A phase III, multi-centre, randomised placebo-controlled trial of oral iron supplementation for the prevention of maternal anaemia

PANDA Prevention of Anaemia

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Protocol Signature Page

The undersigned confirms that the following protocol has been agreed and accepted and the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:
Signature: ..... Date: ...../...../.....
Name (please print): .....
Position: .....

Chief Investigator(s):
Signature: ..... Date: ...../...../.....
Name: (please print): .....

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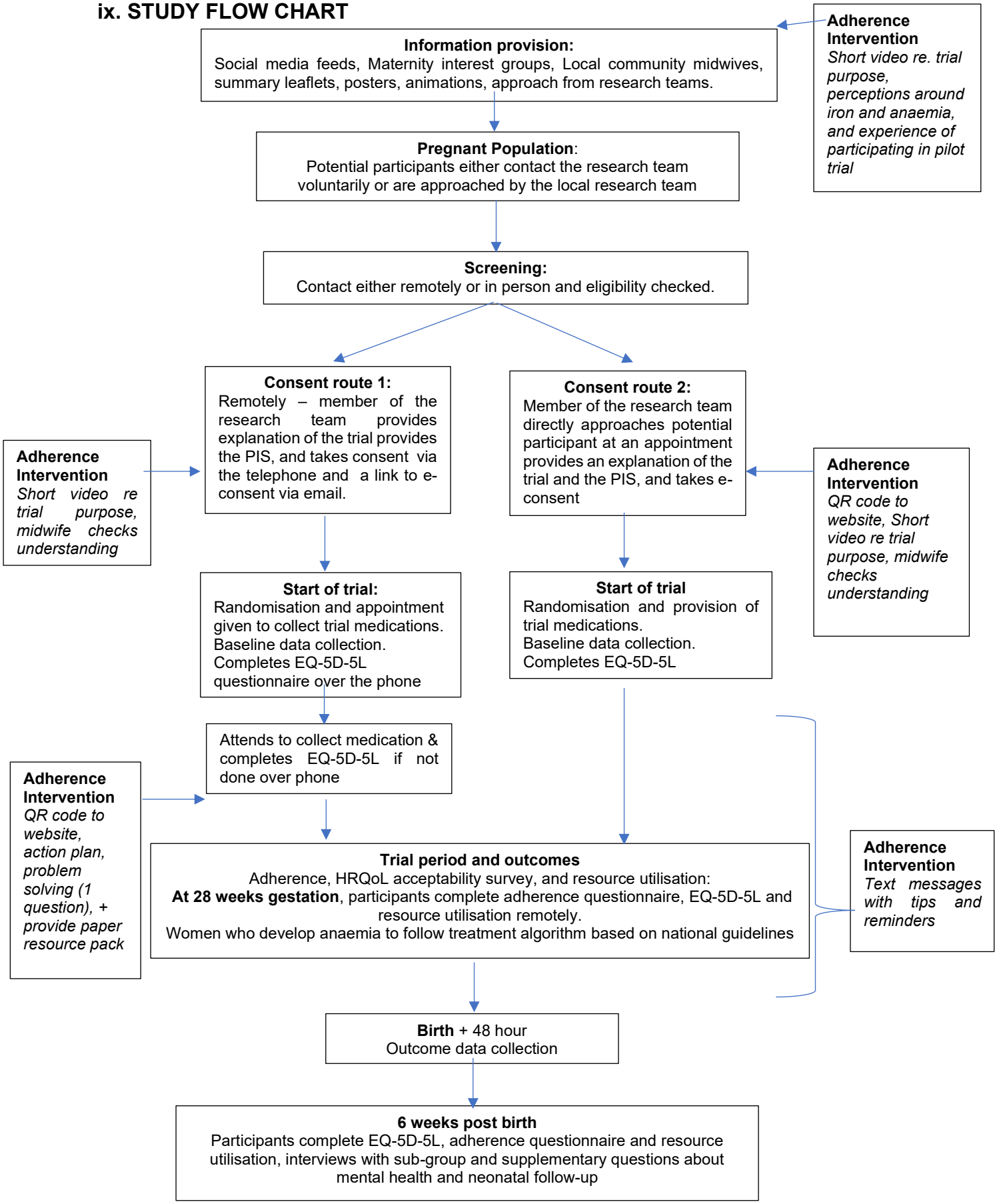
iii. Trial Synopsis

Title of clinical trial	A multi-centre, randomised placebo-controlled trial of oral iron supplementation to prevent maternal anaemia	
Protocol Short Title/Acronym	PANDA Prevention of Anaemia	
Clinical Phase	Phase III	
Study design	Multicentre, multi-arm, double blind randomised trial	
Trial Participants	Non-anaemic pregnant women	
Health Condition(s)	Prevention of anaemia in pregnancy	
Setting	Maternity services	
Planned Sample Size	11,020	
Treatment duration	From time of the booking clinic, the dating ultrasound scan appointment or first antenatal clinic visit until 6 weeks post-birth	
Follow up duration	6 weeks post birth (long-term follow up infants)	
Interventions to be compared	Ferrous Sulphate 200 mg (containing 65 mg elemental iron) or placebo matched to Ferrous Sulphate to mother, with an intervention to support medication adherence (behavioural adherence intervention)	
Primary	Objective: To evaluate the clinical- and cost-effectiveness of a primary prevention strategy for iron deficiency anaemia in pregnancy with an optimised low dose oral iron supplementation intervention.	Outcome: Composite outcome of the proportion of pregnancies with pre-term birth (<37 completed weeks gestation), stillbirth (at 24 weeks gestation or above), neonatal death (up to 28 days) and small for gestational age (SGA) (<10th centile sex-specific weight for age, defined by UK growth charts).
Funding	NIHR PGfAR Programme	National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (project reference RP-PG-NIHR200869).

ix. STUDY FLOW CHART



x. Study Schedule

Procedures	Visits				
	Screening	**Baseline**	**Third trimester 28 weeks**	**Birth plus 48 hours**	**6 weeks post birth follow up**
Eligibility assessment	X				
Informed consent		X			
Randomisation/dispensing		X			
An intervention to support medication adherence (behavioural adherence intervention) including text messaging		X	X		
Demographics	X	X			
Medical history		X			
Past obstetric history		X			
Concomitant medications including supplements taken e.g. vitamins etc		X			
Laboratory tests: Routine haematology bloods		X	X	X	
EQ-5D-5L		X In person assessment	X Remotely completed		X Remotely completed
Healthcare resource utilisation					X
Adherence questionnaire			X Remotely completed		X Remotely completed
Acceptability survey			X Remotely completed		
Post birth questionnaire					X Remotely completed
Acceptability interview (with sub-group sample of women)					X Remotely completed
Outcomes assessment Mother				X	X
Outcomes assessment baby				X	X
Anaemia treatment (if indicated)		X At 2-4 weeks later to assess response	X	X	X
Adverse event assessments			X	X	X
Physician's Withdrawal Checklist			X	X	X
Fidelity checklists		x			

1. BACKGROUND

Maternal anaemia and use of oral iron

Anaemia in pregnancy is common and is primarily caused by iron deficiency. Pregnant women require a greater amount of iron than non-pregnant women to meet the needs of an expanded red blood cell mass in the mother to cope with the physical stresses of childbirth and to support the growing fetus and placenta. Anaemia may develop in around a third of UK women during pregnancy. Anaemia has been reported to be associated with important adverse outcomes including maternal mortality, haemorrhage, preterm birth, stillbirth, and neonatal mortality.

Oral iron is the main form of management of anaemia, but on-going controversy exists as to whether routine iron supplementation, started early in pregnancy, is effective for non-anaemic pregnant women to prevent anaemia. Preventing antenatal anaemia is the focus of a programme of research (Primary prevention of maternal ANaemia to avoid preterm Delivery and other Adverse outcomes) to establish the role of oral iron supplementation in prevention of maternal anaemia, aimed at improving maternal and infant outcomes in the UK.

This protocol describes a clinical study to establish the clinical and cost-effectiveness of universal oral-iron supplementation in association with a behavioural adherence intervention to prevent iron deficiency anaemia during pregnancy. The protocol also incorporates the processes to evaluate the impact of prevention of maternal anaemia on long-term infant neurodevelopment (and maternal outcomes) and (in a subset of women) a process evaluation study to investigate intervention fidelity feasibility and acceptability. In addition, given uncertainties about the effects of current treatment approaches for women who develop anaemia, this study incorporates an algorithm for treatment follow-up, based on national BSH guidelines (Pavord et al).

2. RATIONALE AND RESEARCH QUESTION

Oral iron is the main form of management of anaemia, but it is not known whether routine iron supplementation, started early in pregnancy, to prevent anaemia, has clinical benefits for the mother and infant. Currently, there is no standard of care recommendation for oral iron supplementation and given the high burden of anaemia during later pregnancy, it is likely that many women develop low iron stores during pregnancy.

The trial research question is whether oral iron supplementation using an optimised low-dose schedule given from early pregnancy (first booking clinic) will improve maternal and infant outcomes, by comparison to a placebo. The study hypothesis is that a strategy of universal primary prevention of anaemia during pregnancy with oral iron supplementation will impact the composite primary outcome of pre-term birth, stillbirth, neonatal death and small for gestational age (SGA).

A daily low-dose schedule of oral iron was selected to be offered to pregnant women in this trial. This dose schedule was established by the results of a previous dose-finding randomised study in our PANDA programme of research (WS2), which tested the acceptability and feasibility of different doses of oral iron supplementation for four main outcomes of interest relating to adherence, side effects, maintenance of maternal haemoglobin, and protocol compliance, following earlier publications (Stoffel). One important finding was that many women experienced symptoms of nausea, constipation and heartburn before starting iron supplements, as part of normal physiological pregnancy, and not related to iron use. The use of a placebo in this trial will ensure that any observed effects can be clearly related to the use of oral iron supplementation.

The WS2 study also evaluated intervention strategies to facilitate the decision to initiate, and subsequent adherence to, iron supplementation by pregnant women. This protocol therefore incorporates an intervention to support medication adherence (adherence intervention)

including text messaging. These strategies were developed based on findings from interviews with anaemic and non-anaemic pregnant women during the first workstream (WS1) of PANDA, which identified a range of barriers and enablers to the uptake of, and adherence to, iron supplementation for the prevention of anaemia in pregnancy. The strategies were additionally developed based on stakeholder co-design workshops with key stakeholders (pregnant women representatives, healthcare workers, behavioural scientists, academics).

2.1 Assessment and management of risk

Oral iron (Ferrous sulphate) has a marketing authorisation (MA) in the UK and is currently recommended in national guidelines to manage maternal anaemia. There is extensive clinical experience of the use of oral iron in pregnancy over many years, typically at dose schedules higher than those now adopted in common practice. Even lower doses of oral iron have also been available for pregnant women as part of routine over the counter medication. There is no reason to suspect a different safety profile in this trial population, where oral iron is being given to prevent maternal anaemia at a standard dose. Consequently, this trial is categorised as MHRA Type A.

3. Objectives and Outcome Measures/Endpoints

3.1 Primary objective

To evaluate the clinical- and cost-effectiveness of a primary prevention strategy for iron deficiency anaemia in pregnancy with an optimised low dose oral iron supplementation intervention.

