CLINICAL STUDY PROTOCOL

(ICTU ADOPTED)

Full Study Title: **W**ith**H**olding **E**nteral Feeds **A**round Blood **T**ransfusion – the WHEAT International Trial

Short Study title / Acronym: **WHEAT**

Sponsor: Imperial College London

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This protocol describes the WHEAT trial and provides information about procedures for enrolling participants to the trial. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres enrolling participants for the first time are advised to contact the Trial Coordination centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the Trial Coordination centre.

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
DSMC	Data and Safety Monitoring Committee
eCRF	Electronic Case Report Form
EPR	Electronic Patient Record
GIT	Gastrointestinal tract
HRA	Health Research Authority
ICHNT	Imperial College Healthcare NHS Trust
ICTU	Imperial Clinical Trials Unit
ITT	Intention to Treat
NEC	Necrotising Enterocolitis
NNAP	National Neonatal Audit Programme
NNRD	National Neonatal Research Database
QA	Quality Assurance
REC	Research Ethics Committee
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SIP	Spontaneous Intestinal Perforation
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWAT	Study Within A Trial
TMG	Trial Management Group
TSC	Trial Steering Committee
WHEAT	WithHolding Enteral feeds Around packed red cell Transfusion

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TRIAL SUMMARY

TITLE:

The Withholding Enteral Feeds Around Blood Transfusion (WHEAT) International Trial.

OBJECTIVES:

To determine whether withholding enteral feeds around the time of blood transfusion in preterm infants is superior to continued enteral feeding, in reducing the incidence of necrotising enterocolitis (NEC) and other adverse clinical outcomes before discharge from neonatal care.

DESIGN

Pragmatic, unblinded, international, multicentre, randomised, controlled, parallel-group superiority trial

SAMPLE SIZE

The UK sample size is 2,167

INCLUSION/EXCLUSION CRITERIA

Inclusion
Preterm birth at less than 30 weeks gestation

Exclusion
1. Parent(s) opt-out of trial participation.

2. Packed red cell transfusion with concurrent enteral feeds prior to enrolment.

NB. Infants who have previously received a packed red cell transfusion while nil-by-mouth or minimal enteral nutrition (<15ml/kg/day feeds) at the time of transfusion; defined as before, during and for at least 4 hours after transfusion, are eligible.

3. Infants who are not being fed at the time of randomisation or where enteral feeding is contraindicated for example, major congenital abnormality of the gastrointestinal tract.

4. Previous episode of NEC or spontaneous intestinal perforation (SIP) prior to first packed cell transfusion.

INTERVENTION / MAIN STUDY PROCEDURES

The two care pathways to be compared are:

Withholding feeds around transfusion: Enteral feeds will be paused for 4 hours before, during and 4 hours after transfusion. Hydration and blood glucose will be maintained according to local practice, commonly by parenteral nutrition or intravenous dextrose. Feeds will be restarted at the same rate and type of milk, and the same concentration of fortifier as used before transfusion.

Continuing feeds around transfusion: Enteral feeds will continue to be given before, during and after the transfusion at the same rate and type of milk and concentration of fortifier as used before the decision to transfuse.

Infants will receive the same care pathway for repeated transfusions through their stay until they reach 34 weeks + 6 days postmenstrual age or are discharged from neonatal care.

OUTCOME MEASURES

All clinical outcomes will be assessed from randomisation to 40+0 weeks of gestation or neonatal unit discharge, whichever occurs first.

PRIMARY ENDPOINT

Necrotising enterocolitis (≥ Stage II, Bell's criteria) after the first trial transfusion

SECONDARY ENDPOINT(S)

Severe NEC; death; late-onset sepsis; number of days with central venous line in situ; number of central line-associated bloodstream infections; duration of parenteral nutrition; growth; spontaneous intestinal perforation (SIP); duration of hospital stay; bronchopulmonary dysplasia (BPD)/chronic lung disease; retinopathy of prematurity (ROP); severe brain injury

WHEAT TRIAL FLOWCHART

Inclusion Criteria:
- Gestation at birth <30^{+0} weeks^{+days}

Exclusion Criteria:
- Previous red cell transfusion with enteral feeds
- Enteral feeding contraindicated in first 7 days
- Parent(s) opted out
- Previous episode of NEC or SIP prior to first blood transfusion

Eligibility
Flagged to health professionals through clinical screening or existing Electronic Patient Record (EPR) systems (BadgerNet or BadgerEPR)

Consent
Simplified opt-out consent where approved/written informed consent otherwise

Randomisation (1:1 allocation ratio)

WITHHOLD FEEDS AROUND TRANSFUSION FOR 4 HOURS BEFORE, DURING AND FOR 4 HOURS AFTER

CONTINUE FEEDS AROUND TRANSFUSION BEFORE, DURING AND AFTER TRANSFUSION

The allocated care pathway (transfusion feeding practice) should be applied around all blood transfusions up to and including 34^{+6} gestational weeks^{+days} or discharge (if sooner)

Trial data extracted from the UK National Neonatal Research Database (NNRD) which hold curated and validated EPR data recorded as part of routine clinical care or the Canadian Neonatal Network (CNN) Database
Follow up to 40 weeks corrected gestation or neonatal unit discharge if sooner
Primary Outcome
- NEC Bell's Stage II or greater, after the first trial blood transfusion

Secondary Outcomes: Early components of the neonatal Core Outcome Set
- Severe NEC
- Death
- Late-onset sepsis
- Number of days with a central venous line in situ
- Number of central line-associated bloodstream infections
- Duration of parenteral nutrition
- Growth
- SIP
- Duration of hospital stay
- BPD/Chronic lung disease
- ROP
- Severe brain injury

1. BACKGROUND

Necrotising enterocolitis (NEC) is among the most potentially devastating neonatal diseases and has a mortality of up to 33%, the most severe form (requiring surgery or resulting in death) affects about 5% of infants born at <30 gestational weeks[1]; survivors are at high risk of long-term health[2] and developmental problems.[3,4] Prevention of NEC has been identified as one of the most important research uncertainties in the field of preterm birth.[5] A temporal association between red cell transfusion and the subsequent development of the disease is well described.[6,7] This 'transfusion-associated NEC' may also be more severe[8] with higher mortality.[9,10] Very preterm or extremely low birth weight infants are among the most frequently transfused patients: between 56% and 90–95% have at least one transfusion, and those transfused receive a mean of 5 transfusions in their neonatal stay.[11,12] Withholding milk feeds during red cell transfusion may reduce the risk of NEC by decreasing postprandial mesenteric ischemia but there may be harmful effects of pausing enteral feeds.[13] However, due to a lack of good quality evidence, there is no consensus regarding the optimal feeding strategy during a blood transfusion.

