

Trial Title: Developmental Outcomes of Long-term Feed Supplementation in Neonates - The DOLFIN randomised controlled trial

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Funder:	NIHR HTA programme – NIHR130925

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There are no conflicts of interest to declare.

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1. KEY TRIAL CONTACTS

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2. SYNOPSIS

Trial Title	Developmental Outcome of Long-term Feed Supplementation in Neonates - The DOLFIN randomised controlled trial
Internal ref. no. (or short title)	NuTH REF: 9707
Trial registration	ISRCTN: 62323236
Sponsor	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder	NIHR HTA programme – NIHR 130925
Clinical Phase	Phase III
Trial Design	Multicentre, blinded, stratified, randomised controlled trial (with an internal pilot and alongside economic evaluation). Strata are defined as (1) infants born < 28 weeks of gestation and (2) infants born at ≥ 35 weeks of gestation receiving therapeutic hypothermia for Hypoxic Ischaemic Encephalopathy (HIE)
Trial Participants	Stratum 1. Infants born less than 28 weeks of gestation (preterm stratum) Stratum 2. Infants born at 35 weeks of gestation or more receiving therapeutic hypothermia for HIE (HIE stratum) Infants will be recruited from approximately 40 UK NHS Neonatal Units.
Sample Size	1,010 infants; 538 infants for the preterm stratum, and 472 infants for the HIE stratum. Both strata are powered to detect a 6 point difference between the two arms on the PARCA-R non-verbal cognitive scale standardised score, with 90% power and a 2-sided 5% significance, assuming a population mean score of 88 and standard deviation of 19. An inflation factor of 14% is applied to the preterm stratum to allow for clustering within multiple births. Prevalence of multiple births in the HIE stratum is expected to be negligible.
Planned Trial Period	Trial duration: 69 months Duration of participant involvement: • Intervention phase: to 12 months post Estimated Date of Delivery (EDD). • Follow up phase: to 24 months post EDD.
Planned Recruitment period	Approximately 27 months
Aims: Primary:	To evaluate whether nutritional supplementation with a nutrient blend containing long-chain polyunsaturated fatty acids (LCPUFAs), choline, uridine-5'-Monophosphate (UMP), and cytidine-5'- monophosphate (CMP) plus usual care from birth to 12 months post EDD improves cognitive development at 24 months post EDD, compared to infants receiving a matched control supplement plus usual care (comparator), for (1) infants born <28 weeks of gestation (and up to 3 months post EDD) and (2) infants

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	born at ≥ 35 weeks of gestation receiving therapeutic hypothermia for HIE (and up to EDD plus 28 days).
Secondary:	To evaluate whether nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP and CMP plus usual care from birth to 12 months post EDD alters the following outcomes compared to infants receiving a matched control supplement plus usual care (comparator), for (1) infants born <28 weeks of gestation and (2) infants born at ≥ 35 weeks of gestation receiving therapeutic hypothermia for HIE: • neurodevelopmental outcomes: cognitive; language; motor; emotional, conduct, hyperactivity/inattention, peer relationship problems and prosocial behaviour at 24 months post EDD • infant growth, clinical outcomes, safety, infant tolerability, parental acceptability, maternal quality of life to 24 months post EDD • Health Economics outcomes
Objectives:	For each stratum separately:- <u>Primary</u> • To compare cognitive development of infants randomised to receive nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP, and CMP compared to those randomised to receive a matched control supplement, at 24 months post EDD. <u>Secondary</u> • To compare the effects of nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP, and CMP with a matched control supplement on secondary neurodevelopmental outcomes, at 24 months post EDD. • To investigate the effect of nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP, and CMP on infant growth outcomes to 24 months post EDD. • Investigate the effect of nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP, and CMP on clinical outcomes up to discharge. To investigate the safety, infant tolerability, adherence to and parental acceptability of nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP, and CMP to 12 months post EDD. Safety monitoring will continue for two weeks after the end of the intervention period. • To investigate the impact of nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP, and CMP on maternal health-related quality of life to 24 months post EDD.

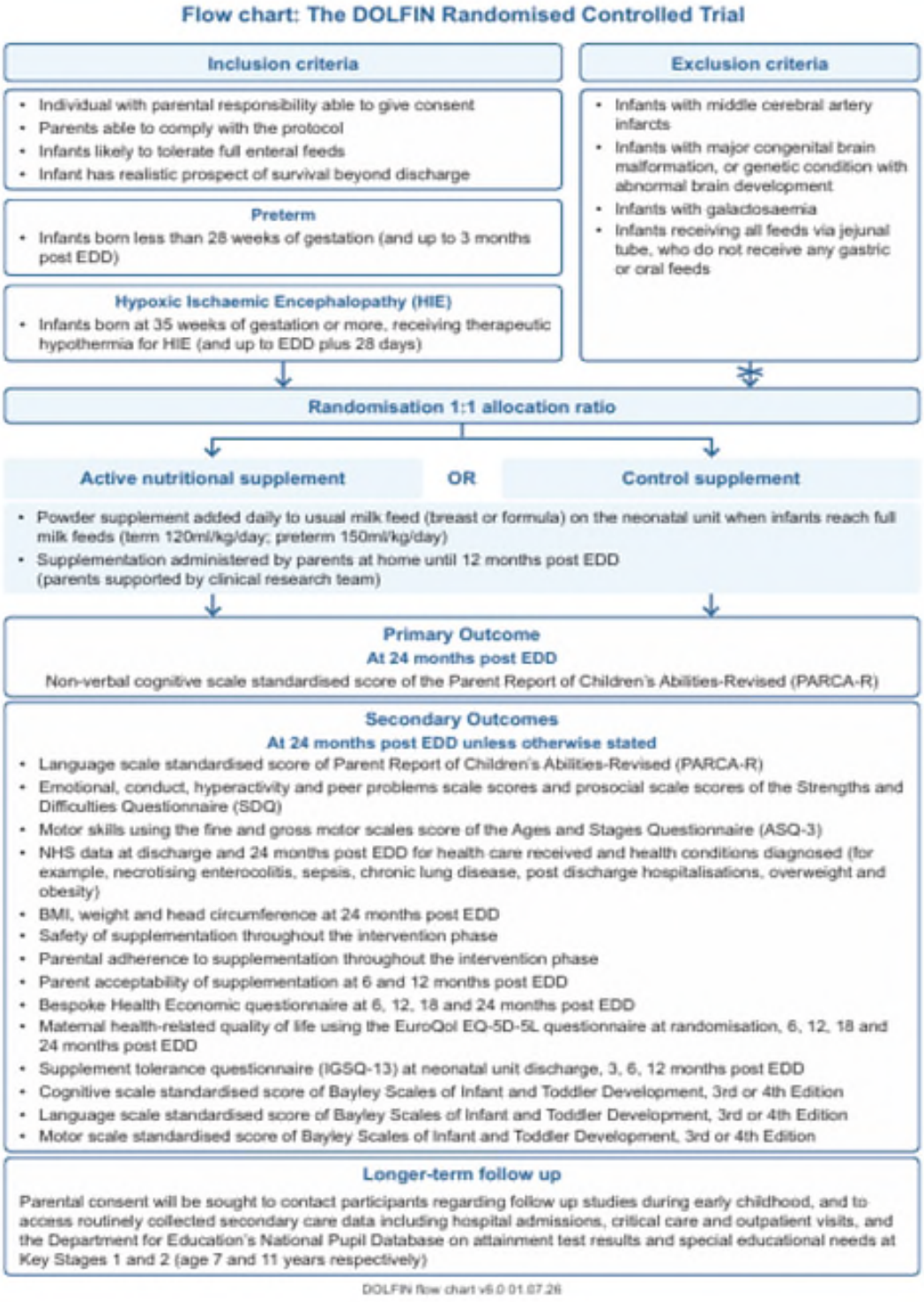
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	• To investigate the cost-effectiveness of nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP, and CMP in relation to health and social care resource use, and wider societal implications including family expenses, paid employment and informal care. To investigate the effect of nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP and CPM on clinical diagnoses up to 24-months post EDD.
Intervention(s)	Micronutrient breast milk/formula milk/food supplement containing a nutrient blend of LCPUFAs, choline, UMP, and CMP. Powder supplement added daily to usual milk feed (breast or formula) on the neonatal unit when infants reach full milk feeds (approx. 120–150ml/kg/day*). Infants can start supplementation following transfer to a Continuing Care Site or post-discharge if required. Supplementation administered by parents at home until 12 months post EDD.
Comparator	Matched control supplement, contains fractions of the active components in the investigational product and no UMP or CMP. Identically packaged and delivered powder supplement indistinguishable from the active treatment. Powder supplement added daily to usual milk feed (breast or formula) on the neonatal unit when infants reach full milk feeds (approx. 120-150ml/kg/day*). Infants can start supplementation following transfer to a Continuing Care Site or post-discharge if required. Supplementation administered by parents at home until 12 months post EDD.

*'The exact definition of full feeds will vary by site and infant according to local feeding practices but this represents a typical threshold'.

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3. FLOW CHART



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4. ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
ASQ-3	Ages and Stages Questionnaire, Third Edition
BAYLEY/BSID	Bayley Scales of Infant and Toddler Development
CEAC	Cost-effectiveness acceptability curves
CI	Confidence Interval
CI	Chief Investigator
CMP	Cytidine-5'-Monophosphate
CRF	Case Report Form
CRN	Clinical Research Networks
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DBM	Donor Breast Milk
DHA	Docosahexaenoic Acid
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EBM	Expressed Breast Milk
EDD	Estimated Date of Delivery
EP	Extreme preterm
EPA	Eicosapentaenoic Acid
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
GCP	Good Clinical Practice
GP	General Practitioner
HEAP	Health Economics Analysis Plan
HIE	Hypoxic Ischaemic Encephalopathy
HRA	Health Research Authority
IB	Investigator's Brochure
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product

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JLA PSP	James Lind Alliance Priority Setting Partnership
LCPUFA	Long Chain Polyunsaturated Fatty Acid
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NGT	Nasogastric Tube
NICE	National Institute for Health and Care Excellence
NNU	Neonatal Unit
NPEU CTU	National Perinatal Epidemiology Unit Clinical Trials Unit
RES	Research Ethics Service
PARCA-R	Parent Report of Children's Abilities-Revised
PI	Principal Investigator
PIL	Participant/Patient Information Leaflet
PMG	Project Management Group
QALY	Quality-Adjusted Life Years
R&D	NHS Trust R&D Department
RCT	Randomised Control Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDQ	Strengths and Difficulties Questionnaire
SDV	Source Data Verification
SEN	Special Educational Needs
SFS	Supplemental Feeding System
SOP	Standard Operating Procedure
USAR	Unexpected Serious Adverse Reaction
TMF	Trial Master File
TSC	Trial Steering Committee (TSC)
UMP	uridine-5'-monophosphate
WASI	Wechsler Abbreviated Scale of Intelligence

