

Developmental outcomes of long-term feed supplementation in newborn babies

Submission date 06/05/2022	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 16/05/2022	Overall study status Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 14/04/2025	Condition category Neonatal Diseases	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

Plain English summary of protocol

Background and study aims

This study is designed to test whether adding a daily nutrient supplement (food substance) to the normal milk and weaning foods of babies born very early can help improve their brain development, and their neurological child development (such as how they think, communicate, play and interact with others). The supplement contains substances that occur naturally in a healthy diet and are often used as food supplements (long-chain polyunsaturated fatty acids, uridine-5'-monophosphate, cytidine-5'-monophosphate, and choline). A small UK study has been carried out and the results were promising, but we need to find out more. The aim is to include about 500 babies born very early and 500 babies who receive cooling treatment in order to be confident of finding out whether the supplement improves the babies' brain development, and neurological child development, or not. If the study shows that the supplement is effective, it might be given to babies as part of future NHS care.

Who can participate?

Babies born more than 12 weeks early and babies born less than 5 weeks early who have received cooling treatment for hypoxic-ischaemic encephalopathy (HIE)

What does the study involve?

Once consent is provided, the infant will receive either the supplement or a substance that looks the same but does not contain the nutrients (a placebo). There is a 50% chance of receiving the supplement and a 50% chance of receiving placebo. The supplement will be given daily to the infant until he/she is 12 months after the Estimated Date of Delivery (EDD). Parents will be asked to complete questionnaires when they join the study, at hospital discharge and at 3, 6, 12, 18 and 24 months of age.

What are the possible risks and benefits of participating?

The supplement has been used in a smaller study of around 100 babies and infants without any problems or side effects. All babies will be monitored very closely throughout the study by the clinical team in the Neonatal Intensive Care or Special Care Unit, and by the local NHS Paediatrician and clinical team following discharge from hospital. Participants who take part in the trial to the time their child is age 24 months will receive a £25 voucher.

Where is the study run from?

The National Perinatal Epidemiology Unit, Clinical Trials Unit (NPEU CTU) at the University of Oxford, in partnership with Newcastle University (UK)

When is the study starting and how long will it run for?

September 2021 to May 2027

Who is funding the study?

The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (UK)

Who is the main contact?

NPEU Clinical Trials Unit National Perinatal Epidemiology Unit (NPEU)
dolphin@npeu.ox.ac.uk

Study website

<https://www.npeu.ox.ac.uk/dolphin>

Contact information

Type(s)

Principal Investigator

Contact name

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Type(s)

Scientific

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Additional identifiers

EudraCT/CTIS number

Nil known

IRAS number

303421

ClinicalTrials.gov number

Nil known

Secondary identifying numbers

CPMS 51833, IRAS 303421

Study information

Scientific Title

Developmental Outcomes of Long term Feed supplementation In Neonates (DOLFIN)

Acronym

DOLFIN

Study objectives

This study is designed to test whether adding a daily nutrient supplement (food substance) to the normal milk and weaning foods of babies born with hypoxic ischaemic encephalopathy (where the brain did not receive enough oxygen around the time of birth) or babies born premature (born less than 28 weeks of gestation) can help improve their neurological development in later childhood (such as how they think, play and interact with others).

Ethics approval required

Old ethics approval format

Ethics approval(s)

Approved 14/03/2022, Bristol Research Ethics Committee Centre, Ground Floor, Temple Quay House, BS1 6PN, UK; +44 (0)207 104 8029; centralbristol.rec@hra.nhs.uk), ref: 22/SW/0009

Study design

Randomized; Both; Design type: Treatment, Dietary, Health Economic

Primary study design

Interventional

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

<https://www.npeu.ox.ac.uk/dolphin/parents/resources>

Health condition(s) or problem(s) studied

Babies born with hypoxic ischaemic encephalopathy (where the brain did not receive enough oxygen around the time of birth) or babies born premature (born less than 28 weeks of gestation)

Interventions

This trial aims to establish whether or not early life nutritional supplementation with a nutrient blend of long-chain polyunsaturated fatty acids (LCPUFAs), choline, uridine-5'-monophosphate (UMP), and cytidine-5'-monophosphate (CMP) improves infants' cognitive development at 24 months post Estimated Date of Delivery (EDD), compared to controls, in two clearly defined strata:

1. Preterm stratum: Infants born less than 28 weeks of gestation
2. HIE stratum: Infants born at 35 weeks of gestation or more, receiving therapeutic hypothermia for HIE.

1,010 infants; 538 preterm and 472 infants born at or after 35 weeks of gestation with HIE cared for in neonatal units across the UK participate. A 9-month internal pilot phase incorporates "stop-go" criteria to evaluate the feasibility of recruitment and other trial processes. With informed consent from parents, clinicians in each unit will use a randomisation website to randomly allocate infants to receive either:

1. Treatment supplement: micronutrient breast milk/formula milk/food supplement containing LCPUFAs, choline, UMP, and CMP.
- or
2. Matched placebo control supplement: identically packaged and delivered powder supplement indistinguishable from the active treatment.

