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Imperial Clinical Trials Unit – ICTU

COLLABORATE

Site Initiation Visit

Imperial College London

FUNDED BY
NIHR | National Institute for Health and Care Research

COLLABORATE

Improving newborn care together

An efficient, UK-wide, real-world-data-enabled, adaptive, 2-randomisation, controlled trial to determine clinical efficacy, effect size, and safety of widely used enteral feeds in reducing necrotising enterocolitis, mortality, and cognitive impairment in preterm babies born below 29 weeks' gestation

Supported by:
NEC UK, Bliss, Adult Preemie Advocacy Network, British Association for Neonatal Neurodevelopmental Follow-Up, Neonatal Nurses Association, British Association of Paediatric Surgeons, and The George Institute for Global Health

AGENDA

- Study organisation
- Background and Objectives
- Design, eligibility, endpoints
- Study Procedures
  - Consent, randomisation, interventions
  - Data collection, OpenClinica EDC
  - Safety reporting
  - Compliance and withdrawals
  - Sub-study
- Monitoring
- Staff training
- Additional information
- ISF, current study documents, API scheme, responsibilities, greenlight

Sponsor	Imperial College London
Chief Investigator	Professor Neena Modi
Co-chief investigator	Professor Victoria Cornelius (methodology lead)
Co-investigators	Professor James Boardman (University of Edinburgh) Mr Peter Bradley, (Bliss) Ms Lauren Ingledow (Adult Preemie Advocacy Network) Dr Annemarie Lodder, (Imperial College London) Professor Ramon Luengo-Fernandez (University of Oxford) Professor Andrew Morris (Health Data Research UK) Professor John Norris (University of Belfast) Professor Shalini Ojha (University of Nottingham) Dr David Quine (Simpson Memorial Maternity Hospital, Edinburgh) Dr Sabita Uthaya (Imperial College London) Professor James Wason (University of Newcastle) Dr Hilary Wong (University of Cambridge)
Trial Management	Imperial Clinical Trials Unit (ICTU); COLLABORATE Trial Manager - Rosie Way Operations Manager – Rahi Jahan
Funder	National Institute for Health and Care Research (NIHR)
Management and Oversight groups	Trial Management Group, Trial Steering Group, Independent Data Monitoring Committee, Parent Advisory Group, Scientific Advisory Group

Objectives and background

Study Objectives

Randomised study primary objectives

- To assess, in babies born **<29 weeks gestation**, the efficacy of **pasteurised Human Donor Milk** (pHDM) compared with **Preterm Formula**, when used as a **supplement** should there be insufficient milk from their own mother (Own Mother's Milk), on “survival to 34 weeks postmenstrual age without surgical necrotising enterocolitis (NEC)” (primary outcome), language and cognitive development at age 2-years, and other outcomes

- To assess, in babies born **<29 weeks gestation**, the efficacy of **routine cow-milk based protein-carbohydrate fortification** of human milk feeds (Own Mother’s Milk and pHDM) compared with **no routine fortification** on “survival to 34 weeks postmenstrual age without surgical necrotising enterocolitis (NEC)” (primary outcome), language and cognitive development at age 2-years, and other outcomes

Mechanistic objective (sub-study led by Professor James Boardman, University of Edinburgh)

- To determine if **pHDM** and **Preterm Formula** exert **different effects on neurodevelopment** through the mechanism of **altered cerebral white matter** microstructure (sub-study)

NHS Value objective (led by Professor Ramon Luengo-Fernandez, University of Oxford)

- To establish if the **additional cost of pHDM to the NHS is justified** through a reduction in NEC

Background

Own mother's milk is best for babies, but often the volume available is insufficient so a top-up feed is needed

Uncertainty on whether pHDM or preterm formula should be used if there is insufficient Own Mother's Milk

Variation in current practice for babies born <29 weeks gestation regarding whether to use formula or pHDM to top up

No definitive evidence on which is best

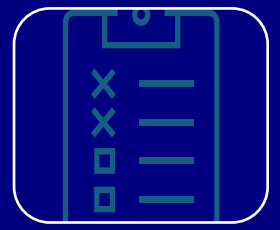
- Possible risk of NEC with formula
- Possible risk of impaired neurodevelopment with pHDM
- High cost of pHDM with no conclusive evidence of benefit

Other considerations

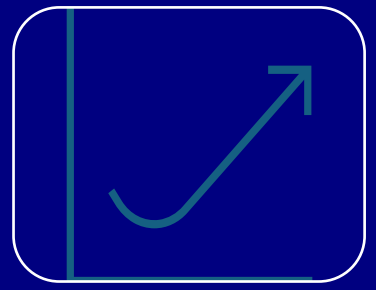
- Possible adverse effect on maternal lactation if pHDM is perceived as equivalent to Own Mother's Milk
- Adverse effects of a growing commercial human milk industry

Background

Uncertainty on whether human milk should have routine protein-carbohydrate fortification



No benefit for routine fortification shown to date



No benefit to long term growth

Risk of neurodevelopmental and other harms from routine fortification through excessive protein intake

Background

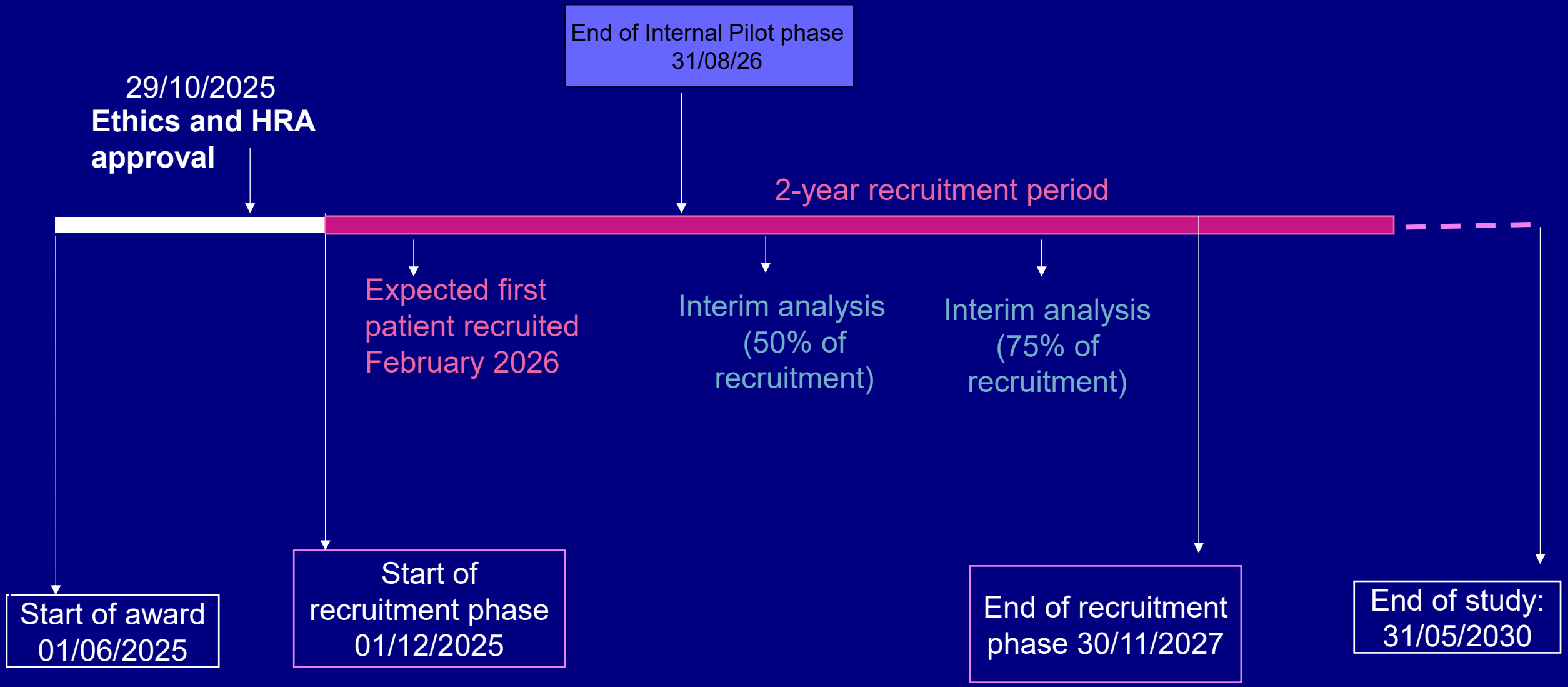
Need for this research and lack of strong evidence highlighted by:

- UK **neonatal priority setting partnership exercises** (all in last decade)
- **Parents** who want the uncertainties resolved
- **British Association of Perinatal Medicine** (2023)
- **UK National Institute of Health and Care Excellence guidance** (2010, reviewed 2018)
- The current **European Society of Paediatrics Gastroenterology** and Nutrition recommendations

Background – mechanistic study

James to add relevant background text

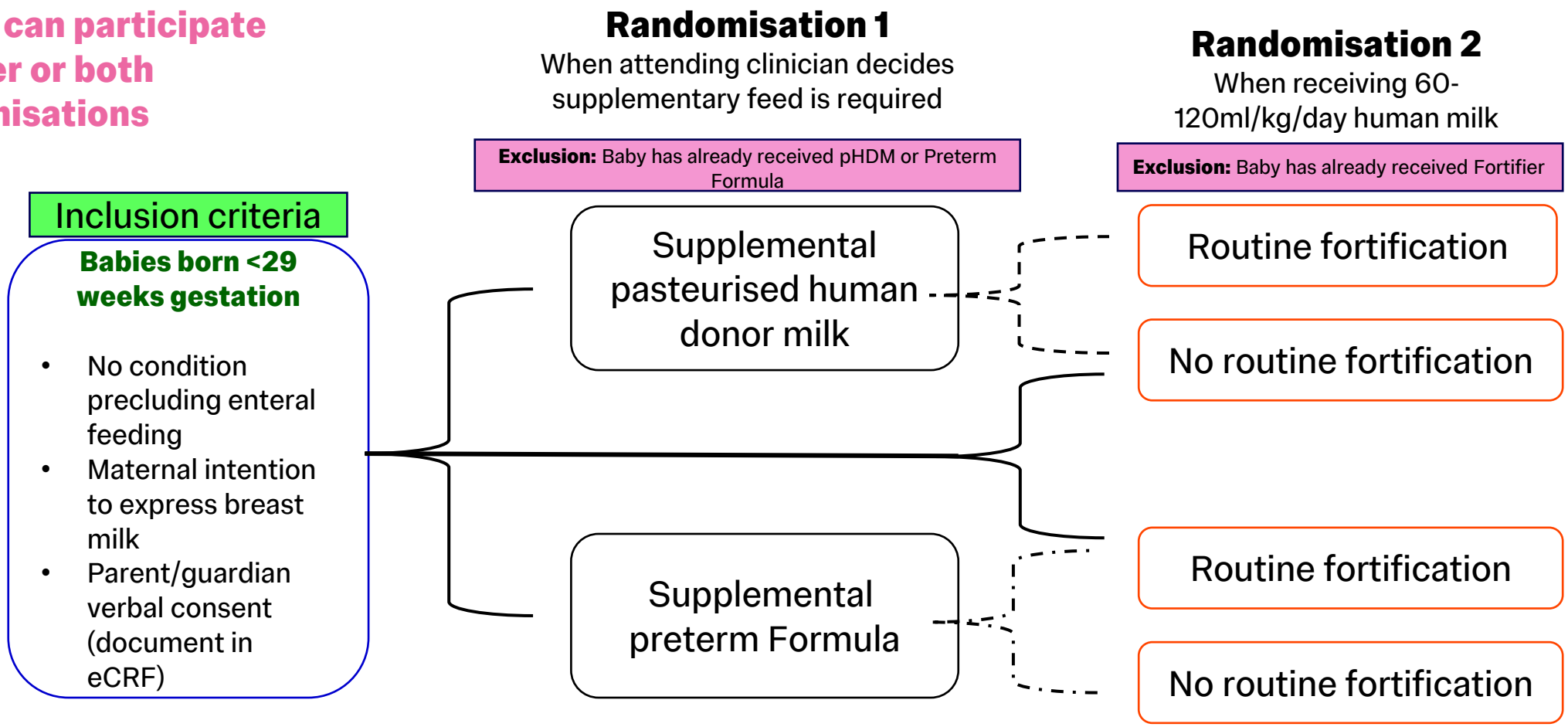
Timelines


End of Internal Pilot phase 31/08/26
29/10/2025
Ethics and HRA approval
2-year recruitment period
Expected first patient recruited February 2026
Interim analysis (50% of recruitment)
Interim analysis (75% of recruitment)
Start of award 01/06/2025
Start of recruitment phase 01/12/2025
End of recruitment phase 30/11/2027
End of study: 31/05/2030

Design, eligibility, endpoints

2-randomisation design, eligibility criteria

Babies can participate in either or both randomisations



Recruitment and sites

- **80** Neonatal Intensive Care Units and Local Neonatal units as **recruiting sites**
- Setting up all other neonatal units as **continuing care sites**
  - Responsible for continuing randomised treatments, safety reporting, protocol compliance reporting, minimal data entry at discharge (if applicable), maintain ISF
- Maximum sample **3252** (2168 in each randomisation, 1084 per arm)
  - If >50% babies co-enrolled to R1 and R2, maximum sample size will be smaller
- **Adaptive design: interim analysis** at 50% and 75% of recruitment (allows study to be stopped early if predefined stopping rules met)

Key design points

Real world data enabled study

- **Majority of COLLABORATE data come from the National Neonatal Research Database (NNRD)**
  - Parents can opt out for inclusion of their baby's data (less than 1% do so).