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5. BACKGROUND AND RATIONALE

Nutrients DHA, choline and UMP are particularly important for brain development and may improve neurodevelopmental outcomes[1,2]. The Dolphin neonatal external pilot RCT used a micronutrient active supplement (a nutrient blend containing LCPUFAs, choline, UMP, and CMP) given for 24 months in newborns at risk of neurological impairment[3]. A total of 59 neonates were randomised. Treatment was feasible and acceptable to families and professionals. No active nor placebo supplement-related serious adverse events or safety concerns were reported. The primary outcome was the Bayley Scales of Infant and Toddler Development III Cognitive Scale[4], following supplementation for 24 months. The treatment group had higher mean cognitive scale scores (mean difference: 9·0 (95% confidence interval (CI) (-0·2 to 18·2)), and language scale scores (mean difference: 8·6, 95% CI (-1·1 to 18·2)) compared to the placebo control group. There was little (between group) difference in mean motor scale scores (mean difference: -1.2 (95% CI (-11.9 to 9.5)). Parent reports of neurodevelopmental outcomes showed similar results[3]. The parallel Dolphin infant trial (infants age 1-18 months; n=40) reported similar findings[5]. Pre-school follow-up studies (at age 4–6 years) showed treatment group advantage (increase of 8.9 IQ points (95% CI: -4.4, 22.2) in cognitive development/IQ (assessed by the Kaufman Assessment Battery for Children II)[6] compared to controls (Andrew MJ et al, in preparation), as well as treatment group advantage in attention assessed by the Early Childhood Attention Battery subtests[7,8]. High dose DHA supplementation of infants born before 29 weeks' gestational age who participated in the N3RO trial assessing the effect of DHA supplementation on bronchopulmonary dysplasia had higher Full Scale Intelligence Quotient scores at 5 years of age compared with controls[9].

Our study includes infants at high risk of adverse neurodevelopmental outcomes. Children born extremely preterm have substantial cognitive deficits that are present in infancy and persist throughout childhood and adolescence, with deficits in IQ of a similar magnitude in adulthood as in childhood [10 11]. Up to 40% of extremely preterm children born at less than 26 weeks' gestation have moderate/severe learning difficulties and 2 in 3 have special education needs (SEN) by the end of primary education[12] resulting in reduced wealth, occupational status and economic potential in adulthood[13]. Fewer than half these infants have radiological evidence of brain injury. Infants born prematurely receive inadequate nutrient intake due to multiple challenges including high nutritional needs, prolonged parenteral nutrition, and delayed breastmilk supplementation; current nutritional protocols do not deliver sufficient DHA, choline and UMP.

Hypoxic Ischaemic Encephalopathy (HIE) is a clinical diagnosis of babies born at or near term. HIE often results in lifelong disability even in the absence of radiological abnormalities. Cognitive deficits, particularly in attention and executive functions, are identified in children following moderate-severe hypoxic ischaemic encephalopathy HIE [14,15,16]. The impact of these deficits on school attainment and social functioning are significant[17].

As these two infant populations are extremely heterogeneous, the trial is stratified for extremely preterm and HIE infant strata. Each stratum is separately powered and will be analysed separately.

The trial primary outcome measure is the Parent Report of Children's Abilities-Revised (PARCA-R) non-verbal cognitive scale score at 24 months of age (corrected for prematurity)[18]. The PARCA-R is a reliable and valid parent completed norm-referenced assessment from which age- and sex-standardised scores

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(Mean 100; SD 15) are derived for cognitive and language development[18]. It was used as an outcome measure in recent landmark perinatal trials (SIFT, INIS, INFANT), and is recommended for developmental surveillance of children born very preterm at age 2 years[19,20].

This trial aims to establish whether or not early life nutritional supplementation with LCPUFAs, choline, UMP, and CMP improves infants' cognitive development at 24 months post EDD, compared to controls, in two clearly defined strata:

1) Preterm stratum: Infants born less than 28 weeks of gestation (and up to 3 months post EDD)

2) HIE stratum: Infants born at 35 weeks of gestation or more, receiving therapeutic hypothermia for HIE (and up to EDD plus 28 days)

6. OBJECTIVES AND OUTCOME MEASURES

For each stratum separately:-

	Objective	Outcome Measures and mode of data collection	Time point(s) (post EDD)
Primary*	To compare cognitive development of infants randomised to receive nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP, and CMP compared to those randomised to receive a matched control supplement, at 24 months post EDD	Non-verbal cognitive scale standardised score of the Parent Report of Children's Abilities-Revised (PARCA-R) questionnaire	At 24 months
Secondary*	To compare the effects of nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP, and CMP	Language Development Scale standardised score of the PARCA-R questionnaire	At 24 months

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	with a matched control supplement on secondary neurodevelopmental outcomes, at 24 months post EDD	Parent reported emotional, conduct, peer problems, hyperactivity, prosocial and total score using the Strengths and Difficulties Questionnaire	
		Parent reported motor skills using the fine and gross motor scales score of the Ages and Stages Questionnaire (ASQ-3)	
Secondary**		Standardised scores of the Bayley Scales of Infant and Toddler Development, 3rd or 4th Edition: • Cognitive Scale • Language Scale • Motor Scale (where available from routine clinical assessments)	At 24 months
Secondary*	To investigate the effect of nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP, and CMP on infant growth outcomes to 24 months post EDD	Weight standard deviation score	At 24 months
		Head circumference standard deviation score	
		Overweight or obese (BMI ≥ 85th percentile)	At 24 months
	Investigate the effect of	Microbiologically-confirmed late-onset invasive infection	Up to discharge home

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	nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP, and CMP on clinical outcomes up to discharge	Necrotising enterocolitis requiring surgery	from neonatal unit
		Retinopathy of prematurity treated medically/surgically (preterm stratum only)	
		Chronic lung disease (preterm stratum only)	
Secondary**	To investigate the safety, infant tolerability, adherence to and parental acceptability of nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP, and CMP to 12 months post EDD	Safety and Adverse Events	Up to 12 months plus two weeks after the end of the interventi on period
		Parent reported infant tolerability of supplement (IGSQ)	Discharge home from neonatal unit, 3, 6 and 12 months
		Parent reported adherence	Up to 12 months
		Parent reported acceptability of supplement	6 and 12 months
Secondary*	To investigate the impact of nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP, and CMP on maternal health-related quality of life up to 24 months post EDD	Maternal health-related quality of life using the EuroQol EQ-5D-5L questionnaire	Baseline, 6, 12, 18 and 24 months
		Maternal quality adjusted life years (QALYs)	Up to 24 months

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Secondary*	To investigate the cost-effectiveness of nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP, and CMP in relation to health and social care resource use, and wider societal implications including family expenses, paid employment and informal care	Health and social care resource use and costs and out-of-pocket costs incurred by families Productivity costs and informal care	Up to 24 months
		Cost per life year without moderate/severe neurodevelopmental impairment (within-trial cost-effectiveness analysis)	At 24 months
		Cost per QALY gained (long-term cost effectiveness analysis)	Modelled to 18 years post EDD
Secondary**	To investigate the effect of nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP and CPM on clinical diagnoses up to 24-months post EDD.	Fit or seizure within the last 12 months	Up to 24 months
		Presence of a feeding tube of any type	
		Receiving supplemental oxygen or any respiratory support	
		Confirmed or suspected diagnosis of cerebral palsy	
		Hydrocephalus treated with a third ventriculostomy or ventriculo-peritoneal shunt	

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*Listed outcomes will be compared between trial arms using formal statistical methods

**Listed outcomes will be described using summary statistics only.

TRIAL DESIGN

Trial design: Multicentre, blinded, stratified, randomised controlled trial (with internal pilot and integrated economic evaluation). Strata are defined as (1) infants born < 28 weeks of gestation (and up to 3 months post EDD) (preterm stratum) and (2) infants born at ≥ 35 weeks of gestation receiving therapeutic hypothermia for HIE (and up to EDD plus 28 days) (HIE stratum).

This research will take place within UK NHS neonatal units and in participant homes. A 9-month internal pilot phase incorporates "stop-go" criteria to evaluate feasibility of recruitment and other trial processes (see section 6.1).

Trial data collection will be from trial entry until 24 months post EDD, including screening, consent, supplementation and follow-up. Outcome information will be collected by case report forms (CRFs), with clinical data collection from medical records at hospital sites. Participant weight and adherence to daily supplementation during the intervention period will be reported via a parent report and/or clinical teams. Parental questionnaires will be completed at randomisation and then sent to the parent/carer after discharge and when the child is 3, 6, 12, 18 and 24 months post EDD. Consent will be obtained to invite parents to participate in future pre-school and school age follow-up studies and to obtain routinely collected education and health data.

6.1. Internal pilot

The internal pilot will assess site and participant recruitment as pre-specified progression criteria, separately for the two strata (preterm and HIE). Other measures will include: parental uptake (expected to be 50%); retention of participants (expected around 90%); acceptability of supplementation and adherence by parents; safety; and completeness of data collection. Pre-defined stop-go criteria will be considered by the Trial Steering Committee (TSC) to assess trial viability.

The length of the internal pilot will be 9 months (one-third of the total recruitment period of 27 months) and will aim to recruit one fifth of the target sample size of 1010 (202 infants). Assuming a monthly recruitment of 1.5 infants (0.8 preterm and 0.7 HIE) per centre by month 3, with centres taking 3 months to reach stable recruitment, 30 centres will have to be actively recruiting by month 9. The internal pilot will assess the following assumptions:

% Threshold	Red	Amber	Green
Sites open	<22	≥22	≥30
Preterm patient strata			
Recruitment per site per month	<0.6	≥0.6	≥0.8
Total participants recruited	<81	≥81	108
HIE patient strata			

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Recruitment per site per month	<0.53	≥0.53	≥0.7
Total participants recruited	<70	≥70	94

Green: continue into the main trial
Amber: open new centres as appropriate, assess and address reasons for lower than anticipated recruitment, review in 6 months
Red: urgent detailed review of options with the TSC and funder

7. PARTICIPANT IDENTIFICATION

7.1. Trial participants

The trial population consists of two clearly defined strata:

Preterm stratum - Preterm infants born less than 28 weeks of gestation

and

HIE stratum - Infants born at 35 weeks of gestation or more who receive therapeutic hypothermia for hypoxic ischaemic encephalopathy (irrespective of neuroimaging findings).