3.2 Secondary objectives

To conduct a process evaluation to assess the fidelity, feasibility, and acceptability of iron supplementation and the adherence intervention. This will inform interpretation of the clinical trial results, intervention refinement and subsequent scalability and implementation.

3.3 Outcome measures/endpoints

3.3.1 Primary outcome

The primary outcome is a composite outcome of the proportion of pregnancies with pre-term birth (<37 completed weeks gestation), stillbirth (at 24 weeks gestation or above), neonatal death (up to 28 days) and small for gestational age (SGA) (<10th centile sex-specific weight for age, defined by UK growth charts, for example Royal College Paediatrics and Child Health).

3.3.2 Secondary outcomes

Secondary outcomes relating to the mother are as follows:

- Components of the composite primary outcome:
  - Pre-term birth (<37 completed weeks gestation)
  - Small for gestational age (<10th centile sex-specific weight for age)
  - Stillbirth (at 24 weeks gestation or above)
  - Neonatal death (up to 28 days)
- Proportion of women developing anaemia during pregnancy
- Transitions in haemoglobin from recruitment to 28 weeks & birth
- Proportion of women with primary postpartum haemorrhage (PPH)
- Proportion of women requiring red cell transfusions prior to discharge but not more than 48 hours post birth
- Proportion of women receiving an iron infusion prior to discharge and up to 6 weeks after birth

- Proportion of women with an infection and or sepsis before discharge and up to six weeks after birth
- Proportion of women breastfeeding or providing breast milk for baby at discharge from maternity care and at 6 weeks
- Proportion of women with postpartum depression assessed at 6 weeks post birth
- Median adherence to medication at 28 weeks and at 6 weeks post birth, as measured using the MARS-5 score
- Health-related quality of life (HRQoL) using EQ-5D-5L at baseline, 28 weeks and at 6 weeks post birth
- Healthcare utilisation over trial period

Secondary outcomes relating to the infant are as follows:

- Mean birthweight
- Mean gestation at birth
- Apgar score at 5 minutes
- Proportion of infants treated for neonatal early onset infection, defined as culture-positive, occurring within 72 hours or prior to discharge home, whichever occurs first.
- Admission to neonatal unit
- Healthcare utilisation including initial hospital stay, subsequent hospital readmissions, up to 6 weeks post birth

Secondary outcomes relating to the process evaluation (WS4)

- Intervention fidelity (i.e. whether intervention delivered and engaged with as planned)
- Intervention acceptability
- Intervention feasibility

3.3.3 Exploratory outcomes

Exploratory outcomes, relating to the infants, are:

- Proportion of infants with:
    - hypoxic ischaemic encephalopathy (HIE) (moderate or severe),
    - severe intraventricular haemorrhage (IVH), defined as grade III or IV,
    - necrotising enterocolitis (NEC),
    - late onset infection,
    - bronchopulmonary dysplasia,
    - retinopathy of prematurity requiring treatment, e.g. laser, cryotherapy or intravitreal injection

Exploratory outcomes, relating to the treatment of anaemia when this occurs in women recruited to PANDA (prevention) are:

- Adherence to the clinical treatment algorithm based on national BSH guidelines, defined as correct primary treatment administered and haemoglobin taken 2-4 weeks after commencement.
- Response rate to initial course of oral iron at 2-4 weeks, assessed by change in:
    - haemoglobin,
    - reticulocytes, where collected routinely
    - other markers of iron haemostasis, where collected routinely
- Impact of treatment on HRQoL and other outcomes, including post-partum haemorrhage and mode of delivery

4. Trial Design

This is a phase III, multicentre, multi-arm, double blind randomised trial.

- The design is a two-arm parallel-group, with 11,020 women being allocated in a 1:1 ratio to 200 mg ferrous sulphate (65mg iron) once daily vs a matched placebo.
- Participants at study sites will also receive an intervention to support medication adherence (behavioural adherence intervention), aimed at supporting the decision to start taking, and subsequent adherence to, trial drug intervention.

5. Trial Setting

Healthy non-anaemic pregnant women will be provided with information and recruited from UK maternity services, at the booking clinic, the dating ultrasound scan appointment or antenatal clinic visit (15 weeks + 6 days gestation or less).

The recruitment target of 11,020 women will require 25 (or more) maternity units to engage with the study. The trial is designed to be pragmatic and aligned with current pathways of care. Acknowledging that units will vary in size, serve differing populations, and have different operational structures, the recruitment plan aims to provide participating sites with a series of options to use when recruiting participants, to make recruitment as efficient as possible.

6. Participant Eligibility Criteria

Eligibility for enrolment will be assessed with reference to inclusion and exclusion criteria. To be eligible for the trial, all inclusion criteria must be met, and no exclusion criteria may apply. Any uncertainty around the eligibility of a participant must be resolved before enrolment.

6.1 Participant Inclusion Criteria

- Healthy non-anaemic pregnant women of all parities (haemoglobin concentration (Hb) ≥110 g/l measured by the first trimester blood profile) at booking or screening
- A live fetus on a first trimester ultrasound scan carried out for viability or dating.
- 15 weeks + 6 days gestation or less at consent
- Age 18 and above
- Able to give informed consent and willing to fulfil trial requirements

6.2 Participant Exclusion Criteria

Women with the following conditions will be excluded:

- Known haemoglobinopathies (women with haemoglobinopathy trait are still eligible)
- Anaemia of any type, defined by BSH guidelines
- Haematological conditions that require ongoing treatments with either regular oral or intravenous iron or transfusions, e.g. syndromes of bone marrow failure.
- Severe gastrointestinal disease, requiring on-going treatments, and potentially affecting tolerability of oral iron
- Chronic renal failure (requiring replacement therapy)
- Allergies to iron
- Multiple pregnancies, given the higher iron demands
- Known haemochromatosis
- Recent red cell transfusion, within 30 days

Women who elect to take iron-containing (over the counter) supplements will not be excluded, but data on this form of supplement use will be collected.

7. Trial Procedures

7.1 Recruitment

Women will be provided with information about the trial as early as possible, potentially ahead of their first appointment. If they have not received information about the trial by then, the research team will provide these when they attend the antenatal clinic.

A full explanation will be given of the trial, intervention options and the manner of treatment allocation. By this time their 'booking blood tests', the routine screening bloods taken in the first trimester, will have been reported and the records can be screened for the exclusion criteria. Informed consent to enter the trial will be taken by Good Clinical Practice (GCP) trained and delegated research staff, including research midwives and nurses.

Participants may only be recruited into PANDA workstream 3 once and cannot be re-randomised with subsequent pregnancies.

7.1.1 Participant identification

Participants will be identified using any of the following methods:

- A summary of the trial provided in the booking pack sent to women registering their pregnancy. This would include links to the trial website and local research staff for more detailed information about the trial. Adherence intervention information videos will be available on the PANDA website and other digital media platforms such as electronic patient records (EPRs).
- Community midwives may direct women to sources of information about the trial when the woman is being registered and her history taken.
- For maternity units with an electronic patient record (EPR) system that has the relevant functionality, a push notification may be sent to the woman's smart phone or other device directing her to the PANDA website and the relevant information. This may also be done via text message.
- A summary of the trial may be included with routine appointment letters
- Information may be provided directly to women by their midwife in antenatal clinics, ultrasound dating appointments and early pregnancy assessment units. This will include access to the adherence intervention webpages (accessed via a QR code in waiting rooms) providing information about the purpose of the trial, testimonials from women who took part in earlier PANDA workstreams, trial updates, facts and myths about use of iron in pregnancy and support for taking iron as recommended
- Information will be available through public-facing research pages for each maternity unit, PPI groups, social media and trial website including adverts
- Posters and adverts may also be presented in relevant clinics. Potential participants will be able to contact the research team at the site directly if they wish to participate
- Potential participants can be contacted by the care team via telephone and/or posted the trial information pack. These women will be identified through hospital's clinic lists or other databases
- Use of websites and/or social media advertising including information about the trial, directing women research staff at participating sites or to allow them to express interest through a website
- Use of wider publicity, including the media and through relevant patient groups, to raise awareness of the trial

7.1.2 Screening

Blood tests performed at ≤ week 15+6 days gestation as part of routine care will be used to screen pregnant women for eligibility. Medical history may be initially assessed using potential participants' medical records. Eligibility will be confirmed when women are seen in the clinic before consent. Confirmation of participant eligibility will be made by the PI or a suitably

qualified delegate including midwives and nurses named on the trial delegation log. An eligibility checklist will be completed.

For potential participants with medical conditions listed below, eligibility should be confirmed by a delegated, GCP trained doctor:

• Inflammatory diseases of the gastrointestinal tract, Crohns disease or ulcerative colitis.
• Any disease of the liver.
• Any haematological disease.
• Chronic renal failure.
• A history of malignancy.

7.1.3 Co-enrolment guideline

The intention is to support co-enrolment with other trials and discussions would be held between CI's to review relevant protocols.

7.1.4 Payment

Participants will not receive any payment for participating in this trial.

7.2 Consent

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the taking of informed consent of participants at their site. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

The PI may delegate other suitably qualified members of the research team, including doctors, research midwives and nurses, to obtain informed consent from the participant and enrol the participant into the PANDA prevention trial. As part of the informed consent procedure and e-consent module, educational content created for the adherence intervention in the form of information videos (developed based on formative work in the earlier PANDA WS1 that identified knowledge gaps and misperceptions of pregnant women about use of iron in pregnancy) will be delivered that provide participants with a) information about the purpose of the trial, b) facts and myths about use of iron during pregnancy and c) testimonials from pregnant women who took part in WS2 of PANDA. Pregnant women will also be provided with a QR code to access the PANDA webpages which provide information about the purpose of the trial, trial updates, facts and myths about iron and support for taking study medication as recommended.

The purpose of delivering this information as part of the e-consent procedure is to facilitate pregnant women making a fully informed choice to take part in the study, an important and essential facet of providing fully informed consent. Informed consent must be obtained prior to the participant undergoing any remaining procedures that are specifically for the purposes of the trial and are out with standard routine care at the participating site. Participants who agree to take part will sign a e-Consent Form, which will also be signed by the PI or an appropriately delegated professional. The informed consent process must be documented in patients' medical records.

The investigator or designee will explain that trial entry is entirely voluntary. It will also be explained that the participant may withdraw at any time during the trial, without having to give a reason and that their decision will not affect the standard of care they receive.

Women will receive a verbal and written explanation of the trial prior to being asked to sign the consent form. The verbal explanation may be provided face-to-face, over the telephone, or using a video conference facility such as Microsoft Teams. The approved Participant Information Sheet may be provided in a paper format or via an e-Consent platform. Both the

participant and health professional taking consent will sign an electronic consent form through the e-Consent. The electronic consent form must be countersigned by the health care professional taking consent within 24 hours of the participant signing the consent form.

7.3 The randomisation scheme

A randomisation list will be generated by an independent statistician using permuted blocks of variable undisclosed size to ensure balance and unpredictability. Kit numbers will be added in consultation with the packaging and distribution company. The independent statistician will be custodian of the final randomisation schedule and will monitor the implementation of the allocations.

