DOLFIN

FUNDED BY NIHR | National Institute for Health Research

NHS The Newcastle upon Tyne Hospitals NHS Foundation Trust

NPEU Clinical Trials Unit

Nuffield Department of POPULATION HEALTH Medical Sciences Division

UNIVERSITY OF OXFORD

Site Initiation Visit (SIV) - Training

Presentation Overview

- ✓Study Overview,
- ✓Management and Procedures
- ✓Safety Reporting
- ✓CRF & Data Management
- ✓Site Folder & e-ISF
- ✓Study Management
- ✓Staff Training

Presentation Overview

Part 1

Study Overview

- Background Information & Study Objectives
- Study Design
- Primary & secondary outcomes/endpoints

Study Procedures

- Inclusion/Exclusion criteria
- Informed consent procedure. In person and remote.
- Randomisation
- Preparation of supplement.
- Administration of supplement
- Supply of supplement.
- Support for parents
- Change of consent
- Hospital transfers

Presentation Overview

Safety Reporting

- Definitions
- SAE's and reporting
- Incident reporting and breaches
- Unblinding

Part 2

- **CRF's and data management**
- **Investigator Site file & eISF**

Study Management

- Green light release process

Staff Training

- Delegation logs
- Training logs
- Archiving/storage

Background – DOLPHIN Pilot

DOLPHIN pilot – 2009 to 2013 in 3 UK Neonatal Units

Aim: To investigate whether a micronutrient supplement containing long-chain fatty acids improves neurodevelopment in neonates at risk for neurodevelopmental impairment.

Method:
62 neonates recruited
59 neonates randomised (HIE and preterm)
53 neonates started supplementation
29 assigned supplement; 24 completed follow up
30 were assigned the placebo; 21 completed follow up.

DOLPHIN Findings

Results:

Higher mean cognitive scale scores BSID-III

Higher mean language scale scores BSID-III

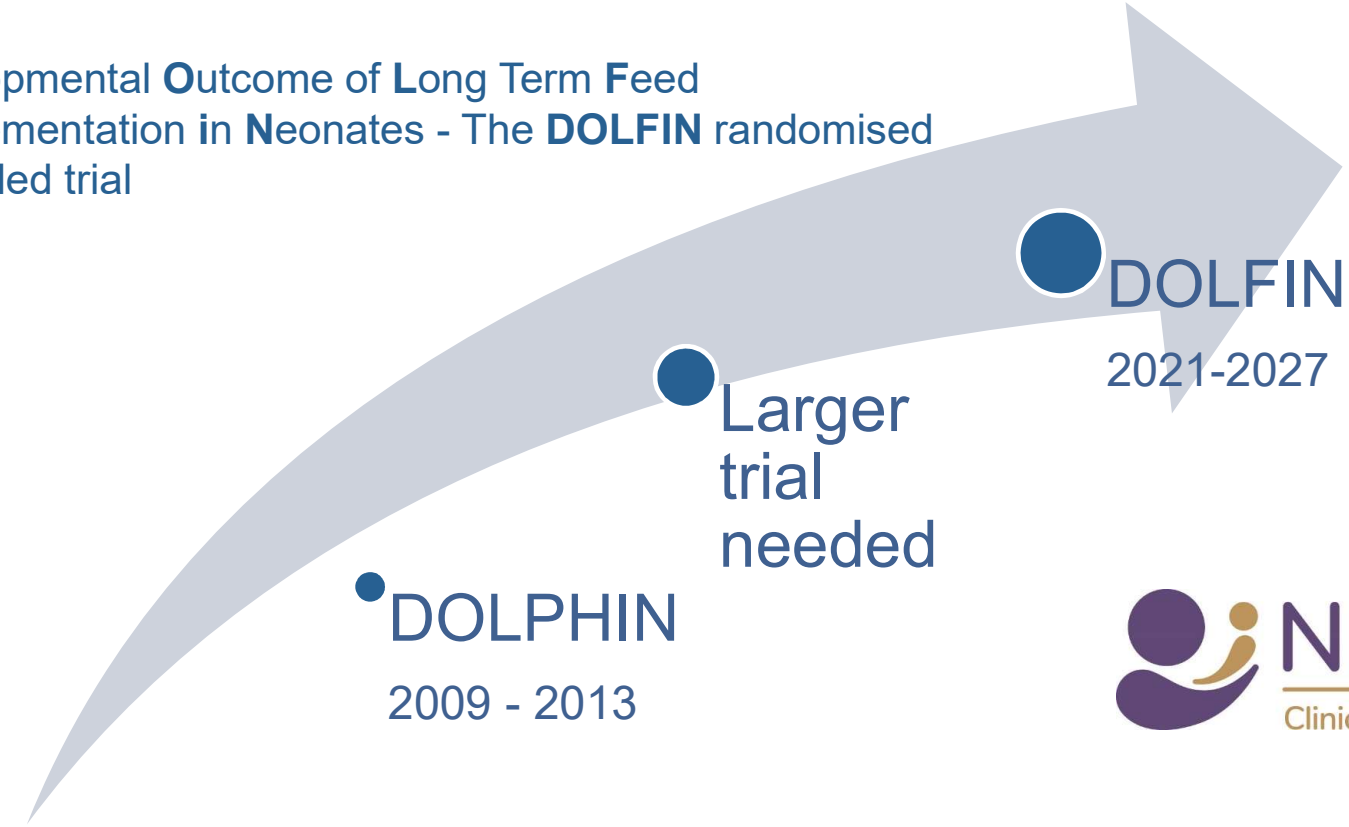
No difference between groups in mean motor scale scores

Parental reports of neurodevelopmental outcomes showed similar results

A larger multicentre trial exploration is warranted:

DOLPHIN to DOLFIN

Developmental **O**utcome of **L**ong Term **F**eed Supplementation **i**n **N**eonates - The **DOLFIN** randomised controlled trial



NPEU
Clinical Trials Unit

Study Objectives

Does nutritional supplementation with a nutrient blend containing long-chain polyunsaturated fatty acids, choline, Uridine-5'-Monophosphate , and cytidine-5'- monophosphate plus usual care from birth to 12 months post EDD improve cognitive development at 24 months post EDD, compared to infants receiving a matched control supplement plus usual care:

Infants born less than 28 weeks of gestation

Infants born at 35 weeks or more of gestation receiving therapeutic hypothermia for HIE

Primary Outcome Measure: Non-Verbal Cognitive Scale standardised score, Parent Report of Childrens Abilities-Revised (PARCA-R)

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

Study Design

- Non-IMP
- Phase III
- Multicentre, blinded, randomised placebo-controlled alongside health economic evaluation
- 1010 infants (538 preterm, 472 HIE from 30 UK NNU)
- Stratified
  - infants born <28 weeks of gestation
  - infants born ≥ 35 weeks of gestation receiving therapeutic hypothermia for HIE)
- Trial duration 69 months, recruitment period 27 months
  Internal pilot 9 months

Inclusion Criteria

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 <28 weeks of gestation

Hypoxic Ischaemic Encephalopathy (HIE)

- Infants born at 35+ weeks of gestation receiving therapeutic hypothermia for HIE

HIE babies are a small group; it is imperative that we do not overlook this population

Exclusion Criteria

- Infants with middle cerebral infarcts.
- Infants with major congenital brain malformation, or genetic condition with abnormal brain development.
- Infants with galactosaemia.
- Infants receiving jejunal feeds.

