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# Withholding enteral feeds around packed red cell transfusion

| Submission date | Recruitment status | [X] Prospectively registered |
|---|---|---|
| 23/07/2018 | No longer recruiting | [X] Protocol |
| **Registration date** | **Overall study status** | [_] Statistical analysis plan |
| 24/07/2018 | Completed | [X] Results |
| **Last Edited** | **Condition category** | [_] Individual participant data |
| 04/08/2023 | Neonatal Diseases | |

## Plain English summary of protocol

Background and study aims
The aim of this study is to compare two practices that are widely used in neonatal units across the UK and around the world to see if one reduces the risk of necrotising enterocolitis (NEC) in babies born early (premature). NEC is a serious gut disease that affects about 1 in 20 very premature babies (about 500 each year). About 1 in 3 of these babies will die of NEC and survivors often have long-term health and developmental problems. In 2014 prevention of NEC was ranked the third most important research priority by parents and perinatal health professionals. Premature babies receive frequent milk feeds (every 1-3 hours) and they often need blood transfusions because they become anaemic (they do not have enough red blood cells). Some doctors worry that feeding babies during a blood transfusion may increase the risk of NEC. Others, however, think that it is more dangerous to stop feeds. Because of this, the way babies are cared for during blood transfusions varies across the country; some babies have milk feeds stopped before, during and after a transfusion (around 12 hours in total) while others have feeds continued. The aim of this study is to determine which approach is best.

Who can participate?
Premature babies (gestational age at birth less than 30 weeks)

What does the study involve?
Babies are recruited shortly after birth (and therefore before they are scheduled to have a blood transfusion in most cases). Blood transfusion is almost universal in babies of this gestational age (90-95% need at least one blood transfusion). The babies are randomly allocated to either have feeds stopped or to have feeds continued for 4 hours before, during and for 4 hours after blood transfusions. The trial uses information that is recorded by doctors and nurses in a baby's existing electronic health record, rather than collecting it all over again; this makes the trial much simpler and easier. Because this is a new way of collecting information, this 'point of care' approach is tested in a "pilot trial" which is a smaller, shorter "test" trial.

What are the possible benefits and risks of participating?
Both of the feeding approaches are currently acceptable to doctors but it is not known if one is

safer. For babies not taking part in this study, it depends on the unit looking after the baby as to whether feeds are given or withheld around blood transfusions. Taking part in the study may be beneficial for the baby. No risks are anticipated.

Where is the study run from?
1. Chelsea and Westminster Hospital (UK)
2. West Middlesex University Hospital (UK)
3. Hillingdon Hospital (UK)
4. Northwick Park Hospital (UK)
5. St Mary's Hospital (UK)
6. Queen Charlotte's and Chelsea Hospital (UK)
7. Birmingham Heartlands Hospital (UK)
8. Good Hope Hospital (UK)
9. Birmingham Women's Hospital (UK)
10. Birmingham Children's Hospital (UK)
11. Birmingham City Hospital (UK)
12. University Hospital Coventry (UK)
13. Princess Royal Hospital (UK)
14. Walsall Manor Hospital (UK)
15. Leicester Royal Infirmary (UK)
16. Hereford County Hospital (UK)
17. New Cross Hospital (UK)

When is the study starting and how long is it expected to run for?
April 2018 to March 2020

Who is funding the study?
Medical Research Council (MRC) (UK)

Who is the main contact?
1. Mrs Kayleigh Stanbury
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2. Dr Chris Gale
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### Study website
https://www.npeu.ox.ac.uk/wheat

# Contact information

### Type(s)
Scientific

### Contact name
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### Type(s)
Scientific

### Contact name
Dr Chris Gale

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## Additional identifiers

### EudraCT/CTIS number

### IRAS number
154432

### ClinicalTrials.gov number

### Secondary identifying numbers
38523, IRAS 154432

## Study information

### Scientific Title
WithHolding Enteral feeds Around packed red cell Transfusion to prevent necrotising enterocolitis in preterm neonates: a multi-centre, electronic patient record (EPR), randomised controlled point-of-care pilot trial

### Acronym
WHEAT

### Study objectives

The purpose of WHEAT is to compare two practices that are widely used in neonatal units across the United Kingdom and around the world to see if one reduces the risk of necrotising enterocolitis (NEC) in babies born early (premature).