7.3.1 Method of implementing the randomisation/allocation sequence

Participating sites will be supplied with sealed individually numbered kits. Kits containing active ferrous sulphate or matched placebo will be indistinguishable. 20 kits will be packaged in a larger dispensing box which permits only the next numbered pack to be withdrawn. Women will be randomised by the allocation of the next numbered pack once consent and eligibility are established. A tear-off section bearing the kit number will be retained in the participant's medical record or stock balance log at sites and the kit number entered into the eCRF as soon as possible upon allocation.

Participants should receive their IMP kit as soon as possible following consent. Participants consented at or around 15 weeks + 6 days gestation must receive their IMP within 10 days of consent (i.e. no later than 17 weeks + 2 days gestation). This is a pragmatic approach to allow for unavoidable delays with collection or delivery of IMP.

7.4 Blinding

Indistinguishable kits containing either active Ferrous sulphate tablets or matched placebo tablets will be supplied to participating sites. In this trial neither the participants, site staff nor investigators should know which intervention a participant is receiving until the clinical trial is completed and the trial database is locked. Emergency unblinding will be handled as described in section 7.5; if a participant needs to be unblinded due to a SUSAR this and onward reporting will be done by a designated unblinded person. Requests for unblinding for any other reason must be made in writing to the CIs stating the reason for the request.

7.5 Emergency Unblinding

An emergency unblinding facility will be available 24 hours per day 7 days a week provided by WGK Ltd. Upon accessing the unblinding facility the clinician may obtain the participant's allocation by providing the kit number/study number. The details of the person requesting unblinding, and the reason for the unblinding request will be recorded. Clinicians requesting emergency unblinding must be satisfied that knowledge of the participant's allocation (to either ferrous sulphate tablets or matched placebo) is necessary for urgent clinical management.

7.6 Behavioural intervention unblinding

For the purpose of the acceptability interviews, to be held with a sub-group of participants towards the end of the study, unblinding is required in order to identify participants who received the active treatment. Once a minimum of 400 participants have completed all other data collection, the independent statistician will randomly select a sub-group of 200 participants who received iron and pass on this information to the behavioural intervention team for them to contact participants for interview. The behavioural intervention team will not disclose to the rest of the study team who has been contacted. Selection and interviews will be timed as to not exceed beyond the end point of the study.

7.7 Development of anaemia

Women who develop anaemia will be offered treatment. A common practical algorithm will be agreed, based on national guidelines (Pavord et al. 2020) and after survey consultation with participating sites. Women who develop anaemia will remain in the PANDA trial for data collection purposes (and contribute to the analysis) but will discontinue taking the trial IMP. After commencing iron treatment (most commonly oral iron initially using the medication available at local hospitals), response to treatment will be assessed at 2-4 weeks follow-up, as per national guidelines.

Limited additional information will be collected in women on the treatment algorithm pathway. This will include the level of haemoglobin and any other tests performed at diagnosis or assessment of response at 2-4 weeks (e.g. reticulocyte count, ferritin, vitamin B12 and folic acid), the oral iron treatment prescribed and given, the need for intravenous iron and the response to treatment, both clinical (including HrQOL) and haematological.

7.8 Baseline data collection

Data collected at baseline will include the following:

- Medical history, physical examination, including
    - Weight and height
    - Smoking status
    - Previous pregnancy outcomes, pathology, and post-partum haemorrhages
    - Assessment of haemoglobinopathy screening
    - Medical history including previous anaemia and treatment
- Record of demographic data (including ethnicity and socioeconomic status/marker of deprivation e.g. postcode)
- Record of baseline concomitant medication, including frequency and dose, particularly, iron-containing supplements as some women may elect to take iron-containing vitamin supplements such as Pregnacare (e.g., 14-17mg elemental iron per tablet).
- Full blood count (FBC)
- Adherence intervention: assessment of fidelity of intervention delivery during the kit allocation appointment. Intervention providers will complete a brief, electronic delivery checklist for all participants following the appointment.
- EQ-5D-5L (electronic or paper questionnaire). This should be completed as close to baseline as possible, but must be completed within 28 days of randomisation.

To enable data linkage and the assessment of socioeconomic status, the following will also be collected at baseline:

- Name;
- NHS/CHI Number;
- Postcode;
- Date of Birth;

7.9 Trial Assessments and data collection points

The activities described under this section are presented at required timepoints but can be performed within multiple visits if required.

28 weeks +/- 2 weeks

- Full blood count (FBC) (if collected as part of routine care)
- Adherence questionnaire (electronic or paper questionnaire)
- Adherence intervention fidelity, acceptability, and feasibility assessments via surveys to all participants (electronic or paper questionnaire)

- Healthcare resource utilisation
- EQ-5D-5L (electronic or paper questionnaire)

Additionally, for women who develop anaemia

- Haemoglobin and reticulocyte counts (measured as local practice for diagnosis and follow-up, and at any later timepoints including delivery, as per main PANDA trial, described below)
- Type of oral iron used, including dose and frequency of administration and prescribing period.
- Intravenous iron type and dose used, if administered.
- Ferritin, Vitamin B12, Folic acid, and other tests (if measured, as routine local practice)

Clinical response to treatment including HrQOL (EQ-5D-5L) at 2- 4 weeks); other clinical outcomes will be as per main PANDA trial.

Delivery + 48 hours

- Date and time of birth
- Outcome of pregnancy
- Method of delivery
- Maternal data including mode of delivery
- Estimated blood loss at delivery and any transfusions required
- Prescription of oral or intravenous iron at or prior to discharge
- Infections requiring prescription of iv antibiotics or re-hospitalisation/hospitalisation
- Maternal peripheral/full blood count (FBC) nearest to time of birth, (if collected as part of routine care)
- Details of any anaemia diagnosis and treatment
- Infant birthweight (grams) and sex
- Infant gestational age at birth (weeks + days)
- Apgar score at 5 minutes
- Admission to a neonatal unit, level of care provided, and main reason for admission including early onset infection
- To enable data linkage: NHS/CHI Number, DoB, Postcode.

6 weeks (+/- 1 week) postpartum/postnatal

This may be conducted as a remote assessment, e.g. online or telephone

- EQ-5D-5L (electronic or paper questionnaire)
- Adherence questionnaire
- Fidelity, acceptability, and feasibility interview with 30 participants on the active treatment arm
- Healthcare resource utilisation
- Details of any infections (maternal and neonatal): A short questionnaire will be used to ask the women about episodes of infection in the baby and themselves (up to 6 weeks after birth), and further details will then be collected locally or by data linkage.
- Details of any anaemia diagnosis and treatment
- Self-report of breastfeeding
- Self-report of postpartum depression
- Details of any babies affected by a pathological process (e.g. HIE, NEC, brain injury, infection, chronic lung disease, ROP)

Data linkage

It is intended that healthcare resource utilisation and neonatal data will be collected from hospital IT systems, however there may be restrictions to this ability at different units. Thus a contingency whereby the data may be collected from registry organisations has been put in

place. Data collected via linkage with the specified organisations will occur throughout the study duration. Neonatal admissions and deaths between birth to 6 weeks postnatal may be collected via the National Neonatal Research Database (NNRD). Admissions and deaths for infants, who are not in a neonatal unit, may be captured via NHS England (HES) Hospital episode statistics and (ONS) office of national statistics, SAIL for those based in Wales or equivalents in other devolved nations. Maternal admissions from entry point into the study until 6 weeks postpartum of the study until may be captured via linkage to the same datasets.

7.10 Long Term Follow-Up Assessments

Within the trial, all participants will be followed for up to 6 weeks following delivery. For these outcomes in women who have provided consent, and to assess long-term infant development and cognitive outcomes, we propose to interrogate data from several national databases. This includes linked datasets on maternal health including Hospital Episode Statistics (HES) for readmissions, outpatient hospital visits and mental health services; infant and childhood hospital admissions and outpatient visits from HES (e.g. infection); neurodevelopmental follow-up at 2 years age for study infants born preterm from the National Neonatal Research Database; and school data on the Foundation Stage and later assessments to conduct follow-up of longer-term child outcomes from the National Pupil Database up to age of 16 years, and their equivalents in the devolved nations. Additional funding will be sought to complete this long-term follow-up which is outside the timelines of this trial. As part of this trial, consent will be obtained for the planned long-term follow up, including linkage to national databases described above; this means collection of the name of the mother and their postcode, date of birth and NHS number.

7.11 The intervention to support iron supplement adherence (adherence intervention)

The intervention to support iron supplement adherence will be delivered to all participants recruited into the trial irrespective of the trial arm they are randomised to (see **Figure 1 and Table 2**). It aims to support the initial decision to take iron supplements, and subsequent ongoing adherence.

The adherence intervention is multi-faceted and was informed by WS1 then piloted in WS2 of the PANDA programmer, as delivered to 60 women. Data was collected from participants and midwives delivering the intervention to understand intervention acceptability, fidelity, and feasibility. Based on this data, revisions to the intervention have been made to further increase acceptability, feasibility, and fidelity of delivery, as well as increase engagement by pregnant women and in the context of busy maternity departments. Proposed changes were discussed in a series of workshops with PPI representatives and the multidisciplinary research team.

Figure 1 presents the timepoints for adherence intervention delivery that correspond to the different recruitment pathways women may take into the study.