Informed Consent

- **Must be undertaken by a trained, PI-delegated team member.**
- **Delegated individual must be listed on the DOLFIN Site Delegation Log.**
- Clinical research team at sites will screen infants admitted to Neonatal Unit (NNU) for eligibility.
- Clinical research team to make initial approach to parents with legal responsibility.
- Parents should be provided with the Parent Information Leaflet (PIL), given time to read it, and discuss it with the clinical team.

PRETERM
- Consented prior to discharge from NNU or Continuing Care Site (CCS)

HIE
- Consented at NNU, CCS or at home

Informed Consent Pathways: In-Person

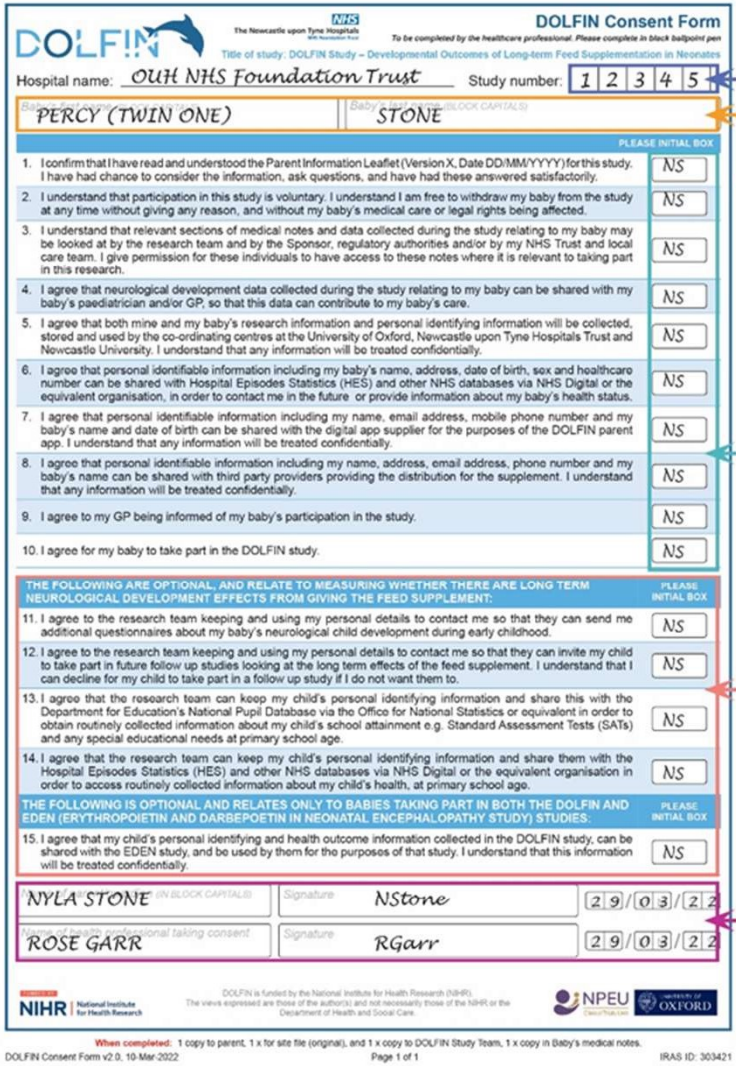
Consent can be obtained from either parent or another person who has legal parental responsibility (as defined in the protocol and consent guidance sheet).
For parents, if the father signs, the mother should countersign as soon as practically possible for maternal data collection.

IN-PERSON – Key points to discuss:

- Participation is voluntary.
- Infants have an equal chance of being randomised to active supplement or placebo.
- Parents will be required to give infants the supplement until 12 months of age, post EDD.
- Parents are asked to complete questionnaires at randomisation, discharge, 3,6,12,18 and 24 months (post EDD).
- Parents will be asked to submit daily adherence data for the first 3 months.
- Parents will be asked to submit infant weights monthly.

Completing the In-Person Consent Form

- The health professional taking consent should read through the consent form with the parents
- The form must be initialled (not ticked) by the parent with legal responsibility.
- It must be signed and dated by the parent.
- It must be signed and dated by the delegated health professional taking consent.
- Copy to parent, e-ISF, infant's medical notes and uploaded to NPEU CTU



DOLFIN

The Newcastle upon Tyne Hospitals NHS Foundation Trust

DOLFIN Consent Form

To be completed by the healthcare professional. Please complete in black ballpoint pen

Title of study: DOLFIN Study – Developmental Outcomes of Long-term Feed Supplementation in Neonates

Hospital name: OUH NHS Foundation Trust

Study number: 1 2 3 4 5

Baby's first name (in BLOCK CAPITALS): PERCY (TWIN ONE)

Baby's last name (in BLOCK CAPITALS): STONE

	PLEASE INITIAL BOX
1. I confirm that I have read and understood the Parent Information Leaflet (Version X, Date DD/MM/YYYY) for this study. I have had chance to consider the information, ask questions, and have had these answered satisfactorily.	NS
2. I understand that participation in this study is voluntary. I understand I am free to withdraw my baby from the study at any time without giving any reason, and without my baby's medical care or legal rights being affected.	NS
3. I understand that relevant sections of medical notes and data collected during the study relating to my baby may be looked at by the research team and by the Sponsor, regulatory authorities and/or by my NHS Trust and local care team. I give permission for these individuals to have access to these notes where it is relevant to taking part in this research.	NS
4. I agree that neurological development data collected during the study relating to my baby can be shared with my baby's paediatrician and/or GP, so that this data can contribute to my baby's care.	NS
5. I agree that both mine and my baby's research information and personal identifying information will be collected, stored and used by the co-ordinating centres at the University of Oxford, Newcastle upon Tyne Hospitals Trust and Newcastle University. I understand that any information will be treated confidentially.	NS
6. I agree that personal identifiable information including my baby's name, address, date of birth, sex and healthcare number can be shared with Hospital Episodes Statistics (HES) and other NHS databases via NHS Digital or the equivalent organisation, in order to contact me in the future or provide information about my baby's health status.	NS
7. I agree that personal identifiable information including my name, email address, mobile phone number and my baby's name and date of birth can be shared with the digital app supplier for the purposes of the DOLFIN parent app. I understand that any information will be treated confidentially.	NS
8. I agree that personal identifiable information including my name, address, email address, phone number and my baby's name can be shared with third party providers providing the distribution for the supplement. I understand that any information will be treated confidentially.	NS
9. I agree to my GP being informed of my baby's participation in the study.	NS
10. I agree for my baby to take part in the DOLFIN study.	NS

THE FOLLOWING ARE OPTIONAL, AND RELATE TO MEASURING WHETHER THERE ARE LONG TERM NEUROLOGICAL DEVELOPMENT EFFECTS FROM GIVING THE FEED SUPPLEMENT:	PLEASE INITIAL BOX
11. I agree to the research team keeping and using my personal details to contact me so that they can send me additional questionnaires about my baby's neurological child development during early childhood.	NS
12. I agree to the research team keeping and using my personal details to contact me so that they can invite my child to take part in future follow up studies looking at the long term effects of the feed supplement. I understand that I can decline for my child to take part in a follow up study if I do not want them to.	NS
13. I agree that the research team can keep my child's personal identifying information and share this with the Department for Education's National Pupil Database via the Office for National Statistics or equivalent in order to obtain routinely collected information about my child's school attainment e.g. Standard Assessment Tests (SATs) and any special educational needs at primary school age.	NS
14. I agree that the research team can keep my child's personal identifying information and share them with the Hospital Episodes Statistics (HES) and other NHS databases via NHS Digital or the equivalent organisation in order to access routinely collected information about my child's health, at primary school age.	NS
THE FOLLOWING IS OPTIONAL AND RELATES ONLY TO BABIES TAKING PART IN BOTH THE DOLFIN AND EDEN (ERYTHROPOIETIN AND DARBEPOETIN IN NEONATAL ENCEPHALOPATHY STUDY) STUDIES:	**PLEASE INITIAL BOX**
15. I agree that my child's personal identifying and health outcome information collected in the DOLFIN study, can be shared with the EDEN study, and be used by them for the purposes of that study. I understand that this information will be treated confidentially.	NS

Name of parent providing consent (in BLOCK CAPITALS)	Signature	Date
NYLA STONE	NStone	29/03/22
Name of health professional taking consent	**Signature**	**Date**
ROSE GARR	RGarr	29/03/22

NIHR | National Institute for Health Research

DOLFIN is funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

NPEU Clinical Trials Unit | University of Oxford

When completed: 1 copy to parent, 1 x for site file (original), and 1 x copy to DOLFIN Study Team, 1 x copy in Baby's medical notes.