Parents will be offered information about the trial and will have ample time to consider whether they wish their baby to take part. Eligible babies will be recruited up to 40 weeks of gestation plus 28 days.

Powder supplement will be added daily to the usual milk feed (breast or formula) on the neonatal unit when infants reach full milk feeds (120–150 ml/kg/day), and have reached 1 kg body weight.

Supplementation will be continued on discharge and given at home by parents until 12 months of age post EDD. Neither the clinicians, nor the caregivers, parents or carers will be aware of whether each individual infant is receiving active treatment or a placebo.

No additional (trial-specific) blood tests or other investigations will be required.

Parents will receive support from their local clinical teams whilst on the Neonatal unit and throughout the entire trial period.

Data will be collected on bespoke data collection forms from the time of randomisation up until the child reaches 24 months of age, post EDD. Parents will be asked to complete questionnaires when their child reaches 6, 12, 18 months of age post EDD and record if the supplement has been given on an App (or alternative method of parents choosing). The researchers will undertake an economic evaluation to determine whether supplementation is a cost-effective treatment.

Consent will be obtained to facilitate future school-age follow-up.

Intervention Type

Supplement

Primary outcome measure

Cognitive development measured using the non-verbal cognitive scale standardised score of the Parent Report of Children's Abilities-Revised (PARCA-R) questionnaire at age 24 months

Secondary outcome measures

1. Secondary neurodevelopmental outcomes measured at 24 months of age post EDD:
 - 1.1. Language Development Scale standardised score of the PARCA R questionnaire
 - 1.2. Parent-reported emotional, conduct, peer problems, hyperactivity, prosocial and total score measured using the Strengths and Difficulties Questionnaire
 - 1.3. Parent-reported motor skills measured using the fine and gross motor scales score of the Ages and Stages Questionnaire (ASQ-3)
2. Infant growth outcomes measured at 24 months of age post EDD:
 - 2.1. Weight standard deviation score
 - 2.2. Head circumference standard deviation score
 - 2.3. Overweight or obese (BMI \geq 85th percentile)
3. Clinical outcomes measured at discharge home from the neonatal unit:
 - 3.1. Microbiologically confirmed late-onset invasive infection
 - 3.2. Necrotising enterocolitis requiring surgery
 - 3.3. Retinopathy of prematurity treated medically/surgically (preterm stratum only)
 - 3.4. Chronic lung disease (preterm stratum only)
4. Safety, infant tolerability, adherence to and parental acceptability measured using:
 - 4.1. Safety and adverse events until age 12 months plus 2 weeks after the end of the intervention period
 - 4.2. Parent-reported infant tolerability of supplement (IGSQ) at discharge home from neonatal unit, 3, 6 and 12 months
 - 4.3. Parent-reported adherence until age 12 months
 - 4.4. Parent-reported acceptability of the supplement at 6 and 12 months
5. Maternal health-related quality of life measured using:
 - 5.1. EuroQol EQ-5D-5L questionnaire at baseline, 6, 12, 18 and 24 months
 - 5.2. Maternal quality-adjusted life years (QALYs) up to 24 months
6. Healthcare and social care resource use and costs, costs borne by families, and wider societal implications including family expenses and employment, measured using:
 - 6.1. Health and social care resource use and costs and out-of-pocket costs incurred by families up to 24 months
 - 6.2. Productivity costs and informal care up to 24 months
 - 6.3. Cost per life-year without moderate/severe neurodevelopmental impairment (within-trial cost-effectiveness analysis) at 24 months
 - 6.4. Cost per QALY gained (long-term cost-effectiveness analysis) modelled to 18 years of age

Overall study start date

01/09/2021

Completion date

31/05/2027

Eligibility

Key inclusion criteria

1. Preterm stratum: Infants born less than 28 weeks of gestation, up to discharge home from neonatal unit (NNU) or step-down site, and no more than 3 months post-estimated date of delivery (EDD)
2. Hypoxic ischaemic encephalopathy (HIE) stratum: Infants born at 35 weeks of gestation or more, who have received therapeutic hypothermia for HIE, up to 40 weeks of gestation plus 28 days
3. 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
4. Parents able to comply with the protocol
5. Infants likely to tolerate full enteral feeds
6. Infant has a realistic prospect of survival beyond discharge

Participant type(s)