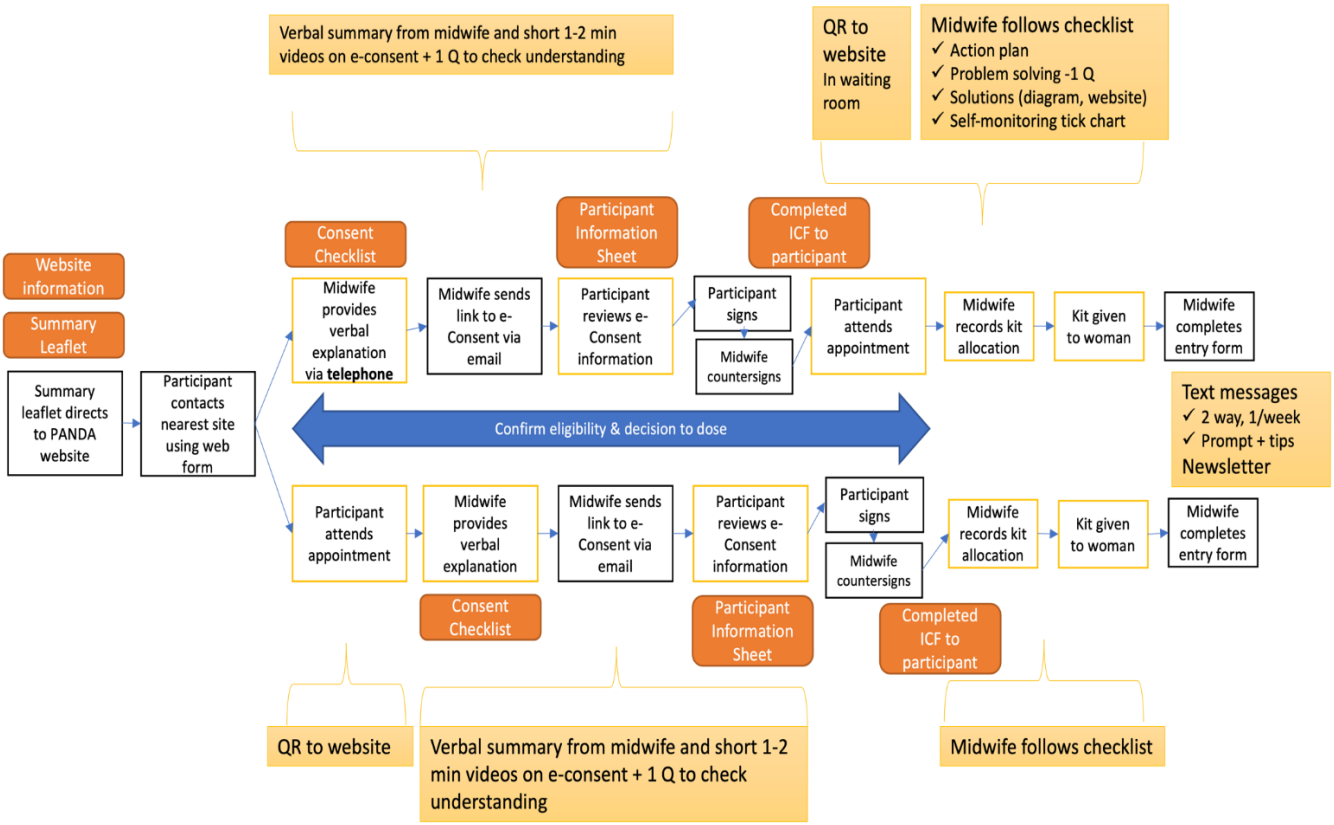

Verbal summary from midwife and short 1-2 min videos on e-consent + 1 Q to check understanding
QR to website
In waiting room
Midwife follows checklist
✓ Action plan
✓ Problem solving -1 Q
✓ Solutions (diagram, website)
✓ Self-monitoring tick chart
Consent Checklist
Participant Information Sheet
Completed ICF to participant
Website information
Summary Leaflet
Summary leaflet directs to PANDA website
Participant contacts nearest site using web form
Midwife provides verbal explanation via telephone
Midwife sends link to e-Consent via email
Participant reviews e-Consent information
Participant signs
Midwife countersigns
Participant attends appointment
Midwife records kit allocation
Kit given to woman
Midwife completes entry form
Confirm eligibility & decision to dose
Text messages
✓ 2 way, 1/week
✓ Prompt + tips
Newsletter
Participant attends appointment
Midwife provides verbal explanation
Midwife sends link to e-Consent via email
Participant reviews e-Consent information
Participant signs
Midwife countersigns
Midwife records kit allocation
Kit given to woman
Midwife completes entry form
Consent Checklist
Participant Information Sheet
Completed ICF to participant
QR to website
Verbal summary from midwife and short 1-2 min videos on e-consent + 1 Q to check understanding
Midwife follows checklist

Table 2: The adherence intervention. The table presents the individual intervention components, the time they will be delivered and the mode of delivery. Text in bold indicates activities research midwives will be administering and non-bold text indicates activities that participants will carry out independently

Timing of delivery / Week of gestation	Mode of delivery	Intervention component	Description of the intervention component
e-consent module at recruitment / Approx. 9-15 weeks + 6 days gestation or less	Website (via signposting SMS/QR codes) / at recruitment and/or randomisation and provision of medication appointment and in community	PANDA videos	Information videos embedded within e-consent module and on PANDA website to provide the following content: - Information about the purpose of the trial - Facts and myths about using iron in pregnancy and for prevention of anaemia - Testimonials from women in WS2 on their experiences of taking iron and participating in the PANDA study
At recruitment and/or randomisation and provision of medication appointment and when in community / Approx. 9-15 weeks + 6 days gestation or less and beyond when in community	Website (via signposting SMS/QR codes)	PANDA website	When women attend the clinic at point of recruitment/kit visit**, they will be given a QR code** to access the PANDA website which can be read whilst waiting for the appointment. The website will include: - Information about the purpose of the trial - Information about anaemia and iron for prevention - Problem solving strategies to help women identify any challenges with adherence to iron and potential solutions they can try - PANDA newsletters
At randomisation and provision of medication appointment / Approx. 9-15 weeks + 6 days gestation or less	Face-to-face	Verbal midwife support	Midwives will ask women 2 questions. Question 1, when discussing the trial prior to consent, will check women's understanding of information provided about the purpose of the trial and use of iron during pregnancy. Question 2 at the point women are given their iron tablets, will ask women if they anticipate any challenges to taking iron as recommended. Midwives will use PANDA resources described below to identify solutions to the challenges.

Timing of delivery / Week of gestation	Mode of delivery	Intervention component	Description of the intervention component
At randomisation and provision of medication appointment and when in community / Approx. 9-15 weeks + 6 days gestation or less and beyond when in community	Paper materials provided through initial verbal communication Materials will also be available to view on the PANDA website	Paper materials	3 paper materials will be provided and briefly discussed: - **Provision of a paper document** presenting a diagram of common challenges and potential solutions to adhering to iron regimen (also available on PANDA website). - **Action plan** to be completed in writing between midwife and participant following discussion of iron regimen and any predicted challenges with taking. - A **self-monitoring tick chart** presenting days of the week in columns and number of weeks in rows. Women will be asked to record each day they take their iron, These materials will be used independently by participants when in the community.
1 per week when in community for up to 31 weeks / throughout pregnancy when in community once enrolled into study	SMS messages	Text messages	**Midwives will check that women opt in to receive text messages.** One weekly text message which will include a sequence of alternating messages covering topics such as: - A reminder to take iron - And either a) signposting to website content or b) an embedded Behaviour Change Technique that provides advice on how to help adherence to iron regimen e.g. “PANDA: Setting daily alarms on your phone can help you get into the habit of taking your iron tablets. See [insert URL] for more help and support.”
When in community quarterly / throughout pregnancy when in community once enrolled into study	Website (via signposting SMS) Email	PANDA newsletter	Quarterly newsletter providing women with updates on rates of recruitment, any emerging evidence about use of iron in pregnancy and if appropriate testimonials from midwives and women involved in the study (fully anonymised)

7.11.1 Questionnaires

Questionnaires including the EQ-5D-5L will be managed within OpenClinica Participate and sent to participant's email address for self-reporting. Responses will be considered source data when completed electronically by participants in the eCRF. Participants may elect to complete a paper copy of the questionnaire, which will then be data entered into the eCRF by site staff. In this case the paper copy must be retained within the investigator site file as it is the source. Paper questionnaires may be source data verified during on site monitoring. At the end of the trial, the site will be provided with a full copy of the data for participants managed at that site, including questionnaire responses, prior to access to the database being revoked.

7.12 Patient transfers

If a patient moves from the area, a copy of the patient's eCRFs should be provided to the new hospital site with a copy of the consent form. The core research staff will check whether the research staff at the original (host) site are able to continue responsibility for follow-up and data collection. The original (host) site should ensure the participant still has possession of the IMP. The core research team will complete a transfer form to note the participants new site and return a copy to both original and new site. Once this has been done, the new site takes responsibility for the patient; until it is done, the patient remains the responsibility of the original site.

7.13 Loss to Follow-Up and withdrawal criteria

A participant will be deemed fully lost to follow up only in the (uncommon) circumstance where it is not possible to contact/locate the participant, and they have not withdrawn from the trial. Every effort will be made to collect primary and secondary outcome data. All data collected up to the point of withdrawal/lost to follow up will be used in the analysis of the study.

Permanent cessation of trial drug does not constitute participant withdrawal. If the trial drug is stopped permanently for any reason, the participant is to continue participating and data collection will continue until the final study follow-up time point. If a participant expresses a wish not to complete questionnaires, they should remain in the study and other trial-related data will be obtained from medical records review, and/or other treating physicians, unless the participant withdraws consent for any further data collection, including linkage. Every effort will be made to determine each participant's status on the components of the primary outcome. Consent forms at study entry will also include consent to data linkage and all other legal means to determine mother and baby status. The integrity and validity of the study relies on following up randomised participants for the number of primary outcome events which occurred. Unless specified by the participant in the occurrence of transfer to a non-active site, data collection via linkage will still occur.

7.14 End of trial

The End of Trial is defined as the date when follow-up data is completed for all participants at delivery + 6weeks.

In instances of pregnancy loss (miscarriage, termination, and stillbirth), all delivery visit eCRFs should be completed with the relevant details. Lab results at delivery may be taken up to 72 hours after the pregnancy loss as part of any resulting admission. The participant is also considered to have reached end of study, without completing the trial, so an End of Study Form is expected. The end of study date should be the pregnancy end date, or the delivery lab results date, whichever is latest.

8. Trial Treatment (CTIMP)

8.1 Introduction

PANDA Prevention of Anaemia will compare ferrous sulphate 200 mg (65 mg elemental iron) tablets with matched placebo. WGK Ltd, a wholesale distributor of human medicinal products, have been contracted to project manage and coordinate the supply of IMP for the trial. Active ferrous sulphate tablets are sourced from Lomapharm GmbH. Development and manufacture of the matched placebo tablets will be undertaken by Lomapharm GmbH (DE_NI_02_MIA_2020_0022). Packaging, labelling and QP release for clinical trial use will be undertaken by Royal Free London NHS Foundation Trust Pharmacy Manufacturing Unit (MIA(IMP) 11149).

8.2 Regulatory status of the drug

Ferrous Sulphate has a marketing authorisation (MA) in the UK.

8.3 Reference Safety Information

The reference safety information (RSI) will be section 4.8 of the Summary of Product Characteristics (SmPC) for ferrous sulphate submitted as part of the clinical trials authorisation. The SmPC will be checked regularly by the NHSBT CTU for any updates. If an update to the RSI is deemed necessary during the trial this will be made as a substantial protocol amendment.

8.4 Drug storage and supply

Following manufacture and release the IMP will be stored by WGK Clinical Services Ltd and distributed to participating hospitals. Shipments of kits containing a mix of both active ferrous sulphate and placebo will be received by hospital pharmacies and stored on the maternity unit (or other appropriate area) for allocation to trial participants for use at home. The study permits appropriately qualified and trained non-medical clinicians, such as midwives, with delegated authority from the PI to consent, prescribe and supply the IMP to participants. This pragmatic arrangement reflects the competency and scope of practice of midwifery staff and is supported by the trial risk assessment. Local procedures should be followed where trust policy does not permit this for clinical trials of investigational products (CTIMPs). This study also permits the posting of the kits to participants where the local participating site pharmacy allows and has existing procedures in place. Full GCP training is not a requirement where prescribing is part of an individual's usual job remit, however prescribing staff must still be listed on the study delegation log and have undertaken the required PANDA SIV training, which contains the required elements of GCP.

8.5 Preparation and labelling of Investigational Medicinal Product

Ferrous sulphate and matched placebo tablets will be packaged into individually labelled blister packs each containing 10 tablets. Blisters are assembled into individually labelled and numbered kits each containing 24 blisters. Kits contain sufficient doses to last from 12 weeks gestation up to delivery +6weeks. It is not expected that a significant number of participants will start the study before 12 weeks gestation, nor expected that many will delivery later than 41+ weeks. Participants will receive a maximum of 240 tablets.

8.6 Dosage schedules

Ferrous sulphate 200 mg (65mg iron) or matched placebo will be taken daily. The participants will be given sufficient tablets to last from 12 weeks gestation up to their delivery + 6 weeks. General advice on prescribing will be provided to the local research teams.

