DOLFIN

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NHS The Newcastle upon Tyne Hospitals NHS Foundation Trust

NPEU Clinical Trials Unit

OXFORD POPULATION HEALTH NPEU

Developmental Outcome of Long Term Feed Supplementation in Neonates - The DOLFIN randomised controlled trial

Site Initiation Visit (SIV) – Training for Continuing Care sites

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Presentation Overview

- Study Overview
- Continuing care site responsibilities
- Supplement
- Safety Reporting
- Data Management
- FAQ’s
- Trial team contact details

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DOLFIN - Trial Design

- Multicentre, blinded, randomised placebo-controlled trial. **NOT A CTIMP**
- Does giving a nutritional supplement plus usual care from birth to 12 months post EDD improve cognitive development at 24 months post EDD compared to a matched placebo plus usual care?
- Active supplement contains:
  - Long-chain polyunsaturated fatty acids (LCPUFAs)
  - Choline
  - Uridine-5’-monophosphate (UMP)
  - Cytidine-5’-monophosphate (CMP)
- Control supplement contains:
  - Tiny amounts of same ingredients except UMP and CMP

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DOLFIN Outcomes

Primary Outcome

At 24 months post estimated delivery date (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

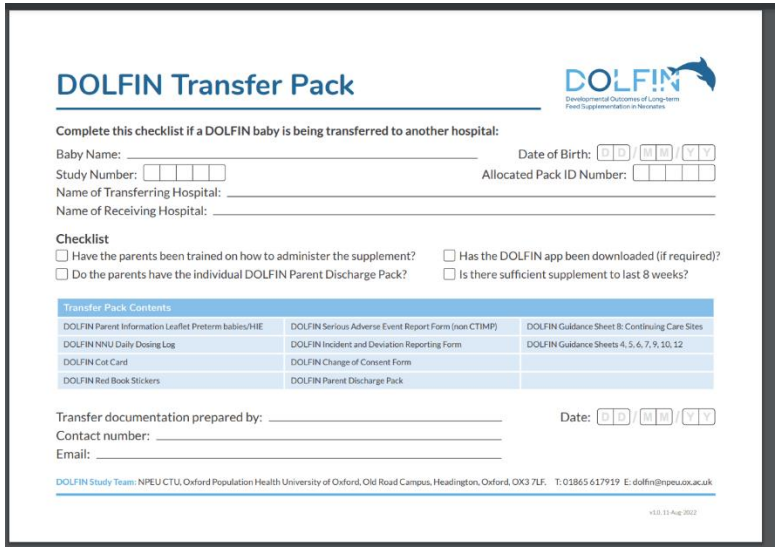
- Language scale standardised score of Parent Report of Children's Abilities Revised (PARCA-R)
- Emotional, conduct, hyperactivity and peer problems scale scores and prosocial scale scores of the Strengths and Difficulties Questionnaire (SDQ)
- Motor Skills using the Fine and Gross Motor scales score of the Ages and Stages Questionnaire (ASQ-3)
- NHS data at discharge and 24 months for health (including necrotising enterocolitis, sepsis, chronic lung disease, post discharge hospitalisations, overweight and obesity)
- Weight and head circumferance at birth, and height, weight and head circumferance at 24 months
- Safety of supplementation throughout the intervention phase
- Parental adherence to supplementation throughout the intervention phase
- Parent acceptability of supplementation at 6 and 12 months post EDD
- Bespoke Health Economic questionnaire at 6, 12, 18 and 24 months
- Parental health-related quality of life using the EuroQol EQ-5D-5L questionnaire at randomisation, discharge, 6, 12, 18 and 24 months
- Supplement tolerance questionnaire (IGSQ) at NNU discharge, 3, 6, 12 months

All trial outcomes are measured at 24 months post estimated delivery date (EDD)

DOLFIN Transfer Pack

The infant will be transferred with a **DOLFIN Transfer Pack**. The contents include:

- DOLFIN supplement
- Parent Information Leaflet (Recruiting site contact details are on the back)
- Serious Adverse Event Report form
- Incident and deviation Form
- Red Book Stickers (to use on notes)
- Cot card
- Daily dosing log
- Guidance sheet 8 for Continuing Care Sites
- Guidance sheets relating to trial procedures
- Parent Discharge Pack



DOLFIN Transfer Pack

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Complete this checklist if a DOLFIN baby is being transferred to another hospital:

Baby Name: _____ Date of Birth: D D / M M / Y Y

Study Number: _ _ _ _ _ Allocated Pack ID Number: _ _ _ _ _

Name of Transferring Hospital: _____

Name of Receiving Hospital: _____

Checklist

☐ Have the parents been trained on how to administer the supplement?
☐ Has the DOLFIN app been downloaded (if required)?
☐ Do the parents have the individual DOLFIN Parent Discharge Pack?
☐ Is there sufficient supplement to last 8 weeks?

Transfer Pack Contents		
DOLFIN Parent Information Leaflet Preterm babies/HIE	DOLFIN Serious Adverse Event Report Form (non CTIMP)	DOLFIN Guidance Sheet 8: Continuing Care Sites
DOLFIN NNU Daily Dosing Log	DOLFIN Incident and Deviation Reporting Form	DOLFIN Guidance Sheets 4, 5, 6, 7, 9, 10, 12
DOLFIN Cot Card	DOLFIN Change of Consent Form	
DOLFIN Red Book Stickers	DOLFIN Parent Discharge Pack	

Transfer documentation prepared by: _____ Date: D D / M M / Y Y

Contact number: _____

Email: _____

DOLFIN Study Team: NPEU CTU, Oxford Population Health University of Oxford, Old Road Campus, Headington, Oxford, OX3 7LF. T: 01865 617919 E: dolfin@npeu.ox.ac.uk

v1.0, 11 Aug 2022

Continuing Care Site responsibilities

- Continuing Care sites are responsible for completing the following:
- **Serious Adverse Event Form**
- **Incident and Deviation Form**
- **NNU Daily Dosing log** (in some cases parents will be reporting via the app so dosing log completion is not required)
- Continuing Care site is *not* responsible for Case Report Forms (CRFs) completion:
  - recruiting site responsibility
    - CCS do not have study database (OpenClinica) access.

Supporting supplementation

- The infant will be transferred with sufficient supply of supplement to use at the Continuing Care Site.
- Videos explaining how to make up the supplement can be found on the DOLFIN website: https://www.npeu.ox.ac.uk/dolfin/parents/resources
- Or direct link:

  https://youtu.be/VtggW8vmvBM

  https://youtu.be/4zVvDSDbNPw

Administration of supplement

- Each box of supplement contains 1g measuring scoops
  - These are not single use. Please do not discard!
- Measured dose dissolved in infants usual feed. e.g. oral, nasogastric tube, gastrostomy tube.
- **The infant must be on full milk feeds before starting supplement**
  - Supplement may be stopped for a short period according to clinical need
- Breastfeeding mothers are supported in this trial; the DOLFIN breastfeeding materials outline options for supplement delivery

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Supplement Dosing

- Dose is 1g (1 scoop) per whole kilogram body weight
  - E.g.an infant weighing 3.0-3.99kg will receive 3 scoops daily.
- Each 1g of supplement requires a minimum of 15mls milk
  - E.g. a 3kg infant having 3 scoops will have a total feed volume of at least 45mls.
- Supplement ‘shot’ for breast fed babies:
  - Each 1g of supplement is mixed with 3mls of milk and given ahead of feed
  - Baby put to breast immediately after supplement given
- Total daily supplement dose can be divided across more than one feed.

