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Sponsor Protocol Number:	22IC7569

Trial Procedures Guide

(Study Specific Procedures Manual)

WHEAT Trial

IRAS 309894

- **Patient Identification & Eligibility Assessment**
- **Approach and Consent**
- **Co-Enrolment**
- **Randomisation**
- **Trial Intervention Procedures**
- **Safety Reporting**
- **Incident (Protocol Deviation/Violation) Reporting**

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Approved by: **Name:**	**Title:**	**Signature:**
Christopher Gale	**Chief Investigator**	

Contents

Associated Documents

Document Title:	Current Version and Date:
WHEAT Trial Protocol	V1.3 13 JUN 2023
WHEAT Parent Information Sheet	V2.0 21 Jun 2022
WHEAT Opt-Out Consent Guidance	V2.0 19 Jun 2023
WHEAT Protocol Deviation/Protocol Violation (Incident) Report Form	V1.0 04 Oct 2022
WHEAT Safety Reporting Procedures Manual (Sites)	V2.0 20Oct 2022
Screening & Enrolment Log	V1.1 19 Jan 2023
Paper Notes – Eligibility Labels	V1.0 04 Oct 2022
Paper Notes – Consent Labels	V1.0 04 Oct 2022
Cot Cards – Eligibility	V1.0 04 Oct 2022
Cot Cards – Continue Arm	V1.0 04 Oct 2022
Cot Cards – Withhold Arm	V1.0 04 Oct 2022
Paper Notes Randomisation Labels – Continue Arm	V1.0 04 Oct 2022
Paper Notes Randomisation Labels – Withhold Arm	V1.0 04 Oct 2022
WHEAT Summary Flowchart	V2.0 22 Jun 2023

1. Introduction

The purpose of this document is to provide clarity on the research procedures and activities involved in the following aspects of the WHEAT Trial **for recruiting sites:**

- Patient Identification & Eligibility Assessment
- Parent/Guardian Approach & Consent
- Randomisation
- Trial Intervention Procedures
- Data Collection in Badger (both BadgerNet EPR and Badger Summary)
- Incident Reporting

2. Scope

This procedure manual is applicable to all delegated personnel working on the WHEAT Trial at all **recruiting sites.**

NB. It is not the intention that this manual be read as a standalone document and the current version of the protocol and associated guidance documents should also be read in conjunction.

3. Abbreviations

AE	Adverse Event
CI	Chief Investigator
eCRF	(electronic) Case Report Form
EDC	Electronic Data Capture
ICTU	Imperial Clinical Trials Unit
PI	Principal Investigator
SAE	Serious Adverse Event
SSPM	Study Specific Procedure Manual

4. Responsibilities

Chief Investigator (CI)	• Review the SAE reports form from site • Determine whether SAE is related to the trial/trial-related activities • Provide advice and guidance to participating sites where required
Principal Investigator (PI)	• Take overall responsibility for the trial at the site • Ensure facilities and staff resources and education are appropriate to carry out the trial • To train members of the site team in the trial intervention and procedures • Delegate tasks responsibly and ensure these are documented • Be available to give advice, support and to sign documents as required • Confirming patient eligibility for the trial • Discussing the trial with parent(s)/guardian(s) and outlining the opt-out consent process • Patient randomisation • Ensuring all members of the site research team adhere to the trial protocol • Ensuring accurate data is entered into BadgerNET Summary/BadgerNET EPR • Signing-off documentation i.e. protocol deviation/violation report forms
Study Physician/Sub-Investigator	• Duties delegated by the PI • Confirming patient eligibility for the trial • Discussing the trial with parent(s)/guardian(s) and outlining the opt-out consent process • Patient randomisation • Ensuring accurate data is entered into BadgerNET Summary/BadgerNET EPR
Study Nurse/Coordinator	• Duties delegated by the PI. • Discussing the trial with parent(s)/guardian(s) and outlining the opt-out consent process • Ensuring accurate data is entered into BadgerNET Summary/BadgerNET EPR • Patient randomisation • Documenting protocol deviations/violations and ensuring PI sign-off
Study Manager/ Monitor	• Ensure facilities and staff resources and education are appropriate to carry out the trial • Provide sites with all relevant documentation and training to enable them to conduct the trial • Monitor progress of sites (recruitment, data entry)

	• Monitor sites' compliance with the protocol through central, remote and on-site monitoring and assessment of protocol deviations/violations • Be available to give advice and support to the research team

5. References

See 'Associated Documents' on page 3.

