PANDA
Primary prevention of maternal ANaemia to avoid preterm Delivery and other Adverse outcomes

NHS Blood and Transplant

A phase III, multi-centre, randomised placebo-controlled trial of oral iron supplementation for the prevention of maternal anaemia (**PANDA Prevention of Anaemia**)

Workstream 3, 4 & 5 of the NIHR-funded 'PANDA' research programme

(**P**rimary prevention of maternal **AN**aemia to avoid preterm **D**elivery and other **A**dverse outcomes)

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Site Initiation Visit Presentation slides V2.0

CIs: Prof Simon Stanworth & Prof Marian Knight
Lead Obstetrician: Prof David Churchill

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Outline

- Background
- Trial design
- Trial visits and assessments
- IMP
- Data collection
- Behavioural intervention
- Safety monitoring
- Monitoring
- Contact information

Why do the research?

Around 1 in 3 women in the UK develop anaemia during pregnancy.

Anaemia is associated with adverse outcomes.

These adverse outcomes include haemorrhage, prematurity, stillbirth, and maternal and neonatal mortality.

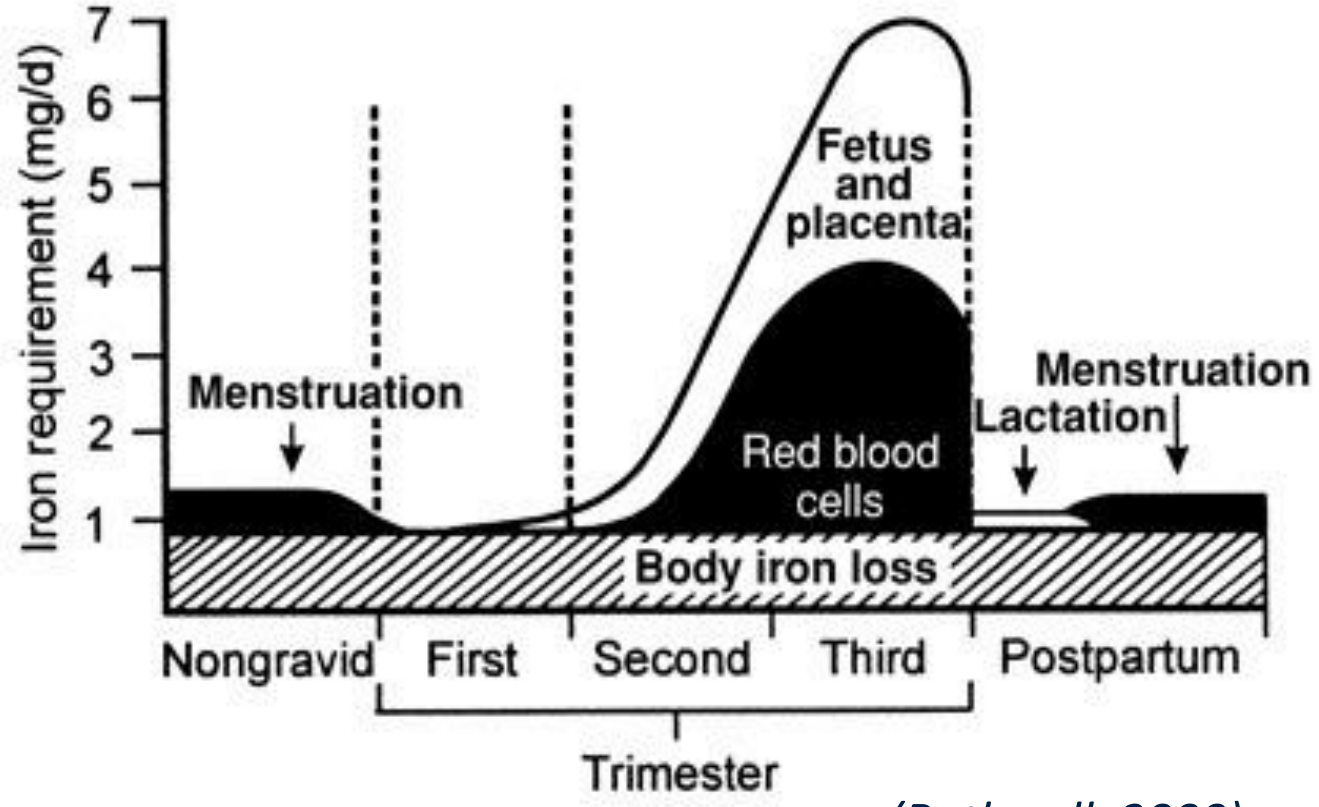
Anaemia is treatable in pregnancy, but we would like to prevent it.