Dosing for babies weighing less than 1kg

- Infants weighing less that 1kg should be dosed as follows:
- 0.5kg -0.749kg, make up as for 1g/3ml and discard half
- 0.75-0.99kg, make up as for 1g/3ml and discard one quarter The daily dose of supplement can be split across feeds to allow the smallest babies to start supplementation as early as possible.
  - each 0.25g of supplement needs to be accompanied by 3.8mls feed.

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Dosing examples

- 1.2kg baby on 2 hourly feeds of 150mls/kg/day (180mls @ 15ml per feed):
  - Dose = 1g in 15mls milk (min. volume)
    - Add 1g of supplement to 15mls milk.
- 900g baby on 2 hourly feeds of 150mls/kg/day (135mls @ 11.2ml per feed):
  - Dose = 0.75g with a minimum milk feed volume of 11mls
    - Add 1g of supplement to 3mls milk; discard one quarter
    - Add the supplement mix to milk feed to make up to 11.2ml
    - If preferred, give the supplement mix as a shot first and then top up with remaining feed volume

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Splitting doses

- 600g baby on hourly feeds 150mls/kg/day (90 mls per day = 3.8mls per feed):
- Daily supplement dose is 0.5g
  - Each 0.25g of supplement needs to be accompanied by 3.8mls milk so the supplement will have to be split across two feeds. (i.e. 0.25g supplement per feed)

➢ Add 1g supplement to 3mls of milk

➢ Discard half

➢ Add the supplement mix to feed to make up 7.6ml (for 2 feeds).

➢ Give 3.8ml for the first feed and store the remaining 3.8ml for the next feed

Note: Milk containing supplement should be used within 1 hour.

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Supplement guidance

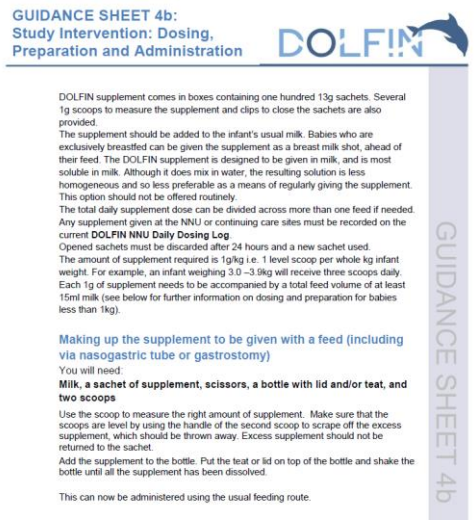
- The volume of milk given with the supplement counts towards the total feed volume.
- Opened sachets must be discarded after 24 hours and a new sachet used.
- Dispose of in a domestic bin or according to trust policy.
- Supplement should be stored at ambient temperature.
- There are no contraindicated medication or dietary supplements. Infants will be able to have all medicines and fortifiers normally prescribed.
- You may choose to omit fortifier from the feed containing DOLFIN.

Supplementation Guidance

- The transfer pack contains guidance sheet 4a & 4b explaining more about the supplement as well as dosing, preparation and administration.
- Further supplement will be delivered directly to the family home on final discharge.

Dosing charts can be found in the transfer pack and online at:

https://www.npeu.ox.ac.uk/dolfin/parents/resources



GUIDANCE SHEET 4b:
Study Intervention: Dosing, Preparation and Administration

DOLFIN

DOLFIN supplement comes in boxes containing one hundred 13g sachets. Several 1g scoops to measure the supplement and clips to close the sachets are also provided.
The supplement should be added to the infant's usual milk. Babies who are exclusively breastfed can be given the supplement as a breast milk shot, ahead of their feed. The DOLFIN supplement is designed to be given in milk, and is most soluble in milk. Although it does mix in water, the resulting solution is less homogeneous and so less preferable as a means of regularly giving the supplement. This option should not be offered routinely.
The total daily supplement dose can be divided across more than one feed if needed. Any supplement given at the NNU or continuing care sites must be recorded on the current **DOLFIN NNU Daily Dosing Log**.
Opened sachets must be discarded after 24 hours and a new sachet used.
The amount of supplement required is 1g/kg i.e. 1 level scoop per whole kg infant weight. For example, an infant weighing 3.0 –3.9kg will receive three scoops daily. Each 1g of supplement needs to be accompanied by a total feed volume of at least 15ml milk (see below for further information on dosing and preparation for babies less than 1kg).