6. Procedures

6.1. Patient Identification & Eligibility Assessment

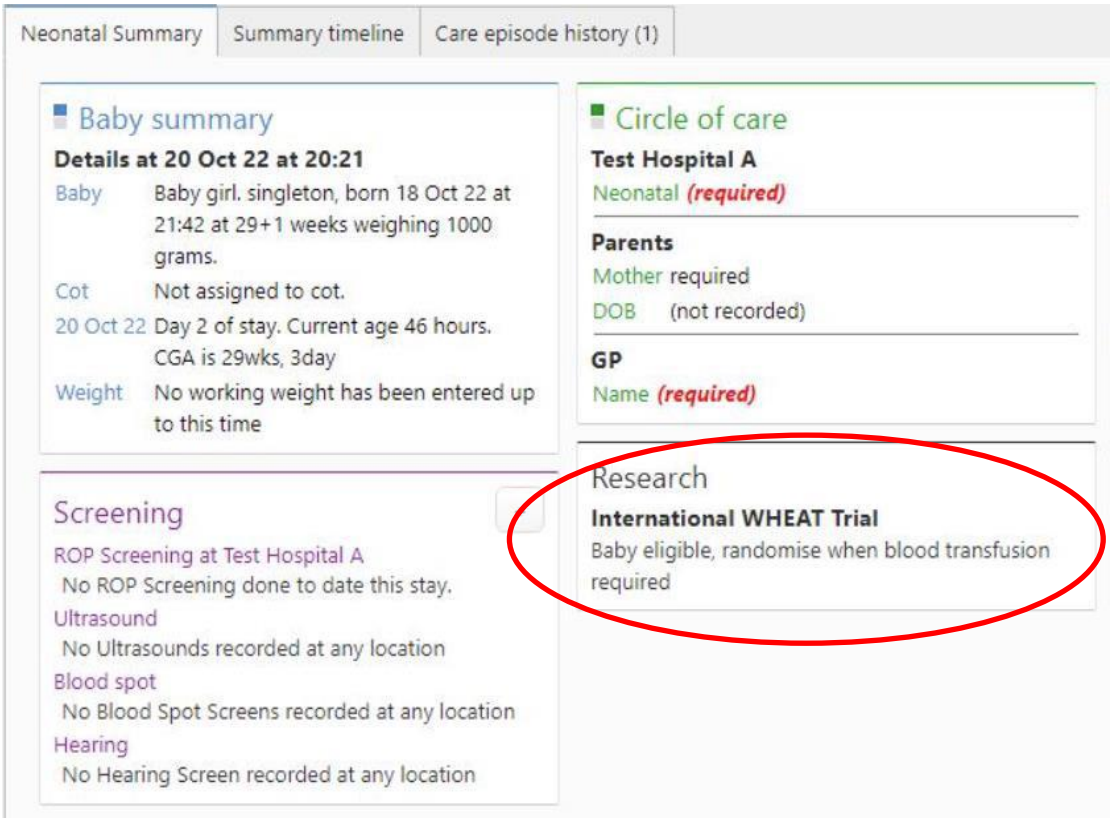
Patient Identification

Babies eligible to take part in the WHEAT trial are automatically partially identified, based on the gestational age of the baby at birth, through BadgerNET Summary/BadgerNET EPR and the system has built-in alerts to notify you when a baby is potentially eligible for the trial.

- BadgerNet will display the following message in the research block if the baby meets the following inclusion criteria:

  - <30+0 weeks gestation at birth **AND**
  - <35+0 weeks corrected age

Below is a screenshot of the eligibility alert generated by the BadgerNET Summary/BadgerNET EPR system:



Note that BadgerNET will flag a baby as eligible even if they do not yet require a blood transfusion. In this instance, please confirm the eligibility and present the trial information to the parents/guardians – this will save time at the point of randomisation and prevent babies from being 'missed'.

Eligibility Assessment

- You must still check the exclusion criteria according to Protocol V1.3, when seeing the eligibility flag on Badger, to fully determine the baby's eligibility
- Enrolment can take place at any time during an infant's neonatal stay providing they meet the eligibility criteria (below)
- Please note that babies will only be randomised to a WHEAT intervention arm when they require a blood transfusion, but please confirm eligibility and provide trial information to the parents/guardians ahead of this.

WHEAT Trial Eligibility Criteria

Inclusion Criteria

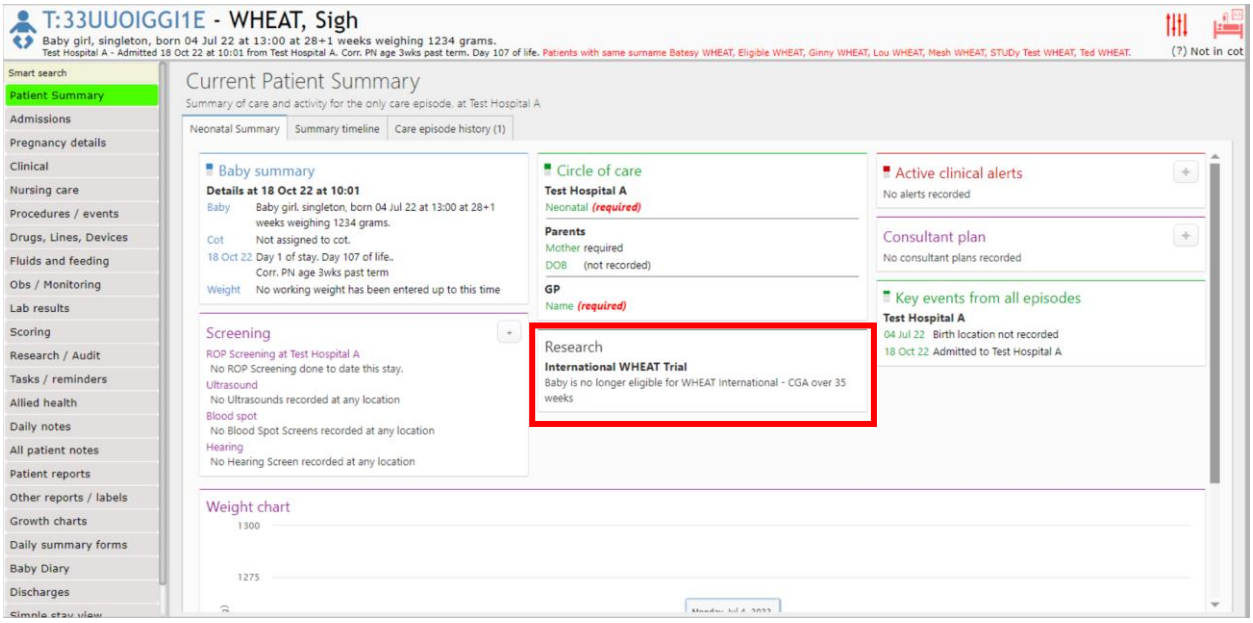
- Preterm birth at <30+0 gestational weeks + days

Exclusion Criteria

- Parent(s) opt-out of trial participation.
- Packed red cell transfusion with concurrent enteral feeds prior to enrolment. ***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***
- 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***.
- Previous episode of necrotising enterocolitis (NEC) or spontaneous intestinal perforation (SIP) prior to first packed cell transfusion.

