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Nutritional Evaluation and Optimisation in Neonates (NEON) trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition: a randomised double-blind controlled trial

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Abstract

Nutritional Evaluation and Optimisation in Neonates (NEON) trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition: a randomised double-blind controlled trial

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Background: Parenteral nutrition (PN) is central to the care of very immature infants. Early intakes of higher amounts of amino acids and the use of lipid emulsions containing fish oils are recommended by current international recommendations.

Objective: To confirm the safety and demonstrate efficacy of the immediate introduction of the recommended daily intake of amino acids (Imm-RDI) and soya bean oil, medium-chain triglycerides, olive oil and fish oil lipid in PN to increase non-adipose (lean) body mass and decrease intrahepatocellular lipid (IHCL) content.

Design: Multicentre, double-blind, 2 × 2 factorial and randomised controlled trial (RCT).

Setting: Neonatal units in London and south-east England, UK.

Participants: Extremely preterm infants born before 31 weeks of gestation without major congenital or life-threatening abnormalities who could to be randomised to receive PN within 24 hours of birth.

Interventions: Infants were randomised within 24 hours of birth to receive PN containing either high [RDI of amino acids (Imm-RDI)] or low [incremental amino acids (Inc-AA) control] levels of amino acids. In addition, infants were randomised to receive either 20% SMOFlipid® (Fresenius Kabi AG, Richmond Hill, ON, Canada) or 20% Intralipid® (Fresenius Kabi AG, Richmond Hill, ON, Canada) (control). This resulted in four groups: (1) Inc-AA/Intralipid, (2) Inc-AA/SMOFlipid, (3) Imm-RDI/Intralipid and (4) Imm-RDI/SMOFlipid. The intervention was continued until infants were receiving 150 ml/kg/day of enteral feeds for 24 hours.

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Primary outcome measure: For the amino acid intervention, this was non-adipose or lean body mass measured by magnetic resonance imaging. For the lipid composition intervention, this was IHCL content as measured by hepatic magnetic resonance spectroscopy. Primary outcomes were measured at term age equivalent, between 37 and 44 weeks postmenstrual age.

Results: We randomised 168 infants born before 31 weeks of gestation. We evaluated outcomes, at term, in 133 infants. There were no significant differences in non-adipose mass between the Imm-RDI and Inc-AA groups [adjusted mean difference 1.0 g, 95% confidence interval (CI) –108 to 111 g] or in levels of IHCLs between the SMOFlipid and Intralipid groups (adjusted mean SMOFlipid to Intralipid ratio 1.1, 95% CI 0.8 to 1.6). Infants receiving the Imm-RDI were more likely than Inc-AA infants to have blood urea nitrogen levels > 7 mmol/l [75% vs. 49% ($p < 0.01$)] and > 10 mmol/l [49% vs. 18% ($p < 0.01$)]. Furthermore, head circumference at term was smaller in the Imm-RDI group (mean difference –0.8 cm, 95% CI –1.5 to –0.1 cm; $p = 0.02$). There were no significant differences in any prespecified secondary outcomes, including adiposity, liver function tests, weight, length and mortality.

Limitations: Not all eligible babies were available for recruitment, as pharmacy staff trained in clinical trial procedures were unavailable at weekends in three of the four centres. We were able to assess brain volumes in only one-third of participants, as imaging was carried out while the participants were sleeping naturally and we measured primary outcomes first and continued to brain imaging only if the infant remained asleep.

Conclusions: Immediate delivery of the recommended daily intake of parenteral amino acids does not benefit body composition or growth to term and may be harmful; SMOFlipid does not affect IHCL content.

Future work: The long-term functional outcomes of early administration of RDI of amino acids and the use of SMOFlipid, including neurodevelopment, body composition and metabolic health, should be evaluated.

Trial registration: Current Controlled Trials ISRCTN29665319 and EudraCT 2009-016731-34.

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List of abbreviations

AE	adverse event
AT	adipose tissue
CI	confidence interval
DMEC	Data Monitoring and Ethics Committee
eCRF	electronic case record form
EME	Efficacy and Mechanism Evaluation
FOV	field of view
ICTU	Imperial Clinical Trials Unit
IHCL	intrahepatocellular lipid
Imm-RDI	immediate introduction of the recommended daily intake of amino acids
Imm-RDI/ Intralipid	immediate introduction of the recommended daily intake of amino acids and 20% Intralipid
Imm-RDI/ SMOFlipid	immediate introduction of the recommended daily intake of amino acids and 20% SMOFlipid
IMP	investigational medicinal product
Inc-AA	incremental amino acids
Inc-AA/ Intralipid	incremental amino acids and 20% Intralipid
Inc-AA/ SMOFlipid	incremental amino acids and 20% SMOFlipid
IQR	interquartile range
IVRS	interactive voice recognition system
LBM	lean body mass
LCT	long-chain triglyceride
MCT	medium-chain triglyceride
MHRA	Medicines and Healthcare products Regulatory Agency
MR	magnetic resonance
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NEON	Nutritional Evaluation and Optimisation in Neonates
NICU	neonatal intensive care unit
NIHR	National Institute for Health Research
PIS	parent information sheet
PN	parenteral nutrition
QUICKI	quantitative insulin sensitivity check index
RCT	randomised controlled trial
RDI	recommended daily intake
SAE	serious adverse event
SD	standard deviation
SMOFlipid	a mixture of soya bean oil, MCTs, olive oil and fish oils, supplemented with vitamin E
SpAE	specific adverse event
SSCNAAT	superficial subcutaneous non-abdominal adipose tissue
TSC	Trial Steering Committee

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Plain English summary

Infants born extremely preterm (defined as born before 31 weeks of gestation) spend several weeks and months in intensive care and are subject to various complications relating to their prematurity. Outside the womb, meeting the nutritional demands of these infants presents challenges. Experts have called for changes in how we feed babies, but we do not know if giving more nutrition is better for babies. We studied two aspects of parenteral nutrition, a fluid used to feed babies through their veins to overcome gut immaturity. First, we compared a stepwise increase in protein intake with giving the baby what is the recommended daily intake. Second, we compared the type of fat currently used in parenteral nutrition with a newer combination of fat that has been shown to be less harmful to the liver. Babies were allocated to one or the other group by chance. This is so that both groups are similar at the start of the study so that any difference that is found at the end can be explained by the difference in the nutrition we gave them. Using special magnetic scans (to measure body muscle mass and fat in the liver) we studied the babies around the time of their due date. We found that, provided extremely preterm babies were fed milk from the start, giving the recommended daily intake of protein from birth instead of gradually increasing the intake did not result in any difference in muscle mass at term age. In addition, the new type of fat did not show any benefit over the old type of fat.

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Scientific summary

Background

Delivering nutrition to very immature babies is challenging. Parenteral nutrition (PN) requires reliable intravenous access, pharmacist support and clinical expertise in minimising and treating complications. Gastrointestinal immaturity precludes early administration of milk volumes sufficient to support growth. In practice, PN and milk feeds are commenced at variable intervals after birth, with nutrient delivery increased incrementally. As a consequence, cumulative nutrient deficits are common and, by term, the majority of very preterm infants are lighter and shorter than healthy term-born counterparts. Although optimal postnatal growth velocity is uncertain, the association between slower growth and greater likelihood of neurodevelopmental impairment and cerebral palsy has provided justification for early PN provision. High amino acid intakes have been advocated, with the recommended daily intake (RDI) calculated on the basis of redressing cumulative deficits as well as matching intrauterine growth velocity. Intravenous lipid preparations containing fish oils have been recommended on the basis of clinical observations suggesting that they may be protective against hepatic dysfunction, a frequent concomitant of PN.

A diet with a low protein-to-energy ratio results in lower lean body mass and greater adiposity. Thus, in the short term, weight gain, though a widely used outcome measure, may not be as revealing as body composition. Monitoring lipid tolerance is problematic, as normative ranges for circulating lipids remain inadequately defined in very preterm babies and relationships to long-term outcomes are unclear. Whole-body magnetic resonance imaging (MRI) can be employed to assess body composition directly and in vivo magnetic resonance spectroscopy (MRS) to non-invasively assess hepatic lipid; the latter compares favourably with the gold standard, liver biopsy, for the quantitative assessment of hepatic steatosis.

We designed a clinical trial to test the hypotheses that the immediate delivery of the RDI of parenteral amino acids compared with incremental provision is more efficacious in increasing lean (non-adipose) body mass at term, and a mechanism of action of 20% soya bean oil, medium-chain triglycerides, olive oil, fish oil lipid (SMOFlipid®; Fresenius Kabi AG, Richmond Hill, ON, Canada) compared with 20% Intralipid® (Fresenius Kabi AG, Richmond Hill, ON, Canada) is to reduce intrahepatocellular lipid (IHCL) content.

Objectives

Amino acid intervention

To evaluate whether or not immediate rather than incremental introduction of the RDI of amino acids (Imm-RDI) in extremely preterm infants results in:

- greater accrual of non-adipose (lean) body mass at term (primary objective)
- increased brain volume at term (secondary objective)
- reduced insulin resistance at term (secondary objective)
- reduced ratio of internal to subcutaneous adipose tissue (AT) at term (secondary objective)
- a lower drop in weight standard deviation (SD) score between birth and term equivalent (secondary objective).

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Lipid intervention

To evaluate whether or not 20% SMOFlipid (with a lower ratio of *n*-6 to *n*-3 fatty acids) compared with 20% Intralipid in extremely preterm infants results in:

- reduced IHCL content at term age equivalent (primary objective)
- reduced incidence of hypertriglyceridaemia and hyperbilirubinaemia (secondary objective).

Methods

Trial design

This was a multicentre, randomised, 2 × 2 factorial and double-blind controlled trial in four UK centres, in London and south-east England. Eligible preterm infants were randomised, within 24 hours of birth, to receive (1) either incremental amino acids (Inc-AA) in PN or the RDI of amino acids (Imm-RDI) from day 1; and (2) either 20% Intralipid or 20% SMOFlipid.

There were four randomised groups:

1. Inc-AA and 20% Intralipid (Inc-AA/Intralipid)
2. Inc-AA and 20% SMOFlipid (Inc-AA/SMOFlipid)
3. Imm-AA and 20% Intralipid (Imm-RDI/Intralipid)
4. Imm-AA and 20% SMOFlipid (Imm-RDI/SMOFlipid).

Participants

Preterm infants (born before 31 weeks of gestation) requiring nutritional support in the form of PN.

Inclusion criteria

- Preterm infants born before 31 weeks of gestation (defined as ≤ 30 weeks and 6 days).
- Written informed consent from parents.

Exclusion criteria

- Major congenital or life-threatening abnormalities.
- Inability to randomise in time to allow administration of trial PN within 24 hours of birth.

Interventions

There were two interventions: (1) the amount of amino acids in PN and (2) the type of lipid formulation. All other components of PN were consistent across the four treatment groups. The intervention was commenced within 24 hours of birth. Nutritional intake, both parenteral and enteral, was guided by prespecified protocols that were provided in an investigator's manual. In the control arm of amino acid intake, infants received 1.7 g/kg/day amino acids on day 1 of postnatal life. This increased to 2.1 g/kg/day on day 2 and a maximum of 2.7 g/kg/day from day 3. In the intervention group, infants received 3.6 g/kg/day from day 1. On days 1 and 2, PN was provided in an aqueous form at a concentration of 90 ml/kg/day increasing to 120 ml/kg/day from day 3 onwards. Carbohydrate intake was 8.6 g/kg/day from day 1. Lipid intake was 2 g/kg/day on day 1 increasing to 3 g/kg/day from day 2 onwards. Infants were also randomised to receive lipid as either 20% Intralipid or 20% SMOFlipid. Day 1 was defined as the duration between birth and when the first bag of PN was changed. Bag changes occurred daily at 17.00. PN was dispensed only between 09.00 and 17.00. The duration of day 1 was variable and dependent on infant time of birth. Subsequently, all infants received the intended volumes as described above.

The interventions ceased once the infant was established on milk feeds of 150 ml/kg/day for at least 24 hours. If the infant was subsequently placed nil by mouth after this point, PN was prescribed in accordance with local practice as determined by the supervising clinician.

Outcomes

Primary outcomes

Efficacy of the early introduction of the RDI of amino acids was assessed by whole-body MRI to measure non-adipose or lean mass. The efficacy of lipid composition was assessed by MRS to measure IHCL content. These assessments were done at term age equivalent, between 37 and 44 weeks postmenstrual age.

Measurement of lean body mass

Lean body mass was calculated by subtracting AT mass from the weight of the baby on the day of the scan.

Measurement of intrahepatocellular lipid content

Efficacy of SMOFlipid was assessed by liver MRS to measure IHCL content. This was done at term age equivalent, between 37 and 44 weeks postmenstrual age.

Secondary outcomes

- Quantity and distribution of AT.
- Total and regional brain volumes.
- Metabolic index of insulin sensitivity [as measured by the quantitative insulin sensitivity check index (QUICKI)].
- Serum lipids and bilirubin.
- Incidence of death.
- Anthropometry.

Sample size and statistical analysis

The sample size was based on the estimate that 64 infants in each pairwise group (Imm-RDI vs. Inc-AA) would provide 80% power (two-sided; 5% significance) to detect a 200-g difference in non-adipose mass assuming a SD of 400 g. This represents half the difference in non-adipose mass identified between very preterm and term-born infants in a prior experimental cohort. We have previously reported IHCL values for very preterm babies at term [mean lipid-to-water ratio 1.75 (SD 1.85), range 0.14–7.72]. As the distribution is positively skewed, a $\log_e$-transformation was used to provide IHCL mean lipid-to-water ratio [0.121 (SD 1.052); range –1.97 to 2.04]. It was calculated that 64 infants in each pairwise group would provide 80% power (5% significance) to detect a difference in mean IHCL values of 0.53 on the logarithmic scale. Back-transforming to the original scale of measurement, this is equivalent to a 40% decrease in IHCL content in the intervention group. It was assumed there would be no interaction between the interventions. Allowing for a 10% mortality and up to 10% dropout (including babies still in hospital at 44 weeks postmenstrual age), the aim was to recruit 160 infants or until 64 infants in each pairwise group completed primary outcome evaluations.

A modified intention-to-treat analysis was used, as it was anticipated that it would not be possible to obtain primary outcome measures in all infants. For the amino acid and lipid interventions, a multiple regression was used with non-adipose mass (g) or IHCL content (natural logarithmic scale) as the dependent variable and amino acid group (Inc-AA or Imm-RDI), lipid group (Intralipid or SMOFlipid), stratifying variables (gestational age, birthweight and centre), sex and age at assessment as the independent variables. An interaction term was added to assess if the effect of amino acid regimen is influenced by lipid type. In a planned secondary analysis, illness severity and nutritional intake was incorporated in the regression models to investigate their role as potential effect modifiers. All analyses were performed using Stata 13 (StataCorp LP, College Station, TX, USA).

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Results

Of the 437 infants born before 31 weeks of gestation, 168 infants were randomised. A total of 133 infants were available for assessment of the primary outcome measures. Baseline characteristics of sex, gestational age at birth, anthropometry, maternal demographics, mode of delivery, antenatal steroid use, blood pressure on admission and time to commencing PN were similar across the four groups.

The median time to achieve a milk intake of 150 ml/kg/day for 24 hours for all infants randomised was similar across the four groups {Inc-AA/Intralipid: 12 days [interquartile range (IQR) 9–17.5 days]; Inc-RDI/SMOFlipid: 11.5 days [IQR 9–16 days]; Imm-RDI: 11 days [IQR 10–14 days]; and Imm-RDI/SMOFlipid: 13 days [IQR 9.5–18 days]}. The median length of hospital stay for all infants randomised was similar across the four groups [Inc-AA/Intralipid: 69.5 days (IQR 52–95 days); Inc-RDI/SMOFlipid: 61 days (IQR 45–88 days); Imm-RDI: 63 days (IQR 45–95 days); and Imm-RDI/SMOFlipid: 66.5 days (IQR 44–98 days)].

Nutritional intake from trial PN during the first week was similar across the four groups, except in the intake of protein. For ease of comparison between enteral and parenteral intakes, we express parenteral amino acid intake as protein (1 g of amino acids ≡ 0.89 g of protein). Trial PN protein intake was higher in the Imm-RDI arms, and carbohydrate and lipid intakes were similar across the four groups.

In relation to primary outcome measures, there were no significant differences in the quantity of non-AT mass between the groups randomised to Inc-AA and those randomised to the Imm-RDI {adjusted mean difference Imm-RDI, 1 g [95% confidence interval (CI) –108 to 111 g]; $p = 0.98$}. For the lipid composition intervention, there was no significant difference in IHCL content between the groups randomised to receive 20% Intralipid than for 20% SMOFlipid (adjusted mean ratio of lipid to water 1.1, 95% CI 0.8 to 1.6; $p = 0.58$).

There were no significant differences between the groups in the proportion of infants with abnormal biochemical indices namely serum glucose, worst base deficit in the previous 24 hours, total serum bilirubin, conjugated bilirubin, serum cholesterol, serum triglycerides, serum sodium, serum potassium, serum phosphate, serum calcium, serum creatinine, and alanine transaminase. However, Imm-RDI infants were more likely than Inc-AA infants to have blood urea nitrogen levels > 7 mmol/l [75% vs. 49% ($p < 0.01$)] and and > 10 mmol/l [49% vs. 18% ($p < 0.01$)]. Head circumference at term was smaller in the Imm-RDI group (mean difference –0.8 cm, 95% CI –1.5 to –0.1 cm; $p = 0.02$).

There were no significant differences, at term age equivalent, in secondary outcome measures of the quantity and distribution of AT, measure of insulin sensitivity (QUICKI), total cerebral volume, whole-brain volume, weight and length.

Conclusions

We conclude that commencement within 24 hours of birth of an Inc-AA regimen providing a maximum of 2.7 g/kg/day together with the early introduction of milk feeds, compared with the immediate provision of an amino acid intake of 3.6 g/kg/day, does not appear to be detrimental to body composition and may be safer. In addition, SMOFlipid does not reduce IHCL accumulation.

Extremely preterm infants at term age equivalent, with the early provision of PN according to a standardised regimen, can achieve the body composition nearer that of healthy term-born infants.

Before either of the interventions studied in this trial can be recommended as routine practice, long-term follow-up of functional outcomes of neurodevelopment as well as long-term body composition and metabolic health of both the trial interventions is essential.

The results do not support the calls for more aggressive nutrition in the extremely preterm infant nor the routine use of SMOFlipid as reflected in international consensus statements (higher amounts of amino acids) or as is increasingly seen in current practice.

A key ancillary observation of this trial is that the use of standard PN regimens is feasible, is acceptable to clinicians, even when blinded, can deliver desired nutritional intake without manipulation and is safe. In our opinion, standardised regimens that have been tested in the context of a randomised controlled trial should be adopted in routine clinical practice to reduce the clinical risk to infants from variation in practice.

We suggest that high amounts of amino acids be used only in the context of randomised clinical trials. Optimal amino acid intakes and intravenous lipid formulations for extremely preterm infants remain to be established.

Trial registration

This trial is registered as ISRCTN29665319 and EudraCT 2009–016731–34.

Funding

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Chapter 1 Introduction

Background

Preterm infants

Extremely preterm infants, born before 31 weeks of gestation, account for 1–1.5% of deliveries in the UK. Of around 70,000 infants born preterm in the UK each year, about 8000 are born before 31 weeks of gestation. The UK has one of the highest rates of preterm birth in Europe, as well as one of the highest rates of neonatal mortality. These infants spend a prolonged period in hospital and are subject to long periods of poor nutrition. By the time preterm infants reach term age, the overwhelming majority exhibit 'growth failure' when compared with healthy term-born infants.[1] Long-term follow-up studies show that there appears to be catch-up growth in infancy and through adolescence.[2] Although this may be reassuring, catch-up growth is associated with adverse metabolic health and renal impairment.[3,4] However, growth failure is associated with neurodevelopmental impairment and cerebral palsy.[5,6]

Rationale for trial

Nutrition is a major factor influencing growth and possibly long-term metabolic health. Protein deficiency and a high-fat, high-carbohydrate diet characterises preterm nutrition during this period regardless of whether it is provided intravenously or enterally. A low-protein diet and low protein-to-energy ratio in preterm infants results in a decrease in lean body mass (LBM) and increased deposition of adipose tissue (AT).[7] Thus, weight gain per se may not be as important as weight gain composition. In preterm infants, a low-protein, high-carbohydrate diet has also been shown to be associated with insulin resistance in adolescence.[8] Preterm infants, at present, do not receive routine metabolic follow-up assessments and so the exact burden of subsequent metabolic ill health cannot be quantified.[9]

There is good evidence that there are critical periods in development where nutrition has long-term effects on later health. It has been shown that by the end of the first week of life, cumulative energy and protein deficits in infants born before 30 weeks of gestation are 400 kcal/kg and 14 g/kg, respectively.[10,11] Preterm formulae and fortified maternal milk meet the recommended daily intake (RDI) of macronutrients, but deficits accumulated in the period after birth combined with factors that increase requirements result in a progressive deficit that is not made up or increases the magnitude of later catch-up growth.

Preterm infants have increased prepubertal insulin resistance compared with term-born infants.[12] Compared with term-born infants, as adults they have higher blood pressure[13,14] and are more likely to have glucose intolerance,[15] insulin resistance and dyslipidaemia.[16] Insulin resistance in prepubertal children born extremely preterm has been associated with neonatal nutrition. Preterm infants were found to be insulin resistant compared with term-born infants. The diet of preterm infants was characterised as being low in protein in the first month and high in fat subsequently. Those who gained most weight in infancy were most insulin resistant and found to have a high carbohydrate intake in the first month of life.[8]

Another group has demonstrated that a period of nutritional deprivation (though not specifically of any one macronutrient) in the early postnatal period may have beneficial effects on insulin resistance in preterm infants in adolescence.[17] We have previously shown aberrant AT partitioning, increased intrahepatocellular lipid (IHCL) content and increased insulin resistance in preterm infants at term age equivalent compared with healthy term infants.[18,19] Our data suggest that, even as early as at term equivalent age, preterm infants demonstrate the manifestations of cardiovascular risk factors.

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Improving the quality and quantity of nutrition in this period has the potential to improve not just short-term outcomes but also the long-term neurodevelopmental and metabolic health of this vulnerable group of infants. Preterm infants constitute a group that continues to utilise NHS resources throughout life because of the long-term sequelae of prematurity. On average, health and societal costs for preterm children at 6 years of age exceed that of a child born at term by approximately threefold.[20]

Nutritional requirements of preterm babies

Traditionally, RDIs have been based on the composition of fetal and newborn weight gain. Source data are derived from the studies of Fomon and Nelson[21] and Ziegler *et al.*[22] on fetal cadavers of different gestational ages. Based on the weight-gain composition at different periods of gestation and hence the accretion rate of lean mass and fat mass, the dietary intake of energy necessary for preterm newborns to achieve an intrauterine growth rate has been estimated as:

$$E_{\text{intake}} = E_{\text{excreted}} + E_{\text{stored}} + E_{\text{expended}}, \quad (1)$$

where excreted energy comprises faeces and urine, stored energy is energy stored as protein and fat (based on fetal accretion rate) and expended energy = resting metabolic rate + energy of activity + thermoregulation (based on studies in growing preterm infants).

Using the above data, the American Academy of Pediatrics and the European Society for Paediatric Gastroenterology Hepatology and Nutrition have published RDIs for preterm infants.[23–25] These RDIs have been used to inform this study. Putet *et al.*[7] have pointed out that knowledge of growth rate is insufficient to derive the optimum nutritional intake of preterm infants. The authors suggests that knowledge of weight gain composition (lean and fat mass) is essential to estimate the ideal ratio of protein to energy in order to avoid the deposition of excess energy as fat. Our previous work lends strength to this concept as we have shown that preterm infants receiving current conventional intakes have a carbohydrate and fat-rich diet, with a deficiency of protein and that they have a higher proportion of AT than term-born infants.[11]

In a non-randomised study, Roggero *et al.*[26], used whole-body plethysmography to measure weight gain and LBM accural at 1 month post-term age in preterm infants fed either a high-protein diet (> 3 g/kg/day) ($n = 26$) or a low-protein diet (< 3 g/kg/day) ($n = 22$). Weight gain was significantly lower in the high-protein group than in the low-protein group {mean [standard deviation (SD)]: 946.7 g [375.2 g] vs. 1238 g [407 g]; $p < 0.05$}, but LBM accrual was asignificantly higher (approximately 4% higher as a percentage of body weight).

Recent reviews have concluded that current nutritional practices contribute to long-term impairment and recommend early introduction of the RDI of macronutrients.[27,28] However, the evidence for this is based on tolerability and growth outcomes, and not on body composition.

Parenteral nutrition

Early nutritional intake in extremely preterm infants is wholly or in part delivered intravenously as parenteral nutrition (PN) because of immaturity of the gastrointestinal system. The median duration of PN after birth in infants born before 31 weeks of gestation is 12 days. Often PN is recommenced later in an infant's neonatal course if the clinical condition precludes enteral feeding. Each day of PN costs the NHS £80–100 per infant. A typical tertiary neonatal unit spends up to £150,000 per year on PN. There are currently various PN preparations in routine use that vary in both composition and usage, but none has previously been tested in this country in the setting of a large randomised controlled trial (RCT). Some solutions are commercially prepared, whereas others are made up in local hospital pharmacies.

This has been the focus of a scoping exercise that was commissioned by the Department of Health because of serious concern of clinical risk to patients.[29] The survey carried out as part of the exercise confirmed that current practice among neonatologists with respect to PN varies widely and is based on limited evidence. There was also considerable variation in the preparation of PN and guidelines for use. One hundred and sixteen hospitals reported providing PN to neonates and completed the survey relating to neonates. The principal investigator was a member of the clinical group that developed and analysed the survey and prepared the report. The report, which was published in November 2011, called for urgent measures to standardise practice in both the technical and clinical aspects of use of PN in neonates and children, and for the development of evidence-based guidelines for the use of PN.[29] A further report from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD), to which the principal investigator contributed, came to similar conclusions.[30]

Current widespread practice is to institute PN several hours to days after birth and to introduce macronutrients in PN at a dose below that of the RDI and increase the quantity slowly over a period of 3–4 days, sometimes longer, often not achieving the RDI. This practice is non-evidence based and results in cumulative deficits in protein and energy over the first 2 weeks of life. This practice is more prevalent with respect to amino acids than carbohydrates and fat. Long-term use of PN results in liver impairment and even failure. This is a particular problem in neonatal units caring for infants with bowel problems that preclude or limit enteral feeding. There are now newer preparations of fat (SMOFlipid®; Fresenius Kabi AG, Richmond Hill, ON, Canada) that have been found to be liver protective and are currently used in infants on long-term PN.[31] There is a need for studies to investigate the efficacy of these newer lipid solutions in reducing liver impairment.

Previous studies of parenteral nutrition

Recent reviews have concluded that current nutritional practices contribute to growth failure and recommend early introduction of the RDI of macronutrients in PN.[27,28] However, the quality of the evidence on which this is based is grade B (RCT with minor limitations, overwhelming consistent evidence from observational studies) and only based on outcomes such as tolerability and growth, despite recognition that the ideal postnatal growth rate of a preterm infant is unknown. No data exist on the effect on body composition.

We have shown that the body composition of preterm infants is different from that of healthy term-born infants. Preterm infants had a significantly reduced LBM and pattern of AT distribution associated with metabolic complications.[19] Tan *et al.*[32,33] studied the effect of hyperalimentation on head growth. No differences between the two groups were found, but non-randomised analyses showed protein and energy deficits to be correlated with poor head growth. Eighty per cent of babies in the intervention group had significant protein/energy deficits at the end of the first 4 weeks. A major drawback of this study was that participants in this study were recruited up to 7 days after birth, by which time significant deficits are known to have developed. The study was also underpowered to detect a significant effect on the primary outcome.

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A systematic review of the effect of early administration of PN on growth outcomes in preterm infants included eight RCTs and 13 observational studies.[34] The review was limited by the disparate growth outcome measures. Early PN reduced the time to regain birthweight by (a mean) 2.2 days [95% confidence interval (CI) 1.1 to 3.2 days] in RCTs and 3.2 days (95% CI 2.0 to 4.4 days) in observational studies. The maximum percentage weight loss with early PN was lower by (a mean) 3.1% (95% CI 1.7% to 4.5%) for RCTs and by 3.5% (95% CI 2.6% to 4.3%) for observational studies. Early PN also improved weight at discharge or 36 weeks postmenstrual age by (a mean) 14.9 g (95% CI 5.3 to 24.5 g) in observational studies, but no benefit was shown for length or head circumference.[34]

A trial comparing two different amounts of amino acids (2.4 g/kg/day vs. 3.6 g/kg/day, with a lipid intake of 2–3 g/kg/day; and an additional third arm of 2.4 g/kg/day of amino acids, with a delayed introduction of lipids) from birth demonstrated an improved nitrogen balance on day 2 in the arms with early initiation of lipids. There was no improvement in nitrogen balance with greater amounts of amino acids.[35]

A systematic review of the early introduction of lipids (defined as introduction within the first 2 days after birth) and the use of new lipid emulsions included 14 RCTs.[36] Early initiation of lipids had no impact on any of the outcome measures, including death, bronchopulmonary dysplasia, necrotising enterocolitis, patent ductus arteriosus, sepsis, intraventricular haemorrhage, significant jaundice and hypertriglyceridaemia. The meta-analysis of the effects of lipid emulsions that are not purely soya bean based showed no difference in outcomes of death, duration of respiratory support or rate of weight gain. There was a lower rate of sepsis with the lipid emulsions that were not purely soya bean based, but the difference was not statistically significant. However, the authors concluded that large-scale RCTs are needed to determine the efficacy of newer lipids.[36]

We recently published a systematic review of preterm PN summarising the evidence to date.[37] The review concludes that the evidence base for current recommendations is based on historical evidence and there are no long-term studies of the impact of PN on health and neurodevelopment.