Preventing anaemia may have long-term benefits for the mother and child

Does universal primary prevention of anaemia during pregnancy with oral-iron supplementation have an incremental benefit on reducing adverse maternal and infant outcomes?

Background

Iron Requirements in Pregnancy



(Bothwell, 2000)

Results **Epi**

bjh research paper

Association between maternal haemoglobin and stillbirth: a cohort study among a multi-ethnic population in England

Table III. Association of maternal anaemia with adverse infant outcomes.

	Stillbirth (n = 14001 singleton babies born at or after 24^{+0} of gestation)					
Maternal anaemia	Stillborn (%)	Live born (%)	Unadjusted OR (95% CI)	P-value for trend	†Adjusted OR (95% CI)	P-value for trend
First visit (Hb, g/l)						
Normal Hb (≥110)	59 (77·6)	11 529 (82·8)	1 (ref)	0·025	1 (ref)	0·018
Mild (100–109)	2 (2·6)	767 (5·5)	0·51 (0·12–2·09)		0·56 (0·13–2·30)	
Moderate-severe (<100)	6 (7·9)	273 (2·0)	4·29 (1·84–10·03)		4·97 (2·09–11·79)	
Missing	9 (11·8)	1356 (9·7)	1·29 (0·64–2·62)		1·50 (0·73–3·11)	
28 weeks (Hb, g/l)*						
Normal Hb (≥110)	26 (41·9)	7833 (56·6)	1 (ref)	0·008	1 (ref)	0·059
Mild (100–109)	12 (19·4)	3007 (21·7)	1·20 (0·61–2·39)		1·30 (0·64–2·61)	
Moderate-severe (<100)	10 (16·1)	988 (7·1)	3·05 (1·47–6·34)		2·81 (1·25–6·30)	
Missing	14 (22·6)	2014 (14·6)	2·09 (1·09–4·02)		1·84 (0·91–3·74)	

NATIONAL GUIDELINES

Guideline	BSH (2019)[16]*	RANZCOG (2015)[17,18]	ACOG (2021)[19]	WHO (2016)[20]
Routine Screening				
Haemoglobin	Booking and 28 weeks. Additional screening for high-risk pregnancies	Booking and 28 weeks.	1st trimester and 24-28 weeks gestation	Hb screening at least once during pregnancy. Additional screening for high-risk groups.
Ferritin	Ferritin screening for people with known haemoglobinopathy or risk factors for iron deficiency**.	Ferritin screening for those with anaemia risk factors.	Not routinely recommended; may be used if iron deficiency is suspected.	Not stated
Diagnosis				
Anaemia	<110 g/L (1st trimester), <105 g/L (2nd & 3rd)	<110 g/L (1st trimester), <105 g/L (2nd & 3rd)	<110 g/L (1st trimester), <105 g/L (2nd & 3rd)	<110 g/L (1st trimester), <105 g/L (2nd & 3rd)
Iron Deficiency	SF <30 µg/L	SF <30 µg/L	SF <30 µg/L	SF <15 µg/L
Oral Iron Treatment				
Indication	Anaemia. Prophylactic iron may be given to high-risk patients	Iron deficiency or iron deficiency anaemia.	Routine low dose iron supplementation	Prophylactic iron for all pregnant women
Preparation	Ferrous fumarate or other equivalent salts	Not specified	Not specified	Not specified
Dose	40-80 mg elemental iron daily	20-80 mg elemental iron daily (IDWA) 100-200 mg elemental iron daily (IDA)	Not Specified	30-60 mg elemental iron daily (prophylactic dose) 120 mg elemental iron daily for anaemia treatment
IV Iron Treatment				
Indication	Hb <70 g/L, anaemia at >34 weeks, or failure or intolerance of oral iron.	Failure of oral iron, poor oral iron tolerance or compliance and rapid iron store needed.	Failure or intolerance to oral iron and for severe iron deficiency late in pregnancy.	Severe anaemia (Hb <70 g/L), late pregnancy, failure or intolerance of oral iron.
Preparation	Ferric carboxymaltose, ferric derisomaltose, iron hydroxide.	Not specified	Not specified	-
Monitoring Post Oral Iron Treatment				
Biomarker	Hb	Hb	Not specified	Hb
Timing	2-3 weeks	Not specified	Not specified	-
Response	Hb rise of 20 g/L over 3-4 weeks	Not specified	Not specified	Aim Hb >110 g/L