7.2. Inclusion criteria

- Preterm stratum: Infants born less than 28 weeks of gestation, up to discharge home from hospital (and up to 3 months post EDD)
- HIE stratum: Infants born at 35 weeks of gestation or more, who have received therapeutic hypothermia for HIE (and up to EDD plus 28 days)
- Individual with parental responsibility able to give consent. In the event that the mother is unable to give consent, or does not have parental responsibility consent can be given by another person who has parental responsibility. Maternal consent for the purposes of maternal data collection will be sought as soon as practical
- Parents able to comply with the protocol
- Infants likely to tolerate full enteral feeds
- Infant has realistic prospect of survival beyond discharge

7.3. Exclusion criteria

The infant is not eligible if ANY of the following apply:

- Infants with middle cerebral artery infarcts
- Infants with major congenital brain malformation, or genetic condition with abnormal brain development
- Infants with galactosaemia

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- Infants receiving all feeds via jejunal tube, who do not receive any gastric or oral feeds

8. TRIAL PROCEDURES

8.1. Schedule of trial procedures

PROCEDURES	BEFORE TRIAL ENTRY	AFTER TRIAL ENTRY	AFTER TRIAL ENTRY							
	Screening	Baseline	Randomisation	Intervention and Data collection						
				Post-randomisation	Around hospital discharge	3 months post EDD	6 months post EDD	12 months post EDD	18 months post EDD	24 months post EDD
Eligibility assessment	X									
Informed consent		X								
Randomisation			X							
Supplement				X	X	X	X	X		
Parent completed baseline/outcome questionnaires				X	X	X	X	X	X	X
Parent completed tolerance questionnaire					X	X	X	X		
Acceptability questionnaire							X	X		
NHS clinical data collection		X	X		X					X
Adverse events assessments *(SAEs, SUSARs etc) throughout intervention period			X	X	X	X	X	X		

*safety monitoring occurs throughout the intervention period and will continue for two weeks after the end of the intervention period.

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8.2. Completion of outcome measures

All infants will be followed up during the trial to 24 months post EDD. An electronic communication (e.g. via the study app, email, WhatsApp, text message) will be used to prompt parents to complete and return questionnaires at randomisation, around discharge from NNU, 3 , 6, 12, 18 and 24 months post EDD. A pre-paid envelope will be supplied to families who opt to complete paper copies of the questionnaires. Participants who do not complete the outcome measures will be contacted with a further request for completion. Thereafter, failure to complete the outcome questionnaires will trigger contact from a member of the local clinical team or from the research team to check if there are any barriers to completion and offer support in completing the questionnaires. Support may include, for example, an offer to complete the questionnaire over the phone at a time convenient to the family. If absolutely necessary, a home visit from the local research nurse may be offered if this is necessary to ensure the completion of outcome measures. Primary outcome (PARCA-R) and secondary outcome neurodevelopmental data will be shared with the local neonatologist or paediatrician, or GP for participants no longer under hospital follow-up; information about norms will be provided to aid local clinician interpretation. Participating families will be sent a £25 gift voucher as a thank you for their participation in the trial at the time that 24 month parent completed outcome measures are requested.

PARCA-R scores will also be obtained from clinical records for all infants where this has been recorded during routine 2-year clinic visits. This will help to maximise the availability of data for the primary outcome. Scores from developmental assessments carried out using the Bayley Scales of Infant and Toddler Development Third or Fourth Edition (Bayley-III or Bayley-IV) will also be obtained for all infants where this has been recorded during routine 2-year clinic visits.

We will seek parental consent to send parents additional neurodevelopmental measures during early childhood, as part of a planned separately funded study; we will submit an ethics amendment to provide details about this stage at a later date.

We will also seek parental consent to access the following routinely collected secondary care data at age 7 and 11 years: NHS data including hospital admissions, critical care and outpatient visits, developmental progress and diagnoses; Department for Education's National Pupil Database on school attainment tests and SEN at what is now known as Key Stages 1 and 2 (currently at ages 7 and 11 respectively, or at the corresponding ages if these change over the intervening period). We will apply for separate funding to investigate the long-term clinical, developmental and educational outcomes of nutritional supplementation.

8.3. Recruitment

Infants will be recruited from UK NHS neonatal units (NNUs). Information about the trial will be widely available using posters and banners throughout the NNUs, on information leaflets and information and videos on the study website. Eligible infants will be identified by the clinical care team and recruited by appropriately trained, delegated individuals.

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Preterm infants must be recruited prior to discharge from hospital, either at a recruiting site or at a Continuing Care Site via remote consent. Infants in the HIE stratum can be recruited post-discharge from hospital.

8.4. Sites and Continuing Care Sites

Participating neonatal units will be either:

1. A recruiting site where parents' consent is obtained (in-person or remotely) and infants are recruited, randomised, and commence participation in the trial.

2. A Continuing Care Site, where supplement will be administered by either hospital staff or parents, and trial data collected if a participating infant is transferred in from a recruiting site or is remotely consented by the recruiting site following transfer.

In the event of a hospital transfer, the infant will be transferred with sufficient supply of supplement for use at the Continuing Care Site if approvals are obtained. Supplement may also be sent directly to the parent's home via the distribution service, for parents to bring in to the Continuing Care Site e.g. if a baby was remotely consented by a recruiting site after being transferred to a Continuing Care Site. Supplementation should continue at the Continuing Care Site whenever possible. Local approvals will be sought and in place for local hospital staff to continue any trial related activities at Continuing Care Sites.

For the neonatal stay where local approvals are in place and considered clinically appropriate by the treating clinician, parents can administer supplement whilst in hospital.

Where supplement is administered by hospital staff this will be recorded by hospital staff on a dosing log that is sent to the recruiting site for data entry. Where parents are administering the supplement at the hospital, parents can record giving of supplement on the study app or via an agreed alternative method. Further supplement will be delivered to the family home on final discharge using the approved distribution service.

The responsibility for data collection and for supporting families will lie with the recruiting site. Regulatory approvals will be in place to continue any trial related activities at continuing care sites.

Where approvals are not given and supplement administration is paused at a Continuing Care Site, administration should be recommenced as soon as possible after discharge home.

8.5. Screening and eligibility assessment

Infants admitted to the NNU will be screened for eligibility by the clinical care team. Parents with legal responsibility will be approached to discuss the trial. Eligibility will be reconfirmed at the point of randomisation.

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8.6. Informed consent

Parents with legal parental responsibility for infants identified as being potentially eligible will be approached to discuss the trial further and to request consent. Parents will be given the opportunity to consider the information, and to ask questions of the research team or other independent parties to decide whether they will participate in the trial. A trained and delegated individual must obtain appropriate informed consent from one parent with legal parental responsibility prior to any trial related procedures being undertaken. If the mother cannot be approached, maternal consent for the purposes of maternal data collection will be requested as soon as practically possible. Virtual or remote consent (via telephone or video call) will be accepted and will be documented on the paper based Remote Consent Form.

If consent is being taken in-person, the person with legal responsibility must sign and date the latest approved consent form and the delegated individual taking consent will sign and date the form. If the consent discussion takes place remotely, the person with legal responsibility will be provided with a patient information sheet either as a physical paper copy prior to consent being taken, or as an electronic copy via an email or as a digital download. The Remote Consent Form will be used to record the consent process.

Some HIE stratum infants may be transferred to Continuing Care Sites, or discharged home (before parents have had adequate time to consider the trial, or for consent to be obtained. These infants should be identified by the recruiting site. In this event, the recruiting site will approach parents to provide trial information, address parental queries and complete the consent and supplement training process in-person or remotely if parents wish to participate. Consent and training may be done by remote video or telephone discussion or in person at home or hospital. This will be documented using the paper based Remote Consent Form.

Regardless of the method of consent, a copy of the completed consent form will be provided to the parent by the recruiting site, a copy will be stored in the site file, a copy will be stored in the infant's medical notes and a copy will be sent to the NPEU CTU. A copy of the consent form should also be provided to a Continuing Care Site on request.

8.7. Randomisation

Randomisation will occur as soon as possible after consent is obtained. For the preterm stratum randomisation must occur before the infant is discharged home. For the HIE stratum randomisation may occur pre or post discharge home.

Randomisation will use a 1:1 allocation ratio, with twins (or higher order multiple births) allocated to the same arm, to either:

(1) Active supplement: Micronutrient breast milk/formula milk/food supplement containing LCPUFAs, choline, UMP, and CMP.

or

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(2) Matched control supplement, contains fractions of the active components in the investigational product and no UMP or CMP.

Randomisation of infants will be managed via a secure web-based randomisation facility hosted by the National Perinatal Epidemiology Unit Clinical Trials Unit (University of Oxford) with telephone backup available at all times (365 days per year). Randomisation will be stratified according to the two strata: (1) Preterm infants born less than 28 weeks of gestation (and up to 3 months post EDD); and (2) Infants born at 35 weeks of gestation or more who receive therapeutic hypothermia for hypoxic ischaemic encephalopathy (irrespective of neuroimaging findings) (and up to 28 days post EDD). The randomisation program will use a separate minimisation algorithm within each stratum to ensure balance between the intervention and control arms with respect to recruiting hospital and sex, and in addition for the preterm strata, gestational age at delivery (by week of gestation) and multiple births.

A Senior Trials Programmer at the NPEU CTU will write the web-based randomisation program and hold the treatment allocation codes. Pack numbers will be added by the Senior Trials Programmer, who will liaise directly with the packaging and distribution company. The Senior Trials Programmer and Trial Statisticians will monitor implementation of the randomisation procedure throughout the trial. Reports will be provided to the Data Monitoring Committee (DMC). An integrated web-based pack management system will track supplies of active supplement and control supplement ensuring a balance of stock across sites and resupplies are according to the allocated arm.

8.8. Blinding and code-breaking

Families and clinical teams caring for the infant will be blinded to trial allocation. Centres will be supplied with sealed numbered packs containing active supplement or control supplement. Once consent and eligibility are established, infants will be allocated a pack containing the trial allocation generated by the randomisation process; the trial allocation itself will not be revealed. All investigators and CTU staff with the exception of the Senior Trials Programmer and Trial Statisticians will be blinded to trial allocation.

In the event of an emergency, unblinding can be performed by the clinician at the recruiting site by logging in to the randomisation website using a single-use access code provided in a sealed envelope. The reason for unblinding must be recorded in the randomisation database. Clinicians will be reminded to exercise discretion when the allocation has been unblinded.