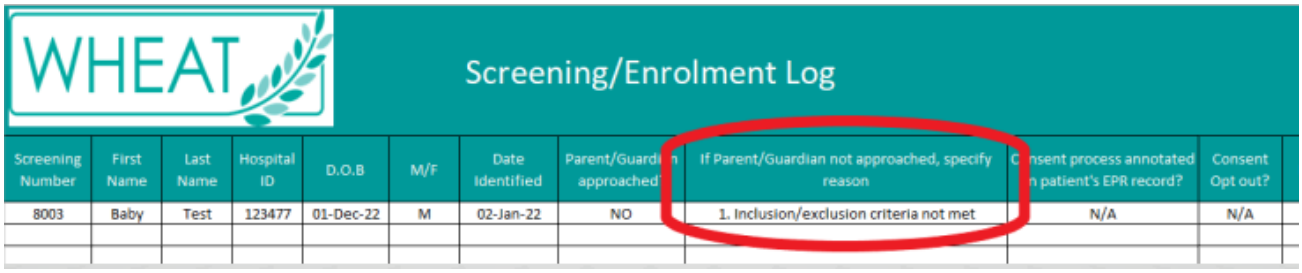
- The Badger system has been configured to partially assess babies for eligibility and for the system to generate an alert once an eligible baby has been identified.
    - ***Badger uses routinely-entered clinical gestational age data from the baby's admission summary in EPR to make an assessment of their suitability for the WHEAT Trial***
    - ***Please check the exclusion criteria when seeing the eligibility alert in Badger***
    - ***Some babies may have other reasons why they are not eligible for the WHEAT trial – these will be assessed at randomisation***

Babies can only be randomised if they are ≤34+6 (weeks+days) corrected gestational age. If a baby initially met the eligibility criteria (p.8) and participation was discussed with parents but sufficient time has lapsed such that the baby is now ≥35 weeks CGA, then Badger will display the following message on the *Summary* view:



- If you have any doubts about the eligibility of a baby, speak with the PI in the first instance before escalating to the WHEAT Trial Manager/Monitor via WHEAT@imperial.ac.uk

- The eligibility assessment of each baby identified must be recorded on the WHEAT Screening & Enrolment Log:



Screening/Enrolment Log

Screening Number	First Name	Last Name	Hospital ID	D.O.B	M/F	Date Identified	Parent/Guardian approached?	If Parent/Guardian not approached, specify reason	Consent process annotated in patient's EPR record?	Consent Opt out?
8003	Baby	Test	123477	01-Dec-22	M	02-Jan-22	NO	1. Inclusion/exclusion criteria not met	N/A	N/A

6.2. Approach and Consent

- Once a baby eligible for WHEAT has been flagged, approach the parent/guardian with the *Patient Information Sheet (PIS)*. A copy of this is available through Badgersystem, and a copy was sent to your site during set-up, so please make sure you have saved a copy of this on your files and you are using the current version.

- **Please provide WHEAT trial information to the parents/guardians if you encounter an eligible baby even if they do not yet require a blood transfusion. This will allow for any discussions that parents may wish to have about the trial to occur in advance and allow time for parents to opt-out of their baby be enrolled into the WHEAT trial if they so choose.**

- You must have received training on the trial to take consent from parents/guardians and have completed the WHEAT training (either by attending the SIV or from your PI). If you have not received trial training, or are unsure of what to do, please speak to your Principal Investigator and/or Research Nurses/Midwives before approaching parents.

- Babies eligible for the trial are automatically opted-in to the research unless parents specifically opt-out for their baby, which is an unusual but ethically-approved method of enrolment for this trial. Therefore, there is **no informed consent form for the trial.**

- Parents must be informed about the WHEAT trial – this can be done by giving them the PIS and through the WHEAT trial posters that should be displayed on the unit, especially in parent facing areas (like the expressing room).

- Please ensure you discuss the trial with the parent/guardian when asked to give them the opportunity to consider their baby's participation in the WHEAT Trial. If the parent(s) decide to opt-out, it must be made clear that their baby will not be enrolled in the trial and therefore will receive local standard of care.

- The Parent Information Sheet for the trial has been translated into the following languages and copies are available on the trial website:

    - Polish
    - Romanian
    - Urdu
    - Punjabi
    - Gujarati
    - Bengali
    - Arabic
    - Portuguese
    - Spanish
    - Chinese (Mandarin)
    - Welsh

- Where parents require an interpreter, the WHEAT trial and opt-out consent should be discussed with them alongside standard clinical updates when an interpreter is used.

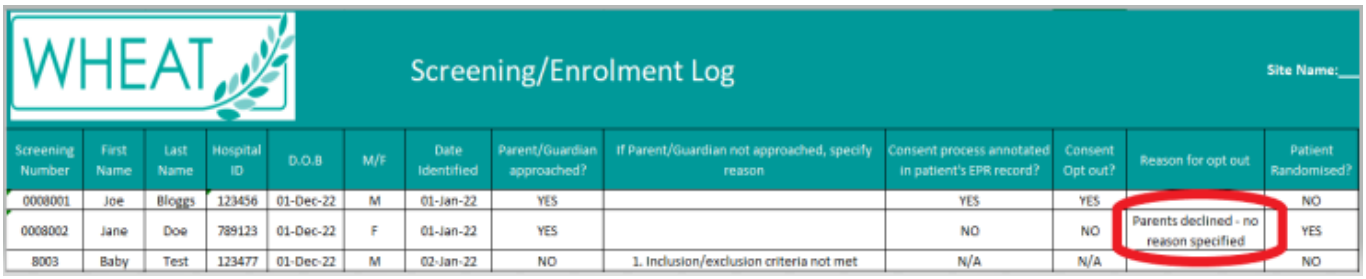
- Where parents are unable to understand the WHEAT trial and the concept of opt-out consent, their baby should not be enrolled in the trial

Use the WHEAT Opt Out Consent Guidance V2.0 dated 19JUN2023 as a point of reference to direct the conversation.

- Where possible, both parents should be informed about the WHEAT trial

<u>Parent(s)/Guardian Opt-Out</u>

- If the parent/guardian wishes to opt-out, please record this on the WHEAT Screening & Enrolment Log.
    - Parents/guardians do not have to give a reason for opting-out, but please collect the reason if specified and record it on the WHEAT Screening & Enrolment Log:



Screening/Enrolment Log

Site Name:

Screening Number	First Name	Last Name	Hospital ID	D.O.B	M/F	Date Identified	Parent/Guardian approached?	If Parent/Guardian not approached, specify reason	Consent process annotated in patient's EPR record?	Consent Opt out?	Reason for opt out	Patient Randomised?
0008001	Joe	Bloggs	123456	01-Dec-22	M	01-Jan-22	YES		YES	YES		NO
0008002	Jane	Doe	789123	01-Dec-22	F	01-Jan-22	YES		NO	NO	Parents declined - no reason specified	YES
8003	Baby	Test	123477	01-Dec-22	M	02-Jan-22	NO	1. Inclusion/exclusion criteria not met	N/A	N/A		NO

<u>Record of Consent</u>

- Whether the parent/guardian chooses for their baby to participate in the WHEAT Trial, or to opt-out, please record the discussion of consent for the trial in the patient's medical records. For example:

"16 AUG 2022. Parents/guardian provided with a copy of the WHEAT Parent Information Sheet (V2.0 21JUN2022) and they opted-in to their baby's enrolment in the trial."