Making up the supplement to be given with a feed (including via nasogastric tube or gastrostomy)

You will need:
Milk, a sachet of supplement, scissors, a bottle with lid and/or teat, and two scoops

Use the scoop to measure the right amount of supplement. Make sure that the scoops are level by using the handle of the second scoop to scrape off the excess supplement, which should be thrown away. Excess supplement should not be returned to the sachet.
Add the supplement to the bottle. Put the teat or lid on top of the bottle and shake the bottle until all the supplement has been dissolved.

This can now be administered using the usual feeding route.

GUIDANCE SHEET 4b

GUIDANCE SHEET 4a:
Study Intervention

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Micronutrient Supplement & Matched Placebo

The active supplement contains a specific nutrient blend containing long chain polyunsaturated fatty acids (LCPUFAs), choline, Uridine-5'Monophosphate (UMP), and Cytidine-5'Monophosphate (CMP). The matched placebo contains fractions of the active components contained in the active supplement and no UMP or CMP. The placebo product contains higher levels of lactose. The active and the placebo products are isocaloric and have similar levels of fat and comparable energy content. The supplement long-chain polyunsaturated fatty acids 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. Some families may wish to discuss this further with their religious leader.

ALLERGENS
Both supplement and matched placebo contain fish, egg and/or milk products

Packaging

DOLFIN supplement comes in boxes containing one hundred 13g sachets. Several 1g scoops to measure the supplement and clips to close the sachets are also provided. Each box and sachet carries the ID of that box.
The packaging may vary across batches and during the trial. There is no correlation between the type of packaging and the active supplement or matched placebo.

Pack Allocation

Each infant will be allocated a first treatment pack ID number during randomisation. Enter this treatment pack ID on the first **DOLFIN Dosing Log**. When this pack runs out a new pack will be allocated and a new dosing log bearing this pack ID should commence.