DOLFIN Consent Form v2.0, 10-Mar-2022 Page 1 of 1 IRAS ID: 303421

After consent, obtain a study number from the Randomisation website and write study number here

Differentiate between multiples (for example, infants can be named as TWIN ONE, TWIN TWO). Where first name is not yet confirmed, write down as Baby

Initial the boxes, not tick

This is optional consent and can be left blank if they do not wish to be contacted in the future

Both the parent providing consent and the health professional taking consent must be on the same date.

Mother must counter-sign and date even if the other parent provides consent initially, as soon as practically possible.

Informed Consent - Remote

REMOTE

- Consent may be obtained remotely (via telephone or video call) if an infant has been discharged home or to a continuing care site and so in-person consent is not possible.
- Remote consent should be of the same standard as in person consent.
- Provide parent with hard copy or electronic of PIL prior to discharge.
- Prior to taking consent identity checks of the parent must be completed:

✓ Confirm parent's name and address.

✓ Confirm infant's name, date of birth and address

Informed Consent - Remote

- Delegated research staff completes the REMOTE consent form on behalf of parent by initialling each box with own initials.
- Parent signature **not required.** Delegated individual signs instead.
- Delegated individual to declare that identity checks have taken place.
- Copy sent to parent either electronically or by post, a copy is filed in:

✓ e-ISF

✓ infant's medical notes

✓ and uploaded to NPEU CTU.

DOLFIN

The Newcastle upon Tyne Hospitals NHS Foundation Trust

DOLFIN Remote Consent Form

To be completed by the healthcare professional.
Please complete in black ballpoint pen

"The healthcare professional taking consent should indicate in each box – using their own initials – that the parent has understood and verbally agreed to each statement.

Title of study: DOLFIN Study – Developmental Outcomes of Long-term Feed Supplementation in Neonates

Hospital name: _____ Study number: ☐☐☐☐☐

Baby's first name (BLOCK CAPITALS) | Baby's last name (BLOCK CAPITALS)

Healthcare Professional Declaration: I confirm that I have undertaken participant identity checks (including parent's name, baby's name, date of birth of baby and address) and I have confirmed the identity of both the parent and the baby.

Name of health professional taking consent | Signature | D D / M M / Y Y

Parent name (BLOCK CAPITALS) | Parent surname (BLOCK CAPITALS)

		PLEASE INITIAL BOX*
1.	I confirm that I have read and understood the Parent Information Leaflet (Version X, Date DD/MM/YYYY) for this study. I have had a chance to consider the information, ask questions, and have had these answered satisfactorily.	
2.	I understand that participation in this study is voluntary. I understand that I am free to withdraw my baby from the study at any time without giving any reason, and without my baby's medical care or legal rights being affected.	
3.	I understand that relevant sections of medical notes and data collected during the study relating to my baby may be looked at by the research team and by the Sponsor, regulatory authorities or by my NHS Trust and local care team. I give permission for these individuals to have access to these notes where it is relevant to taking part in this research.	
4.	I agree that neurological development data collected during the study relating to my baby can be shared with my baby's paediatrician and/or GP, so that this data can contribute to my baby's care.	
5.	I agree that both mine and my baby's research information and personal identifying information will be collected, stored and used by the co-ordinating centres at the University of Oxford, Newcastle upon Tyne Hospitals Trust and Newcastle University. I understand that any information will be treated confidentially.	
6.	I agree that personal identifiable information including my baby's name, address, date of birth, sex and healthcare number can be shared with Hospital Episodes Statistics (HES) and other NHS databases via NHS Digital or the equivalent organisation, in order to contact me in the future or provide information about my baby's health status.	
7.	I agree that personal identifiable information including my name, email address, mobile phone number and my baby's name and date of birth can be shared with the digital app supplier, Newcastle University for the purposes of the DOLFIN parent app. I understand that any information will be treated confidentially.	
8.	I agree that personal identifiable information including my name, address, email address, phone number and my baby's name can be shared with third party providers providing the distribution for the supplement. I understand that any information will be treated confidentially.	
9.	I agree to my GP being informed of my baby's participation in the study.	
10.	I agree for my baby to take part in the DOLFIN study.	
	THE FOLLOWING ARE OPTIONAL, AND RELATE TO MEASURING WHETHER THERE ARE LONG TERM NEUROLOGICAL DEVELOPMENT EFFECTS FROM GIVING THE FEED SUPPLEMENT:	**PLEASE INITIAL BOX**
11.	I agree to the research team keeping and using my personal details to contact me so that they can send me additional questionnaires about my baby's neurological child development during childhood.	
12.	I agree to the research team keeping and using my personal details to contact me so that they can invite my child to take part in future follow up studies looking at the long term effects of the feed supplement. I understand that I can decline for my child to take part in a follow up study if I do not want them to.	
13.	I agree that the research team can keep my child's personal identifying information and share this with the Department for Education's National Pupil Database via the Office for National Statistics or equivalent in order to obtain routinely collected information about my child's school attainment e.g. Standard Assessment Tests (SATs) and any special educational needs at primary school age.	
14.	I agree that the research team can keep my child's personal identifying information and share them with the Hospital Episodes Statistics (HES) and other NHS databases via NHS Digital or equivalent organisation in order to access routinely collected information about my child's health, at primary school age.	
	THE FOLLOWING IS OPTIONAL AND RELATES ONLY TO BABIES TAKING PART IN BOTH THE DOLFIN AND EDEN (ERYTHROPOETIN AND DARBEPOETIN IN NEONATAL ENCEPHALOPATHY STUDY) STUDIES:	**PLEASE INITIAL BOX**
15.	I agree that my child's personal identifying and health outcome information collected in the DOLFIN study, can be shared with the EDEN study, and be used by them for the purposes of that study. I understand that this information will be treated confidentially.	

Healthcare Professional Declaration: I confirm that I have read all of the statements above to the participant and that the participant has verbally confirmed their consent to take part in the study. I have indicated this by providing my initials next to the relevant statements where the participant has provided their consent.

Name of health professional taking consent | Signature | D D / M M / Y Y

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NPEU Clinical Trials Unit

When completed: 1 copy to parent, 1 x for site file (original), and 1 x copy to DOLFIN Study Team, 1 x copy in Baby's medical notes.