Risks and benefits of parenteral nutrition

Parenteral nutrition is an independent risk factor for sepsis in neonates, associated with a 40-fold greater risk, which makes its judicious use a priority. The risks associated with any form of PN are metabolic disturbances (hyperglycaemia, hyperlipidaemia, electrolyte imbalances), infection[38] and catheter-related complications. However, these risks are unavoidable as PN is the only option for feeding extremely preterm infants until they are established on enteral nutrition.

Parenteral nutrition is also associated with cholestasis and liver impairment.[39] Instituting PN containing the RDI of amino acids on the day of birth, as in the intervention arm, may result in a higher incidence of metabolic acidosis and high concentrations of urea nitrogen in the blood. Until now, only one study has investigated the efficacy of the early introduction of amino acids (3.5 g/kg/day) combined with a lipid emulsion (3 g/kg/day), in high concentrations, within the first 2 hours of life. Early lipid introduction resulted in an increased positive nitrogen balance without an increased incidence of metabolic or respiratory complications.[40] However, there was a small, but statistically significant, increase in serum bilirubin, without clinical implications. Other studies in preterm infants using this approach have not found an increased incidence of this problem.[40–42]

The lipid solution currently used, Intralipid 20% (Fresenius Kabi AG, Richmond Hill, ON, Canada), is a first-generation lipid emulsion based on soya bean oil, which is very rich in *n*-6 polyunsaturated fatty acids. However, an excess intake of *n*-6 polyunsaturated fatty acids in PN is associated with an unbalanced fatty acid pattern in cell membranes, with possible modified function, and with increased lipid peroxidation.[43] Second-generation emulsions are represented by medium-chain triglyceride (MCT) and long-chain triglyceride (LCT) mixtures, and emulsions containing olive oils. MCT–LCT mixtures are cleared from the

bloodstream more quickly and generate more immediate energy. Emulsions containing olive oils provide a more physiological mixture of fatty acids with less lipid peroxidation. An example of a third-generation emulsion is SMOFlipid (a mixture of soya bean oil, MCTs, olive oil and fish oils, supplemented with vitamin E). This emulsion is designed to increase the amount of *n*-3 fatty acids, thereby reducing the ratio of *n*-6 to *n*-3 fatty acids (in accordance with current recommended levels).[43] SMOFlipid 20% is well tolerated in infants without changing lipid peroxidation parameters,[31,44] and beneficial effects on liver function and serum triglyceride concentrations have been described.[31]

Need for the Nutritional Evaluation and Optimisation in Neonates trial

In spite of evidence demonstrating that introducing the RDI of macronutrients early appears to be safe and results in improved protein retention and better growth in the short term, clinical practice has remained variable because of the absence of evidence from RCTs with clinically meaningful outcomes. If early introduction of the RDI of macronutrients was shown, in the setting of a RCT, to improve not just growth measured by anthropometry, but a better measure of growth (i.e. increase in LBM and better brain growth, with the long-term benefits that in turn result from these) it has the potential to impact the vast majority of neonatal unit graduates. There is an urgent need for therapy with PN to be evidence based.

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Chapter 2 Research objectives

The two main research objectives were to study the effects of two parenteral nutrition interventions (amino acid quantity and lipid composition) in extremely preterm infants.

Amino acid intervention

To evaluate whether or not immediate rather than incremental introduction of the RDI of amino acids (Imm-RDI) in extremely preterm infants results in:

- higher non-adipose (lean) body mass at term (primary objective)
- increased brain volume at term (secondary objective)
- reduced insulin resistance at term (secondary objective)
- lower ratio of internal to subcutaneous AT at term (secondary objective)
- the standard deviation (SD) score for weight undergoing a smaller drop between birth and term equivalent (secondary objective).

Lipid intervention

To evaluate whether or not 20% SMOFlipid (with a lower ratio of *n*-6 to *n*-3 fatty acids) compared with 20% Intralipid in extremely preterm infants results in:

- reduced IHCL content at a term age equivalent (primary objective)
- a reduced incidence of hypertriglyceridaemia and hyperbilirubinaemia (secondary objective).

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Chapter 3 Methods

Trial design

This was a multicentre, randomised, 2 × 2 factorial and double-blind controlled trial in four London and south-east England centres in the UK. Eligible preterm infants were randomised within 24 hours of birth to receive (1) either incremental amino acids (Inc-AA) in PN or the Imm-RDI from day 1; and (2) either 20% Intralipid or 20% SMOFlipid.

There were four randomised groups:

1. Inc-AA and 20% Intralipid (Inc-AA/Intralipid)
2. Inc-AA and 20% SMOFlipid (Inc-AA/SMOFlipid)
3. Imm-RDI and 20% Intralipid (Imm-RDI/Intralipid)
4. Imm-RDI and 20% SMOFlipid (Imm-RDI/SMOFlipid).

Participants

Preterm infants (born before 31 weeks of gestation) requiring nutritional support in the form of PN.

Inclusion criteria

- Preterm infants born before 31 weeks of gestation (defined as ≤ 30 weeks and 6 days).
- Written informed consent from parents.

Exclusion criteria

- Major congenital or life-threatening abnormalities.
- Inability to randomise in time to allow administration of trial PN within 24 hours of birth.

Interventions

There were two main interventions, namely the amount of amino acids in PN and the type of lipid formulation. All other components of PN were consistent across the four treatment groups. The intervention was commenced within 24 hours after birth. Nutritional intake, both parenteral and enteral, was guided by prespecified protocols that were provided in an investigator's manual.

The interventions ceased once the infant was established, for at least 24 hours, on enteral feeds of 150 ml/kg/day. If the infant was subsequently nil by mouth after this point, PN was prescribed in accordance with local practice as determined by the supervising clinician.

A summary of the interventions is provided in *Table 1*.

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TABLE 1 Summary of interventions

Intervention component	Day 1	Day 2	Day 3 onwards
Inc-AA/Intralipid			
Volume (excluding lipid volume) (ml/kg/day)	90	90	120
Protein (g/kg/day)	1.5	1.9	2.4
Amino acid equivalent (g/kg/day)	1.7	2.1	2.7
Carbohydrate (glucose) (g/kg/day)	8.6	8.6	8.6
20% Intralipid (g/kg/day)	2	3	3
Inc-AA/SMOFlipid			
Volume (excluding lipid volume) (ml/kg/day)	90	90	120
Protein (g/kg/day)	1.5	1.9	2.4
Amino acid equivalent (g/kg/day)	1.7	2.1	2.7
Carbohydrate (glucose) (g/kg/day)	8.6	8.6	8.6
20% SMOFlipid (g/kg/day)	2	3	3
Imm-RDI/Intralipid			
Volume (excluding lipid volume) (ml/kg/day)	90	90	120
Protein (g/kg/day)	3.2	3.2	3.2
Amino acid equivalent (g/kg/day)	3.6	3.6	3.6
Carbohydrate (glucose) (g/kg/day)	8.6	8.6	8.6
20% Intralipid (g/kg/day)	2	3	3
Imm-RDI/SMOFlipid			
Volume (excluding lipid volume) (ml/kg/day)	90	90	120
Protein (g/kg/day)	3.2	3.2	3.2
Amino acid equivalent (g/kg/day)	3.6	3.6	3.6
Carbohydrate (glucose) (g/kg/day)	8.6	8.6	8.6
20% SMOFlipid (g/kg/day)	2	3	3

Outcomes

Primary outcomes

The efficacy of the early introduction of the RDI of amino acids was assessed by whole-body magnetic resonance imaging (MRI) to measure lean mass, and by the quantity and distribution of AT. This assessment was done at term age equivalent. The infants were scanned between 37 and 44 weeks postmenstrual age.

Measurement of lean body mass

Lean body mass was calculated by subtracting AT mass from the weight of the infant on the day of the scan.

Measurement of intrahepatocellular lipid content

The efficacy of SMOFlipid was assessed by liver magnetic resonance spectroscopy (MRS) to measure IHCL content. This was done at term age equivalent, between 37 and 44 weeks postmenstrual age.

Secondary outcomes

- Quantity and distribution of AT.
- Total and regional brain volumes.
- Metabolic index of insulin sensitivity [qualitative insulin sensitivity check index (QUICKI)].
- Serum lipids and bilirubin.
- Incidence of death.
- Anthropometry.

Data collection

Electronic case record form

Data management was through the InForm 4.6 (SP0c, build 1088; Oracle Corporation, Redwood, CA, USA) integrated trial management system, a web-based data entry system that builds an Oracle Database 10g (Enterprise Edition release 10.2.0.4.0 – 64bit; Oracle Corporation, Redwood, CA, USA) for each individual clinical trial. Trial data were captured on a bespoke web-based electronic case record form (eCRF) with built-in validation rules to identify data entry errors in real time and a full audit trail of data entry and changes.
All persons entering data were trained prior to start-up and given personal login details, with access to forms restricted according to site and role. The eCRF was designed in accordance with the requirements of the trial protocol and access to the eCRF was password protected and included a controlled level of access.

Timescale of trial evaluations

Daily evaluations

The first daily evaluation started at the time of birth and was completed when the first bag of trial PN was changed and on the first day of postnatal life. Subsequent evaluations occurred 24 hours from this time point (± 2 hours), every day from birth and until 37 weeks postmenstrual age or discharge from the neonatal intensive care unit (NICU) (where days were calculated from the date PN was initiated).

Weekly evaluations

The first weekly evaluation occurred 7 ± 2 days from randomisation and each 7 days (± 2 days) thereafter until 37 weeks corrected age or discharge from the NICU.

Monthly evaluation

The first monthly evaluation occurred 30 days (± 5 days) from randomisation and each 30 days (± 5 days) thereafter until 37 weeks corrected age or discharge from the NICU.

For infants who received long-term PN, which is for at least 28 continuous days, serum trace elements were measured.

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The 37-week evaluation

This evaluation took place when the infant reached 37 weeks postmenstrual age (± 1 week) or when the infant was discharged from the NICU, whichever occurred sooner.

The end-of-study evaluation

The end-of-study evaluation took place as soon as possible after the infant was discharged from the NICU at 37–44 weeks postmenstrual age. In the case of one hospital (Chelsea and Westminster NHS Foundation Trust) with onsite access to a magnetic resonance (MR) scanner, infants aged between 37 and 44 weeks postmenstrual age who were otherwise well but not ready for discharge, were scanned prior to discharge.

Schedule of investigations

A summary of tests and investigations performed is provided in *Table 2*.

TABLE 2 Summary of tests and investigations

Evaluation	Baseline	Daily	Weekly	Monthly	37 weeks corrected age	End of study (37–44 weeks and discharge from the NICU)
Informed consent	✓					
Eligibility	✓					
Randomisation	✓					
Weight	a	a,b	a			✓
Length	a		a			✓
Head circumference	a		a			✓
Blood pressure	a		✓			✓
Nutritional intake	✓	✓				
Safety						
Blood glucose (highest and lowest in previous 24 hours)		a,b				
Worst base deficit on blood gas (in previous 24 hours)		a,b				
Serum bilirubin, LFTs, serum urea, creatinine and electrolytes		a,b			a	
Serum lipid and cholesterol			a,b			
Trace elements (zinc, copper, manganese, aluminium and selenium)				a,b		
AE tracking		✓	✓		✓	✓
Efficacy						
QUICKI					✓	
Whole-body and brain MRI, MRS						✓
Blood spot	✓				✓	
Urine sample and stool sample			✓			

✓, for research purposes; AE, adverse event; LFT, liver function test.
a Routine care.
b While on PN.

Clinical investigations

Anthropometry

Weight, length and head circumference measurements are routinely used to monitor infant growth. Weight was recorded on a daily basis until discharge and at the end of study visit while the infant received PN, and weekly when the infant did not receive PN. Length and head circumference were recorded on a weekly basis until discharge and at the end of study visit.

Blood pressure measurements

Systolic and diastolic blood pressure were measured in the right upper limb using a non-invasive blood pressure monitor and a cuff that covered at least two-thirds of the right upper limb and encompassed the entire arm in the resting state.

Magnetic resonance imaging

The MRI measurements were carried out during normal sleep without the need for sedation. All the MRI measurements (body composition, hepatic MRS and brain MRI) took a total of 45–60 minutes. The infants were monitored with pulse oximetry and a trained neonatal doctor was present throughout the scan. Parents were invited to be present in the console room.

Magnetic resonance imaging body composition

Acquisition of images

Scans were undertaken after discharge from hospital at the Robert Steiner MR Unit, Imperial College Healthcare NHS Trust at a dedicated research scanning facility on a 1.5-T Phillips Achieva scanner (Philips, Best, the Netherlands). Babies born at the lead site (Chelsea and Westminster NHS Foundation Hospital) who were still inpatients between 37 and 44 weeks postmenstrual age and unlikely to be discharged home in time to be scanned in the research scanner were scanned while inpatients at Chelsea and Westminster NHS Foundation Hospital scanner on a 1.5-T Siemens Avanto scanner (Siemens, Erlangen, Germany).

For images that were acquired on the Phillips 1.5-T system, a T1-weighted rapid-spin-echo sequence (repetition time of 500 milliseconds, echo time of 17 milliseconds, echo train length of 3) using a Q body coil was used. The slice thickness was 5 mm and the interslice difference was 5 mm. Voxel size was $0.31 \times 0.31 \times 0.31$ cm. Acquisition time was approximately 12 minutes. For images acquired on the Siemens scanner a T1 turbo-spin-echo sequence was used (with a repetition time of 514 milliseconds and an echo time of 11 milliseconds).

Analysis of images

Analysis of all MR images was undertaken independently of the investigators, blind to subject identity and treatment, by Vardis Group (London, UK; www.vardisgroup.com). Images were analysed by a single observer, using a commercially available software program (SliceOMatic, Version 4.2; Tomovision, Montreal, QC, Canada). A filter was used to distinguish between different grey-level regions on each slice. This was then verified and, where necessary, edited using the interactive slice editor program. AT area (cm^2) for each slice was calculated as the sum of the voxels multiplied by the voxel area. AT volume (cm^3) for each slice was calculated by multiplying the tissue area by the sum of the slice thickness and the interslice distance. The coefficient of variation for these measurements was $< 3\%$.[45] AT volume in litres was converted to AT mass in kg, assuming a value for the density of AT of 0.90 kg/l.[46,47]

$$\text{AT mass, kg} = (\text{AT volume, l}) \times 0.90. \quad (2)$$

Adipose tissue mass was used to determine percentage AT as:

$$\text{Percentage AT mass} = (\text{AT mass, kg})/(\text{body mass, kg}). \quad (3)$$

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Total AT volume was calculated as the sum of six individually quantified AT compartments – superficial subcutaneous abdominal AT, superficial subcutaneous non-abdominal AT, deep subcutaneous abdominal AT, deep subcutaneous non-abdominal AT, internal abdominal AT and internal non-abdominal AT – as previously described[45] (*Figure 1*). Total subcutaneous AT was calculated as the sum of abdominal superficial subcutaneous, abdominal deep subcutaneous, non-abdominal superficial subcutaneous and non-abdominal deep subcutaneous AT. Total internal AT was calculated as the sum of internal abdominal and internal non-abdominal AT.

Hepatic magnetic resonance spectroscopy

Acquisition of spectra

Hydrogen-1 (^{1}H) MR spectra were acquired at 1.5 T from the right lobe of the liver using a point-resolved spectroscopy sequence (repetition time 1500 milliseconds/repetition time 135 milliseconds) without water saturation and with 128 signal averages. Transverse images of the liver were used to ensure accurate positioning of the (20 × 20 × 20 mm) voxel in the liver, avoiding blood vessels, the gall bladder and fatty tissue. For spectra acquired on the 1.5-T Siemens Avanto scanner a voxel size of 15 × 15 × 15 mm was used.

Analysis of spectra

Spectra were analysed in the time domain using the advanced method for accurate robust and efficient spectral fittings algorithm included in the Java-based MR user interface software package (version 1.3; MRUI consortium; www.jmrui.eu/) by a single investigator (LT) who was blind to the treatment category.[48–50] Peak areas for all resonances were obtained and lipid resonances were quantified with reference to water resonance, after correcting for T1 and T2. Hepatic water, known to be relatively constant, was used as an internal standard and the results are presented as the percentage ratio of fat CH_2 to water.

Brain magnetic resonance imaging

Acquisition of images

Brain imaging was performed on infants using a dedicated eight-channel paediatric coil. Three-dimensional T1-weighted fast-gradient echo images were acquired in a sagittal plane with using the following parameters: field of view (FOV) 220 × 158 mm; 192 slices; slice thickness 1 mm; an acquired voxel size 0.82 × 0.97 mm; matrix 256; echo time 4.6 milliseconds; repetition time 17 milliseconds; flip angle 13°; and acquisition time 6 minutes.

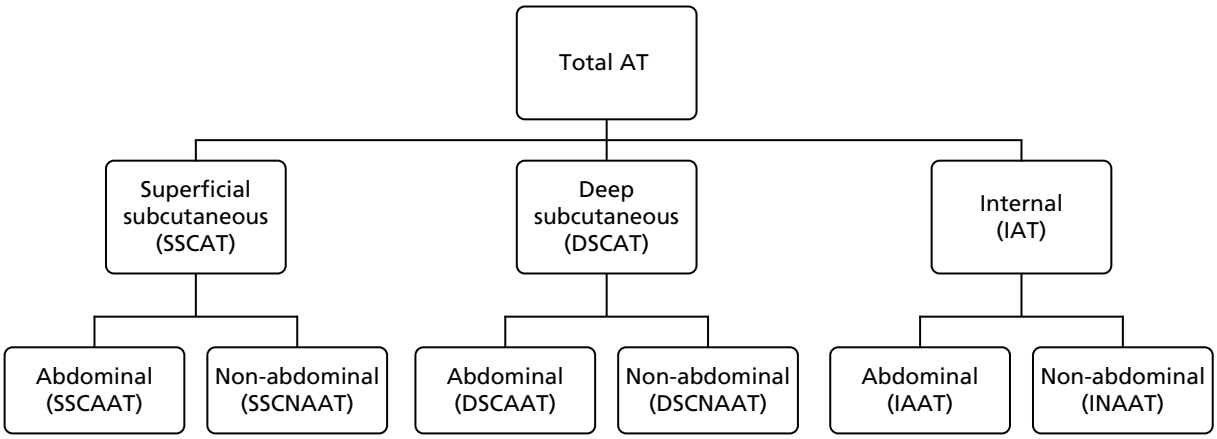

FIGURE 1 Classification of AT depots. DSCAAT, deep subcutaneous abdominal adipose tissue; DSCAT, deep subcutaneous adipose tissue; DSCNAAT, deep subcutaneous non-abdominal adipose tissue; IAAT, internal non-abdominal adipose tissue; IAT, internal adipose tissue; INAAT, internal non-abdominal adipose; SSCAAT, superficial subcutaneous abdominal adipose tissue; SSCAT, superficial subcutaneous adipose tissue; SSCNAAT, superficial subcutaneous non-abdominal adipose tissue. Adapted with permission from Modi N *et al.*, *Pediatric Research* 2009;**65**:584–7.[45]

Whenever possible, and with time permitting, the following brain scans were also undertaken:

- T2-weighted turbo-spin-echo sequence acquired in an axial plane with FOV 220 × 220 mm; 94 slices; slice thickness 2 mm; acquired voxel size 1.15 × 1.42 mm; slice gap 1 mm; matrix 256; echo time 160 milliseconds; repetition time 15,077 milliseconds; flip angle 90°; and acquisition time 2 minutes.
- A three-dimensional time-of-flight MR angiography sequence to assess the anterior cerebral artery, middle cerebral artery and posterior cerebral artery. The imaging parameters used were FOV 175 × 144 mm; 75 slices; one stack; slice thickness 0.8 mm; slice gap 0 mm, voxel size 0.61 × 0.61 mm; echo time 12 milliseconds; repetition time 23 milliseconds; flip angle 16°; matrix 512; and acquisition time 5 minutes.
- Fifteen direction diffusion tensor imaging for assessment of white matter integrity also formed part of the protocol, with the following imaging parameters: FOV 224 × 224 mm; 49 slices; slices thickness 2.5 mm; slice gap 0 mm; acquired voxel size 2 × 2 mm; matrix 128; echo time 49 milliseconds; repetition time 49,709 milliseconds; maximum b factor 750; number of b factors 2; and acquisition time 6 minutes.

Analysis of images

A specialist in neonatal neurology reported all brain MRI images for clinical purposes. A note was made of any congenital or acquired lesions. The type and severity of these was recorded for all cases. Scans with parenchymal brain lesions were excluded from subsequent quantitative analysis.

A quantitative whole-brain segmentation program was used to segment the brain and its constituent structures using the T2-weighted image data.[51] These volumetric data could be obtained only from images that were of adequate quality with good signal-to-noise ratio and absence of motion artefact.

The following outcomes were measured:

- total cerebral volume: sum of the volumes of basal ganglia, thalami (deep grey matter), cerebrospinal fluid, grey matter, white matter and lateral ventricles
- whole-brain volume: sum of the volumes of basal ganglia, thalami (deep grey matter), grey matter and white matter
- posterior fossa volume: sum of the volumes of cerebellum and brainstem.

Quantitative insulin sensitivity check index

The QUICKI is a marker of insulin resistance calculated from pre-feed serum insulin and blood glucose. Homeostatic model assessment is the gold standard for measuring insulin resistance, but is invasive and cannot be justified ethically in this patient group. Furthermore, the QUICKI has been validated against homeostatic model assessment[52] and has been used in neonates before.[53] Measurement of the QUICKI was carried out at term age and samples taken at the time of routine (pre-feed) blood tests.

Pharmacovigilance definitions and procedures

Serious adverse events

An adverse event (AE) was defined as any untoward medical occurrence in a patient administered an investigational medicinal product (IMP), in accordance with clinical trial regulations. An AE was considered serious and reportable via the eCRF if any of the following criteria occurred:

- it resulted in death
- it was life-threatening
- it resulted in prolongation of existing inpatient hospitalisation
- it resulted in persistent or significant disability or incapacity.

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Expectedness and causality of serious adverse events

The trial protocol specified that a range of serious adverse events (SAEs) would be expected, either as a consequence of preterm birth or if they were listed in any of the summaries of product characteristics, and this expectedness was recorded on the eCRF for each SAE report.

Causal relationship to the IMP was defined according to *Table 3*.

Reporting of adverse events

The trial eCRF included dedicated forms for reporting SAEs. Investigators were advised to report SAEs via the eCRF within 24 hours of becoming aware of the event and to include an assessment of expectedness and causality in the SAE report. The clinical trials unit and chief investigator reviewed each SAE report within 2 working days.

Adverse events

The only non-serious AEs that were reportable were values of triglycerides, bilirubin and other safety parameters above or below prespecified levels, and these are summarised in *Table 4*. These were labelled as 'specific adverse events' (SpAEs) reportable via the eCRF. The eCRF incorporated in-built checks to flag any occurrence of a SpAE during the data entry process to the local teams. Guidance for the management of these events was provided to the participating centres in a trial-specific investigator's manual. SpAEs related to safety parameters were collected daily during the period of trial PN administration.

As the levels selected for SpAEs were consistent with normal ranges used in standard neonatal clinical care and, in accordance with the new Medicines and Healthcare products Regulatory Agency (MHRA) guidance on risk-adapted approach to managing clinical trials, the Nutritional Evaluation and Optimisation in Neonates (NEON) trial was equivalent to standard care, additional reporting and review of SpAEs were not required. The trial Data Monitoring and Ethics Committee (DMEC) reviewed a selection of SpAEs throughout the duration of the trial.

The thresholds for SpAEs as well as those requiring reporting to the DMEC are summarised in *Table 4*.

TABLE 3 Definitions for assessment of causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible[a]	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable[a]	There is evidence to suggest a causal relationship and the influence of other factors is unlikely
Definitely[a]	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship

SUSAR, suspected unexpected serious adverse reaction.

a SUSAR: if an AE was considered serious, unexpected and related to the IMP (possible, probable or definitely related) this would have met the definition of SUSAR requiring expedited reporting to the MHRA, Research Ethics Committee and sponsor. There were no SUSARs for the NEON trial.

TABLE 4 Definitions of SpAEs including thresholds for reporting to the DMEC

Assessment (blood test)	Level requiring SpAE report	Level requiring reporting to the DMEC
Glucose	< 2.6 mmol/l or > 15 mmol/l	Not reported to the DMEC
Worst base deficit in previous 24 hours	> 15 mmol/l	> 15 mmol/l
Total serum bilirubin	> 150 µmol/l	> 150 µmol/l, only after 3 weeks on PN[a]
Conjugated bilirubin	> 40 µmol/l	> 40 µmol/l
Cholesterol	> 6 mmol/l	> 10 mmol/l
Triglycerides	> 2.5 mmol/l	> 5 mmol/l
Sodium	< 131 mmol/l or > 150 mmol/l	Not reported to the DMEC
Potassium	< 3.2 mmol/l or > 9 mmol/l	Not reported to the DMEC
Phosphate	< 1.5 mmol/l or > 3 mmol/l	Not reported to the DMEC
Calcium	< 1 mmol/l or > 3 mmol/l	Not reported to the DMEC
Urea	< 1.5 mmol/l or > 7 mmol/l	> 10 mmol/l
Creatinine	> 170 µmol/l	Not reported to the DMEC
Alanine transaminase	> 60 IU/l	Not reported to the DMEC
Zinc	< 8 µmol/l	Not reported to the DMEC
Copper	< 2 µmol/l	Not reported to the DMEC
Manganese	> 30 nmol/l	Not reported to the DMEC
Aluminium	> 0.4 µmol/l	Not reported to the DMEC
Selenium	< 20 µg/l	Not reported to the DMEC

a The infant must have been on PN for at least 3 weeks for this to meet the requirements for reporting to the DMEC.

Annual safety reports

Annual safety reports were provided to the Research Ethics Committee and MHRA, in accordance with clinical trial regulations, on the anniversary of the clinical trial authorisation each year. A total of three annual safety reports were submitted over the course of the trial.

Statistical considerations

Sample size

The mean directly measured LBM of preterm infants when studied in 2003 was 2.1 kg (SD 0.4 kg).[17] The mean in healthy term-born infants was 2.6 kg (SD 0.21 kg; mean difference 450 g, 95% CI 300 to 610 g). A sample size of 64 infants in each group was therefore chosen, as this would allow detection of a 200 g difference between the groups with 80% power and at 5% significance. This was considered a clinically important increase in lean mass.

Since the publication of our paper on IHCL,[18] measurements were available for a total of 15 infants with gestational ages ranging from 24 weeks to 32.6 weeks. IHCL had a mean lipid-to-water ratio of 1.75 (SD 1.85, range 0.14–7.72); the distribution is clearly positively skewed. A $\log_e$-transformation was therefore used to achieve approximate normality. On the natural logarithmic scale the mean IHCL lipid-to-water ratio was 0.121 (SD 1.052, range –1.97 to 2.04). A sample size of 64 infants in each group would therefore have 80% power to detect a difference in means of 0.526 on the logarithmic scale as significant at the 5% significance level (with a *t*-test). Transforming back to the original scale of measurement, this is equivalent to a 40% decrease in IHCL content in the intervention group.

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Assuming a 10% mortality prior to term and a 10% dropout rate, the aim was to recruit 80 infants to each group or until 64 infants in each group had undergone MRI and MRS, a total of 128 scans.

Randomisation

Randomisation was performed using an interactive voice recognition system (IVRS) telephone randomisation system. Sealed Envelope Ltd (London, UK) provided the IVRS and randomisation list.

Randomisation was performed using minimisation, with a 25% chance of simple random allocation (based on the procedure outlined in Pocock[54]). Randomisation was stratified by gestational age at birth (23–26 or 27–31 completed weeks of gestation), birthweight (< 500 g, 500–1000 g, > 1000 g) and centre. Multiple births were randomised individually.

Blinding

Unblinded trial PN was delivered to the pharmacy department at each participating centre. Trained pharmacy staff were responsible for blinding the trial PN prior to dispensing the supply for administration to each infant.

Secure copies of the randomisation list were held by each pharmacy team in case of the need for emergency unblinding. There was no requirement for unblinding at any point over the course of the study.

Statistical methods

The analysis of this 2 × 2 factorial randomised trial was performed 'at the margins' of the 2 × 2 table, assuming that the two factors are operating independently. In addition, summary measures were presented for each cell of the 2 × 2 table and an interaction ratio/difference was calculated.[55] A 'modified' intention-to-treat method was used to analyse the results as it was accepted that a proportion of infants would not be able to attend for MRI. With the exception of infants in whom MRI assessment was not completed, all infants were analysed according to their allocation.

The primary outcome measures for this trial were non-adipose (lean) body mass and IHCL content; the secondary outcomes were growth (weight, length and head circumference), brain growth and development (assessed by MRI) and measure of insulin sensitivity (by the QUICKI). Growth parameters are the only outcomes that were measured sequentially; all other outcomes, including the two primary outcomes, were measured on a single occasion at term age equivalent.

For outcomes measured on a single occasion, a regression model containing the stratifying variables (gestational age, birthweight and centre), nutritional interventions (amino acid and lipid), sex and age at time of measurement were used to estimate the effects of each intervention.

For the amino acid intervention primary outcome, a multiple regression was used with non-adipose body mass (g) as the dependent variable and amino acids (incremental vs. RDI), lipids (20% SMOFlipid vs. Intralipid), gestational age, birthweight, centre, sex and age at MRI as the independent variables to assess the effect of amino acids on non-adipose body mass. An interaction term was also included to assess whether or not the effect of amino acids regimen on non-adipose body mass is influenced by choice of lipids.