Clinicians carrying out emergency unblinding must be satisfied that it is a genuine emergency and that knowledge of the treatment allocation (either active supplement or control) is needed to guide the appropriate clinical management of the infant. In most cases, appropriate clinical management will be possible without unblinding, by treating the infant as if they have received the active supplement. Clinicians considering emergency unblinding are encouraged to discuss the need to do so with the PI or any clinician on the delegation log beforehand, if possible and safe to do so.

Where the infant has been transferred from the recruiting site for onward care, the treating health care professional should contact the PI or any clinician on the delegation log at the recruiting site to discuss unblinding.

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As long-term neurodevelopmental follow-up of the cohort in future studies is planned, participants will not be unblinded at the end of the trial or until all future follow-up studies are completed. Thus, all other requests for unblinding must be made in writing to the NPEU CTU, who will consider the request in discussion with the Chief Investigator or delegate.

Participants will be made aware of the unblinding process/criteria in the Parent Information Sheet prior to consent being obtained.

8.9. Study data collection

Data for the trial include:

1) Parent completed measures:

At randomisation:

The mother (or other person with parental responsibility) will be asked to complete a baseline questionnaire seeking demographic information and a health related quality of life questionnaire (the EuroQol EQ-5D-5L).

Following discharge home:

The mother (or person with parental responsibility) will be asked to complete questionnaires to assess method of supplement delivery (including breast milk or infant formula feeding), supplement tolerability, any community health and social care contacts, any costs incurred by families, parental time away from work and informal care provided by friends or family. The mother will also be asked to complete the EuroQol EQ-5D-5L questionnaire. These questionnaires will be completed at regular intervals as listed in section 6, and alongside the neurodevelopmental outcome questionnaire measures at 24 months post EDD.

Respondents will be given the option of receiving and completing all questionnaires in paper copy by post, or electronically. All data will be entered on to the study database.

2) Routinely collected clinical data:

a. Until discharge home from the Neonatal Unit:

Clinical data relating to birth and NNU admission/stay will be collected from hospital records and the BadgerNet or equivalent electronic data collection systems, from trial entry to hospital discharge home. All data will be entered on trial specific paper or electronic CRFs. If the infant is transferred to another hospital, a transfer/discharge CRF must be completed at the time of transfer to another hospital and at the point of discharge home from the hospital the infant is transferred to. If the recruiting site is not able to obtain clinical information from hospital records for an infant that has been transferred, the recruiting site may contact the transfer hospital to request required clinical information. The recruiting site will be responsible for data collection.

b. Post-discharge home (24 months post EDD):

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Clinical data and scores from routinely conducted neurodevelopmental assessments will be collected from hospital records.

All data will be entered on trial specific paper or electronic CRFs. If the recruiting site is not able to obtain clinical information from hospital records for an infant that has been transferred, the recruiting site may contact the transfer hospital to request required clinical information. The recruiting site will be responsible for data collection.

Parental consent will be obtained at trial entry requesting permission to follow up infants in the future using routine national databases.

8.10. Withdrawal of participants

8.10.1. Withdrawal of participants/change of consent

Parents will have the right to change their consent for their infant's participation in the trial at any time (withdrawal). Change of consent will not affect their infant's ongoing clinical care. They may change consent for any aspect of the study and/or data collection. Data collected up to the point of change of consent will be used in the trial. Any change of consent will be recorded on the Change of Consent form.

Parents who wish to discontinue trial supplementation will be asked if they are still happy to complete data collection and give permission for the trial team to complete data collection using medical records. In addition, the treating clinician may discontinue the trial supplement at any time if they consider it to be in the best interests of the infant's health and wellbeing. The reason for discontinuation will be recorded on an eCRF, if a reason is given.

Infants who have died, or for whom a change of consent has been received where this results in discontinuation of supplement and/or little to no data collection, within 28 days of commencing the supplement, will be replaced through additional trial recruitment.

8.10.2. Discontinuation of supplement

Parents will have the right to permanently discontinue administration of the trial supplementation. They will be asked if they continue to agree to complete data collection and give permission for the trial team to complete data collection using medical records. In addition, the treating clinician may discontinue the trial supplement at any time if they consider it to be in the best interests of the infant's health and wellbeing. The reason for discontinuation will be recorded on the Supplement Discontinuation CRF, if a reason is given.

8.11. Definition of end of trial

The end of the trial will be defined as the date when the trial database is locked. An end of trial declaration will be made to the approving REC.

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9. TRIAL INTERVENTIONS

This trial is classified as A Clinical Trial of a non-IMP. The active supplement is not classifiable as an investigational medicinal product therefore clinical trials authorisation from the MHRA is not required.

The active and control supplements have been developed, quality control checked and provided by Nutricia, a company that makes foods for medical nutrition. Nutricia is the only supplier of this particular supplement. Nutricia were not involved in the design of the study, nor will they be involved in the collection or analysis of trial data. Depending on the findings of the trial, organisations such as the National Institute of Health and Care Research can decide if it should be offered through the NHS.

9.1. Intervention description

The intervention is a novel micronutrient breast milk/formula milk/food active supplement powder. The active supplement consists of a specific nutrient blend containing long-chain polyunsaturated fatty acids (LCPUFAs), choline, uridine-5'-Monophosphate (UMP), and cytidine-5'-monophosphate (CMP).

A matched control supplement will be an identically packaged and delivered powder supplement indistinguishable from the active supplement. The control supplement contains fractions of the active components in the investigational product and no UMP or CMP. The control supplement contains higher levels of lactose. The active and the control supplements are isocaloric, and have similar levels of fat and comparable energy content.

Powder supplement will be added daily to usual milk feed (breast or formula) on the neonatal unit after infants have reached full milk feeds (120–150ml/kg/day). For HIE stratum babies, -in the event an eligible infant is discharged home without joining the trial, and/or starting supplementation, consent, training to give supplement, and commencement of supplement can be undertaken at home up to 28 days post discharge. The infant will be randomised in accordance with section 8.6. Supplementation will be continued on discharge until 12 months post EDD and can be added to weaning foods.

Nutricia Research, the Netherlands designed, produced, and supplied the supplements for the original Dolphin Trials [3,5]. Subsequent market research with Dolphin Trials' parent participants and product development work refined the supplement products and improved the overall product experience and acceptability, as confirmed during product testing with Dolphin Trials' parent participants.

The long-chain polyunsaturated fatty acids in the active supplement are from a fish source. The supplements contain small amounts of cow's milk protein. The supplements do not contain pork. They are not certified kosher and halal compliant.

To prepare the supplement in a clean and correct way the factory will clean the production line after each production. They will test the quality and safety of the supplements, (including microbiological safety testing). The supplements will be produced by the factory in 13g sachets. The sachets will be boxed in the factory. When the supplements are produced, tested and boxed they will be sent to an external warehouse where the boxes containing the supplements will be labelled for the study purposes.

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Each box will have a unique identifier code supplied by the NPEU CTU. Nutricia will store the boxed sachets and transport them to the UK. Boxes of supplement sachets will be stored in the UK and delivered to recruiting sites and to the participants' homes by a distribution company subcontracted by Newcastle upon Tyne Hospitals NHS Foundation Trust. Nutricia will have no access to child, parent or professional identifiable information (see Section 12, Data Management). Their branding will not be on the sachets or trial materials.

9.1.1. Blinding of supplement

The control supplement and the active treatment will be packaged in either a white or a foil sachet. The colour of the sachet bears no correlation as to whether it is the control supplement or the active treatment, and the content will be indistinguishable. See section 8.7 Blinding and code-breaking for further details.

9.1.2. Commencing and continuing supplement

Powder supplement will be added daily to usual milk feed (breast or formula) or sterile water on the neonatal unit after infants have reached full milk feeds as per local feeding practices, unless there is clinical indication not to do so.

The definition of 'full milk feeds' will vary slightly between NNUs and infants, but in term infants these are typically around 120ml/kg/day whilst in preterm infants they are around 150ml/kg/day, or when parenteral nutrition is no longer considered necessary (exact timing at the discretion of the clinical consultant managing their care), unless there is clinical indication not to do so. Infants recruited post-discharge will commence supplementation as soon as possible after randomisation.

Whilst on the NNU, the supplement will be added to milk or sterile water by milk-kitchen or nursing staff, or parents, according to each NNUs standard approach. The supplement will be continued at home by parents post-discharge and continued to 12 months post EDD. This date will be provided to parents in the discharge information pack, and to local teams on infant trial entry.

For HIE stratum babies, in the event an eligible infant is discharged without joining the trial, and/or starting supplementation, consent can be undertaken up to EDD plus 28 days. In these circumstances, supplement will be sent directly from the UK storage facility to the parents using the distribution service. Training to give supplement can be undertaken remotely. Commencement of supplement should take place as soon as possible.

For preterm infants consented remotely by a recruiting site whilst at a Continuing Care Sites, training to give supplement can be undertaken remotely. The supplement will be sent directly from the UK storage facility to the parents using the distribution service and brought to the Continuing Care Site by parents if supplementation is to commence prior to discharge.

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On discharge, parents will continue the supplement at home for 12 months post EDD. The date to stop supplement will be provided to parents in the discharge information pack, and to local teams on infant trial entry.

For paediatric readmissions or short break stays away from home during the intervention period (up to 12 months post EDD), where locally permitted, parents can continue to give their infant supplement in line with local policies, and considered clinically appropriate by the treating clinician.

Where approvals are not given and supplement administration is paused during a paediatric admission, administration should be recommenced as soon as possible after discharged.

9.1.3. Administration of supplement

The supplement will be provided in labelled sachets. Each box of supplement will contain a 1g scoop, with which to measure out supplement from the sachet. The measured supplement dose will either be dissolved into the infants' milk feed, or dissolved in a small volume of infant milk and given ahead of a feed.

If a breast-feeding mother is unable to or does not wish to express milk with which to mix the supplement, and does not wish to use infant formula milk, the supplement can be mixed with a minimum volume of sterile water (3ml sterile water per 1g supplement) and given ahead of the feed where clinically appropriate. Once an infant is established on solids, the supplement can also be mixed with appropriate infant foods.

The daily amount of supplement will be 1g/kg i.e. 1 scoop per whole kilogram child weight i.e. an infant weighing 3.0 –3.9kg will receive 3 scoops daily. Infants weighing less than 1kg will receive a proportionate amount of supplement based on pre-defined weight bands i.e. an infant who weighs 0.5-0.74kg will receive 0.5g supplement; infants weighing 0.75-0.99kg will receive 0.75g of supplement. To make up 0.5g of supplement, NNU staff will follow guidance for making up 1g supplement (in a minimum of 3ml milk) then discard 50% of the total volume of milk mixed with supplement. To make up 0.75g of supplement, NNU staff will follow guidance for making up 1g supplement (in a minimum of 3ml milk) then discard 25% of the total volume of milk mixed with supplement. The daily supplement dose can be given with one milk feed or meal, or split across more than one milk feed or meal depending on infant feed volumes and preference.