- At the point the baby requires a blood transfusion and is ready to be randomised, there is no requirement to re-discuss participation with the parents/guardians.

If a transfusion is not yet required:

- Use the *Eligibility Cot Cards (V1.0 dated 04 OCT 2022)* to highlight to the clinical team that the baby is eligible for WHEAT

- If you use EPR, set an alert to notify the clinical team the baby is to be randomised in WHEAT at the point they require a transfusion.

  The baby must be ≤34+6 (weeks + days) corrected gestational age in order to be randomised.

- If you use paper medical records, apply one of the labels to the patients paper notes to alert the clinical team to notify the baby is to be randomised in WHEAT at the point they require a transfusion
  - Use the *Paper Notes Eligibility Labels* V1.0 dated 04OCT2022

Once the baby is ready to be randomised, see the steps to follow in Section 6.4 below.

6.3. Co-Enrolment

Babies can be co-enrolled in the WHEAT trial and the following trials

- neoGASTRIC
- DOLFIN
- POLAR

Please contact the WHEAT trial team to discuss co-enrolment with other trials.

6.4. Randomisation

6.4.1 Timing of Randomisation

Babies should be randomised at the point they require a non-emergency blood transfusion.

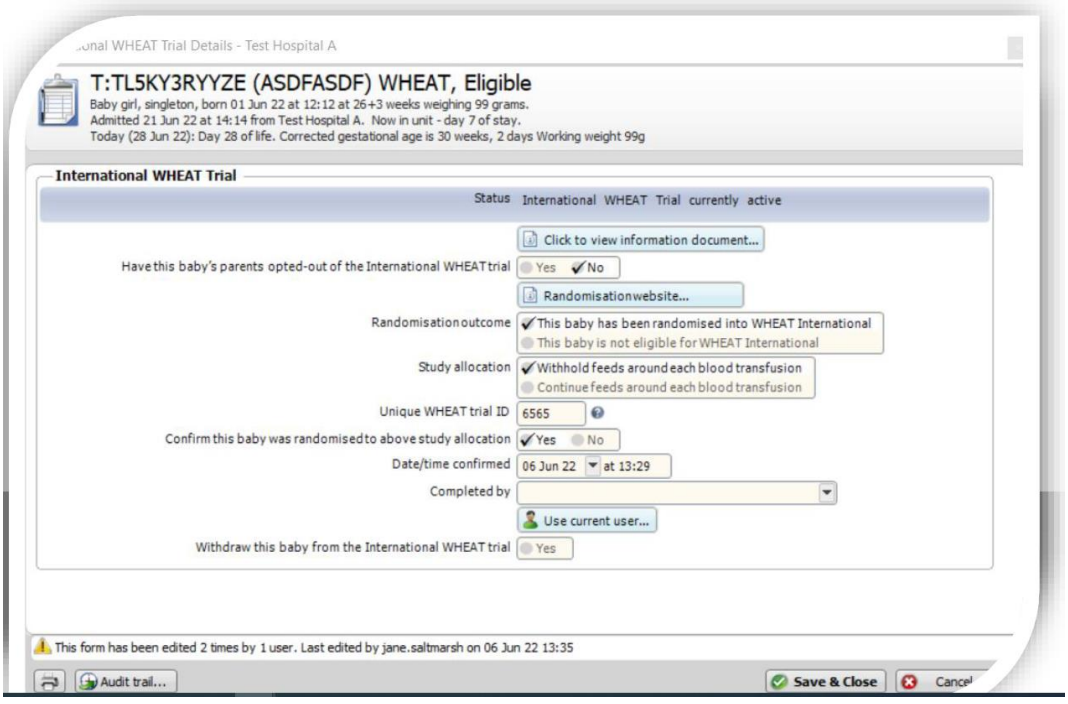
If a baby requires an emergency blood transfusion this should be given **immediately** and the baby should **not** be randomised into the WHEAT trial at this point – they can be randomised into the WHEAT trial when they need a non-emergency blood transfusion in future.

There is no need to re-discuss participation with their parents/guardians, providing this was done at the point the baby was identified as eligible for WHEAT.

6.4.2 Randomisation Walk-Through

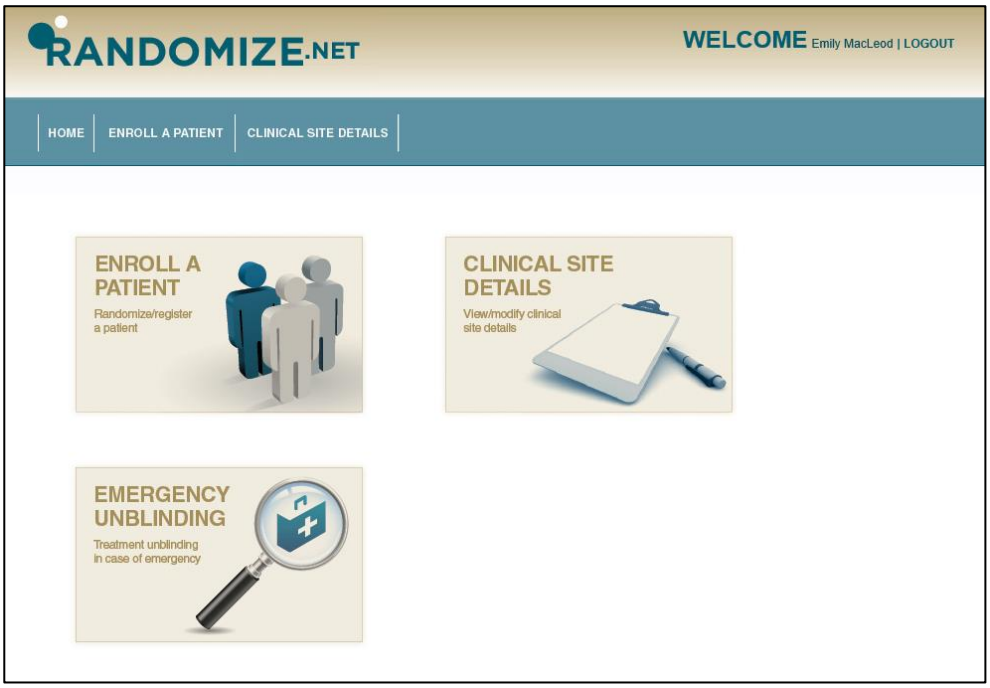
Once the baby requires a blood transfusion, follow the steps below to randomise the baby into the WHEAT Trial.