Similarly, for the lipid intervention primary outcome, a multiple regression was used with IHCLs at natural logarithmic scale as the dependent variable and amino acid (incremental vs. RDI), lipids (20% SMOFlipid vs. Intralipid), gestational age, birthweight, centre, sex and age at MRI as the independent variables to assess the effect of lipids on IHCL content. Again, an interaction term was included to assess whether or not the effect of lipids on IHCL content is affected by amino acid quantity.

A planned secondary analysis was used to investigate the role of illness severity and nutritional intake as potential modifiers of the effects of each intervention by adding these variables to the regression models.

The secondary analysis investigated the role of illness severity, maternal breast milk and post-PN intake, including PN period and post-PN period, as potential modifiers of the effects of each intervention by adding these variables to the regression model. All analyses were performed using Stata 13 (StataCorp LP, College Station, TX, USA).

All analyses were performed on an intention-to-treat basis, but as the primary outcomes can be ascertained in only those infants attending the end of study evaluation, up to 20% of primary outcomes are expected to be missing. We have assumed that these outcomes are missing at random.

Missing data

Owing to the nature of this study, it was expected that a number of infants would not undergo the end-of-study MRI (primarily because of death, ill-health or withdrawal of the subject). This was taken into account when calculating the sample size. The statistical analysis plan prespecified that we would analyse only those infants who could be scanned. The reasons for non-attendance were recorded in the withdrawal form. We aimed to comment on the implications that the missing data patterns had on the results from the analysis.

No missing data imputation was carried out except for infant weight over study period. Infant weight was recorded every day during the trial study period and weekly once infants were off the trial. As the daily infant weight was used in the descriptive analysis only, we did not carry out multiple imputations. Instead, we used simple imputation by using the nearest measured weight, either before or after the day of missing weight, to impute the missing data.

Statistical analysis plan

A statistical analysis plan was prepared by the trial investigators and trial statistician and reviewed and agreed by the Trial Steering Committee (TSC) and DMEC prior to the end of the recruitment period.

Trial organisation

Trial management

The UK Clinical Research Collaboration-registered Imperial Clinical Trials Unit (ICTU) was responsible for trial management, quality assurance, trial statistics, and development and maintenance of the trial database. The Clinical Trials and Evaluation Unit at the Royal Brompton and Harefield NHS Foundation Trust carried out trial and data management, which was one of the ICTU groups at the time of the trial.

The ICTU core staff and the InForm team are supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London.

Trial sponsor

The sponsor of the trial was Imperial College London. The sponsor's role is clearly set out in the European Clinical Trials Directive (http://ec.europa.eu/health/human-use/clinical-trials/directive/index_en.htm) and NHS Research Governance documents (www.gov.uk/government/uploads/system/uploads/attachment_data/file/139565/dh_4122427.pdf). Imperial College London signed a clinical trial agreement with each of the participating centres prior to the start of the trial.

Ethical considerations

The trial was conducted in accordance with the Declaration of Helsinki on research involving human subjects. The study protocol, parent information sheet (PIS) and consent form were submitted to the Research Ethics Committee prior to the start of the study and a favourable opinion was obtained on 8 December 2009.

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Consent

Where possible, parents were approached prior to their infant's birth to give them the PIS and discuss the trial. Full written informed consent was taken after birth using the ethically approved PIS and consent form.

Research governance

The trial was carried out in accordance with the NHS Research Governance Framework, and local NHS permission was granted by the research and development departments at each participating site prior to recruitment commencing.

Regulatory requirements

As a randomised trial of an IMP, the NEON trial was conducted in accordance with the European Clinical Trials Directive and the Medicines for Human Use (Clinical Trials) Regulations 2004.[56] The trial received clinical trials authorisation from the MHRA on 8 January 2010 and was registered in the European Community with the European Clinical Trials Database (EudraCT) number 2009-016731-34.

Trial registration

The trial was registered on the International Standard Randomised Controlled Trial Number (ISRCTN) clinical trial database with reference ISRCTN29665319.

National Institute for Health Research Clinical Research Network portfolio

The NEON trial was adopted on the NIHR Clinical Research Network and Medicines for Children Research Network portfolios. Accrual data were uploaded onto the NIHR Clinical Research Network database on a monthly basis.

Summary of protocol amendments

The ethics committee and MHRA made the following amendments to the trial protocol following approval of the first version of the document:

- Protocol version 2:
  - Clarifications implemented following review by TSC:
    - clarification that randomisation would be performed by minimisation with 25% chance of random allocation
    - randomisation to be stratified by birthweight in addition to existing factors (centre and gestational age at birth)
    - addition of a monthly evaluation to assess trace elements for infants on PN for > 28 days.
  - Administrative corrections.
  - Addition of a metabonomic substudy (funded separately and not reported in this article).
- Protocol version 3:
  - Additional blood samples on days 1 and 5 of life to assess inflammatory markers and lipid profile. The intention was to conduct a substudy to collect these samples at the lead site but it was never implemented.
  - Clarification of randomisation time window. The protocol previously stated that infants must be randomised within 12 hours of birth. The purpose of this time window was to allow adequate time for preparation and dispensing of trial PN. The time window was revised for this version of the protocol so that infants needed to be randomised in enough time to allow administration of PN within 24 hours.
  - Administrative corrections.

- Protocol version 4:
  - The protocol was amended to include a follow-up visit for neurodevelopmental outcomes at 2 years corrected age using the Bayley Scale of Infant Development, the Hammersmith Optimality Score as well as parental questionnaires (Social-Emotional scale of the Bayley Scales and the Quantitative Checklist for Autism in Toddlers). A funding application for this additional visit was not successful, so the additional visit was not implemented.

Trial committees

Trial steering committee

A TSC was established to oversee the conduct of the study. The TSC met three times over the course of the trial: on 26 February 2010, 14 December 2011 and 22 November 2012. Copies of the minutes from each meeting were sent to the funder, the Efficacy and Mechanism Evaluation (EME) programme of the NIHR. The TSC approved the trial protocol prior to the start of the study and received regular recruitment reports throughout the duration of the trial.

The TSC membership is listed below.

- Independent members:
  - Professor Richard Cooke (chairperson).
  - Mrs Lorraine Dob (parent representative).
  - Dr Paul Clarke.
  - Professor Robert Hume.
- Investigators:
  - Dr Sabita Uthaya (chief investigator).
  - Professor Neena Modi.
  - Caroline Doré.
  - Professor Ian Wong.
  - Professor Jimmy Bell.
  - Professor Deborah Ashby.

Data Monitoring and Ethics Committee

An independent DMEC was established to review SAE reports and the results of interim analyses. The DMEC meetings took place on 2 August 2010, 13 October 2011 and 27 September 2012.

The first DMEC meeting, to agree the charter outlining operational details and responsibilities, took place early in the trial, on 2 August 2010. The second meeting to review interim data for the first 32 infants was on 13 October 2011 and the final interim analysis for 64 infants took place on 27 September 2012. The DMEC provided feedback reports for each meeting to the chairperson of the TSC and this was reviewed, as applicable, at subsequent TSC meetings.

Data Monitoring and Ethics Committee membership:

- Professor Peter Brocklehurst (chairperson).
- Professor Tim Cole (independent statistician).
- Professor Tony Nunn.
- Dr Helen Mactier.

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Data management

Predefined data ranges were included in the eCRF, which raised automated queries if data outside of the expected range were entered. In addition to the automated queries, the trial data were reviewed on a regular basis by the data manager to look for discrepancies and errors. Furthermore, the trial statistician also performed a series of checks on snapshots of data to look for inconsistencies. The checks performed by the data manager and statistician were documented in a prespecified data management plan, which was updated over the course of the study as required.

Risk assessment and monitoring plan

A risk assessment was performed by the ICTU quality assurance manager prior to the start of the trial. The result of the risk assessment indicated that the study was low risk and that 20% of trial data, 100% consent forms and 100% SAEs should be source verified. A monitoring plan was prepared in accordance with the risk assessment to specify the frequency of monitoring visits and number of source data verification required.

Monitoring visits

A site initiation visit was performed at all participating centres. Interim monitoring visits were carried out approximately annually, depending on the recruitment rate, and closeout visits were carried out at all centres following the final follow-up visit for the last patient recruited. The monitoring visits were conducted by the trial manager.

Investigational medicinal product manufacturer

The IMP for the NEON trial was manufactured by Bath-ASU (Wiltshire, UK), a MHRA-licensed manufacturing unit, with expertise in producing aseptic products.

Patient and public involvement

The TSC membership included a parent representative who was invited to attend all TSC meetings and included in all relevant correspondence. The long-term follow-up of the infants involved in the trial was something parents of babies who took part in the study were keen to see.

Parents were consulted during preparation of the PIS and the charity Bliss was also approached during the design phase of the study. Parent representatives contributed by suggesting changes to the PIS, including reducing the length and complexity of information.

Chapter 4 Results

Participant flow

The flow of patients is summarised in *Figure 2*, including the number of patients screened, randomised and completing the trial.

Screening

Four hundred and sixty infants below 31 weeks of gestational age were admitted to the participating hospitals over the duration of the trial. Of the 382 infants meeting the eligibility criteria, 168 were randomised to the trial. *Figure 3* summarises the percentage of eligible patients recruited to the trial and reasons for non-recruitment.

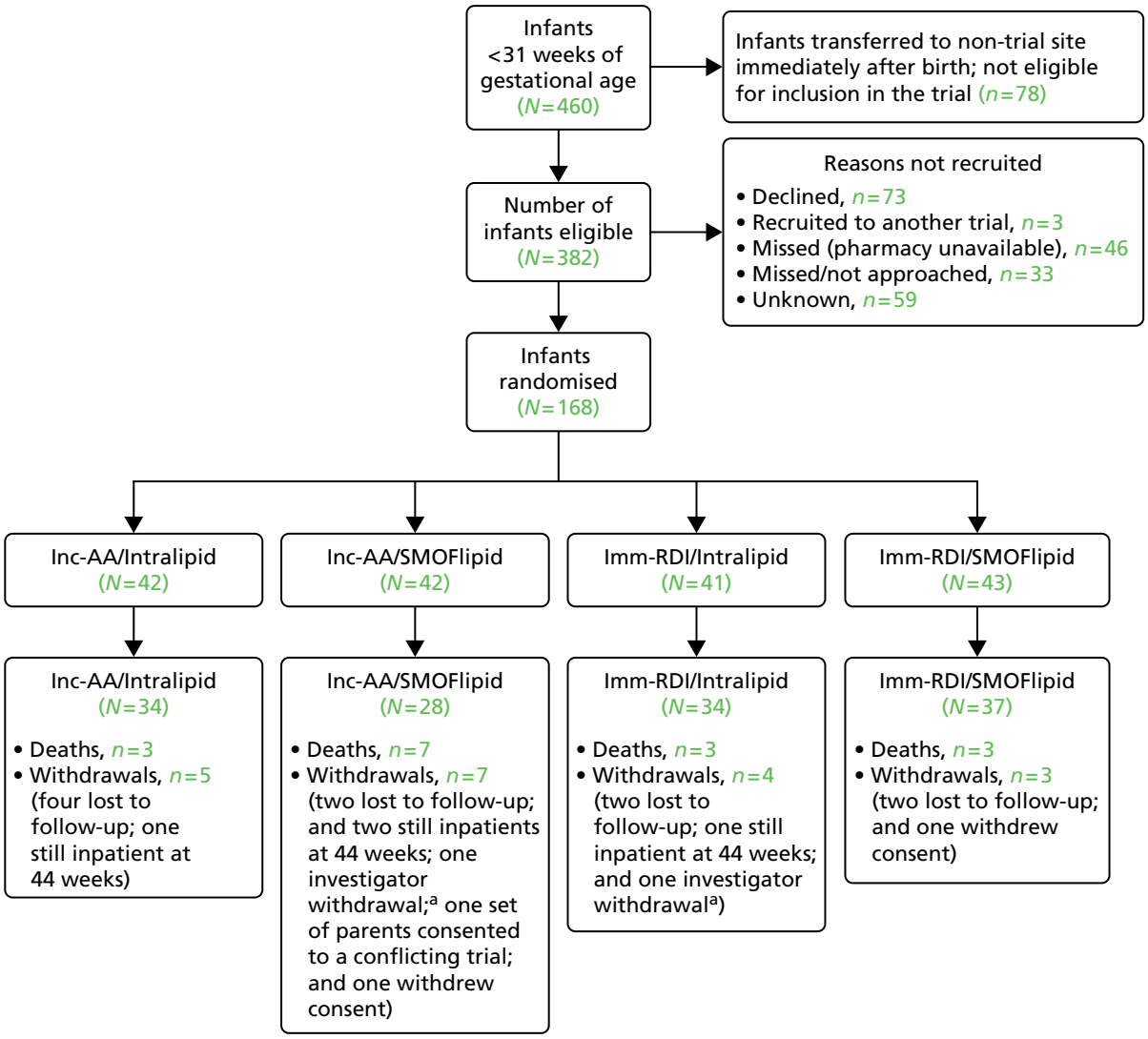

FIGURE 2 The Consolidated Standards of Reporting Trials diagram. a, Investigator withdrawal: in both cases, this occurred when the infant was transferred to a non-trial site very soon after randomisation and was therefore unable to receive the trial intervention.

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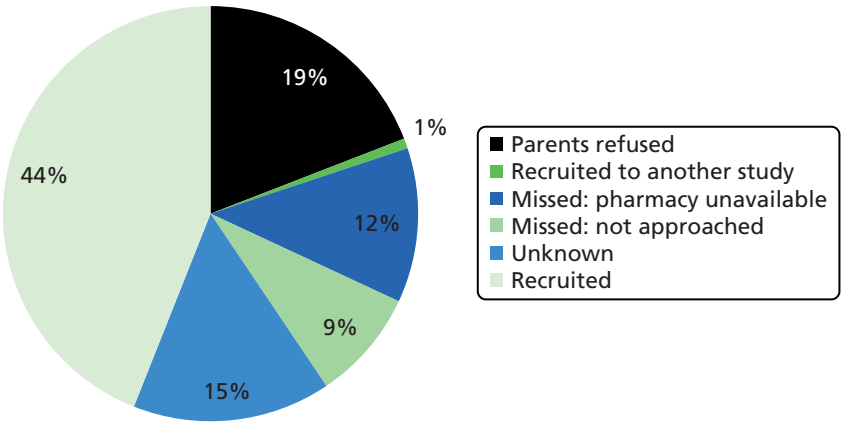

FIGURE 3 Summary of screening data for all trial sites.

Recruitment and retention

Recruitment lasted for 3 years; the first infant was recruited on 6 July 2010 and the last on 31 July 2013. The actual recruitment period was longer than the original target of 2.5 years because of delays starting the trial at all sites. The delays in starting the trial were associated with the following:

(a) Identifying a suitable manufacturer for the trial with an IMP licence to produce PN and the capacity to support the trial.
(b) Agreement from each centre to support excess treatment costs because of the cost difference between standard hospital PN and trial PN supply, including signing a procurement contract for each participating pharmacy.
(c) Obtaining NHS permission at each site was lengthy, the procurement process was a factor for this.
(d) Inability to recruit during weekends and holidays. Pharmacy departments at three out of four sites could not support recruitment at weekends or during Christmas and Easter, which reduced the recruitment rate.

Recruitment rate

The target recruitment rate for the study was six patients per month, based on all four centres recruiting. The average monthly recruitment rate once all centres were activated (January 2012) was consistent with the target, that is, six patients per month.

Figures 4–6 summarise cumulative recruitment and retention over the course of the study, and recruitment and retention per centre.

Baseline data

The baseline characteristics of the infants recruited to the study and those who completed the MR assessment of primary outcome measures are shown in *Tables 5* and *6*, respectively. Of the 437 infants born before 31 weeks of gestation, 168 infants were randomised. A total of 133 infants were available for assessment of the primary outcome measures. Baseline characteristics of sex, gestational age at birth, anthropometry, maternal demographics, mode of delivery, antenatal steroid use and time to commencing PN were similar across the four groups.

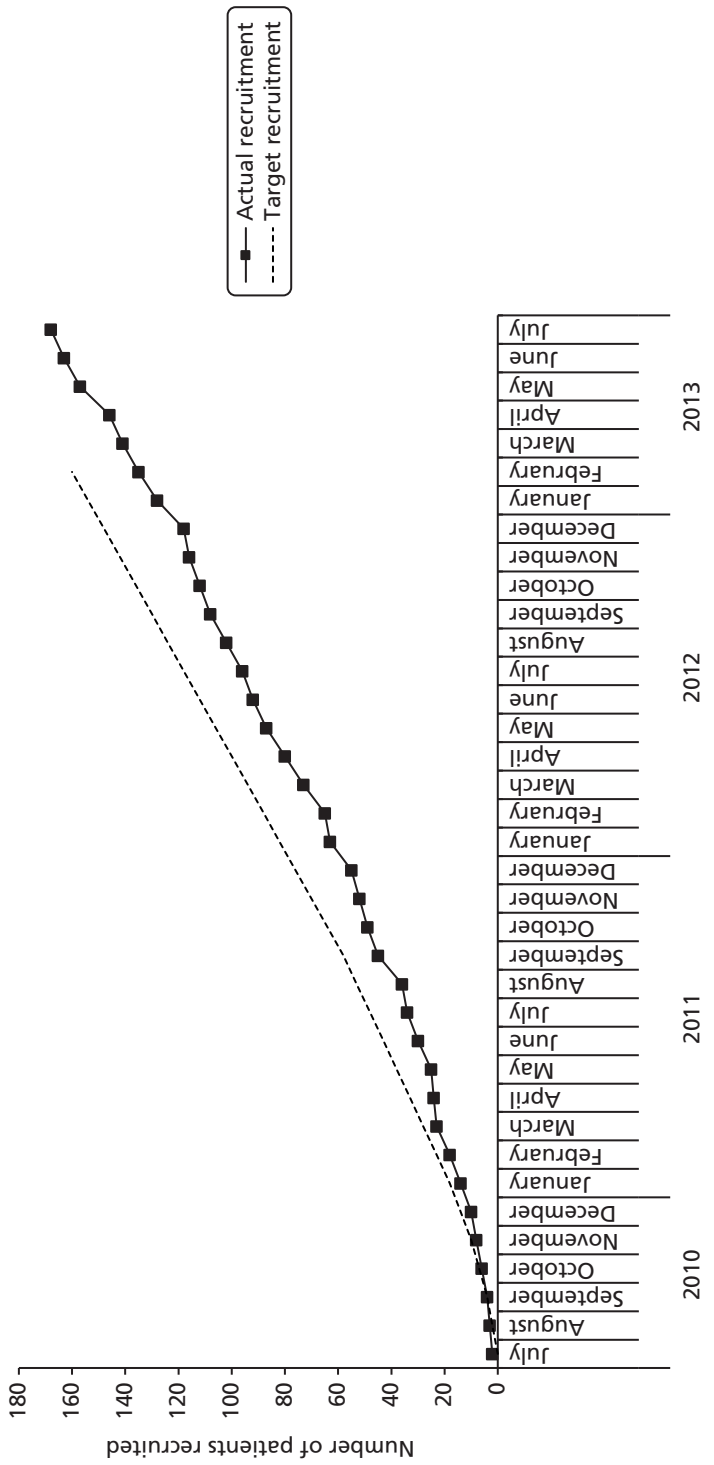

FIGURE 4 Cumulative recruitment vs. target recruitment for the duration of the trial.

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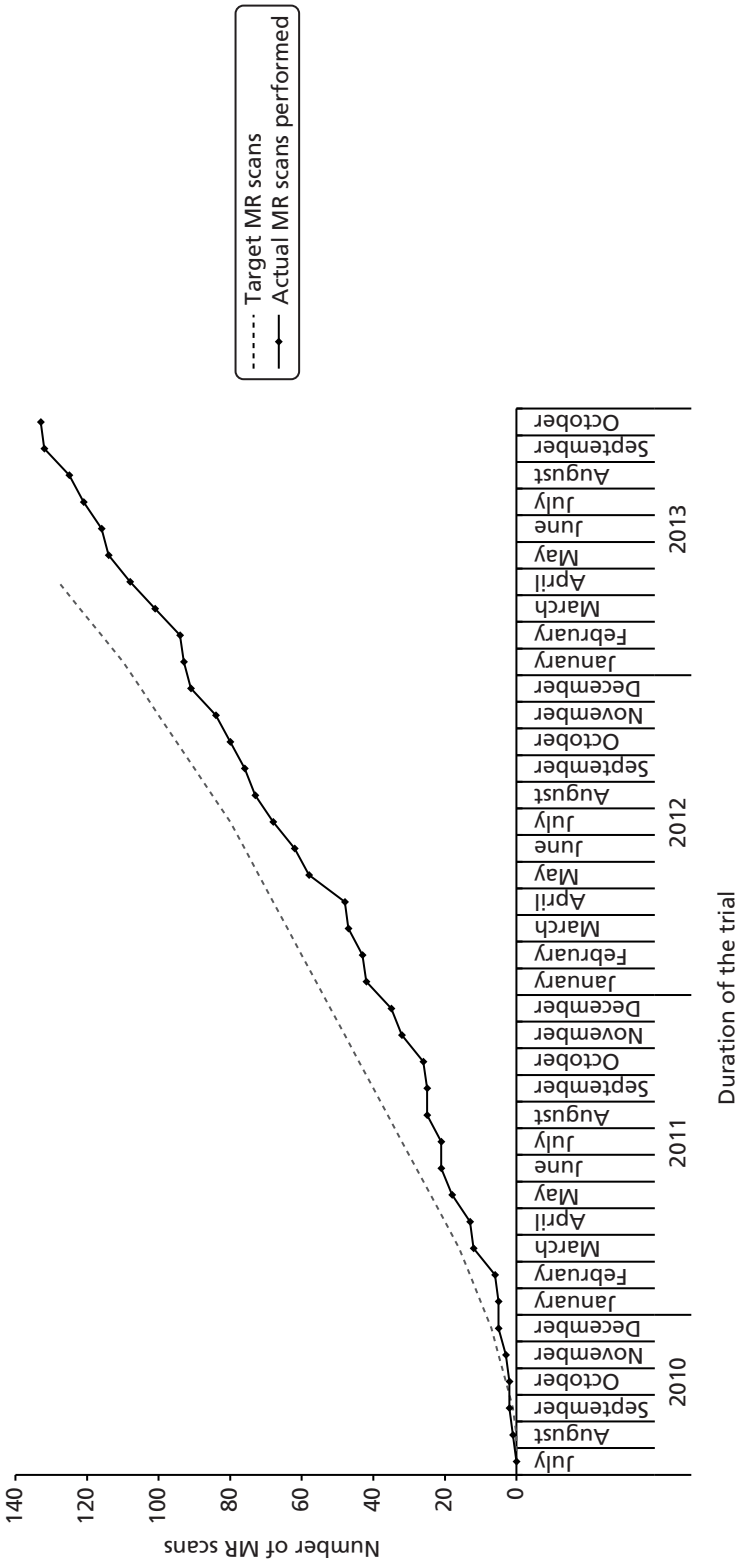

FIGURE 5 Cumulative retention (number of MR scans) vs. target retention for the duration of the trial.

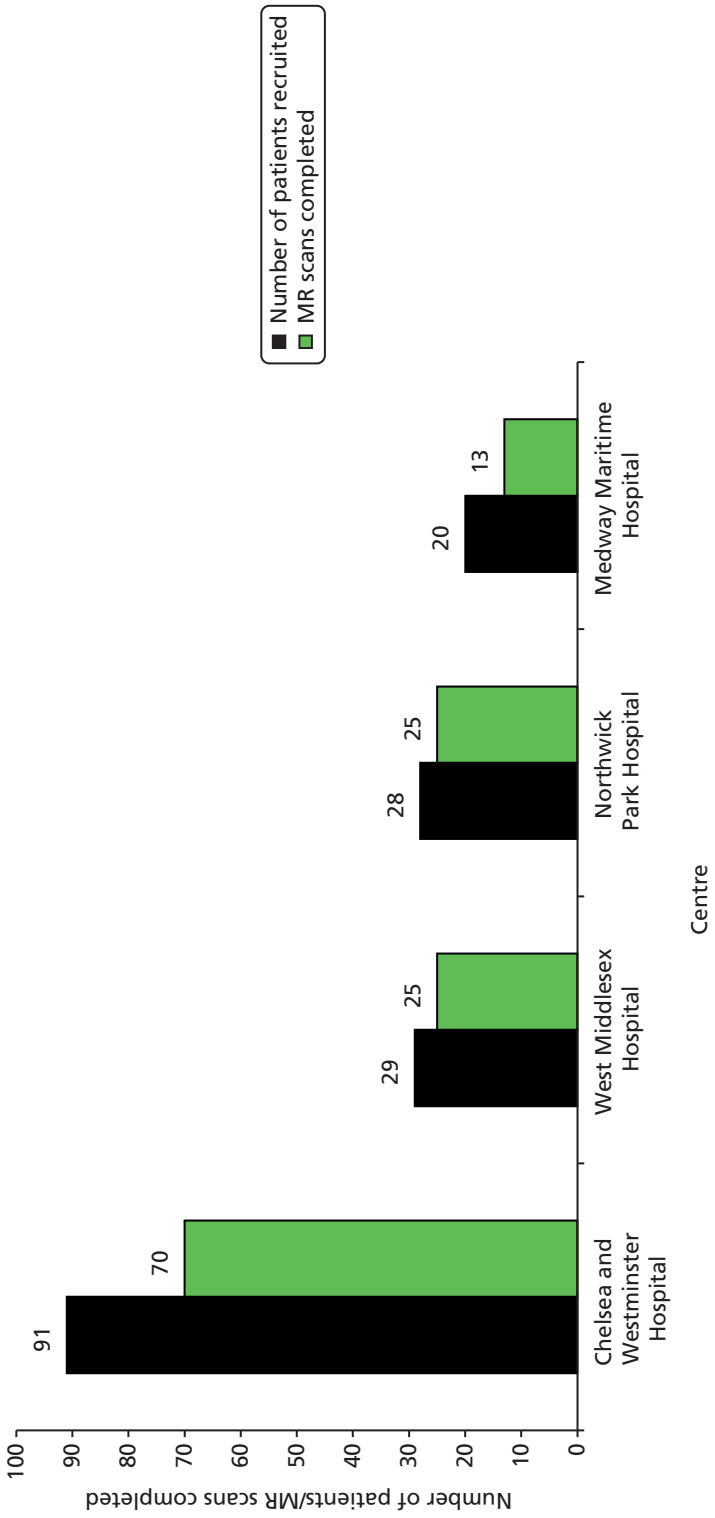

FIGURE 6 Total recruitment and retention per centre.

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TABLE 5 Baseline characteristics for all infants randomised[a]

Characteristic	Inc-AA/Intralipid (*N* = 42)	Inc-AA/SMOFlipid (*N* = 42)	Imm-RDI/ Intralipid (*N* = 41)	Imm-RDI/ SMOFlipid (*N* = 43)
Infant sex, *n* (%)				
Male	28 (66.7)	26 (61.9)	21 (51.2)	22 (51.2)
Gestational age (weeks), mean (SD)	27.8 (1.9)	27.5 (2.4)	28.1 (2.1)	27.8 (2.1)
Multiple births, *n* (%)				
Yes	6 (14.3)	6 (14.3)	9 (22.0)	15 (34.9)
Birthweight (kg), mean (SD)	1.03 (0.29)	1.05 (0.34)	1.04 (0.28)	1.06 (0.29)
Birth length (cm), mean (SD)	35.1 (3.5); *n* = 31	34.6 (4.2); *n* = 32	35.1 (3.9); *n* = 26	35.2 (5.2); *n* = 32
Head circumference (cm), mean (SD)	25.3 (2.0); *n* = 41	25.0 (3.0); *n* = 40	25.3 (1.9); *n* = 37	25.6 (2.9); *n* = 39
Birthweight (*z*-score), mean (SD)	–0.2 (1.0); *n* = 42	0.1 (1.0); *n* = 41	–0.2 (1.0); *n* = 41	0 (0.9); *n* = 43
Birth length (*z*-score), mean (SD)	–1.0 (1.0); *n* = 30	–0.9 (1.2); *n* = 24	–1.1 (1.0); *n* = 25	–0.8 (1.5); *n* = 29
Head circumference (*z*-score), mean (SD)	–0.5 (0.9); *n* = 41	–0.3 (1.0); *n* = 39	–0.7 (0.9); *n* = 37	–0.2 (1.6); *n* = 41
Mother's age (years), mean (SD)	32.9 (5.3); *n* = 42	31.3 (7.7); *n* = 42	32.9 (6.3); *n* = 40	32.5 (6.6); *n* = 43
Mother's weight (kg),[b] mean (SD)	66.4 (13.3); *n* = 34	65.9 (11.4); *n* = 25	64.9 (13.0); *n* = 30	68.5 (15.2); *n* = 33
Mother's height (cm),[b] mean (SD)	161.9 (7.8); *n* = 33	164.9 (7.7); *n* = 27	161.3 (9.2); *n* = 27	164.5 (8.6); *n* = 32
Father's weight (kg),[b] mean (SD)	80.8 (10.7); *n* = 27	82.3 (13.2); *n* = 22	85.3 (16.1); *n* = 24	86.3 (14.9); *n* = 31
Father's height (cm),[b] mean (SD)	178.4 (6.5); *n* = 28	179.6 (6.8); *n* = 22	175.7 (10.0); *n* = 22	182.0 (9.7); *n* = 30
Mother's ethnicity, *n* (%)				
White	16 (38.1)	19 (45.2)	21 (51.2)	21 (48.8)
Asian	14 (33.3)	7 (16.7)	12 (29.3)	12 (27.9)
Black	6 (14.3)	13 (31.0)	6 (14.6)	6 (14.0)
Mixed	2 (4.8)	2 (4.8)	1 (2.4)	2 (4.7)
Other	3 (7.1)	0 (0)	1 (2.4)	2 (4.7)
Missing	1 (2.4)	1 (2.4)	0 (0)	0 (0)
Mode of delivery, *n* (%)				
Vaginal	8 (19.1)	18 (42.9)	16 (39.0)	17 (39.5)
Elective caesarean	7 (16.7)	3 (7.1)	4 (9.8)	2 (4.7)
Emergency caesarean	27 (64.3)	21 (50.0)	21 (51.2)	24 (55.8)
Antenatal steroids, *n* (%)				
Yes	30 (71.4)	34 (81.0)	32 (78.1)	35 (81.4)
No	7 (16.7)	6 (14.3)	7 (17.1)	4 (9.3)
Unknown	5 (11.9)	2 (4.8)	2 (4.9)	4 (9.3)
Time from birth to starting PN, (hours),[c] median (IQR)	18.4 (12.3–22.7); *n* = 42	19.5 (13.6–22.8); *n* = 41	20.4 (12.6–23.6); *n* = 40	17.7 (13.0–22.4); *n* = 43

IQR, interquartile range.
a Data presented are means (SD) for continuous variables and frequency (percentage) for categorical variables.
b Anthropometries measured at booking.
c Data presented are medians (IQR, lower quartile, upper quartile).