Each 1g of supplement must be given with a total milk volume of at least 15ml of milk to ensure appropriate osmolality. For breastfed babies, 1g supplement can be mixed with a minimum volume of 3ml of milk and given before a feed, as long as the total feed volume is at least 15ml for each 1g of supplement. Infants who weigh less than 1kg will require a proportionate total feed volume i.e. infants receiving 0.5g of supplement will have a minimum total feed volume of 7.5ml, and infants receiving 0.75g of supplement will have a minimum feed volume of 11ml.

Infants receiving supplement dissolved in their usual milk feed will be given this via their normal feeding route e.g. oral, nasogastric tube, gastrostomy tube. Mothers of infants who are fed via nasogastric or

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gastrostomy tube will be supported with supplement delivery by a funded NHS clinical team at sites and via specifically developed trial materials.

Breastfeeding mothers will be provided with a range of options for delivering the supplement before a breast feed, including for example, use of a supplemental feeding system, syringe, teat, finger-feeder, or a cup. Depending upon the supplement delivery method chosen, breastfeeding mothers who choose to express the required volume of milk with which to mix the supplement, will be supported to do this through funded NHS clinical team at sites and specifically developed trial materials.

9.1.4. Adherence to trial supplement prior to discharge

Prior to hospital discharge, if the clinical team are administering the supplement, adherence to giving the supplement will be recorded on paper dosing logs and entered on to the study database, completed by the local research team. If parents are administering the supplement, adherence to giving the supplement will be recorded on the study app or paper diary by the parents.

9.1.5. Development of food intolerance during supplementation

The following allergens (according to directive 2003/89/EC) may be present in the product:

- Eggs and products thereof
- Fish and products thereof
- Milk and products thereof (including lactose)

If any of the following food intolerances/conditions are suspected and an exclusion diet trialled in an attempt to reach a conclusion, then supplementation will be suspended for the duration of the exclusion trial then re-started once an intolerance has been excluded:

- Established or expected cow's milk protein allergy
- Lactose intolerance
- Intolerance of eggs and products thereof
- Galactosaemia
- Fish protein allergy

This information is provided to parents in the discharge pack. The infant should continue with the trial procedures as documented in this protocol despite stopping supplementation.

9.2. Parent support and training to give supplement

The supplement can be given to infants who are breastfeeding, bottle feeding (either maternal breastmilk or DBM or formula milk), or nasogastric/gastrostomy tube (NGT/GT) feeding. Breastfeeding mothers will be provided with a range of options for delivering the supplement, including, for example, use of a supplemental feeding system, syringe, teat, finger-feeder or cup, or another system if that is preferred and used by local sites. In the days or weeks prior to hospital discharge, parents will be taught to mix and give the supplement to their infant by NNU staff. Supplement training may be completed remotely when in person training has not taken place. At discharge each family will be provided with

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aparent discharge pack, which will contain an initial supply of supplement, written support materials and access to online information and videos specific to each feeding method detailing: how to mix and give the supplement, dosing schedules, a personalised study timeline (with the infant's supplement end date and outcome measurement dates), and contact information for the infant's local NHS professionals and the research team. Families of preterm infants and HIE infants recruited post-transfer, or HIE infants recruited post-discharge, will be sent the discharge pack by the recruiting site. Generic versions of the materials will also be available via the trial website (https://www.npeu.ox.ac.uk/dolfin), which will include: videos on how to mix the supplement, breastfeeding support materials, nasogastric and gastrostomy tube feeding support materials.

There will also be a frequently asked questions page, which will be regularly updated. Parents will also be signposted to the trial website via the app (or text) during app (or text) contacts.

9.3. Promotion, protection and maintenance of breastfeeding

The DOLFIN trial will utilise existing appropriate materials that are available widely or locally to support breastfeeding mothers. Prior to the trial commencing, focus groups with breastfeeding mothers of preterm and term infants will facilitate co-design of breastfeeding support materials for use during the trial. This will include written and video materials providing population specific breastfeeding advice, and demonstration of available methods for giving EBM mixed with supplement. Informed by this Patient and Public Involvement (PPI) work, methods to promote, protect and maintain breastfeeding will be employed as follows:

1. Recruiting NNUs will receive funding for breast pumps for use by trial mothers when their infants are on the NNU, or at home post-discharge.

2. Breastfeeding mothers will have a choice of delivery methods for giving the supplement. These include: use of a supplemental feeding system (SFS) known to be effective and acceptable to mothers (a thin flexible tube is taped to the nipple, the other end is placed in a plastic bottle containing supplement and breast milk; sucking facilitates simultaneous draw from the breast and from the bottle, the infant controls the flow rate), mixing the supplement with maternal choice of milk and giving via a syringe, teat, finger-feeder, or cup, or another safe system if that is preferred and used by local sites.

3. Signposting to local and national breastfeeding support.

4. Breastfeeding mothers will also be supported by local lactation consultants as per usual care.

5. The DOLFIN study team includes lactation consultants who can respond to queries from sites or parents upon request.

9.4. Support for parents post discharge

Parents will be supported throughout the trial by their local neonatal and local post discharge clinical teams including paediatricians, dietitians, lactation consultants, as per usual care. Parents will be provided with information on who to contact with trial related queries (local research nurses or local

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post discharge clinical team, depending on local set-up). Members of the Project Management Group (PMG) will respond to queries from local neonatal and local post discharge clinical teams as needed. The PMG may respond to direct queries from parents relating to trial processes, data collection or resupply of supplement; they will not become involved with queries relating to the clinical care of their infant. Queries relating to the clinical care of infants will be directed to the local neonatal and local post discharge clinical teams. If needed, the PMG will liaise with parents and with the local post discharge clinical team at sites as required to best support participating families.

9.5. Trial communication and adherence app

During the trial, parents will be invited to download a bespoke trial app, created in partnership with NuTH, and produced by Newcastle University, to facilitate communication with the research team and collection of adherence data (this will be GDPR compliant, and Sponsor approved). Parents will also be able to contact the research team directly via individual WhatsApp accounts (text messages will be used for parents unwilling/unable to use the app or WhatsApp). WhatsApp, text message or email will only be used as a communication tool and will not be used to collect trial data. Any queries regarding clinical care will be directed to the local neonatal or local post discharge clinical team as appropriate, with whom the research team will liaise as required (see section 9.4 Support for parents post discharge and 9.6 – Support to local clinical teams).

9.6. Support to local clinical teams

Local neonatal and post discharge clinical teams will be supported by the clinical trial research team comprising paediatricians, dietitians, a research nurse and a lactation consultant. The research team nurse and co-investigator team will provide comprehensive training to local neonatal and post discharge nurses, lactation consultants, dieticians, and medical staff at site set-up. This will include face-to-face (remote or in person) training on the study and provision of comprehensive written trial reference materials within the site trial pack. The professionals' page hosted on the NPEU website will contain comprehensive materials and a frequently asked questions document. The research team will be in regular contact with local clinical teams, during the set up and recruitment and supplementation phases, to allow early identification and resolution of any challenges.

9.7. Supplement storage and supply

Nutricia will transport the supplement through the intervention phase to the UK storage facility. The supplement will be distributed to participating NNUs and direct to family homes via the distributor. Participants will be discharged with an initial supply of supplement, then receive further deliveries of supplement through the supplementation stage. The number of deliveries will be determined by final product shelf-life, anticipated to be 9 months by trial commencement, or longer if Nutricia testing shows this is appropriate. The resupply of supplement across all sites will be closely monitored using an online pack management system that will track stock levels (including expiry dates) across sites and families. This will ensure full accountability of packs and resupply to families is in line with protocol requirements. The supplement should be stored at ambient room temperature in a naturally cool area with a range of 2-25 degrees Celsius. The supplement is stable up to 30 degrees Celsius if it does not reach 25-30

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degrees Celsius for more than 30 consecutive days. The supplement does not require temperature monitoring at sites or in parent's homes.

9.8. Post discharge supplementation period

9.8.1. Altering the amount of supplement received

During supplementation, parents will receive monthly requests for information about their infant's weight (regularly measured as standard care for this population; parents will be requested to weigh their infant monthly at a health clinic and enter the weight in a banding - for example 3-4 kg, 6-7kg). Parents can submit monthly weights via the study app, or for parents not using the study app parents will be sent (using text or email) a link to an OpenClinica Participate form into which they will enter their infant's current weight. The study app and the OpenClinica Participate form reference the trial website and flag that the dosing schedule for each weight band can be accessed here. Parents will also have a paper version of the dosing schedule in their discharge pack. Supplement dose will be equivalent to 1 scoop per whole kg child body weight (each scoop 1g), up to a maximum daily dose of 12g (for example a 3.6kg infant in the 3-4kg weight band receives 3 scoops). For the first 6 months, the local research nurse will telephone parents monthly to confirm the current correct dose on receipt of weight information, supported by the trial dietitians. If parents are confident of the dosing method, dose confirmation calls will cease thereafter. The app is not considered a medical device.

9.8.2. Adherence monitoring following discharge

For the first month of supplementation post discharge, parents will be asked to confirm that they have given the supplement, via study app, or by responding to a daily email or text. In response to PPI input, the frequency of reminders will then reduce to prevent contact fatigue; parents will be able to request to continue/discontinue daily reminders if they wish. This will allow the research team to identify parents who may need additional support to give the supplement. After the first month post discharge, parents will receive a weekly email, text or app prompt asking them to report the proportion of supplement they have managed to deliver over the previous week from a drop down menu. In cases of non-adherence, the research team will liaise with the post discharge clinical team to identify barriers to supplementation and offer appropriate support to improve subsequent adherence. Parents can also opt to complete a paper diary to record adherence if they do not wish to use email/text or study app reporting.

9.8.3. Accountability of the trial supplement

Families will be advised to dispose of unused or expired supplement by placing it in a domestic bin. There will be no product reconciliation. Adherence monitoring will be parent reported via the reporting mechanisms described in section 9.8.3.

9.8.4. Concomitant medications and dietary supplementation

There are no contraindicated medications or dietary supplements, and infants will be able to have all medicines and supplements normally prescribed for this population during the course of the trial. If

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parents choose to give additional dietary LCPUFA to their infant, this is not a concern as commercially available LCPUFA supplements are low and will not significantly alter the overall LCPUFA intake of participating infants.