Primary endpoint (from NNRD):

- 34 weeks PMA: Survival without surgical NEC

Secondary endpoints (majority obtained from NNRD):

- All core neonatal outcomes
- Cognitive and language development at age 2-years, assessed using an electronic version of the PARCA-R

Key design points

Minimal research data entry required

- At recruitment: eligibility, consent, randomisation
- During NNU admission: protocol deviations/violations, safety reporting, withdrawals
- At NNU discharge (or before transfer to another unit if data is available):
  - Minimal clinical outcome data
    - 3 items, if surgery for NEC additional 6 fields
  - 3 laboratory results required (maximum serum urea, creatine, alkaline phosphatase)
  - Sign parents up to electronic 2-year PARCA-R questionnaire

Verbal consent being used

- Confirmation of verbal consent entered directly into eCRF

No research related follow up visits for main study

Design: sub-study

MRI scan
Weekly stool samples from birth to neonatal unit discharge and at time of MRI scan

Inclusion criteria

- Participants in **randomisation 1** recruited at the Royal Infirmary of Edinburgh
- Written Parent Consent

Exclusion criteria (MRI)

- Infants with congenital anomalies: structural or functional (e.g., metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth or later in life (WHO definition)
- Infants with a contraindication to MRI at 3Tesla

No exclusion criteria for stool samples

Written consent required (parents can choose to consent to both parts or just one) and transcribed into eCRF

120 participants (60 in pHDM supplement arm, 60 in formula supplement arm)

Study Flowchart

After NNU admission, study discussed at an appropriate time with parent:

- **Eligibility checked**
- PIS provided

Participant recruited:

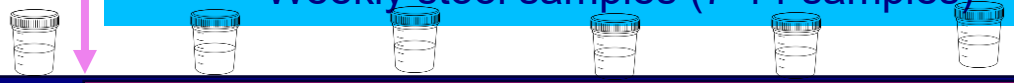
Participant **randomised** to **R1** (formula top up or pHDM top up) **and/or R2** (fortifier or no fortifier) when criteria met

Outcome data from EPR is automated into the eCRF from the NNRD

Sub-study: MRI (37- 44 weeks)

2-year PARCA-R assessment sent electronically to parent

Weekly stool samples (7-14 samples)



Safety reporting from randomisation until discharge or 34 weeks PMA if earlier

Randomised interventions received:
Intervention continued from randomisation until 34 weeks PMA

Parent **verbally consents to R1 and/or R2 prior** to any supplemental feed or fortifier

Sub-study: Written consent for baby's in R1

At discharge: Ancillary outcome data entered into eCRF
Participant signed up to ePARCA-R

Study procedures : consent, randomisation, interventions

Eligibility and Consent

Eligibility assessed by member of the clinical care team after admission to NNU

Parents must consent to their baby's data to be included in NNRD

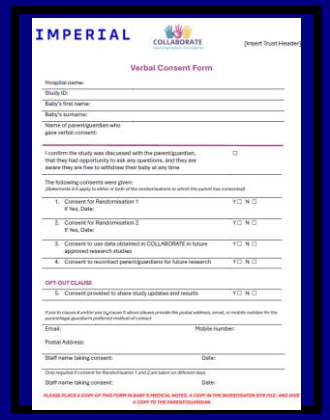
Screening log kept locally and documented with reasons for declining

Verbal consent

- **Study discussed at an appropriate time and prior to any supplemental feed or fortifier**
- Provide PIS part 1 and 2, ensure parents have adequate time to consider
  - Parent information will be available in English, Welsh and the ten other most prevalent UK languages
  - Verbal consent statement completed by site staff electronically in Open Clinica
  - Back up paper statement, if used should be transcribed into OpenClinica as soon as possible
  - R1 and/or R2, can consent to R2 later
- **Copy of consent statement provided to parent**
- **Participation documented in medical/research records**

Patient facing and engagement material

Verbal Consent statement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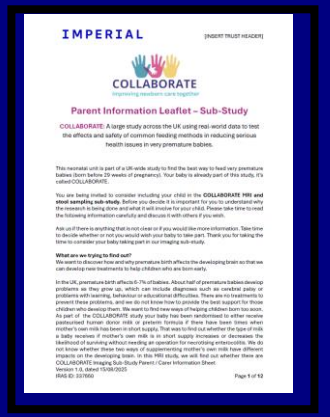
Verbal Consent Form

Videos explaining the study, randomisation and NNRD

https://www.imperial.ac.uk/neonatal-data-analysis-unit/collaborate/

Sub Study PIS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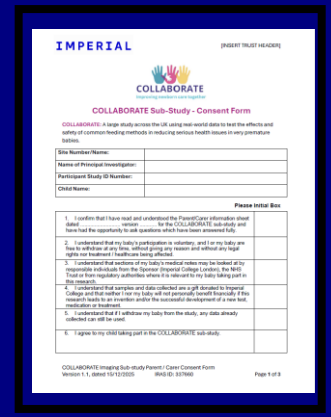
Parent Information Leaflet – Sub-Study

Sub Study written consent statement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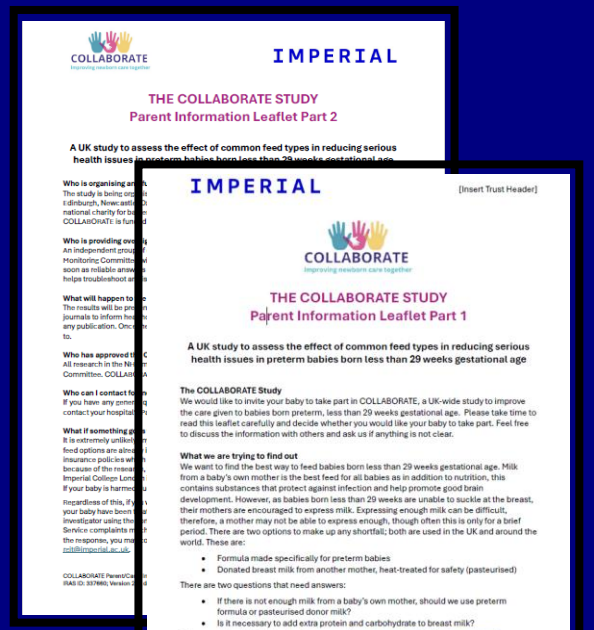
COLLABORATE Sub-Study - Consent Form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THE COLLABORATE STUDY

Parent Information Leaflet Part 2

A UK study to assess the effect of common feed types in reducing serious health issues in preterm babies born less than 29 weeks gestational age

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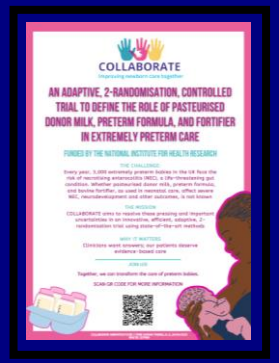
THE COLLABORATE STUDY

Parent Information Leaflet Part 1

A UK study to assess the effect of common feed types in reducing serious health issues in preterm babies born less than 29 weeks gestational age