Causal Mechanisms

The pathogenesis of NEC is incompletely understood. Mesenteric blood flow is generally increased in response to milk feeds. However, this postprandial increase is absent in infants who develop NEC suggesting that gut hypoperfusion may contribute to its pathogenesis. Red cell transfusion suppresses the normal postprandial increase in mesenteric blood flow and alters intestinal barrier function based on animal [14, 15] and human studies. [16,17,18] Milk feeds during red cell transfusion may thus precipitate NEC in preterm infants by reducing mesenteric blood flow and intestinal barrier function. Stopping milk feeds during packed red cell transfusion may reduce gut hypoperfusion and reduce the risk of NEC. However, this hypothesis has not been reliably tested in a large, randomised trial. Understanding the link between NEC and blood transfusion is of particular importance given that almost all very preterm babies will have a red cell transfusion, and many will receive multiple transfusions.[12]

Current Evidence

Stopping milk feeds around the time of packed red cell transfusion is currently practised in some neonatal settings to reduce the risk of NEC, putatively by maintaining more physiological intestinal blood flow.[19] This practice has not, however, been tested in an adequately powered randomised trial, and there are physiological reasons why stopping milk feeds in preterm infants may lead to harm. Interrupting enteral feeding prolongs the time taken to reach full milk feeds, which is associated with invasive infection[20] and may paradoxically be associated with an increased risk of NEC.[21] Only three small randomised trials[16, 22, 23] with a total of just 175 babies have been published on this issue; these lack power to assess the effect of this intervention on NEC rates even with ongoing studies. The Cochrane review[24] on this topic concluded that "Randomised controlled trial evidence is insufficient to show whether stopping feeds has an effect on the incidence of subsequent NEC or death. Large, adequately powered RCTs are needed to address this issue". A meta-analysis of seven 'before-after' non-randomised studies in 7,492 preterm infants reported a substantial reduction (by 53%) in the relative risk of NEC within 48-72 hours of transfusion.[13] However, these studies were at high risk of bias, including regression to the mean, publication and ascertainment bias. The authors concluded that adequately powered randomised controlled trials are needed to confirm these findings.

Current randomised trials: A review of clinical trial registries identified six trials assessing effects of enteral feeding around blood transfusion on NEC in preterm infants. The largest

of these is the WHEAT pilot trial 25 (https://www.npeu.ox.ac.uk/wheat) that recruited 179 infants over ten months. The projected total from all six trials is only 332 infants, providing inadequate power to reliably assess key outcomes like NEC and death even when combined. The WHEAT pilot trial demonstrated the feasibility and acceptability of a randomised trial and developed the materials and systems to run the large trial.

Practice Variation

Our research team recently designed and conducted an international survey with research end-users, consumers and parents (unpublished). Of 830 respondents in 22 countries, 84% agreed or strongly agreed that a large RCT is needed to test if continuing or withholding feeds during transfusion reduces the risk of NEC. The table demonstrates the substantial practice variation in 220 responding NICUs. Among all 830 respondents, 425 (51%) identified themselves as neonatal clinicians, defined as neonatal nurses, neonatal nurse practitioners, neonatal physicians or trainees. As individuals, neonatal clinicians reported substantial practice variation.

Table 1; Enteral feed policy for infants <30 weeks gestation in 220 NICUs worldwide

Practice	continue/reduce feeds during transfusion	withhold feeds during transfusion	either: depends on attending consultant	Total
No. of responses	123 (29%)	122 (29%)	180 (42%)	425

There is wide variation in the United Kingdom (UK) and United States (US) in relation to enteral feeding during transfusion in preterm infants. In a survey with a 68% response rate, 35% of UK units withheld enteral feeds during transfusion. A survey of US units found that in 17% of units, feeds were withheld around blood transfusion.[26] Such variation reflects a significant gap in the evidence.

Relevance

Prevention of NEC has been ranked as one of the most important research priorities in the field of preterm birth by over 500 parents, patients, doctors, nurses and researchers.[5] The UK National Blood and Transplant Serious Hazards Of Transfusion report has also highlighted the need for trials in this area[27] and this question has been identified as a research priority in transfusion medicine.

1.1 Clinical setting

Neonatal intensive care units in Canada and UK

1.2 Intervention details

The intervention in this study is withholding enteral feeds around the time of blood transfusion in pre-term infants. The comparator is enteral feeding around the time of blood transfusion in pre-term infants.

1.3 Rationale for the study

If withholding enteral feeds around the time of packed red cell transfusion reduces the risk of NEC, then implementing this simple practice will reduce the mortality and long-term complications of NEC. Conversely, if the safety of continued feeding can be demonstrated,

this will facilitate increased and consistent feeding, which has well described short-term and long-term benefits.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

To determine if withholding enteral feeds around blood transfusion is superior to continued enteral feeding, in reducing incidence of NEC and other adverse clinical outcomes before discharge from neonatal care.

2.2 Primary Endpoint

Necrotising enterocolitis (NEC) stage II or greater after the first trial transfusion (modified Bell staging criteria) based on clinical features and abdominal imaging findings, or on surgical or histological findings of NEC.

2.3 Secondary Endpoints

1. Severe NEC
2. Death
3. Late onset sepsis
4. Number of days with a central venous line in situ.
5. Number of central line-associated bloodstream infections.
6. Duration of any parenteral nutrition in days.
7. Growth
8. Spontaneous intestinal perforation (SIP)
9. Duration of neonatal care
10. Bronchopulmonary dysplasia (BPD)/Chronic lung disease
11. Retinopathy of Prematurity (ROP)
12. Severe brain injury

2.4 Summary Table of Objectives and Endpoints

Objective	Outcomes	Timepoint(s) of evaluation of this outcome
Primary Objective 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.	**Primary outcome:** Stage II or greater NEC recorded after the first trial blood transfusion; defined according to the modified Bell staging criteria: Clinical signs and symptoms plus pneumatosis, pneumoperitoneum or portal/hepatic air diagnosed by x-ray or other imaging techniques according to National Neonatal Audit Programme criteria[28]	Between randomisation and discharge or 40^{+0} weeks gestation (whichever's first)
	Secondary outcomes	
Secondary Objectives. Is withholding enteral feeds around blood transfusion superior to continued enteral feeding, in reducing incidence of the following clinical outcomes before discharge from neonatal care.	Severe NEC: Histologically or surgically confirmed or recorded on the death certificate. These infants will be identified as described in Battersby et al.,[1] which will include infants recorded as being transferred for surgery.	Between randomisation and discharge or 40^{+0} weeks gestation (whichever's first)
	Death: All-cause mortality	Between randomisation and discharge or 40^{+0} weeks gestation (whichever's first)
	Late-onset sepsis: Positive blood and/or cerebrospinal fluid culture, after two days of age	Between randomisation and discharge or 40^{+0} weeks gestation (whichever's first)
	Number of days with central venous line in-situ	From birth to discharge home
	Number of central line associated bloodstream infections: Includes laboratory-confirmed bloodstream infection and clinical sepsis	Between randomisation and discharge or 40^{+0} weeks gestation (whichever's first)
	Duration of parenteral nutrition in days	From birth to discharge home
	Growth: Weight & head circumference z-score	At discharge or 40^{+0} weeks (whichever's first)
	Spontaneous intestinal perforation: Histologically or surgically confirmed or recorded in the death certificate	Between randomisation and discharge or 40^{+0} weeks gestation (whichever's first)
	Duration of neonatal unit stay: Total duration of neonatal care in days including all levels of care (intensive care, high dependency care, special care and ordinary care)	From birth to discharge home
	Bronchopulmonary dysplasia/Chronic Lung Disease: Requiring respiratory support at 36 weeks gestation	At 36 weeks gestation

