DOLFIN

Developmental Outcome of Long-term Feed Supplementation in Neonates

Summary Protocol

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Research Question

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 estimated date of delivery (EDD) improves cognitive development at 24 months post EDD, compared to infants receiving a matched control supplement plus usual care (comparator).

Trial eligibility

The trial population are two clearly defined groups:

- All infants born less than 28 weeks of gestation (and up to 3 months post EDD) (preterm)
- All infants born at 35 weeks of gestation or more, receiving therapeutic hypothermia for hypoxic ischaemic encephalopathy (and up to EDD plus 28 days) (HIE)

Trial design

Multicentre blinded randomised controlled trial of 1,010 infants in approx. 40 UK NHS tertiary neonatal units; 538 infants in the preterm group and 472 infants in the HIE group.

Trial Intervention

Infants will be randomised as soon as possible after consent is obtained, using a 1:1 allocation ratio, to either:

- Active supplement: Micronutrient breast milk/formula milk/food supplement of LCPUFAs, choline, UMP, and CMP, or
- Matched control supplement, contains fractions of the active components in the investigational product and no UMP and CMP

Powder supplement is added daily to usual milk feed (breast or formula) on the neonatal unit when infants reach full milk feeds (approx. 120–150ml/kg/day). Supplementation administered on discharge and given by parents at home until 12 months post EDD.

Primary outcome

Non-verbal cognitive scale standardised score of the Parent Report of Children's Abilities-Revised (PARCA-R) questionnaire (parent report) at 24 months post EDD.

Secondary outcomes

- Neurodevelopmental outcomes at 24 months post EDD:
  - Language scale standardised score of Parent Report of Children's Abilities-Revised (PARCA-R)
  - Emotional, conduct, hyperactivity and peer problems scale scores and prosocial scale scores of the Strengths and Difficulties Questionnaire (SDQ)
  - Motor Skills using the fine and gross motor scales score of the Ages and Stages Questionnaire (ASQ-3)
- NHS data at discharge and 24 months post EDD for health care received and health conditions diagnosed (for example necrotising enterocolitis, sepsis, chronic lung disease, post discharge hospitalisations, overweight and obesity)
- BMI, weight and head circumference at 24 months post EDD
- Safety of supplementation throughout the intervention phase
- Parental adherence to supplementation throughout the intervention phase
- Maternal acceptability of supplementation at 6 and 12 months post EDD
- Bespoke Health Economic questionnaire at 6, 12, 18 and 24 months post EDD
- Parental health-related quality of life using the EuroQol EQ-5D-5L questionnaire at randomisation, 6, 12, 18 and 24 months post EDD
- Supplement tolerance questionnaire (IGSQ-13) at neonatal unit, 3, 6, 12 months post EDD

Number of participants required:	1,010	Number of centres:	40
Planned recruitment start and end dates:	January 2022 to May 2024		
Funding source:	NIHR Health Technology Assessment (HTA) Programme		

Flow chart: The DOLFIN Randomised Controlled Trial

Inclusion criteria

- Individual with parental responsibility able to give consent
- Parents able to comply with the protocol
- Infants likely to tolerate full enteral feeds
- Infant has realistic prospect of survival beyond discharge

Preterm

- Infants born less than 28 weeks of gestation (and up to 3 months post EDD)

Hypoxic Ischaemic Encephalopathy (HIE)

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

Exclusion criteria

- Infants with middle cerebral artery infarcts
- Infants with major congenital brain malformation, or genetic condition with abnormal brain development
- Infants with galactosaemia
- Infants receiving all feeds via jejunal tube, who do not receive any gastric or oral feeds

Randomisation 1:1 allocation ratio

Active nutritional supplement OR **Control supplement**

- Powder supplement added daily to usual milk feed (breast or formula) on the neonatal unit when infants reach full milk feeds (term 120ml/kg/day; preterm 150ml/kg/day)
- Supplementation administered by parents at home until 12 months post EDD (parents supported by clinical research team)

Primary Outcome

At 24 months post EDD

Non-verbal cognitive scale standardised score of the Parent Report of Children's Abilities-Revised (PARCA-R)

Secondary Outcomes

At 24 months post EDD unless otherwise stated

- Language scale standardised score of Parent Report of Children's Abilities-Revised (PARCA-R)
- Emotional, conduct, hyperactivity and peer problems scale scores and prosocial scale scores of the Strengths and Difficulties Questionnaire (SDQ)
- Motor skills using the fine and gross motor scales score of the Ages and Stages Questionnaire (ASQ-3)
- NHS data at discharge and 24 months post EDD for health care received and health conditions diagnosed (for example, necrotising enterocolitis, sepsis, chronic lung disease, post discharge hospitalisations, overweight and obesity)
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Longer-term follow up

Parental consent will be sought to contact participants regarding follow up studies during early childhood, and to access routinely collected secondary care data including hospital admissions, critical care and outpatient visits, and the Department for Education's National Pupil Database on attainment test results and special educational needs at Key Stages 1 and 2 (age 7 and 11 years respectively)

DOLFIN flow chart v5.0 01.03.24

DOLFIN Contact details

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