8.7 Dosage modifications

Participants should aim to maintain the once daily schedule. If a dose is missed or forgotten, then the next scheduled dose should be taken as usual.

8.8 Known drug reactions

Ferrous sulphate or matched placebo is contraindicated in the event of:

- Known hypersensitivity to ferrous sulphate H_2O, ponceau 4R (E124); ponceau 4R aluminium salt (E124). For a full list of excipients please refer to the SmPC
- Rare hereditary problems of galactose intolerance, fructose intolerance, lactase deficiency, glucose-galactose malabsorption.

8.9 Concomitant medication

There are no contraindicated concomitant medications. Iron salts have been reported to affect absorption of a range of drugs including antibiotics as described in SmPC. Absorption of iron may be affected by concomitant use of a range of drugs including antacids, as described in the SmPC. Advice will follow national guidance (https://bnf.nice.org.uk/interactions/iron/)

8.10 Assessment of adherence to treatment

Adherence will be assessed by use of MARS-5 questionnaire at the 28 weeks and + 6 weeks of delivery timepoints.

9. Safety Reporting

The principles of ICH-GCP will be followed, which require Investigators and Sponsors to follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section.

9.1 Definitions

In this trial only Serious Adverse Events/Reactions will be reported. The definitions to be applied to serious adverse events recorded in this study are given in the Table below.

Term	Definition
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening* • requires inpatient hospitalisation or prolongation of existing hospitalisation** • results in persistent or significant disability/incapacity Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. *The term "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.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information:

Reaction (SUSAR)	• in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

9.2 Operational definitions for SAEs

Ferrous sulphate used in this trial is licensed for use in pregnancy to prevent maternal anaemia and has well characterised safety profiles. Non-serious adverse events will not be routinely recorded as the IMP is a licensed product which is being given at a standard dose. However adverse events which are part of the study outcomes will be recorded in the eCRF.

All SAEs will be reported immediately, at least within 24 hours; except the following SAEs which are either not considered to be causally related to the trial intervention, or a foreseeable event in pregnancy which will be collected as a pre-specified trial outcome:

- Birth defect/congenital anomaly
- Stillbirth
- Preterm birth
- Small for gestational age
- Pre-eclampsia or pregnancy induced hypertension
- Gestational diabetes
- Infections contracted during pregnancy or post birth (up to 6 weeks)
- Sepsis during pregnancy or post birth period (up to 6 weeks)
- Antepartum or post-partum haemorrhages of any cause
- Babies admitted to the neonatal unit (NICU, neoHDU, SCBU or transitional care)
- Postnatal depression
- Puerperal sepsis
- Hospitalisation for:
    - Routine treatment or monitoring, or general care
    - Any elective procedure that was planned and scheduled prior to trial entry
    - Birth/delivery
    - management of pregnancy loss

In addition, we do not require SAE reporting of obstetric conditions that can occur and affect any pregnant woman, whether they are taking iron or not. Examples are listed below.

Maternal

- Routine admissions for monitoring of high-risk pregnancies with known maternal complications such hypertension, pre-eclampsia, diabetes, cardiac disease, etc.
- Any vaginal bleeding in pregnancy, threatened miscarriage, antepartum haemorrhage or abruption
- Hyperemesis gravidarum where symptoms preceded trial entry
- Threatened preterm labour
- Urinary tract infections of any kind
- Admission for assessment of abdomino-pelvic pain or labour
- Surgical procedures such as insertion of cervical suture or emergency procedures e.g. appendicitis, return to theatre for infection or bleeding.

Fetal

- Routine admissions for monitoring of high-risk pregnancies with known fetal complications such as fetal growth restriction, hydrops, etc.
- Assessment of reduced fetal movements
- Monitoring for anomalous antibodies / Rhesus disease

9.3 Recording and reporting of SAEs, SARs AND SUSARs

All SAEs, SARs AND SUSARs will be reported to the NHSBT CTU using the trial specific electronic SAE Form. For each SAE/SAR and SUSAR the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality
- Expectedness (Expectedness assessment will only be undertaken if an event is deemed to be related)

Any change of condition or other follow-up information will be updated within the electronic SAE Form in the trial database as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or the final outcome has been reached.

Serious Adverse Events (SAE)

All SAEs that occur between consent and delivery follow-up (+6 weeks) will be submitted to the NHSBT CTU by completing the electronic SAE form in the trial database within 24 hours of observing or learning of the event. All sections on the electronic SAE form will be completed. Details will be recorded in the participants' medical record.

Serious Adverse Reaction (SAR)

All SARs that occur between administration of the first dose of IMP and delivery follow up (+6 weeks) will be submitted to the NHSBT CTU by completing the electronic SAE (eSAE) form in the trial database within 24 hours of observing or learning of the event. All sections on the eSAE form will be completed. In the event that the database was not accessible, a paper copy of the eSAE form will be provided to site to use and email to the NHSBT CTU SAE inbox (Serious_Adverse_Events@nhsbt.nhs.uk). Details will be recorded in the participants' medical record.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Reporting is required between administration of the first dose of IMP and end of delivery follow up (+6 weeks). Details will be recorded in the participants' medical record and reported to the NHSBT CTU within 24 hours of becoming aware of the event using the trial electronic SAE form.

All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to the IMP and unexpected (as compared to the RSI) will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The NHBT CTU will inform the Sponsor, the MHRA, and the REC of SUSARs within the required expedited reporting timelines.

9.4 Responsibilities for reporting and reviewing safety information

Principal Investigator (PI):

- The PI will ensure that all SAEs are recorded and reported to the NHSBT CTU within 24 hours of becoming aware of the event and provide further follow up information

as soon as available. The PI will ensure that SAEs are chased with the NHSBT CTU if a record of receipt is not received within 2 working days of initial reporting

- All SAEs must be followed up until resolution and until there are no further queries. Information not available at the time of the initial report (e.g., an end date for the SAE, discharge summaries, lot numbers, laboratory data) which are received after the initial report must be documented and submitted on a follow-up form.

Chief Investigator (CI) / delegate or independent clinical reviewer:

- The CIs will retain clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit
- The CIs or delegate will review specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan
- The CIs or delegate will prepare the clinical sections and final sign off of the Development Safety Update Report (DSUR)

PANDA Steering Committee (PSC): In accordance with the Trial Terms of Reference for the PSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC): In accordance with the Trial Terms of Reference for the DMC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

9.5 Overdose

Ferrous sulphate overdose will be diagnosed and managed as per the drug SmPC and local practice guidelines. Overdose should also be reported as a SAE including the number of tablets ingested. The IMP label will include ‘keep away from children’ to avoid overdose in children..

9.6 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 MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

9.7 The type and duration of the follow-up of participants after adverse reactions.

Events will be followed up until the event has been resolved or a final outcome has been reached.

9.8 Development safety update reports

The NHSBT CTU in collaboration with the CIs will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or as necessary, to the Competent Authority (MHRA), where relevant the Research Ethics Committee and the sponsor. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

10. PROCESS EVALUATION

10.1.1 Process evaluation

A parallel process evaluation (WS4) will explore the extent of implementation and mechanisms of change that may contribute to interpretation of observed results from WS3. We will explore fidelity of the adherence intervention (i.e. whether the intervention was delivered and enacted as planned) delivery by midwives and engagement by participating

women). We will also explore intervention acceptability and feasibility. Finally, the target behavioural outcome (oral iron supplementation adherence) and the factors influencing this (barriers/enablers) will be explored. Data collection for this process evaluation was piloted on a smaller scale, in WS2 during the dose finding trial, with 24 women and 6 midwives taking part in interviews and 27 women completing surveys.
Findings from the process evaluation will aid interpretation of observed trial outcomes and inform the development of an implementation strategy if the oral iron supplementation strategy is found to be effective and is thus rolled out and/or implemented on a larger scale. Alternatively, it may also inform intervention refinement and optimisation if implementation and adherence are found to be sub-optimal.

10.1.2 Fidelity

We have based our proposed mixed-methods fidelity assessment on best-practice guidance provided by the National Institute of Health Behaviour Change Consortium Fidelity framework (Bellg et al., 2004), and will assess extent of, and variation, in fidelity across multiple domains including: fidelity of training (i.e. the extent to which training is delivered as planned to all intervention providers), fidelity of delivery (i.e. extent to which the intervention is delivered as intended by midwives), fidelity of receipt (i.e. the extent to which the women initially understood the intervention; e.g. how/when to take iron supplements, how to complete the self-monitoring chart for medication adherence); subsequent fidelity of enactment (i.e. engagement with the intervention, performance of any intended planning, monitoring, problem solving strategies, and extent of the target behavioural outcome (oral iron supplementation adherence)).

To enhance the reliability and internal validity of the study, a fidelity enhancement strategy will be put in place, described in more detail below. Briefly, training will be standardised through the production of pre-recorded training sessions and training manuals. Further, intervention providers will be given checklist to follow when delivering the intervention to act as a prompt/cue for the provider to ensure they deliver everything they need to.

Fidelity will be assessed and analysed in the following ways:

- Pre-recorded training videos will be delivered to all midwives delivering the intervention:
    - Midwives will complete training logs capturing the number who complete training, their site and role
    - Midwives may be asked to complete a questionnaire following training asking about their perceived confidence to deliver the intervention, understanding of the intervention and perceived acceptability of the intervention.
    - Web analytics will also be collected to explore access to the training.
    - Descriptive statistics will be generated from training logs, web analytics and the questionnaire.
- Midwives will complete a fidelity checklist after each session, indicating the extent to which they delivered protocol specified intervention components/behaviour change techniques (0-not at all, 1-partially, 2-fully). Descriptive statistics will be generated.
- Content analyse of trial logs and electronic records may take place to check that other intervention components, such as text messages, were delivered at the intended frequency and time point to participants.
- Fidelity of delivery will be quantified in terms of the percentage of protocol-specified components delivered as intended; with high fidelity classified as 80-100% delivered; medium 51-78%, and low fidelity as < 50% (Borrelli et al. 2011).
- Website analytics of the PANDA website will facilitate assessment of women's exposure to and engagement with the website content.
- Data collected from semi-structured interviews (described below) at +6 weeks delivery, surveys (described below) and the adherence questionnaire at 28 weeks gestation will also support assessment of fidelity.

10.1.3 Intervention feasibility and acceptability

A mixed-methods approach will combine in-depth qualitative interviews with a sub-sample of participants (pregnant women and midwives) and quantitative surveys (with pregnant women) in up to the full trial sample, to explore variation in how participants responded to the intervention and their perceived acceptability. Interviews will also explore midwives willingness to deliver the intervention. The interview guide and survey items will be informed by the domains of both the Theoretical Framework of Acceptability (Sekhon et al., 2017) and the Theoretical Domains Framework (TDF; Cane et al, 2012) or Capability, Opportunity and Motivation Model of behaviour (COM-B; Michie et al 2011).

10.1.4 Interviews

We will use a maximum variation sampling strategy, aiming for representation across sites, and demographic groups (e.g. ethnicities) to recruit 30 pregnant women for interviews; sample size contingent on whether thematic saturation is reached (Francis et al 2010)). We will conduct semi-structured interviews to explore women's understanding and perceived acceptability of the oral iron and adherence intervention, plus reported barriers/enablers to initiating iron supplementation and on-going adherence. These interviews will last approximately 30-60 minutes. Consent to be contacted about taking part in the interview will be sought as part of the initial trial consent taking processes. Women who agree to be contacted will be contacted via email or phone, by a member of the research team, in order to ascertain their interest, to answer any questions and to schedule a time for interview.