	Retinopathy of prematurity: defined according to the International Classification of Retinopathy of Prematurity (ICROP) and requiring treatment (laser or intraocular anti-VEGF injection)	At discharge or 40^{+0} weeks gestation (whichever's first)
	Severe brain injury: Intraventricular haemorrhage (IVH) grade 3 or 4 or cystic periventricular leukomalacia (PVL)	At discharge or 40^{+0} weeks (whichever's first)

3. STUDY DESIGN

The WHEAT trial is a randomised controlled, unblinded, international, multicentre, parallel-group superiority trial comparing two clinical pathways. Participants will be randomised to either pathway.

The WHEAT trial will be performed at approximately 40 investigational sites in Canada and the United Kingdom (around 36 in the UK). The duration of the study will be 3 years.

4. PARTICIPANT ENTRY

4.1 Patient population

(i) Inclusion criteria

Preterm birth at <30+0 gestational weeks + days

(ii) Exclusion criteria

1. Parent(s) opt-out of trial participation.

2. Packed red cell transfusion with concurrent enteral feeds prior to enrolment.

NB. Infants who have previously received a packed red cell transfusion while nil-by-mouth or minimal enteral nutrition (<15ml/kg/day feeds) at the time of transfusion; defined as before, during and for at least 4 hours after transfusion, are eligible.

3. Infants who are not being fed at the time of randomisation or where enteral feeding is contraindicated, for example major congenital abnormality of the gastrointestinal tract.

4. Previous episode of NEC or SIP prior to first packed cell transfusion.

4.2 Participating sites

4.2.1 Main Sites

The WHEAT trial will be conducted at an estimated 36 NHS Trusts across England, Scotland and Wales who will be responsible for all trial activities listed in this protocol.

The requirement for a main site, as defined in this protocol, is any NHS neonatal unit which has the facilities and capacity to treat pre-term births <30 weeks corrected gestation age and to perform packed red cell transfusions on this patient population.

4.2.2 Continuing Care Sites

Continuing Care Sites for the WHEAT trial will be responsible for the continuation of the trial intervention, if receiving a baby within the trial intervention period (<35 weeks post-menstrual age) and allowing for the extraction of routine clinical data until the end of the follow-up period (40 weeks corrected gestational age or until final discharge home). This is in line with the current, approved trial protocol and the only difference in activities between a Main Site (see Section 4.2.1) and a Continuing Care Site is that the latter will not be identifying, recruiting nor randomising babies into the trial.

4.2.3 Data Collection Sites

This refers to NHS neonatal units which are not undertaking any research activity, either through lack of research capacity or clinical equipoise concerns regarding the trial itself but will permit the extraction of de-identified clinical data from babies transferred in from main/continuing care sites.

See Section 10 for the data extraction process, which is the same for all site types.

5. PROCEDURES AND MEASUREMENTS

5.1 Identification and recruitment of participants

In the UK, baseline data for all infants admitted to neonatal units are routinely entered into the Electronic Patient Record (EPR) admission summary as part of usual clinical care. In participating units, data entered electronically into the admission summary will be interrogated by the EPR platform in real-time to identify and flag infants meeting the WHEAT trial inclusion criteria. When an infant in a participating unit meets the inclusion criteria, this will result in an electronic reminder appearing on the EPR platform at the participating unit. This 'flag' will inform the health professional that the infant is eligible for the WHEAT trial. Research participants/their parents/carers will not receive any payments for taking part in this research.

5.2 Screening and pre-randomisation evaluations

When an infant in a participating unit meets the inclusion criteria, this will result in an electronic reminder appearing on the EPR platform at the participating unit. This 'flag' will inform the health professional that the infant is eligible for the WHEAT trial.

5.3 Randomisation and Blinding

Infants will be randomly assigned shortly before receiving the first trial blood transfusion via a secure website to either care pathway. Randomisation can take place up until the baby reaches 35+0 weeks+days gestational age. Randomisation will be in a 1:1 allocation ratio as per a computer-generated randomisation sequence using permuted blocks of various sizes with stratification as described below. The block sizes will not be disclosed to ensure allocation concealment. Stratification will be by:

1. The neonatal unit of enrolment
2. Gestational age at birth, dichotomised as follows
    A) <28+0 weeks+days
    B) 28+0 to 29+6 weeks+days

Infants who are part of the multiple birth set (twins, triplets or higher-order multiples) will be randomised as a set to the same pathway of care following feedback from parent representatives, parent organizations including Bliss and TAMBA (Twins and Multiple Births Association) and research involving parents and adult ex-preterm twins. [3]

Allocation concealment

Infants will be randomised using an online secure central randomisation – randomise.net. Sites will submit patient information to a web-based randomisation platform which will allocate the care pathway.

Blinding

The WHEAT trial will be unblinded as it is not possible to mask the different care pathways.

5.4 Visit Schedule

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT	After birth, before allocation	0	Transfusion 1 (t_1)	t_2	t_3 etc.	Discharge from neonatal unit or 40 + 0 postmenstrual age
ENROLMENT						
Eligibility screen	X					
Informed opt out consent	X					
Allocation		X				
INTERVENTION						
Withhold feeds			X	X	X	
Control			X	X	X	
ASSESSMENTS						
Baseline variables	Collected from routine data extracted by the NNRD - no involvement of participant					
Outcome variables	Collected from routine data extracted by the NNRD and from Badger - no involvement of participant					
Other variables	Collected from routine data extracted by the NNRD and from Badger - no involvement of participant					
Expected Serious Adverse Events (SAEs)		Collected from routine data extracted by the NNRD - no involvement of participant* *see section 7.3 for a comprehensive list of expected SAEs for this study population which do not require reporting				
Unexpected and/or trial-related Serious Events (SAEs)		Reported from participating site to Trial Manager				

5.5 Follow-up

Follow-up and evaluation of outcomes will be up to 40+0 postmenstrual age or neonatal unit discharge (if earlier). Recruitment is planned for 36 months, with data collection continued, until all trial infants have finished follow-up at 40+0 corrected gestational weeks or neonatal discharge if sooner.

As routine data will be collected at sites through their electronic patient records and there are no research samples or additional procedures then there won't be any incidental findings known only to the research team that require reporting back to the clinical team.