9.8.5. Recruitment to other trials

Co-recruitment to other trials is permitted, except for intervention trials which have a neurodevelopmental primary outcome. Co-recruitment to another trial with a neurodevelopmental primary outcome may be possible following discussion and agreement between trial Chief Investigators.

9.8.6. Post-trial supplementation

There will not be the provision of the supplement beyond the trial period.

10. SAFETY REPORTING

10.1. Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a trial supplement has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a participant which is related to the trial supplement.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: 1. results in death 2. is life-threatening 3. requires inpatient hospitalisation or prolongation of existing hospitalisation 4. results in persistent or significant disability/incapacity 5. consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to the trial supplement, based on the information provided.

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Unexpected Serious Adverse Reaction	An SAE that, in the opinion of the PI, CI or safety delegate, is a result of the trial supplement and is not an expected event (in the opinion of the CI or safety delegate.

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

10.2. Procedures for reporting Adverse Events

The safety reporting window for this trial will be from starting the supplement up to two weeks after completing the trial supplement period (12 months post EDD) for each participant if no discontinuation date is recorded; otherwise until 2 weeks post date of discontinuation of supplement. All trials run by the NPEU Clinical Trials Unit (NPEU CTU) follow the unit’s safety reporting Standard Operating Procedure (Safety Reporting in Trials not using IMPs).

In this population we anticipate day-to-day fluctuations of pre-existing conditions, new conditions, and we anticipate a small number of deaths. As a result, many adverse events are foreseeable due to the nature of the participant population and their routine care/ treatment. Consequently, only those adverse events identified as serious will be reported for the trial.

10.2.1. Foreseeable SAEs which do not require expedited reporting via a SAE form

The following foreseeable SAEs are pre-defined trial outcomes or are events that could be reasonably expected to occur in this population. They do not require reporting by trial centres as SAEs unless considered that they may be causally related to the trial supplement, in which case they should be reported as detailed in Section 10.3:

Foreseeable serious adverse events:

1. Abnormalities of tone, posture and/or movement
2. Accidental injury
3. Acute cardio-respiratory event or failure
4. Anaemia
5. Clinically significant intracranial abnormality on cranial ultrasound scan – intracranial haemorrhage or white matter injury
6. Chronic lung disease / Broncho pulmonary dysplasia
7. Coagulopathy requiring treatment
8. Congenital anomalies
9. Constipation
10. Death (unless unforeseen in this population)
11. Difficulty establishing enteral feeding
12. Dysphagia/neurological feeding and drinking difficulties

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13. Epilepsy
14. Food intolerances leading to exclusion diet (cow's milk, lactose, eggs, fish)
15. Fluid retention
16. Fine motor impairment
17. Gastrointestinal bleeding
18. Gastro-oesophageal reflux disease
19. Gastrostomy insertion
20. Global developmental impairment
21. Gross motor impairment
22. Haematuria
23. Haemothorax
24. Hearing impairment
25. High blood creatinine level (defined as >100 µmol/L)
26. Hyperbilirubinemia (jaundice)
27. Hyperglycaemia
28. Hypoglycaemia
29. Hypotension
30. Hypoxic ischaemic encephalopathy
31. Hydrocephalus
32. Impaired renal function (urine output <0.5 ml/kg/hour, and or serum creatinine > 100 µmol/L)
33. Incarcerated hernia
34. Jejunostomy or gastrojejunostomy extension tube insertion
35. Low sodium level/hyponatremia
36. Liver dysfunction
37. Non-iatrogenic meningitis
38. Necrotising enterocolitis
39. Neutropenia (defined as <1.0 mmol/L)
40. Metabolic bone disease
41. Metabolic disturbance of electrolytes or minerals
42. Patent ductus arteriosus
43. Pneumothorax or air leaks
44. Pneumonia (including aspiration pneumonia)
45. Pulmonary haemorrhage
46. Pulmonary hypertension requiring treatment
47. Respiratory failure
48. Retinopathy of prematurity
49. Seizures
50. Sepsis / infection (except when associated with culture/growth of an unusual organism, see section 10.2.2 below)
51. Sleep disordered breathing
52. Spontaneous intestinal perforation
53. Speech and language impairment
54. Sudden and Unexpected Death in Infancy

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55. Thrombocytopenia
56. Tracheostomy placement
57. Upper airway obstruction
58. Ventriculo-peritoneal shunt insertion or replacement
59. Visual impairment

10.2.2. SAEs which require expedited reporting via SAE reporting form:

All SAEs other than those listed as foreseeable (section 10.2.1), and not deemed causally related, will be reported. Reporting procedures will be followed as per section 10.3. In particular, the following events will need to be reported:

- Serious prolonged gastrointestinal disturbance (except from necrotising enterocolitis)
- Serious prolonged gastrointestinal disturbance associated with culture/growth of an unusual organism
- Sepsis associated with culture/growth of an unusual organism

All SAEs deemed causally related to the trial supplement must also be reported as per section 10.3, irrespective if they feature in the list under 10.2.1.

10.3. Reporting procedures for Serious Adverse Events

During NNU admission, all unforeseeable SAEs, and foreseeable SAEs deemed causally related to the trial supplement (as defined in section 10.2.2) must be reported on the SAE Reporting Form to the NPEU CTU trial team as soon as possible after the site becomes aware of the event being defined as serious.

Following discharge from the NNU, parents will be asked to report SAEs to their local research nurse or post discharge clinical team using contact details provided in discharge trial packs. Parents will be reminded via the study app or an agreed alternative (text message or email) to report unplanned hospital admissions. When a report is received the site will be asked to assess whether the hospital admission requires reporting as an SAE. Parents will also be asked about the occurrence of SAEs at the time of parent reported outcome measure completion at 3, 6 and 12 months post EDD. SAEs reported to the local research nurse or post discharge clinical team (which meet the reporting criteria listed above), must be reported to the NPEU CTU trial team via the SAE Reporting Form as soon as possible after the individual being made aware of the event being defined as serious.

Sites may use one of the following SAE reporting methods:

1. Paper or electronic forms, with instructions, will be provided with the trial documentation to enable anyone to report an SAE. The completed SAE form must be emailed to NPEU CTU.
2. Staff with access to the trial electronic database should complete the SAE form online. An automatic email notification to the NPEU CTU staff will be triggered for SAEs reported electronically.

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3. Where the above routes are not possible, then the SAE may be reported to NPEU CTU by telephone and the SAE form will be completed by NPEU CTU staff in compliance with internal NPEU CTU safety reporting Standard Operating Procedures (SOPs).

Follow-up SAE information should be reported as necessary by the site staff and sent back to the NPEU CTU electronically or by email.

All reportable SAEs as defined in this protocol will be forwarded to Nutricia as set out in the Product Supply Agreement.

10.4. Assessment of causality

The relationship of each adverse event to the trial supplement must be determined by a medically qualified individual according to the following definitions:

- **Unrelated** – where an event is not considered to be related to the trial supplement.
- **Possibly** – although a relationship to the trial supplement cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.
- **Probably** – the temporal relationship and absence of a more likely explanation suggest the event could be related to the trial supplement.
- **Definitely** – the trial supplement is the most likely cause.

All SAEs labelled possibly, probably or definitely will be considered as related to the trial supplement.

10.5. Review of SAEs

The NPEU CTU will forward a copy of the SAE form to the CI / safety delegate as soon as possible on receipt. The CI /safety delegate will also (as well as the site PI) assess whether the SAE was related to the trial supplement (i.e. is it an SAE or a SAR). If assessed to be related, the CI / safety delegate will proceed to assess expectedness (see Section 10.5.1). All completed SAE forms will also be sent to the sponsor.

10.5.1. Assessment of expectedness

Assessment of whether a serious adverse reaction is an expected event will be made by the CI / safety delegate.

10.6. Reporting Unexpected Serious Adverse Reactions

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the PI, CI or safety delegate the event was 'related' (resulted from administration of the trial supplement) and, in the opinion of the CI or safety delegate, 'unexpected' in relation to the trial supplement. Reports of related and unexpected SAEs should be submitted within 15 working days of the CI or safety delegate becoming aware of the event, using the HRA report of serious adverse event form (see HRA website)."

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As the study is blinded, the blind will be broken for the participant concerned by the Senior Trials Programmer or delegate, who will then carry out the required reporting. These unexpected SARs will also be reported to the DMC in an unblinded format. The Sponsor, Site PIs and relevant R&D offices will receive a summary of the USAR in a blinded format to prevent unnecessary unblinding. The NPEU CTU/ NUTH will forward all required safety events to Nutricia as detailed in the Product Supply Agreement Safety Reporting Schedule.

11. STATISTICS

11.1. Sample size determination

To detect a 6 point difference between two trial arms on the PARCA-R non-verbal cognitive scale standardised score (for both strata), with 90% power and a 2-sided 5% significance, assuming a population mean score of 88 and standard deviation of 19, 212 infants per arm are required for each stratum (424 in the preterm stratum and 424 in the HIE stratum). The estimated mean and standard deviation are from infants born less than 28 weeks of gestation in the PANDA study (used as validation sample for PARCA-R standardisation)(6); we assume similarly for infants of ≥ 35 weeks gestation with HIE.

An inflation factor of 14% applied to the preterm stratum allows for clustering due to infants from multiple births being randomised to the same allocation and gives a total of 484 infants (assuming prevalence of multiples of 30% and intra-cluster correlation coefficient of 0.77, data from SIFT trial)(15). Prevalence of multiples in the HIE stratum is expected to be negligible. Allowing for 10% loss to follow-up at 2 years of age gives an overall sample size of 538 (269 per arm) in the preterm stratum and 472 (236 per arm) in the HIE stratum. The total target sample size is 1,010 infants.

11.2. Statistical analysis plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan that will be available prior to the first DMC review of interim data. The SAP will be finalised before final data lock takes place.

11.3. Description of statistical methods

The trial is powered to detect differences in the two trial strata (preterm and HIE) separately, and data will be analysed and presented separately for each stratum. Overall results by allocation for the two strata combined will not be presented. The primary inference will be based on a modified intention to treat (ITT) analysis, i.e. infants with outcome data will be analysed in the groups into which they were randomly allocated, regardless of allocation received.

The flow of participants through each stage of the trial will be summarised by randomised group using a CONSORT diagram, separately for the preterm and HIE strata. The number and percentage of infants lost to follow-up will be reported with the reasons recorded. Socio-demographic characteristics of the mothers, and clinical characteristics of the infants at baseline will be reported by trial allocation. For binary

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and categorical variables, the number and percentage in each category will be presented. For continuous variables, the mean and standard deviation or the median and the interquartile range will be presented. There will be no planned tests of statistical significance performed for differences between randomised groups on any baseline variable.