Recruitment to other trials

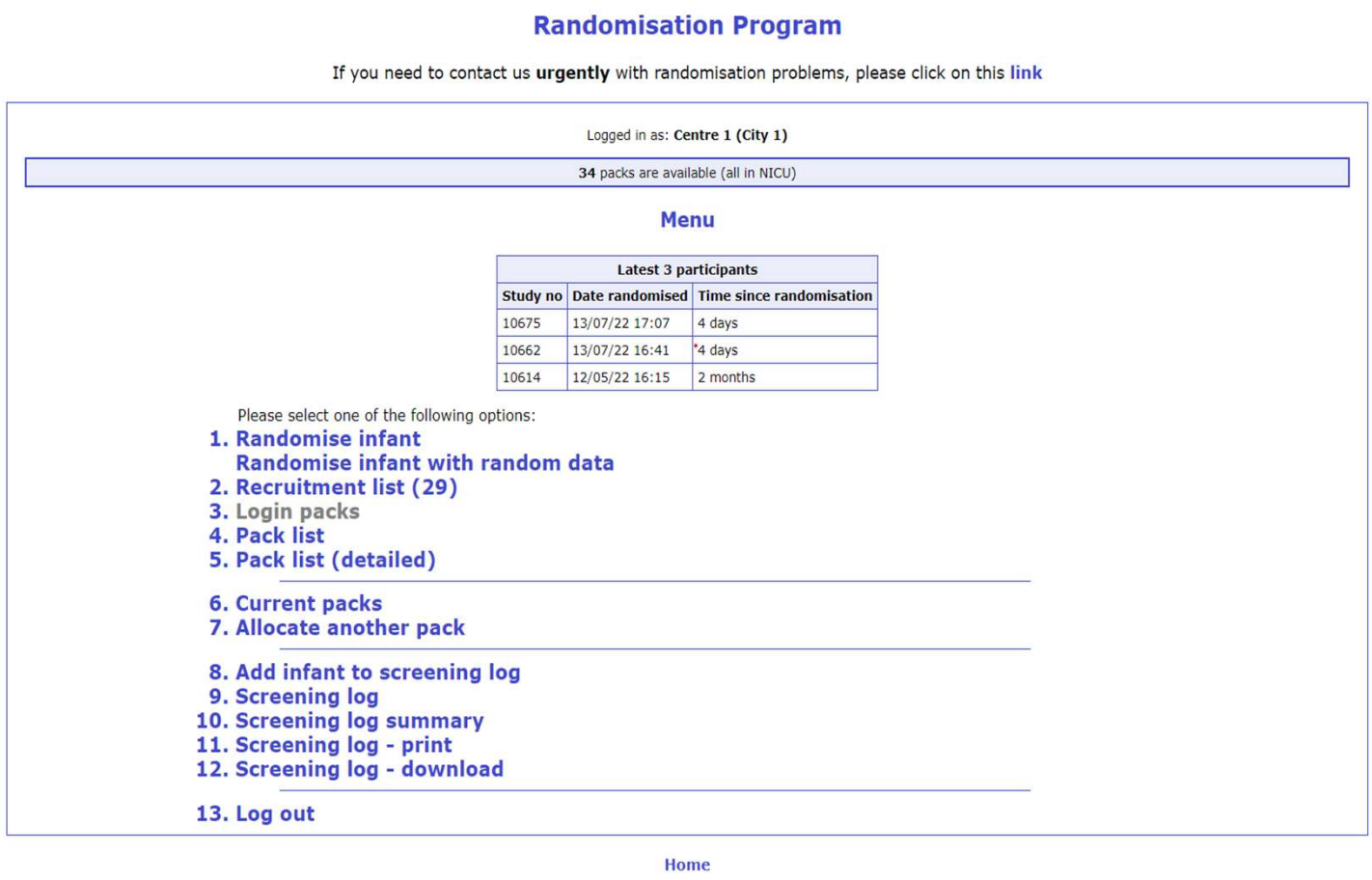
- Co-recruitment to other trials permitted, except for intervention trials which have a neurodevelopmental primary outcome.
- If this scenario arises please contact NPEU CTU who will refer to the Chief Investigators.
- Co-recruitment to the EDEN study is permitted for infants in the HIE stratum.

Randomisation

- As soon as possible after informed consent obtained
- Preterm infants randomised prior to discharge from NNU/CCS.
- HIE infants randomised until 40 weeks of gestation plus 28 days, may occur pre or post discharge home
- Ensure written consent has been obtained.
- 1:1 allocation ratio
- Multiple births allocated to the same arm

Micronutrient Supplement **OR** **Matched Placebo**

Randomisation



Randomisation Program

If you need to contact us **urgently** with randomisation problems, please click on this **link**

Logged in as: **Centre 1 (City 1)**

34 packs are available (all in NICU)

Menu

Latest 3 participants		
Study no	**Date randomised**	**Time since randomisation**
10675	13/07/22 17:07	4 days
10662	13/07/22 16:41	4 days
10614	12/05/22 16:15	2 months

Please select one of the following options:

1. **Randomise infant**
   Randomise infant with random data
2. **Recruitment list (29)**
3. **Login packs**
4. **Pack list**
5. **Pack list (detailed)**

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6. **Current packs**
7. **Allocate another pack**

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8. **Add infant to screening log**
9. **Screening log**
10. **Screening log summary**
11. **Screening log - print**
12. **Screening log - download**

---

13. **Log out**

Home

Section A: Eligibility

Time of randomisation: 18 Jul 2022 16:29

Section A: Infant details

A1. What is the infant's date and time of birth?	/ / : 24hr clock
A2. Expected date of delivery (EDD – by maternal scan if available, if not LMP)	/ /
A3. What is the infant's sex?	
A4. What is the infant's current weight (g)?	
A5. Is this infant one of a multiple pregnancy?	
A6. Is this infant currently an inpatient?	

Inclusion criteria

A7.1. Has written informed parental consent been obtained from an individual with parental responsibility?	
A7.1.1 Who signed the consent form?	
A7.1.2 Please enter name of person who obtained consent	
A7.2. Does this infant have a realistic prospect of survival beyond discharge?	
A7.3. Are the parents able to comply with the protocol?	
A7.4. Is this infant likely to tolerate full enteral feeds?	

