The WHEAT pilot trial

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

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of covariance
CI	Chief Investigator
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
EPR	Electronic Patient Record
GCP	Good Clinical Practice
HRA	Health Research Authority
ISRCTN	International Standard Randomised Controlled Trial Number
NEC	Necrotising enterocolitis
NHS R&D	National Health Service Research & Development
NNAP	National Neonatal Audit Programme
NNRD	National Neonatal Research Database
NPEU	National Perinatal Epidemiology Unit
NRES	National Research Ethics Service
PMG	Project Management Group
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDS	Standard Deviation Score
SHOT	Serious Hazards of Transfusion
SOP	Standard Operating Procedure
TAMBA	Twins And Multiple Births Association
TSC	Trial Steering Committee
UK	United Kingdom
USA	United States of America

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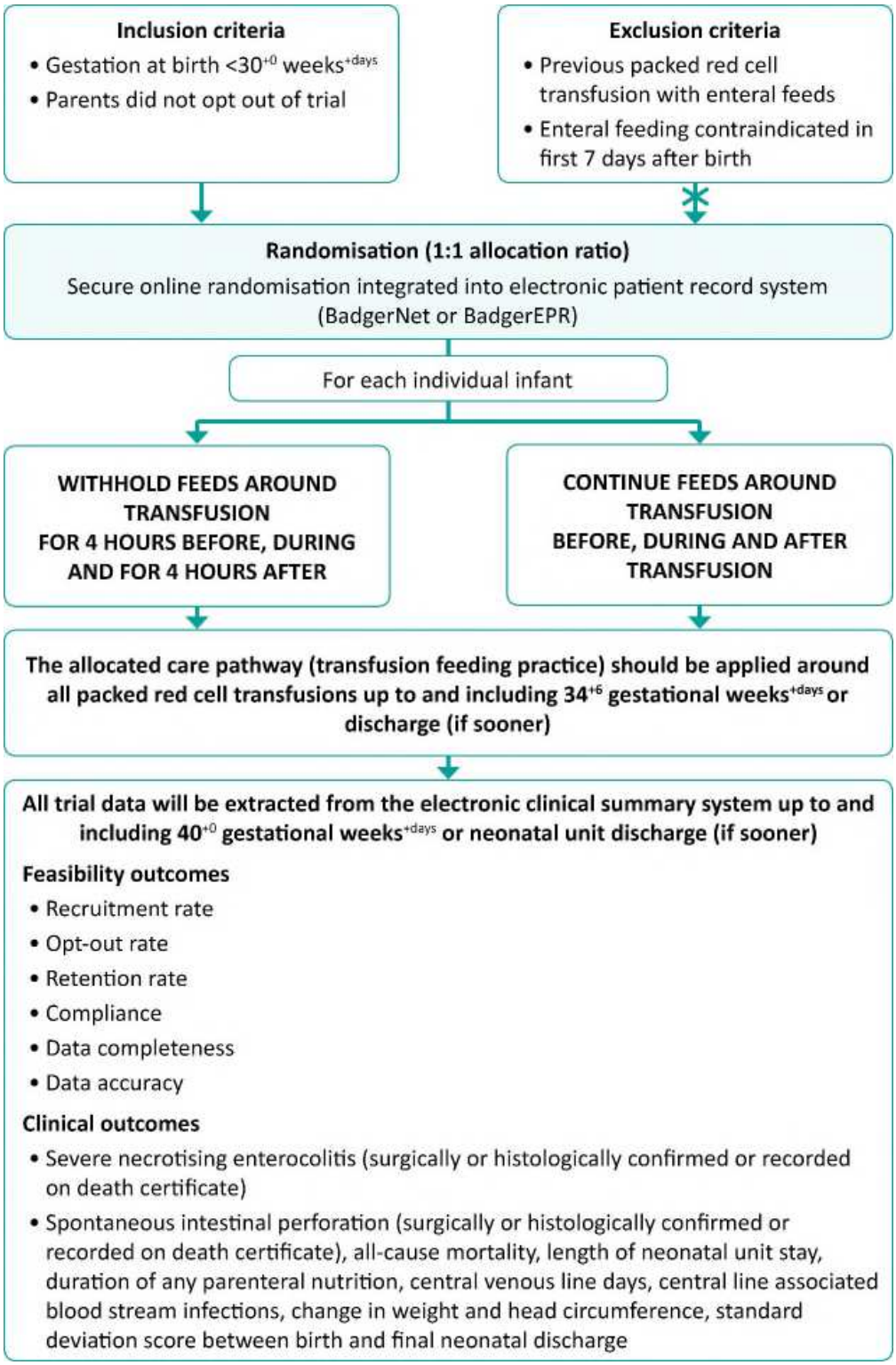
TRIAL SUMMARY