The mean and standard deviation will be presented for the standardised PARCA-R non-verbal cognitive scale score at 24 months post EDD by randomised group. A mixed-effects linear regression model will be fitted, adjusting for minimisation factors and the correlation between infants from multiple births. Recruiting hospital will be treated as a random effect in the model, with mother's identification nested within site and all other minimisation factors fitted as fixed effects. A similar analysis approach will be adopted for other continuous outcomes, unless they are highly skewed, in which case quantile regression methods will be used and median differences with 95% confidence intervals will be presented.

Standardised PARCA-R scores cannot be calculated for infants if questionnaires are completed outside of 23.5 to 27.5 months post EDD, although their raw scores may be available. A multiple imputation analysis will be performed, imputing standardised scores for such infants. Estimates from the multiple imputation analysis will be presented as the primary inference and further sensitivity analyses will be documented in the SAP.

For dichotomous outcomes, risk ratios and 95% confidence intervals will be estimated using a log-binomial regression model, or a Poisson regression model with robust variance estimator if the binomial model fails to converge. Growth measurements (weight and head circumference) will be converted to standard deviation scores and analyses will be adjusted for baseline growth scores. These models will also be adjusted for minimisation factors and the correlation between infants from multiple births.

The consistency of the effect of the active supplement on the primary outcome will be assessed across specific subgroups of infants using the statistical test of interaction. Effect estimates and 95% confidence intervals will be presented for each subgroup, plus the interaction p-value.

The subgroup categories are:

- Gestational age at birth by week of gestation for the preterm stratum
- Severity of Hypoxic Ischaemic Encephalopathy (normal/mild, moderate, severe) according to neurological examination on days 1, 2 and 3 of therapeutic hypothermia for the HIE stratum.

A two-sided 5% level of significance will be used for all statistical tests, and 95% confidence intervals will be presented for all pre-specified outcome comparisons including subgroup analyses.

11.4. Health economics analysis

A cost-effectiveness analysis to determine whether the potential benefits of active supplement added to usual milk feed compared to usual milk without supplement represents value for money will be conducted separately for the preterm and HIE strata. A health economics analysis plan (HEAP) with extended details of the summarised costs-effectiveness methods presented in this proposal will be

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prepared in a separate document. The HEAP will be prepared and finalised before final data lock takes place.

We have designed a two-stage economic evaluation to assess: 1) whether the resources needed to deliver active supplement in practice are justified by the additional benefits achieved at 24 months; and 2) to estimate the cost-effectiveness of the intervention compared to the control group up to 18 years of age. In the first stage, we will conduct two within-trial cost-effectiveness analyses using: 1) Life years without moderate/severe neurodevelopmental impairment, and 2) the trial primary outcome, as the health outcome measure for the economic evaluation. Results of the within-trial cost-effectiveness analysis will also be presented as a cost-consequence evaluation in a secondary analysis. In the second stage, we will estimate a cost-utility analysis using a decision analytical model.

Stage 1: Within-trial cost-effectiveness analysis at 24 months corrected age

An NHS health care and societal perspective will be used in the within-trial cost-effectiveness analysis with categories of resource use relevant to each perspective captured. To minimise burden to families, we will extract secondary care data from hospital records at each site. We will circulate parents a questionnaire when infants are 6, 12, 18 and 24 months corrected age to collect health care utilisation details not available in hospital records (primary and community health and social care usage), any major specialist items purchased by families or home adaptations for the care of their infants; changes in parents' work pattern or time away from work, additional informal care/support required. We will conduct a micro-costing approach to determine the cost of delivering the intervention in practice to the NHS and families. Categories of resource use will be costed using national average unit costs from established sources including, for example, NHS Reference Costs and the Personal and Social Services Research Unit.

We will also collect maternal EuroQol EQ-5D-5L data to understand whether the intervention also affects mothers' health-related quality of life over the trial period.

Mean incremental analysis of costs and life-years without moderate/severe impairment between active and control supplements will be synthesised using the incremental cost-effectiveness ratio (ICER), which will be expressed as:

1) incremental cost per life year without moderate/severe impairment. Moderate/severe impairment will be defined as having moderate or severe impairment in any of the following:

- cognitive (PARCA-R non-verbal cognition standard score <70);
- language (PARCA-R language standard score <70);
- gross motor (inability to walk independently; unable to sit independently);
- hearing (hearing loss corrected with aids; some hearing loss not corrected by aids; deafness);
- visual (reduced vision uncorrected with aids; blindness in one eye; blindness/can perceive light only).

2) incremental cost per unit increase in the standardised PARCA-R non-verbal cognitive scale score at 24 months post EDD. Uncertainty around that estimate will be presented using parametric and non-

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parametric confidence intervals for the ICER (if appropriate) and cost-effectiveness acceptability curves (CEAC). Cost-effectiveness results will be presented separately for infants born <28 weeks gestation and those born at term who receive therapeutic cooling.

As a secondary analysis, we will also present the Stage 1 within-trial economic evaluation using a cost-consequence analysis. Costs will be presented alongside the key primary and secondary outcomes by treatment arm with associated uncertainty (for example PARCA-R, SDQ, parental acceptability, maternal health-related quality of life) an approach which will enable various stakeholders (for example parents, clinicians) to contemplate the impact of active supplement on the outcomes of most relevance to them.

Stage 2: Long-term cost-effectiveness analysis

If intervention with a nutrient enriched diet is shown to be cost-effective in Stage 1 for any of the infant population strata, we will develop a decision analytical model to estimate the cost-effectiveness of the intervention up to 18 years of age. This analysis will be conducted from a societal perspective and the main outcome measure in the economic evaluation will be child quality-adjusted life years (QALYs). A Markov model will be constructed representing the natural history of infants born <28 weeks gestation or born at term who receive therapeutic cooling to extrapolate the within-trial cost-effectiveness results using annual cycles. The structure of the model will be established and agreed within the research team. Observed outcomes and health care resource utilisation for randomised infants will be used to inform the characteristics of a hypothetical cohort entering the model. Transition probabilities indicating movement across health states during the first two years will be obtained from the trial, whereas transition probabilities after the second year will be informed through literature searches. Health care costs and health-related quality of life estimates incurred annually in each health state after the second year will be obtained from the literature. Data on informal care and impact on productivity of parents to inform cost parameters in the model will also be obtained from the literature.

Costs and QALYs will be combined and synthesised using the ICER and the net-benefit statistic. Uncertainty will be assessed using probabilistic sensitivity analysis and CEACs. These results will be presented from an NHS perspective and a societal perspective. One-way sensitivity analysis will be carried out to explore the impact of parameters not subject to probabilistic uncertainty (e.g. cost of active supplement to the NHS) on cost-effectiveness results.

11.5. Procedures for reporting any deviation(s) from the original statistical plan

Deviations from the Original Statistical Plan agreed by the co-investigators will be reported to the Trial Steering Committee, and the NIHR.

12. DATA MANAGEMENT

The data management aspects of the trial will be fully described in the Data Management Plan to ensure that high quality data are produced for statistical analysis.

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12.1. Source data

Source documents are where data are first recorded, and from which infants' CRF data are obtained. CRF entries will be considered source data if the CRF is the site of the original recording (i.e. there is no other written or electronic record of data). Parent reported data (for example, adherence data collected via the app, Quality of life data and PARCA-R questionnaires) will be considered source data.

12.2. Access to data

Direct access will be granted to authorised representatives from the Sponsor, funder, research team, host institution (NHS trust) and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Site staff will have authenticated and restricted access to the Clinical Database Management System (OpenClinica), ensuring they are only able to see data on participants recruited at their Trust. Access to the electronic data is strictly controlled using individual passwords for all staff accessing the electronic databases.

There will be no direct sharing of patient identifiable information or professionals' details with Nutricia. NuTH will share data with Nutricia as per the conditions stated in the Product Supply Agreement (which has been reviewed by the NIHR IP Team). Data will be shared with Nutricia in either a wholly anonymised format or pseudo-anonymised format, as per the terms of the Product Supply Agreement between Newcastle upon Tyne Hospitals NHS Foundation Trust and Nutricia.

12.3. Data recording and record keeping

All clinical data will be entered into the clinical database either directly or from paper CRFs by the local NHS site staff. The clinical database will be validated and maintained in accordance with NPEU CTU Standard Operating Procedures (SOPs). Data entered will at the point of entry undergo a number of validation checks to verify the validity and completeness of the data captured. A separate administrative database application will be used to store the participants' names and any other identifiable details. Trial participants will be identified by a unique trial number, which is used to link the clinical and administrative database applications.

Regarding the DOLFIN parent app that will be created during the trial period, the digital app supplier will hold some personal details such as names, email address and contact details to facilitate usage of the app but will not share this with other organisations. Consent forms containing the infant and parent's names will be sent securely electronically (using encryption) or in pre-addressed envelopes to the NPEU CTU. All data will be processed in line with the NPEU CTU Data Management SOPs. It is the responsibility of all parties involved (Sponsor, NPEU CTU, and the NHS organisations) to ensure confidentiality of participant information is maintained.

Electronic files, such as eCRFs and other electronic or scanned documents containing personal/sensitive information, will be stored on a restricted access (named individuals) server that can be accessed only by members of the NPEU CTU DOLFIN trial team with permissions to access data at specified levels, held in

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a secure location. The data are backed up daily. Authorised access to the NPEU CTU is via an electronic tag entry system and individual rooms are kept locked when unoccupied. Authorised staff will process data via a secure network, which requires individual login name and password (changed regularly). No data are stored on individual workstations.

Archiving will follow the completion of the trial and publication of results as detailed in NPEU SOPs and in line with NHS guidelines for a minimum of 25 years. At this point, the requirements to continue to archive these data will be reviewed in line with the applicable data protection guidelines.

All paper and electronic data will be stored securely in strict compliance with data protection regulations.

At the end of the trial, all participant clinical and parent-reported data (collected within OpenClinica) will be transferred to the research team at Newcastle University and NuTH. In addition, all participant names and NHS numbers, and parent names and contact details, will be transferred to the research team at Newcastle University and NUTH in order to allow Newcastle University and NuTH to contact parents if required at the end of the study or (for those who have consented) with regards to planned long-term follow-up, and in compliance with any applicable Data Sharing Agreement.

13. QUALITY ASSURANCE PROCEDURES

13.1. Risk assessment

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and SOPs. A risk assessment (RA) and monitoring plan (MP) will be prepared before the trial opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. Monitoring

The PI will be responsible for the running of the trial at their site. This will include ensuring successful recruitment, staff education and training, and trial data completeness and quality.