Exclusion criteria

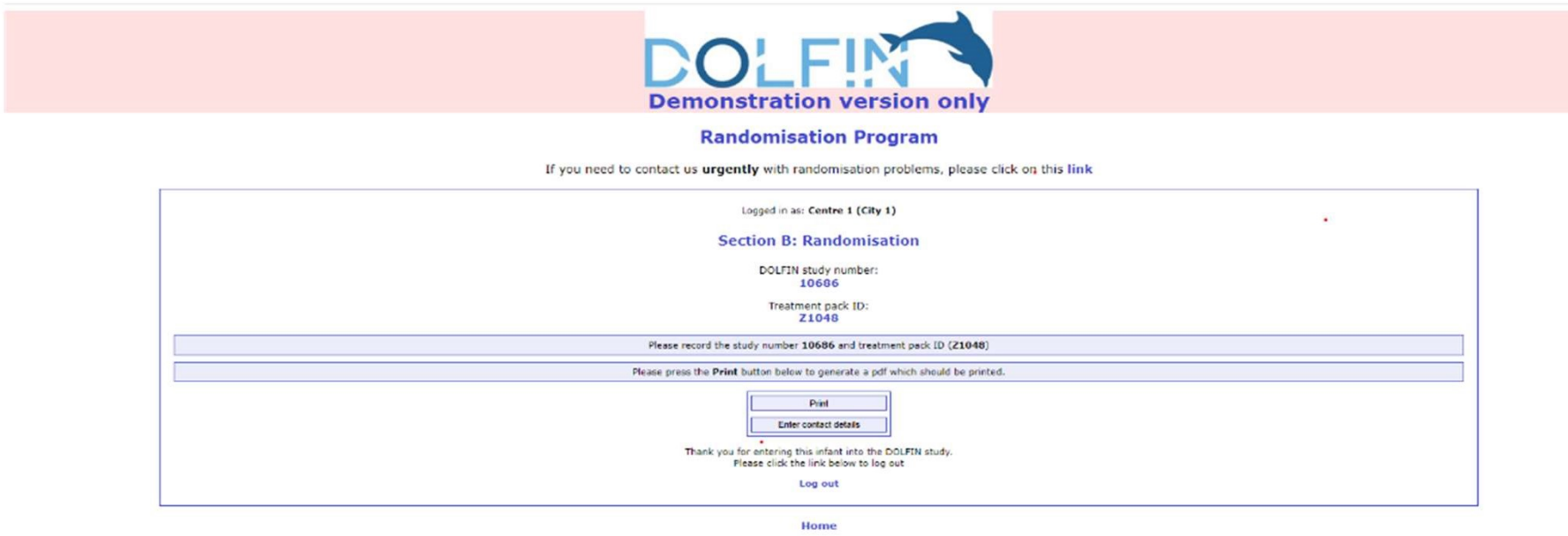
A8.1. Does this infant have a middle cerebral artery infarct?	
A8.2. Does this infant have a major congenital brain malformation, or genetic condition with abnormal brain development?	
A8.3. Does this infant have galactosaemia?	
A8.4. Is this infant receiving jejunal feeds?	

Please sign off this form once complete

Surname	
Forename	
Professional email	

Continue

Cancel



It is important to record the infant and mother's healthcare number (e.g. NHS number), email address, telephone number and postal address.
Once completed, sms/email will be sent requesting completion of the DOLFIN Baseline Questionnaire

Pack Management and accountability

- Not a CTIMP.
- Pharmacy involvement is a site level decision.
- Pack management will be via the randomisation system.
- Pack resupply will be monitored closely using the pack management system which tracks stock levels and expiry dates across sites and families.
- Packs received direct to the NNU should complete the DOLFIN Supplement Management and Control log.

Trial Intervention

- A breast milk/infant formula/food active supplement.
- Active and placebo supplement have similar levels of fat and comparable energy content.
- Identically packaged.
- Supplied by Nutricia and delivered to sites and parents homes by distribution company, IPS.
- Quality and safety tested at the factory.
- Supplied in 13g sachets.
- No branding on sachets or trial materials

Trial Intervention

- **Infants must have reached full milk feeds prior to commencing the supplement however training can take place as soon as the infant is randomised.**
- Sachets should be stored in an area which will be kept at 2-25 degrees Celsius.
- Opened sachets should be used within 24 hours of opening.
- Once added to the infant's milk, give as soon as possible and within 1 hour of preparation.
- Record supplement given on the DOLFIN NNU Daily Dosing Log including the treatment pack ID allocated at randomisation.

HIE Infant supplement training

- If randomised remotely, training on preparation of supplement and administration can be undertaken up to 28 days post discharge.
- Training can take place remotely or by home visit.
- Site staff must be confident that parents know how to administer the supplement safely prior to commencing the daily supplementation.
- Signpost to the videos online.

Supplement Preparation

- There are 2 videos on our website showing preparation of the supplement.
- https://youtu.be/VtggW8vmvBM
- https://youtu.be/4zVvDSDbNPw
- https://www.npeu.ox.ac.uk/dolfin/parents/resources

Administration of supplement

- Each box contains a 1g scoop to measure out supplement.
- Measured dose to be dissolved in infants usual milk feed.
- The infant must be on full milk feeds.
- Infant weights will be reported by parents via the App or OpenClinica form to ensure correct doses are being administered once discharged home.

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 must be given with 15mls milk
  - E.g. a 3kg infant having 3 scoops will have a total feed volume of at least 45mls.
- Breast fed babies can be given a 3ml breastmilk-supplement shot, ahead of their feed.
- 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.
- If splitting the total daily dose of supplement into more than one feed, then each 0.25g of supplement needs to be accompanied by 3.8 mls feed.

Administration of supplement

- The supplement is given to the infant via their normal feeding route e.g. oral, nasogastric tube, gastrostomy tube.
- Breastfeeding mothers should be provided with options for delivering the supplement and signposted to DOLFIN breastfeeding materials.
- Breastfeeding mothers should be supported by local lactation consultants as per usual care.
- Flexible funding available to sites for equipment to support breastfeeding e.g. hospital grade breast pumps.

Parent support and training to give supplement

- At discharge each participant will be supplied with an individual Discharge Pack containing:

✓ Supply of supplement

✓ Written support materials

✓ Information about accessing online training materials and support

✓ Dosing charts

✓ Personalised study timeline

✓ Contact information for local NHS professionals and study team

✓ A letter will also be sent to GP and Health Visitor to ensure access to community weighing facilities and support as required.

Parent support and training to give supplement

- DOLFIN website www.npeu.ox.ac.uk/dolfin will have a range of materials including:

✓ How to mix the supplement

✓ Breastfeeding support materials

✓ Nasogastric and gastrostomy tube feeding support materials

✓ FAQ page for parents which will be updated in response to participant queries

- Also supported by local neonatal and local post discharge team including GP and Health Visitor as per usual care

DOLFIN Study App

- Bespoke App created.
- Collect adherence data (GDPR compliant and Sponsor approved).
- Regular supplement administration reminders sent (or via sms or email if not using the App).
- Daily for first 3 months post discharge then weekly thereafter until end of supplementation.
- In cases of non-adherence, research team to liaise with parents and post discharge team to identify any barriers.

Unblinding Procedure

- Must be satisfied that it is a genuine emergency and that knowledge of allocation is needed to guide appropriate clinical management of the infant.
- Log into the randomisation website using the single access code provided in the sealed envelope in the document box.
- Reason for unblinding must be recorded in the randomisation database.

Safety Reporting – Serious Adverse Events (SAE's)

- All SAE's other than those listed as foreseeable in the protocol and are not deemed causally related, must be reported.
- Reporting window will be from supplement start to 12 months and 2 weeks post EDD.
- 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

SAE Reporting

- The Principal Investigator (PI) and site study team have responsibility for safety reporting at site. They must inform the DOLFIN study team of all SAEs that occur, and of other relevant safety issues.
- Any member of the team can report SAEs, DO NOT wait for the causality assessment to be completed.

- SAEs must be reported as soon as possible and within 24 hours of the site becoming aware of it.
- SAEs should be reported from randomisation up until the infant is 12 months and 2 weeks post EDD.

- SAEs can reported by phone, email or online (do not send patient identifiable information to the DOLFIN email address.

Internal Use Only
Study ID _____ SAE ID _____ Form ID _____

DOLFIN
Developmental Outcomes of Long-term Feed Supplementation in Neonates

Serious Adverse Event Report Form (Non CTIMP)

Form completion instructions overleaf

1. **Report type** *(tick one)* Initial report ☐ Follow-up information ☐

2. **Site name:** _____

3. **Participant details**

Study number _____

Participant's initials *(please delete row for collection of participants initials before printing form if PID not been collected in house)* _____

Date of birth __/__/____

Sex Male ☐ Female ☐ Indeterminate ☐

Weight _____ *g* OR __.__ *kg*
(last known weight and delete as applicable)

4. **ADVERSE EVENT DESCRIPTION:**

(Please record diagnosis if known, an account of the event including signs and symptoms if diagnosis not known, any interventions given to manage the event including dates for these, any sequelae and if event fatal, cause of death if known):

5. **Start date and time of SAE** __/__/____ __:__

6. **Stop date and time of SAE** __/__/____ __:__ Or ongoing ☐

7. **Date and time site became aware of SAE:** __/__/____ __:__

Please complete and send this form immediately, as soon as possible after becoming aware of the SAE.