We will also carry out semi-structured interviews with midwives who have delivered the intervention (at least one midwife per trial site (n=20)), to explore intervention acceptability and to understand any barriers or enablers to implementation. These interviews will last approximately 30-60 minutes. Midwives from the study sites will be contacted via email to ascertain expressions of interest in taking part in interview. A participant information sheet will be sent to midwives at this time explaining the purpose of the interviews and their rights as a participant. A copy of this participant information sheet is enclosed with this ethics application. Fully informed written or verbal consent will be sought prior to interview. Consent can be obtained by midwives sending a signed copy of the consent form back to the research team, by emailing the following statement: "I have read and understood the participant information sheet dated xxx and agree to take part in the study" or, in the last instance, by providing verbal consent where the researcher reads out each consent statement and checks agreement from the midwife. All instances of verbal consent will be recorded and transcribed.

All interviews will be conducted by a member of the behavioural science team who is trained in theory informed qualitative interview techniques. All interviews will be audio recorded and transcribed verbatim via MS teams transcription (where applicable) or through external GDPR compliant transcription services. Verbal assent will be sought from participants taking part in interviews in order to gain explicit consent from the participant that they are happy to be audio recorded. This will be included in the transcript.

The topic guides (one for pregnant women and one for midwives, see Appendices) will be based on the Theoretical Framework of Acceptability (Sekhon et al., 2017), and the Theoretical Domains Framework (TDF) (Cane et al., 2012). Interviews will be conducted via telephone or video call, lasting approximately 30-60 minutes. The interviews will be audio-recorded, transcribed verbatim and fully anonymised. Indicative topic guides are included within this ethics application. These guides may be subject to change following piloting.

A combined deductive framework and inductive thematic analysis approach will be taken to analyse the data, categorising generated themes according to domains of the Theoretical Domains Framework and Theoretical Framework of Acceptability. Analysis software, such as NVIVO, will be used.

10.1.5 Surveys

The survey, delivered as part of the adherence intervention process evaluation to assess participant fidelity, feasibility and acceptability, will be administered electronically to all women participating in the trial via OpenClinica Participate. A paper version will be available for those with no access to the internet and transcribed onto the database by the site team. The survey will be administered at the 28-week antenatal visit in a single pack alongside the adherence questionnaire and EQ-5D-5L. The (full) survey will take up to approximately 15 minutes to complete. Participants will receive a survey containing items taking the form of belief statements corresponding to each of the domains from the COM-B (Michie et al. 2011) and each of the domains from the Theoretical Framework of Acceptability (Sekhon et al. 2017). This will enable exploration of the barriers/enablers to adherence and the perceived intervention acceptability. Participants will rate their agreement on a 5-point Likert type scale. Consent will be sought to take part in this survey as part of the full trial consent form.

Survey data will be analysed using software such as SPSS. Survey data will be summarised descriptively and where appropriate inferential statistics will be generated to explore relationships between intervention acceptability, reported barriers to adherence and adherence.

11. STATISTICS AND DATA ANALYSIS

11.1 Sample size calculation

The primary outcome is a composite of pre-term birth, stillbirth, neonatal death and small-for-gestational age (SGA). A Wolverhampton and London study of 14,001 women (Nair et al., 2017) showed that 17.4% of pregnancies resulted in stillbirths, neonatal deaths, SGA births, and preterm births. A Cochrane Review of pregnancy iron supplementation (Peña-Rosas et al., 2015) reported the relative risk of pre-term birth for iron versus placebo as 0.82 (95% CI 0.58-1.14), and similar relative risks for low birthweight and neonatal death (0.84 (95% CI 0.69-1.03) and 0.91 (95% CI 0.71-1.18), respectively. As some infants may experience multiple components of the composite outcome (e.g. preterm babies are more likely to die in the neonatal period), the number experiencing the composite outcome will not be additive. Therefore, to address whether prophylactic iron reduces the composite outcome rate, assuming, conservatively, a relative risk of 0.85, baseline rate of 15%, and target rate of 12.75%, the required sample size is 4959 in each group (9918 total), with 90% power and a significance level of 5%.

Based on other studies and UK antenatal trial data (CLASP (Collaborative Low dose Aspirin Study in Pregnancy) Collaborative Group, 1994; Rotchell et al., 1998; Poston et al., 2006), a 10% drop-out was allowed for, and therefore the total number of participants required is 11020. Data from Workstream 2 of the PANDA Programme confirmed that 10% drop out is appropriate; there were 23 withdrawals and 2 further participants lost to follow up from the 300 participants recruited.

An interim analysis will be performed to re-assess the sample size calculation after the primary outcome is reported for 2000 participants. This calculation will be based on an estimate of the overall primary outcome rate and the drop-out rate.

11.2 Planned recruitment rate

The 11,020 pregnant women will be recruited across at least 20-25 maternity units. The number of participants required from each maternity unit, if spread equally, is around 600 over 18 months, or 30 participants per month, depending on number of sites. The % of eligible women in each maternity unit is estimated to exceed 70% (a conservative estimate) of the population of women booking in a typical maternity unit of 4500 births/annum (a pool of 3150 from which to recruit).

11.3 Statistical analysis plan

Analyses will be described in detail in a full Statistical Analysis Plan (SAP). This section summarises the main issues. Unless otherwise specified, all analyses will be on an intention-to-treat basis, with all participants included in the arm to which they were randomised.

11.3.1 Summary of baseline data and flow of patients

Characteristics of all randomised participants will be tabulated by arm of the trial to describe the cohort. These will include: demographics, pregnancy details, obstetric history, medical history (including prior anaemia), haemoglobin at randomisation, whether the participant is taking iron containing supplements at baseline. Categorical variables will be presented as N and percentages, whereas mean and standard deviation (or median and interquartile range, depending on the distribution of the data) will be presented for continuous variables.

A CONSORT diagram will be presented to show the flow of participants through the trial.

11.3.2 Primary outcome analysis

The primary outcome for the trial is a composite of pre-term birth (<37 weeks' gestation), stillbirth (≥ 24 weeks' gestation), neonatal death (in the first 28 days) and SGA (<10th centile as per the national Royal College Paediatrics and Child Health (RCPCH) growth charts). This binary outcome will be analysed using mixed logistic regression to allow for adjustment for centre as a random effect. The number needed to treat, and summary statistics (N and percentages) will also be presented.

As a sensitivity, a per-protocol analysis of the primary outcome will be conducted which will exclude those who withdrew from the trial, were randomised in error, were lost to follow-up, and who experienced clinically significant protocol deviations.

11.3.3 Secondary outcome analysis

Maternal outcomes:

Binary outcomes, including the composite parts of the primary outcome (pre-term birth, stillbirth, neonatal death, SGA), will all be analysed similarly to the primary outcome; each binary outcome will be analysed using a mixed logistic regression model adjusting for centre as a random effect. Descriptive statistics will also be presented, summarising the number and percentage with each of the outcomes by arm and overall. Additionally, descriptive statistics will be presented for:

- Haemoglobin, gestation at diagnosis of anaemia, and treatment prescribed for those who develop anaemia during pregnancy. Those diagnosed with anaemia at birth and in the first six weeks post-birth will also be summarised together with the treatment prescribed (outcome: proportion developing anaemia during pregnancy);
- Total blood loss in the first 24 hours (outcome: incidence of PPH);
- Number of units of red blood cells transfused (outcome: proportion requiring red cells prior to discharge);
- Number of iron infusions split by whether administered antenatally and postnatally (outcome: proportion requiring iron infusion up to six weeks after birth);
- Proportion admitted to hospital with infection/sepsis (outcome: proportion with infection and/or sepsis up to six weeks after birth);
- Method of feeding (outcome: proportion breastfeeding at six weeks after birth).

The mean (SD) haemoglobin at 28 weeks and adjusted mean change in haemoglobin between baseline and 28 weeks will be analysed using a mixed Normal model with the adjustment for centre as a random effect. The latter will additionally adjust for the participant's haemoglobin levels at baseline. A similar approach will be taken with haemoglobin at delivery and its adjusted mean change between baseline and delivery. However, as haemoglobin at delivery is more likely to be reported in those who develop

anaemia or experience pre-term delivery, no formal statistical comparisons will be performed to compare between the two treatment arms.

Adherence with medication at 28 weeks and +6 weeks delivery as captured by MARS-5 with scores (0-25) will be summarised descriptively. It is anticipated that this data will not be Normally distributed and therefore appropriate transformations will be applied to formally test for differences between the two treatment arms. These approaches will be fully detailed in the SAP.

Neonatal outcomes:
For these outcomes, the analysis population will include only those pregnancies which resulted in a live birth. Similar analysis approaches to the maternal outcomes will be taken as appropriate: binary outcomes will be analysed using mixed logistic regression models, and continuous outcomes analysed using mixed Normal regression models. For all models, centre will be included as a random effect. As before, descriptive statistics by arm and overall will also be presented for each outcome, with additional descriptive summaries provided including:

- Gestation at birth in categories e.g. <28 weeks, 28-<34 weeks, 34-<37 weeks, 37 weeks+ (outcome: infant gestation at birth);
- Recognised pathogenic organism(s) detected in a blood culture (outcome: proportion with neonatal early onset infection);
- Types of higher level of care/intervention received and the duration of the admissions (outcome: proportion admitted to neonatal/transitional care);

Safety outcomes:
SAEs will be summarised separately for maternal and infants, by treatment arm and overall. No formal statistical comparisons will be made, beyond those which also form a maternal or neonatal outcome. Detailed listings will also be produced. Given the proportionate approach being taken to SAE reporting, full details of the SAEs that should be reported are documented in Section 9.

11.3.4 Exploratory outcome analysis (through data linkage or hospital IT systems)

For the neonatal exploratory outcomes, summary statistics will be presented by treatment arm and overall. Due to the small numbers likely to experience these events, statistical models will only be considered or adjusted if appropriate. Apart from late onset infection, which will include all those with a livebirth pregnancy outcome, the analysis populations used for each outcome will align with those used in the National Neonatal Audit Programme (NNAP). NNAP definitions for the outcomes will be used, where applicable.

In addition to descriptive summary statistics (N and percentages), for the number of neonates with each of the outcomes, descriptive statistics will also summarise:

- If they received therapeutic hypothermia for moderate or severe HIE (outcome: proportion with HIE);
- Hospital admissions or treatment courses for infection (outcome: proportion with late onset infection);
- Definition of late onset infection met, either requiring antibiotics, culture positive, or both (outcome: proportion with late onset infection)

For the exploratory outcomes relating to the treatment of anaemia when this occurs in women recruited to PANDA, summary statistics will be presented for all outcomes with no formal statistical testing. Specifically,

- Adherence to the clinical treatment algorithm will be presented using Ns and percentages for overall adherence, and for each of its two components (given the correct treatment, haemoglobin taken 2-4 weeks after starting).
- Response rates will be summarised both categorically and continuously.