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
DESIGN	A randomised, controlled, unblinded, pragmatic, superiority pilot trial, embedded within an electronic patient record system (point-of-care trial), comparing two parallel care pathways
AIMS	Pilot trial objective: To demonstrate the feasibility and efficiency of a point-of-care trial approach embedded within an electronic patient record (EPR) system Clinical objective of planned main trial: To test whether the practice of withholding enteral feeds around packed red cell transfusion in preterm infants reduces the incidence of severe necrotising enterocolitis
POPULATION	Preterm infants (born less than 30^{+0} gestational weeks^{+days}) admitted to participating UK neonatal units
ELIGIBILITY	Inclusion criteria: • Preterm birth at less than 30^{+0} gestational weeks^{+days} (up to and including 29^{+6} gestational weeks^{+days}) Exclusion criteria: • 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) • Infants where enteral feeding is contraindicated in the first 7 days after birth (e.g. congenital abnormalities)
CARE PATHWAYS TO BE COMPARED	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)
OUTCOME MEASURES	Pilot trial endpoints: • Recruitment rate • Opt-out rate • Retention rate • Compliance • Data completeness of clinical endpoint data items • Data accuracy of clinical endpoint data items

	Secondary (clinical) endpoints: • Severe necrotising enterocolitis (surgically or histologically confirmed or recorded on death certificate) • Spontaneous intestinal perforation surgically or histologically confirmed or recorded on death certificate) • All-cause mortality • Total duration of neonatal care (days) • Duration of any parenteral nutrition (days) • Length of time with a central venous line in situ (days) • Number of central line associated blood stream infections (defined as per National Neonatal Audit Programme, NNAP, 2017 definition) • Growth: change in weight and head circumference for gestational age standard deviation score between birth and final neonatal discharge
DURATION	Follow-up and evaluation of outcomes will be up to and including 40^{+0} gestational weeks^{+days} or neonatal unit discharge (if earlier).

WHEAT TRIAL FLOWCHART



1. INTRODUCTION

1.1. BACKGROUND

Necrotising enterocolitis (NEC) is among the most devastating of neonatal diseases. UK population data from National Neonatal Research Database (NNRD) indicates that severe NEC (requiring surgery or resulting in death) affects about 5% of infants born at less than 30 gestational weeks, and has a mortality of about 33% (1); NEC is also a major cause of long-term gastrointestinal morbidity and the leading cause of paediatric short bowel syndrome (2). The inflammatory process extends the effects of the disease systemically, and affected infants are at substantially increased risk of neurodevelopmental impairment (3, 4). In England over 2012–13, 531 infants developed severe NEC and one third of these died of the disease (1).

A temporal association between red cell transfusion and the subsequent development of NEC was originally described in the 1980s (5), and continues to be described in observational studies (6). In comparison with classical NEC, transfusion associated NEC cases are anecdotally described as more severe (7) with higher rates of surgical intervention (8) and higher mortality (9, 10).

1.1.1. Proposed mechanisms linking transfusion and necrotising enterocolitis

The pathogenesis of NEC is not completely understood. It is believed that NEC arises from "an uncontrolled exuberant inflammatory response to bacterial colonization that characterises the intestine of the preterm infant" (11). The innate immune system, and specifically up-regulation of toll like receptor 4, mediate this inflammatory response (12), while altered commensal intestinal microbiota and impaired intestinal epithelial integrity are contributory. Factors that are believed to increase an infant's risk of NEC are those that alter the commensal intestinal flora (such as prolonged treatment with antibiotics, absence of human milk feeds), or impair mucosal integrity (such as prolonged absence of milk or formula feeding, or profound hypotension) (13).

Milk feeds during packed red cell transfusion may precipitate NEC by influencing mesenteric blood flow and thus intestinal barrier function. Mesenteric blood flow is increased in response to milk feeds (14, 15), and absence of this normal postprandial increase is seen in infants who subsequently develop NEC (16), leading to speculation that this relative gut hypoperfusion may predispose infants to NEC (16, 17).

Packed red cell transfusion results in a failure of the normal postprandial increase in mesenteric blood flow in preterm lamb (18) and piglet models (19), and in human preterm infants (7, 17, 20, 21). The cessation of milk feeds around the time of packed red cell transfusion may therefore be beneficial in limiting the influence on intestinal blood flow (22). This practice has not, however, been tested in a published randomised trial.

1.1.2. Potential adverse effects of interrupting milk feeds

Conversely, stopping milk feeds around blood transfusions among preterm infants at high risk of necrotising enterocolitis, may lead to harm. Interrupting milk feeding may prolong the time taken to reach full enteral feeds, which is associated with increased risk of invasive

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infection (23). Furthermore, in preterm infants, a higher number of days where feeds are withheld is associated with an increased risk of necrotising enterocolitis (24), raising the possibility that the intervention proposed to reduce transfusion associated necrotising enterocolitis (withholding milk feeds) may, in fact, lead to the very disease it is aiming to prevent.

1.1.3. Red cell transfusion in preterm infants

Preterm infants are among the most transfused patient groups; 90–95% of infants born at <30 weeks of gestation receive at least one blood transfusion (25); those transfused received a mean of 4 (range 1–27) transfusions during their neonatal unit stay (population level data from NNRD). Of note is that randomised trials aiming to reduce the number of packed red cell transfusions received by preterm infants, though succeeding in this aim, did not show any associated reduction in NEC (26, 27).