TABLE 6 Baseline characteristics for all infants completing MRI assessment[a]

Characteristic	Inc-AA/Intralipid (*N* = 34)	Inc-AA/SMOFlipid (*N* = 28)	Imm-RDI/ Intralipid (*N* = 34)	Imm-RDI/ SMOFlipid (*N* = 37)
Infant sex, *n* (%)				
Male	20 (58.8)	18 (64.3)	17 (50.0)	19 (51.4)
Gestational age (weeks), mean (SD)	28.0 (1.8)	28.0 (2.1)	28.4 (2.1)	27.7 (2.0)
Multiple births, *n* (%)				
Yes	4 (11.8)	3 (10.7)	8 (23.5)	13 (35.1)
Birthweight (kg), mean (SD)	1.06 (0.29)	1.10 (0.32)	1.09 (0.28)	1.06 (0.29)
Birth length (cm), mean (SD)	35.5 (3.5); *n* = 28	35.1 (4.0); *n* = 24	35.6 (3.5); *n* = 24	34.9 (4.9); *n* = 27
Head circumference (cm), mean (SD)	25.3 (2.0); *n* = 34	25.6 (2.6); *n* = 26	25.5 (1.9); *n* = 32	25.7 (2.9); *n* = 34
Birthweight (*z*-score), mean (SD)	–0.1 (0.9)	0 (1.0)	–0.2 (1.0)	0.1 (0.9)
Birth length (*z*-score), mean (SD)	–0.9 (1.1); *n* = 28	–1.0 (1.3); *n* = 21	–1.0 (1.0); *n* = 23	–1.1 (1.4); *n* = 25
Head circumference (*z*-score), mean (SD)	–0.5 (0.9); *n* = 34	–0.4 (1.0); *n* = 26	–0.7 (0.9); *n* = 32	–0.2 (1.7); *n* = 34
Mother's age (years), mean (SD)	32.6 (5.4); *n* = 34	30.3 (7.8); *n* = 26	32.2 (6.4); *n* = 33	32.7 (6.7); *n* = 34
Mother's weight (kg),[b] mean (SD)	67.6 (14.5); *n* = 27	63.8 (11.5); *n* = 17	64.7 (13.3); *n* = 26	68.5 (16.1); *n* = 29
Mother's height (cm),[b] mean (SD)	162.4 (7.2); *n* = 26	165.1 (7.3); *n* = 19	162.1 (9.1); *n* = 23	164.8 (9.1); *n* = 28
Father's weight (kg),[b] mean (SD)	82.3 (11.5); *n* = 21	81.5 (14.0); *n* = 15	84.1 (15.9); *n* = 22	87.8 (14.7); *n* = 28
Father's height (cm),[b] mean (SD)	177.8 (6.1); *n* = 22	179.3 (7.4); *n* = 15	175.6 (10.2); *n* = 20	182.8 (9.6); *n* = 27
Mother's ethnicity, *n* (%)				
White	13 (38.2)	11 (39.3)	17 (50.0)	19 (51.4)
Asian	10 (29.4)	6 (21.4)	11 (32.4)	9 (24.3)
Black	5 (14.7)	10 (35.7)	5 (14.7)	6 (16.2)
Mixed	2 (5.9)	1 (3.6)	0 (0)	2 (5.4)
Other	3 (8.8)	0 (0)	1 (2.9)	1 (2.7)
Missing	1 (2.94)	0 (0)	0 (0)	0 (0)
Mode of delivery, *n* (%)				
Vaginal	6 (17.6)	9 (32.1)	13 (38.2)	15 (40.5)
Elective caesarean	5 (14.7)	2 (7.1)	4 (11.8)	1 (2.7)
Emergency caesarean	23 (67.7)	17 (60.7)	17 (50.0)	21 (56.8)
Antenatal steroids, *n* (%)				
Yes	24 (70.6)	21 (75.0)	26 (76.5)	30 (81.1)
No	5 (14.7)	5 (17.9)	6 (17.7)	4 (10.8)
Unknown	5 (14.7)	2 (7.1)	2 (5.9)	3 (8.1)
Time from birth to starting PN, (hours),[c] median (IQR)	16.9 (10.5–22.3); *n* = 34	19.4 (12.1–22.3); *n* = 28	20.0 (12.4–23.5); *n* = 34	17.7 (13.2–22.4); *n* = 37

IQR, interquartile range.
a Data presented are means (SD) for continuous variables and frequency (percentage) for categorical variables.
b Anthropometries measured at booking.
c Data presented are medians (IQR, lower quartile, upper quartile).

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The time to achieve a milk intake of 150 ml/kg/day for 24 hours for all infants randomised was similar across the four groups [Inc-AA/Intralipid, median 12 days, interquartile range (IQR) 9–17.5 days; Inc-AA/SMOFlipid, median 11.5 days, IQR 9–16 days; Imm-RDI/Intralipid, median 11 days, IQR 10–14 days; Imm-RDI/SMOFlipid, median 13 days, IQR 9.5 –18 days]. The length of hospital stay for all infants randomised was similar across the four groups (Inc-AA/Intralipid, median 69.5 days, IQR 52–95 days; Inc-AA/SMOFlipid, median 61 days, IQR 5–88 days; Imm-RDI/Intralipid, median 63 days, IQR 45–95 days; Imm-RDI/SMOFlipid, median 66.5 days, IQR 44–98 days) (*Tables 7* and *8*).

TABLE 7 Parenteral nutrition details and blood culture results for all infants randomised

Characteristic	Inc-AA/Intralipid (*N* = 42)	Inc-AA/SMOFlipid (*N* = 42)	Imm-RDI/ Intralipid (*N* = 41)	Imm-RDI/ SMOFlipid (*N* = 43)
Route of PN administration, median (IQR)				
Peripheral (days)	0 (0–2); *n* = 42	1 (0–5); *n* = 41	0.5 (0–2.5); *n* = 40	1 (0–3); *n* = 43
Central (days)	11.5 (8–20); *n* = 42	13 (8–20); *n* = 41	11 (9–15.5); *n* = 40	12 (9–18); *n* = 43
Days from delivery to achieve milk intake of 150 ml/kg/day for 24 hours	12 (9–17.5); *n* = 32	11.5 (9–16); *n* = 28	11 (10–14); *n* = 30	13 (9.5–18); *n* = 36
Reason for stopping PN,[a] frequency (%)				
Investigator's decision	5 (11.9)	3 (7.1)	3 (7.3)	9 (20.9)
Investigator's decision and investigator manual	0 (0)	1 (2.4)	0 (0)	0 (0)
Investigator's manual	2 (4.8)	1 (2.4)	2 (4.9)	2 (4.7)
Operational	2 (4.8)	1 (2.4)	2 (4.9)	3 (6.7)
Withdrawal	1 (2.4)	0 (0)	0 (0)	0 (0)
SAE	0 (0)	2 (4.8)	0 (0)	0 (0)
Positive blood culture,[b] frequency (%)	15	13	9	14
Fungus	2 (13.3)	1 (7.7)	0 (0)	1 (7.1)
Gram-negative bacilli	5 (33.3)	4 (30.8)	3 (33.3)	1 (7.1)
Gram-positive bacilli	1 (6.7)	0 (0)	0 (0)	0 (0)
Gram-positive cocci CoNS	2 (13.3)	3 (23.1)	4 (44.4)	7 (50.0)
Gram-positive cocci excluding CoNS	3 (20.0)	4 (30.8)	1 (11.1)	5 (35.7)
Gram-positive cocci not specified	2 (13.3)	1 (7.7)	1 (11.1)	0 (0)
Positive blood cultures (while on PN)[b]	8	9	8	8
Length of stay in hospital (days), median (IQR)	69.5 (52–95); *n* = 38	61 (45–88); *n* = 33	63 (45–95); *n* = 38	66.5 (44–98); *n* = 38

CoNS, coagulase-negative staphylococci.
a There can be more than one reason for each infant.
b Growth of a known pathogen on culture; data presented are the number of infants who had at least one positive result.

TABLE 8 Parenteral nutrition details and blood culture results for all infants completing MRI assessment

Characteristic	Inc-AA/Intralipid (*N* = 34)	Inc-AA/SMOFlipid (*N* = 28)	Imm-RDI/ Intralipid (*N* = 34)	Imm-RDI/ SMOFlipid (*N* = 37)
Route of PN administration, median (IQR)				
Peripheral (days)	0 (0–2)	1 (0–5.5)	1 (0–3)	1 (0–3)
Central (days)	11 (8–17)	13.5 (8.5–19.5)	10.5 (9–15)	12 (9–18)
Days from delivery to achieve milk intake of 150 ml/kg/day for 24 hours, median (IQR)	11 (9–16); *n* = 28	11.5 (9–16); *n* = 22	11 (10–13.5); *n* = 28	13 (10–18); *n* = 33
Reason for stopping PN,[a] frequency (%)				
Investigator's decision	3 (8.8)	2 (7.1)	3 (8.8)	6 (16.2)
Investigator's manual	2 (4.8)	1 (2.4)	2 (4.9)	1 (2.7)
Operational	2 (4.8)	1 (2.4)	2 (4.9)	3 (8.1)
Positive blood culture,[b] frequency (%)	9	4	5	12
Fungus	2 (22.2)	0 (0)	0 (0)	1 (8.3)
Gram-negative bacilli	3 (33.3)	3 (75.0)	3 (60.0)	0 (0)
Gram-positive bacilli	0 (0)	0 (0)	0 (0)	0 (0)
Gram-positive cocci CoNS	1 (11.1)	0 (0)	1 (20.0)	6 (50.0)
Gram-positive cocci excluding CoNS	2 (22.2)	0 (0)	0 (0)	5 (41.7)
Gram-positive cocci not specified	1 (11.1)	1 (25.0)	1 (20.0)	0 (0)
Positive blood cultures (while on PN)[b]	5	3	4	7
Length of stay in hospital (days), median (IQR)	69.5 (55–96); *n* = 34	59 (44–85); *n* = 28	60.5 (44–88); *n* = 34	67 (47–98.5); *n* = 36

CoNS, coagulase-negative staphylococci.
a There can be more than one reason for each infant.
b Growth of a known pathogen on culture; data presented are the number of infants who had at least one positive result.

Nutritional intake from trial PN during the first week was similar across the four groups, except for the intake of protein. On day 4, for all infants randomised, when infants randomised to Inc-AA intake achieved the maximum intake, the protein intake was 2.5 g/kg and 2.6 g/kg in the Inc-AA/Intralipid and Inc-AA/SMOFlipid groups, respectively, compared with 3.3 g/kg and 3.1 g/kg in the Imm-RDI/Intralipid and Imm-RDI/SMOFlipid groups, respectively for all infants randomised (*Table 9*). *Table 10* shows data for babies who completed the MR scan. The median cumulative protein intake from trial PN during the first 2 weeks after birth for all randomised infants in the incremental arm was 22.4 g (IQR 16.0–28.4 g) and 20.9 g (IQR 15.3–28.4 g) in the Inc-AA/Intralipid and Inc-AA/SMOFlipid groups, respectively, compared with 25.9 g (IQR 22.6–32.5 g) and 29.5 g (IQR 23.2–37.2 g) in the Imm-RDI/Intralipid and Imm-RDI/SMOFlipid groups, respectively. The median cumulative protein intake from all sources between birth and 34 weeks postmenstrual age for all babies randomised was 138.2 g (IQR 109.9–170.7 g) and 119.0 g (IQR 91.1–161.0 g) in the Inc-AA/Intralipid and Inc-AA/SMOFlipid groups, respectively, compared with 124.8 g (IQR 103.1–175.3 g) and 148.3 g (IQR 122.1–170.7 g) in the Imm-RDI/Intralipid and Imm-RDI/SMOFlipid groups, respectively. *Tables 11–13* show data of nutritional intake for all babies randomised. *Tables 14* and *15* show data of nutritional intake for babies who completed the MR scan.

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TABLE 9 Trial PN intake during the first 7 days for all infants randomised

Trial PN intake by day	Inc-AA/Intralipid (*N* = 42)	Inc-AA/SMOFlipid (*N* = 42)	Imm-RDI/ Intralipid (*N* = 41)	Imm-RDI/ SMOFlipid (*N* = 43)
Day 1,[a] mean (SD)	*n* = 39	*n* = 34	*n* = 37	*n* = 41
Aqueous volume (ml/kg)	71.1 (36.2)	69.5 (34.3)	69.2 (36.7)	68.1 (35.6)
Lipid volume (ml/kg)	8.8 (5.2)	8.6 (4.6)	8.5 (5.3)	7.9 (4.5)
Protein (g/kg)	1.2 (0.7)	1.2 (0.6)	2.5 (1.3)	2.4 (1.3)
Carbohydrate (g/kg)	6.8 (3.5)	6.7 (3.3)	6.6 (3.5)	6.4 (3.4)
Fat (g/kg)	1.8 (1.0)	1.7 (0.9)	1.7 (1.1)	1.6 (0.9)
Day 2, mean (SD)	*n* = 39	*n* = 38	*n* = 39	*n* = 42
Aqueous volume (ml/kg)	96.5 (20.8)	89.9 (31.1)	94.9 (16.8)	94.5 (20.9)
Lipid volume (ml/kg)	14.8 (9.9)	12.8 (5.2)	13.7 (2.6)	14.1 (4.0)
Protein (g/kg)	2.1 (0.5)	1.9 (0.7)	3.1 (0.5)	3.1 (0.7)
Carbohydrate (g/kg)	8.6 (1.8)	8.1 (2.8)	8.4 (1.4)	8.2 (1.8)
Fat (g/kg)	3.0 (2.0)	2.6 (1.0)	2.7 (0.5)	2.8 (0.8)
Day 3, mean (SD)	*n* = 39	*n* = 37	*n* = 38	*n* = 42
Aqueous volume (ml/kg)	114.4 (22.4)	112.8 (29.1)	112.6 (25.1)	114.0 (23.2)
Lipid volume (ml/kg)	14.3 (3.2)	14.7 (3.8)	13.4 (3.8)	13.4 (4.8)
Protein (g/kg)	2.5 (0.5)	2.5 (0.7)	3.1 (0.7)	3.1 (0.7)
Carbohydrate (g/kg)	8.5 (1.8)	8.3 (2.1)	8.4 (1.8)	8.3 (1.8)
Fat (g/kg)	2.8 (0.6)	2.9 (0.7)	2.6 (0.8)	2.6 (0.9)
Day 4, mean (SD)	*n* = 40	*n* = 37	*n* = 38	*n* = 40
Aqueous volume (ml/kg)	111.4 (26.0)	117.0 (21.5)	123.4 (14.7)	115.9 (20.2)
Lipid volume (ml/kg)	14.2 (5.3)	14.6 (4.2)	15.3 (4.4)	14.0 (4.1)
Protein (g/kg)	2.5 (0.6)	2.6 (0.5)	3.3 (0.4)	3.1 (0.5)
Carbohydrate (g/kg)	8.1 (2.1)	8.4 (1.6)	8.9 (1.1)	8.4 (1.4)
Fat (g/kg)	2.6 (1.0)	2.7 (0.8)	2.8 (0.8)	2.5 (0.7)
Day 5, mean (SD)	*n* = 42	*n* = 38	*n* = 38	*n* = 41
Aqueous volume (ml/kg)	106.5 (29.9)	111.3 (23.7)	114.0 (25.1)	112.4 (22.1)
Lipid volume (ml/kg)	14.4 (4.7)	14.9 (4.3)	14.8 (4.1)	13.7 (4.7)
Protein (g/kg)	2.4 (0.7)	2.5 (0.5)	3.0 (0.7)	3.0 (0.6)
Carbohydrate (g/kg)	7.7 (2.2)	8.1 (1.6)	8.2 (1.8)	8.1 (1.6)
Fat (g/kg)	2.5 (0.8)	2.6 (0.7)	2.6 (0.7)	2.4 (0.8)
Day 6, mean (SD)	*n* = 42	*n* = 38	*n* = 38	*n* = 41
Aqueous volume (ml/kg)	100.9 (34.0)	103.0 (31.6)	103.0 (31.3)	107.5 (27.8)
Lipid volume (ml/kg)	13.1 (5.4)	13.8 (4.9)	13.2 (6.0)	12.8 (5.7)
Protein (g/kg)	2.3 (0.8)	2.3 (0.7)	2.8 (0.8)	2.9 (0.7)
Carbohydrate (g/kg)	7.3 (2.5)	7.4 (2.3)	7.4 (2.3)	7.7 (2.0)
Fat (g/kg)	2.3 (1.0)	2.4 (0.9)	2.3 (1.0)	2.3 (1.0)

TABLE 9 Trial PN intake during the first 7 days for all infants randomised (*continued*)

Trial PN intake by day	Inc-AA/Intralipid (*N* = 42)	Inc-AA/SMOFlipid (*N* = 42)	Imm-RDI/ Intralipid (*N* = 41)	Imm-RDI/ SMOFlipid (*N* = 43)
Day 7, mean (SD)	*n* = 41	*n* = 36	*n* = 36	*n* = 38
Aqueous volume (ml/kg)	93.4 (35.7)	92.4 (31.3)	101.3 (28.2)	100.9 (25.6)
Lipid volume (ml/kg)	11.1 (6.1)	11.1 (6.0)	13.1 (7.5)	11.6 (5.6)
Protein (g/kg)	2.1 (0.8)	2.1 (0.7)	2.7 (0.8)	2.7 (0.7)
Carbohydrate (g/kg)	6.8 (2.6)	6.7 (2.3)	7.3 (2.0)	7.3 (1.8)
Fat (g/kg)	2.0 (1.1)	1.9 (1.0)	2.3 (1.3)	2.1 (1.0)

a Day 1 is defined from birth to first 17.00.

TABLE 10 Trial PN intake during the first 7 days for all infants completing MRI assessment

Trial PN intake by day	Inc-AA/Intralipid (*N* = 34)	Inc-AA/SMOFlipid (*N* = 28)	Imm-RDI/ Intralipid (*N* = 34)	Imm-RDI/ SMOFlipid (*N* = 37)
Day 1,[a] mean (SD)	*n* = 32	*n* = 25	*n* = 31	*n* = 36
Aqueous volume (ml/kg)	69.5 (36.2)	70.1 (34.4)	70.9 (37.6)	67.8 (36.0)
Lipid volume (ml/kg)	8.4 (5.0)	8.7 (4.5)	8.9 (5.5)	8.1 (4.7)
Protein (g/kg)	1.2 (0.7)	1.2 (0.6)	2.5 (1.3)	2.4 (1.3)
Carbohydrate (g/kg)	6.7 (3.5)	6.7 (3.3)	6.8 (3.6)	6.4 (3.4)
Fat (g/kg)	1.7 (1.0)	1.7 (0.9)	1.8 (1.1)	1.6 (0.9)
Day 2, mean (SD)	*n* = 33	*n* = 27	*n* = 34	*n* = 36
Aqueous volume (ml/kg)	92.9 (18.5)	89.5 (22.6)	97.3 (15.3)	97.1 (20.2)
Lipid volume (ml/kg)	14.7 (10.7)	13.2 (4.4)	13.8 (2.6)	14.6 (3.8)
Protein (g/kg)	2.0 (0.4)	1.9 (0.5)	3.2 (0.5)	3.1 (0.6)
Carbohydrate (g/kg)	8.3 (1.7)	8.0 (1.9)	8.5 (1.3)	8.4 (1.7)
Fat (g/kg)	2.9 (2.1)	2.7 (0.9)	2.7 (0.5)	2.9 (0.7)
Day 3, mean (SD)	*n* = 32	*n* = 28	*n* = 34	*n* = 36
Aqueous volume (ml/kg)	116.8 (21.5)	112.2 (32.7)	111.8 (26.3)	117.5 (19.2)
Lipid volume (ml/kg)	14.6 (3.4)	14.4 (4.3)	13.3 (4.0)	13.9 (4.6)
Protein (g/kg)	2.6 (0.5)	2.5 (0.7)	3.1 (0.7)	3.2 (0.6)
Carbohydrate (g/kg)	8.6 (1.8)	8.3 (2.4)	8.4 (1.9)	8.6 (1.6)
Fat (g/kg)	2.8 (0.6)	2.8 (0.8)	2.6 (0.8)	2.7 (0.9)

continued

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TABLE 10 Trial PN intake during the first 7 days for all infants completing MRI assessment (*continued*)

Trial PN intake by day	Inc-AA/Intralipid (*N* = 34)	Inc-AA/SMOFlipid (*N* = 28)	Imm-RDI/ Intralipid (*N* = 34)	Imm-RDI/ SMOFlipid (*N* = 37)
Day 4, mean (SD)	*n* = 33	*n* = 28	*n* = 34	*n* = 35
Aqueous volume (ml/kg)	112.4 (26.8)	117.4 (24.4)	123.2 (14.9)	118.5 (14.6)
Lipid volume (ml/kg)	13.9 (5.6)	14.8 (4.7)	15.6 (3.7)	14.4 (3.5)
Protein (g/kg)	2.5 (0.6)	2.6 (0.5)	3.3 (0.4)	3.2 (0.3)
Carbohydrate (g/kg)	8.2 (2.1)	8.5 (1.8)	8.9 (1.1)	8.6 (0.9)
Fat (g/kg)	2.5 (1.0)	2.7 (0.8)	2.8 (0.7)	2.6 (0.6)
Day 5, mean (SD)	*n* = 34	*n* = 28	*n* = 34	*n* = 36
Aqueous volume (ml/kg)	107.6 (32.1)	111.0 (25.2)	113.3 (26.2)	112.3 (23.1)
Lipid volume (ml/kg)	14.3 (5.1)	15.2 (4.1)	14.7 (4.3)	13.5 (5.0)
Protein (g/kg)	2.4 (0.7)	2.5 (0.6)	3.0 (0.7)	3.0 (0.6)
Carbohydrate (g/kg)	7.7 (2.3)	8.0 (1.8)	8.2 (1.9)	8.1 (1.7)
Fat (g/kg)	2.5 (0.9)	2.7 (0.7)	2.6 (0.7)	2.4 (0.9)
Day 6, mean (SD)	*n* = 34	*n* = 28	*n* = 34	*n* = 35
Aqueous volume (ml/kg)	101.4 (36.8)	104.6 (33.7)	101.5 (32.5)	111.0 (24.1)
Lipid volume (ml/kg)	13.1 (5.8)	13.9 (5.4)	13.0 (6.1)	13.2 (5.6)
Protein (g/kg)	2.3 (0.8)	2.4 (0.8)	2.7 (0.9)	3.0 (0.6)
Carbohydrate (g/kg)	7.3 (2.7)	7.5 (2.4)	7.3 (2.3)	8.0 (1.7)
Fat (g/kg)	2.3 (1.0)	2.4 (0.9)	2.3 (1.1)	2.3 (1.0)
Day 7, mean (SD)	*n* = 33	*n* = 26	*n* = 32	*n* = 33
Aqueous volume (ml/kg)	93.8 (35.6)	93.2 (34.8)	101.9 (29.2)	103.1 (26.3)
Lipid volume (ml/kg)	11.3 (6.0)	11.4 (6.3)	13.3 (7.8)	12.3 (5.4)
Protein (g/kg)	2.1 (0.8)	2.1 (0.8)	2.7 (0.8)	2.8 (0.7)
Carbohydrate (g/kg)	6.8 (2.6)	6.7 (2.5)	7.3 (2.1)	7.4 (1.9)
Fat (g/kg)	2.0 (1.1)	2.0 (1.1)	2.4 (1.4)	2.2 (1.0)

a Day 1 is defined from birth to first 17.00.

TABLE 11 Total nutrition intake during the first 7 days, 3 weeks, 4 weeks and by 34 weeks of gestational age for all infants randomised

	Inc-AA/Intralipid (*N* = 42)	Inc-AA/SMOFlipid (*N* = 42)	Imm-RDI/ Intralipid (*N* = 41)	Imm-RDI/ SMOFlipid (*N* = 43)
Day 1,[a] mean (SD)	*n* = 40	*n* = 36	*n* = 39	*n* = 41
Protein (g/kg)	1.3 (0.7)	1.2 (0.7)	2.4 (1.4)	2.5 (1.3)
Carbohydrate (g/kg)	7.2 (3.6)	6.6 (3.6)	6.6 (3.9)	6.8 (3.6)
Fat (g/kg)	1.8 (1.1)	1.8 (1.1)	1.7 (1.2)	1.7 (1.0)
Total energy (kcal/kg)	50.1 (26.5)	47.5 (25.8)	51.5 (31.4)	52.7 (28.3)
Day 2, mean (SD)	*n* = 41	*n* = 39	*n* = 39	*n* = 42
Protein (g/kg)	2.1 (0.6)	2.0 (0.8)	3.3 (0.6)	3.2 (0.7)
Carbohydrate (g/kg)	9.1 (2.0)	8.7 (3.4)	9.1 (1.6)	9.0 (2.1)
Fat (g/kg)	3.1 (2.0)	2.9 (1.3)	3.0 (0.7)	3.1 (1.0)
Total energy (kcal/kg)	73.0 (21.7)	68.5 (27.4)	76.8 (13.4)	77.1 (18.7)
Day 3, mean (SD)	*n* = 41	*n* = 38	*n* = 38	*n* = 42
Protein (g/kg)	2.7 (0.8)	2.8 (0.9)	3.4 (0.8)	3.4 (0.8)
Carbohydrate (g/kg)	9.7 (2.3)	9.6 (3.0)	9.8 (2.5)	9.7 (2.5)
Fat (g/kg)	3.2 (1.0)	3.5 (1.3)	3.3 (1.1)	3.3 (1.3)
Total energy (kcal/kg)	78.1 (17.5)	81.2 (26.0)	82.3 (21.9)	82.3 (23.1)
Day 4, mean (SD)	*n* = 42	*n* = 38	*n* = 38	*n* = 43
Protein (g/kg)	2.7 (0.8)	3.1 (0.8)	3.7 (0.5)	3.4 (1.1)
Carbohydrate (g/kg)	9.8 (2.8)	10.3 (2.9)	10.7 (1.8)	9.9 (3.1)
Fat (g/kg)	3.3 (1.3)	3.7 (1.2)	3.7 (1.2)	3.3 (1.4)
Total energy (kcal/kg)	79.4 (22.5)	86.4 (24.4)	91.0 (18.7)	83.2 (28.6)
Day 5, mean (SD)	*n* = 42	*n* = 38	*n* = 38	*n* = 42
Protein (g/kg)	2.9 (0.8)	3.2 (0.7)	3.7 (0.8)	3.6 (0.7)
Carbohydrate (g/kg)	9.9 (3.0)	10.8 (2.7)	11.1 (2.7)	11.0 (2.8)
Fat (g/kg)	3.7 (1.4)	4.1 (1.3)	4.1 (1.5)	3.7 (1.2)
Total energy (kcal/kg)	84.3 (27.1)	92.8 (24.9)	95.8 (26.9)	91.2 (20.1)
Day 6, mean (SD)	*n* = 41	*n* = 38	*n* = 38	*n* = 43
Protein (g/kg)	3.0 (0.7)	3.2 (0.7)	3.6 (0.7)	3.6 (0.9)
Carbohydrate (g/kg)	10.4 (2.7)	11.2 (2.6)	11.2 (2.4)	10.9 (2.7)
Fat (g/kg)	3.9 (1.6)	4.4 (1.3)	4.3 (1.6)	3.9 (1.7)
Total energy (kcal/kg)	89.2 (26.6)	97.2 (24.2)	97.7 (25.3)	93.2 (28.1)

continued

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TABLE 11 Total nutrition intake during the first 7 days, 3 weeks, 4 weeks and by 34 weeks of gestational age for all infants randomised (*continued*)

	Inc-AA/Intralipid (*N* = 42)	Inc-AA/SMOFlipid (*N* = 42)	Imm-RDI/ Intralipid (*N* = 41)	Imm-RDI/ SMOFlipid (*N* = 43)
Day 7, mean (SD)	*n* = 42	*n* = 38	*n* = 38	*n* = 41
Protein (g/kg)	3.0 (0.7)	3.1 (0.6)	3.7 (0.6)	3.6 (0.8)
Carbohydrate (g/kg)	10.5 (2.5)	11.0 (2.4)	11.5 (2.1)	11.2 (2.5)
Fat (g/kg)	3.9 (1.6)	4.3 (1.6)	4.6 (1.7)	4.1 (1.8)
Total energy (kcal/kg)	89.2 (25.2)	94.8 (24.6)	102.1 (23.3)	96.0 (27.6)
First 3 weeks, mean (SD)	*n* = 42	*n* = 41	*n* = 40	*n* = 43
Protein (g)	61.4 (23.0)	58.8 (29.5)	70.7 (26.0)	71.2 (29.7)
Carbohydrate (g)	238.7 (90.1)	223.7 (109.8)	248.4 (90.4)	243.0 (103.6)
Fat (g)	105.5 (47.8)	99.2 (56.2)	109.4 (48.8)	104.1 (52.8)
Total energy (kcal)	2150 (875)	2023 (1057)	2261 (893)	2193 (1003)
First 4 weeks, mean (SD)	*n* = 42	*n* = 41	*n* = 40	*n* = 43
Protein (g)	85.5 (32.0)	80.4 (42.7)	96.3 (38.1)	98.1 (41.0)
Carbohydrate (g)	339.5 (120.8)	313.7 (158.2)	349.5 (131.0)	346.9 (144.7)
Fat (g)	156.1 (65.8)	143.9 (80.7)	159.0 (72.0)	155.2 (76.2)
Total energy (kcal)	3105 (1193)	2871 (1521)	3215 (1308)	3177 (1419)
Until 34 weeks postmenstrual age, mean (SD)	*n* = 42	*n* = 41	*n* = 40	*n* = 43
Protein (g)	143.7 (55.9)	117.6 (57.9)	133.5 (51.9)	144.6 (47.3)
Carbohydrate (g)	574.7 (200.8)	481.9 (228.1)	525.7 (196.9)	544.8 (185.9)
Fat (g)	272.0 (98.7)	225.0 (111.2)	237.2 (94.1)	249.3 (97.0)
Total energy (kcal)	5321 (1890)	4424 (2123)	4772 (1784)	5001 (1768)

a Day 1 is defined from birth to first 17.00.