A. Access the randomisation site through BadgerNet:

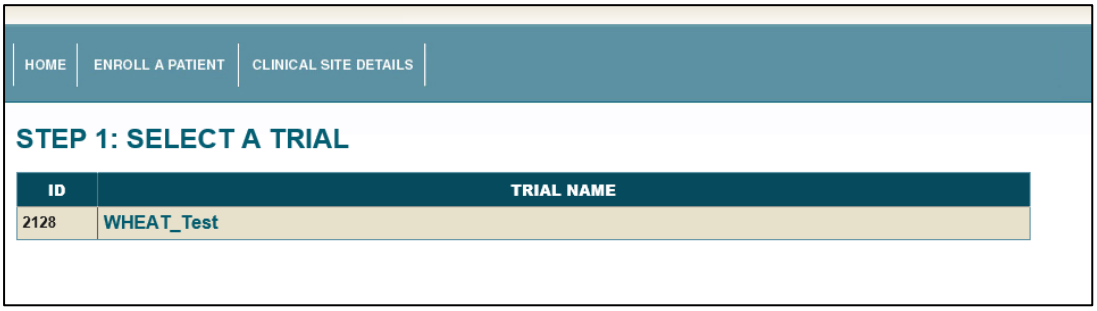


Login in using the details provided by the Trial Manager during set-up. Contact WHEAT@imperial.ac.uk if you need access.

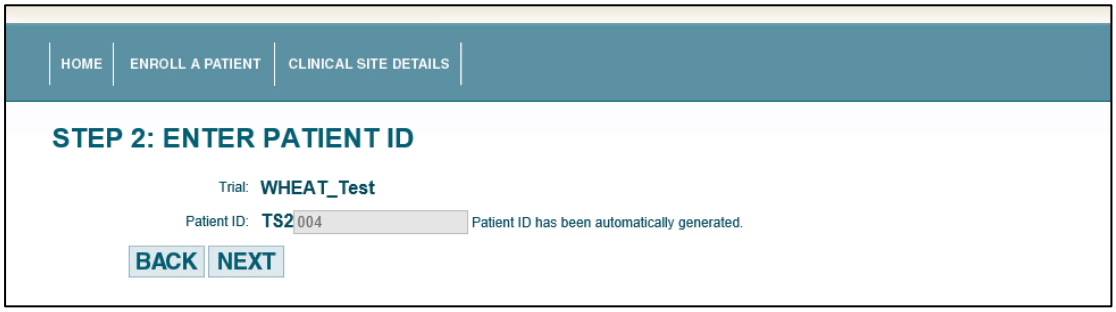
B. Click on "Enroll a Patient"



C. Select "WHEAT International" on the Step 1: Select Trial page

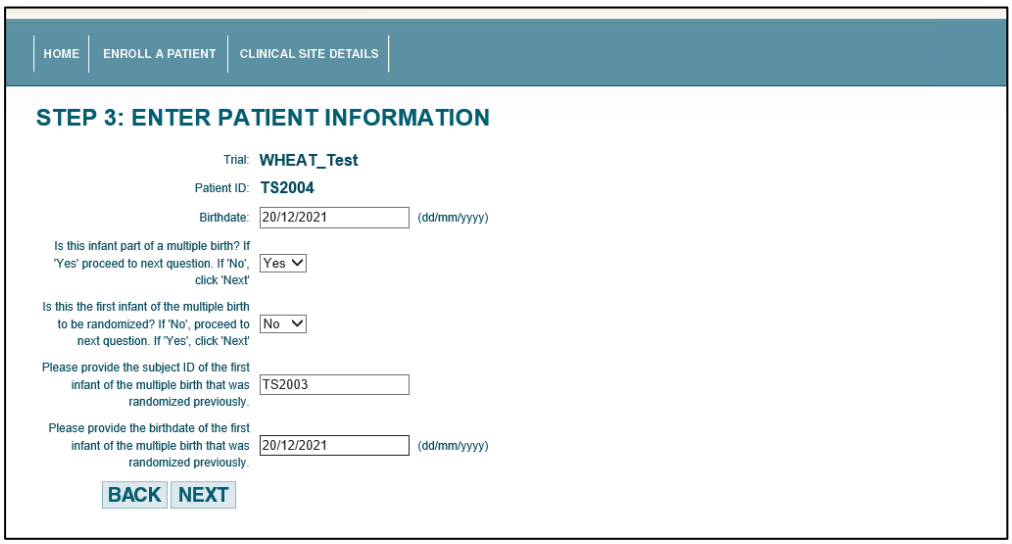


D. Click "Next "on the Step 2: Enter Patient ID page
The Patient ID on this page is automatically generated. Please record this number in the WHEAT Screening and Enrolment log and in BadgerNET Summary/BadgerNET EPR.



E. Enter the baby's birthdate and answer the relevant questions regarding multiple births on the Step 3: Enter Patient Information page. Click "Next".

If the participating baby is part of a multiple birth and a previous baby in that set of multiples has already been randomised you will need to enter the birthdate and study ID of the first multiple randomised. This information can be found in the WHEAT Screening and Enrolment log.

