Total Cost	Total Units
Commercial Supplier(includes NHS PAMU not locally dispensing iv lipid)	Standard infusions bulk manufactured but selected according to named patient prescription	Complete lipid infusion ordered from commercial supplier			
Pharmacy Aseptic Manufacturing Unit (PAMU)		No further manipulation of lipid infusion required			
Pharmacy Dispensing Service	Named patient prescription submitted	Dispensing process: Coordinates prescription, manufacturing order and dispensing			
Neonatal Service	Patient prescription checked against lipid infusion	Total waste cost: all unused standardised lipid infusions			

Standardised parenteral nutrition: supplementary component

Standardised supplementary infusions (usually glucose) are sometimes used to supplement standardised PN regimens (eg to correct electrolyte or mineral deficiency). They are an integral part of a standardised concentrated PN regimen to given flexibility at the cotside to manage glucose, electrolyte and mineral derangement. While their use is determined by individual patient laboratory data, the infusions are standardised concentrations. Non-standardised supplementary infusions are not considered part of the PN regimen in this document.. The tables below describe the steps involved in the manufacture of standardised supplementary infusions and provide the framework for annual costs to be calculated.

Table s1aq is the framework for supplementary infusions manufactured from scratch in a NHS Pharmacy Aseptic Manufacturing Unit (PAMU). Table i2aq is the framework for supplementary infusions purchased from a commercial supplier and further manipulated in a (local) PAMU to produce a modified standard lipid infusion (eg addition of vitamins). Although not recommended, this includes ward manipulation (eg added electrolytes to a prepared glucose infusion). Table s3aq is the framework for supplementary infusions purchased from a commercial supplier and dispensed locally without further manipulation. One costing framework should be used for each supplementary infusion supplier (usually one).

Table s1supp	Prescribing process	Supplementary infusion manufacture	RAG	Total Cost	Total Units
Commercial Supplier		Standardised PN components: Glucose +Electrolytes +Minerals +Other			
Pharmacy Aseptic Manufacturing Unit (PAMU)	Standard supplementary infusions bulk manufactured but selected according to named patient prescription	Manufacturing process: On costs: - Fully automated (compounder) - Partially automated - Manual preparation Consumables			
		Quality assurance: Microbiological testing Quality control Consumables			
Pharmacy Dispensing Service	Named patient prescription submitted	Dispensing process: Coordinates prescription, manufacture and dispensing			
Neonatal Service	Patient prescription checked against infusion	Total waste cost: all unused standardised supplementary infusions			

Table s2supp	Prescribing process	Supplementary infusion manufacture	RAG	Total Cost	Total Units
Commercial Supplier (includes NHS PAMU not locally dispensing iv PN supplements)		Standardised PN components: Glucose ±Electrolytes ±Minerals ±Other			
Pharmacy Aseptic Manufacturing Unit (PAMU)	Standard infusions bulk manufactured and then further manipulated (in bulk) locally to complete standard formulation Selected according to named patient prescription	Manufacturing process: On costs Partially automated and/or manual addition of: - ±Vitamins - ±Other Consumables			
		Quality assurance: Microbiological testing Quality control Consumables			
Pharmacy Dispensing Service	Named patient prescription submitted	Dispensing process: Coordinates prescription, manufacture and dispensing			
Neonatal Service	Patient prescription checked against lipid infusion	Total waste cost: all unused standardised supplementary infusions			

Table s3supp	Prescribing process	Supplementary infusion manufacture	RAG	Total Cost	Total Units
Commercial Supplier (includes NHS PAMU not locally dispensing iv PN supplements)	Standard infusions bulk manufactured but selected according to named patient prescription	Complete supplementary infusion ordered from commercial supplier			
Pharmacy Aseptic Manufacturing Unit (PAMU)		No further manipulation of supplementary infusion required			
Pharmacy Dispensing Service	Named patient prescription submitted	Dispensing process: Coordinates prescription, manufacturing order and dispensing			
Neonatal Service	Patient prescription checked against lipid infusion	Total waste cost: all unused standardised supplementary infusions			