The NPEU CTU will develop an appropriate central monitoring plan for the trial, based on the RA. Recruitment patterns at sites and within the data will be monitored. Any unexpected patterns, issues, or outlier data will be investigated and may trigger ‘for cause’ site monitoring. No other routine monitoring or auditing will be conducted unless the central monitoring triggers cause to do so.

13.3. Trial committees

The trial will be run on a day-to-day basis by the Project Management Group (PMG), which reports to the Trial Steering Committee (TSC), which in turn is responsible to the NIHR HTA programme (as per the NIHR HTA contract). The PMG will consist of the Chief Investigator(s), CTU Director, Clinical CTU Director,

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Senior Trials Manager, the Trial Statistician, Sponsor and other project staff. The PMG will meet every month.

The Co-Investigator Group (CIG), an extended PMG, will comprise all members of the co-applicant group and the members of the PMG to review progress, troubleshoot and plan strategically.

The trial will be overseen by a TSC consisting of an independent chair and other members to include clinicians, statisticians and Patient and Public Involvement (PPI) representatives. Committee members will be deemed independent if they are not involved in trial recruitment. The chair and members of the TSC will be nominated as per the guidance outlined by the NIHR HTA for their approval. The TSC will aim to meet in person or virtually at least annually.

The TSC terms of reference are specified by the NIHR HTA. The TSC will monitor the progress of the trial and its conduct and advise on its scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC and ultimately carry the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

The Data Monitoring Committee (DMC) members will be independent of the trial team and the TSC, and will include a chair, clinician and statistician. During the recruitment phase, the committee will meet annually or more often as appropriate, review trial conduct, progress and accumulating data, and make recommendations to the TSC. Details about the roles, responsibilities and conduct of the committee will be set out in a DMC Charter, which will be agreed at the first meeting.

14. PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process) or from GCP or any applicable regulatory requirements. Any deviations from the protocol will be documented in incident forms and, where applicable, the relevant corrective and preventative action completed. All incidents will be recorded in an Incident Log database.

15. SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected, the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

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16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The NPEU CTU will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Other ethical considerations

There are no other ethical considerations associated with the trial.

16.5. Reporting

The CI shall submit once a year throughout the study, or on request, an annual progress report to the REC Committee, HRA (where required), host organisation, Sponsor and funder (where required). In addition, an end of study notification and final report will be submitted to the same parties.

16.6. Transparency in research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

16.7. Participant confidentiality

The trial will comply with the GDPR and Data Protection Act 2018. All documents will be stored securely at the NPEU CTU and will only be accessible by trial staff and authorised personnel. The trial staff will safeguard the privacy of participants' personal data.

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All personal identifiers details and trial data will be stored in a separate database also held at the NPEU CTU and at Newcastle University. These databases will only be linked by the infant's trial number. After the trial has been completed and the reports published, the data will be archived in a secure physical or electronic location with controlled access.

16.8. Expenses and benefits

Parents will receive a £25 thank you voucher for completion of the questionnaires; this will be sent as the 2 year parent completed outcome measure completion is requested.

16.9. Funding

This trial is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) [NIHR130925]. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Nutricia will fund active and control supplement production, supply and distribution to Trusts and homes. The Terms and Conditions of supply, including data sharing, are described in the Product Supply Agreement between Newcastle upon Tyne Hospitals NHS Foundation Trust and Nutricia.

16.10. Insurance

The Newcastle upon Tyne Hospitals NHS Foundation Trust is the sponsor for the trial. They have NHS indemnity in place which would operate in the event of any participant suffering harm as a result of their involvement in the research. NHS indemnity operates in respect of the clinical treatment which is provided. Newcastle University will indemnify the design of the trial.

16.11. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

17. PUBLICATION POLICY

The success of the trial depends on a large number of neonatal nurses, neonatologists, and parents support of the trial. Credit for the trial findings will be given to all who have collaborated and participated in the trial, including all local co-ordinators and collaborators, members of the trial committees, the DOLFIN Co-ordinating Centre and trial staff. Authorship at the head of the primary results paper will take the form "[name], [name] and [name] on behalf of the 'The DOLFIN Collaborative Group'". The drafting of the paper will be the responsibility of a writing committee. All contributors to the trial will be listed at the end of the main paper, with their contribution identified. It is the intention of the DOLFIN Collaborative Group to publish the protocol and peer-reviewed articles including the analysis of key outcomes. All published material will contain an acknowledgement of funding, as required by the NIHR HTA.

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Parents will be emailed a copy of the trial results, and trial results will be disseminated through the trial website. A full dissemination plan will be developed by the PMG.

18. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees rests with the employer.

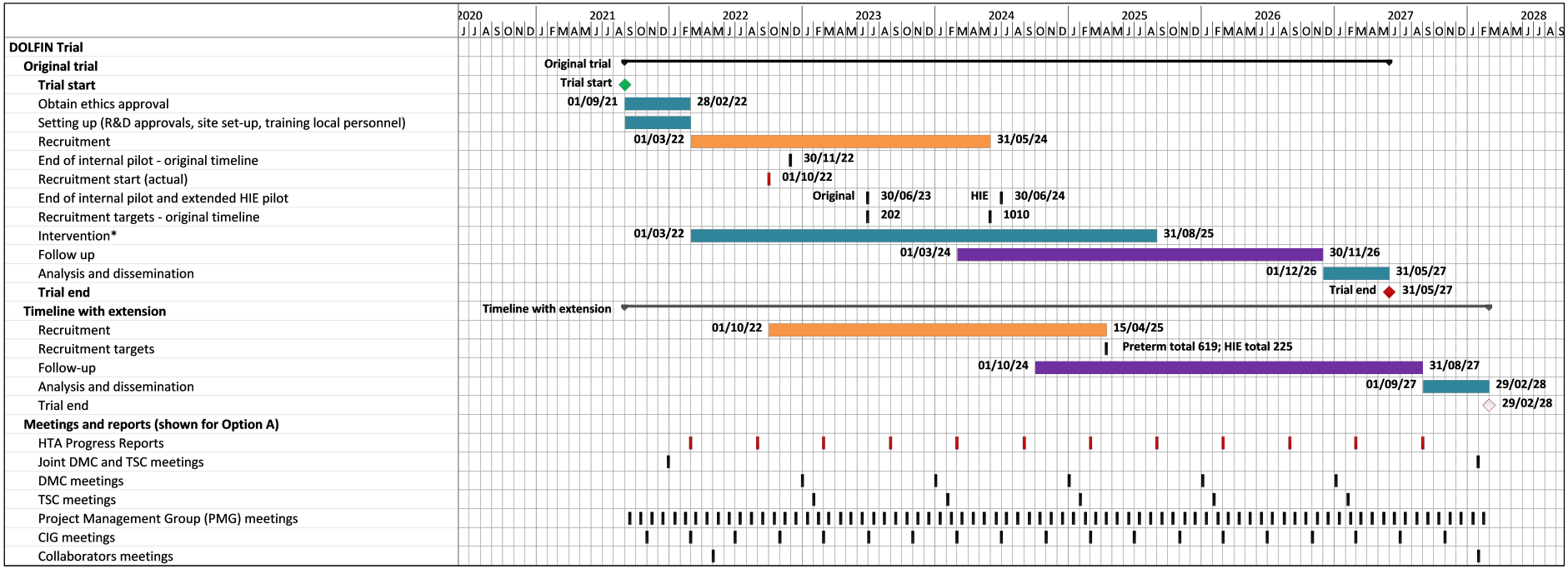
Ownership of IP generated by employees of NuTH vests in NuTH. The protection and exploitation of any new IP will be managed by Newcastle University's IP team.

19. ARCHIVING

Archiving will follow the completion of the trial and publication of results as detailed in NPEU Standard Operating Procedures (SOPs) and in line with Sponsor's guidelines for a minimum of 25 years. At this point, the requirements to continue to archive these data will be reviewed in line with the applicable data protection guidelines.

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20. ANTICIPATED TIMELINE



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21. REFERENCES

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22. APPENDIX D: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	3.0	09.06.2022	Sarah Turner	Minor wording amends including improvements in delivering the study supplement to a baby has been bench tested. The supplement can now be prepared with 3ml of milk for each 1g of supplement. Previously 15ml of milk was required for each 1g of supplement. With lower ml of milk required per 1g of supplement, a baby can now begin the supplement once they have reached full feeds, and no longer needs to wait until they have reached 1kg. Further information has been added to the protocol to inform participants about the supplement supplier (Nutricia's) involvement in the study. Explicit detail has be added to the protocol and supporting documentation regarding the supplement's suitability for participants on vegan, halal or kosher diets.
2	4.0	22.09.2023	Victoria Stalker	- Clarification of existing inclusion/exclusion criteria. - Preterm infants can be remotely consented prior to discharge home from hospital. - Clarification of eligibility criteria for HIE stratum - can be consented up to EDD plus 28 days (remotely or in-person) - Parents can give supplement in hospital. Processes and text updated throughout to reflect these changes. - Further information and clarification for transfer of infants to Continuing Care Site. - Additional information and clarification relating to supplementation – constituents, storage, administration, adherence reporting. - Minor rewording for clarification on change of consent. - Additional foreseeable SAEs. - Removal of EDEN co-enrolment.
3	5.0		Usharani Wahengbam	- Update of section 10.5.1. Assessment of expectedness

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				- Update of section 10.6. Reporting Unexpected Serious Adverse Reactions - Update of abbreviation column- removed SUSAR and added USAR - Update from placebo to control or matched control supplement throughout. Correction of eligibility criteria for HIE and preterm stratum to remove 'can be consented' - Amend to trial timeline
4	6.0		Usharani Wahengbam	- Addition of a new secondary objective " To investigate the effect of nutritional supplementation with a nutrient blend containing LCPUFAs, choline, UMP and CPM on clinical diagnoses up to 24-months post EDD" with five outcome measures. - Update of section 11.3 Description of statistical methods. - Development of a Parent newsletter template which will be designed and used to circulate parent newsletters for the trial as part of parent engagement and retention in the trial. - Update to parent communications schedule document - minor edits / corrections to some of the parent-facing messages - Current version 4.0 Parent information leaflets are adapted for Scottish sites.
5	7.0		Usharani Wahengbam	- Addition of secondary outcome: Standardised scores of the Bayley Scales of Infant and Toddler Development, 3rd or 4th Edition - Update of section 8.2: Completion of outcome measures - Update of section 8.9: Study data collection - Update of section 10.2: Procedures for reporting Adverse Events - Update of section 11.4: Health economics analysis - Update of Trial Flowchart - Update of protocol summary - Update of Gantt Chart - Update of Abbreviation table

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