PLEASE FAX/EMAIL FORM TO: Trial Co-ordinating Centre
+44 (0)1865 289740 dolfin@npeu.ox.ac.uk

SAE Report in Open Clinica – Initial report

1. Report type
If this is the first time the SAE has been reported, please select "Initial report". If you are submitting new, updated or corrected information for a previously reported SAE, please select "Follow-up information".

(•) Initial report ( ) Follow-up information

SAE number
If this CRF relates to the patient's first SAE, enter 1. If the patient has had more than one SAE, please record the SAE number that this applies to

1

Form number (for this SAE)
If this is the initial report, enter 1. If this is a follow-up form, please record the number of CRFs you have attempted to complete for this SAE, including this one

1

2. Site

Site name

Leicester Royal Infirmary

3. Participant details

DOB on Entry Form: 2020-09-25

Date of birth

2020-09-25

Sex

( ) Male (•) Female ( ) Indeterminate

Enter participant's last known weight either in grams OR kilograms

Weight in grams
(g)

3835

Weight in kilograms
(kg)

3.835

Review of SAE's

- Relationship of each adverse event to the trial supplement must be determined by a medically qualified individual as:
  - Unrelated, Possibly, Probably or definitely.

- If determined possibly, probably or definitely related to the trial supplement further information will be requested from site.

Causality Assessment

- ✓Any member of the team can report an SAE
- ✓Causality assessment can only be completed by medically qualified delegated individuals
- ✓If the initial **SAE Form** was completed online, print the form in order to obtain causality assessment from a delegated individual
- ✓**We recommend more than one person is delegated to complete causality assessment**
- ✓DO NOT WAIT FOR THIS ASSESSMENT TO REPORT THE SAE.

SAE Follow up information

- ✓ If new relevant or missing information is obtained, site staff can send an updated version of the original report form, or use a new SAE Report Form
  - ✓ If adding minimal data, e.g., end date, this could be added to existing SAE report form
  - ✓ Extensive information should be on new SAE form.

- ✓ If updating the original report form, new information should be added in a **GCP compliant** manner
  - E.g., it should be made clear ***who*** has added the information and ***when*** it was added by signing ***initials and date*** next to each of the new entries made

- ✓ This is applicable to both electronic (OpenClinica) or paper reporting form.

Incident reporting

Incidents & Breaches

- **What is an incident?** It can be defined as a deviation from:
  - Protocol
  - Study specific procedures
  - Good Clinical Practice
  - Regulatory requirements.

  For example:

  1. Parent consented by an individual not on the delegation log.
  2. Superseded version of a form used.

Anyone on the delegation log can report incidents.

Incidents and protocol deviations will be defined as a **serious breach** if the incident is likely to affect to a significant degree either:

- The safety, physical or mental integrity of the subjects of the trial
- The scientific value of the trial

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Incident and Deviation Reporting Form

Site Name

Principal Investigator:

Participant Study Number (if applicable):

Participant day and month of date of birth (if applicable): /

Incident number: *(to be completed by NPEU CTU)*

Date incident occurred (started): / /

Detail of incident:

Resolution: *(include actual and planned corrective and preventative action at site)*

If this information is not available at the time the incident is first reported, please send without this information and send this information later.

Details of Reporter:

Name:

Role:

Signature: **Date:** / /

List any relevant documentation included with this form:

Please complete and send immediately after becoming aware of the incident.

One copy to NPEU CTU, along with relevant documentation, and one to be filed in the Investigator Site File.

Please fax/email form to:

DOLFIN Coordinating Centre

Email: dolfin@npeu.ox.ac.uk

Fax: +44 (0)1865 289740

NPEU CTU Receipt:

Received at NPEU CTU by:

Name:

Role:

Signature: **Date:** / /

NPEU CTU comments to reporting site:

Name:

Role:

Signature: **Date:** / /

Incident reporting

- Sites can complete forms as:

✓An editable electronic PDF (in e-ISF) OR

✓A paper form (in DOLFIN Document box)

- DO NOT EMAIL WITH PATIENT IDENTIFIABLE DATA
- If unable to complete the resolution section, send the partially completed form and re-send with resolution at a later date.

Participant Change of Consent

- Parents have the right to change consent for their infant at any time.
- Parents may withdraw consent for any aspect of the study and /or data collection.
- Data collected up to the point of change of consent will be used.
- If parents wish to discontinue trial supplementation they should be asked if they are happy to complete data collection.
- If there is a permanent or temporary discontinuation of supplement by parent or clinician, this does not constitute a withdrawal, only change of consent.

Transfer to Continuing care sites

- Continuing care (CCS) sites will be set up as part of the study set up.
- Please notify DOLFIN study team of a transfer as soon as possible.
- Supplementation will only continue where there are regulatory permissions in place at the cc site and supplementation has already started at the recruiting site.
- Transfer with sufficient supply of supplement and the DOLFIN transfer pack (see guidance sheet 7)
- Complete the Transfer Form on OpenClinica

Transfer to Continuing Care Site

- Contact the receiving site and inform them that the infant is in DOLFIN.
- Provide a copy of the NNU Daily Dosing Log.
- CCS site responsible for reporting SAE's and incidents.
- CC site must inform recruiting site when infant is transferred to a different hospital or home.
- Recruiting site continue to have responsibility for completion of CRF's and supporting the family after transfer.

Any Questions??

Part 2

- **CRF’s and data management**
- **Investigator Site file & eISF**

Study Management

- Green light release process

Staff Training

- Delegation logs
- Training logs
- Archiving and storage

DCF

Completed by site staff / Completed by parents	Infant recruit type: Preterm	Infant recruit type: HIE randomised in hospital	Infant recruit type: HIE randomised post-discharge	Where/how completed	When to complete
Consent form	✓	✓	✓	As self-carbonating paper copy	As soon as parent decides to take part (having had appropriate time to consider and ask questions) and before any data is collected
Randomisation web form	✓	✓	✓	Through DOLFIN randomisation website	As soon as possible after the consent form is completed
Contact details form	✓	✓	✓		
Entry form	✓	✓	✓	Data from randomisation website automatically copied to first section; second section via data entry on OpenClinica	
HIE infants neonatal encephalopathy questionnaire		✓	✓	As data entry on OpenClinica	
Post-discharge form			✓		
Parent baseline questionnaire	✓	✓	✓	Through link emailed to parent, onto OpenClinica (paper available if requested)	
Supplement starter form	✓	✓		As data entry on OpenClinica	As soon as the infant receives first dose of in-hospital supplement
Dosing log	✓	✓		As paper copy which is then entered onto OpenClinica	While infant is in hospital, once supplement has begun
Transfer/discharge form	✓	✓		As data entry on OpenClinica	Whenever infant is transferred to another hospital, when they are discharged home, or if they die
Parent discharge questionnaire	✓	✓	✓	Through link emailed to parent, onto OpenClinica (paper available if requested)	Two weeks after infant is discharged from hospital

CRF completion – Clinical data

- Routine data collection: Clinical data relating to birth and NNU admission/stay collected from hospital records.
- All data should be input on eCRF's directly into the database (OpenClinica).
- **Entry Form** – section A & B copied from randomisation site.
- **The Transfer/Discharge Form** will be completed at discharge from each hospital by the recruiting site.
- Please ensure DOLFIN study team are informed about the infant's transfer/discharge or death.