TIAP: Response to iron therapy
The two definitions

Categories	Post oral iron therapy follow-up (V2&V3)		End of iron therapy follow-up (V5 end of treatment 3 months after the diagnosis)	
	N	Incidence [1] (95% CI)	N	Incidence [1] (95% CI)
Haematological response[2]	35	36.5 (27.6 – 46.4) 40.2 (30.4 – 50.7) §	55	57.3 (47.3 – 66.7) 70.5 (59.8 – 79.7) §
Haematological and/or gestational response[3]	53	55.2 (45.3 – 64.8) 60.9 (50.4 – 70.7) §	69	71.9 (62.2 – 79.7) 88.5 (80.0 – 94.1) §
Attrition [4]	9	9.4 (5.0 – 16.9)	18	18.7 (12.2 – 27.0)

1 Incidence of response, attrition, remission and overall retention calculated based on total eligible antenatal population (N=96). § Incidence of response, non-response and remission calculated based on participants with observed outcomes, i.e., n=87 at V2/V3 and n=78 at V5.

DFT - Methods and Study

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QUESTION: What is the optimal dose of oral iron to take forward to further definitive trials of iron supplementation to prevent anemia in pregnancy?

CONCLUSION: A daily dosing schedule might give the best opportunity for delivering an adequate iron load during pregnancy in nonanemic women.

Population

300 participants **5 NHS Trusts**

Healthy nonanemic pregnant women
<14 weeks' gestation
No known contraindications for iron

Median age: 31
Median gestation (weeks): 12.7

Randomized 1:1:1

Intervention

Ferrous Sulphate 200mg administered between randomization and 28 weeks' gestation, and taken:

Daily	Alternate	3x per week
n = 98	n = 99	n = 103

Four main outcomes of interest

Adherence
Transitions in hemaglobin
Side effects
Protocol compliance

Adherence: Tablet count

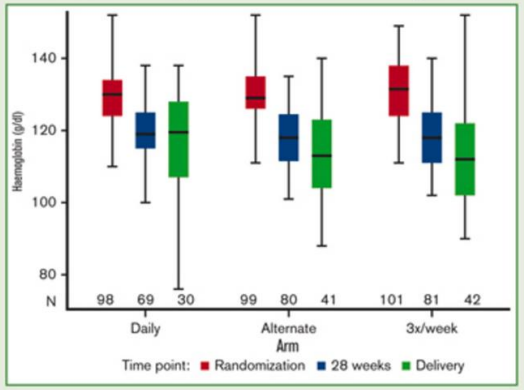
Daily	Alternate	3x per week
33/70, 47.1% (35.1-59.4)	**49/79, 62.0%** (50.4-72.7)	**48/79, 60.8%** (49.1-71.6)

Mean # tablets per week

5.1	**3.1**	**2.6**

Transitions in hemaglobin

Smaller reduction between randomization and 28 weeks' gestation for the daily arm