TABLE 12 Nutritional intake over the first 2 weeks for all infants randomised[a]

	Inc-AA/Intralipid (*N* = 42)	Inc-AA/SMOFlipid (*N* = 42)	Imm-RDI/ Intralipid (*N* = 41)	Imm-RDI/ SMOFlipid (*N* = 43)
Had maternal expressed breast milk, *n* (%)	40 (95.2)	38 (90.5)	38 (92.7)	42 (97.7)
Cumulative maternal expressed breast milk (l), median (IQR)	0.76 (0.42–1.56); *n* = 40	0.94 (0.21–1.33); *n* = 38	0.68 (0.34–1.44); *n* = 38	0.59 (0.17–1.11); *n* = 42
Had formula milk, *n* (%)	12 (28.6)	11 (26.2)	16 (39.0)	13 (30.2)
Cumulative formula intake (l), median (IQR)	0.03 (0.01–0.29); *n* = 12	0.16 (0.04–1.10); *n* = 11	0.47 (0.03–1.00); *n* = 16	0.37 (0.02–1.56); *n* = 13
Had trial PN, *n* (%)	42 (100.0)	41 (97.6)	40 (97.6)	43 (100.0)
Time on trial PN (days), median (IQR)	11.0 (8.0–14.0); *n* = 42	12.0 (9.0–14.0); *n* = 41	11.0 (9.0–13.0); *n* = 40	12.0 (9.0–14.0); *n* = 43
Cumulative trial PN intake, median (IQR)				
Aqueous volume (l)	1.02 (0.74–1.29); *n* = 42	0.93 (0.70–1.30); *n* = 41	0.93 (0.81–1.18); *n* = 40	1.04 (0.81–1.36); *n* = 43
Lipid volume (l)	0.13 (0.09–0.17); *n* = 42	0.11 (0.08–0.17); *n* = 41	0.12 (0.10–0.15); *n* = 40	0.13 (0.09–0.18); *n* = 43
Protein (g)	22.4 (16.0–28.4); *n* = 42	20.9 (15.3–28.4); *n* = 41	25.9 (22.6–32.5); *n* = 40	29.5 (23.2–37.2); *n* = 43
Carbohydrate (g)	76.6 (57.7–96.1); *n* = 42	69.3 (53.1–96.6); *n* = 41	69.8 (61.1–87.8); *n* = 40	79.5 (62.7–100.4); *n* = 43
Fat (g)	23.6 (16.7–31.6); *n* = 42	21.0 (15.1–31.4); *n* = 41	21.4 (17.5–27.7); *n* = 40	24.6 (16.7–31.8); *n* = 43
Received non-trial PN, *n* (%)	3 (7.1)	1 (2.4)	1 (2.4)	3 (7.0)
Time on non-trial PN (days), median (IQR)	4.0 (3.5–4.0); *n* = 3	1.0 (1.0–1.0); *n* = 1	1.0 (1.0–1.0); *n* = 1	2.0 (1.5–5.0); *n* = 3
Cumulative non-trial PN intake, median (IQR)				
Aqueous volume (l)	0.46 (0.40–0.47); *n* = 3	0.02 (0.02–0.02); *n* = 1	0.07 (0.07–0.07); *n* = 1	0.37 (0.20–0.44); *n* = 3
Lipid volume (l)	0.02 (0.01–0.04); *n* = 3	0.00 (0.00–0.00); *n* = 1	0.00 (0.00–0.00); *n* = 1	0.03 (0.01–0.03); *n* = 3
Protein (g)	1.34 (1.17–1.54); *n* = 3	0.07 (0.07–0.07); *n* = 1	0.15 (0.15–0.15); *n* = 1	1.04 (0.57–1.21); *n* = 3
Carbohydrate (g)	42.57 (40.82–45.99); *n* = 3	2.47 (2.47–2.47); *n* = 1	3.35 (3.35–3.35); *n* = 1	29.75 (17.04–35.48); *n* = 3
Fat (g)	4.40 (2.20–7.90); *n* = 3	0.30 (0.30–0.30); *n* = 1	0.53 (0.53–0.53); *n* = 1	4.44 (2.61–5.85); *n* = 3
Cumulative non-trial and trial PN intake, median (IQR)				
Aqueous volume (l)	1.04 (0.81–1.29); *n* = 42	0.93 (0.70–10.30); *n* = 41	0.94 (0.81–1.18); *n* = 40	1.04 (0.81–1.36); *n* = 43
Lipid volume (l)	0.13 (0.09–0.17); *n* = 42	0.11 (0.08–0.17); *n* = 41	0.12 (0.10–0.15); *n* = 40	0.13 (0.09–0.18); *n* = 43
Protein (g)	22.4 (16.0–28.4); *n* = 42	20.9 (15.3–28.4); *n* = 41	25.9 (22.6–32.5); *n* = 40	29.5 (23.2–37.2); *n* = 43
Carbohydrate (g)	78.0 (61.8–96.1); *n* = 42	69.3 (53.1–96.6); *n* = 41	70.3 (61.1–87.8); *n* = 40	79.5 (62.7–100.4); *n* = 43
Fat (g)	23.6 (16.8–31.6); *n* = 42	21.0 (15.1–31.4); *n* = 41	21.4 (17.5–27.7); *n* = 40	24.6 (16.7–31.8); *n* = 43

a Data presented are medians (IQR, lower quartile, upper quartile).

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TABLE 13 Nutritional intake during the study period for all infants randomised[a]

	Inc-AA/Intralipid (*N* = 42)	Inc-AA/SMOFlipid (*N* = 42)	Imm-RDI/Intralipid (*N* = 41)	Imm-RDI/SMOFlipid (*N* = 43)
Glucose and insulin, median (IQR)				
Cumulative intravenous dextrose (g)	15.2 (5.39–50.2); *n* = 42	18.1 (7.20–54.0); *n* = 41	11.8 (5.23–45.7); *n* = 40	22.2 (7.99–55.5); *n* = 43
Received insulin, *n* (%)	11 (26.2)	12 (28.6)	5 (12.2)	10 (23.3)
Electrolytes, median (IQR)				
Additional sodium (mmol)	17.54 (8.96–24.4); *n* = 14	7.46 (5.12–18.4); *n* = 14	12.18 (9.01–42.7); *n* = 9	10.01 (5.44–22.5); *n* = 14
Additional potassium (mmol)	9.97 (6.79–11.73); *n* = 8	2.73 (1.47–4.88); *n* = 8	2.93 (1.73–8.24); *n* = 8	3.72 (1.64–7.14); *n* = 10
Received donor milk, *n* (%)	15 (35.7)	12 (28.6)	13 (31.7)	17 (39.5)
Cumulative donor milk (l, total volume per baby), median (IQR)	0.38 (0.08–1.07); *n* = 15	0.30 (0.02–0.47); *n* = 12	0.38 (0.05–1.10); *n* = 13	0.19 (0.03–0.36); *n* = 17
Received maternal breast milk, *n* (%)	41 (97.6)	38 (90.5)	38 (92.7)	43 (100.0)
Cumulative maternal expressed breast milk (l, total volume per baby), median (IQR)				
During trial PN phase	0.72 (0.45–0.88); *n* = 41	0.61 (0.43–0.81); *n* = 38	0.57 (0.30–0.81); *n* = 38	0.63 (0.26–0.89); *n* = 43
During non-trial PN phase	1.92 (0.38–4.82); *n* = 8	4.01 (1.83–5.08); *n* = 8	1.79 (0.44–4.51); *n* = 8	2.78 (0.70–4.50); *n* = 8
Over study period	8.05 (4.50–13.2); *n* = 41	7.16 (1.94–12.1); *n* = 38	6.74 (1.27–12.1); *n* = 38	7.61 (1.73–15.7); *n* = 43
Number of days having Fortifier, median (IQR)	13.0 (10.0–24.0); *n* = 23	23.0 (14.5–41.8); *n* = 12	14.0 (1.0–29.0); *n* = 17	27.0 (13.0–44.0); *n* = 17
Received formula milk, *n* (%)	30 (71.4)	23 (54.8)	29 (70.7)	29 (67.4)
Cumulative formula intake (l, total volume per baby), median (IQR)				
During trial PN phase	0.02 (0.01–0.13); *n* = 10	0.24 (0.02–0.52); *n* = 10	0.28 (0.04–0.60); *n* = 15	0.30 (0.04–0.39); *n* = 14
During non-trial PN phase	2.05 (0.44–3.60); *n* = 6	2.09 (0.00–4.35); *n* = 4	0.78 (0.00–2.12); *n* = 7	2.30 (0.95–5.06); *n* = 6
Over study period	5.86 (1.22–10.87); *n* = 30	6.39 (0.41–9.36); *n* = 23	8.44 (2.21–13.04); *n* = 29	6.70 (3.86–12.63); *n* = 29
Received trial PN, *n* (%)	42 (100.0)	41 (97.6)	40 (97.6)	43 (100.0)
Time on trial PN (days), median (IQR)	11.0 (8.00–16.8); *n* = 42	12.0 (9.00–17.0); *n* = 41	11.0 (9.75–13.2); *n* = 40	12.0 (9.00–17.0); *n* = 43
Cumulative trial PN intake				
Aqueous volume (l)	1.04 (0.77–1.56); *n* = 42	0.97 (0.71–1.39); *n* = 41	0.95 (0.81–1.33); *n* = 40	1.19 (0.86–1.56); *n* = 43
Lipid volume (l)	0.13 (0.09–0.19); *n* = 42	0.13 (0.08–0.18); *n* = 41	0.12 (0.10–0.16); *n* = 40	0.14 (0.10–0.19); *n* = 43
During trial PN phase, median (IQR)				
Protein (g)	22.8 (16.9–34.4); *n* = 42	21.6 (15.3–30.5); *n* = 41	26.7 (23.2–37.5); *n* = 40	33.5 (24.0–42.5); *n* = 43
Carbohydrate (g)	78.0 (57.7–116.0); *n* = 42	72.7 (55.0–104.8); *n* = 41	71.9 (62.6–101.3); *n* = 40	90.4 (64.8–114.6); *n* = 43
Fat (g)	23.9 (16.7–35.7); *n* = 42	23.6 (15.1–33.0); *n* = 41	21.6 (18.0–29.5); *n* = 40	25.0 (18.6–35.0); *n* = 43
Received non-trial PN, *n* (%)	10 (23.8)	8 (19.0)	8 (19.5)	10 (23.3)

TABLE 13 Nutritional intake during the study period for all infants randomised[a] (*continued*)

	Inc-AA/Intralipid (*N* = 42)	Inc-AA/SMOFlipid (*N* = 42)	Imm-RDI/Intralipid (*N* = 41)	Imm-RDI/SMOFlipid (*N* = 43)
Time on non-trial PN (days), median (IQR)	5.5 (3.25–19.8); *n* = 10	22.0 (14.50–28.5); *n* = 8	28.5 (9.50–58.5); *n* = 8	12.0 (3.00–15.8); *n* = 10
Cumulative non-trial PN intake, median (IQR)				
Aqueous volume (l)	0.47 (0.39–2.44); *n* = 10	2.12 (1.89–2.37); *n* = 8	2.91 (0.87–9.50); *n* = 8	1.23 (0.47–2.44); *n* = 10
Lipid volume (l)	0.06 (0.02–0.26); *n* = 10	0.33 (0.32–0.39); *n* = 8	0.38 (0.13–1.40); *n* = 8	0.16 (0.05–0.26); *n* = 10
During trial PN phase, median (IQR)				
Protein (g)	0.0 (0.0–0.00); *n* = 10	0.0 (0.0–0.00); *n* = 8	0.0 (0.0–0.04); *n* = 8	0.0 (0.0–0.07); *n* = 10
Carbohydrate (g)	0.0 (0.0–0.00); *n* = 10	0.0 (0.0–0.00); *n* = 8	0.0 (0.0–0.84); *n* = 8	0.0 (0.0–3.25); *n* = 10
Fat (g)	0.0 (0.0–0.00); *n* = 10	0.0 (0.0–0.00); *n* = 8	0.0 (0.0–0.13); *n* = 8	0.0 (0.0–0.59); *n* = 10
Over study period, median (IQR)				
Protein (g)	1.65 (1.34–6.54); *n* = 10	7.32 (5.60–7.66); *n* = 8	10.76 (4.60–31.95); *n* = 8	3.09 (0.39–4.28); *n* = 10
Carbohydrate (g)	49.4 (41.1–220.6); *n* = 10	222.7 (188.6–265.4); *n* = 8	338.7 (166.7–1136.4); *n* = 8	108.6 (11.3–146.3); *n* = 10
Fat (g)	10.5 (4.04–46.5); *n* = 10	58.8 (56.76–69.1); *n* = 8	66.0 (23.68–247.1); *n* = 8	28.3 (8.78–46.4); *n* = 10
Cumulative non-trial and trial PN intake, median (IQR)				
Aqueous volume (l)	1.12 (0.85–1.85); *n* = 42	1.30 (0.83–1.64); *n* = 41	1.06 (0.87–1.48); *n* = 40	1.38 (0.95–2.04); *n* = 43
Lipid volume (l)	0.17 (0.10–0.24); *n* = 42	0.16 (0.10–0.21); *n* = 41	0.13 (0.11–0.20); *n* = 40	0.18 (0.12–0.24); *n* = 43
During trial PN phase, median (IQR)				
Protein (g)	22.8 (16.9–34.4); *n* = 42	21.6 (15.3–30.5); *n* = 41	26.7 (23.2–37.5); *n* = 40	33.5 (24.0–42.5); *n* = 43
Carbohydrate (g)	78.0 (60.9–116.0); *n* = 42	72.7 (55.0–104.8); *n* = 41	71.9 (62.6–101.3); *n* = 40	90.4 (66.3–114.6); *n* = 43
Fat (g)	23.9 (16.8–35.7); *n* = 42	23.6 (15.1–33.0); *n* = 41	21.6 (18.0–29.5); *n* = 40	25.0 (18.6–35.0); *n* = 43
Over study period, median (IQR)				
Protein (g)	23.7 (18.0–36.4); *n* = 42	23.9 (17.8–31.6); *n* = 41	29.5 (24.1–38.4); *n* = 40	33.5 (25.2–42.5); *n* = 43
Carbohydrate (g)	87.8 (64.5–139.6); *n* = 42	94.8 (64.0–136.5); *n* = 41	81.0 (65.1–113.4); *n* = 40	101.4 (70.8–149.7); *n* = 43
Fat (g)	31.3 (18.8–43.6); *n* = 42	28.2 (19.0–37.4); *n* = 41	23.2 (19.3–36.4); *n* = 40	32.0 (22.6–44.1); *n* = 43
Cumulative nutritional intake from birth until 34 weeks postmenstrual age (includes PN and milk intake), median (IQR)				
Protein (g)	138.2 (109.9–170.7); *n* = 42	119.0 (91.1–161.0); *n* = 41	124.8 (103.1–175.3); *n* = 40	148.3 (122.1–170.7); *n* = 43
Carbohydrate (g)	565.6 (446.6–756.7); *n* = 42	557.9 (338.4–673.2); *n* = 41	508.0 (399.7–682.4); *n* = 40	590.4 (440.4–680.9); *n* = 43
Fat (g)	272.8 (217.2–346.5); *n* = 42	246.1 (157.6–306.1); *n* = 41	235.7 (182.7–295.7); *n* = 40	261.5 (201.9–313.0); *n* = 43

a Data presented are medians (IQR, lower quartile, upper quartile) for continuous variables and frequency (percentage) for categorical variables.

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TABLE 14 Nutritional intake over first 2 weeks for all infants completing MRI assessment[a]

	Inc-AA/Intralipid (*N* = 34)	Inc-AA/ SMOFlipid (*N* = 28)	Imm-RDI/Intralipid (*N* = 34)	Imm-RDI/SMOFlipid (*N* = 37)
Had maternal expressed breast milk, *n* (%)	32 (94.1)	27 (96.4)	33 (97.1)	36 (97.3)
Cumulative maternal expressed breast milk (l), median (IQR)	0.79 (0.60–1.63); *n* = 32	0.97 (0.54–1.62); *n* = 27	0.77 (0.42–1.54); *n* = 33	0.76 (0.29–1.14); *n* = 36
Had formula milk, *n* (%)	10 (29.4)	9 (32.1)	14 (41.2)	11 (29.7)
Cumulative formula intake (l), median (IQR)	0.03 (0.01–0.19); *n* = 10	0.26 (0.09–1.11); *n* = 9	0.35 (0.03–1.12); *n* = 14	0.37 (0.05–1.32); *n* = 11
Had trial PN, *n* (%)	34 (100.0)	28 (100.0)	34 (100.0)	37 (100.0)
Time on trial PN (days), median (IQR)	11.0 (8.00–14.0); *n* = 34	12.0 (9.00–14.0); *n* = 28	11.0 (9.25–13.0); *n* = 34	12.0 (9.00–14.0); *n* = 37
Cumulative trial PN intake, median (IQR)				
Aqueous volume (l)	1.02 (0.74–1.30); *n* = 34	1.03 (0.81–1.33); *n* = 28	0.94 (0.86–1.21); *n* = 34	1.07 (0.81–1.39); *n* = 37
Lipid volume (l)	0.13 (0.09–0.18); *n* = 34	0.13 (0.10–0.18); *n* = 28	0.12 (0.10–0.16); *n* = 34	0.13 (0.09–0.18); *n* = 37
Protein (g)	22.4 (16.0–28.9); *n* = 34	22.3 (17.6–29.1); *n* = 28	26.2 (23.9–33.2); *n* = 34	31.0 (23.0–37.9); *n* = 37
Carbohydrate (g)	76.6 (57.7–97.2); *n* = 34	79.1 (59.7–100.1); *n* = 28	70.6 (64.4–89.6); *n* = 34	83.7 (62.0–102.1); *n* = 37
Fat (g)	24.3 (17.0–32.2); *n* = 34	24.5 (18.1–32.2); *n* = 28	21.7 (18.1–28.4); *n* = 34	25.0 (17.1–32.9); *n* = 37
Received non-trial PN, *n* (%)	2 (5.9)	1 (3.6)	1 (2.9)	2 (5.4)
Time on non-trial PN (days)	4.0 (4.0–4.0); *n* = 2	1.0 (1.0–1.0); *n* = 1	1.0 (1.0–1.0); *n* = 1	5.0 (3.5–6.5); *n* = 2
Cumulative non-trial PN intake, median (IQR)				
Aqueous volume (l)	0.47 (0.47–0.48); *n* = 2	0.02 (0.02–0.02); *n* = 1	0.07 (0.07–0.07); *n* = 1	0.44 (0.41–0.47); *n* = 2
Lipid volume (l)	0.01 (0.01–0.02); *n* = 2	0.00 (0.00–0.00); *n* = 1	0.00 (0.00–0.00); *n* = 1	0.03 (0.03–0.04); *n* = 2
Protein (g)	1.37 (1.18–1.55); *n* = 2	0.07 (0.07–0.07); *n* = 1	0.15 (0.15–0.15); *n* = 1	1.21 (1.12–1.29); *n* = 2
Carbohydrate (g)	45.99 (44.28–47.69); *n* = 2	2.47 (2.47–2.47); *n* = 1	3.35 (3.35–3.35); *n* = 1	35.48 (32.62–38.34); *n* = 2
Fat (g)	2.20 (1.10–3.30); *n* = 2	0.30 (0.30–0.30); *n* = 1	0.53 (0.53–0.53); *n* = 1	5.85 (5.14–6.56); *n* = 2
Cumulative non-trial and trial PN intake, median (IQR)				
Aqueous volume (l)	1.04 (0.82–1.30); *n* = 34	1.03 (0.81–1.33); *n* = 28	0.95 (0.86–1.21); *n* = 34	1.07 (0.81–1.39); *n* = 37
Lipid volume (l)	0.13 (0.09–0.18); *n* = 34	0.13 (0.10–0.18); *n* = 28	0.12 (0.10–0.16); *n* = 34	0.13 (0.09–0.18); *n* = 37
Protein (g)	22.4 (16.0–28.9); *n* = 34	22.3 (17.6–29.1); *n* = 28	26.2 (23.9–33.2); *n* = 34	31.0 (23.0–37.9); *n* = 37
Carbohydrate (g)	78.0 (63.0–97.2); *n* = 34	79.1 (60.5–100.1); *n* = 28	71.7 (64.4–89.6); *n* = 34	83.7 (62.0–102.1); *n* = 37
Fat (g)	24.3 (17.0–32.2); *n* = 34	24.5 (18.4–32.2); *n* = 28	21.7 (18.1–28.4); *n* = 34	25.0 (17.1–32.9); *n* = 37

a Data presented are medians (IQR, lower quartile, upper quartile).

TABLE 15 Nutritional intake during the study period for all infants completing MRI assessment[a]

	Inc-AA/Intralipid (*N* = 34)	Inc-AA/SMOFlipid (*N* = 28)	Imm-RDI/Intralipid (*N* = 34)	Imm-RDI/SMOFlipid (*N* = 37)
Glucose and insulin, median (IQR)				
Cumulative intravenous dextrose (g), median (IQR)	9.27 (4.56–54.8); *n* = 34	23.64 (7.04–75.1); *n* = 28	11.81 (5.68–25.9); *n* = 34	22.20 (8.89–53.4); *n* = 37
Insulin (number of babies who received insulin), *n* (%)	7 (20.6)	6 (21.4)	4 (11.8)	7 (18.9)
Electrolytes, median (IQR)				
Additional sodium (mmol)	20.93 (11.81–34.2); *n* = 10	11.13 (5.00–22.6); *n* = 11	9.85 (8.87–13.5); *n* = 7	10.01 (5.44–22.5); *n* = 14
Additional potassium (mmol)	10.38 (6.45–12.29); *n* = 7	3.71 (1.62–5.58); *n* = 7	2.18 (1.46–5.00); *n* = 7	4.19 (1.60–7.85); *n* = 9
Received donor milk, *n* (%)	11 (32.4)	9 (32.1)	12 (35.3)	15 (40.5)
Cumulative donor milk (l, total volume per baby), median (IQR)	0.38 (0.08–1.07); *n* = 11	0.27 (0.02–0.44); *n* = 9	0.24 (0.04–1.15); *n* = 12	0.19 (0.03–0.84); *n* = 15
Received maternal expressed breast milk, *n* (%)	33 (97.1)	27 (96.4)	33 (97.1)	37 (100.0)
Cumulative maternal expressed breast milk (l), median (IQR)				
During trial PN phase	0.73 (0.57–0.88); *n* = 33	0.62 (0.45–0.83); *n* = 27	0.62 (0.32–0.82); *n* = 33	0.65 (0.36–0.90); *n* = 37
During non-trial PN phase	1.75 (0.33–4.46); *n* = 5	4.16 (2.86–5.13); *n* = 7	1.79 (0.50–3.16); *n* = 6	2.78 (0.70–4.50); *n* = 8
Over study period	8.46 (5.90–14.6); *n* = 33	7.86 (2.79–13.5); *n* = 27	5.97 (1.53–12.3); *n* = 33	8.86 (3.32–15.9); *n* = 37
Number of days having fortifier, median (IQR)	13.0 (10.0–21.0); *n* = 21	20.0 (16.0–36.0); *n* = 9	13.0 (1.0–28.2); *n* = 16	25.5 (13.0–45.0); *n* = 16
Received formula milk, *n* (%)	25 (73.5)	19 (67.9)	25 (73.5)	26 (70.3)
Cumulative formula intake (l), median (IQR)				
During trial PN phase	0.02 (0.00–0.16); *n* = 9	0.41 (0.13–0.53); *n* = 8	0.13 (0.04–0.66); *n* = 13	0.28 (0.05–0.38); *n* = 11
During non-trial PN phase	2.34 (1.76–4.02); *n* = 5	2.09 (0.00–4.35); *n* = 4	0.78 (0.00–3.45); *n* = 5	2.30 (0.95–5.06); *n* = 6
Over study period	2.81 (0.99–14.37); *n* = 25	8.04 (2.96–9.93); *n* = 19	8.44 (2.21–13.04); *n* = 25	7.26 (3.90–12.61); *n* = 26
Received trial PN (number of babies), *n* (%)	34 (100.0)	28 (100.0)	34 (100.0)	37 (100.0)
Time on trial PN (days), median (IQR)	11.0 (8.0–16.0); *n* = 34	12.5 (9.0–16.0); *n* = 28	11.0 (10.0–13.0); *n* = 34	13.0 (9.0–17.0); *n* = 37

continued

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TABLE 15 Nutritional intake during the study period for all infants completing MRI assessment[a] (*continued*)

	Inc-AA/Intralipid (*N* = 34)	Inc-AA/SMOFlipid (*N* = 28)	Imm-RDI/Intralipid (*N* = 34)	Imm-RDI/SMOFlipid (*N* = 37)
Cumulative trial PN intake, median (IQR)				
Aqueous volume (l)	1.04 (0.77–1.56); *n* = 34	1.06 (0.83–1.39); *n* = 28	0.96 (0.86–1.32); *n* = 34	1.19 (0.82–1.57); *n* = 37
Lipid volume (l)	0.14 (0.09–0.19); *n* = 34	0.13 (0.10–0.19); *n* = 28	0.12 (0.10–0.16); *n* = 34	0.14 (0.10–0.20); *n* = 37
During trial PN phase, median (IQR)				
Protein (g)	22.8 (16.9–34.4); *n* = 34	23.0 (18.2–30.6); *n* = 28	27.2 (23.9–36.9); *n* = 34	33.5 (23.5–42.5); *n* = 37
Carbohydrate (g)	78.0 (57.7–118.5); *n* = 34	81.6 (62.1–105.2); *n* = 28	73.4 (64.4–99.6); *n* = 34	90.4 (63.4–114.6); *n* = 37
Fat (g)	25.0 (17.0–35.7); *n* = 34	24.9 (18.1–33.9); *n* = 28	21.7 (19.1–28.4); *n* = 34	25.0 (19.0–35.6); *n* = 37
Received non-trial PN (number of babies), *n* (%)	6 (17.6)	7 (25.0)	6 (17.6)	9 (24.3)
Time on non-trial PN (days), median (IQR)	13.5 (4.0–27.5); *n* = 6	19.0 (13.0–26.0); *n* = 7	43.5 (25.8–69.5); *n* = 6	12.0 (3.0–16.0); *n* = 9
Cumulative non-trial PN intake, median (IQR)				
Aqueous volume (l)	1.77 (0.40–3.76); *n* = 6	2.13 (1.86–2.48); *n* = 7	6.26 (2.52–10.83); *n* = 6	1.24 (0.74–2.76); *n* = 9
Lipid volume (l)	0.18 (0.02–0.58); *n* = 6	0.33 (0.32–0.35); *n* = 7	0.90 (0.32–1.58); *n* = 6	0.17 (0.07–0.29); *n* = 9
During trial PN phase, median (IQR)				
Protein (g)	0.0 (0.0–0.00); *n* = 6	0.0 (0.0–0.00); *n* = 7	0.0 (0.0–0.12); *n* = 6	0.0 (0.0–0.00); *n* = 9
Carbohydrate (g)	0.0 (0.0–0.00); *n* = 6	0.0 (0.0–0.00); *n* = 7	0.0 (0.0–2.51); *n* = 6	0.0 (0.0–0.00); *n* = 9
Fat (g)	0.0 (0.0–0.0); *n* = 6	0.0 (0.0–0.0); *n* = 7	0.0 (0.0–0.4); *n* = 6	0.0 (0.0–0.0); *n* = 9
Over study period, median (IQR)				
Protein (g)	4.88 (1.44–12.63); *n* = 6	7.44 (4.66–7.69); *n* = 7	19.86 (6.68–37.40); *n* = 6	3.98 (1.07–4.28); *n* = 9
Carbohydrate (g)	159.4 (47.9–431.8); *n* = 6	242.2 (186.9–267.0); *n* = 7	701.5 (239.8–1339.7); *n* = 6	139.6 (30.7–147.6); *n* = 9
Fat (g)	31.2 (2.96–101.7); *n* = 6	58.2 (56.47–62.2); *n* = 7	159.0 (55.66–278.5); *n* = 6	30.4 (13.16–50.8); *n* = 9
Cumulative non-trial and trial PN intake, median (IQR)				
Aqueous volume (l)	1.11 (0.85–1.85); *n* = 34	1.34 (0.96–1.80); *n* = 28	1.12 (0.89–1.43); *n* = 34	1.53 (0.97–2.05); *n* = 37
Lipid volume (l)	0.17 (0.10–0.25); *n* = 34	0.18 (0.13–0.25); *n* = 28	0.13 (0.11–0.20); *n* = 34	0.18 (0.13–0.25); *n* = 37

TABLE 15 Nutritional intake during the study period for all infants completing MRI assessment[a] (*continued*)

	Inc-AA/Intralipid (*N* = 34)	Inc-AA/SMOFlipid (*N* = 28)	Imm-RDI/Intralipid (*N* = 34)	Imm-RDI/SMOFlipid (*N* = 37)
During trial PN phase, median (IQR)				
Protein (g)	22.8 (16.9–34.4); *n* = 34	23.0 (18.2–30.6); *n* = 28	27.2 (23.9–36.9); *n* = 34	33.5 (23.5–42.5); *n* = 37
Carbohydrate (g)	78.0 (61.2–118.5); *n* = 34	81.6 (62.1–105.2); *n* = 28	73.4 (64.4–99.6); *n* = 34	92.7 (66.4–114.6); *n* = 37
Fat (g)	25.0 (17.0–35.7); *n* = 34	24.9 (18.4–33.9); *n* = 28	21.7 (19.1–28.4); *n* = 34	25.0 (19.0–35.6); *n* = 37
Over study period, median (IQR)				
Protein (g)	23.7 (18.0–36.5); *n* = 34	26.1 (20.5–31.6); *n* = 28	30.3 (24.9–37.9); *n* = 34	34.4 (25.8–42.5); *n* = 37
Carbohydrate (g)	85.5 (64.5–139.6); *n* = 34	101.9 (72.2–145.1); *n* = 28	83.5 (67.2–110.6); *n* = 34	112.0 (71.9–152.7); *n* = 37
Fat (g)	30.3 (18.8–45.5); *n* = 34	31.8 (23.5–46.0); *n* = 28	23.6 (20.2–35.7); *n* = 34	32.9 (22.8–45.6); *n* = 37
Cumulative nutritional intake from birth until 34 weeks postmenstrual age (includes PN and milk intake), median (IQR)				
Protein (g)	138.2 (115.8–185.8); *n* = 34	144.3 (115.5–165.4); *n* = 28	124.2 (104.5–176.6); *n* = 34	154.7 (133.1–171.7); *n* = 37
Carbohydrate (g)	565.6 (489.3–767.7); *n* = 34	596.2 (476.4–703.0); *n* = 28	508.0 (402.8–684.2); *n* = 34	607.7 (508.9–690.0); *n* = 37
Fat (g)	284.3 (235.7–370.6); *n* = 34	282.2 (233.8–320.1); *n* = 28	245.2 (185.1–295.2); *n* = 34	279.1 (213.3–323.2); *n* = 37

a Data presented are medians (IQR, lower quartile, upper quartile) for continuous variables and frequency (percentage) for categorical variables.