6. INTERVENTION

Withholding feeds around transfusion:

All enteral feeds will be discontinued (the infant will be placed nil by mouth) for at least 4 hours prior to packed red cell transfusion, during the packed red cell transfusion and until at least 4 hours post packed red cell transfusion. During this period (~12 hours), hydration and blood glucose will be maintained according to local practice, commonly by providing parenteral nutrition or intravenous dextrose. Four hours after the red cell transfusion has finished, feeds will be recommenced in the manner they were being given prior to the decision to transfuse – at the same rate and type of milk and concentration of fortifier as used before the decision to transfuse. This duration of withholding feeds will follow the approach used in other trials[23] and observational studies,[13] and identified as the most acceptable in a survey of UK neonatal units. It gives time for milk in the small bowel to transit into the large bowel before the transfusion and for the circulation to stabilise after the transfusion before milk feeds given into the stomach pass through into the small intestine. Infants will remain allocated to the same care pathway until 34+6 weeks+days gestational age.

Continuing feeds around transfusion:

Enteral feeds will continue to be given prior, during and after the packed red cell transfusion, in the manner in which they were being given prior to the decision to transfuse – at the same rate and type of milk and concentration of fortifier as used before the decision to transfuse. Infants will remain allocated to the same care pathway until 34+6 weeks+days gestational age.

After 34+6 weeks+days gestational age the choice of continuing or withholding enteral feeds around blood transfusion will be determined by the clinical team.

Clinical care

In order to ensure that this pragmatic trial is as generalisable as possible to current practice, blood transfusions will be administered when clinically indicated according to local blood transfusion guidelines. Data will be collected on the pre-transfusion haemoglobin level for trial participants. Other concomitant care, including speed of increase of enteral feeds and choice of milk, will be according to locally defined practice for both care pathways.

In situations where a baby has feed intolerance during packed red cell transfusion (e.g. vomiting), management will be in accordance with clinical practice considered appropriate by the local clinical team. The infants' usual clinical care, including the administration of any regular medications (enterally or otherwise), should continue throughout the trial.

6.1 Permanent discontinuation of study intervention and withdrawal from study

(i) Permanent discontinuation of study intervention

Participants may discontinue study intervention for the following reasons:

- At the request of a participating infant's parent or guardian.

- If the investigator considers that an infant's health will be compromised due to adverse events (any untoward medical occurrence in a patient or clinical study subject) or concomitant illness that develop after entering the study.
- If an infant is diagnosed with NEC

If the study intervention is discontinued then the choice of withholding or continuing feeds during blood transfusion will be determined by local guideline, or by clinical choice in the absence of a guideline.

(ii) Withdrawal from Study

Withdrawal from the study refers to discontinuation of study intervention and study procedures and can occur for the following reasons:

- Parental decision
- Loss to follow-up

(iii)Procedures for Withdrawal from Study

If parents choose to withdraw their infant from receiving the allocated pathway of care, they will be asked for permission for continuing data collection and follow-up.
The attending clinician may withdraw the infant from the allocated pathway of care if they consider this to be in the infant's best interest and well-being.

Reason for withdrawal will be recorded in the EPR system in a study specific data item, and in the infant's medical records.

7. SAFETY REPORTING

7.1 Adverse Event (AE)

Due to the nature of the patient population, neonates in intensive care, a high incidence of adverse events is foreseeable during their routine care and treatment. Consequently, only those adverse events identified as serious will be recorded for the trial.

7.2 Serious Adverse Events (SAE)

(i) Definition of SAE

An SAE is defined as any event that

- Results in death
- Is life-threatening*
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect

* "Life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. SAEs are to be reported from randomisation until the end of trial follow-up (40^{+0} gestational weeks^{+days} or neonatal unit discharge, if earlier).

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation

but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

7.3 Safety Events Reporting

Non-serious adverse events will not be reported to the Clinical Trials Unit nor Sponsor as the trial is comparing two accepted pathways of care that are both widely practised in the United Kingdom.

The following are serious adverse events that could be reasonably anticipated to occur in this population of infants during the course of the trial or form part of the outcome data. They do not require reporting by the trial sites as SAEs but do require relevant data to be captured in the summary EPR systems (BadgerNet or BadgerEPR) as part of routine clinical care:

- Death (unless cause not anticipated in this population)
- Necrotising enterocolitis or gastrointestinal perforation
- Bronchopulmonary dysplasia (or chronic lung disease)
- Intracranial abnormality (haemorrhage or focal white matter damage) on cranial ultrasound scan or other imaging
- Pulmonary haemorrhage
- Pneumothorax
- Anaemia requiring blood transfusion
- Hyperbilirubinaemia
- Hyperglycaemia
- Hypoglycaemia
- Coagulopathy requiring treatment
- Hypotension
- Hypertension
- Impaired renal function
- Patent ductus arteriosus (PDA)
- Retinopathy of prematurity
- Sepsis
- Fractures
- Clinically significant liver failure
- Clinically significant extravasation injury
- Clinically significant left ventricular hypertrophy on echocardiography
- Hydrocephalus
- Surgery for a condition not anticipated in this population

Only if these events are thought to be causally related to the allocated pathway of care would they require urgent reporting to the trial centre as outlined below.

Unforeseen SAEs and SAEs related to the allocated trial intervention must be reported to ICTU by a member of site staff within 24hours of becoming aware of the event. Site staff may email a completed SAE form to ICTU (WHEAT@imperial.ac.uk). Paper forms, with instructions, will be made available with the trial documentation to enable anyone to report an SAE. If this is not possible, site staff may report the SAE to ICTU by telephone and will follow up this notification with an SAE report form by email as soon as possible. If following

the reporting of an SAE additional information becomes available, a new SAE form should be completed. The PI at the site will assess whether the SAE was as a result of trial related activities (related).

ICTU will forward a copy of the SAE form to the Chief Investigator (CI) as soon as possible on receipt. The CI will review whether the SAE was as a result of trial related activities (related). If the assessments of the PI and CI do not agree further discussion can take place and/or if either assesses the SAE to be related and unexpected it will be further reported as below.

All related and unexpected SAEs reported will be submitted to the Research Ethics Committee (REC) that gave a favourable opinion of the trial within 15 working days of the CI becoming aware of the event, using the HRA report of serious adverse event form (see HRA website). In addition, all unexpected SAEs will be reported to the sponsor and the Canadian trial team (IWK) and be reported to the DMC and relevant R&D offices including IWK.

Related and unexpected SAEs are defined as:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Contact details for reporting SAEs
Email: wheat@imperial.ac.uk and christopher.gale@imperial.ac.uk
Please scan and email SAE forms to the WHEAT Trial Coordinating Centre
Tel: 0207 594 7271 (Mon to Fri 09.00–17.00)

The WHEAT study team will forward any related and unexpected SAEs to RGIT@imperial.ac.uk

7.4 Annual reporting of Safety Events

Annual Progress reports will be submitted to the Sponsor and the Ethics Committee in accordance with local requirements. The Annual Progress Report will detail all reported events.