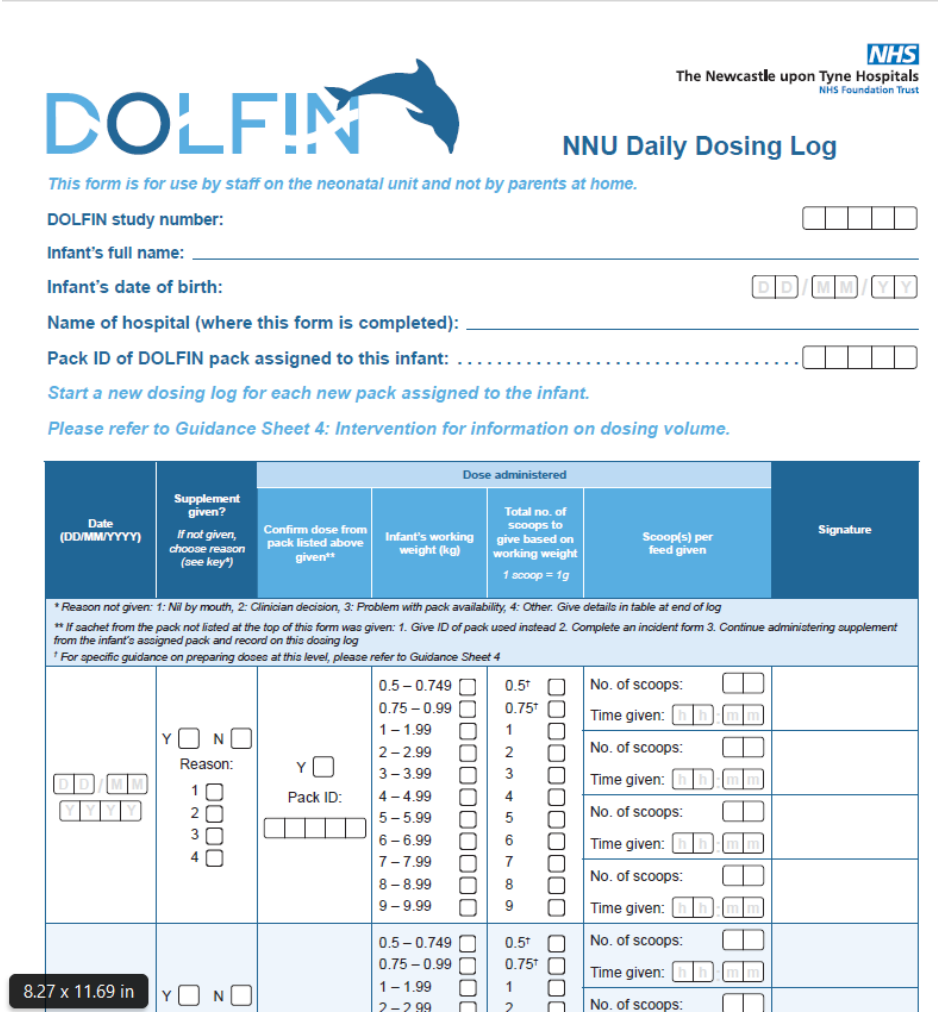
Starting supplementation on the unit

The study supplement and study procedures must only be started once informed consent and randomisation has been completed.

GUIDANCE SHEET 4a

NNU Daily Dosing log

- The NNU daily dosing log will be sent in the transfer pack. This only needs to be completed if the parents are not recording dosing via the DOLFIN App.
- Complete daily when the infant receives the dose.
- If the infant does not receive the supplement on any given day, please record the reason on the log.
- If the infant transfers to another site please send the daily dosing log, transfer pack and supplement with the infant.
- **Once the infant is discharged home, please send the Daily Dosing log to the research nurse at the recruiting site**.



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NNU Daily Dosing Log

This form is for use by staff on the neonatal unit and not by parents at home.

DOLFIN study number: ☐☐☐☐☐

Infant's full name: _____

Infant's date of birth: D D / M M / Y Y

Name of hospital (where this form is completed): _____

Pack ID of DOLFIN pack assigned to this infant: ..... ☐☐☐☐☐

Start a new dosing log for each new pack assigned to the infant.

Please refer to Guidance Sheet 4: Intervention for information on dosing volume.

Date (DD/MM/YYYY)	Supplement given? *If not given, choose reason (see key*)*	Dose administered: Confirm dose from pack listed above given**	Dose administered: Infant's working weight (kg)	Dose administered: Total no. of scoops to give based on working weight *1 scoop = 1g*	Dose administered: Scoop(s) per feed given	Signature
** Reason not given: 1: Nil by mouth, 2: Clinician decision, 3: Problem with pack availability, 4: Other. Give details in table at end of log* *** If sachet from the pack not listed at the top of this form was given: 1. Give ID of pack used instead 2. Complete an incident form 3. Continue administering supplement from the infant's assigned pack and record on this dosing log* *† For specific guidance on preparing doses at this level, please refer to Guidance Sheet 4*						
D D / M M / Y Y Y Y	Y ☐ N ☐ Reason: 1 ☐ 2 ☐ 3 ☐ 4 ☐	Y ☐ Pack ID: ☐☐☐☐☐	0.5 – 0.749 ☐ 0.75 – 0.99 ☐ 1 – 1.99 ☐ 2 – 2.99 ☐ 3 – 3.99 ☐ 4 – 4.99 ☐ 5 – 5.99 ☐ 6 – 6.99 ☐ 7 – 7.99 ☐ 8 – 8.99 ☐ 9 – 9.99 ☐	0.5† ☐ 0.75† ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐	No. of scoops: ☐☐ Time given: h h m m No. of scoops: ☐☐ Time given: h h m m No. of scoops: ☐☐ Time given: h h m m No. of scoops: ☐☐ Time given: h h m m	
	Y ☐ N ☐		0.5 – 0.749 ☐ 0.75 – 0.99 ☐ 1 – 1.99 ☐ 2 – 2.99	0.5† ☐ 0.75† ☐ 1 ☐ 2	No. of scoops: ☐☐ Time given: h h m m No. of scoops:	