1.1.4. Evidence from non-randomised studies

There have been no adequately powered randomised studies that have examined the question "Does withholding feeds during transfusion reduce the occurrence of transfusion associated NEC?"

Non-randomised studies were recently reviewed by Jasani et al in September 2017 (28). This systematic review identified seven non-randomised studies, including 7,492 infants. Included studies were historical control studies and were therefore at high risk of bias, including regression to the mean and ascertainment bias. Pooled results from the identified non-randomised studies suggest that withholding feeds during the peri-transfusion period may reduce the risk of transfusion associated necrotising enterocolitis in preterm infants. The authors conclude that adequately powered randomised controlled trials are needed to confirm these findings.

1.1.5. Current randomised studies

Review of clinical trial registries (WHO ICTRP, searched 1/8/2017) identified two single centre randomised controlled trials examining enteral feeding around blood transfusion in preterm infants. Neither trial is powered to examine clinically relevant outcomes such as NEC.

1. FEEding DURing Red Cell Transfusion (FEEDUR): The effects of feeding on blood flow to the gut in preterm infants receiving red blood cell transfusion; ANZCTR identifier ACTRN12616000160437, Newborn Care Centre Royal Hospital for Women, Sydney, Australia. The primary outcome is a non-clinical outcome, cerebro-splanchnic oxygenation ratio measured using near infrared spectroscopy. The planned sample size is 60 infants; the trial is still recruiting.
2. Tx-TRAGI trial, ClinicalTrials.gov identifier NCT02132819, Zekai Tahir Burak Maternity and Teaching Hospital, Turkey. The primary outcome is increase in abdominal circumference and NEC defined using Bell's staging criteria (29). The planned sample size is 150 infants; the trial is still recruiting.

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1.1.6. Current practice

Considerable variation in current UK practice exists in relation to withholding enteral feeds during packed red cell transfusion in preterm infants, reflecting the limited evidence base for this approach. A 2011 electronic survey of UK neonatal units (68% response rate) demonstrated that 35% of UK units routinely withheld enteral feeds during packed red cell transfusion (30). We updated this survey in 2014 and found similar results; 106/163 neonatal units responded, 28% routinely withhold enteral feeds during transfusion, in 22% the decision to withhold feeds was left up to the individual clinician and 50% did not routinely withhold enteral feeds during transfusion. A survey carried out in the USA in 2009 recorded that 17% of American units practised withholding enteral feeds around blood transfusion (31).

1.1.7. Importance

If withholding enteral feeds around the time of packed red cell transfusion reduces the risk of NEC, then this simple practice will provide a way to reduce the mortality and long-term health and neurodevelopmental burden associated with this disease.

Conversely, given that human milk contains a number of growth factors and immunological agents, it is biologically plausible that episodes of withholding feeds in preterm might adversely affect intestinal integrity and development, and paradoxically increase the risk of NEC or poor growth. Given how widespread the practice of withholding enteral feeds is in the UK and internationally, demonstrating harm will mean that this practice can be safely discontinued.

1.1.8. Relevance

Prevention of NEC has been identified by service users and clinicians as the third most important treatment uncertainty in the field of preterm birth (32). The National Blood and Transplant Serious Hazards Of Transfusion (SHOT) report in 2012 and 2013 reported cases of NEC possibly associated with packed red cell transfusion and called for prospective studies to investigate a causal relationship (33, 34), and in 2016 transfusion associated NEC was identified as a research gap in transfusion medicine (35). There have been multiple published calls for a large scale randomised controlled trial from academics, clinicians (13, 20, 22, 36-39) and nursing professionals (40, 41).

1.2. RATIONALE FOR CURRENT TRIAL

1.2.1. Research question

Among preterm infants (Patient), does the practice of withholding enteral feeds around the time of blood transfusion (Intervention), compared with continued enteral feeding around the time of blood transfusion (Comparator), lead to a reduction in severe necrotising enterocolitis (Outcome)?

This is a pilot trial (not an internal pilot) to determine whether a large multi-centre trial addressing this research question is feasible, and whether clinical trial processes (identifying participants, randomisation and data collection) can be successfully integrated into existing

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neonatal Electronic Patient Record (EPR) systems: the BadgerNet clinical summary system, and the BadgerEPR full electronic patient record system.

The clinical question that underpins the WHEAT trial is an important source of clinical uncertainty in the United Kingdom and internationally, and has been identified as an important research priority by multiple groups. Because the substantive clinical outcome (necrotising enterocolitis) is rare, a trial powered to detect a clinically important reduction would need to be very large: larger than any previous randomised controlled trial among preterm infants carried out anywhere in the world. It is for this reason that the WHEAT pilot trial is evaluating the feasibility of using an existing neonatal EPR system to apply a point-of-care trial methodology.