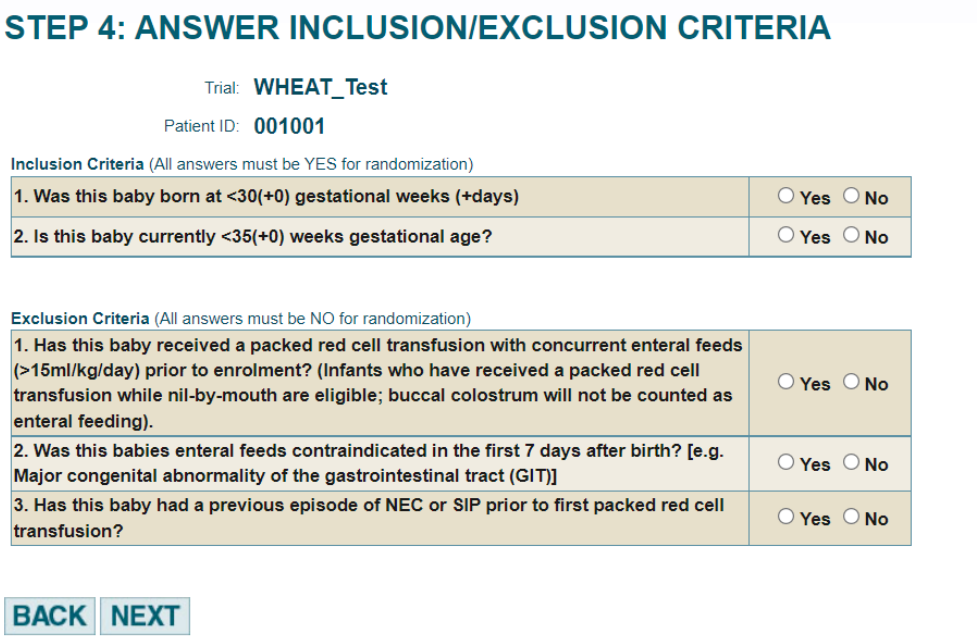


F. Answer the inclusion/exclusion criteria questions to ensure the baby is still eligible to participate in the study.

Click "Next".

Prior to answering these questions confirm with someone on the babies care team that the baby has not had a previous episode of necrotising enterocolitis (NEC) or spontaneous intestinal perforation (SIP) and that the baby has not had enteral feeds contraindicated in the first 7 days of life, for example due to a major anomaly of the gastrointestinal system.

Remember, babies must be ≤34+6 (weeks+days) corrected age in order to randomise and receive the trial intervention.



STEP 4: ANSWER INCLUSION/EXCLUSION CRITERIA

Trial: WHEAT_Test

Patient ID: 001001

Inclusion Criteria (All answers must be YES for randomization)

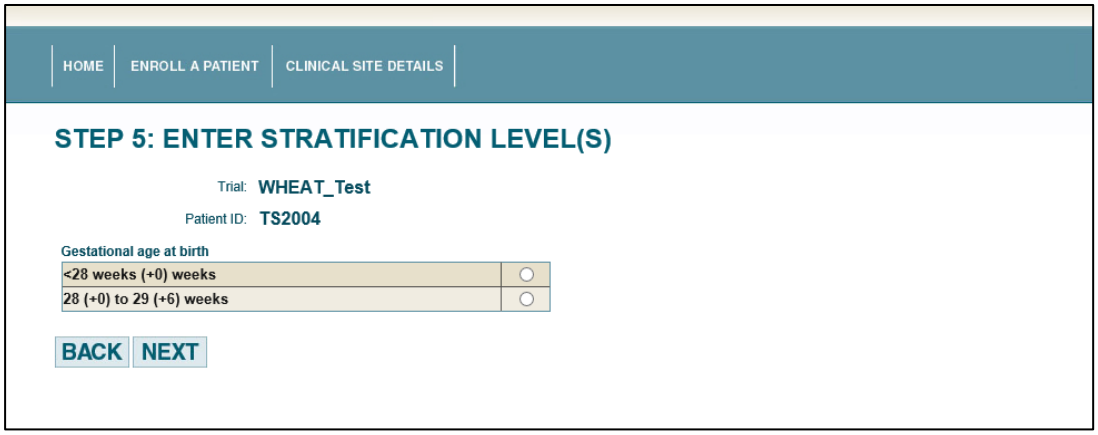
1. Was this baby born at <30(+0) gestational weeks (+days)	○ Yes ○ No
2. Is this baby currently <35(+0) weeks gestational age?	○ Yes ○ No

Exclusion Criteria (All answers must be NO for randomization)

1. Has this baby received a packed red cell transfusion with concurrent enteral feeds (>15ml/kg/day) prior to enrolment? (Infants who have received a packed red cell transfusion while nil-by-mouth are eligible; buccal colostrum will not be counted as enteral feeding).	○ Yes ○ No
2. Was this babies enteral feeds contraindicated in the first 7 days after birth? [e.g. Major congenital abnormality of the gastrointestinal tract (GIT)]	○ Yes ○ No
3. Has this baby had a previous episode of NEC or SIP prior to first packed red cell transfusion?	○ Yes ○ No