    - Ns and percentages will summarise the proportion whose values either increase from baseline and/or return to within normal ranges after 2-4 weeks treatment.
    - Mean (and standard deviation) of haemoglobin, reticulocytes and other iron markers at diagnosis and 2-4 weeks treatment, and of the difference between the two time points will be presented.
    - Adjusted mean differences will be calculated using linear regression adjusted for the value at diagnosis. 95% confidence intervals for the adjusted means will also be presented.
- HRQoL will be summarised using descriptive statistics. For those diagnosed around the 28 week visit, additional descriptive statistics will summarise changes between EQ-5D-5L at 28 weeks and the 2-4 weeks treatment timepoint, similar to the approach taken for response rates.
- Other outcomes, including PPH and mode of delivery will be summarised in line with the descriptive statistics presented for the corresponding secondary outcome, as outlined above.

11.4 Subgroup analyses

Additionally, the primary outcome analysis will be replicated in several subgroup analyses to explore differential treatment effects on outcomes. These are:

- Maternal age (<25 years vs 25-35 years vs >35 years): Younger and older women may have different burdens of low/borderline iron stores reflecting either childhood nutrition deficiencies or longer durations of menstrual blood losses, increasing the likelihood of experiencing the primary outcome.
- Ethnicity (white and ethnic minority groups): It is anticipated that the iron status and physiological responses to iron may differ between ethnicities, resulting in differences in proportions experiencing the primary outcome (Churchill 2022).
- Markers of iron status at randomisation: Lower Haemoglobin concentrations (Hb<130g/L) or MCV<82fl) may indicate borderline/low iron stores and participants may respond better to oral iron supplementation, reducing the likelihood or experiencing the primary outcome.
- Time since last pregnancy (less than or greater than 18 months between birth and due date for the current pregnancy): Those with more recent pregnancies are likely to have a higher burden of iron deficiency (Pavord 2020) and therefore be at higher risk of the primary outcome.
- Gestational age at randomisation (<12 weeks vs >12 weeks): It is anticipated that those who commence iron therapy earlier will have a longer time to accrue greater irons stores and therefore have a reduced likelihood of experiencing the primary outcome.

11.5 Interim analysis and criteria for the premature termination of the trial

An interim analysis will be performed to re-assess the sample size calculation after the primary outcome is reported for 2000 participants. This calculation will be based on an estimate of the overall primary outcome rate (not calculated by arm) and the drop-out rate, with all other assumptions remaining the same. As part of the interim analysis, the recruitment rate of eligible participants will also be assessed and opening of further sites may be considered if necessary.

The results of this interim analysis will be reviewed by the DMC who will advise the PSC if a sample size adjustment should be considered. The DMC will also review accruing unblinded trial data, in particular safety data, twice a year as part of their overall assessment of the trial. They will have overall oversight and can recommend terminating the trial early for any safety concerns. Based on recommendations from the DMC, the ultimate decision on continuation of the study lies with the PSC.

11.6 Participant population

For the primary analysis of the primary outcome, and secondary maternal outcomes (unless otherwise specified), the analysis population will be intention-to-treat, with all participants in the arm to which they were randomised included. A per-protocol sensitivity analysis of the primary outcome is also planned, with all participants in the arm to which they were randomised, but excluding those: who withdrew from the trial, were randomised in error, were lost to follow-up, and who experienced clinically significant protocol deviations. Except for in the per-protocol sensitivity analysis, participants who withdraw prior to the end of the trial will be included in analyses, where possible.

For many of the secondary infant outcomes, the population to be used will include all participants who experienced a live birth. Apart from late onset infection, which will include all those with a livebirth pregnancy outcome, the intention-to-treat populations will align with the NNAP definitions for all exploratory infant outcomes.

SAEs will be reported and analysed using the arm to which the participant was assigned in the intention-to-treat population.

11.7 Procedure(s) to account for missing or spurious data

Data completeness will be regularly reviewed by the data and trial managers as the trial progresses and any missing data will be requested. Any outstanding missing data at the end of the trial will be assumed to be missing at random and will be summarised. For the main analysis, missing data will not be imputed for primary and secondary outcome measures, and missing data will be excluded from the relevant analyses.

To explore if missing values have an undue impact on the primary outcome result, a sensitivity analysis using multiple imputation will be performed if the primary outcome is missing in more than 10% of the participants included in the intention to treat analysis. If the proportion of participants with a missing primary outcome is less than or equal to 10% then this sensitivity analysis will not be performed.

However, as the primary outcome is identifiable through routine data collection at delivery, it is anticipated that this should minimise missing data arising due to loss to follow-up.

11.8 Other statistical considerations

Any deviations from the original statistical plan will be described, reported and justified in the final data analysis report.

An outline of the health economics plan is provided below, with a separate more comprehensive description set out in a separate health economics analysis plan. This analysis will address the outcomes of health-related quality of life (at baseline, 28 weeks, and 6 weeks after birth), and healthcare utilisation over the trial period.

11.9 Economic evaluation

A separate health economics analysis plan will be produced and will provide a more comprehensive description of the planned within-trial economic evaluation that is only briefly outlined below. Our aim is to determine whether the additional benefits of 200mg ferrous sulphate versus a matched placebo are justified by the additional costs needed to deliver the interventions in an NHS setting. An NHS perspective and a time horizon of 6-weeks postpartum will be employed. The economic evaluation will assess whether the use of ferrous sulphate as a preventive measure translates into differences between groups in costs or outcomes driven by changes in any of the individual components of the composite outcome (pre-term birth, stillbirth, neonatal death and SGA), or secondary outcomes (e.g. maternal mental health).

Conducting an economic evaluation of oral iron supplementation during pregnancy is challenging because the intervention has the potential to affect both mothers and their babies. We do not have yet an approach to incorporate mother and baby outcomes in a

single metric (e.g. QALYs). Therefore, we propose to present the economic evaluation of our study using two different strategies. Our primary strategy will be to use a cost-consequence analysis where maternal/infant cost and outcomes will be presented in a disaggregated manner over the trial period. No attempt will be made in this approach to combine differences in costs and effects among the alternatives into an incremental cost-effectiveness ratio (ICER). A second strategy will be to present the results of the economic evaluation using the more familiar cost-utility analysis from the mother's perspective using quality-adjusted life years (QALYs) over the trial period.

Maternal/infant health-care resource use will be captured using a variety of methods as described above, and to minimise burden on sites and missing data. Data on admissions/readmissions may be collected through hospital PAS systems. We will collect additional maternal health care resource use beyond the usual antenatal/postnatal care, and will include only secondary care. For babies, we will collect detailed information about their original hospital stay, any subsequent hospital readmissions, up to 6-weeks postpartum (this will be linked to National Neonatal Research Database), and seek information on episodes of infection in babies at the time of virtual follow-up contacts (followed by additional targeted data collection at sites).

We will employ unit costs from national catalogues and the literature to estimate costs in each arm of the trial. Maternal QALYs up to 6-weeks postpartum in each trial arm will be estimated as the area under the mother-specific utility profile generated using utility values from the EQ-5D-5L instrument. The currently NICE-recommended crosswalk will be used to derive utilities and these will be connected using a straight-line relationship between follow-up points.

For the primary strategy and the cost-consequence analysis, the composite primary outcome of the trial, a selected number of secondary outcomes (e.g. maternal EQ-5D-5L and mental health data), and maternal/infant costs will be used as consequences in the analysis. EQ-5D-5L profile data will be analysed using the Paretian Classification of Health Change (PCHC) between follow-ups to identify improvements in domains associated to utility values. Consequences will be presented a disaggregated and tabulated manner over the trial period. Main outcomes for the cost-consequence analysis will be presented as mean estimates with associated 95% confidence interval (CI) for each alternative. For the cost-utility analysis, mean differences in maternal costs and QALYs between trial arms will be combined using an incremental analysis of mutually exclusive interventions. Mean differences in costs and QALYs will be synthesised using the ICER expressed as cost per QALY gained. Current value judgements from the National Institute for Health and Clinical Excellence will be followed to determine which of the alternatives is a cost-effective use of NHS resources. Uncertainty around cost-effectiveness results will be presented using parametric and non-parametric confidence intervals for the ICER (if appropriate), and net-benefits. The cost-effectiveness acceptability curve will be constructed to derive the probability of ferrous sulphate to be cost-effective for different values of willingness to pay for maternal QALY gained compared with placebo. For both cost-consequence and cost-utility analysis, mean differences and associated 95% CI between alternatives will be estimated using a normal mixed-effect model with centre as random effect and also adjusted (if necessary) for potential imbalances at baseline. Missing data in costs and utilities will be imputed if necessary, using multiple imputation approaches. We will follow current guidance on methods of technology appraisal to report the results of the economic analysis.

12. DATA MANAGEMENT

12.1 Data collection tools and source document identification

ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in

source documents (original records or certified copies)." The basic concept of source data is that it permits not only reporting and analysis but also verification at various steps in the process for the purposes of confirmation, quality control, audit or inspection.

Source Documents

ICH E6 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

Source documents in this trial include:

- Informed consent form
- Hospital records (Paper or electronic)
- Laboratory test results
- Records kept at the Pharmacy such as prescriptions and accountability log
- Electronic participant questionnaires

Case report forms (CRFs)

All case report forms will be electronic (eCRF). Sites will be granted access to the eCRF system following approval of all site registration documentation and completion of training provided by NHSBT CTU. Sites must adhere to the instructions and submission schedule outlined in the protocol. The eCRFs must be completed directly onto the database system.

NHSBT CTU staff will be in regular contact with local site personnel to check on progress and to help with any queries that may arise. Incoming electronic forms will be checked for completeness, consistency, timeliness, and compliance with the protocol. CRFs as Source Documents are as follows:

- EQ5D-5L
- MARS-5
- Acceptability questionnaire.

12.2 Data handling and record keeping

The Principal Investigator has overall responsibility for data collection at Site. Participant data will be entered onto the trial database designed and administered by the NHSBT CTU data management team using OpenClinica. The OpenClinica database will be used for electronic data capture (EDC) management and reporting on this trial. Training and instructions for completion of eCRFs will be given to each site at site activation. Data sourced through linkage applications will be held securely in accordance to the organisations data security standards within NHSBT.

All case report forms will be electronic. Sites will be granted access to the EDC system following approval of all site registration documentation and completion of training by the NHSBT CTU office. Sites must adhere to the instructions and submission schedule outlined in the protocol. The eCRFs must be completed directly onto the EDC system (i.e., Database).

The NHSBT CTU staff will be in regular contact with local site personnel to check on progress and to help with any queries that may arise. Incoming electronic forms will be checked for completeness, consistency, timelines and compliance with the protocol.

Interviews will be audio recorded (onto an encrypted recording device) with the permission of the participant and transcribed by an approved and General Data Protection Regulations (GDPR) compliant, external transcription service. Interview transcripts will be fully anonymised, so that no individual or organisation may be identified from the transcripts and

reported data. Participants will be asked if they would like to receive a copy of their transcript for review and will be given the opportunity to clarify or remove information if they wish from the transcript. Audio recordings, transcripts and midwife consent will be stored in UCL data safe haven.

12.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits, and inspections.

12.4 Archiving

Archiving will be authorised by the Sponsor following submission of the end of trial report. All essential documents will be archived at least 15 years in accordance with national law, whichever is longer after completion of trial. Destruction of essential documents will require authorisation from the Sponsor. The sponsor will be responsible for archiving the TMF. Following completion of analysis, the trial database will be archived in accordance with the Trial Sponsor policies.