A point-of-care trial embeds trial processes, including the identification, recruitment, randomisation and trial data collection into an existing data collection structure, in this case an existing neonatal EPR (the BadgerNet clinical summary system and the BadgerEPR full electronic patient record system). Applying a point-of-care trial methodology offers the potential for large improvements in efficiency, and hence the possibility of studying much larger participant numbers. However, feasibility and data quality have not yet been demonstrated for the UK neonatal EPR systems (BadgerNet and BadgerEPR) for the purposes of a point-of-care trial.

It is these feasibility questions that the WHEAT pilot trial will address, in preparation for a future trial that will be powered to address the clinically important outcome necrotising enterocolitis.

2. TRIAL OBJECTIVES

	Objective	Outcomes
Feasibility	To determine whether a point-of-care trial methodology (embedding trial processes and data collecting within an existing EPR system) is feasible for an individually randomised trial that includes preterm infants delivered at less than 30^{+0} gestational $weeks^{+days}$, carried out in NHS neonatal units. Outcomes will be measured up to and including 40^{+0} gestational $weeks^{+days}$ or neonatal unit discharge (if sooner).	Recruitment rate: Percentage of eligible cases where parents agree to trial involvement and the infant is randomised. Opt-out rate: Percentage of eligible cases where parents opted out of their infant being involved in the trial. Retention rate: Percentage of recruited infants who complete follow-up. Compliance: Percentage of cases where the allocated care pathway was adhered to. Data completeness: Percentage of recruited infants where trial data items are complete.

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		Data accuracy: Percentage of recruited infants where data items are correctly recorded when compared to source data.
Clinical	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 Outcomes will be measured up to and including 40^{+0} gestational $weeks^{+days}$ or neonatal unit discharge (if sooner).	Necrotising enterocolitis: Histologically or surgically confirmed, or recorded in part 1 of the death certificate Spontaneous intestinal perforation: Histologically or surgically confirmed, or recorded in part 1 of the death certificate All-cause mortality Length of neonatal unit stay: in days and including all levels of care Duration of any parenteral nutrition: in days Number of days with a central venous line in situ Number of central line associated blood stream infections: defined according to NNAP criteria Growth: change in weight and head circumference for gestational age standard deviation score between birth and final neonatal discharge

3. TRIAL DESIGN

3.1. OVERALL DESIGN

The WHEAT trial is a randomised, controlled, unblinded, multi-centre, superiority pilot trial of two care pathways. The primary metrics of feasibility are recruitment, data completeness and data accuracy. The clinical outcomes include mortality and NEC. Groups will be randomised with a 1:1 allocation ratio with varied block sizes and stratified within neonatal unit by gestational age at birth and infant sex. Trial processes will be embedded within neonatal EPR systems and all outcome data will be extracted from data that is routinely recorded within the existing neonatal EPR systems (BadgerNet and BadgerEPR), and held in the National Neonatal Research Database.

The WHEAT trial is a stand-alone pilot trial to demonstrate that the point-of-care methodology applied in WHEAT is efficient and results in complete and accurate trial data.

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3.2. DURATION

Recruitment: 9 months

Randomised care pathway phase: Until all trial infants have finished the randomised care pathway (all enrolled infants are older than a gestational age of 34^{+6} gestational weeks^{+days})

Follow-up phase: Until all trial infants have finished the follow-up period (40^{+0} gestational weeks^{+days} or neonatal unit discharge, if earlier)

Number of infants to be recruited:

- Estimated number of eligible infants in 2 neonatal networks recruiting to the WHEAT trial: in the region of 375 (annual number of <30 gestational week infants cared for in the proposed trial networks in 2016 was 500, from NNRD data)
- Estimated recruitment rate of 65–70%
- Estimated recruitment over 9 months of 250

3.3. GEOGRAPHICAL AREA

The WHEAT trial will recruit patients from neonatal networks in England.

4. PARTICIPANTS

4.1. INCLUSION CRITERIA

1. Preterm birth at less than 30^{+0} gestational weeks^{+days} (up to and including 29^{+6} gestational weeks^{+days})
2. Parents did not opt out of trial participation

4.2. 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)

Infants enrolled in other interventional studies are eligible for participation in the WHEAT trial unless contraindicated (Chief Investigators to discuss on a case-by-case basis).

Use of any concomitant medication used for neonatal clinical care or as part of an interventional research trial is permitted during the WHEAT trial.

4.3. WITHDRAWAL CRITERIA

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/or follow-up.

The attending clinician may withdraw the infant from the allocated pathway of care if they consider this to be in the best interest of the infant's health and well-being.

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4.4. SETTING

Neonatal units in England caring for very preterm infants.

4.5. INTER-HOSPITAL TRANSFER

Participating neonatal units will be either:

1. A recruiting site where infants may be recruited, randomised, and commence participation in the trial
2. A continuing care site where the allocated care pathway (withhold feeds or feed as usual during transfusion) will continue to be followed and routine data collected if a participating infant is transferred in from a recruiting site

From recent experience, about 50% of participating infants are likely to be transferred from their recruiting neonatal care unit to a continuing care site.