Calculating the number of PN days

It is the total cost of each PN day that is the object of this costing exercise. Working through manufacturing, dispensing, wastage and unit costs will give a true cost of each PN day. Total PN days will be calculated for each neonatal Operational Delivery Network (ODN) and each PN provider within an ODN. This will be done by collecting data on Badger.net as described in Appendix A. The method of data collection will separately identify PN administered on day 1-14 (costs within tariff) and PN administered after day 14 (costs claimed from CCG).

Appendix 4.1

Calculating PN days

Methodology for extracting and analysing TPN usage data from Badgernet

Purpose

To work out the frequency and length of time TPN is being administered by ODN, locality and unit.

Method

This method is intended to show a simple way of viewing the data and is not intended to be prescriptive. It is accepted that many ODNs will have established ways of querying the data which may be more efficient and in line with their current practices.

1. Download the Neonatal episode summary (anonymous) data for all required units and time period from Badgernet.

2. Create a pivot table based on the data with the following fields:

   Filters: NetworkName, CareLocationName

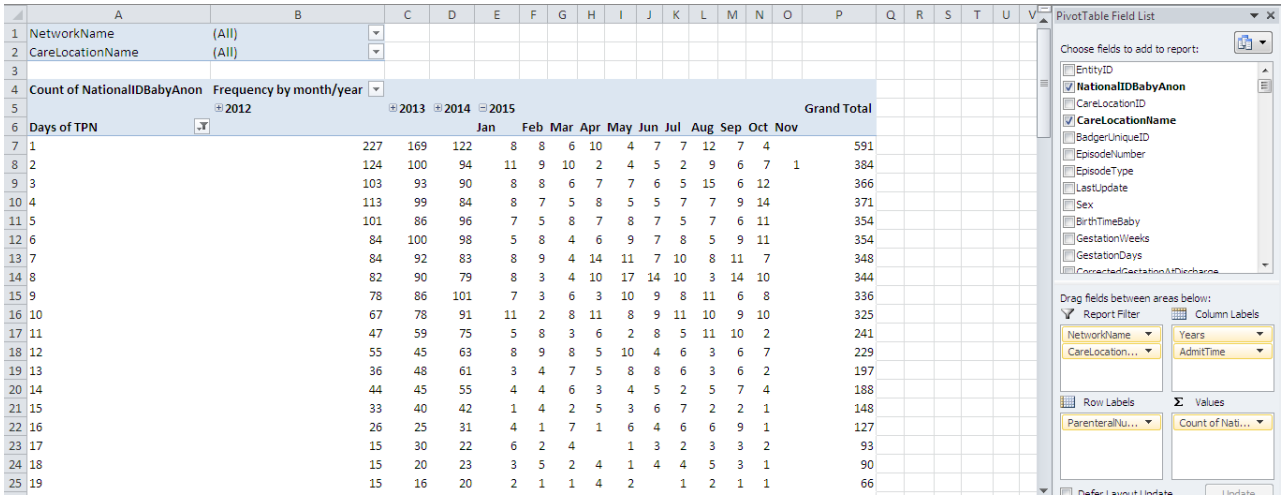
   Columns: AdmitTime (grouped to years and months in this example)

   Rows: ParenteralNutritionDays

   Values: NationalIDBabyAnon

3. Remove zero and blanks from the Row Labels.

4. You should now have something that looks similar to the snip below, showing the number of days in each TPN episode and the frequency by month/year:



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	NetworkName	(All)														
2	CareLocationName	(All)														
3																
4	Count of NationalIDBabyAnon	Frequency by month/year														
5		2012	2013	2014	2015											Grand Total
6	Days of TPN				Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	
7	1	227	169	122	8	8	6	10	4	7	7	12	7	4		591
8	2	124	100	94	11	9	10	2	4	5	2	9	6	7	1	384
9	3	103	93	90	8	8	6	7	7	6	5	15	6	12		366
10	4	113	99	84	8	7	5	8	5	5	7	7	9	14		371
11	5	101	86	96	7	5	8	7	8	7	5	7	6	11		354
12	6	84	100	98	5	8	4	6	9	7	8	5	9	11		354
13	7	84	92	83	8	9	4	14	11	7	10	8	11	7		348
14	8	82	90	79	8	3	4	10	17	14	10	3	14	10		344
15	9	78	86	101	7	3	6	3	10	9	8	11	6	8		336
16	10	67	78	91	11	2	8	11	8	9	11	10	9	10		325
17	11	47	59	75	5	8	3	6	2	8	5	11	10	2		241
18	12	55	45	63	8	9	8	5	10	4	6	3	6	7		229
19	13	36	48	61	3	4	7	5	8	8	6	3	6	2		197
20	14	44	45	55	4	4	6	3	4	5	2	5	7	4		188
21	15	33	40	42	1	4	2	5	3	6	7	2	2	1		148
22	16	26	25	31	4	1	7	1	6	4	6	6	9	1		127
23	17	15	30	22	6	2	4		1	3	2	3	3	2		93
24	18	15	20	23	3	5	2	4	1	4	4	5	3	1		90
25	19	15	16	20	2	1	1	4	2		1	2	1	1		66

5. It is possible to filter by locality/unit and month/year in this example. It's also possible to group the times differently so that you can filter by quarter if preferred.

6. Using this table the total number of PN days exceeding 14 days PN for each infant can be calculated for both ODN and individual provider:
    a. the total number of PN days in all infants who exceeding 14 days PN can be calculated using the SUM function.
    b. the total number of infants exceeding 14 days PN can also be calculated using the SUM function.
    c. The total number of PN exceeding 14 days PN for each infant is a-(bx14)

Summary

The essence of what we're looking at is the ParenteralNutritionDays field and the frequency of this field at a particular unit or locality in a given time frame. It is something that should be fairly straightforward to build into a regular reporting cycle. If anyone has any questions or suggestions, please contact richard.williams23@nhs.net

5. Neonatal PN Improving Value Roadmap

5.1. Initiate project

The Operational Delivery Network (ODN) will identify project champion and establish a Core Network Nutrition Group (CNNG). This will comprise a multidisciplinary team to represent all PN providers within the ODN. This will include representatives from clinicans, nurses, dietitians, clinical pharmacists, preparatory services and the Quality Control Pharmacist. The champion will be responsible for developing the regional communication strategy and coordinating support from the QIPP team and toolkit. Early links should be initiated with the relevant procurement hub/team and the local processes for procurement must be agreed at the beginning. The implications of existing PN tenders need to be clarified (see 10).

5.2. Review the current ODN PN guidelines and formulations

The CNNG will develop a central repository of all guidelines and policies within the ODN. Local areas of best practice and strategies to improve PN provision should be recognised. Differences in clinical practice should be acknowledged and discussed. Include comparisons with the formulations in regional use: the CoMPaSS concept (NW ODN) and the East of England (EOE) ODN PN regimen.

5.3. Categorise the current PN supply chain

The CNNG will identify all PN providers within the ODN and find the closest match for their current PN supply chain within the categories defined in the toolkit. There should be a least one aqueous PN and one lipid supply chain. Group centres that share (or could share) common supply chains.

5.4. Estimate the baseline costs

Each PN provider will enter all known costs using the costing table for each supply chain. The CNNG will develop a work stream to estimate the local costs for parts of the supply chain that are currently unknown. National data can be used (if needed) in the interim while waiting for the workstream to complete. Calculate the number of PN days achieved by each provider using the toolkit guide. This will allow separation of PN days 1-14 from PN days after day 14. This process could be coordinated nationally by Neonatal Database Analysis Unit (NDAU).