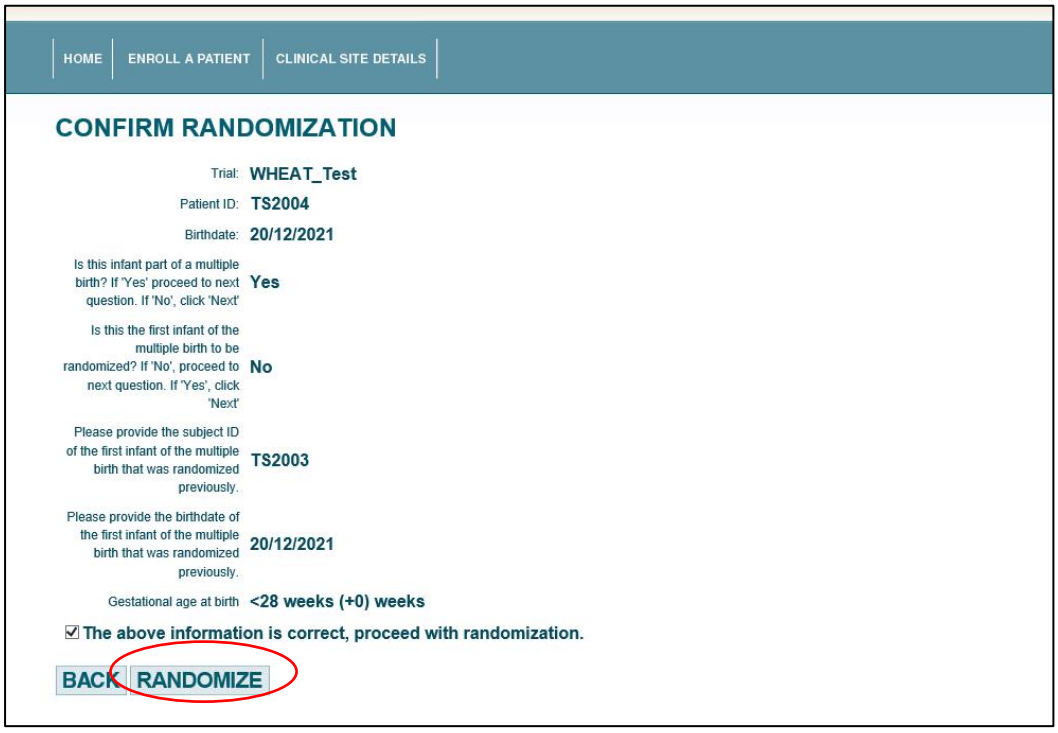
BACK NEXT

G. Select the gestational age at birth of the participating baby. Click "Next".



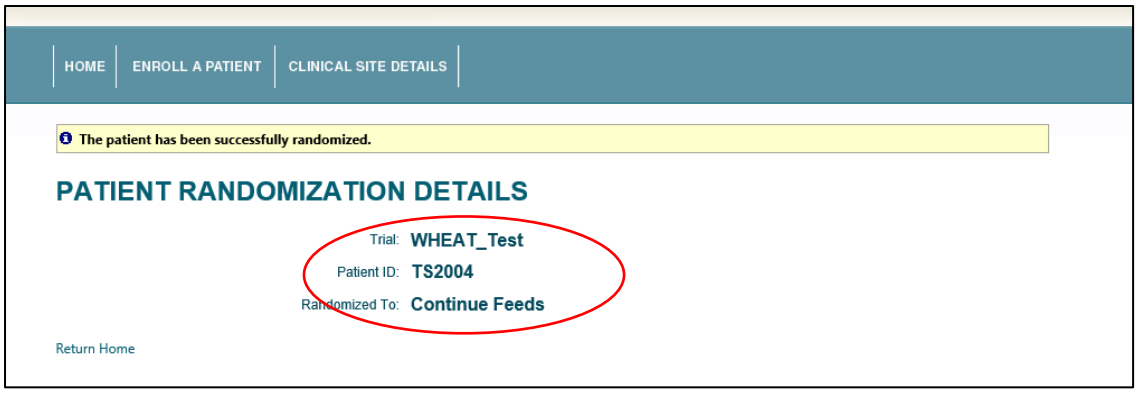
H. Confirm that the randomisation details are correct by checking the box at the bottom.

Click "Randomize".



I. **Success – you've randomised the baby! The study arm will be listed at the bottom.**

Please record the Study Arm in the WHEAT Study Screening and Enrolment log and on BadgerNET Summary or BadgerNET EPR.



The WHEAT Sponsor Office will also be automatically notified, via email, that a baby has been randomised.

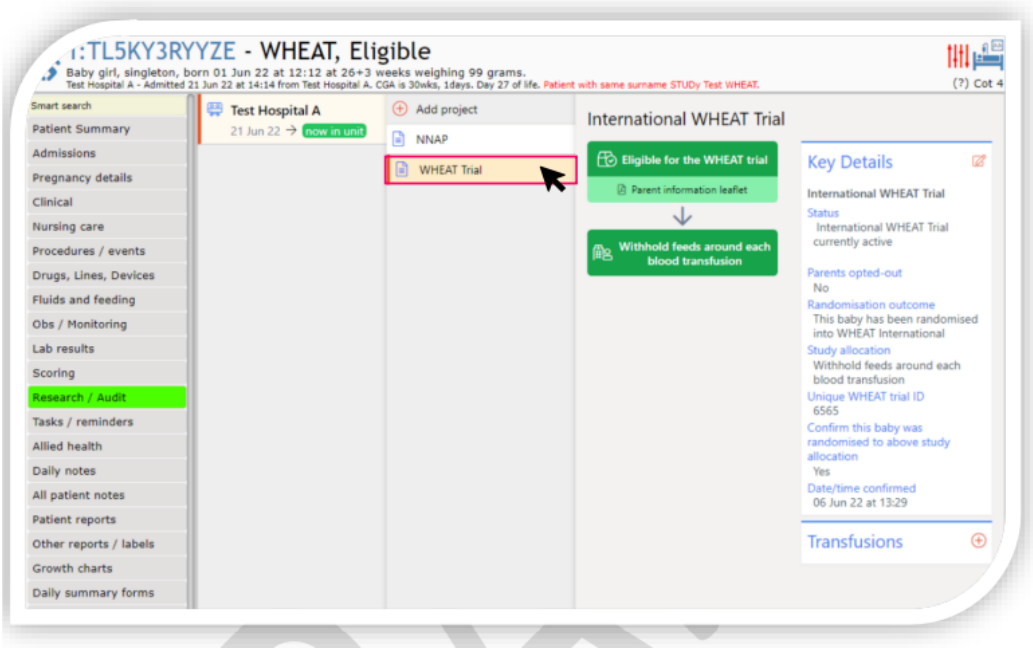
*** If you receive an error message when you select "Randomize" it is often an indication that the questions regarding the previous baby in a set of multiples were not correct (i.e. the Study ID provided doesn't match the birthdate, etc.). Reconfirm these details and try again. If the message persists, contact the WHEAT Trial Office at Imperial Clinical Trials Unit via WHEAT@imperial.ac.uk.**