There were no significant differences between the groups in the proportion of infants with abnormal biochemical indices, namely serum glucose, worst base deficit in the previous 24 hours, total serum bilirubin, conjugated bilirubin, serum cholesterol, serum triglycerides, serum sodium, serum potassium, serum phosphate, serum calcium, serum creatinine and alanine transaminase. *Tables 16–18* show infant safety data, with *Tables 16* and *18* including data for all infants randomised and *Table 17* showing safety data for only those infants who completed the MR scan.

However, there were significantly more infants with blood urea nitrogen levels > 7 mmol/l (50% and 47.6% in the groups Inc-AA/Intralipid and Inc-AA/SMOFlipid, respectively, vs. 70.7% and 79.1% in Imm-RDI/Intralipid and Imm-RDI/SMOFlipid, respectively; $p < 0.01$) and > 10 mmol/l (14.3% and 21.4% in the groups Inc-AA/Intralipid and Inc-AA/SMOFlipid respectively, vs. 43.9% and 53.5% in Imm-RDI/Intralipid and Imm-RDI/SMOFlipid, respectively; $p < 0.01$).

There was a significant interaction ($p = 0.05$) between the two interventions for non-adipose mass (*Figure 7*).

In relation to primary outcome measures, there were no significant differences in the quantity of non-AT mass between the groups randomised to Inc-AA and the group randomised to the RDI of amino acids (adjusted mean difference 1 g, 95% CI –108 g to 111 g; $p = 0.98$). For the lipid composition intervention, there was no significant difference in IHCL content between the group randomised to receive 20% Intralipid and the group randomised to receive 20% SMOFlipid (adjusted geometric mean ratio of lipid to water 1.1, 95% CI 0.8 to 1.6; $p = 0.58$). Primary and secondary outcomes for all infants randomised are shown in *Table 19*. AT volumes are shown in *Table 20*.

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TABLE 16 Safety data: summary of laboratory AEs by treatment for all infants randomised[a]

SpAE	Inc-AA/Intralipid, (*N* = 42)	Inc-AA/SMOFlipid (*N* = 42)	Imm-RDI/ Intralipid (*N* = 41)	Imm-RDI/ SMOFlipid (*N* = 43)	*p*-value for amino acid	*p*-value for lipid
Glucose, *n* (%)						
Low (< 2.6 mmol/l)	12 (28.6)	19 (45.2)	15 (36.6)	16 (37.2)	1.0	0.32
High (> 15 mmol/l)	8 (19.0)	11 (26.2)	3 (7.3)	7 (16.3)	0.10	0.25
Worst base deficit in previous 24 hours, *n* (%)						
> 15 mmol/l	5 (11.9)	3 (7.1)	5 (12.2)	8 (18.6)	0.35	1.0
Total serum bilirubin, *n* (%)						
> 150 µmol/l	30 (71.4)	27 (64.3)	26 (63.4)	31 (72.1)	1.0	1.0
Conjugated bilirubin, *n* (%)						
> 40 µmol/l	6 (14.3)	4 (9.5)	3 (7.3)	4 (9.3)	0.61	0.96
Cholesterol, *n* (%)						
> 6 mmol/l	0 (0)	2 (4.8)	1 (2.4)	0 (0)	0.56	0.57
> 10 mmol/l	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Triglycerides, *n* (%)						
> 2.5 mmol/l	15 (35.7)	13 (31.0)	14 (34.1)	12 (27.9)	0.87	0.55
> 5 mmol/l	2 (4.8)	2 (4.8)	1 (2.4)	2 (4.7)	0.70	0.72
Sodium, *n* (%)						
Low (< 131 mmol/l)	9 (21.4)	7 (16.7)	10 (24.4)	9 (20.9)	0.70	0.65
High (> 150 mmol/l)	5 (11.9)	10 (23.8)	4 (9.8)	5 (11.6)	0.27	0.3
Potassium, *n* (%)						
Low (< 3.2 mmol/l)	5 (11.9)	6 (14.3)	11 (26.8)	7 (16.3)	0.22	0.63
High (> 9 mmol/l)	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Phosphate, *n* (%)						
Low (< 1.5 mmol/l)	17 (40.5)	12 (28.6)	14 (34.1)	19 (44.2)	0.63	1.0
High (> 3 mmol/l)	4 (9.5)	5 (11.9)	5 (12.2)	4 (9.3)	1.0	1.0
Calcium, *n* (%)						
Low (< 1 mmol/l)	0 (0)	1 (2.4)	0 (0)	2 (4.7)	0.56	0.08
High (> 3 mmol/l)	0 (0)	0 (0)	3 (7.3)	2 (4.7)	0.02	0.63
Urea, *n* (%)						
Low (< 1.5 mmol/l)	13 (31.0)	11 (26.2)	5 (12.2)	8 (18.6)	0.15	0.55
High (> 7 mmol/l)	21 (50.0)	20 (47.6)	29 (70.7)	34 (79.1)	< 0.01	0.78
High (> 10 mmol/l)	6 (14.3)	9 (21.4)	18 (43.9)	23 (53.5)	< 0.01	0.30
Creatinine, *n* (%)						
> 170 µmol/l	0 (0)	0 (0)	0 (0)	3 (7.0)	0.08	0.08
ALT, *n* (%)						
> 60 IU/l	5 (11.9)	2 (4.8)	4 (9.8)	4 (9.3)	1.0	0.56

TABLE 16 Safety data: summary of laboratory AEs by treatment for all infants randomised[a] (*continued*)

SpAE	Inc-AA/Intralipid, (*N* = 42)	Inc-AA/SMOFlipid (*N* = 42)	Imm-RDI/ Intralipid (*N* = 41)	Imm-RDI/ SMOFlipid (*N* = 43)	*p*-value for amino acid	*p*-value for lipid
Zinc, *n* (%)						
< 8 µmol/l	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Copper, *n* (%)						
< 2 µmol/l	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Manganese, *n* (%)						
> 30 nmol/l	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Aluminium, *n* (%)						
> 0.4 µmol/l	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Selenium, *n* (%)						
< 20 µg/l	0 (0)	1 (2.4)	0 (0)	0 (0)	0.32	0.32

ALT, alanine transferase; NA, not applicable.
a Biochemical indices were measured while the infant was on PN as part of routine monitoring whether on trial or non-trial PN.

TABLE 17 Safety data: summary of laboratory AEs by treatment for all infants completing MRI assessment

SpAE	Inc-AA/Intralipid, (*N* = 34)	Inc-AA/SMOFlipid (*N* = 28)	Imm-RDI/ Intralipid (*N* = 34)	Imm-RDI/ SMOFlipid (*N* = 37)	*p*-value for amino acid	*p*-value for lipid
Glucose, *n* (%)						
Low (< 2.6 mmol/l)	8 (23.5)	12 (42.9)	13 (38.2)	14 (37.8)	1.0	0.32
High (> 15 mmol/l)	6 (17.6)	5 (17.9)	3 (8.8)	5 (13.5)	0.1	0.25
Worst base deficit in previous 24 hours, *n* (%)						
> 15 mmol/l	2 (5.9)	0 (0.0)	2 (5.9)	6 (16.2)	0.35	1.0
Total serum bilirubin, *n* (%)						
> 150 µmol/l	24 (70.6)	21 (75.0)	23 (67.6)	28 (75.7)	1.0	1.0
Conjugated bilirubin, *n* (%)						
> 40 µmol/l	4 (11.8)	3 (10.7)	2 (5.9)	3 (8.1)	0.61	0.96
Cholesterol, *n* (%)						
> 6 mmol/l	0 (0.0)	1 (3.6)	1 (2.9)	0 (0.0)	0.56	0.57
> 10 mmol/l	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Triglycerides, *n* (%)						
> 2.5 mmol/l	10 (29.4)	7 (25.0)	11 (32.4)	10 (27.0)	0.87	0.55
> 5 mmol/l	2 (5.9)	0 (0.0)	1 (2.9)	2 (5.4)	0.7	0.72

continued

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TABLE 17 Safety data: summary of laboratory AEs by treatment for all infants completing MRI assessment (*continued*)

SpAE	Inc-AA/Intralipid, (*N* = 34)	Inc-AA/SMOFlipid (*N* = 28)	Imm-RDI/ Intralipid (*N* = 34)	Imm-RDI/ SMOFlipid (*N* = 37)	*p*-value for amino acid	*p*-value for lipid
Sodium, *n* (%)						
Low (< 131 mmol/l)	7 (20.6)	3 (10.7)	9 (26.5)	7 (18.9)	0.7	0.65
High (> 150 mmol/l)	3 (8.8)	3 (10.7)	4 (11.8)	4 (10.8)	0.27	0.3
Potassium, *n* (%)						
Low (< 3.2 mmol/l)	2 (5.9)	4 (14.3)	9 (26.5)	6 (16.2)	0.22	0.63
High (> 9 mmol/l)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Phosphate, *n* (%)						
Low (< 1.5 mmol/l)	12 (35.3)	8 (28.6)	13 (38.2)	17 (45.9)	0.63	1.0
High (> 3 mmol/l)	4 (11.8)	3 (10.7)	4 (11.8)	3 (8.1)	1.0	1.0
Calcium, *n* (%)						
Low (< 1 mmol/l)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.4)	0.56	0.08
High (> 3 mmol/l)	0 (0.0)	0 (0.0)	3 (8.8)	1 (2.7)	0.02	0.63
Urea, *n* (%)						
Low (< 1.5 mmol/l)	10 (29.4)	10 (35.7)	5 (14.7)	7 (18.9)	0.15	0.55
High (> 7 mmol/l)	14 (41.2)	14 (50.0)	25 (73.5)	29 (78.4)	< 0.01	0.78
High (> 10 mmol/l)	1 (2.9)	4 (14.3)	16 (47.1)	18 (48.6)	< 0.01	0.3
Creatinine, *n* (%)						
> 170 µmol/l	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.4)	0.08	0.08
ALT, *n* (%)						
> 60 IU/l	3 (8.8)	2 (7.1)	3 (8.8)	2 (5.4)	1.0	0.56
Zinc, *n* (%)						
< 8 µmol/l	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Copper, *n* (%)						
< 2 µmol/l	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Manganese, *n* (%)						
> 30 nmol/l	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Aluminium, *n* (%)						
> 0.4 µmol/l	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Selenium, *n* (%)						
< 20 µg/l	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)	0.32	0.32

ALT, alanine transferase; NA, not applicable.

TABLE 18 Safety data: summary of SAEs by treatment[a]

Variable	Inc-AA/Intralipid (*N* = 42)	Inc-AA/SMOFlipid (*N* = 42)	Imm-RDI/Intralipid (*N* = 41)	Imm-RDI/SMOFlipid (*N* = 43)
Number of infants who experience a SAE, *n* (%)	6 (14.3)	12 (28.6)	8 (19.5)	9 (20.9)
SAE classification, *n* (%)[b]				
Death, *n* (%)	3 (7.1)	7 (16.7)	3 (7.3)	3 (7.0)
Life-threatening, *n* (%)	3 (7.1)	3 (7.1)	4 (9.8)	4 (9.3)
Prolongation of existing inpatient hospitalisation, *n* (%)	2 (4.8)	2 (4.8)	1 (2.4)	3 (7.0)
Persistent or significant disability or incapacity, *n* (%)	0 (0.0)	1 (2.4)	0 (0.0)	1 (2.3)
Sepsis (diagnosis on SAE form), *n* (%)[c]	2 (4.8)	6 (14.3)	1 (2.4)	1 (2.3)
Necrotising enterocolitis, *n* (%)[c]	3 (7.1)	4 (9.5)	1 (2.4)	4 (9.3)

a All SAEs were classified by local investigators on the SAE reporting form.
b One infant may have more than one SAE.
c Growth of known pathogen on culture; data presented are number of infants who had at least one positive result.

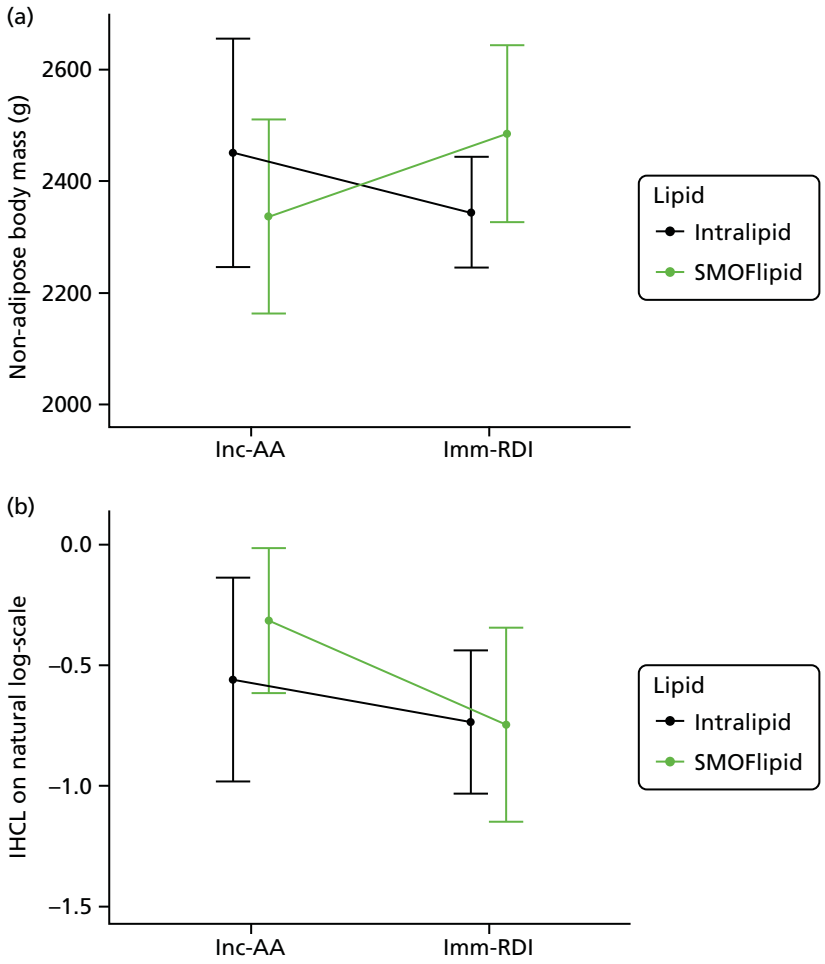

FIGURE 7 Means (95% CIs) of Inc-AA and Imm-RDI in two lipid subgroups for (a) non-adipose body mass; and (b) IHCL content on a log-scale.

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TABLE 19 Baseline characteristics and trial outcomes (all infants completing primary outcome assessments)

	Inc-AA/Intralipid ($N = 34$)	Inc-AA/SMOFlipid ($N = 28$)	Imm-RDI/Intralipid ($N = 34$)	Imm-RDI/SMOFlipid ($N = 37$)	Adjusted mean difference (Imm-RDI minus Inc-AA)[a]	Adjusted mean difference (SMOFlipid minus Intralipid)[a]	Interaction (p-value)
Gestational age (weeks), mean (95% CI)	28.0 (27.3 to 28.6)	28.0 (27.2 to 28.9)	28.4 (27.7 to 29.2)	27.7 (27.1 to 28.4)	–	–	–
Birthweight (g), mean (95% CI)	1064 (962 to 1166)	1103 (979 to 1226)	1090 (993 to 1186)	1059 (962 to 1155)	–	–	–
Sex, male (%), mean (95% CI)	58.8 (40.7 to 75.4)	64.3 (44.1 to 81.4)	50.0 (33.4 to 67.6)	51.4 (34.4 to 67.5)	–	–	–
Age (weeks) at scan, mean (95% CI)	12.5 (11.3 to 13.7)	12.4 (10.9 to 14.0)	12.1 (10.8 to 13.4)	13.3 (12.0 to 14.5)	–	–	–
Primary outcomes							
Non-adipose mass (g), mean (95% CI)	2450 (2246 to 2655)	2337 (2164 to 2510)	2344 (2244 to 2444)	2485 (2327 to 2643)	1 (–108 to 111); $p = 0.98$	–41 (–150 to 68); $p = 0.46$	216 (0 to 432); $p = 0.05$
IHCL, mean (95% CI)[b]	0.6 (0.4 to 0.9); $n = 34$	0.7 (0.5 to 1.0); $n = 28$	0.5 (0.4 to 0.6); $n = 34$	0.5 (0.3 to 0.7); $n = 36$	0.7 (0.5 to 1.1); $n = 132$	1.1 (0.8 to 1.6); $n = 132$	0.8 (0.4 to 1.7); $n = 132$
					$p = 0.11$	$p = 0.58$	$p = 0.53$
Secondary outcomes							
Total cerebral volume (cm^3), mean (95% CI)[c]	468 (419 to 518); $n = 13$	480 (425 to 534); $n = 10$	468 (414 to 523); $n = 11$	511 (440 to 583); $n = 15$	15 (–42 to 71); $n = 49$	24 (–32 to 80); $n = 49$	–26 (–142 to 90); $n = 49$
					$p = 0.61$	$p = 0.40$	$p = 0.66$
Whole-brain volume (cm^3), mean (95% CI)[d]	339 (304 to 373); $n = 13$	352 (319 to 385); $n = 10$	344 (296 to 393); $n = 11$	365 (321 to 410); $n = 15$	9 (–29 to 47); $n = 49$	14 (–24 to 52); $n = 49$	–29 (–107 to 49); $n = 49$
					$p = 0.64$	$p = 0.47$	$p = 0.46$
Posterior fossa volume (cm^3), mean (95% CI)[e]	30 (26 to 33); $n = 13$	31 (28 to 34); $n = 10$	30 (27 to 34); $n = 11$	35 (29 to 38); $n = 15$	1.44 (–1.99 to 4.87); $n = 49$	2 (–2 to 5); $n = 49$	–2 (–9 to 5); $n = 49$
					$p = 0.41$	$p = 0.35$	$p = 0.64$

	Inc-AA/Intralipid ($N = 34$)	Inc-AA/SMOFlipid ($N = 28$)	Imm-RDI/Intralipid ($N = 34$)	Imm-RDI/SMOFlipid ($N = 37$)	Adjusted mean difference (Imm-RDI minus Inc-AA)[a]	Adjusted mean difference (SMOFlipid minus Intralipid)[a]	Interaction (p-value)
QUICKI, mean (95% CI)[52]	0.18 (0.17 to 0.19); $n = 11$	0.19 (0.18 to 0.20); $n = 6$	0.19 (0.18 to 0.20); $n = 11$	0.18 (0.17 to 0.20); $n = 11$	0.01 (0 to 0.02); $n = 39$ $p = 0.20$	0.01 (–0.01 to 0.02); $n = 39$ $p = 0.28$	–0.01 (–0.04 to 0.02); $n = 39$ $p = 0.46$
Weight (g), mean (95% CI)	3060 (2780 to 3340)	2924 (2686 to 3162)	2932 (2780 to 3085)	3151 (2934 to 3368)	17 (–136 to 170); $p = 0.83$	–35 (–187 to 117); $p = 0.65$	293 (–8 to 593); $p = 0.06$
Length (cm), mean (95% CI)	47.7 (46.4 to 49.0)	48.0 (46.6 to 49.4)	48.2 (47.4 to 49.0)	49.1 (47.8 to 50.3)	0.5 (–0.3 to 1.3); $p = 0.20$	0.2 (–0.6 to 1.0); $p = 0.56$	0.5 (–1.1 to 2.1); $p = 0.56$
Head circumference (cm), mean (95% CI)	36.0 (34.9 to 37.1)	35.3 (34.6 to 36.0)	34.8 (34.3 to 35.3)	35.2 (34.5 to 35.9)	–0.8 (–1.5 to –0.1); $p = 0.02$	–0.2 (–0.9 to 0.5); $p = 0.56$	1.1 (–0.2 to 2.5); $p = 0.09$
Superficial subcutaneous AT (g), mean (95% CI)	515 (437 to 593)	495 (431 to 559)	493 (431 to 554)	564 (499 to 629)	12 (–44 to 68); $p = 0.67$	9 (–46 to 64); $p = 0.75$	73 (–38 to 183); $p = 0.20$
Internal AT (g), mean (95% CI)	67.2 (55.5 to 79.0)	65.0 (52.4 to 77.5)	69.1 (57.2 to 81.0)	71.2 (59.8 to 82.5)	2.5 (–7.5 to 12.6); $p = 0.62$	–3.4 (–13.4 to 6.6); $p = 0.50$	0.1 (–19.9 to 20.1); $p = 0.99$
Deep subcutaneous abdominal AT (g), mean (95% CI)	14.2 (11.0 to 17.3)	13.0 (10.7 to 15.2)	14.9 (12.3 to 17.5)	17.8 (14.8 to 20.7)	2.0 (–0.5 to 4.4); $p = 0.11$	0.4 (–2.0 to 2.8); $p = 0.74$	3.5 (–1.3 to 8.3); $p = 0.15$
Internal abdominal AT (g), mean (95% CI)	14.8 (12.2 to 17.3)	14.1 (11.0 to 17.2)	15.9 (12.8 to 18.9)	16.5 (13.6 to 19.3)	1.4 (–1.2 to 4.1); $p = 0.28$	–0.8 (–3.4 to 1.8); $p = 0.56$	0.5 (–4.8 to 5.7); $p = 0.86$
Superficial subcutaneous AT tissue (g), mean (95% CI)	87.0 (72.4 to 101.6)	84.5 (72.8 to 96.2)	85.2 (73.8 to 96.5)	102.6 (87.2 to 118.1)	5.2 (–6.5 to 17.0); $p = 0.38$	5.0 (–6.7 to 16.6); $p = 0.40$	16.3 (–7.0 to 39.6); $p = 0.17$
Total AT (g), mean (95% CI)	610 (518 to 702)	587 (509 to 664)	589 (514 to 663)	666 (589 to 743)	16 (–51 to 82); $p = 0.64$	6 (–60 to 72); $p = 0.85$	77 (–55 to 208); $p = 0.25$
Total AT as a percentage of body weight (%), mean (95% CI)	19.4 (17.9 to 20.9)	19.7 (18.4 to 21.0)	19.6 (17.8 to 21.4)	20.8 (19.4 to 22.3)	0 (–0.01 to 0.02); $p = 0.56$	0.01 (–0.01 to 0.02); $p = 0.45$	0.01 (–0.02 to 0.03); $p = 0.72$

continued

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TABLE 19 Baseline characteristics and trial outcomes (all infants completing primary outcome assessments) (*continued*)

	Inc-AA/Intralipid (*N* = 34)	Inc-AA/SMOFlipid (*N* = 28)	Imm-RDI/Intralipid (*N* = 34)	Imm-RDI/SMOFlipid (*N* = 37)	Adjusted mean difference (Imm-RDI minus Inc-AA)[a]	Adjusted mean difference (SMOFlipid minus Intralipid)[a]	Interaction (*p*-value)
Safety outcomes[f]							
Triglycerides > 2.5 mmol/l (%), mean (95% CI)[g]	29.4 (15.1 to 47.5)	25.0 (10.7, 44.9)	32.4 (17.4 to 50.5)	27.0 (13.8 to 44.1)	1.15 (0.48 to 2.74) $p = 0.76$	0.68 (0.28 to 1.62) $p = 0.38$	0.71 (0.12 to 4.06) $p = 0.70$
Total serum bilirubin > 150 µmol/l (%), mean (95% CI)[g]	70.6 (52.5 to 84.9)	75.0 (55.1 to 89.3)	67.6 (49.5 to 82.6)	75.7 (58.8 to 88.2)	0.92 (0.41 to 2.04) $p = 0.83$	1.32 (0.59 to 2.94) $p = 0.50$	1.29 (0.26 to 6.47) $p = 0.75$
Conjugated bilirubin > 40 µmol/l (%), mean (95% CI)[g]	11.8 (3.3 to 27.5)	10.7 (2.3 to 28.2)	5.9 (0.7 to 19.7)	8.1 (1.7 to 21.9)	0.47 (0.12 to 1.85) $p = 0.28$	0.93 (0.24 to 3.54) $p = 0.92$	1.65 (0.11 to 25.34) $p = 0.72$
ALT > 60 IU/l (%), mean (95% CI)[g]	8.8 (1.9 to 23.7)	7.1 (0.9 to 23.5)	8.8 (1.9 to 23.7)	5.4 (0.7 to 18.2)	0.99 (0.22 to 4.41) $p = 0.99$	0.45 (0.09 to 2.12) $p = 0.31$	0.59 (0.03 to 12.69) $p = 0.74$

ALT, alanine transferase.
a Adjusted for: age at MRI, sex, gestational age, birthweight and centre; body mass components are derived from body mass volumes.
b Log-transformation was used in the regression model with the results transformed back from the log-scale.
c Total of basal ganglia, thalami (deep grey matter), cerebrospinal fluid, grey matter, white matter and lateral ventricles volumes.
d Total of basal ganglia, thalami (deep grey matter), grey matter and white matter.
e Total of cerebellum and brainstem volumes.
f Percentages of babies.
g Logistic regression was used for modelling and odds ratios are reported.

TABLE 20 Adipose tissue compartments in litres for all infants completing MRI assessment

	Inc-AA/20% Intralipid ($n = 34$)	Inc-AA/20% SMOFlipid ($n = 28$)	Imm-RDI/20% Intralipid ($n = 34$)	Imm-RDI/20% SMOFlipid ($n = 37$)	Adjusted mean difference (Imm-RDI – Inc-AA),[a] *p*-value	Adjusted mean difference (20% SMOFlipid – 20% Intralipid),[a] *p*-value	Interaction, *p*-value
Total internal AT (l) mean (95% CI)	0.07 (0.06 to 0.09)	0.07 (0.06 to 0.09)	0.08 (0.06 to 0.09)	0.08 (0.07 to 0.09)	0 (–0.01 to 0.01); $p = 0.62$	0 (–0.01 to 0.01); $p = 0.50$	0 (–0.02 to 0.02); $p = 0.99$
Superficial AT (l) mean (95% CI)	0.57 (0.49 to 0.66)	0.55 (0.48 to 0.62)	0.55 (0.48 to 0.62)	0.63 (0.55 to 0.7)	0.01 (–0.05 to 0.08); $p = 0.67$	0.01 (–0.05 to 0.07); $p = 0.75$	0.08 (–0.04 to 0.2); $p = 0.20$
Deep subcutaneous AT (l) mean (95% CI)	0.03 (0.03 to 0.04)	0.03 (0.02 to 0.03)	0.03 (0.03 to 0.03)	0.03 (0.03 to 0.04)	0 (0 to 0); $p = 0.55$	0 (0 to 0); $p = 0.71$	0 (0 to 0.01); $p = 0.24$
Internal abdominal AT (l) mean (95% CI)	0.02 (0.01 to 0.02)	0.02 (0.01 to 0.02)	0.02 (0.01 to 0.02)	0.02 (0.02 to 0.02)	0 (0 to 0); $p = 0.28$	0 (0 to 0); $p = 0.55$	0 (–0.01 to 0.01); $p = 0.86$
Superficial subcutaneous abdominal AT (l) mean (95% CI)	0.1 (0.08 to 0.11)	0.09 (0.08 to 0.11)	0.09 (0.08 to 0.11)	0.11 (0.1 to 0.13)	0.01 (–0.01 to 0.02); $p = 0.38$	0.01 (–0.01 to 0.02); $p = 0.40$	0.02 (–0.01 to 0.04); $p = 0.17$
Deep subcutaneous abdominal AT (l) mean (95% CI)	0.02 (0.01 to 0.02)	0.01 (0.01 to 0.02)	0.02 (0.01 to 0.02)	0.02 (0.02 to 0.02)	0 (0 to 0); $p = 0.11$	0 (0 to 0); $p = 0.74$	0 (0 to 0.01); $p = 0.15$
Total AT (l)	0.68 (0.58 to 0.78)	0.65 (0.57 to 0.74)	0.65 (0.57 to 0.74)	0.74 (0.65 to 0.83)	0.02 (–0.06 to 0.09); $p = 0.64$	0.01 (–0.07 to 0.08); $p = 0.85$	0.09 (–0.06 to 0.23); $p = 0.25$

a Adjusted for: age at scan, sex, gestational age, birthweight and centre.