7.5 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

8. STATISTICAL ANALYSES

8.1 Sample Size and power considerations

Assuming an annual proportion of 5.2% infants developing ≥ Stage II Bells NEC and that 75% (3.9%) of these infants develop NEC after their first blood transfusion,[32] representing

the population who may benefit from withholding feeds during transfusion; a total of 4,333 infants will have >80% power to show a 40% relative risk reduction (RRR) in the primary outcome (from 3.9% to 2.34%), with a two-tailed test (www.sealedenvelope.com). This accounts for an inflation of the sample size by 1% to account for multiple births (based on the NEC incidence data from the SIFT trial). This estimated RRR is 40%, more conservative than the RRR of 53% in the meta-analysis by Jasani et al. [13] Planned recruitment rate

2,167 infants will be recruited from 20 sites over 3 years. Each site will recruit approximately 6 infants per month. The Canadian sites will also aim to recruit 2,167 infants.

8.2 Statistical Analysis

A statistical analysis plan will be prepared and finalised prior to analysing the data. All randomised participants will be eligible for inclusion in efficacy analyses in accordance with the intention-to-treat analysis (ITT) principle. Participants will be analysed according to the care pathway they actually received to compare the rates of Serious Adverse Events that are unexpected. Methods to account for missing, unused or spurious data will be described in the statistical analysis plan.
Continuous variables will be summarised using means and SD unless their distributions are skewed, in which case medians, 25th quartiles, 75th quartiles and the range (lowest and highest values) will be presented. Dichotomous variables will be presented as frequencies and percentages.

Subgroup Analysis

The following subgroup analyses are prespecified:
1. Gestational age at birth (<28 weeks; ≥ 28 weeks postmenstrual age)
2. Sex
3. Multiplicity

Interim Analysis

Interim analyses will be performed by the Study Statistician and reviewed by the combined Trial Steering Committee (TSC) and Data Safety and Monitoring Committee (DSMC) according to a pre-agreed Charter[34] in line with the ICTU DSMC Charter. Haybittle-Peto criteria will be used to compare the rates of the primary outcome and key outcomes between study arms. Should a difference in a key outcome emerge beyond reasonable doubt and be judged likely to change clinical practice the joint TSC/DSMC will review the strength of this finding and advise the Trial Management Group (TMG) accordingly. The TMG will also monitor the number of eligible patients, number of patients randomised, number of incorrect randomisations, and number of protocol violations.

Analysis populations

All randomised participants will be eligible for inclusion in efficacy analyses in accordance with the intention-to-treat analysis principle.

Primary Endpoint Analysis

The primary analysis will compare care pathways on the incidence of the primary outcome.

Secondary Endpoints Analysis

Other binary secondary outcomes will be analysed using the same method, while comparable approaches applicable to continuous data will be applied as required. Estimates of the treatment effect adjusted for baseline characteristics will be calculated in sensitivity analyses using the relevant linear modelling approach. These modelling techniques will also be used to identify clinically significant prognostic factors and perform heterogeneity tests in subgroup analyses. Hypothesis tests will be undertaken at the two-sided 5% level of significance. p-values from secondary analyses that are unadjusted for multiple comparisons will be interpreted in proper context.[33]

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

9. REGULATORY, ETHICAL AND LEGAL ISSUES

9.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the 2013 revision of the 1964 Declaration of Helsinki.

9.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

9.3 Research Ethics Committee (REC) Approval

Appropriate approval from a research ethics committee (REC) will be obtained before commencing recruitment. As both the pathways being compared in the trial are standard practice in UK and Canada, the trial will use a simplified opt-out consent process. This approach has been developed with parents and parent charities and has shown to be acceptable in a study of 12 Research Ethics Committees.[36] A qualitative exploration of the opt-out consent and recruitment process and trial procedures were conducted with parents who participated in the WHEAT-UK trial and health professionals from the recruiting sites. Parents were supportive of research like WHEAT-UK, where both comparator arms are routine care. The priority expressed by parents was having the right to decide about trial participation, and they did not see opt-out consent as undermining this.[37]

(i) Initial Approval

Prior to the enrolment of participants, the REC will provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Participant Information Sheet, and any other written information that will be provided to the participants.

(ii) Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval as instructed by the Sponsor. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

The Chief Investigator (CI) or their delegate will submit and, where necessary, obtain approval from the REC for any protocol amendments and changes to the parent information leaflet. The CI/delegate will determine whether the changes are substantial or non-substantial. Changes will be communicated to stakeholders via email and TMGs and will be reviewed by all members of the Protocol Development Group prior to finalising.

(iii) Annual Progress Reports

Annual Progress Reports will be submitted to the Research Ethics Committee (REC) and the Sponsor in accordance with local / national requirements. The Annual Progress Report will also detail all SAEs recorded.

(iv) End of Trial Notification

The trial will end once the study reaches the end of study definition (refer to section 9.10).The REC will be informed about the end of the trial, within the required timelines. The end of trial notification will be submitted within 90 days of the end of trial definition being met.

9.4 HRA approval

Health Research Authority (HRA) approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing.

The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

9.5 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via study specific data items within the EPR system and reviewed by the CI and reported to the ICTU QA manager on a monthly basis. Protocol violations will be reported to the Sponsor.

An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.

A serious breach is defined as:

A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the UK trial participants; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the REC within 7 days of becoming aware of the serious breach.

9.6 Insurance and Indemnity and Sponsor

The Sponsor has civil liability insurance, which covers this study in the United Kingdom.

9.7 Trial Registration

The trial is registered on clinicaltrials.gov NCT05213806

9.8 Informed Consent

Because both care pathways that are being compared are part of standard Canadian and UK practice, WHEAT is using a simplified model of consent where this is approved by the local research ethics boards in Canada or the research ethics committee in the UK. This means that parents will be informed about the trial and see posters and leaflets in the unit and be given the opportunity to 'opt out' if they do not want their infant to be randomised and enrolled in the trial.

There is no upper time limit when trial discussions can occur with parents, except before a blood transfusion occurs; any discussions about the trial should occur when most appropriate for the parents. Parents are able to opt-out of the WHEAT trial at any point. If parents opt out, this will be recorded on a screening log. If parents do not opt out, randomisation will occur through a web-based system at the point when a blood transfusion is indicated or shortly before. Enrolment of the infant and the allocation will be notified to the local team through an online electronic randomisation system. Because of the opt-out nature of WHEAT, there will not be a signed consent form.

A screening log at each site or embedded within the EPR system will be used to record how many babies are eligible but don't need a transfusion or are eligible but parents opt out or do not give consent.

Recruitment is planned for 36 months, with data collection continued, until all trial infants have finished follow-up at 40+0 corrected gestational weeks or neonatal discharge if sooner. Some infants will not receive a packed red cell transfusion during their neonatal unit stay. These infants will not be randomised and not included in the primary analysis of clinical outcomes.