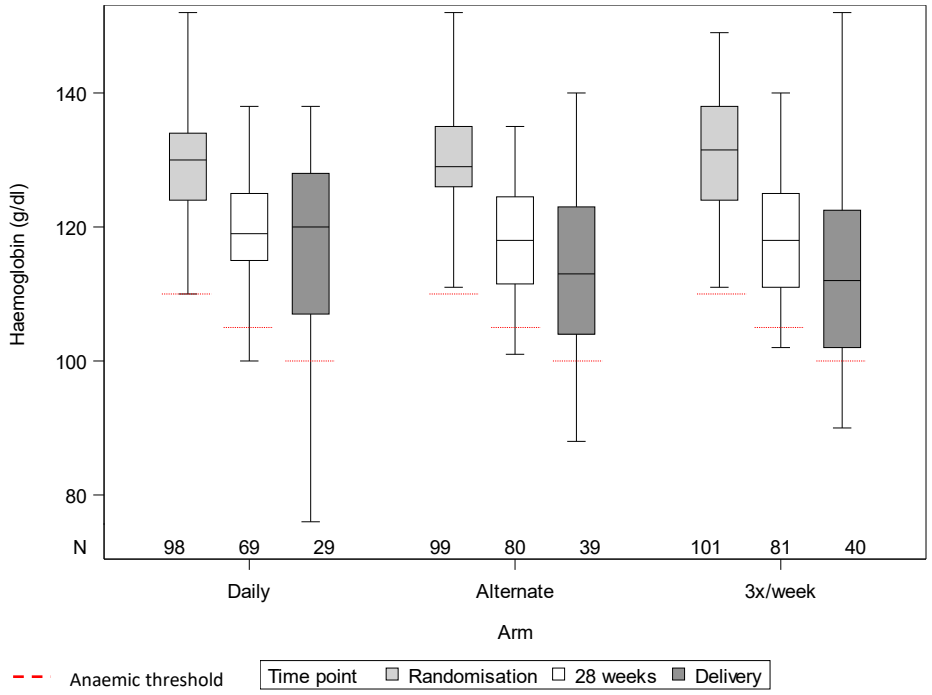
Side effects

Symptoms improved during pregnancy with overlap in proportions between treatment arms

The impact of different doses of oral iron supplementation during pregnancy: a randomized trial *(Stanworth et al., 2024)*

Workstream 2

Boxplot of haemoglobin by visit



% maintaining above diagnostic thresholds

	Daily 98	Alternate 99	3x/week 103	Total 300
28 weeks				
n/N (%)	66/69 (95.7%)	73/80 (91.3%)	78/81 (96.3%)	217/230 (94.3%)
95% CI	(87.8%-99.1%)	(82.8%-96.4%)	(89.6%-99.2%)	(90.5%-97.0%)
Delivery				
n/N (%)	24/29 (82.8%)	33/39 (84.6%)	32/40 (80.0%)	89/108 (82.4%)
95% CI	(64.2%-94.2%)	(69.5%-94.1%)	(64.4%-90.9%)	(73.9%-89.1%)

All participants were above the diagnostic threshold for anaemia at randomisation

Evidence

Rukuni et al. BMC Pregnancy and Childbirth (2015) 15:269
DOI 10.1186/s12884-015-0679-9

BMC Pregnancy & Childbirth

RESEARCH ARTICLE Open Access

Screening for iron deficiency and iron deficiency anaemia in pregnancy: a structured review and gap analysis against UK national screening criteria

Ruramayi Rukuni[1*], Marian Knight[1†], Michael F Murphy[2†], David Roberts[2†] and Simon J Stanworth[2†]

BJHaem BRITISH JOURNAL OF HAEMATOLOGY — British Society for Haematology

Research Paper | Open Access

Association between maternal haemoglobin and stillbirth: a cohort study among a multi-ethnic population in England

Manisha Nair, David Churchill, Susan Robinson, Cathy Nelson-Piercy, Simon J. Stanworth, Marian Knight

First published: 26 October 2017 | https://doi.org/10.1111/bjh.14961 | Citations: 30

BJHaem BRITISH JOURNAL OF HAEMATOLOGY — British Society for Haematology

ORIGINAL PAPER

Maternal iron deficiency anaemia in pregnancy: Lessons from a national audit

David Churchill, Hind Ali, Mahmoud Moussa, Ciara Donohue, Sue Pavord, Susan E. Robinson, Katherine Cheshire, Paul Wilson, John Grant-Casey, Simon J. Stanworth

First published: 03 August 2022 | https://doi.org/10.1111/bjh.18391 | Citations: 1