Patient

Age group

Neonate

Upper age limit

3 Months

Sex

Both

Target number of participants

Planned Sample Size: 1143; UK Sample Size: 1143

Key exclusion criteria

1. Infants with middle cerebral artery infarcts
2. Infants with major congenital brain malformation, or genetic condition with abnormal brain development
3. Infants with galactosaemia
4. Infants receiving continuous enteral feeds, including jejunal feeds

Date of first enrolment

10/10/2022

Date of final enrolment

15/04/2025

Locations

Countries of recruitment

England

Northern Ireland

United Kingdom

Wales

Study participating centre

Addenbrooke's Hospital

Hills Road

Cambridge

United Kingdom

CB2 0QQ

Study participating centre

Birmingham Heartlands Hospital

Bordesley Green East

Birmingham

United Kingdom

B9 5SS

Study participating centre

Birmingham Women's and Children's Hospital

Steelhouse Lane

Birmingham

United Kingdom

B4 6NH

Study participating centre

Bradford Teaching Hospital

Duckworth Lane

Bradford

United Kingdom

BD9 6RJ

Study participating centre

Chelsea and Westminster Hospital
369 Fulham Road
London
United Kingdom
SW10 9NH

Study participating centre
James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Leeds General Infirmary
Great George Street
Leeds
United Kingdom
LS1 3EX

Study participating centre
Liverpool Women's Hospital
Liverpool Womens Hospital
Crown Street
Liverpool
United Kingdom
L8 7SS

Study participating centre
Medway Maritime Hospital
Windmill Road
Gillingham
United Kingdom
ME7 5NY

Study participating centre
New Cross Hospital
Wolverhampton Rd
Heath Town

Wolverhampton
United Kingdom
WV10 0QP

Study participating centre
Norfolk and Norwich University Hospital
Colney Lane
Colney
Norwich
United Kingdom
NR4 7UY

Study participating centre
Nottingham City Hospital
Hucknall Road
Nottingham
United Kingdom
NG5 1PB

Study participating centre
Queen's Medical Centre
Derby Rd
Lenton
Nottingham
United Kingdom
NG7 2UH

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Princess Anne Hospital
Coxford Road
Southampton
United Kingdom
SO16 5YA

Study participating centre
Queen Alexandras Hospital
Southwick Hill Road
Cosham
Portsmouth
United Kingdom
PO6 3LY

Study participating centre
Royal London Hospital
Whitechapel
London
United Kingdom
E1 1BB

Study participating centre
Royal Jubilee Maternity Hospital
274 Grosvenor Rd
Belfast
United Kingdom
BT12 6BA

Study participating centre
The Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
United Kingdom
TS1 4LP

Study participating centre
Southmead Hospital
Southmead Road
Westbury-on-trym
Bristol
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BS10 5NB

Study participating centre

St Mary's Hospital
Oxford Rd
Manchester
United Kingdom
M13 9WL

Study participating centre
St Michael's Hospital
Southwell St
Bristol
United Kingdom
BS2 8EG

Study participating centre
St Peter's Hospital
Guildford St
Lyne
Chertsey
United Kingdom
KT16 0PZ

Study participating centre
Sunderland Royal Hospital
Kayll Road
Sunderland
United Kingdom
SR4 7TP

Study participating centre
The Grange University Hospital
Caerleon Road
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NP44 8YN

Study participating centre
University Hospital of Wales
Heath Park
Cardiff
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CF14 4XW

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Clifford Bridge Road
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United Kingdom
CV2 2DX

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Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
William Harvey Hospital
Kennington Road
Willesborough
Ashford
United Kingdom
TN24 0LZ

Study participating centre
Royal Stoke University Hospital
Newcastle Road
Stoke-on-trent
United Kingdom
ST4 6QG

Study participating centre
Bolton NHS Foundation Trust
The Royal Bolton Hospital
Minerva Road
Farnworth
Bolton
United Kingdom
BL4 0JR

Study participating centre
Burnley General Hospital
Casterton Avenue
Burnley
United Kingdom
BB10 2PQ

Sponsor information

Organisation

Newcastle upon Tyne Hospitals NHS Foundation Trust

Sponsor details

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NE3 3HD
+44 (0)1912824454
tnu-tr.sponsormanagement@nhs.net

Sponsor type

Hospital/treatment centre

Website

<http://www.newcastle-hospitals.org.uk/>

ROR

<https://ror.org/05p40t847>

Funder(s)

Funder type

Government

Funder Name

NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: NIHR130925

Results and Publications

Publication and dissemination plan

Planned publication in a high-impact peer-reviewed journal.

Intention to publish date

31/12/2027

Individual participant data (IPD) sharing plan

At the end of the trial, all participant clinical and parent-reported data will be transferred to the research team at Newcastle University and NuTH (Trial Sponsor). 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.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 3.0	09/06/2022	18/10/2022	No	No
HRA research summary			28/06/2023	No	No
Protocol file	version 6.0	10/10/2024	21/03/2025	No	No