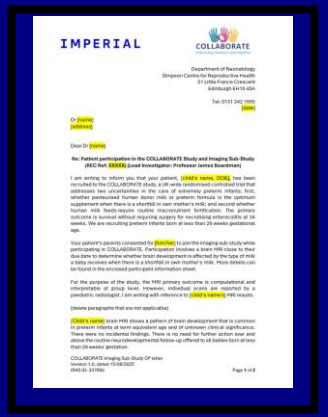
Main study PIS part 1&2

Posters/flyers



Cot cards and paper note labels

Sub Study GP letter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Randomisation

Timings

- **R1 (Formula top up vs pHDM top up):** When a supplemental feed is required because own mother's milk is insufficient
- **R2: (routine fortification vs no routine fortification):** When the baby is receiving between 60-120 ml/kg/day of human milk feeds (Own Mother's Milk and/or pHDM). (Immediate or incremental increase to full strength fortification according to local practice)

Process

- **Randomise via OpenClinica**, enter minimisation criteria, click randomise, allocation will be documented in the eCRF, record in medical notes
  - In order to randomise, staff will need individual OpenClinica account with COLLABORATE access granted
- Cot cards and stickers for paper medical notes to remind staff and parents of study and allocation, add flag to electronic records

Interventions

All interventions (formula, pHDM, fortifier) are standard hospital stock used as part of standard of care

Additional guidance: fortification

- No routine fortification arm

  Babies randomised to no routine fortification recommended to receive routine vitamins and oral phosphate supplements in accordance with unit policy (refer to COLLABORATE mineral and vitamin supplementation guidance).

Study procedures :
data entry, Open Clinica

Clinical data entry

1. **Please ensure EPR data is complete and timely**
2. **Additional minimal clinical data** for study to be entered into eCRF
3. **ePARCA-R registration**
    1. **ePARCA-R registration prior to discharge/transfer to another unit**

Refer to: eCRF data entry guide

Open Clinica EDC

1. EDC platform is **OpenClinica**, training to be completed online:

   https://www.imperial.ac.uk/clinical-trials-unit/clinical-data-systems/cds-openclinica/training-openclinica-40/

   The code is CDSTraining_123

2. At least one staff member, plus the PI, to complete training prior to enrolling any participants
3. After completing OpenClinica role(s) based training, users must submit an OpenClinica User Activation Form to request an account
4. Send the completed User Activation Form to collaborate@imperial.ac.uk
5. Once your OpenClinica account is set up, any technical queries should be directed to Clinical Data Systems Production support: cds_support@imperial.ac.uk

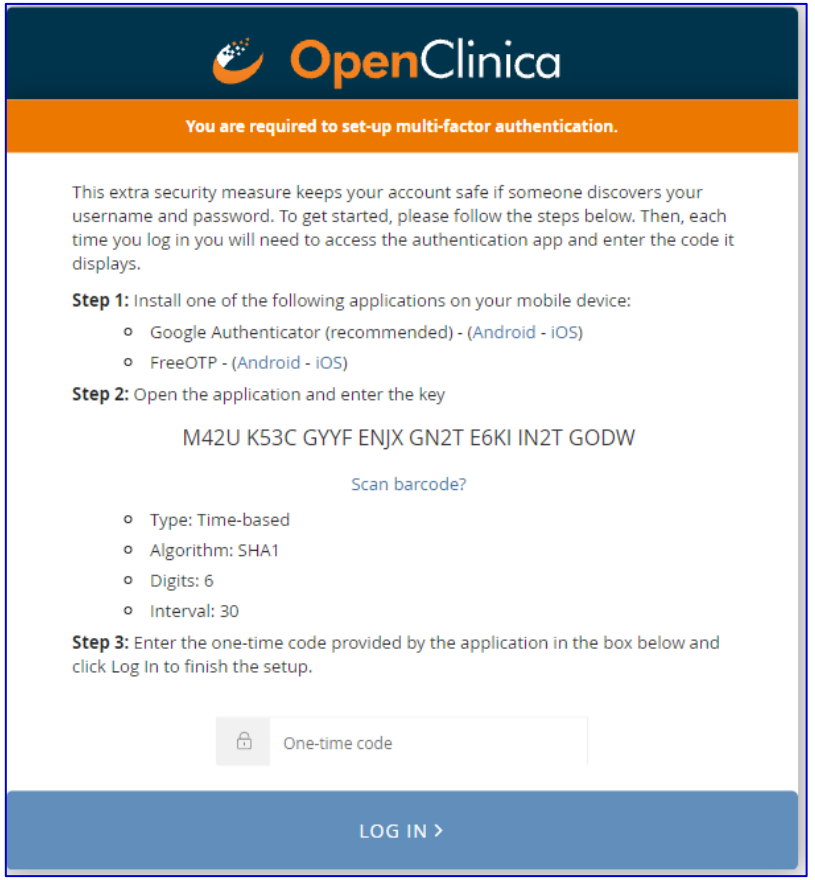
Refer to: eCRF data entry guide

Open Clinica EDC

Account Setup

When you first access OpenClinica, you will be provided with a 6-digit code on your mobile device after scanning the QR code on the computer screen

If you are unable to scan the QR code, click on the '**Unable to scan**' link on OpenClinica webpage after entering your username and password. This will provide you with a 32-key code.

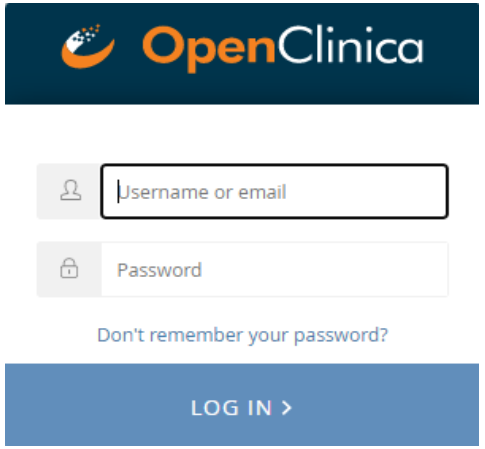


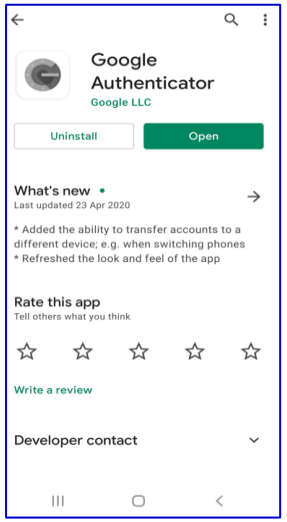
Refer to: eCRF data entry guide

Open Clinica EDC

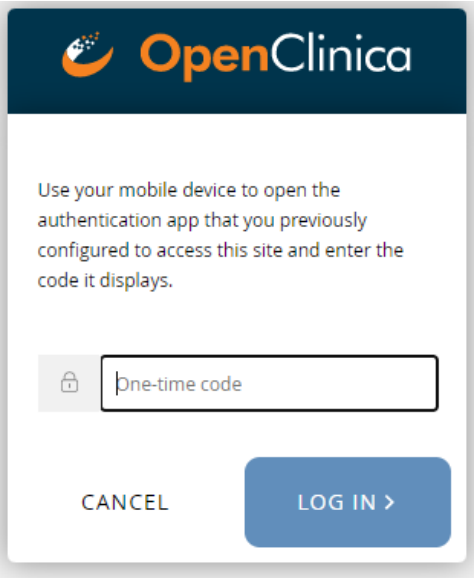
Log In

You will be required to download an **Authenticator app** to retrieve a code before you can access the study.