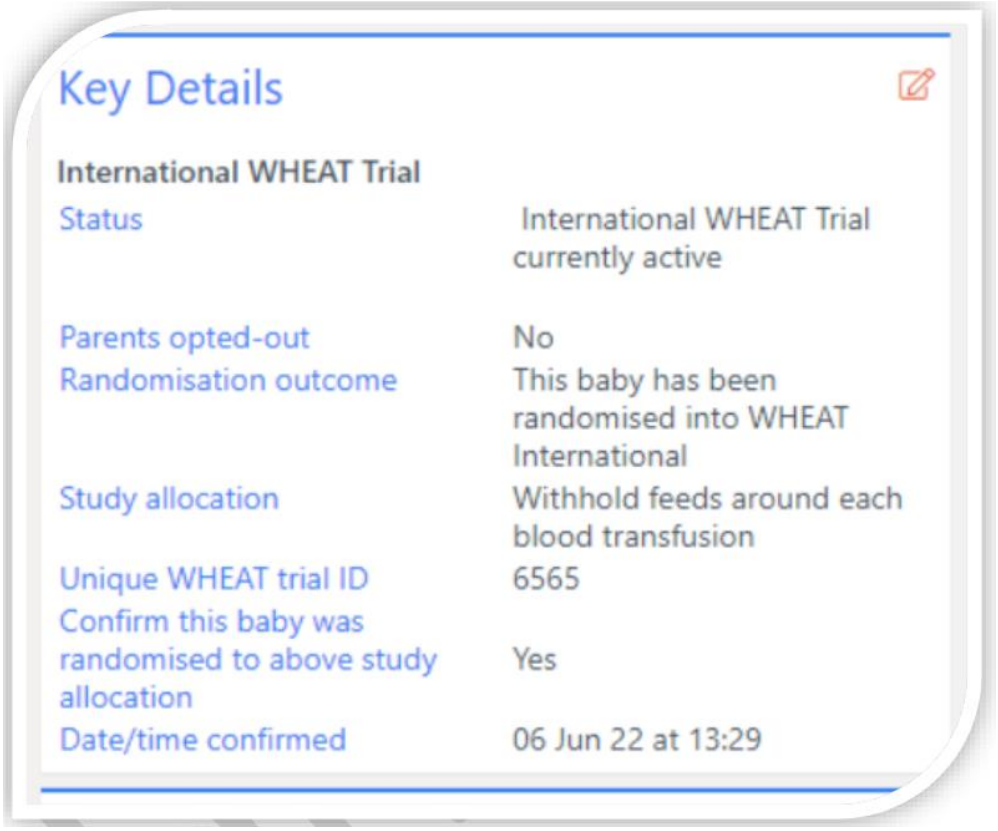
K. **Update Badger, Study Identifier stickers and cot cards.**
Patient stickers and cot cards are provided in your Investigator Site File. Please ensure that all relevant paper medical records, blood transfusion charts and the baby's cot are labelled accordingly, so it is clear to all staff that they are both enrolled on the WHEAT Trial and the arm the baby is randomised to.

- **See the Data Entry Guidelines for instructions on how to record the randomisation outcome**
- **Use the cot card corresponding with the randomisation allocation**
  - **Cot Cards – Withhold Arm V1.0 04OCT2022**
  - **Cot Cards – Continue Arm V1.0 04OCT2022**

- **If your site uses paper medical records, use the paper notes stickers to record the randomisation outcome**
  - **Paper Notes Randomisation Labels – Withhold Arm V1.0 04OCT2022**
  - **Paper Notes Randomisation Labels – Continue Arm V1.0 04OCT2022**

- Once Badger is updated with the randomisation outcome, the key information relating to the baby's participation in WHEAT will be displayed under the *Research/Audit* tab of Badger:





6.5 Trial Intervention

Babies will be allocated to one of the following interventional arms, to be applied at each and every packed red cell transfusion until the baby reaches ≤34+6 (weeks + days) corrected age:

Withhold Feeds

- Baby nil by mouth at the following timepoints:
    - **At least 4 hours before** starting a packed red cell transfusion
    - **During** packed red cell transfusion
    - **At least 4 hours after** packed red cell transfusion finishes

- During the feed withhold period (~12 hours), hydration and blood glucose should be maintained according to **local practice**
- Once the feed withhold period is over – 4 hours post-packed red cell transfusion, feeds will be resumed in **the same manner, including the same rate and type of milk and concentration of fortifier** as they were before the decision was made to transfuse

Continue Feeds

- Enteral feeds will continue to be given before, during and after packed red cell transfusion
- Feeds will be given in **the same manner, including the same rate and type of milk and concentration of fortifier** as they were before the decision was made to transfuse

Transfer to another hospital

Babies transferred onto other neonatal units will continue with the WHEAT trial intervention and data collection.

When a baby is transferred, contact the Trial Manager via 0207 594 7271 or by emailing WHEAT@imperial.ac.uk with:

1. Babies' WHEAT unique ID (taken from Badger)
    a. *Do not send any patient identifiable data to Imperial*
2. Name of Hospital/Unit transferred to
3. Date of transfer
4. A named contact of a clinician/nurse at the transfer site with contact details (telephone or email)

We have an ethical obligation to continue with the trial intervention for babies transferred out, so please notify us in good time.

6.6 Incident (Protocol Deviation/Violation) Reporting

Any deviations from the protocol, trial procedures, principles of Good Clinical Practice or regulatory/ethical requirements must be reported to the WHEAT Trial Office at ICTU.

Any such incidents must be reported as soon as possible by completing the WHEAT Protocol Deviation/Violation Form (V1.0 04AUG22) and emailing it to WHEAT@imperial.ac.uk.

You must ensure that the PI or delegated Sub-Investigator has reviewed the protocol deviation/violation and signed-off the form.

Once received by the WHEAT Trial Office at ICTU, the Chief Investigator will make an assessment of whether the protocol deviation/violation constitutes a serious breach.

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.

Depending on the nature and/or severity of the protocol deviation(s) or violation, further monitoring of site may be undertaken and research activities may be temporarily halted following further investigation.

6.7 Withdrawals

In the event that enrolled infants' parent(s)/guardian(s) decided they no longer wish for their baby to be on the WHEAT trial, then they are

permitted to do this at any time without giving a reason and without prejudice to their baby's routine care.

Please record the withdrawal within Badger and refer to the *Data Entry Guidelines* for instructions on how to do this.

Notify the Trial Team via WHEAT@imperial.ac.uk of the withdrawal.

Also record this on your Screening and Enrolment Log.

6 Revision History

Version	Date Effective	Reason for update
2.0	20 OCT 2022	• Clarification of randomisation procedure • Clarification of eligibility criteria
3.0	12 DEC 2022	• Provided updated screenshot of eligibility notification in Badger, following system upgrade in Dec 2022 • Clarified eligibility criteria as per Non-Substantial Amendment 2 • Clarified and updated protocol co-enrolment
4.0	19 JUN 2023	• Clarification of eligibility criteria • Correction of instruction on how to access randomisation website