BJHaem BRITISH JOURNAL OF HAEMATOLOGY — British Society for Haematology

Guideline | Free Access

UK guidelines on the management of iron deficiency in pregnancy

Sue Pavord, Jan Daru, Nita Prasannan, Susan Robinson, Simon Stanworth, Joanna Girling, on behalf of the BSH Committee

First published: 02 October 2019 | https://doi.org/10.1111/bjh.16221 | Citations: 119

Prevalence of maternal anaemia and its predictors: a multi-centre study

Filipa Barroso • Shubha Allard • Brennan C. Kahan • ... Louise Choo • Khalid Khan • Simon Stanworth •

ejog European Journal of Obstetrics & Gynecology and Reproductive Biology

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EDITORIAL

Anemic Data for Preventive Screening and Supplementation to Address Iron Deficiency Anemia in Pregnancy

Elaine L. Duryea, MD; Catherine Y. Spong, MD

The US Preventive Services Task Force (USPSTF) recently re- sible and important to patients. While there is no readily apparent

- *"The USPSTF attempted to examine the benefits associated with* ***screening for iron deficiency without associated anemia in pregnancy,*** *which is thought to be a precursor to iron deficiency anemia, but* ***evidence was insufficient to recommend for or against*** *the practice."*
- *"There remain* ***significant knowledge gaps in the understanding of the utility of screening for iron deficiency anemia and routine supplementation with iron in pregnancy, especially in the form of rigorous RCTs.*** *However, there are even larger, and perhaps more important, knowledge gaps in relation to health-related social needs which may influence the development of iron deficiency anemia."*

- *JAMA2024*

PANDA Programme Structure

WS1: Qualitative study
Barriers to taking oral iron & development of BI?

WS2: Pilot oral iron dose-finding study
best dose for adherence/side effect rates/Hb?

WS3: Large efficacy 2- arm trial (N=11,020)
Primary outcome: composite of pre-term birth, stillbirth, neonatal death & SGA

WS4: Process evaluation
Assessing the fidelity of intervention delivery

WS5
Data linkage and routine health data
Long term maternal and infant follow up

To improve maternal and infant outcomes by evaluating prevention of anaemia during pregnancy with oral iron supplementation

CI Stanworth, Knight

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The PANDA

(Primary prevention of maternal ANaemia to avoid preterm Delivery and other Adverse outcomes)