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There were no significant differences in secondary outcome measures of the quantity and distribution of AT, measure of insulin sensitivity (as measured by the QUICKI), total cerebral volume, whole-brain volume, weight and length at term age equivalent. There was, however, a significant difference in the mean head circumference at term age equivalent between the group randomised to receive Inc-AA and that randomised to receive the Imm-RDI (adjusted mean difference –0.8 cm, 95% CI –1.5 to –0.1 cm; $p = 0.02$).

In a secondary analysis, after adjusting for covariates, there were no significant differences in primary outcomes (*Tables 21* and *22*).

TABLE 21 Summary of the covariates for secondary analysis

Covariates	Inc-AA/Intralipid ($N = 34$)	Inc-AA/SMOFlipid ($N = 28$)	RDI/Intralipid ($N = 34$)	RDI/SMOFlipid ($N = 37$)
Proportion of level 1 care, median (IQR)	0.11(0.07–0.21)	0.11 (0.06–0.35)	0.12 (0.08–0.31)	0.16 (0.07–0.32)
Proportion of level 2 care, median (IQR)	0.42 (0.21–0.59)	0.30 (0.20–0.46)	0.29 (0.20–0.44)	0.31 (0.21–0.42)
Proportion of MEBM in all milk intake, median (IQR)	0.80 (0.44–1.00); $n = 33$	0.95 (0.28–1.00); $n = 27$	0.65 (0.10–0.99); $n = 33$	0.70 (0.26–1.00); $n = 37$
Trial-PN phase protein intake (g), median (IQR)	31.5 (24.2–46.2)	34.4 (27.8–44.5)	42.8 (36.1–54.1)	48.5 (36.2–63.9)
Trial-PN phase carbohydrate intake (g), median (IQR)	124.6 (98.5–178.7)	139.6 (110.8–173.2)	129.9 (109.6–158.9)	148.2 (111.8–182.6)
Trial-PN phase fat intake (g), median (IQR)	52.8 (35.5–68.6)	51.6 (42.7–68.6)	51.8 (38.1–59.5)	53.1 (38.2–70.2)
Post-trial-PN phase protein intake (g), median (IQR)	213.0 (168.7–449.4)	213.4 (154.0–302.2)	234.5 (155.3–335.4)	257.4 (187.3–365.2)
Post-trial-PN phase carbohydrate intake (g), median (IQR)	969.0 (699.6–1786.1)	867.7 (643.5–1196.1)	1042.9 (644.8–1390.7)	1080.4 (696.3–1531.5)
Post-trial-PN phase fat intake (g), median (IQR)	479.8 (375.0–942.3)	434.8 (329.5–584.4)	515.9 (346.9–613.8)	550.5 (374.9–779.6)

MEBM, maternal expressed breast milk.

TABLE 22 Primary outcomes (pairwise comparisons)

	Adjusted mean difference (Imm-RDI/Inc-AA)[a]	Adjusted mean difference (SMOFlipid/Intralipid)[a]	Interaction (*p*–value)	Adjusted mean difference (Imm-RDI/Inc-AA)[b]	Adjusted mean difference (SMOFlipid/Intralipid)[b]	Interaction (*p*-value)
Non-adipose mass (g), difference (95% CI)	1 (–108 to 111); $p = 0.98$	–41 (–150 to 68); $p = 0.46$	216 (0 to 432); $p = 0.05$	–44 (–226 to 139), $n = 130$; $p = 0.64$	–14 (–114 to 86), $n = 130$; $p = 0.78$	184 (–22 to 390); $p = 0.08$
IHCL content, difference (95% CI)[c]	0.7 (0.5 to 1.1), $n = 132$; $p = 0.11$	1.1 (0.8 to 1.6), $n = 132$; $p = 0.58$	0.8 (0.4 to 1.7), $n = 132$; $p = 0.53$	0.81 (0.37 to 1.80), $n = 129$; $p = 0.61$	0.89 (0.61 to 1.31) $n = 129$; $p = 0.57$	0.86 (0.39 to 1.92), $n = 129$; $p = 0.71$

a Adjusted for age at MRI, sex, gestational age, birthweight and centre.
b Adjusted for age at scan, sex, gestational age, birthweight z-score (UK 1990 growth data),[57] centre, level of care (% time spent receiving intensive and high-dependency care between birth and assessment[32]) and nutritional intake.
c Log-transformation was used in the regression model, the results transformed back from the logarithmic scale and presented as the ratio of intervention to control.

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Weight gain over the study period was similar across groups (*Figure 8*).

Trial PN protein intake was higher in the Imm-RDI arms in the first 2 weeks (*Figure 9*).

Carbohydrate, lipid and energy intakes were similar across all four groups (*Figures 10–12*).

Macronutrient and energy intake from milk and PN from the end of the second week onwards did not differ between groups (*Figures 13–16*).

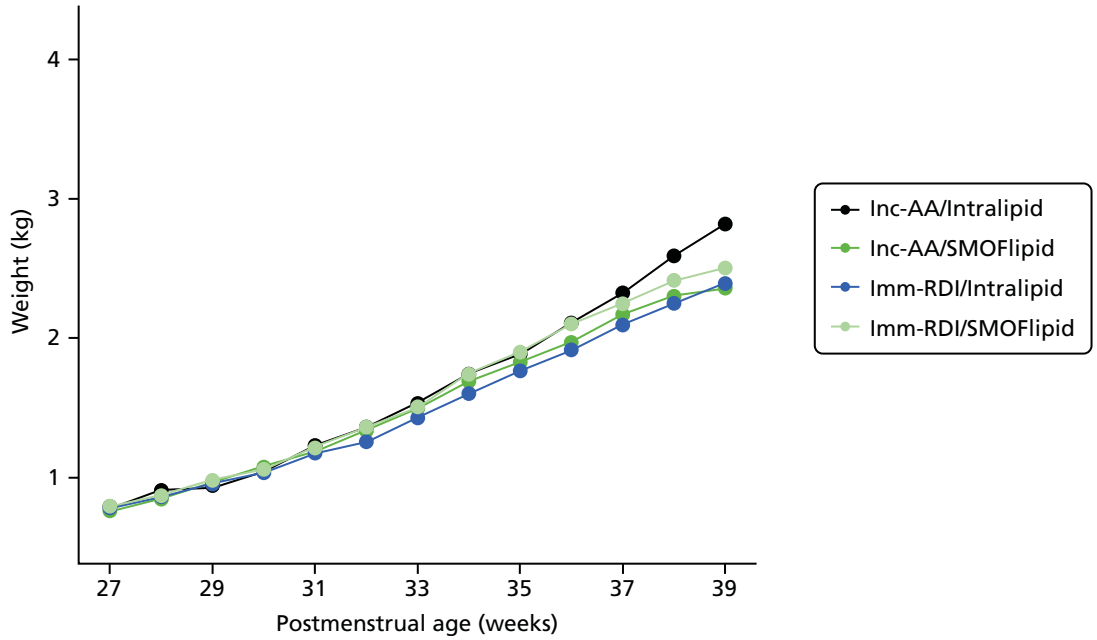

FIGURE 8 Time trend for babies' weights across four groups.

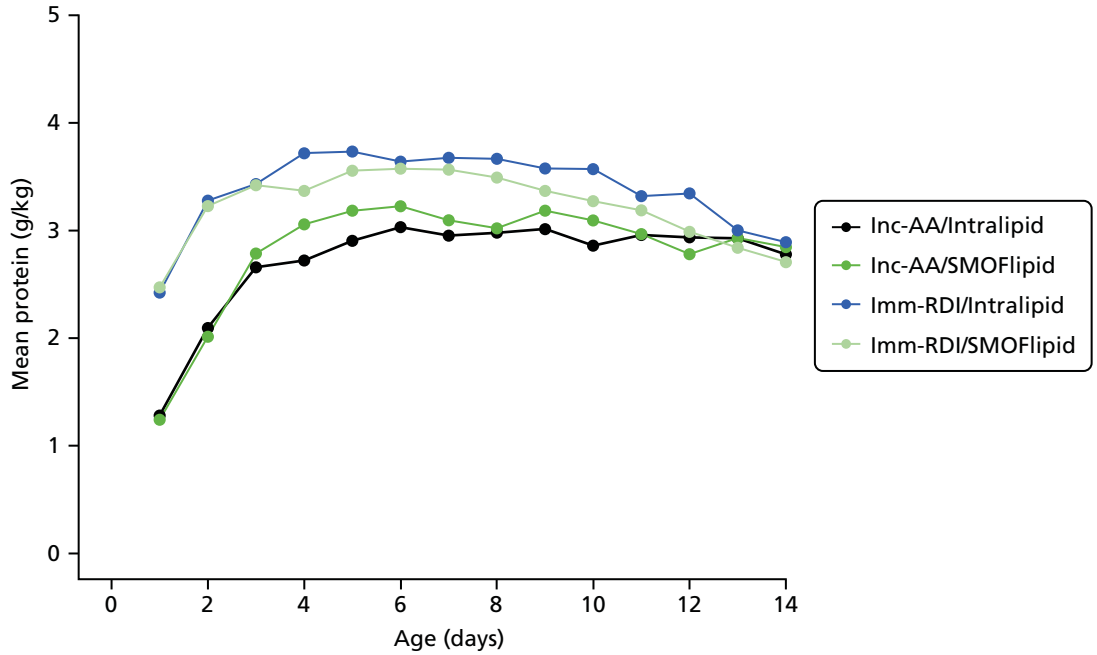

FIGURE 9 Daily protein intake from all sources in the first 2 weeks across four groups.

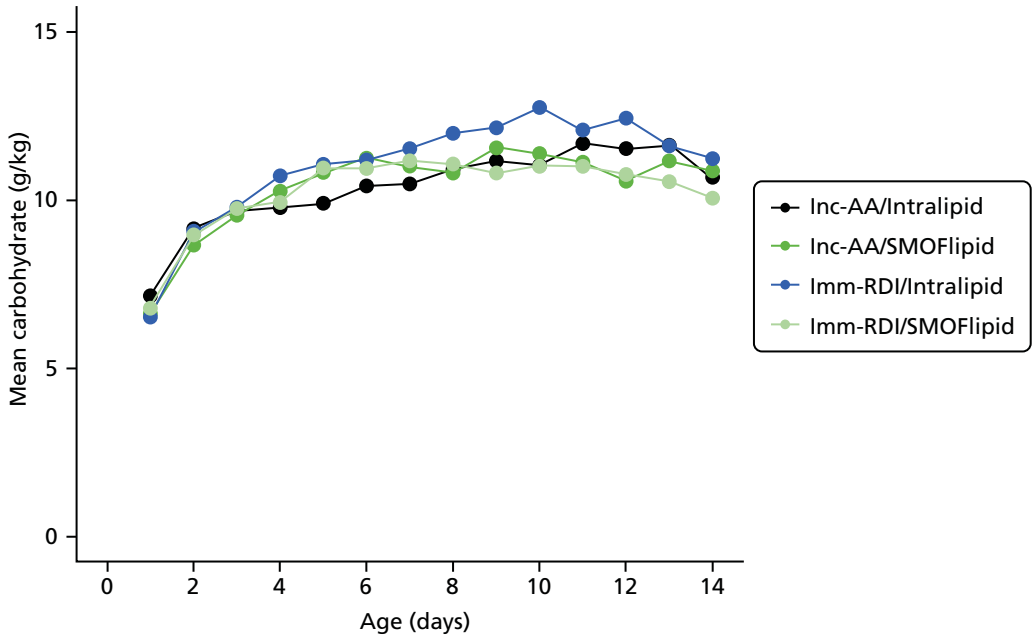

FIGURE 10 Daily carbohydrate intake from all sources in the first 2 weeks across all four groups.

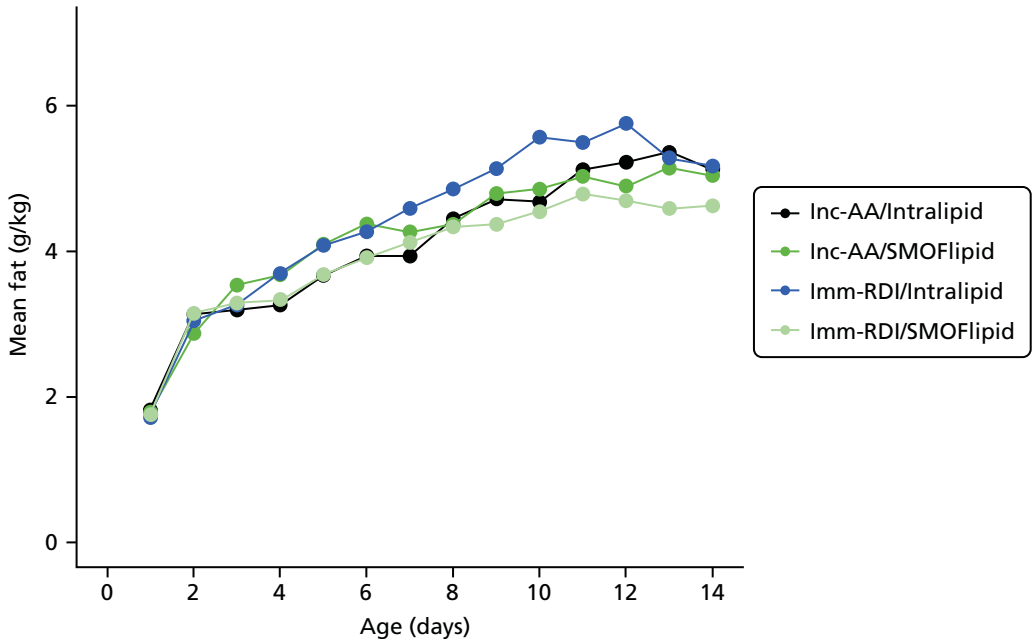

FIGURE 11 Daily fat intake from all sources in the first 2 weeks across all four groups.

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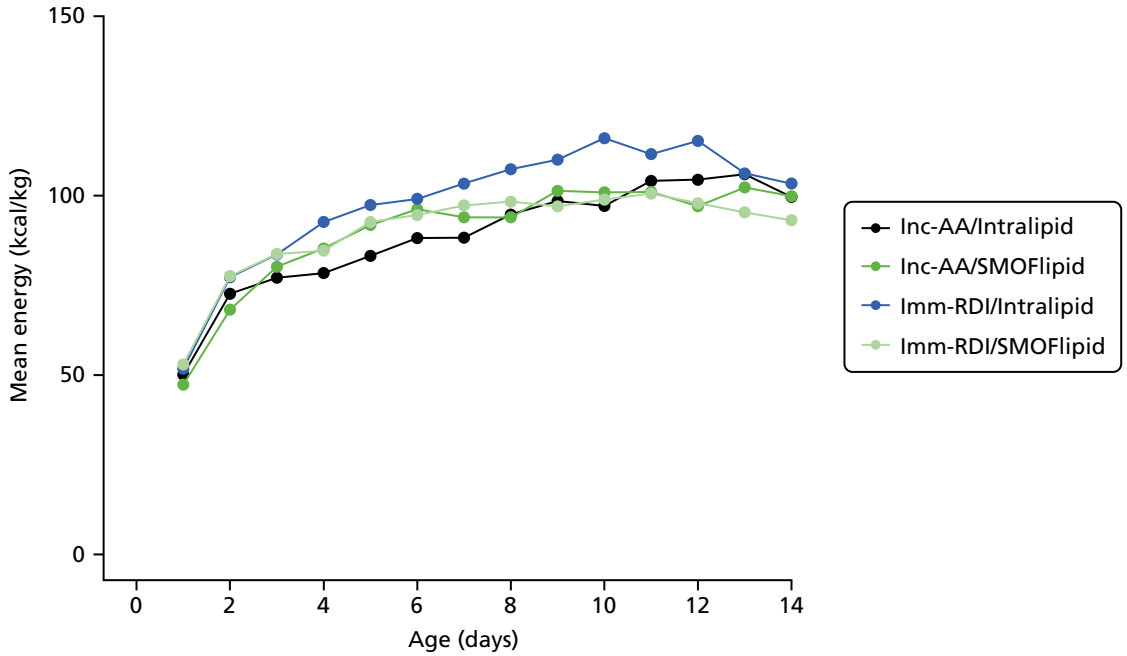

FIGURE 12 Daily energy intake from all sources in the first 2 postnatal weeks.

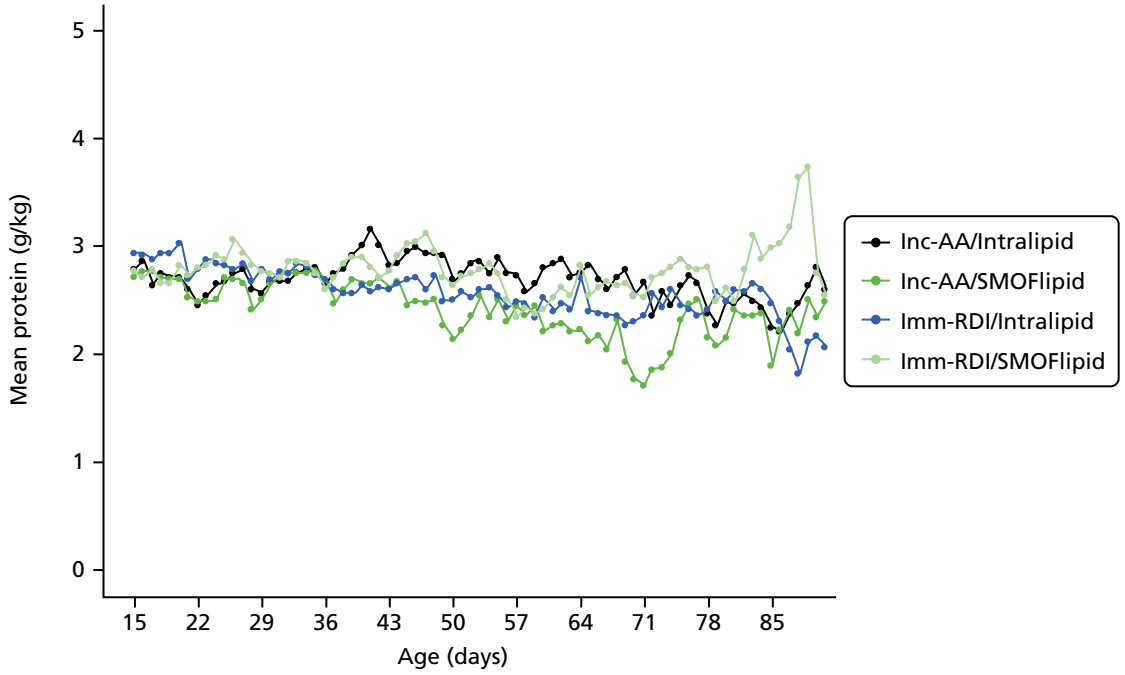

FIGURE 13 Daily protein intake from all sources after first 2 weeks across all four groups.

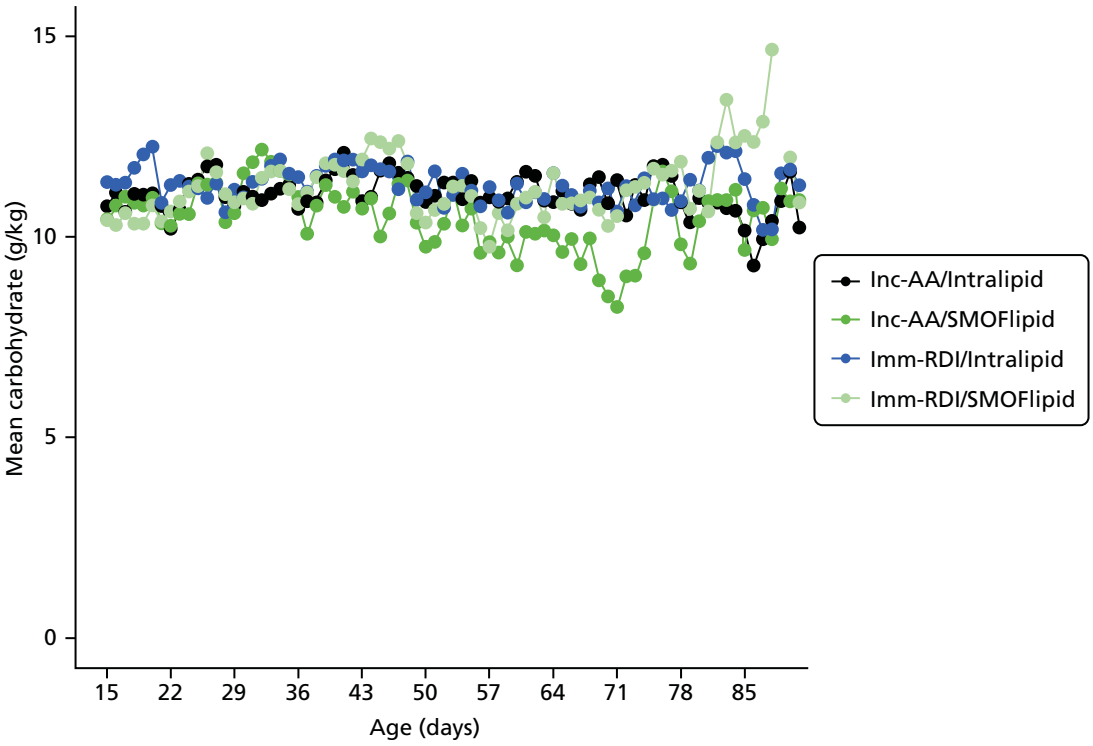

FIGURE 14 Daily carbohydrate intake from all sources after first 2 weeks across all four groups.

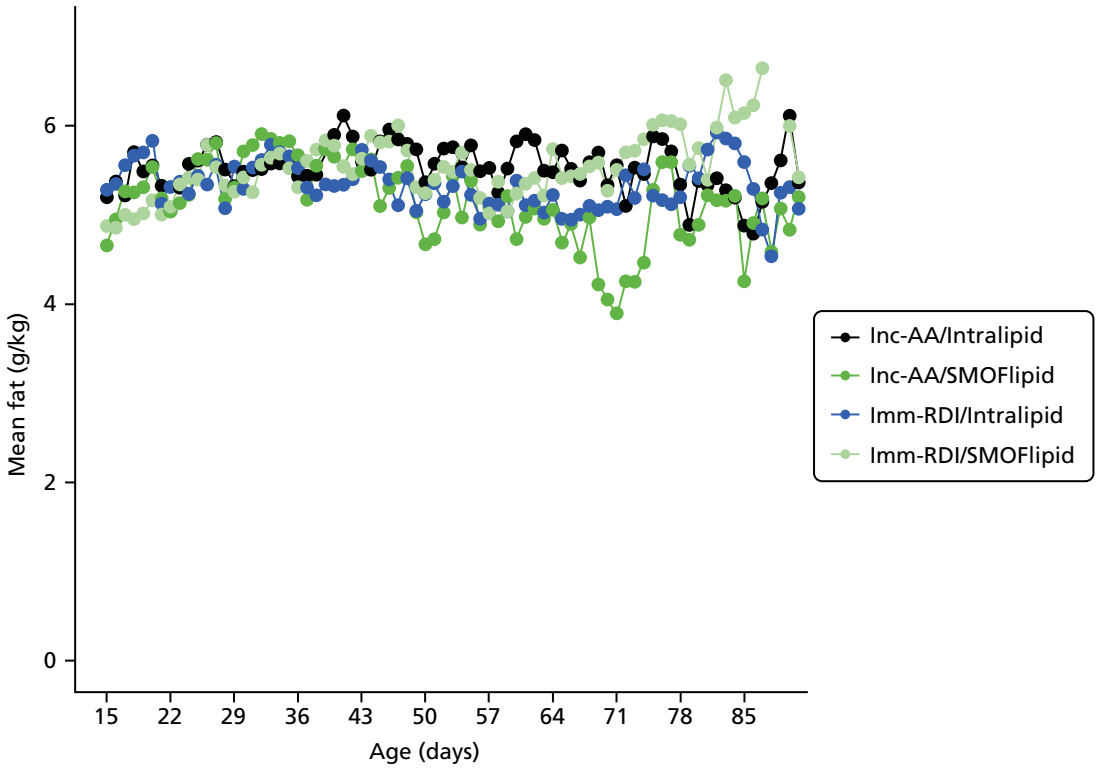

FIGURE 15 Daily fat intake from all sources after first 2 weeks across four groups.

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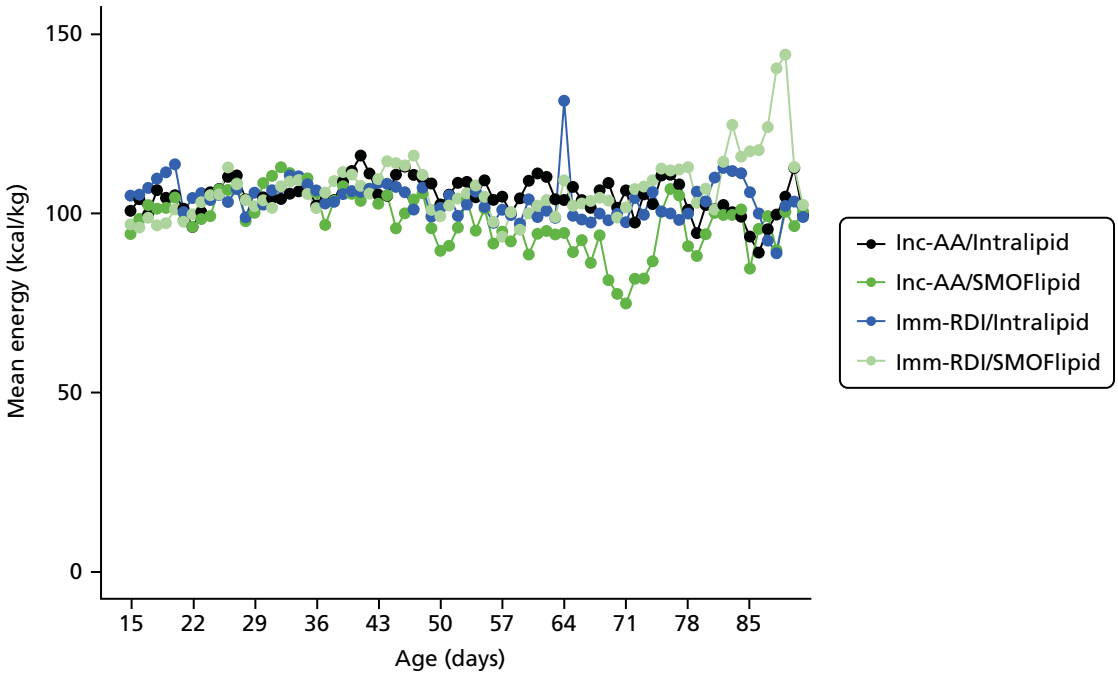

FIGURE 16 Daily energy intake from all sources after the first 2 postnatal weeks.

Chapter 5 Discussion

The key strength of the NEON trial was the excellent trial protocol adherence, including the introduction of milk feeds within 24 hours of birth and a prespecified approach to the management of electrolyte disturbances despite clinician blinding to group allocation. The need for central venous access can limit early commencement, hence the composition of trial PN permitted delivery by peripheral vein. Both gestational age strata (23–26 weeks and 27–31 weeks) were broadly equal across groups making the trial results applicable to the most immature infants. The NEON trial was adequately powered, as the CIs for the mean differences in non-adipose mass and SMOFlipid-to-Intralipid IHCL ratio exclude, respectively, the prespecified difference of 200 g,[19] and decrease of 40%. As we know of no biological reason for lipid type to influence the quantity of non-AT we consider it likely that the between-intervention interaction we detected is due to chance.

This is the first RCT of the impact of amino acids intake in PN on body composition in extremely preterm infants. Despite several guidelines and reviews recommending that extremely preterm infants be given the RDI of protein and calling for more aggressive nutritional management, especially in the early postnatal period, we have shown that this does not have an impact on LBM at term age equivalent. Similarly, the use of 20% SMOFlipid as the primary lipid composition resulted in similar IHCL levels as those found in infants who received 20% Intralipid.

This is the first RCT of SMOFlipid compared with Intralipid in preterm infants to study the impact of lipid composition on IHCL content. Preterm infants are known to have elevated IHCL content compared with term-born infants, and this is correlated with early lipid intake.[58] IHCL content measured with MRS in adults has been shown to have good diagnostic accuracy and compares favourably with the gold standard of liver biopsy for the quantitative measurement of hepatic steatosis.[59] SMOFlipid has been shown to be liver protective in the context of intestinal failure and PN in children and adults. Increasingly, the use of SMOFlipid has been adopted for use in neonates with liver impairment. However, to date, there have been no studies showing benefit for its use to prevent hepatic impairment. Previous studies of SMOFlipid in preterm infants published to date have focused mainly on lipid profiles,[60–63] including one small study on the incidence of retinopathy of prematurity[62] and a further one on the impact on growth outcomes.[60] In contrast to Vlaardingerbroek *et al.*,[60] we did not find any difference in growth outcomes in either weight or head circumference in this study between the group receiving SMOFlipid and the one receiving Intralipid.