4.6. END OF TRIAL

The trial will end when the last trial infant finishes follow-up (reaches 40^{+0} gestational $weeks^{+days}$ or neonatal unit discharge)

5. PATHWAYS OF CARE TO BE COMPARED

5.1. PATHWAYS OF CARE

Both comparator pathways of care are standard in the UK; there is no "experimental care pathway". The WHEAT trial is a comparative effectiveness trial. The two care pathways that will be compared are

1. Withholding feeds around transfusion
2. Continuing feeds around transfusion

Infants will remain allocated to the same care pathway until 34^{+6} $weeks^{+days}$ gestational age.

5.1.1. Withholding feeds around transfusion

Within the *withholding feeds around transfusion* pathway of care, all enteral feeds will be discontinued (the infant will be placed nil by mouth) for a period of 4 hours prior to packed red cell transfusion, during the packed red cell transfusion and until 4 hours post packed red cell transfusion.

During the period of this pathway of care (approximately 12 hours), hydration and blood glucose will be maintained according to local practice, commonly by provision of parenteral nutrition or intravenous dextrose.

Four hours after the red cell transfusion has finished feeds will be restarted in the manner in which they were being received prior to the decision to transfuse.

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5.1.2. Continuing feeds around transfusion

Within the *continuing feeds around transfusion* pathway of care, 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.

5.1.3. Justification for the duration of the withholding feeds arm

Where withholding milk feeds around packed red cell transfusion is practised, there is no consensus regarding the duration of withholding feeds. The most recent UK data show that among neonatal units where milk feeds were routinely stopped for transfusion, 66% stopped feeds only for the duration of the transfusion and the remainder adjusted feeds for a variable period of time ranging from 4 hours before to 4 hours after transfusion (30). In the USA, among neonatal units where milk feeds are stopped, 82% withheld feeds before transfusion and 71% after (the duration was not recorded) (31).

Similar variation exists in studies where the association between withholding feeds and NEC has been examined using historical cohorts. DeRienzo et al (39) stopped enteral feeds 4 hours prior to and for the duration of a transfusion and restarted enteral feeds at 50% volume for 12 hours before advancing to the original volume of feeds. Feeds were omitted for 2–4 hours before and after as well as during packed red cell transfusions by Del Vecchio et al (42), and for 4 hours before and 4 hours after by Perciaccante et al (43), while in the study by El-Dib et al (22) feeds were omitted only for the duration of the transfusion. In the only registered randomised controlled trial (44) feeds are omitted from 4 hours prior until 24 hours post transfusion.

One rationale for withholding enteral feeds before packed red cell transfusion is that unless feeds are discontinued in advance, milk within the stomach will transit into the small intestine (the site most commonly affected by NEC) during packed red cell transfusion, potentially influencing gut haemodynamics. The median oro-caecal transit time (a measure of both gastric emptying and small intestinal transit time) in preterm infants (10 infants, median gestational age at birth 28.9 weeks, median age at examination 19 days) is 3.1 hours; therefore withholding feeds for 4 hours prior should result in passage of milk through the small intestine before transfusion (45).

The rationale for withholding feeds after packed red cell transfusion is less clear. Intestinal haemodynamic effects may persist following blood transfusion, as mesenteric blood flow remains reduced for at least four hours after transfusion in preterm infants with a haemodynamically significant patent ductus arteriosus (46), but the total duration is unclear: no significant differences are detectable by 48–96 hours post transfusion (17).

In the light of considerable variation in practice and incomplete scientific knowledge, a survey was undertaken of neonatal units within the UK Neonatal Collaborative (all 163 neonatal units in England). In total 122 neonatal units (75%) responded, of which 112 expressed an interest in taking part in the WHEAT trial. The most acceptable duration to withhold feeds was for 4 hours prior to transfusion (56% of responders) and for 4 hours following transfusion (60% of responders).

Combining data from available scientific studies, existing practice and clinician preference has led to the decision to define the *withholding feeds around transfusion* pathway of care

as “withholding milk feeds for 4 hours prior to, during, and for 4 hours following transfusion”.

5.1.4. Justification for the continue feeds arm

In both the UK (30) and the USA (31) the most common practice is to continue milk feeds at the previous rate prior to, during and following transfusion, justifying this practice for the control group.

5.2. CONCOMITANT 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 packed red cell transfusion guidelines. Data will be collected about pre-transfusion haemoglobin level for trial participants.

Other concomitant care, including speed of increase of enteral feeds and choice of milk, for both the *withholding feeds around transfusion* pathway and the *continuing feeds around transfusion* pathway of care will be according to locally defined practice.

5.2.1. Feed intolerance

In situations where enteral feeds intolerance is manifest, in either the *withholding feeds around transfusion* pathway or the *continuing feeds around transfusion* pathway, during the period of packed red cell transfusion (for example, vomiting) management will be in accordance with clinical practice considered appropriate by the local clinical team.