5.5. Complete a pre-implementation audit

Use the audit tool within the toolkit to calculate the nutrient (usually protein) target attainment in a minimum of 10 consecutive infants who are PN-dependent from birth. This should be calculated for each provider. The benchmark has been established using post-implementation audit data in the NW ODN (CoMPaSS concept) and the EOE (shares many features with the CoMPaSS concept).

For those units providing partially or mainly individually prescribed and manufactured bags (usually in a local Pharmacy Aseptic Manufacturing Unit) an audit of actual PN prescriptions may provide sufficient evidence that a change to a standardised PN formulation is justified. For example: serial prescriptions in the same patient showing little change in prescription or changes that could still be managed within a standardised regimen (eg electrolytes). An audit of actual nutrient intake will still

be required to establish the baseline (see above) but this will allow more rapid progression through the roadmap to the procurement stage.

5.6. Establish the case for change

Use the baseline cost data to calculate the average cost of a PN day for each provider. This should be benchmarked against the equivalent data in the NW (CoMPaSS concept) and EOE networks to establish a case for changing all or part of the current supply chain for each provider. The same process should be used to identify those providers where target nutrient attainment falls below that set by the NW and EOE ODN data. Notify relevant procurement hub/team.

5.7. Develop an improvement strategy

If providers compare favourably with both quality and cost benchmarks then there is no case for changing practice within this service. However, it is unlikely that all providers within ODN will meet this standard. The ODN must support the CNNG to coordinate an improvement strategy for those units not meeting the quality and/or cost benchmarks. This will utilise the implementation package in the toolkit. This may range from selecting one or two areas for improvement to complete adoption of the CoMPaSS concept.

5.8. Coordinate an improvement strategy

The ODN and CNNG will facilitate implementation in individual providers by supporting collaboration between providers to achieve a common PN supply chain. This will include sharing in the best practice demonstrated by providers meeting both cost and quality benchmarks within the ODN. This will include supporting the necessary procurement processes and should consider a common procurement process for the whole ODN.

5.9. Agree a standard formulation

Multidisciplinary consultation (minimum: neonatologist, senior neonatal nurse, dietitian and pharmacist representation from each provider) facilitated by the CNNG must be used to agree a common formulation and prescribing process. This may result in the adoption of a formulation in current use in another region or from a commercial supplier (see procurement). This must involve the largest regional collaboration possible (ideally the entire ODN).

5.10. Follow the relevant procurement process

Having selected the preferred neonatal PN regimen the CNNG, the procurement process can then identify potential suppliers. This may be complicated by an existing PN tender relating to all or part of the ODN. Timelines may require adapting to take this into account. Detailed specifications (including the robustness of supply with widely fluctuating demand) will be generated in line with local/regional procurement requirements overseen by the ODN. The supplier will be confirmed after the tendering process completed and contracts agreed.

5.11. Implement changes using a locally adapted teaching and training package

CNNG will agree an implementation date and ODN launch event(s) with all regional participants. The Neonatal PN QIPP toolkit will include a framework to implement and support a local teaching and

training package. The regional champion will play a key role in cascade training and ensuring there is a pilot period with troubleshooting advice available.

5.12. Conduct a post-implementation audit

The pre-implementation audit will be repeated post implementation. The audit tool within the toolkit will be used to calculate the nutrient (usually protein) target attainment in a minimum of 10 consecutive infants who are PN-dependent from birth. This will be calculated for each provider. Other quality assessments including biochemical stability/trends will be required. Similarly, the cost data for the new model of PN provision will be compared with pre-implementation data and the projected savings estimated using the crude regional PN usage data. The Champion and CNNG are responsible for cascading the post-implementation audit findings, identifying further changes in practice and sustaining the audit cycle to continue improving PN provision.