9.8.1 Contact with General Practitioner

There is no requirement to inform the general practitioner that an infant was enrolled in the WHEAT trial.

9.8.2 Participant Confidentiality

The investigator must ensure that the participant's confidentiality is maintained. On documents submitted to the Sponsors, participants will be identified by a participant ID number only. Documents that are not submitted to the Sponsor should be kept in a strictly confidential file by the investigator.
The investigator shall permit direct access to participants' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS, Regulatory Authorities and RECs.

9.9 Data Protection and Participant Confidentiality

The investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Data will be pseudonymised.

9.10 End of Trial

The end of the trial definition will be when the final enrolled infant has reached the end of follow up at neonatal unit discharge or 40+0 gestational weeks+days, whichever is first.

9.11 Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor, and for at least twenty years after study completion. Participant files and other source data (including copies of protocols, EPR data, correspondence, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

10. DATA MANAGEMENT

10.1 Source Data

Data entered into the EPR systems, paper-based medical records and completed paper SAE forms will be considered source data.

10.2 Language

Trial data will be recorded in English. All written material to be used by participants must use vocabulary that is clearly understood and be in the language appropriate for the study site.

10.3 Database

Trial processes will be embedded within neonatal EPR systems and all outcome data will be extracted from data that is largely routinely recorded within the existing neonatal EPR systems at participating NHS sites (BadgerNet EPR and BadgerNet Clinical Summary). There is no study-specific eCRF/CRF for the WHEAT Trial.

10.4 Data Collection

The WHEAT Trial seeks to increase efficiency in clinical trial management while reducing the administrative burden on participating NHS sites. There will be no study-specific eCRF

nor paper CRFs for this research. Instead, data collection will be embedded within the UK national electronic patient record used by neonatal units nationwide. A prerequisite to participation is that neonatal units must use the BadgerNet (Clevermed Ltd) electronic patient record system and also be existing contributors to the UK National Neonatal Research Database (NNRD).

10.4.1 National Neonatal Research Database (NNRD)

Baseline characteristics and clinical outcomes will be extracted from the National Neonatal Research Database (NNRD). The NNRD is an existing NHS REC-approved Research Database which exists separately to the WHEAT Trial and for each infant admitted to a neonatal unit in the UK, their clinical data will form the Neonatal Data Set. Extracted from neonatal units across England, Scotland, Wales and the Isle of Man, the Neonatal Data Set (NDS) is an on-going extraction from electronic health records of neonatal units created on a platform called BadgerNet, operated by Clevermed Ltd. The BadgerNet system is updated routinely by clinical staff on neonatal units. Clevermed store all of the generated records on behalf of the NHS Trust for whom they supply BadgerNet. From this data repository Clevermed extract a set of core data items that are known to be part of the Neonatal Data Set. The Neonatal Data Analysis Unit (NDAU), based jointly at the Chelsea & Westminster NHS Foundation Trust and Imperial College London, receives this extract to form the National Neonatal Research Database (NNRD). Caldicott guardian agreements are held by the NDAU with every neonatal unit across England & Wales allowing the transfer of data from Clevermed to an NDAU server based at Chelsea and Westminster NHS Foundation Trust.

Please refer to the NNRD Neonatal Dataset ISB1595 (Release 1, V22) for a full list of the data items collected at individual patient-level (link: https://digital.nhs.uk/data-and-information/information-standards/information-standards-and-data-collections-including-extractions/publications-and-notifications/standards-and-collections/isb-1595-neonatal-data-set).

10.4.2 BadgerNet

Baseline data for all infants admitted to neonatal units in the UK are routinely entered into the EPR admission summary, within BadgerNet, as part of regular clinical care as mentioned in section 10.4.1. NHS sites will use one of two versions of this patient record management system depending on their implementation of either full electronic (BadgerNet EPR) or paper-based (BadgerNet Clinical Summary) medical records. The version of BadgerNet used does not preclude participation in WHEAT as the data collected from each version fulfils the data collection requirements for the WHEAT Trial.

For participating NHS sites, BadgerNet will be modified to include a WHEAT Trial instance that will draw on the admission summary to flag to participating site staff that a baby is eligible for the trial. Upon enrolment, additional research-specific data fields will be enabled within each participating infants' electronic medical record (BadgerNet) to capture data items not routinely collected. For example, WHEAT Trial unique ID, confirmation of consent discussion, randomisation allocation and details of the randomised intervention.

The above data fields which are not collected routinely, but necessary to address the research objectives set out in this protocol, do not form part of the Neonatal Data Set held in the NNRD.

10.4.3 Final Data Set

While BadgerNet (neonatal EPR) is the origin of all data collected in this study, the overall data are stored in two separate repositories. The first is the NNRD Neonatal Data Set (section 10.4.1) which contains all routinely-entered clinical data on an individual infant, but this does not account for the WHEAT Trial research-specific fields built into BadgerNet as described in section 10.4.2. Therefore, further data from the WHEAT Trial instance of BadgerNet will be held in a second dataset.

Clevermed Ltd extract the required dataset for the NNRD (section 10.4.1) and extract an additional dataset containing the additional data fields and outcome data from the WHEAT Trial instance of BadgerNet (section 10.4.2), which are then transferred to the Neonatal Data Analysis Unit (NDAU), based jointly at the Chelsea & Westminster NHS Foundation Trust and Imperial College London.

NHS Trusts authorise the NDAU to receive their data through Caldicott Guardian agreements, which are already in place for each participating NHS site.

The Neonatal Data Set and that generated from the WHEAT Trial instance of BadgerNet are linked by the “Badger Unique Identifier”, which is a unique ID allocated to each infant and associated with their EPR record.

All research data are stored pseudo-anonymised, in an encrypted file on a secure NHS server in the Neonatal Data Analysis Unit in accordance with the associated Data Security and Protection Toolkit.

10.5 Archiving

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 20 years following the end of the study. All electronic and paper documents will be stored securely and kept in strict accordance with current data regulations.

11. STUDY MANAGEMENT STRUCTURE

The trial's coordinating centre will be located at IWK Health Centre, Canada and will be staffed by a full-time study coordinator. There will be a trial manager within Imperial Clinical Trials Unit (ICTU) overseeing the set up and running of the UK documentation, approvals and sites. In collaboration with JD, CG and BS, the study coordinator and trial manager will coordinate with other centres regarding patient recruitment, data handling, data transfer, and study status on a day-to-day basis.

The running of the trial will be managed by a Trial Management Group (TMG) consisting of a sub-group of the local and international collaborators.

Individual researchers will not receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research.

11.1 Combined Trial Steering Committee/Data Safety and Monitoring Committee

A joint Trial Steering Committee/Data Safety and Monitoring Committee (TSC/DSMC) will be convened including as a minimum an independent Chair, independent clinician, the Chief Investigator, Trial Manager and independent public/patient/parent member. The role of the TSC/DMSC is to provide overall supervision of trial conduct and progress, and monitor patient safety and appropriateness of study design.