programme of research

Brief trial summary WS3

NIHR | National Institute for Health Research

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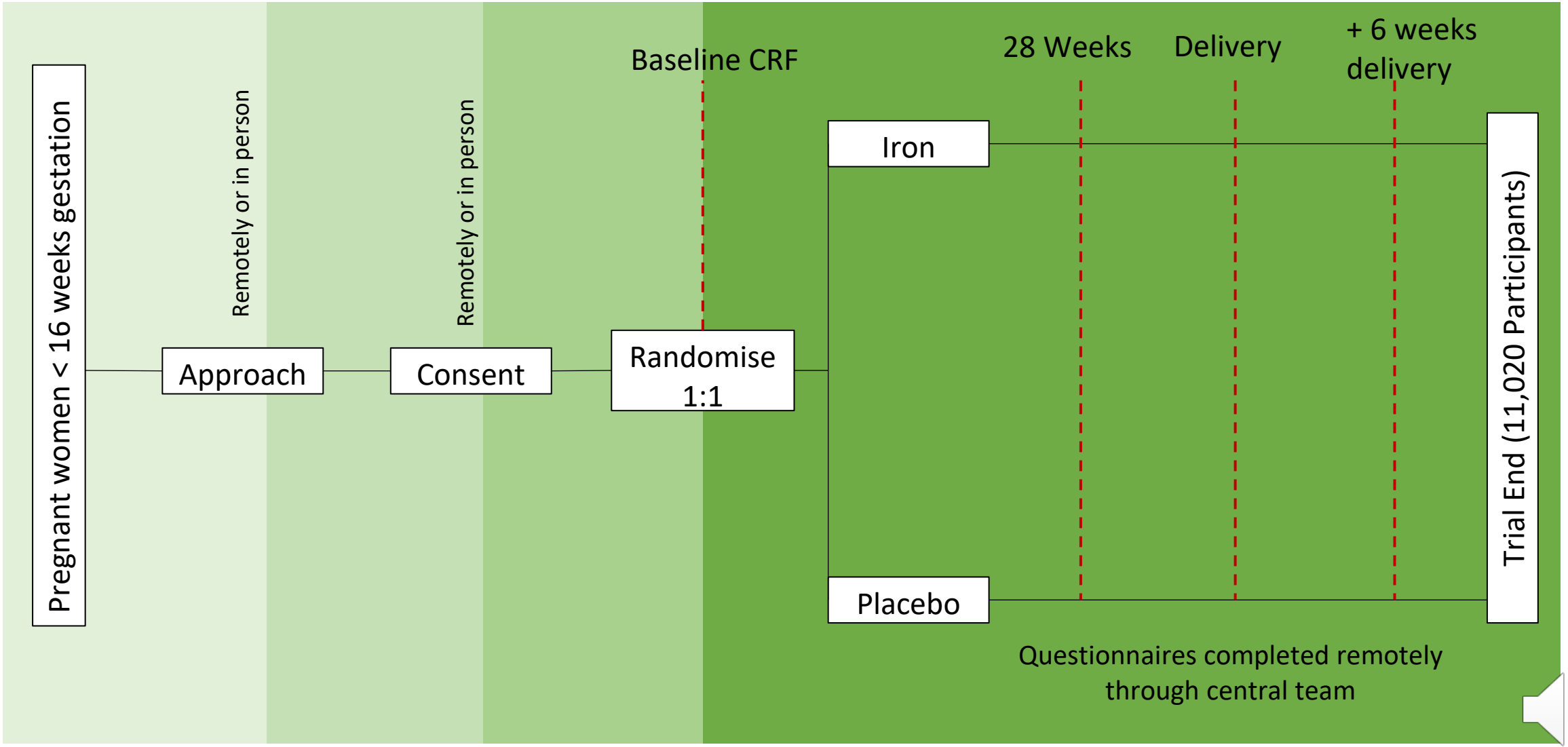
Trial Design

- Multi-centre
- Randomised
- Double-blind
- Two-arm

200 mg Ferrous sulphate vs matched placebo

Trial Schema



Target Population

Inclusion	Exclusion
Healthy non-anaemic pregnant women of all parities (haemoglobin concentration (Hb) ≥110 g/l measured by the first trimester blood profile)	Known haemoglobinopathies (women with haemoglobinopathy trait are still eligible)
Live fetus on a first trimester ultrasound scan	Anaemia of any type
15 weeks + 6 days gestation or less at consent	Severe gastrointestinal disease
Age 18 and above	Allergies to iron
Able to give informed consent	Multiple pregnancies
	Haematological conditions that require ongoing treatment with either regular oral or intravenous iron or transfusions, e.g. dyserythropoiesis or other similar condition/disease.
	Chronic renal disease (requiring replacement therapy)
	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 the form of supplement use will be collected.

Outcomes

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).

Some of the secondary outcomes
Proportion of women developing anaemia
Transitions in haemoglobin
Primary postpartum haemorrhage
Proportion of women who received red cell transfusions
Proportion of women who received iron infusions
Proportion of women with an infection and or sepsis

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Trial visits and assessments

By Eleanor Hounslea & Adela Dann

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Schedule of assessments

Site collection

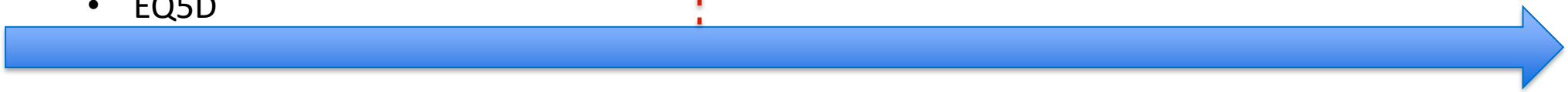
Baseline
- Eligibility
- Consent
- Randomisation
- Demographics
- Obstetric history
- Medical history
- Con-meds
- Lab tests (FBC)
- Fidelity checklist
- EQ5D