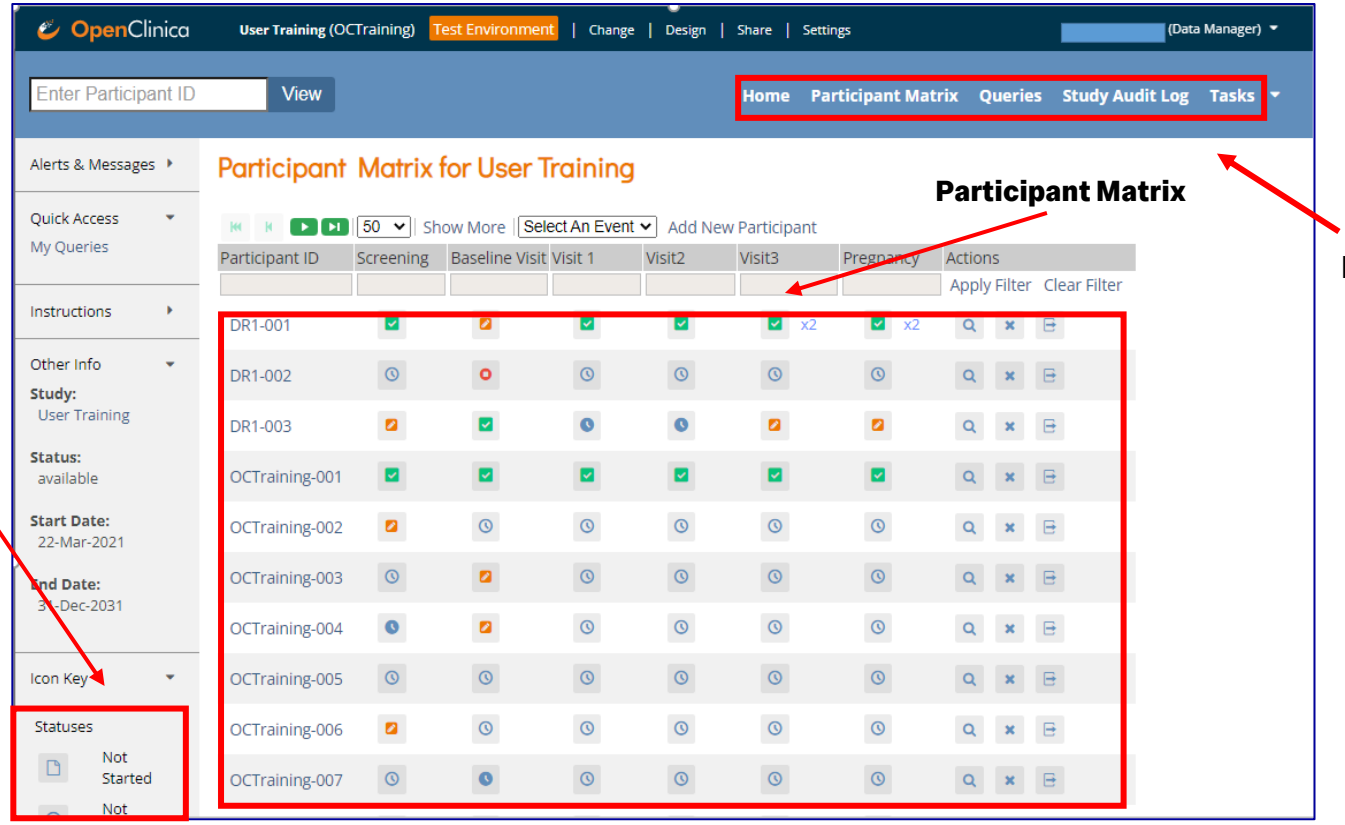
Once these details are entered, click '**LOG IN**'. The system will display a screen to enter your one-time code, this is generated by the Google Authenticator app on your smart phone.



Refer to: eCRF data entry guide

Open Clinica EDC

Home Screen



The system will display the HOME screen which is dependent to your user role

Refer to: eCRF data entry guide

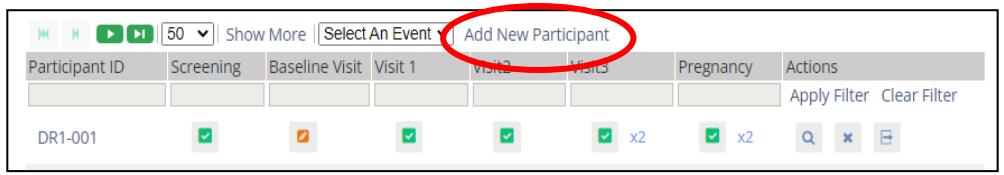
Open Clinica EDC

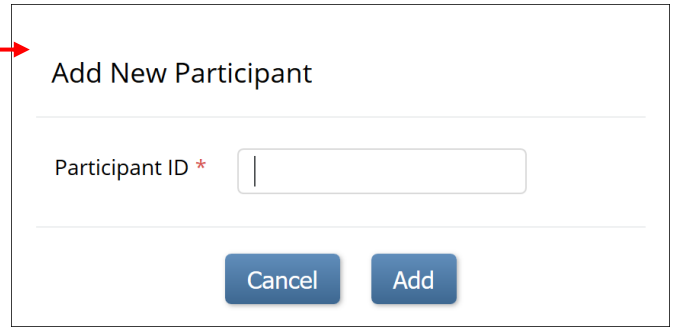
Adding a participant

There are two options to add a participant on OC:

Option 1 - Click on ‘Tasks’ in the Navigation Bar and select **‘Add Participant’**

Option 2 - In the Participant Matrix screen, click **‘Add New Participant’** and a pop-up will appear