6. TRIAL OUTCOME MEASURES

6.1. FEASIBILITY OUTCOMES

1. Recruitment rate: Rate and percentage of eligible cases where parents agree to trial involvement and the infant is randomised in the WHEAT trial
2. Opt-out rate: Percentage of eligible cases where parents opt out of their infant being involved in the trial
3. Retention rate: Rate and percentage of recruited cases where outcome data are available up to the end of the follow-up period (40^{+0} gestational weeks^{+days} or neonatal unit discharge, if earlier)
4. Compliance: Rate and percentage of recruited cases who correctly received their allocated care pathway around all packed red cell transfusions between randomisation and a gestational age of 34^{+6} gestational weeks^{+days}
5. Data completeness: Percentage of eligible cases where trial data items are complete
6. Data accuracy: Percentage of recruited cases where the following data items are correctly recorded when compared to source data (clinical notes where available or electronic patient record data)
    a. Severe necrotising enterocolitis – histologically or surgically confirmed, or recorded in part 1 of the death certificate, all infants with this outcome will have source data verified. All infants recorded as being transferred to stand-

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alone surgical units (e.g. Birmingham Children's Hospital or Great Ormond Street Hospital) will have their source data verified (false-positive rate).

b. All-cause mortality (all infants with this outcome will have source data verified).
c. All infants with necrotising enterocolitis recorded as a diagnosis (any diagnosis of necrotising enterocolitis, of any severity) will have their source data verified to ensure that they do not meet the criteria for severe necrotising enterocolitis or died prior to neonatal unit discharge (assessing false-negative rate).
d.

6.2. CLINICAL OUTCOMES

1. Severe necrotising enterocolitis: histologically or surgically confirmed, or recorded in part 1 the death certificate. These infants will be identified as described in (47), a process which will include infants recorded as being transferred for surgery
2. Spontaneous intestinal perforation: histologically or surgically confirmed, or recorded in part 1 the death certificate.
3. All-cause mortality
4. Total duration of neonatal care in days: including all levels of care (intensive care, high dependency care, special care and ordinary 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 blood stream infections (defined according to National Neonatal Audit Programme (NNAP) 2017 definition)
8. Growth: change in weight and head circumference for gestational age standard deviation score between birth and final neonatal discharge

7. RANDOMISATION AND ENROLMENT PROCEDURE

7.1. RANDOMISATION OR REGISTRATION PRACTICALITIES

Potential participants will be identified through the existing neonatal EPR systems that are widely used across England; BadgerNet (a clinical summary system) or BadgerEPR (a complete electronic patient record system).

Baseline data for all infants admitted to neonatal units in the UK are routinely entered into the EPR *admission summary* as part of normal clinical care. These data are updated in real-time and held securely on BadgerNet and BadgerEPR servers.

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 and link to the parent information leaflet.

The EPR system will use data (neonatal unit, gestational age and sex) entered as part of the *admission summary* to stratify infants.

7.2. CONSENT

Because both the care pathways that are being compared are part of standard UK practice, WHEAT is using a simplified model of consent. This means that parents will have the WHEAT trial explained to them and will be asked to "opt out" if they do not want their infant to be randomised and enrolled in the trial.

Parents will be approached shortly after their infant is admitted to the neonatal unit (in most cases within the first 24 hours). There is no upper time limit as to when trial discussions can take place. Parents will be able to opt out of the WHEAT trial at any point.

Neonatal health professionals will be prompted within the EPR to explain WHEAT to parents of eligible infants and to provide them with an information leaflet. The EPR will subsequently ask the health care professional whether the WHEAT trial and the "opt-out" process have been fully explained to the parents. If parents "opt out" this will be recorded in the EPR. If parents do not "opt out", i.e. are happy for their infant to take part in WHEAT, randomisation will occur through the EPR.

Enrolment of the infant and the allocation will be notified to the local team through the EPR. Enrolment can take place at any time during an infant's neonatal stay providing they meet the inclusion criteria. At the point of randomisation, the trial CI and the Clinical Trials Unit will be automatically notified electronically. Participating infant data will be downloaded regularly to the Neonatal Data Analysis Unit (NDAU).

Because of the opt-out nature of WHEAT there will not be a signed consent form. Prior to randomisation the EPR will ask the health professional to confirm that the parents have been provided with the trial information, have had the trial explained to them, have had an opportunity to ask questions and have not expressed the wish to "opt out". This will be recorded electronically within the EPR.

Due to the common nature of packed red cell transfusion in the trial population (infants born at $<30^{+0}$ gestational weeks^{+days}), health professionals will explain the WHEAT trial and opt-out process shortly after birth (in most cases within the first 24 hours). A minority of infants will not receive a packed red cell transfusion during their neonatal unit stay (estimated to be <5% of eligible infants). These will not be included in the main analysis population of clinical outcomes.

7.3. RANDOMISATION

Infants will be randomly assigned to either pathway of care in a 1:1 allocation ratio as per a computer generated randomisation sequence (stratified by neonatal unit) using permuted blocks of various sizes with stratification by gestational age and infant sex within neonatal unit. The block sizes will not be disclosed to ensure allocation concealment.