Although this study was not powered to detect a significant difference in rates of sepsis, there was a higher rate of sepsis associated with SAE reports in the SMOFlipid group (15.5% vs. 3.6%), although this finding could be due to chance. A systematic review, comparing soya bean with non-soya bean lipid preparations, found a trend towards a lower incidence of sepsis, which did not reach statistical significance, in the group receiving the non-soya bean lipid preparation. In the current study, 20% SMOFlipid did not result in a reduction in IHCL content in preterm infants at term when used as a primary lipid composition. Although there were no differences between the groups, the quantity of IHCLs in the cohort of babies was similar to that in our previously published work comparing preterm infants with term-born infants.[18,64] We utilised IHCL content as a mechanistic marker of lipid tolerance, as levels at term correlate with early lipid intake[58] and are higher in very preterm than in full-term infants[18] and young adults.[65] We also monitored liver function using conventional biochemical markers and identified no between-group differences. Overall, our data support the conclusion of a systematic review and meta-analysis that fish oil-based lipid emulsions do not prevent PN-associated cholestasis[31] although the possibility that other formulations, including those with higher fish oil content, may be beneficial is not precluded.

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Other strengths of this study are that there was a prospective collection of detailed data of nutritional intake from birth to discharge and the proportion of missing nutritional data was < 0.1% for data on trial PN and < 5% for non-trial PN. The cohort, for this reason, lends itself to the long-term study of early nutritional intervention on outcomes such as neurodevelopment and later metabolic health. As evident from *Tables 9* and *10*, the trial interventions were delivered according to protocol both in the commencement of PN within 24 hours (barring a few protocol violations) and in the subsequent immediate postnatal period. By reducing the concentration of glucose, it was possible to commence PN without the need for central access, which can be a rate-limiting factor in the early commencement of PN. Additionally, we were able to demonstrate adherence to the use of a standardised regimen with a standardised prespecified approach to the management of electrolyte disturbances. Previous non-randomised studies comparing standardised with individualised PN have been inconclusive on the effect of these regimens on delivery of the required amounts of nutrition. We have demonstrated that using a standardised PN regimen in the context of a RCT is feasible. This is an important outcome, as increasingly there is recognition that current practices in relation to the prescription, preparation and use of PN pose a potential clinical risk to patients. There are several standard bags and regimens commercially available on the market. However, none of these regimens has been subjected to the rigour of a large RCT with clinically meaningful outcomes and the concurrent collection of a host of safety data. Data collection for this study included daily electrolyte and biochemical data while infants were on trial PN and weekly thereafter.

The study was carried out in four neonatal units in London and the south-east of England. Two of the units were designated NICUs in nature, whereas the remaining two were designated local neonatal units or level 2 units that cared for infants of > 27 weeks of completed gestation. All units serve a varied population in terms of both ethnic and socioeconomic backgrounds. Owing to the lack of MRI facilities for research use on site, the original trial protocol dictated that infants had to be discharged from hospital before the measurement of the primary outcome, as the MRI facility was located at a site separate from the location of the four hospitals and it would have been unethical to transfer a baby for MRI purely for the purpose of research if the baby was not fit to be discharged. This potentially could have resulted in a bias, with the sickest babies being excluded from the measurement of primary outcome. However, early on in the trial the hospital where the majority of infants were recruited was able to scan infants who were still inpatients, resulting in nine infants who were otherwise not fit for discharge to be safely scanned on site. This allowed these infants who would have otherwise been excluded from the primary outcome measure analysis to be included. Four babies were excluded from the analysis of primary outcome measure because they were still hospital inpatients during the window of measurement. There was also concern during the trial design stage that the most immature infants at the highest risk of death may be under-represented in the final results. Therefore, the TSC considered that it might be necessary to stop recruiting to the stratum of infants in the higher gestational age category if this was found to be an issue in the interim analysis (i.e. if more mature babies were being recruited and completing the scans there might have been over representation of the more mature babies). However, this was not found to be the case and, hence, the results are generalisable to not just the sicker infants but the most immature as well. In the group of infants born between 31 and 33 weeks of gestation, or the very growth-restricted, but more mature, infant in whom the use and justification of PN remains uncertain, definite recommendations cannot be made from the results of this study.

There has been previous concern about the use of aggressive nutrition in a study comparing standard intake with 'aggressive' nutrition when the intervention included higher protein and energy intake.[66] The authors terminated the study early as there was an increased rate of sepsis in the intervention group and an association between low serum phosphate levels in the intervention group (despite increased phosphate delivery) and sepsis. In our study both groups received similar intake of electrolytes and there was no significant difference in the incidence of abnormalities in electrolytes.

Previous studies have suggested that the provision of increased early amino acids in PN is safe and not associated with an increased incidence of metabolic acidosis or elevation in blood urea nitrogen.[40,41] We found a significantly higher incidence of elevated blood urea concentrations in the groups receiving the

RDI of amino acids. This is also in keeping with the studies of Vlaardingerbroek *et al.*,[35,67] although there was no associated increased incidence of metabolic acidosis. The significance of elevated blood urea in the early postnatal period in preterm infants is unclear. It may reflect increased amino acid oxidation, but is also dependent on renal function and hydration status. The long-term outcomes of providing increased intake of amino acids from birth require evaluation before this approach can be recommended in practice.

We noted a smaller head circumference at term in babies receiving the higher amino acid intake. The observation is at odds with the Standardised, Concentrated Additional Macronutrients, Parenteral nutrition in very preterm infants (SCAMP) study, in which very preterm neonates randomised to receive higher PN from birth had a larger head circumference at 28 days.[68] Of note is that, although the SCAMP study aimed to deliver large amounts of PN, randomisation occurred up to 120 hours of age (compared with 24 hours in the NEON trial) and hence infants received a lower average energy and amino acid intake over the first 3 postnatal days than the NEON trial infants. The NEON trial was not powered to detect a difference in head circumference, but our observation is a concern as the possibility of adverse effects from higher PN has been raised previously. Choudri *et al.*[69] found smaller brain growth and compromised neurodevelopment despite equivalent weight gain in preterm piglets receiving total parenteral in comparison with total enteral nutrition. Blanco *et al.*[70] found that infants receiving an immediate parenteral amino acid intake of 2 g/kg/day increasing to 4 g/kg/day, compared with a group randomised to receive a lower intake, had a lower mean Mental Development Index at 18 months and lower mean z-scores for weight, length and head circumference. Reassuringly, in the NEON trial we identified no between-group differences in brain volume.

Several studies have shown growth failure in preterm infants in the postnatal period and continuing to adulthood.[2,71] There are calls for a more aggressive approach to early postnatal nutrition to prevent this growth failure.[42,72] Various published guidelines recommend the early introduction of amino acids, with recommended intakes of up to 4 g/kg/day.[23] However, these recommendations are based on limited evidence, and there are no long-term data to support the safety of such an approach. A recent paper with a similar intervention of amino acids demonstrated that the early introduction of parenteral amino acids given in conjunction with lipids improved nitrogen balance. However, higher intake of amino acids from day 1 did not further improve the nitrogen balance, but led to increased amino acid oxidation.[35] Although there is concern that undernutrition is associated with adverse neurodevelopmental outcomes, there is also some suggestion that 'overnutrition' may also be detrimental to neurodevelopment.[73] As noted above, there are animal data reporting an association between PN and adverse neurodevelopment when compared with enteral nutrition.[69] Interestingly, in that study, the pigs fed on the enteral diet showed a slowing of growth before recovery of growth rate to match the PN-fed pigs. The PN-fed pigs showed a positive growth trajectory in the immediate postnatal period, which excludes poor postnatal growth as being the cause of adverse neurodevelopment. This study shows that commencing amino acids within the first 24 and increasing the quantity to a maximum of 2.7 g/kg/day when accompanied by the early introduction of enteral feeds results in an increase in LBM compared with historical controls and no significant difference between the intervention and controls. Our sample size calculation was based on our previous work.[19] Practice in neonatal PN has changed with the emphasis on commencing PN earlier. Data from the UK National Data Analysis Unit show that year on year more infants born before 30 weeks of gestation are started on PN within the first 48 hours after birth, but currently up to one-fifth to one-quarter of babies do not receive PN until day 3.[37] In the incremental group the mean protein intake from parenteral and enteral intake by day 3 was 3.4 g/kg/day. The difference in mean protein intake between the incremental and RDI groups was significant only in the first 2 weeks, when the infants were becoming established on enteral nutrition. It is of note that the CI for the mean difference in lean mass between the groups excludes the deviation of prespecified difference in lean mass on which the sample size calculation was based. The trial was, therefore, adequately powered to detect any clinically important differences between the groups.

Our own work and that of others has shown that LBM in preterm infants at term age equivalent is significantly lower than in healthy term-born infants. A systematic review, including our work, has shown that the magnitude of mean difference between preterm and term-born infants is about 460 g.[74] The mean LBM in the NEON trial cohort was 2.41 kg (SD 0.46 kg). These values of lean mass are higher than

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the mean of our previous cohort of preterm infants of 2.1 kg (SD 0.4 kg), on which the sample size calculation was based, and closer to the mean of our term-born cohort of 2.6 kg (SD 0.21 kg).[19] Furthermore, the values are comparable to the mean lean mass seen in a more recent cohort of preterm infants of 2.49 kg (95% CI 2.45 to 2.54 kg), published after the commencement of this study.[11] As is evident from the National Data Analysis Unit data, babies are increasingly receiving PN earlier. Babies randomised to the standard arm in this trial commenced PN earlier than is routine practice and, hence, were not exposed to deficits that may arise from delaying PN. Despite the difference in early protein intake in the first week, this did not result in differences in LBM at term age equivalent. This suggests that, provided PN is initiated early and established according to a standardised regimen, accompanied by early introduction and advancement of milk feeds, it is possible to achieve LBM in preterm infants at term age equivalent that are closer to that seen in healthy term-born infants.

Parenteral nutrition is a high-cost and widely used neonatal intensive care intervention, yet there have been few previous RCTs and none that has evaluated effects on body composition.[37] We achieved a clear difference in amino acid intake between the Imm-RDI and Inc-AA groups. The possible reasons why this did not translate into a difference in body composition or weight at term merit consideration. First, the incidence of elevated blood urea concentrations was significantly higher the Imm-RDI groups. This suggests that increased delivery above a threshold results in increased amino acid oxidation with no improvement in nitrogen retention or growth, as suggested previously.[35,75,76] We consider it unlikely that impaired utilisation of amino acids was attributable to inadequate non-protein energy delivery, as there were no significant differences between the groups in non-protein energy intakes. Second, trial interventions may have resulted in a short-term difference in body composition that was attenuated when babies transitioned to self-regulated suck feeds. Embleton and Cooke[77] found that babies fed a higher-protein formula by nasogastric tube achieved an increase in LBM that did not persist after a period of self-regulated feeding by bottle.

One of the weaknesses of this study was that the appropriate MR images of the brain required to measure volumes were not availabe for a significant proportion of babies. The brain volumes were derived from T2-weighted images. This sequence followed the longer T1-weighted sequence in the scanning protocol and babies often woke up at the end of the T1-weighted scan. This was a missed opportunity to test the hypothesis that amino acid intake and SMOFlipid influences brain growth and volume by using a direct measure of brain growth instead of the previously used surrogate measure of head circumference.[68] However, in one-third of infants, for whom there were images of sufficient quality to analyse, there were no differences seen between groups in relation to either intervention. If early nutritional intervention at a period of rapid brain development has a long-term impact on neurodevelopment, then it is plausible that a difference in total and regional brain volumes persists beyond the neonatal period. Follow-up of this cohort in which detailed nutritional intake has been captured offers the unique opportunity of studying the long-term impact of early nutrition on brain development as well as neurodevelopment. Establishing the long-term safety of the introduction of higher amino acid intake is of particular importance given the calls for early aggressive nutrition without the accompanying evidence of the lack of harm, both in the short and long term. The QUICKI data were not able to be captured on a number of infants because of the inability of non-lead sites to carry out this assessment, as well as babies being transferred to non-trial sites before reaching 37 weeks postmenstrual age.

Chapter 6 Conclusions and recommendations

In conclusion, commencement within 24 hours of birth of an incremental amino acid regimen providing a maximum of 2.7 g/kg/day together with the early introduction of milk feeds, compared with the immediate provision of an amino acid intake of 3.6 g/kg/day, does not appear to be detrimental to body composition and may be safer, and SMOFlipid does not reduce intrahepatic lipid accumulation.

Extremely preterm infants at term age equivalent can achieve a body composition close to that of healthy term-born infants if provided at an early stage with PN in accordance with a standardised regimen.

The results do not support the calls for more aggressive nutrition in the extremely preterm infant or the routine use of SMOFlipid as reflected in international consensus statements (higher amounts of amino acids) or as is increasingly seen in current practice. In the light of the unexpected finding of a smaller head circumference in those randomised to receive immediate RDI of amino acids, we recommend that large amounts of amino acids be used only in the context of randomised clinical trials. Optimal amino acid intakes and intravenous lipid formulations for extremely preterm infants remains to be established.

Health-care recommendations

A key ancillary observation of this trial was that the use of standard PN regimens is feasible, acceptable to clinicians even when blinded, can deliver desired nutritional intake without manipulation and is safe. In our opinion, standardised regimens that have been tested in the context of a RCT should be adopted in routine clinical practice to reduce the clinical risk to infants from variation in practice.

Research recommendations

1. We recommend that long-term follow-up of functional outcomes of neurodevelopment as well as long-term body composition and metabolic health of both the trial interventions is essential before either of the interventions studied in this trial can be recommended as routine practice.
2. It is essential to develop early biomarkers of nutritional intervention in neonates that are predictive of long-term body composition and health. Demonstration of stability in body composition and IHCL content between term age equivalent and childhood would provide justification for the use of body composition and IHCL content as short-term surrogate outcomes in neonatal nutrition research.
3. This study did not address the role of carbohydrate in PN. The optimal intake of carbohydrate and the management of hyperglycaemia whether by reducing intake of glucose or the use of insulin during PN should be established.

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Data Monitoring and Ethics Committee members

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Contributions of authors

Sabita Uthaya conceived and designed the study; analysed and interpreted the data; and drafted, revised and approved the report.

Xinxue Liu analysed the data, and drafted, revised and approved the report.

Daphne Babalis designed the study, analysed and interpreted the data; and drafted, revised and approved the report.

Caroline Dore designed the study, analysed and interpreted the data; and drafted, revised and approved the report.

Jane Warwick analysed the data and approved the report.

Jimmy Bell acquired and analysed the data, and drafted, revised and approved the report.

Louise Thomas analysed the data, and drafted, revised and approved the report.

Deborah Ashby analysed the data, and drafted, revised and approved the report.

Giuliana Durighel acquired the data, and drafted, revised and approved the report.

Ash Ederies acquired and analysed the data, and drafted, revised and approved the report.

Monica Yanez-Lopez analysed the data, and revised and approved the report.

Neena Modi conceived and designed the study, analysed and interpreted the data; and drafted, revised and approved the report.

Data sharing statement

All available data can be obtained from the corresponding author.

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Appendix 1 Distribution of primary and secondary outcomes after transformation

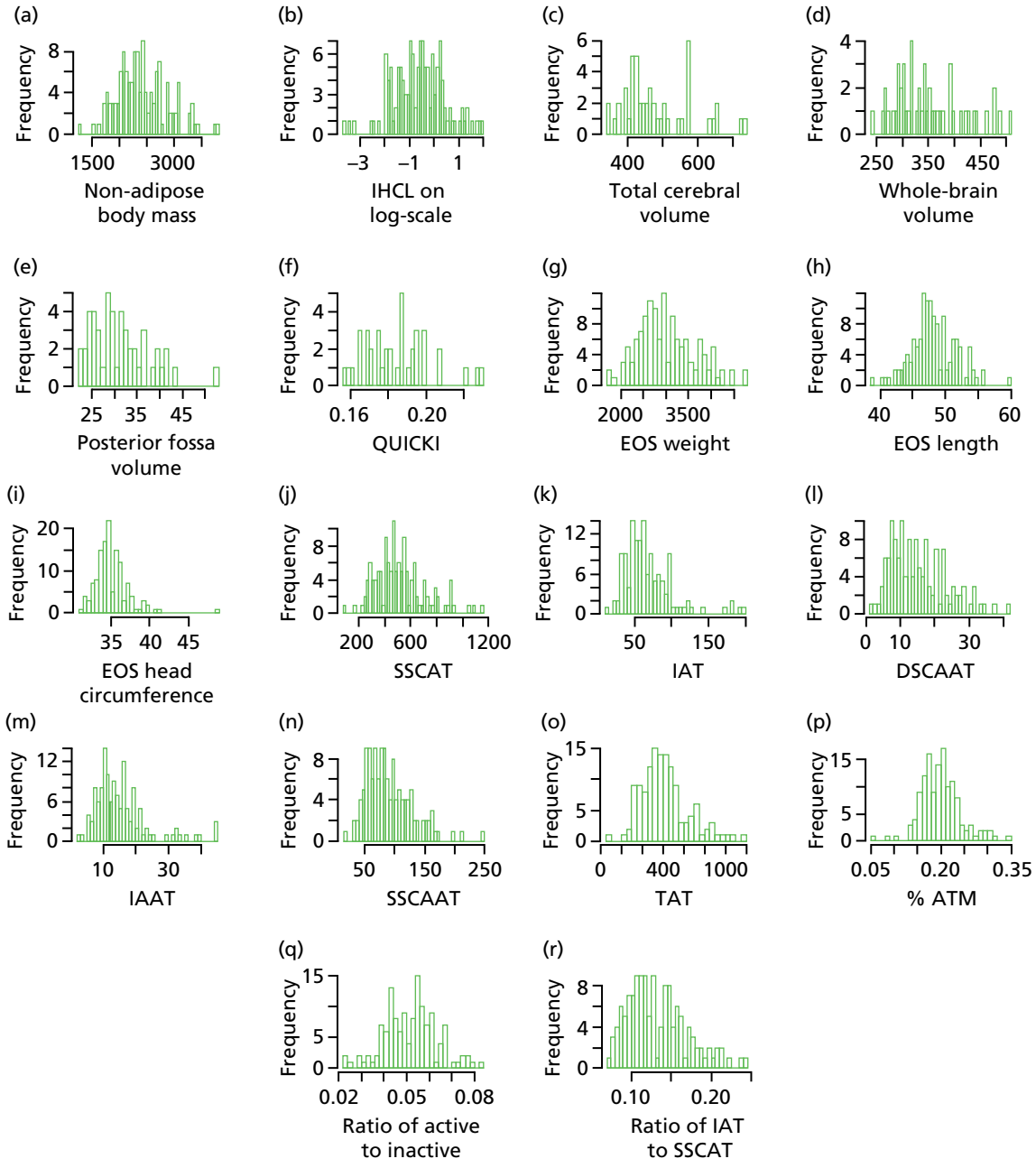

FIGURE 17 Distribution of primary and secondary outcomes after transformation. IHCL values are log-transformed. ATM, adipose tissue mass; DSCAAT, deep subcutaneous abdominal adipose tissue; EOS, end of study; IAAT, internal non-abdominal adipose tissue; IAT, internal adipose tissue; SSCAAT, superficial subcutaneous abdominal adipose tissue; SSCAT, superficial subcutaneous adipose tissue; TAT, total adipose tissue.

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Appendix 2 Parent information sheet, magnetic resonance information sheet and consent form

INFORMATION SHEET FOR PARENTS

Study title: Amino acid regimen and intravenous lipid composition in preterm parenteral nutrition: a randomised controlled trial of Nutritional Evaluation and Optimisation in Neonates (NEON)

Invitation to participate
We would like to invite you to consider giving your consent to include your baby in a research study. Please take time to read this information carefully and discuss it with others if you wish. A member of our team will go through the information sheet with you. Please ask if there is anything that is not clear or if you would like more information.

What is the purpose of the study?
Extremely preterm infants (born less than 31 weeks of gestation) spend several weeks and months in hospital. Feeding babies born so early is difficult. By the time they reach their due date their weight is typically about 1 kg (2 lbs) less than that of a full-term healthy baby.

Food is initially provided as a fluid called parenteral nutrition (PN) that is given into a vein. As extremely preterm babies may have other medical problems, traditionally, the amount of nutrition provided in PN has been gradually increased in a cautious, stepwise manner. This means that it can take several days to reach the full recommended nutritional intake to enable them to grow.

Though necessary, PN has complications, especially if used for several weeks. One complication is damage to the liver. The type of fat used in PN may affect this.

Recent studies have shown that giving preterm babies the recommended amount of nutrition straight away without the stepwise approach, and using a new type of fat (SMOF lipid) that contains soybean oil, olive and fish oil rather than the fat we currently use (Intralipid) which has soybean oil alone is safe. Although these approaches to feeding are used by doctors in day to day practice, we do not know for sure if one has benefit over the other in preterm babies. Before this can be introduced into everyday practice as recommendation we need to make sure this approach is beneficial.

The purpose of this study is to improve the growth and health of preterm babies. We will do this by:

1) comparing “immediate” introduction of Parenteral Nutrition with “stepwise” introduction
2) comparing the currently used fat in PN, with a newer type of fat that we hope is less harmful to the liver.

Why have I been invited?
You have been invited because your baby has been born prematurely (at less than 31 weeks of gestation) and needs Parenteral Nutrition.

Does my baby have to take part?
It is entirely up to you to decide whether or not you wish your baby to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form, a copy of which will be given to you. If you decide to take part

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you are still free to withdraw your baby from the study at any time and without giving a reason. We would ask that you allow us to use any information collected up to that point. A decision not to take part will not affect the standard of care that your baby receives.

What will the study involve?
We will be enrolling 128 babies into this study. Babies will receive one of four different combinations of parenteral nutrition treatment.

Group 1: Stepwise introduction of PN and currently used fat
Group 2: Stepwise introduction of PN and newer lipid
Group 3: Immediate introduction of PN and currently used fat
Group 4: Immediate introduction of PN and newer lipid

The process of allocating which treatment a baby receives is done by 'randomisation'.

Randomisation means that a specially designed computer programme will determine the choice. There is a 50% chance that your baby will receive either type of treatment (like tossing a coin). Randomisation is done in order to ensure that every baby has the same chance of receiving either one or the other treatment. We will not know which treatment your baby receives until the end of the study. This is to prevent any bias in the results of the study.

Your baby will start milk feeds and the study PN within 24 hours as is normal practice. We recommend you provide your own expressed breast milk to your baby. When your baby is tolerating milk feeds well and no longer requires PN this will be stopped. We will collect the following information on your baby:

Routinely collected information
This is collected for any baby receiving care on a neonatal unit. This includes measurement of growth, recording the amount of nutrition (milk or PN) a baby receives and blood tests that show the effect of nutrition on the body.

Information collected for research
This is information that will be collected in addition to routine tests and information. The blood tests will be done at the same time as other routine blood tests and after the tests are done the samples will be destroyed. The samples will be labelled with a unique trial identification number.

The following additional tests will be done:

1. We will take 3 drops of blood in the first week, and additionally, once a week during your baby's stay in hospital, we will collect a few drops of urine (10 drops) and stool from the nappy to measure metabolite levels. The test uses a new technique called magnetic resonance (a method that uses a magnetic field) which allows a large number of metabolites (waste products of food) to be measured in very small quantities of blood or urine.

2. If your baby is born at Chelsea and Westminster hospital, we will take a few drops of blood (0.5 – 1 ml) to measure the type of fat present in the blood on the first and fifth day after birth.

3. When your baby reaches his /her due date we will take a few drops (1ml) of blood to measure sugar, insulin and metabolite levels.

4. In order to determine the results of the treatments on the development of the body, brain and liver, we will arrange a magnetic resonance (MR) scan to obtain pictures of your baby's body and brain. This will be done when you baby has reached his or her due date and has gone home. We will give you more information about this nearer the time of this scan.

Other than the MR scans the study samples may not be taken if your baby is transferred to another hospital. If this is the case we will take a sample of urine when your baby has the MR scan.
After your baby has had his or her scan, involvement in this study will end. Your baby will continue to receive routine care and follow up. If you agree, we may contact you about future research studies looking at how nutrition affects babies in later life.

Expenses and payments
The MR scan is done at the Hammersmith Hospital where we will ask you to come for a morning or an afternoon. We will arrange for a taxi or reimburse your travel and parking costs.

What are the alternatives for diagnosis or treatment?
If you choose not to enter your baby in to the study then your baby will receive standard care which will include PN. It is not routine practice to do MR scanning of the body, liver or brain.

What are the possible disadvantages and risks of taking part?
Parenteral nutrition (PN) is usually unavoidable for extremely preterm infants. The benefits of PN in neonatal intensive care are believed to outweigh the risks. The additional risk from using "immediate" PN from day one is minimal. Previous studies have not shown an increase in complications. SMOF lipid has been used in other studies and is often used in preterm infants receiving prolonged PN.

You will need to travel to the Hammersmith Hospital after discharge for the MR scans. They are not being carried out for clinical diagnosis but there is a possibility that they might show something unexpected. If this occurs, a senior doctor will explain this to you and notify your GP, and discuss whether any further action is necessary.

What are the possible benefits of taking part?
As we do not know if one treatment has benefit over the other there is no direct benefit to your baby. By following a standardised approach to milk feeding as in this study, there may be benefits to your baby. However, the information we obtain from this study may help us to improve nutrition of preterm babies in the future.

What if there is a problem?
All the treatments used in this study are currently used in day to day practice and it is not anticipated that there will be problems related directly to the study. As with all studies, Imperial College London holds insurance policies which apply to this study. If your baby experiences harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If your baby is harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Insert name and contact

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details). The normal National Health Service complaint complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Office.

Will my baby's taking part in the study be kept confidential?
All information which is collected about your baby during the course of the research will be kept strictly confidential, and any information about your baby which leaves the hospital will have your baby's name and address removed so that he /she cannot be recognised. They may be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to your baby as a research participant and we will do our best to meet this duty.

What if relevant new information becomes available?
Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss your baby's options.

What will happen to the results of the research study?
We will publish the results in a scientific journal. No participant will be identified in any publication. We will send a letter summarising the results to the parents of the babies who took part. At this stage should you wish to know which group your baby was in we would be happy to provide you this information.

Who is organising and funding the research?
The research is being organised by Imperial College London. The study is being funded by the Efficacy and Mechanism Programme of the National Institute for Health Research.

Who has reviewed the study?
The study has been reviewed by independent doctors, specialists and parent representatives. All research in the NHS is looked at by independent group of people, called a National Research Ethics Committee, to protect the interests of participants. This study has been reviewed and given favourable opinion by the Hammersmith Hospital Research Ethics Committee

Further information and contact details
If you would like further information about the study please contact

Insert local PI details.

Nutritional Evaluation and Optimisation in Neonates Study: the NEON study.

Version 4: 28 Oct 2010

Nutritional Evaluation and Optimisation in Neonates Study: The NEON Study:

Information Sheet for parents on the Magnetic Resonance Scan:

We thank you for including your baby in the Nutritional Evaluation and Optimisation in Neonates (NEON) Study. This information sheet gives you additional information about the magnetic resonance (MR) scan which is the final part of this study.

As your baby is now preparing to go home we are in a position to arrange the MR scan which will look at how the body, brain and liver have developed. The results of this scan will be compared between the babies who have received different treatments in order to see whether or not one treatment has any benefits over the other. The scan will be done within roughly 2 weeks of your baby going home.

You will need to travel to the Hammersmith Hospital for this scan. We will arrange transport for you and your baby to and from the hospital or reimburse you for parking if you choose to drive yourself.

MR imaging is a technique widely used in infants and we have studied several hundred infants with MR. A MR scanner uses a magnet to take detailed pictures of the body and brain and measures the amount of fat in the liver.

The scan is carried out whilst your baby is in natural sleep without the use of sedatives. The scan normally takes no more than 40 minutes but sometimes additional time is required to settle a baby. You are welcome to be in the adjacent control room and watch your baby during the scan. During the scan your baby will be under the care of a doctor. As the MR scanner makes some noise we use baby ear muffs to protect your baby's ears. After the scan is complete we will measure your baby's growth and blood pressure.

We will be happy to show you the pictures taken of your baby. The scan is not being carried out for clinical diagnosis but there is a possibility that they might show something unexpected. If this occurs, a senior doctor will explain this to you and notify your GP, and discuss whether any further action is necessary. The brain scan however will be reported and the results will be sent to your baby's doctor who will be able to discuss this with you.

NEON Study Information Sheet for parents on MR scan Version 1 261109

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CONSENT FORM FOR PARENTS

Version 2 dated 28th October 2010

Study title: Amino acid regimen and intravenous lipid composition in preterm parenteral nutrition: a randomised controlled trial of Nutritional Evaluation and Optimisation in Neonates (NEON)

Patient's name and hospital sticker

The parent should complete this sheet himself or herself.

Please initial boxes

1. I confirm that I have read and understand the parents information sheet dated 28th October 2010 (version 4) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that I am free to withdraw my baby from the study at any time without giving any reason, without my baby's medical care or legal rights being affected. ☐

3. I understand that relevant sections of any of my baby's medical notes and data collected during the study may be looked at by responsible individuals from the Clinical Trials and Evaluation Unit or staff from regulatory authorities where it is relevant to my baby taking part in research; I give permission for these individuals to have access to my baby's records. ☐

4 I understand that routine information about my baby's care may be collected for the purposes of the study if my baby is transferred to another hospital prior to discharge home. I agree to this information being collected. ☐

5. I agree to be contacted in the future to be informed about follow up studies that may take place. ☐

6. I agree to my baby being included in the above study. ☐

_____ _____ _____

NAME IN BLOCK CAPITALS Date Signature

Relationship to patient: _____

Investigator's signature _____Date _____

(INVESTIGATOR'S NAME IN BLOCK CAPITALS)_____

When completed, 1 for infant's parent; 1 for researcher file; 1 (original) to be kept in medical notes

NEON Consent Form v2.0 dated 28th October 2010

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