The TSC/DSMC will review interim data and other emerging evidence, including relevant RCTs and overviews of RCTs. It will advise the TMG if, in their view, there is proof beyond reasonable doubt of net clinical benefit or harm, for all infants or for a subset of infants, that might reasonably be expected to influence the management of many clinicians. A charter will be prepared detailing the role and responsibility of the TSC/DSMC and operational, decision making, and reporting processes. If required, the TSC/DSMC will liaise with the DSMCs of other WHEAT trials (e.g. the Australian WHEAT trial DSMC) to ensure that the implications of any important impacts are collaboratively considered.

Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

11.2 Trial Management Group

A Trial Management Group (TMG) will be convened as a sub-group of the local and international collaborators, trial coordinator and trial manager. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate terms of Reference. The TMG will also monitor the number of eligible patients, number of patients randomised, number of incorrect randomisations, and number of protocol violations.

11.3 Outcome Adjudication Committee

This is an open-label trial; blinding of the clinicians, nursing staff, and parents is not possible due to impracticality. A blinded endpoint review committee will be set up to examine the relevant pseudonymised data and abdominal X-rays and laboratory results that are deemed required. Two independent clinicians unaware of the trial-group assignments will classify babies for necrotising enterocolitis using standard definitions if outcome report forms are ambiguous or data is missing.

11.4 Early Discontinuation of the Study

If during the interim analysis the TSC/DSMC believe there is proof of harm the study may be discontinued early as detailed in the TSC/DMSC charter.

11.5 Risk Assessment

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of 'low', 'medium' or 'high' to the trial. Risk assessment will be carried out by the ICTU QA Manager in collaboration with the CI and Study Manager and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

11.6 Monitoring

Central monitoring will be used at ICTU to monitor patterns of recruitment at sites and within the data; data completeness and quality; safety reports and outliers in the clinical data will be investigated and may trigger 'for cause' site monitoring.

Direct access will be granted to authorised representatives from trial organisers, the research Sponsor and NHS Trusts to permit trial-related monitoring, audits and inspections. A monitoring plan will be in place for the duration of the study to describe the monitoring that will take place.

11.7 Quality Control and Quality Assurance

Quality Control will be performed according to ICTU procedures. The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection.

The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd Edition).

11.8 Peer review

The study has undergone independent peer review by the Canadian Institute of Health Research (CIHR).

11.9 Patient and Public Involvement

The WHEAT international trial addresses one of the most important research uncertainties in preterm birth, as identified by over 500 parents, patients, health professionals and researchers.[5] The WHEAT trial has been developed in partnership with parents. Over 400 parents and patients have contributed to the selection of trial outcomes through the COIN project.[41] Parents and Bliss, the charity for babies born premature or sick, were involved in developing the opt-out consent process, how this is communicated, in designing information leaflets and posters. The WHEAT trial also has parent representatives on oversight committees. Representatives from Bliss and Canadian Preterm Birth Foundation will help with trial recruitment and material development through parent groups and dissemination and knowledge translation.

11.10 Publication and Dissemination policy

The Trial Management Group will appoint a Publication Committee to draft manuscripts based on the trial data.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor. Therefore all information obtained as a result of the study will be regarded as confidential, at least until appropriate analysis and review by the investigator(s) are completed

Manuscripts will be submitted to a peer-reviewed journal(s). The primary publication will be the report of the full trial results based on the main protocol using the study group name, with subsequent publications of data subsets. The Writing Committee will develop a publication plan, including authorship, target journals, expected dates of publication, and other effective ways of disseminating the results of the study.

Dissemination to academic, nursing and medical professionals will be through peer reviewed publications, conference presentations and through professional networks and organisations. Dissemination of results to parents, patients and the public will be led by the parent and parent advocate members of the trial steering committee and will be via charity websites and social media outlets. Results will also be published on the trial website (www.neoepcoh.com/wheat-trial).

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13. APPENDICES

13.1 APPENDIX 1: STUDY WITHIN A TRIAL (SWAT) UK ONLY

BACKGROUND

The admission of a baby to the neonatal unit is often unexpected and carries a significant negative emotional burden for parents (1) including feelings of fear, depression, anxiety, stress and a loss of control, often compounded by questions and a lack of understanding about the healthcare their infant is receiving (2, 3, 4).

Informed consent in neonatal clinical research

The way that research information is presented and informed consent obtained in a neonatal unit needs to understand and accommodate the challenges faced by parents (5). However, parents and clinicians alike feel strongly that parents must be involved in the decision-making for their baby, including being offered the opportunity to take part in neonatal research (6). Multiple factors affect a parent's decision to provide consent, namely the complexity and severity of their infant's condition, the perceived risk-benefit ratio of the research as well as their relationship with the research team. Effective communications and dialogue between parents and the research team are key to ensuring parents are able to make informed decisions about participation in neonatal research (7).

Multiple different approaches have been developed to provide parents with information about neonatal research that is clear and concise, and to ensure that the process of gaining informed consent in proportionate and appropriate. These include the use of oral assent followed by later written informed consent (8, 9), deferred consent (10) and opt-out consent (11).

The WHEAT trial

The WHEAT trial is a randomised, controlled, comparative effectiveness trial that aims to determine whether withholding enteral feeds around the time of blood transfusion in preterm infants is superior to continued enteral feeding, in reducing the incidence of necrotising enterocolitis (NEC) and other adverse clinical outcomes before discharge from neonatal care. The trial aims to recruit 2,167 babies within 3 years across approximately 36 NHS Trusts. It is currently underway in the UK, Australia and Canada and is using an opt-out approach to consent in the UK. Initial data collected during the first 3 months of recruitment in the trial, shows that out of the 127 parents approached, 23% have opted-out of their infant's participation in the trial. At some participating sites, the opt-out rate has been as high as 45%. Parents do not have to provide a reason for withdrawing their infant from the trial but informal feedback from research teams highlights parental hesitancy around the word 'trial'. It is essential to identify more effective ways to engage parents, alleviate concerns and build trusting relationships with site research teams, not only to increase recruitment into the WHEAT trial, but to ensure parental understanding of research and normalise participation in neonatal clinical research.

The use of routinely recorded clinical data in randomised controlled trials is increasing; it has a number of major benefits including efficiency and simplicity (12). Point-of-care clinical trials describe a design methodology that integrates existing electronic health record systems (13) to allow baseline, treatment and outcome data to be extracted directly from existing electronic records. The WHEAT trial is using such a design.

Digital multimedia as a recruitment tool

Digital multimedia has been used to facilitate written informed consent for clinical research: participant information clips, short videos that provide study-related information to potential research participants or their proxies, are cost-effective and straightforward to produce and implement (14). There is, however, a paucity of data describing the impact of digital multimedia in trials using an opt-out approach to consent or using routinely recorded clinical data (point-of-care trials).