28 weeks
- FBC

- Anaemia treatment
- EQ5D

Delivery
- FBC
- Mother outcomes
- Baby outcomes

+6 weeks delivery
- Mother outcomes
- Baby outcomes
- Healthcare resources



Central team

- EQ5D
- MARS 5
- BI questionnaire

- EQ5D
- MARS 5
- Post birth questionnaire
- Interview

Questionnaires still need to be scheduled by sites. See CRF flow charts if unsure how to complete CRFs in certain circumstances

Health Utilisation data

Some of the data required for PANDA is on hospital admissions, antenatal and postnatal contacts throughout the study for women, and also any neonatal admissions for babies.

We will also be conducting linkage with the NNRD for neonatal data.

Participant identification

The trial information packs can be given/sent to participants through:

- Community midwives
- Electronic patient records (e.g., MyChart BADGER) / other relevant databases
- Directly by research midwives/team during routine clinic visits (i.e. US or pre-natal visits)
- Advertisements in clinics, social media, PPI pages etc.
- Invitation letters/PIS can be email to potential participants also.

Please record all approached participants (provided with PIS) in the OC screening database. All other potential participants should be recorded on internal logs/the paper logs provided in the site file

Participant eligibility & consent

Eligibility:

– Eligibility can be confirmed by non-clinicians (e.g. research midwives/nurses) as per the protocol unless participants have any of the following medical conditions. Then eligibility should be confirmed by a doctor:

• Any 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.

Evidence of eligibility confirmation must still be recorded in the medical notes, including who it was confirmed by and on what date.

Participant eligibility & consent

OpenClinica e-consent:

- Participants can complete e-consent on the unit or over the phone with the consenter
- Please record the consent discussion in the medical notes, including date and name of consenter etc.
- Consent must be countersigned by the consenter immediately after.
- Ensure participant has a copy of the fully signed consent form.
- Consent must be taken by a delegated member of the research team (documented on the delegation log and signed by the PI)

Randomisation

How to randomise participants:

- There is no electronic randomisation system
- Randomisation occurs when the IMP kit is provided to participant
- Randomisation code is the **kit number** of the kit box. This **needs to be logged before providing the kit to the participant** and recorded in the eCRF and accountability log.
- Participants should be provided with an ID card, populated with the kit ID and their unique study ID, to carry with them in cases where unblinding is required.

- Participants who consent at the 15 week + 6 days gestation can receive the IMP no later than 10 days after e.g.(17 weeks + 2 days).

Withdrawal/Stopping IMP

- Participants who become anaemic during the study should stop the trial treatment and start local procedures for the treatment of anaemia.
- Participants should be requested to inform the research team if they have been diagnosed with anaemia.
- Stopping treatment does not mean withdrawal from the overall study, and data collection should continue.
- Participants who elect to withdraw should be asked if they are happy to continue to contribute to data collection, and long-term data collection via linkage if they consented to it.

Potential key reasons for stopping IMP:

- Medical contraindications
- Development of anaemia
- Participant's request
- Clinician's decision

Questions from Clinicians

There is a lot of uncertainty about the prevention and treatment of anaemia in pregnancy and we have been asked many questions in the past. These have been on the rationale for the trial, symptoms versus side effects, ferritin levels, interactions with other medications etc.

To help to address these questions we have produced an information sheet for professionals which can be found on the PANDA website to download.

We have also included one in the trial pack for you to print off and use when you are raising awareness of the trial in your unit.

Co-enrolment

- Co-enrolment is allowed in the PANDA study with CI approval.
- If any participants are identified within another trial please contact us to discuss if participation within PANDA is possible.
- Please also check the co-enrolment requirements of the other identified trial as they may prohibit it.

(Currently allowed studies - MOLI, iHOLDS, INGRID-2, OBS UK study, PROTECT study , CAREFOL-HT, GENERATION)

NIHR Associate PI Scheme

- The Associate PI Scheme is a six month in-work training opportunity, providing practical experience for healthcare professionals starting their research career.
- The healthcare professional works alongside the Local PI for six months
- The Local PI acts as a mentor to the Associate PI
- During their time on the Scheme, the Associate PI must complete a checklist of study activities and a learning pathway on NIHR Learn
- The NIHR Associate PI Scheme team will then issue a certificate https://www.nihr.ac.uk/health-and-care-professionals/career-development/associate-principal-investigator-scheme.htm

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Investigational Medicinal Product (IMP): Ferrous sulphate & matched placebo

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IMP: GCP requirements

- Protecting participant rights and safety - The rights, safety, and well-being of trial subjects are the highest priority.