Refer to: eCRF data entry guide

Open Clinica EDC

Icon Key

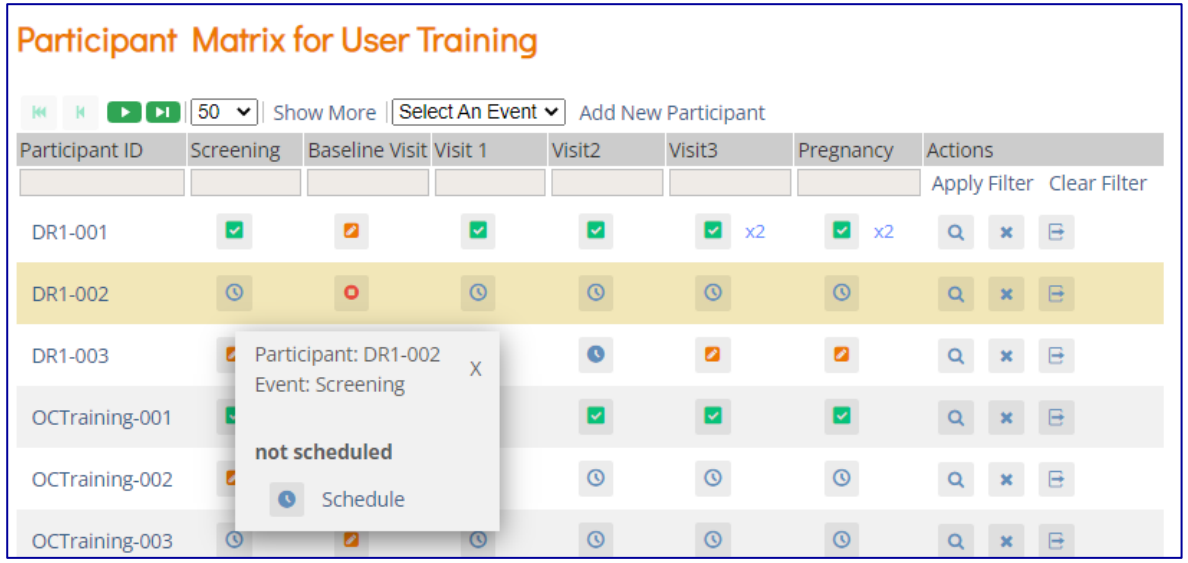
Status/Action	Icon	Description
Not Started		The Event has not been started.
Not Scheduled		The Event has not been scheduled.
Scheduled		The Event has been scheduled, but no data has been entered.
Data Entry Started		A user has started to enter data. If the Event is in 'data entry started', you can't go back to previous Status.
Stopped		The Participant has temporarily stopped participating in the study. this status can be selected from the dropdown menu on the 'Update Event' screen when the current status is data entry started.
Skipped		The user has decided not to complete the Event. Any data that has been entered can still be viewed and/or exported. You can select this setting from the dropdown menu on the Update Event screen when the current status is scheduled.
Completed		A user has completed data entry for at least one Form in the Event. If further changes are needed in that Form, you are required to provide a reason for change.
Signed		The Study Event has been signed off. This icon appears in addition to the status. When the Investigator signs the casebook for a Participant, the OpenClinica system automatically sets the status for all Study Events for that Participant to 'signed.' After an Event status is 'Signed,' any changes to the CRF automatically change the Event status back to 'Completed.'
Locked		The Study Event has been locked. No data can be added, and the Event cannot be removed. This icon appears in addition to the status. This is performed by the Data Manager role. Note: You can set the status for a Study to 'frozen' or 'locked,' and while that does not change the status of any Events in the Study, it does prevent users from changing data.
Archived		The Study Event has been archived. . This icon appears in addition to the status. This is performed in Study Designer.
Removed		The Study Event has been removed for a participant is remove/

The Icon Key displays the icon definitions which show the status of an Event

Refer to: eCRF data entry guide

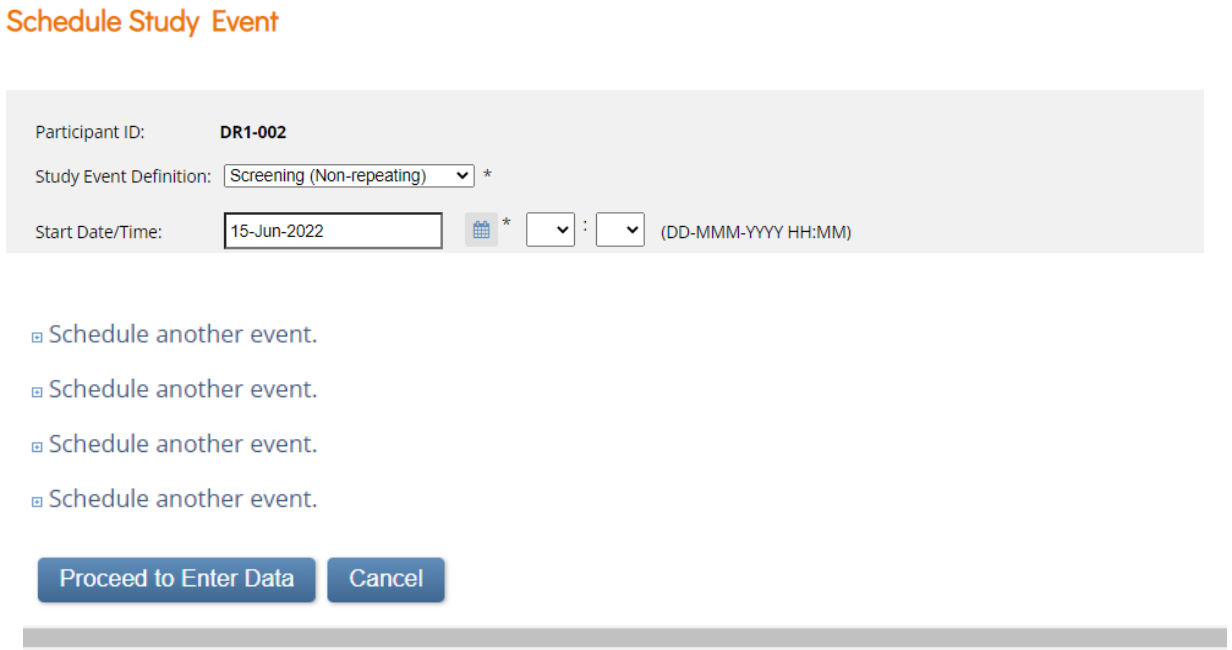
Open Clinica EDC

Study Event



If you want to enter data, you need to schedule the respective Event. This is done in **the 'Participant Matrix'**. Click on the Event you want to schedule. A window pops up and then click on **'Schedule'.**

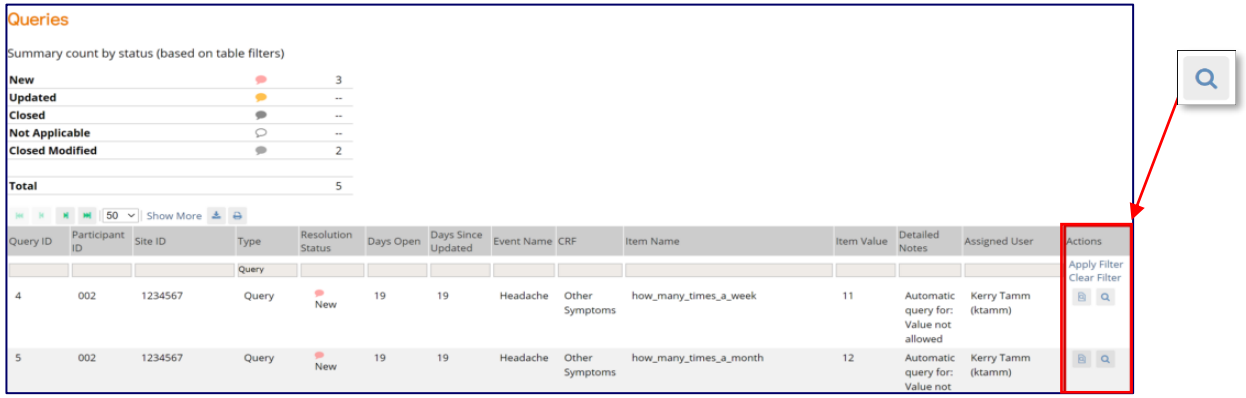
The 'Schedule Study Event screen appears.