CRF Completion cont'd

- **Supplement Starter Form –** complete as soon as the infant receives their first dose of supplement. If infant transferred before starting supplement, please liaise with the continuing care site.
- **Discontinuation of supplement starter form –** complete if infant permanently stops supplement.
- **Post-discharge form –** complete as soon as randomised for infants randomised after discharge home. This form replaces the transfer/discharge form for these infants.

Daily Dosing Log

- Complete the Dosing Log each time the supplement is administered. Make a note of the pack ID at the top of the form to ensure accountability.
- Enter the data from the Dosing Logs onto Open Clinica. (Research Nurse or other delegated individual).
- Store paper dosing logs in the site folder.

HIE Babies Only

- Neonatal Encephalopathy questionnaire should be completed for all infants receiving therapeutic hypothermia for HIE.
- Includes NICHD examination information D1-3
- Needs to signed off by the PI
- See guidance document for signing off on Open Clinica.

HIE Infants Neonatal Encephalopathy Questionnaire

Day 1 of therapeutic hypothermia

Neurological examination - Day 1 of therapeutic hypothermia						
Date of examination						
yyyy-mm-dd						
Signs of neonatal encephalopathy (NE) in each category						
		Alert, responsive to external stimuli (state dependent e.g., Post feeds)	Hyper-alert, has a stare, jitteriness, high-pitched cry, exaggerated response to minimal stimuli, inconsolable	Lethargic	Stupor / coma	Not measured
1. Level of consciousness	*	○	○	○	○	○
		Changes position when awake	Normal or decreased	Decreased activity	No activity	Not measured
2. Spontaneous activity	*	○	○	○	○	○
		Predominantly flexed when quiet	Mild flexion of distal joints (fingers, wrist usually)	Moderate flexion of distal joint, complete extension	Decerebrate	Not measured
3. Posture	*	○	○	○	○	○

Parent daily adherence data	✓	✓	✓	Through link emailed to parent, onto OpenClinica, or via DOLFIN app	Every day for first 3 months of supplement administration once infant is home
Parent weekly adherence data	✓	✓	✓		Every week for months 4 to 12 of supplement administration once infant is home
Parent 3-month questionnaire	✓	✓	✓	Through link emailed to parent, onto OpenClinica (paper available if requested)	When the infant is 3 months old (post-EDD)
Parent 6-month questionnaire	✓	✓	✓		When the infant is 6 months old (post-EDD)
Parent 12-month questionnaire	✓	✓	✓		When the infant is 12 months old (post-EDD)
Serious adverse event (SAE) form	*(✓)*	*(✓)*	*(✓)*	*As data entry on OpenClinica* ***as soon as possible after site becomes aware of event being defined as serious***	***Only** if any SAEs occur from when infant starts supplement up until infant is 12 months and 2 weeks old (post-EDD)*
Parent 18-month questionnaire	✓	✓	✓	Through link emailed to parent, onto OpenClinica (paper available if requested)	When the infant is 18 months old (post-EDD)
Parent 24-month questionnaire	✓	✓	✓		When the infant is 24 months old (post-EDD)
2-year outcomes form	✓	✓	✓	As data entry on OpenClinica	When the infant is 24 months old (post-EDD)
Change of consent	*(✓)*	*(✓)*	*(✓)*		***Only** if the parent no longer wishes to provide data or otherwise change the consent they originally provided*

Parent completed Outcomes

- Parents will complete questionnaires at:
  - **Randomisation** - baseline questionnaire containing a health related quality of life questions.
  - **Discharge** home – method of supplement delivery, tolerability, any community health and social care contacts, costs incurred by families and parental time away from work.
  - **Validated questionnaires** sent at 3,6,12,18 and 24 months post EDD.
  - **2-year outcomes** are measured at 24 months post EDD.
  - They will be given the option to complete the questionnaires electronically or in paper copy.

OpenClinica

Open Source for Clinical Research

- Data entry on OpenClinica can be completed only by trained and delegated staff.
- Log in details will be sent to individual sites.
- Data queries resolution is covered in the OpenClinica training.
- Training materials will be available for clinicians to access on the DOLFIN website

Study Documentation for sites

- Document box containing:

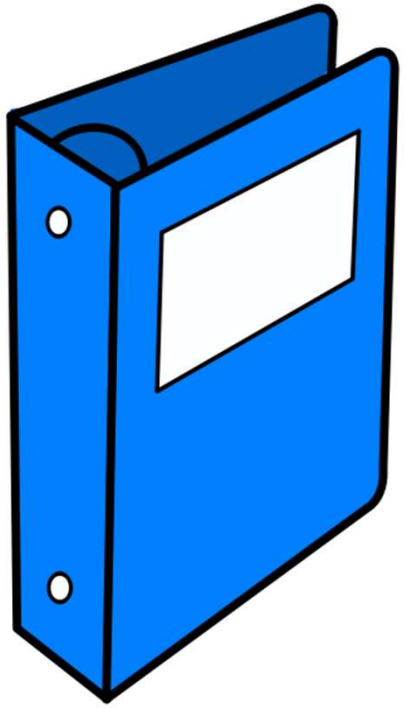
✓ Small investigator site folder
✓ Copies of both PILs
✓ Consent Forms
✓ Guidance Sheets
✓ Discharge and Transfer packs
✓ Site contact details
✓ Randomisation site log in details
✓ Stationery (pens, post it pads) and REC approved posters
✓ Optional – DOLFIN Banner

Site Folder and e-ISF

Site Folder for:

- Consent forms
- Any paper forms i.e.

✓ Delegation log
✓ Training log
✓ Dosing log



A downloadable electronic site file will be sent to sites; all electronic documents should be kept here.
It should be stored and maintained on a backed up and appropriately restricted location.

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The Newcastle upon Tyne Hospitals NHS Foundation Trust

This log should include all relevant study staff and other clinical staff who routinely carry out study procedures or who have specific data collection/interpretation responsibilities.

Add new or replacement staff as appropriate. Please send updated copies to Dolfin@npeu.ox.ac.uk

Note: Please complete the log and obtain the PI's approval before starting study-related responsibilities.

A	Screen Patients/ Confirm Eligibility	E	Data collection/resolution of data queries (Open Clinica)	K	Pack management system (for permissions of allocating)	Page ____ x_____
B	Obtain Informed Consent	F	SAE clinical review/causality assessment & sign off.	L	Provision of parent training on administering supplement	
C	Randomisation	G	Maintain Investigator Site File	M	All of the above	
D	Provide study-related training	H	Prescribing supplement	N	Other (specify)	

						Delegated Individual		Principal investigator	
Full Name *(Please print)*	**Role**	**Responsibilities** *(Use codes listed above)*	**Dates of responsibilities**		**Email address**	**Appropriate GCP?** ✓	**Usual Initials**	**Signature**	**PI's Signature**	**Date**
			Start (DD/MM/YY)	**End** (DD/MM/YY)						

- ✓ **Please ensure your local PI has delegated responsibility (signed off) for staff on the DOLFIN delegation log. If research staff perform duties they are not delegated to carry out it will lead to a reportable incident or breach.**
- ✓ **Whenever the log is updated please remember to scan the entire log to dolfin@npeu.ox.ac.uk**
- ✓ **Only GCP and CV for the PI and Lead research nurse(s) are submitted to the DOLFIN study team. Please maintain records locally for all members of staff.**

Site Delegation Log – Top tips

- Please complete and maintain your Site Delegation Log to avoid incidents and serious breaches.
- Ensure all columns on the log are correct and complete paying particular attention to the **responsibility codes.**
- **Do not strike through** an entry on the log. If there is an error or you need to update an entry, complete a new line for that individual in the log.
- Always complete '**end dates'** for any staff who leave. This is especially important for staff who rotate.

