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Developmental outcomes of long-term feed supplementation in newborn babies

Submission date
06/05/2022

Recruitment status
No longer recruiting

Registration date
16/05/2022

Overall study status
Ongoing

Last Edited
07/01/2026

Condition category
Neonatal Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] 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)
dolfin@npeu.ox.ac.uk

Contact information

Type(s)
Principal investigator

Contact name
Prof Jeremy Parr

Contact details
University of Newcastle upon Tyne
Level 3, Sir James Spence Institute
Royal Victoria Infirmary
Newcastle Upon Tyne
United Kingdom
NE1 4LP
+44 (0)1912825966
Jeremy.parr@newcastle.ac.uk

Type(s)
Scientific

Contact name
Miss Victoria Stalker

ORCID ID
https://orcid.org/0000-0001-5157-7043

Contact details
National Perinatal Epidemiology Unit (NPEU)
Oxford Population Health (Nuffield Department of Population Health)
University of Oxford
Richard Doll Building, Old Road Campus
Oxford
United Kingdom

OX3 7LF
+44 (0)1865 617924
dolfin@npeu.ox.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
303421

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
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

Study type(s)
Treatment

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(s)
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

Key secondary outcome(s))
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 ≥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

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

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
0 months

Upper age limit
3 months

Sex
All

Total final enrolment
0

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
United Kingdom

England

Northern Ireland

Wales

Study participating centre
Addenbrooke's Hospital
Hills Road
Cambridge
England
CB2 0QQ

Study participating centre
Birmingham Heartlands Hospital
Bordesley Green East
Birmingham
England
B9 5SS

Study participating centre
Birmingham Women's and Children's Hospital
Steelhouse Lane
Birmingham
England
B4 6NH

Study participating centre
Bradford Teaching Hospital
Duckworth Lane
Bradford
England
BD9 6RJ

Study participating centre
Chelsea and Westminster Hospital
369 Fulham Road
London
England
SW10 9NH

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

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

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

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

Study participating centre
New Cross Hospital
Wolverhampton Rd
Heath Town
Wolverhampton
England
WV10 0QP

Study participating centre
Norfolk and Norwich University Hospital
Colney Lane
Colney

Norwich
England
NR4 7UY

Study participating centre
Nottingham City Hospital
Hucknall Road
Nottingham
England
NG5 1PB

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

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

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

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

Study participating centre
Royal London Hospital
Whitechapel
London
England
E1 1BB

Study participating centre
Royal Jubilee Maternity Hospital
274 Grosvenor Rd
Belfast
Northern Ireland
BT12 6BA

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

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

Study participating centre
St Mary's Hospital
Oxford Rd
Manchester
England
M13 9WL

Study participating centre

St Michael's Hospital
Southwell St
Bristol
England
BS2 8EG

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

Study participating centre
Sunderland Royal Hospital
Kayll Road
Sunderland
England
SR4 7TP

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

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

Study participating centre
University Hospital Coventry
Clifford Bridge Road
Coventry
England
CV2 2DX

Study participating centre
Leicester Royal Infirmary
Infirmary Square
Leicester
England
LE1 5WW

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

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

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

Study participating centre
Burnley General Hospital
Casterton Avenue
Burnley
England
BB10 2PQ

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

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

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 article		29/12/2025	07/01/2026	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet		11/11/2025	11/11/2025	No	Yes
Protocol file	version 3.0	09/06/2022	18/10/2022	No	No
Protocol file	version 6.0	10/10/2024	21/03/2025	No	No
Study website		11/11/2025	11/11/2025	No	Yes