The sites will be responsible for archiving the Investigator Site Files. The sites must keep the signed Informed Consent forms, all trial documentation and source documents collected during the trial in a secure location (e.g., locked filing cabinets in a room with restricted access). All data must be accessible to the competent authorities and the Sponsor with suitable notice for inspection. All trial documentation must be retained for at least 15 years after trial completion or termination. In addition, the Investigator must not discard or destroy any trial specific materials unless otherwise instructed by the Sponsor.

13. MONITORING, AUDIT & INSPECTION

The frequency, type and intensity for routine monitoring and the requirements for “for cause” monitoring will be detailed in a separate monitoring plan. In addition to potential GCP inspections or audits by the host R&D department, the Sponsor and NHSBT CTU reserve the right to conduct site audits, either as part of its on-going audit programme, or in response to adverse observations.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Research Ethics Committee (REC) Review & Reports

- Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent form and other relevant documents.
- Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial. If necessary, an amendment will also be reviewed and approved by the NHS R&D departments before implementation.
- All correspondence with the REC will be retained in the Trial Master File (TMF).
- An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial has ended.
- It will be the responsibility of the CIs or delegate to produce the annual reports as required.
- The NHSBT CTU on behalf of the CIs will notify the REC of the End of Trial.
- Within one year of the end of the trial, the NHSBT CTU on behalf of the CIs will submit a final report with the results, including any publications/abstracts, to the REC.

14.2 Peer review

The research proposal this protocol has been based on has been independently peer reviewed by the National Institute for Health Research (NIHR) Programme Grants for Applied Research (PGfAR) funding committee.

14.3 Public and Patient Involvement

Patient and Public involvement (PPI) has been embedded in all aspects of the management and governance of the PANDA programme. The PPI model for the PANDA programme involves two members of the Nottingham Maternity Research Network (NMRN) who are co-investigators and members of the PANDA research team. The PPI are led by a Professor of Midwifery, with the full Network available for consultation on a 2-4-monthly basis. The PPI team have reviewed and contributed to this trial protocol and participant facing materials and design. They will continue to be involved in the oversight and management of this trial including data analysis and dissemination of the findings.

14.4 Regulatory Compliance

The trial will not commence until the following approvals are obtained: Clinical Trial Authorisation (CTA) from the MHRA, a favourable opinion from the REC and HRA approval. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol patients into the study, the Chief Investigators/Principal Investigators or designees will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.

For any amendment to the study, the Chief Investigators or designee, in agreement with the Sponsor, will submit information to the appropriate body for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the trial as amended.

14.5 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used, for example it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Accidental protocol deviations can happen at any time and must be reported to the co-ordinating centre at NHSBT CTU. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

14.6 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree:

a) the safety or physical or mental integrity of the participants of the trial; or
b) the scientific value of the trial

The site will inform NHSBT CTU as soon as they are aware of a potential serious breach, so NHSBT CTU can report the breach to the trial Sponsor. The NHSBT CTU and the Sponsor will discuss the breach and decide whether the breach is classified as serious. If the breach is serious, NHSBT CTU will report to the REC and MHRA within 7 days of becoming aware of the breach as per the UK regulatory requirements. NHSBT CTU will notify the REC and MHRA in writing of any serious breach of:

a) the conditions and principles of GCP in connection with that trial; or
b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

14.7 Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the UK Data Protection Act 2018 with regards to the collection, storage, processing, and disclosure of personal information and will uphold the regulations' core principles. The confidentiality standards will be maintained by coding each patient enrolled in the trial through assignment of a unique participant identification number. Only pseudo-anonymous data will be entered into the trial database.

Limited patient identifiable data points will be required, to enable linkage to the datasets (described in section 7.8 and 7.9). Consent will be obtained via the participant to collect these data items. Identifiable information will not be retained for the analysis. The required data will be transferred directly to the trial database with access limited only to the trial team The trial statistician(s) will ensure that any onward data transfer is performed securely and in agreement with the terms of the relevant Data Transfer Agreement.

Consent will be sought from participants to inform their General Practitioner (GP) of their enrolment in the trial.

Data generated by this trial must be available for inspection upon request by representatives of MHRA and other national and local health authorities, NHSBT CTU monitors, representatives, and the REC for each trial site, as appropriate. The data controller for this study is NHSBT.

14.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

At the time of writing the protocol, the Chief Investigators, Principal Investigators and all members of the trial committees had no competing interests that might influence trial design, conduct or reporting. Any potential disclosures arising during the trial will be notified to the Chief Investigators. These will include ownership interests that may be related to products, services or interventions that may be significantly affected by the trial, commercial ties (including pharmaceutical and/or technology company, or behaviour modification) and any non-commercial potential conflicts (e.g. professional collaborations that may impact on academic promotion).

14.9 Indemnity

Insurance for Clinical Trials sponsored and managed by NHSBT is covered by the NHS Resolution Schemes as follows:

- The Clinical Negligence Scheme for Trusts (CNST): for negligent harm. Any clinical negligence liabilities owed to a patient/participant arising out of or in connection with practical implementation of clinical trials sponsored by NHSBT are covered by the Scheme.
- The Liabilities for Third Parties Scheme (LTPS): covers employers' and public liability claims from NHS staff, patients and members of the public. These range from straightforward slips and trips to serious workplace manual handling, bullying and stress claims. LTPS covers claims arising from breaches of the Human Rights Act, the Data Protection Act and the Defective Premises Act, as well as defamation, unlawful detention and professional negligence claims.

14.10 Post-trial care

Once the trial is over, all participants will continue to receive pregnancy standard care. The participants and their treating clinicians will decide whether iron supplementation should continue beyond delivery (+6 weeks) or not, and based on the participant's individual needs.

14.11 Access to the final trial dataset

The final data set will reside with NHSBT. The Chief Investigators will have access and can approve exceptional access for other members of the trial team to facilitate analysis or to cover for absences. Access to the final data set for additional analyses will be permitted under the agreement of the PSC and according to the trial dissemination policy (see below).

15. DISSEMINATION POLICY

15.1 Dissemination policy

- Ownership of the data arising from this trial reside with the Sponsor. On completion of the trial the data will be analysed and tabulated, and a final trial report prepared. Any manuscript(s) will be prepared by the relevant members of the writing group and the PANDA Project Management Group.
- Draft copies of all trial manuscripts will be circulated to all collaborators for review prior to their submission for publication.
- The main trial results will be presented at conferences and published in a peer-reviewed journal(s), on behalf of all collaborators. All presentations and publications related to the trial must be authorised by the PMG.
- The members of the PSC and DMC will be listed with their affiliations in the acknowledgements of the main publication. The funders will be acknowledged within all publications.
- The final report's abstract and reference will be accessible on the PANDA Programme website.
- Participants will be able to access the results through the PANDA Programme website.
- A trial identifier will be included on all presentations and publications (e.g. the ISCRTN).
- No data may be made public before publication and without agreement from the CIs and Sponsor.
- The datasets generated during and/or analysed during the trial will be available upon request from the NHSBT Clinical Trials Unit after de-identification (text, tables, figures and appendices) 9 months after publication and ending 5 years following article publication. Data will be shared with investigators whose use of the data has been assessed and approved by the PSC, and if appropriate an ethics committee, as a methodologically sound proposal.

15.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship on any publications arising from this study will follow the rules laid out by the International Committee of Medical Journal Editors definitions of Authors and Contributors.

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17. Governance and Committees

17.1 Protocol Development Group:

The protocol was written by all members of the PANDA research team.

17.2 Role of trial sponsor and funder

NHS Blood and Transplant (NHSBT) is the primary trial sponsor and overall management of the trial will be undertaken by the NHSBT Clinical Trials Unit. Queries relating to the NHSBT sponsorship of the trial should be addressed to: Yomi Adegbaju, NHS Blood and Transplant, email: research.office@nhsbt.nhs.uk. The Sponsor has overall responsibility for the trial, including final financial decisions and participating in site monitoring visits.
The funder is the National Institute for Health Research (NIHR). NIHR will agree the trial design, conduct, data analysis and interpretation, manuscript writing and dissemination of results.

17.3 Roles and responsibilities of trial management committees/groups and individuals

17.3.1 Programme Steering Committee (PSC)

A Programme Steering Committee (PSC) with an independent Chair, statistician, clinicians, behavioural scientist and patient representative has been appointed and will be responsible for overseeing the progress of the trial. The PSC will convene at least annually either face-to-face, virtually or by teleconference. The PSC will focus on progress of the trial, patient safety, and the consideration of new information relevant to the research question. The PSC will provide advice, through its Chair, to the CIs, the trial Sponsor, the trial Funder, and the Host Institution. The ultimate decision on continuation of the trial lies with the PSC. The PSC Charter includes details of membership as well as roles and responsibilities of the committees' members.

17.3.2 Data Monitoring Committee

The Data Monitoring Committee (DMC) will monitor trial data and will meet regularly for the duration of the trial. The role of its members is to monitor the trial data and make recommendations to the PSC on whether there are any ethical or safety reasons why the trial should not continue. The safety, rights and well-being of the trial participants are paramount.

The NHSBT CTU has a core Data Monitoring Committee (DMC) for all of its transfusion medicine trials, with the addition of two experts relating to the specific trial. The group will act as DMC to this trial, provide advice to the Chair of the PSC and can recommend premature closure of the trial. The DMC Charter includes details of membership as well as roles and responsibilities of the committees' members.

17.3.3 Programme Management Group

The Programme Management Group (PMG) has been set up by the co-CI's and it includes the lead investigators and the overall PANDA programme (Primary prevention of maternal ANaemia to avoid preterm Delivery and other Adverse outcomes) co-applicants, members of the NHSBT CTU and the Sponsor representative. The PMG will convene regularly, either face-to-face, virtually or by teleconference, and will discuss recruitment and other practical aspects of the trial. The day-to-day management of the trial will be co-ordinated through the CIs and NHSBT CTU.

Appendix ii. Abbreviations and Glossary

CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
HRA	Health Research Authority
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trials
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
neoHDU	Neonatal High Dependency Unit
NHS	National Health Service
NHS R&D	National Health Service Research & Development
NHSBT	NHS Blood and Transplant
NICU	Neonatal Intensive Care Unit
NIHR	National Institute for Health and Care Research
PI	Principal Investigator
PIS	Participant Information Sheet
PMG	Programme Management Group
PSC	Programme Steering Committee
QoL	Quality of Life
QP	Qualified Person
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious adverse event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SCBU	Special Care Baby Unit
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

18. Appendices

18.1 **Appendix 1 Amendment History**

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	2.0	03/04/2024	PANDA team	Addition of data collection around anaemia treatment, update to analysis section and some small wording changes throughout.
2	2.1	04/07/2024	PANDA team	Updated wording within the analysis section and also small updates to wording throughout
3	2.2	03/12/2024	PANDA team	Addition of guidance for safety reporting
4	2.3	28Aug2025	PANDA team	Clarifications around consent requirements, when participants must receive IMP by, window for baseline EQ5D completion, known drug reactions and end of trial guidance in instances of pregnancy loss. Minor updates to wording throughout.
5	2.4	20Oct2025	PANDA team	Clarification around who can confirm eligibility and when. Updating wording on GCP requirements for prescribers.