Stratification will be by neonatal unit of enrolment and using the following categories:

1. Gestational age at birth
    - $<28^{+0}$ weeks^{+days}
    - 28^{+0} to 29^{+6} weeks^{+days}
2. Infant sex

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7.3.1. Randomisation of multiple births

Infants that are part of a multiple birth set (twins, triplets or higher order multiples) will be randomised as a multiple – i.e. they will all be allocated to the same pathway of care (withholding feeds around transfusion or feeding as usual around transfusion). This decision is based upon feedback from parent representatives, parent organisations including Bliss and TAMBA (Twins and Multiple Births Association) and international research involving parents and adult ex-preterm twins (48).

7.3.2. Allocation concealment

Infants will be randomised using an online secure central randomisation service which will be embedded into the existing neonatal EPR systems (BadgerNet and BadgerEPR). Randomisation will occur within the EPR to ensure allocation concealment. A unique identifier will be generated within the EPR for each infant to enable trial data to be extracted from routinely entered clinical data.

7.4. BLINDING

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

8. ADVERSE EVENTS

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.

8.1. DEFINITIONS

8.1.1. Serious Adverse Event (SAE)

Adverse events are defined as serious if they:

- Result in death
- Are life-threatening
- Require inpatient hospitalisation or prolongation of existing hospitalisation
- Result in persistent or significant disability/incapacity, or
- Are a congenital anomaly/birth defect

The term “life-threatening” 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).

8.2. REPORTING PROCEDURES

8.2.1. Recording SAEs

Non-serious adverse events will not be routinely recorded as the trial is comparing two accepted pathways of care that are both widely practised in the United Kingdom.

8.2.2. Reporting foreseeable SAEs

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

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 the SAEs associated with the allocated pathway of care must be reported to the NPEU CTU by a member of site staff within 24hours of becoming aware of the event. Site staff may email or fax a completed paper SAE form to NPEU CTU. 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 NPEU CTU by telephone and will follow up this notification with an SAE report form by fax or email as

soon as possible. If following the reporting of an SAE additional information becomes available, a new SAE form should be completed.

The NPEU CTU will forward a copy of the SAE form to the Chief Investigator (CI) as soon as possible on receipt. The CI will assess whether the SAE was as a result of trial related activities (related). All related and unexpected SAEs 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 unforeseen SAEs and the SAEs associated with the allocated pathway of care will be reported to the sponsor and related and unforeseeable SAEs will be reported to the DMC and relevant R&D offices.

Contact details for reporting SAEs

Fax: 01865 289740, Email: WHEAT@npeu.ox.ac.uk

Please scan and email or fax SAE forms to the WHEAT Trial Coordinating Centre

Tel: 01865 617923 (Mon to Fri 09.00–17.00)

9. ASSESSMENT AND FOLLOW-UP

Follow-up will be until neonatal unit discharge or 40^{+0} gestational $weeks^{+days}$, whichever is first. There will be no data collection after neonatal unit discharge.

9.1. DATA COLLECTION BEFORE DISCHARGE

All outcome data for this trial are routinely recorded clinical items held in the patient notes and existing neonatal EPR systems (BadgerNet and BadgerEPR). No additional blood or tissue samples are required for this trial.

Clinical information will be extracted from routinely recorded clinical data entered at the point of care by health professionals into the existing EPR (BadgerNet or the BadgerEPR).

10. STATISTICS AND DATA ANALYSIS

There is no predefined sample size for this pilot trial. Recruitment (absolute numbers and the rate) will be a primary outcome for the pilot trial. 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.

As this is a pilot trialfocusing on feasibility outcomes rather than clinical outcomes, no formal sample size calculation was conducted and the target recruitment was estimated based on practical and realistic assumptions. The pilot trial aims to provide inference for the sample size calculation of the main trial.

As this is a pilot trial, the sample size is not powered to detect any treatment differences; therefore, no formal hypothesis testing will be conducted.

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10.1. DESCRIPTIVE STATISTICS

All baseline and feasibility outcomes will be analysed descriptively. All continuous and normally distributed data will be presented as means and standard deviations and non-normally distributed data will be presented by medians along with 25th and 75th centiles and minimum and maximum values. All categorical and dichotomous variables will have frequencies and percentages presented.

10.2. COMPARATIVE STATISTICS

Feasibility results, including recruitment, data quality and data completeness will be reported as rates or proportions with 95% confidence intervals.

Although no formal hypothesis testing will be conducted, estimated differences in clinical outcomes of efficacy will be calculated.

Data and all essential documentation will be stored for a minimum of 25 years after the completion of the trial, including the follow-up period.

11. MONITORING

11.1. RISK ASSESSMENT

Prior to trial commencement, the NPEU CTU performed a risk assessment of the trial that will be reviewed at regular intervals according to its own Standard Operating Procedure. This trial is a comparison of standard treatments, which does not include a drug treatment, so does not fall under the auspices of the MHRA. Based on the assessment, this trial poses minimal risk, no greater than normal care within a neonatal intensive care unit, to either the participants or the health care professionals delivering the trial.