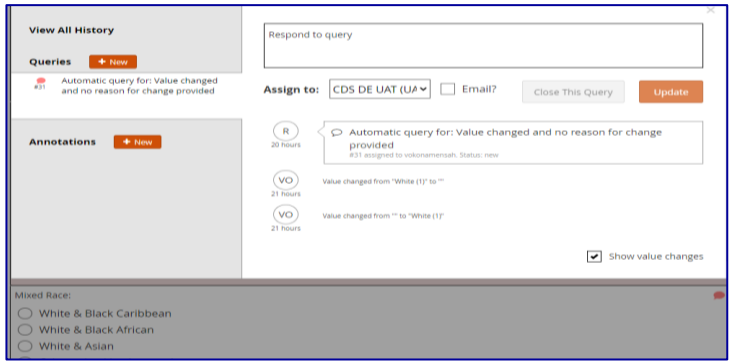


Refer to: eCRF data entry guide

Open Clinica EDC

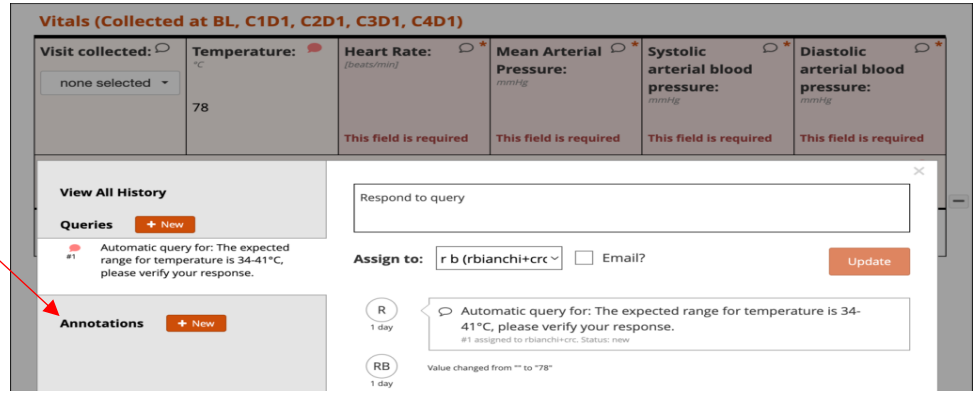
Queries





To review data associated with a query, you can either:

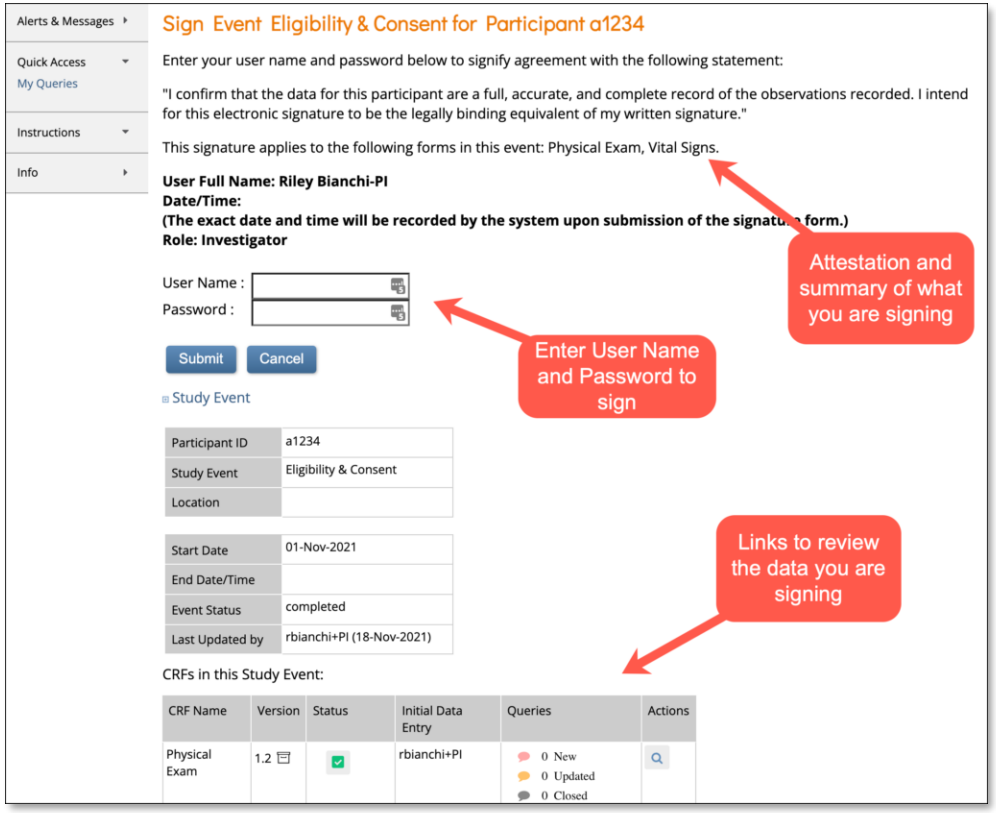
- View Query Only
- View Query within record
- Open Query



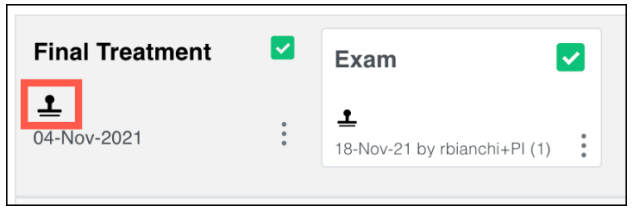
Refer to: eCRF data entry guide

Open Clinica EDC

Electronic signature (by PI)



- Electronic signatures in OC are considered a legal signature and verification of the attestation provided.
- Signatures are applied via an OC account and its associated username and password, so keep this information secure.
- You can see a list of forms in the Event and the status of queries for each of these forms.
- To complete the electronic signature process, you will need to enter your username, password and then click **Submit**.



Refer to: eCRF data entry guide

Participant transfer

ICTU are confirming the process of transferring participants to another site on OpenClinica.

In the meantime, email collaborate@imperial.ac.uk in advance of a participant being transferred to another neonatal unit, for instructions.