Site Training Log

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Developmental Outcomes of Long-term Feed Supplementation in Neonates

The Newcastle upon Tyne Hospitals NHS Foundation Trust

DOLFIN TRAINING LOG

Full Title:	Developmental Outcome of Long Term Feed Supplementation in Neonates - The DOLFIN randomised controlled trial		IRAS ID: 303421
Chief Investigator:	Prof Jeremy Parr (overall Chief Investigator responsibility) Prof Morag Andrew (as per NIHR award)		REC Ref: 22/SW/0009
Site Name:		**Principle Investigator:**	

Full name of Trainee	Position/Role	Trainee Signature	Training Description (include format of training, trainer name, organisation, version number of document or module if applicable)	Date of training *(dd/mm/yy)*	Trainer Signature and Date *

Please ensure site training logs are routinely maintained and kept up to date.
Please keep a copy at site and upload a copy to dolfin@npeu.ox.ac.uk

Central Monitoring and Site Visits

- Remote central monitoring is conducted at monthly Project Management Group meetings at NPEU with Sponsor input.
- Remote central monitoring includes:
  - Supplement administration, Consent Forms, Delegation log, Safety Reporting, CRFs etc.
- Where site monitoring is triggered, the DOLFIN study team will liaise with the local team to arrange a visit.
- Site Monitoring Visit Report will be provided highlighting any issues
- A copy of the monitoring report is filed in the e-ISF.

Archiving

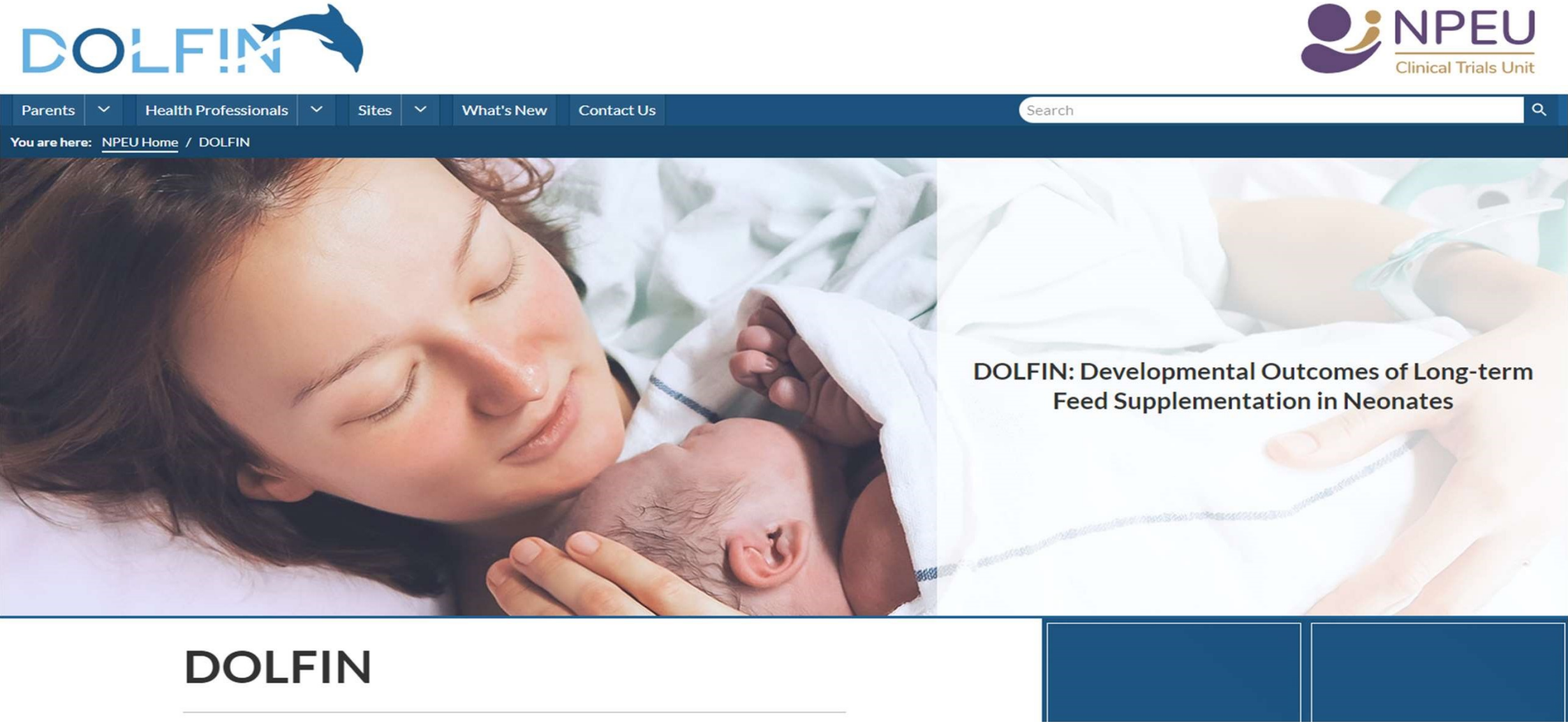
- Ensure that the electronic Investigator Site File (e-ISF) and all study documents are archived appropriately when notified by the Sponsor or DOLFIN Study Team and retained as required by the protocol.

- Essential study documents should be archived once all study-related activity is completed and Clinical Trial Summary Report is available.

- As the study involves minors under 18 years old, essential documents should be archived for a minimum of 25 years.

- Documents must be stored in a way that preserves their accuracy, integrity and legibility, and restricts access to authorised individuals only.

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



Green Light process

- **DOLFIN Green Light Release** form confirms site initiation/training on trial including Open Clinica training.
- Fully executed site agreement
- Confirmation of Capacity and Capability at NHS Trust.
- Receipt of DOLFIN **Document box** and eISF uploaded.
- Log in details for randomisation website and site activated on system.

DOLFIN Study Team

- Chief Investigator: Professor Jeremy Parr
- Co-Chief Investigator: Dr. Morag Andrew


- DOLFIN Trial Manager: Victoria Stalker
- DOLFIN Research Nurse: Clare Edwards
- Data Co-ordinator/Administrative Assistant: Adriana Ortiz



NPEU CTU, University of Oxford

- Pollyanna Hardy (Director, NPEU CTU)
- Charles Roehr (Clinical Director, NPEU CTU)
- Christina Cole (Senior Trials Manager)
- Ann Kennedy (Assistant Trials Manager)
- Andy King (Head of Trials Programming)
- David Murray (Senior Trials Programmer)
- Kayleigh Stanbury (Head Of Operations)
- Joy Wiles (Quality Assurance Manager)
- Richard Welsh (Senior Software Developer)
- Madeleine Hurd (Data Manager)

DOLFIN
Developmental Outcomes of Long-term Feed Supplementation in Neonates

Thank you for listening

DOLFIN Study Team Contact details:

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Email: dolfin@npeu.ox.ac.uk
Website: www.npeu.ox.ac.uk/dolfin

Any Questions??