We hypothesise that if parents are made aware of the value of their baby's routine clinical data used in clinical trials to improve neonatal care, they will be more inclined for their baby to participate in simple point-of-care trials.

AIM

To evaluate the effectiveness of presenting parents with a short video animation explaining the importance of routine data in clinical care and research, on the parental opt-out and withdrawal rates for the WHEAT trial.

OBJECTIVES

Primary Objective

To establish if parents are less likely to opt-out of their infant's participation in the WHEAT trial if they are given information on the use of routine data in clinical research, in addition to WHEAT trial specific parent information.

Secondary Objective(s)

To establish if parents are less likely to withdraw their infant from the WHEAT trial post randomisation if they are given information on the use of routine data in clinical research, in addition to WHEAT trial specific parent information.

DESIGN

A Study Within a Trial (SWAT): A cluster randomised trial nested within participating UK WHEAT trial sites.

Randomisation will be stratified on the level of unit (LNU/SCBU and NICU).

ELIGIBILITY

Inclusion criteria

- Parents of pre-term neonates eligible for inclusion in the WHEAT trial

Exclusion criteria

- Parents who do not speak one of the languages in which the patient information materials and video presentation are available (currently only in English).

INTERVENTION

WHEAT sites will be randomised 1:1 to either:

1. Intervention: A small card containing a link to a short, 3-minute animated video explaining the importance neonatal research and of routinely recorded clinical data for research. This will be delivered to parents at the same time as information about the WHEAT trial is provided to them.

2. Comparator: Information about the WHEAT trial only.

The intervention is a 3-minute animated video hosted on the WHEAT trial website (http://neoepoch.com/wheat-trial) which will be made available to parents by providing them with a small card with a QR code which links directly to the video clip. The video animation gives a plain English explanation of the importance of neonatal research and the use of routine clinical data in research and includes audio from interviews of parents who have had babies involved in research from the WHEAT trial Parent and Public Advisory Group.

Research staff at sites participating in the intervention arm of the SWAT sub-study will present parents of babies eligible for the WHEAT trial with a small card containing a QR code which links to the intervention video on the WHEAT trial website. Parents will be asked to scan the QR code using their own smartphone, from which they will watch the video animation.

Comparator arm sites will continue to approach parents/guardians of potentially eligible babies for the WHEAT trial in the usual way. The stratified block randomisation will be performed via two separate sequences of the arms for each stratum (NICU, LNU/SCBU) generated randomly by a statistical software code with the block size of 4. The randomisation sequence will be concealed from all researchers involving in the study.

OUTCOMES

Primary Outcome

- Parental opt-out rate for the WHEAT trial pre-randomisation

Secondary Outcomes

- Parental withdrawal rate from the WHEAT trial post-randomisation

SAMPLE SIZE

36 NHS Trusts are participating in the WHEAT trial and will be randomly allocated on a 1:1 basis (18 units in each arm) to intervention and comparator arms. Assuming an average cluster size of 50 babies, intraclass correlation of 0.05, and a baseline percentage for opt-out of 32% (based upon initial recruitment), 18 clusters in each arm will provide 80% power to detect a difference of 11.4% in opt-out rates between intervention and control at an alpha of 0.05. Additional participating sites will also be randomised into the SWAT as they open to recruitment to WHEAT.

ANALYSIS

The primary analysis will be based on an intention-to-treat approach; participants with outcome data will be analysed in the SWAT groups to which they are assigned, regardless of deviation from the protocol or procedure received. The comparator group will be used as the reference group in all analyses. For the primary and secondary binary outcomes, risk ratios and confidence intervals will be calculated using a mixed modified Poisson model with a log link and robust variance of error, with cluster as a random effect, and adjusting for level of unit as a fixed effect. Risk differences will also be calculated using a mixed binomial model with an identity link.

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14. REVISION HISTORY

Version	Date	Summary of changes
1.0	20 APR 2022	Original Version
1.1	14 SEP 2022	Minor administrative changes and updates not affecting the scientific validity nor safety of patient participants: • Page 2, Research Ref. Numbers – add REC reference number • Page 3, Contact List – added name of the WHEAT Trial Manager • Page 16, Section 5.3 Randomisation – clarified point at which eligible infant can be randomised • Page 17, Section 5.4 Visit Schedule – clarification that expected serious adverse events (SAEs) will be recorded in the patient electronic medical records and only unexpected SAEs will be reported to Sponsor o This level of SAE reporting was described in the original protocol, but the visit schedule had not been updated • Page 20, Section 7.3 Safety Events Reporting – included email address for unexpected SAEs to be reported to • Page 25, Section 9.8 Informed Consent – clarified that a separate screening log will be maintained by the Research Team at each participating site and that this will not be embedded within the electronic patient record • Page 26, Section 10 Data Management – clarified the flow of research data and explained the different pathways for routine clinical data collected as part of the National Neonatal Research Database and additional research data collected directly from participating site electronic medical records (BadgerNET)
1.2	16 DEC 2022	Page 15, Section 4. Participant Entry – Clarified exclusion criteria (3) to align with Trial Summary p8.

1.3	13 JUN 2023	• Page 15, Section 3. Study Design
		  ○ Updated anticipated number of UK participating sites (n=36)
		• Page 15, Section 4. Participant Entry
		  ○ Further clarifications to eligibility criteria
		  ○ Clarification of participating site types
		• Page 18, Section 6. Intervention
		  ○ WITHHOLD ARM – clarification of duration that feeds are to be withheld for
		• Page 25, Section 9.8 Informed Consent
		  ○ Reference to the SWAT protocol in the UK
		• Page 33, Section 11.3 Outcome Adjudication Committee
		  ○ Removal of late-onset sepsis as outcome to be adjudicated
		• Page 35, Section 13. Appendices – 13.1 Appendix 1: Study Within a Trial (SWAT)
		  ○ Addition of a SWAT sub-study in the UK

SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

The signature below constitutes approval of this protocol by the signatory, on behalf of the Protocol Development Group, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: **W**ith**H**olding **E**nteral Feeds **A**round Blood **T**ransfusion – the WHEAT International Trial

Protocol Number: 22IC7569

Signed: _____

Dr Chris Gale
Consultant Neonatologist

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: **W**ith**H**olding **E**nteral Feeds **A**round Blood **T**ransfusion – the WHEAT International Trial

Protocol Number: 22IC7569

Signed: _____

Name of Sponsor's Representative
Title
Sponsor name

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: **W**ith**H**olding **E**nteral Feeds **A**round Blood **T**ransfusion – the WHEAT International Trial

Protocol Number: 22IC7569

Signed: _____

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: **W**ith**H**olding **E**nteral Feeds **A**round Blood **T**ransfusion – the WHEAT International Trial

Protocol Number: 22IC7569

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____