Please ensure:

1. All data has been completed on OpenClinica
2. Parent has registered for ePARCA-R
3. Receiving site is aware participant is on COLLABORATE study

Refer to: eCRF data entry guide

Study procedures :
safety reporting

Safety reporting

- **Safety reporting window is from randomisation until 34 weeks PMA/discharge from NNU/death (whichever occurs first)**
- **Adverse event (AE):** any untoward medical occurrence in a participant
- **Serious Adverse event (SAE):** results in death, is life-threatening, requires prolongation of hospitalisation, or causes significant disability or incapacity
- **Serious Adverse Reactions (SAR):** an SAE that is considered related to the study intervention
- Majority of events meeting the SAR definition are common and will be collected as study outcomes
- **Only unexpected Serious Adverse Reactions that are serious, related (possible/probable/definite) and unexpected, will be collected**

Action:
Complete unexpected SAR details on eCRF within 24 hours

Refer to: Safety reporting manual

Safety reporting

Causality	
Unrelated	**No evidence** of any causal relationship
Unlikely	There is **little evidence** to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study medication). There is **another reasonable explanation** for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is **some evidence** to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study medication). However, the **influence of other factors may have contributed** to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is **evidence** to suggest a causal relationship and the **influence of other factors is unlikely**.
Definite	There is **clear evidence** to suggest a causal relationship and **other possible contributing factors can be ruled out**.

Severity	
Mild	Awareness of event but easily tolerated
Moderate	Discomfort enough to cause some interference with usual activity
Severe	Inability to carry out usual activity

Refer to: Safety reporting manual

The assignment of causality & severity should be made by the PI*

*If the PI is not medical qualified (e.g. an ANNP) then another medically qualified study member should make this assessment

Study procedures: compliance and withdrawals, end of study

Protocol compliance

Protocol Deviation: A minor non-compliance with the approved protocol with no impact on participant safety or data integrity.

Protocol Violation: A significant or repeated non-compliance with the protocol that may affect participant safety or study integrity (e.g. failure to present parents with study information prior to initiation of study related procedures or assess eligibility correctly).

Action:

Complete protocol deviation or violation eCRF

- Reviewed by ICTU/CI to assess for **serious breach** (a GCP or protocol violation likely to significantly affect participant safety or the study's scientific value)
- Serious breaches will be reported to the sponsor and REC

Discontinuing of study intervention and Withdrawals

- A parent/guardian may withdraw their baby from the study and/or study intervention at any point, without giving a reason
- Study intervention can also be discontinued at the decision of a clinician
  - Investigators who would like to withdraw a participant should discuss with Neena Modi n.modi@imperial.ac.uk /Sabita Uthaya s.uthaya@imperial.ac.uk

Action:

- If intervention is discontinued before 34 weeks PMA, complete **Discontinuation of Study Intervention eCRF**
- And on **End of Study eCRF**:
  1. Confirm the participant **did not** complete the study according to the protocol
  2. Confirm which randomisation the participant withdrew from
  3. Confirm reason for withdrawal

Refer to: eCRF guide

End of study

- End of Study for each participant is defined as at the last outcome timepoint (**2-year** ePARCA-R)
  - Site involvement should not be required at 2-year timepoint, parent registered prior to discharge and questionnaire sent electronically to parent, data collected into separate database

- Last outcome data collected on main database is at discharge

Action:

- Complete End of Study CRF at discharge

Refer to: eCRF guide

Monitoring

Monitoring

Central monitoring will be conducted for all sites routinely:

- Relevant findings discussed with PI/research team
- Remote/onsite monitoring visits will be scheduled if required

Monitoring visits may occur if ‘triggered’ by:

- Unexpected study related SAEs
- Serious protocol violations affecting participant safety or data integrity
- Unresponsive to data queries or high rate of data discrepancies

- In person monitoring visits may be conducted to check sub-study written consents and sample handling

Study procedures :
Sub-study

Additional information

MRI SCAN

- Follow local SOP
- Use earmuffs, continually monitor vital signs (heart rate and oxygen saturation)
- Observations to be recorded every 5 minutes until 1 hour after the infant has woken up
- The scan will be stopped if there are any abnormalities in monitoring.
- Child's general practitioner will be notified of any incidental findings that may be clinically actionable and any relevant NHS services that have been involved, through the clinical care team.
- £20 thankyou voucher provided to each participant for their involvement in the sub-study and travel reimbursement

Sample storage and labelling

- Stored at -80 degrees
- Record sample number, date and ID on eCRF

Staff Training

Staff training

Study manuals

- eCRF data entry guide
- Safety reporting guide
- Eligibility checklist
- Discretionary fortification guidance
- Mineral and vitamin supplementation guidance
- Local SOP manual

Training log

- **Confirm protocol, PIS, SIV visit slides, study manuals have been reviewed**

Actions for site staff (before undertaking any study-related activity):

- **Signed-off on the Delegation Log by the Principal Investigator (PI)**
- **Documented study training on the Training Log**
- **Submitted GCP certificate, signed CV and User Activation Request form**

Additional information

Investigator Site File

Electronic Investigator Site File (eISF): Florence https://www.florencehc.com/

Actions:

1. Allocate a named main administrator (could be PI)
2. Receive welcome link, complete short training
3. Send training certificate to study mailbox
4. Arrange a short ISF handover call prior to activation

Archiving

ICTU will archive for a minimum of 10 years following the end of the study.

Key Study Documents

*To be provided to study team after SIV visit and prior to activation

Document	Version and Date
Protocol	V3.0 09/01/2026
Eligibility checklist*	V1.0 27/01/2026
Parent Information Sheet part 1	V2.1 12/12/2025
Parent Information Sheet part 2	V2.0 22/10/2025
Verbal consent statement	V2.1 12/12/2025
Sub Study PIS	V1.0 15/08/2025
Sub-study Written consent form	V1.1 15/12/2025
Sub Study GP Letter	V1.0 15/08/2025
Flyer	V2.3 04/04/2025
Cot labels	V1.0 15/08/2025
Paper Notes Labels	V1.0 15/08/2025
Mineral and vitamin supplementation*	V1.2 21/01/2026
Discretionary fortification guidance*	V1.2 21/01/2026
eCRF data entry manual*	TBC
Safety reporting manual*	TBC

Associate PI Scheme

- NIHR Associate PI Scheme is a six-month in-work training opportunity for staff to receive accredited research experience
- Local PI will mentor the Associate PI, working alongside them to deliver the study
- Associate PI to complete a checklist of study activities and a learning pathway on NIHR learn
- A certificate will be issued to confirm Associate PI status, endorsed by the NIHR and Royal Colleges
- https://www.nihr.ac.uk/career-development/clinical-research-courses-and-support/associate-principal-investigator-scheme

PI Responsibilities

- Conduct the study in accordance with the approved protocol, GCP, and regulatory requirements.
- Ensure adequate resources, appropriately trained staff, and delegation of duties to qualified personnel.
- Provide appropriate medical care, including study-related medical decisions.
- Ensure informed consent procedures are in place for all participants, including those unable to consent.
- Maintain participant confidentiality and data integrity.
- Ensure accurate, complete, and timely data reporting consistent with source documents.
- Allow access to study documents for monitoring, audits, and inspections.
- Report protocol deviations, serious breaches (where applicable), and unexpected SARs within required timelines.
- Maintain, archive, and securely store study documentation.

Green Light

Actions for site green light:

- Localised documents returned
- Signed PI signature page
- Signed contract (mNCA)
- Confirmation of capacity and capability received from R&D
- CVs, GCPs, training log, delegation log complete for study team
- Database access and training completed
- ISF training and handover

Thank you

collaborate@imperial.ac.uk