8.27 x 11.69 in

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Blinding and code breaking

- Families and clinical teams are blinded to trial allocation
- The treating health care professional should contact the PI at the recruiting site to discuss unblinding.
- Consider treating the infant as if they have received the active supplement.
- Emergency unblinding can be carried out by recruiting site. Non urgent requests should be directed to NPEU for Chief Investigator or safety delegate review.

Safety Reporting – Serious Adverse Events (SAE's)

- The following must be reported:
  - Serious prolonged gastrointestinal disturbance (except NEC)
  - Serious prolonged gastrointestinal disturbance associated with culture/growth of an unusual organism
  - Sepsis associated with culture/growth of an unusual organism

- Reporting window is from supplement start to 12 months and 2 weeks post EDD.
- The DOLFIN protocol lists all foreseeable SAE's which do not require reporting (page 33 of protocol).

SAE Reporting

- Any member of the team can report SAE's.
- Report as soon as you are aware. DO NOT wait for the causality assessment to be completed.
- SAEs can be reported by phone or email (**do not** send patient identifiable information to the DOLFIN email address.)
- Refer to guidance sheet 9 for more information (in transfer pack or on the DOLFIN website.)

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Discharge

- Please let the recruiting site know when baby is discharged home or to another continuing care site.
- Send parents' home with their discharge pack and the remainder of their supplement.
- Ensure parents are provided with information on who to contact with trial related queries (recruiting site, research team and NPEU CTU)
- All follow up questionnaires for parents are sent from NPEU CTU.

FAQ’s

- **Do we need CV/GCP?** We do not require a CV or GCP for staff at continuing care sites due to the limited activity taken place. Please follow your own Trust policies for CV/GCP documentation.
- **Is there any funding available for continuing care sites?** Unfortunately, there is no funding for continuing care sites due to restrictions on funding from the Funder and the limited activity taking place. The study is a CRN portfolio trial and so may be eligible for CRN funding – please contact your local CRN.
- **Do we have any data entry responsibilities or have respond to data queries?** No, all data entry and queries are the responsibility of the recruiting site. Completion of the dosing log to confirm supplementation is the only data recording required, this should be sent to the recruiting site by email or post to enter onto the database.
- **Will the supplement arrive with the baby?** A box of supplement should arrive with the baby alongside a DOLFIN Transfer Pack and DOLFIN Discharge Pack. This should last for the duration of the hospital stay but if more is required please contact us.

FAQ’s

- **Is there training provided for staff for giving supplement?** We provide guidance sheets to sites which detail preparation, administration and storage of supplement. There are also videos available on the DOLFIN website alongside this presentation. The DOLFIN study team can be contacted for further support and training if required.
- **Will we need to train the parents to give supplement when they are discharged?** No, the recruiting site are responsible for training and supporting the parents. If this was not done ahead of transfer, the recruiting site will liaise with the parents to arrange training.
- **How many babies may be transferred to us?** As transfers are unpredictable, we are unable to estimate the number of transfers within the trial and it will vary across hospitals.
- **Can baby have other supplements?** Yes. As previously mentioned, there are no contraindicated medication or dietary supplements. Infants will be able to have all medicines and fortifiers normally prescribed.
- **Can we get training credits or recognition for our contributions?** We can provide certificates to sites for CPD evidence and all continuing care sites will be acknowledged in any publications.

Further Information

https://www.npeu.ox.ac.uk/dolfin

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Thank you for listening

Any Questions??

DOLFIN Study Team Contact details:

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