NEC is a serious gut disease that affects about 1 in 20 very premature babies (approximately 500 each year in the UK); about 1 in 3 of these babies will die of NEC and survivors often have long-term health and developmental problems. In 2014 prevention of NEC was ranked the third most important research priority by parents and perinatal health professionals.

Premature babies receive frequent milk feeds (every 1-3 hours) and they often need blood transfusions because they become anaemic (they do not have enough red blood cells). Some doctors worry that feeding babies during a blood transfusion may increase the risk of NEC. Others, however, think that it is more dangerous to stop feeds. Because of this, the way babies are cared for during blood transfusions varies across the country; some babies have milk feeds stopped before, during and after a transfusion (around 12 hours in total) while others have feeds continued.

The purpose of WHEAT is to determine which approach is best. We will do this by comparing babies who have feeds stopped with those who have feeds continued for 4 hours before, during and for 4 hours after blood transfusions. Whether feeds will be stopped or continued will be decided by randomisation. Randomisation is done by computer and ensures that each baby has an equal chance of receiving either approach. WHEAT will compare standard UK practices and involves nothing new.

The WHEAT trial will use the information that is recorded by doctors and nurses in a baby's existing electronic health record, rather than collecting it all over again; this will make the trial much simpler and easier. Because this is a new way of collecting information for a trial, we will be testing this 'point of care' approach in a "pilot trial" which is a smaller, shorter "test" trial.

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
London - Bloomsbury Research Ethics Committee, 05/07/2018, ref: 18/LO/0900

### Study design
Randomised; Interventional; Design type: Process of Care, Dietary, Management of Care

### Primary study design
Interventional

### Secondary study design
Randomised controlled trial

### Study setting(s)
Hospital

### Study type(s)
Treatment

### Participant information sheet

See additional files

## Health condition(s) or problem(s) studied
Necrotizing enterocolitis

## Interventions
DESIGN: A multicentre, randomised, controlled, unblinded, pragmatic, pilot trial embedded within an electronic patient record system (point of care trial), comparing two parallel care pathways. Central block randomisation, variable block sizes, 1:1 allocation; stratification by site, minimisation by sex, gestational age; comparator arms:

1. WITHHOLD FEEDS AROUND TRANSFUSION: All enteral feeds will be discontinued (the infant will be placed nil by mouth) for a period of 4 hours prior to the transfusion, during the transfusion and until 4 hours post transfusion
2. CONTINUE FEEDS AROUND TRANSFUSION: Continuation of enteral feeding before, during and after transfusion

The same allocated care pathway will be followed for all transfusions a participating infant receives until and including 34+6 gestational weeks+days or discharge (if sooner)

SAMPLE SIZE: The estimated target sample size for the pilot trial is up to 250 based on infant throughput and assuming 65–70% recruitment of eligible infants in the neonatal networks.

TRIAL DATA COLLECTION: All trial data will be obtained from an existing research database, the National Neonatal Research Database (NNRD). This holds patient level clinical data from 2007 to the present extracted quarterly from the electronic health record of all admissions to NHS neonatal units in England and Wales. Data items are a NHS Information Standard and appropriate approvals are held. NNRD data has been validated against clinical trial data and patient notes. During the WHEAT trial, key data items (allocation and outcome data) will be validated by local clinicians using an established national system.

PARTICIPANT TIMELINE: All preterm infants born at <30 weeks gestational age that survive delivery are admitted to a neonatal unit immediately after birth. In UK NHS neonatal units all babies have admission details (such as gestational age and birth weight) entered onto an electronic health record system shortly after admission. In neonatal units participating in the WHEAT trial the electronic health record will be programmed to automatically flag babies that meet the inclusion criteria for the WHEAT trial to clinical staff. Clinical staff will then approach the parents of eligible babies, explain the WHEAT trial and the opt-out consent process, and provide them with a copy of the parent information sheet. The clinical staff member will then record that this explanation has been given to parents on the electronic health record and that the parents were happy for their baby to be randomised in the WHEAT trial.

A nationally agreed UK standard (audited as part of the National Neonatal Audit Programme) is that all parents are spoken to by a senior member of staff within 24 hours of neonatal unit admission, we expect that explanation of the WHEAT trial will occur within the same period.