11.2. MONITORING AT TRIAL COORDINATING CENTRE

Central monitoring will be used at NPEU CTU 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.

11.3. MONITORING AT LOCAL SITE

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.

Trial data accuracy and completeness are outcomes for this pilot trial. Source data verification will be undertaken by the WHEAT trial team for clinical outcome data items, stratification data items, and allocation data items as outlined in section 3.1, trial outcome measures.

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12. REGULATORY ISSUES

12.1. ETHICS APPROVAL

The trial will only start after gaining approval from the Health Research Authority (HRA), and a National Research Ethics Service (NRES) registered ethics committee. Additionally, NHS Trust Research and Development (R&D) Offices will review the trial for Capacity and Capability for individual trial sites. The 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 trial will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. This trial will adhere to the principles outlined in the NHS UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, relevant Data Protection regulations, the principles of GCP and other regulatory requirements as appropriate.

12.2. CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the trial and is registered under relevant Data Protection regulations.

12.3. INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this trial.

12.4. SPONSOR

Imperial College London will act as the Sponsor for this trial. Delegated responsibilities will be assigned to the NHS Trusts taking part in this trial.

This protocol describes the WHEAT trial and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial.

12.5. FUNDING

The United Kingdom Medical Research Council (MRC) are funding this trial. Parents will not be given any financial or material incentive or compensation for enrolling their infants in this trial.

12.6. AUDITS

The trial may be subject to inspection and audit by Imperial College London under their remit as Sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research.

13. TRIAL MANAGEMENT

The trial will be supervised on a day-to-day basis by the Project Management Group (PMG). This group reports to the TSC which is responsible to the trial Sponsor.

The core PMG will consist of Chris Gale (Chief Clinical Investigator), Sena Jawad (Trial Statistician) and NPEU CTU staff including:

- CTU Director
- Senior Trials Managers
- Head of Trials Programming

The Clinical Investigators' Group, (CIG) will meet regularly. This will comprise all members of the co-applicant group and the members of the core PMG.

The trial will be overseen by a Trial Steering Committee (TSC) consisting of an independent chair and at least two other independent members. The Chief Investigator and CTU Director will also sit on the TSC.

A Data Monitoring Committee (DMC) independent of the applicants and of the TSC will review the progress of the trial as agreed and provide advice on the conduct of the trial to the TSC and (via the TSC) to the Sponsor. The DMC will act according to its Charter, which will be agreed at its first meeting.

14. PUBLICATION POLICY

The success of the trial depends on a large number of neonatal health professionals and trials unit staff. Credit for the trial findings will be given to all who have collaborated and participated in the trial including all local coordinators and collaborators, members of the trial committees, the NPEU CTU, and trial staff.

Authorship at the head of the primary results paper will take the form [name], [name]… and [name] on behalf of the WHEAT Trial Collaborative Group, where named authors form part of the writing committee. The writing will be the responsibility of the writing committee which it is anticipated will include all of the investigators. Named authors will be listed in the following order: individual responsible for completing the first draft of the paper, lead analyst, all other members of the writing committee in alphabetical order, lead supervising author. All other contributors to the trial will be listed at the end of the report, with their contribution to the trial identified.

Those responsible for other publications reporting specific aspects of the trial, such as detailed microbiological outcomes, may wish to utilise a different authorship model. Decisions about authorship of additional papers will be discussed and agreed by the trial investigators and the TSC.

Full details of the trial will be made available to parents of infants enrolled in the trial through the trial website: www.npeu.ox.ac.uk/WHEAT.

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RECORD OF CHANGES

Version Stage	Versions No	Version Date	Protocol updated & finalised by	Detail the reason(s) for the protocol update
V2.0 26.07.18	V 1.0	24.04.18	PMG	Amendment 1 (substantial): Change of secondary clinical end points from weight (for gestational age at NICU discharge) to growth (change in weight and head circumference for gestational age between birth and NICU discharge). Additional text clarifying collection of pre-transfusion haemoglobin levels (section 5.2 concomitant care) Changes to source data verification (SDV) percentages (section 6.1). Changing review of NEC cases from 10% of cases to all cases and removing SDV on 5% of cases where NEC is not reported. Clarification that there are no upper limits for consent and enrolment Clarification on why no form sample size calculations are conducted and removing details about formal hypothesis testing for clinical outcomes. Adding ISRCTN number Formatting text throughout document

APPENDIX 1 - Summary of investigations, treatment and assessments

	PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			**Close-out**
TIMEPOINT	**After birth, before allocation**	**0**	**Transfus-ion 1 (t_1)**	**t_2**	**t_3, etc.**	**Discharge from neonatal unit**
ENROLMENT						
Eligibility screen	X					
Informed "opt-out" consent	X					
Allocation		X				
COMPARATOR PATHWAYS OF CARE						
Withholding feeds			X	X	X	
Continuing feeds						
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 – no involvement of participant					
Other variables	Collected from routine data extracted by the NNRD – no involvement of participant					

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