Where parents inform clinical staff that they are happy for their baby to be randomised in the WHEAT trial (they do not to opt out), their baby will be randomised to either be fed or not fed during blood transfusions. In practice this means that when the clinical team looking after a participating baby decide that a blood transfusion is clinically indicated AND the baby is receiving milk feeds the baby will either:

1. Be made nil by mouth from 4 hours before the blood transfusion, during the blood transfusion (this lasts 3-4 hours) and for 4 hours after the blood transfusion is finished (approximately 11-12 hours in total). During this period the baby will be placed on intravenous fluid or nutrition as per local unit policy.
OR
2. Have milk feeds continued before, during and after the blood transfusion.

If the baby requires any further blood transfusions during their neonatal unit stay they will remain allocated to the same intervention group.

There will be no other involvement of the baby or their family in the WHEAT trial. All trial data (including outcome data) will be extracted from existing electronic health record data that is entered in the course of routine clinical care and there will be no follow up questionnaires.

National Perinatal Epidemiology Unit – Clinical Trials Unit will be responsible for the day-to-day trial management and monitoring activities for the trial. This will include: securing regulatory and ethical approvals, site initiation, ensuring trial is carried out in accordance with regulatory and Good Clinical Practice (GCP) guidance, confirming capability and capacity at sites, risk assessment, maintenance of trial master file and safety reporting.

## Intervention Type
Other

## Primary outcome measure
Feasibility outcomes: To determine whether a point-of-care trial methodology (embedding trial processes and data collection within an existing electronic patient record system) is feasible for an individually randomised trial that includes preterm infants delivered at less than 30+0 gestational weeks+days, carried out in National Health Service neonatal units. These include:
1. Recruitment rate: Percentage of eligible cases where parents agree to trial involvement and the infant is randomised
2. Opt-out rate: Percentage of eligible cases where parents opted out of their infant being involved in the trial
3. Retention rate: Percentage of recruited infants who complete follow-up
4. Compliance: Percentage of cases where the allocated care pathway was adhered to
5. Data completeness: Percentage of recruited infants where trial data items are complete
6. Data accuracy: Percentage of recruited infants where data items are correctly recorded when compared to source data
Outcomes will be measured up to and including 40+0 gestational weeks+days or neonatal unit discharge (if sooner)

## Secondary outcome measures
Secondary (clinical) outcomes: To determine if withholding enteral feeds around blood transfusion is superior to continued enteral feeding, in reducing incidence of NEC and other clinical outcomes before discharge from neonatal care. These include:
1. Necrotising enterocolitis: Histologically or surgically confirmed, or recorded in part 1 of the death certificate
2. Spontaneous intestinal perforation: Histologically or surgically confirmed, or recorded in part 1 of the death certificate
3. All-cause mortality
4. Length of neonatal unit stay: in days and including all levels of care
5. Duration of any parenteral nutrition: in days

6. Number of days with a central venous line in situ
7. Number of central line associated bloodstream infections: defined according to National Neonatal Audit Programme criteria (https://www.rcpch.ac.uk/work-we-do/quality-improvement-patient-safety/national-neonatal-audit-programme-nnap)
8. Growth: change in weight and head circumference for gestational age standard deviation score between birth and final neonatal discharge
Outcomes will be measured up to and including 40+0 gestational weeks+days or neonatal unit discharge (if sooner)

### Overall study start date
01/04/2018

### Completion date
31/03/2020

## Eligibility

### Key inclusion criteria
1. Gestational age at birth <30 weeks (up to and including 29+6 weeks)
2. Babies will be recruited shortly after birth (and therefore before they are scheduled to have a blood transfusion in most cases). Blood transfusion is almost universal in babies of this gestational age (90-95% will need at least one blood transfusion prior to discharge)
3. Parents did not opt out of trial participation

### Participant type(s)
Patient

### Age group
Neonate

### Sex
Both

### Target number of participants
Planned Sample Size: 250; UK Sample Size: 250

### Total final enrolment
179

### Key exclusion criteria
1. Packed red cell transfusion with concurrent enteral feeds prior to enrolment (infants who have received a packed red cell transfusion while nil by mouth ARE still eligible)
2. Infants where enteral feeding is contraindicated in the first 7 days after birth (e.g. congenital abnormalities)

### Date of first enrolment
25/09/2018

### Date of final enrolment
30/06/2019

# Locations

## Countries of recruitment
England

United Kingdom

## Study participating centre
**Chelsea and Westminster Hospital (lead centre)**
369 Fulham Rd
Chelsea
London
United Kingdom
SW10 9NH

## Study participating centre
**West Middlesex University Hospital**
Twickenham Road
Isleworth
United Kingdom
TW7 6AF

## Study participating centre
**Hillingdon Hospital**
Pield Heath Road
Uxbridge
United Kingdom
UB8 3NN

## Study participating centre
**Northwick Park Hospital**
Watford Road
Harrow
United Kingdom
HA1 3UJ

## Study participating centre
**St Mary's Hospital**
Praed Street

London
United Kingdom
W2 1NY

**Study participating centre**
**Queen Charlotte's and Chelsea Hospital**
Du Cane Road
London
United Kingdom
W12 0HS

**Study participating centre**
**Birmingham Heartlands Hospital**
Bordesley Green East
Birmingham
United Kingdom
B9 5SS

**Study participating centre**
**Good Hope Hospital, Rectory Road**
Sutton Coldfield
Birmingham
United Kingdom
B75 7RR

**Study participating centre**
**Birmingham Women's Hospital**
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2TG

**Study participating centre**
**Birmingham Children's Hospital**
Steelhouse Lane
Birmingham
United Kingdom
B4 6NH

**Study participating centre**
**Birmingham City Hospital**
Dudley Road
Birmingham
United Kingdom
B18 7QH

**Study participating centre**
**University Hospital Coventry**
Clifford Bridge Road
Coventry
United Kingdom
CV2 2DX

**Study participating centre**
**Princess Royal Hospital**
Apley Castle
Apley
Telford
United Kingdom
TF1 6TF

**Study participating centre**
**Walsall Manor Hospital**
Moat Road
Walsall
United Kingdom
WS2 9PS

**Study participating centre**
**Leicester Royal Infirmary**
Infirmary Square
Leicester
United Kingdom
LE1 5WW

**Study participating centre**
**Hereford County Hospital**
Stonebow Road
Hereford

United Kingdom
HR1 2BN

**Study participating centre**
**New Cross Hospital**
Wolverhampton Road
Wolverhampton
United Kingdom
WV10 0QP

# Sponsor information

**Organisation**
Imperial College London & Imperial College Healthcare NHS Trust

**Sponsor details**
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**Sponsor type**
Hospital/treatment centre

**ROR**
https://ror.org/041kmwe10

# Funder(s)

**Funder type**
Research council

**Funder Name**
Medical Research Council; Grant Codes: MR/N008405/1

**Alternative Name(s)**

Medical Research Council (United Kingdom), UK Medical Research Council, MRC

### Funding Body Type
Government organisation

### Funding Body Subtype
National government

### Location
United Kingdom

# Results and Publications

### Publication and dissemination plan
Protocol will be available on the trial website shortly (https://www.npeu.ox.ac.uk/wheat) and published in a journal prior to recruitment finishing. Planned publication of the results in a high-impact peer reviewed journal.

### Intention to publish date
30/11/2020

### Individual participant data (IPD) sharing plan
All WHEAT Pilot trial data are held in the National Neonatal Research Database (NNRD), an established research database. All neonatal units in England and Wales contribute data to the NNRD, NNRD data are an NHS Information Standard (ISB1595) and are extracted quarterly from real-time neonatal Electronic Health Records. The NNRD is approved by the Caldicott Guardians and Lead Clinicians of all contributing neonatal units, the National Research Ethics Service, (16/LO/1093) and the Confidentiality Advisory Group of the Health Research Authority (805(f)/2010). For more details contact the National Neonatal Research Database (NNRD), Neonatal Data Analysis Unit Manager, Richard Colquhoun, Room G 4.3, Chelsea and Westminster Hospital, ndau@imperial.ac.uk, tel : +44 (0)20 3315 5841. The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication. Please note this relates to aggregated results, the trialists do not supply datasets.

### IPD sharing plan summary
Other

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Participant information sheet | version v2.0 | 26/06/2018 | 24/07/2018 | No | Yes |
| Protocol article | protocol | 20/09/2019 | 23/09/2019 | Yes | No |
| HRA research summary | | | 26/07/2023 | No | No |
| Basic results | | 16/05/2022 | 04/08/2023 | No | No |
| Results article | | 02/11/2020 | 04/08/2023 | Yes | No |