- Ensuring data credibility - All clinical information must be recorded, handled, and stored in a way that allows for accurate reporting, interpretation, and verification while protecting subject confidentiality

- Providing a secure IMP supply chain - storage, transportation, maintaining blinding

- Qualified personnel - Every individual involved in the trial must be qualified through education, training, and experience to perform their tasks

IMP: Ferrous sulphate & Placebo

IMP: 200 mg ferrous sulphate (65 mg iron) sugar-coated oral tablets and matched placebo obtained from WGK Ltd.

- IMP storage – according to local practice and SmPC. Can be stored in the maternity unit if local site approvals are in place.
  - This can be enabled by a local risk assessment of the storage location. Examples of where sites currently do this can be provided.
- Stock management – centrally through WGK but sites should also log stock as per local practice. Accountability logs must be completed throughout the study and returned to the central team on request.
- On receipt of IMP, download data from temperature logger and send to WGK
- If pharmacy allows, IMP can be posted to participants using local procedures.

IMP: Dispensing/Prescription

- On dispensing to participants **the kit code must be recorded** and noted in the medical notes, stock accountability log and entered into the database.
- Sites can use their own prescription templates on approval from the CTU. The PANDA template version is supplied in the ISF.
- Prescriptions can be completed by non-medics if your trust approves this for CTIMPs. Otherwise all prescriptions must be completed by a medic. They do not require full GCP but should be delegated on the delegation log to prescribe and completed the relevant training.
- The IMP kits come in shipper boxes. They must **not be removed from the shipper box** for any other reason other than providing to participant.
- One box should be dispensed per participant, normally at the baseline visit. Sufficient tablets are provided to last for treatment from week 12 of pregnancy to +6 weeks after delivery (240 tablets).

IMP: Dispensing

IMP dispensing box prototype

IMP: Incident/unblinding

- Remind participants to keep IMP out of reach of children and report any incidents e.g. accidental consumption by child or overdose
- Participant ID card to be provided (by research midwife) includes:
  - Participant ID (added by research midwife)
  - Kit ID (added by research midwife)
  - Site contact details
  - Emergency details

  N.B. remind the participant to notify the local research team if they are diagnosed with anaemia
- In the event of an emergency and unblinding is required, the unblinding contact details can be found in the pharmacy and trial manuals.

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Data collection and eCRFs*

**Separate training session.*

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Behavioural intervention*

**Provided in separate training video.*

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Safety reporting

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DEFINITIONS

Serious adverse event (SAE)

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.

In this study, overdose (an excessive and potentially dangerous dose of a drug) will also be reported as an SAE

DEFINITIONS

Serious adverse reaction (SAR)

- Any SAE that is in the opinion of the reporting Investigator, believed with reasonable probability to be due to **Ferrous sulphate**, based on the information provided (Reference Safety Information (RSI) in the SmPC). (Possibly, probably or definitely related)

Suspected unexpected serious adverse reactions (SUSAR)

- A serious adverse reaction, the nature and severity of which is not consistent with the information about Ferrous sulphate set out in the RSI
- Current RSI: approved by MHRA
  - ❑ Section 4.8 of the **Summary of Product Characteristics (SmPC) within the IMPD V4.0 18Nov2025.**
  - ❑ **IMPD/SmPC should be filed in the ISF and pharmacy file.**

Recording and reporting of SAEs

Only SAEs/SARs/SUSARs will be recorded and reported in this trial

Reporting period:

- All SAEs that occur between consent and + 6 week delivery follow-up
- All (SU)SARs: between 1st dose of IMP to + 6 week delivery follow-up

How and when to report:

- Using electronic SAE form within the eCRFs to CTU within 24 hrs of site awareness of the event

Recording and reporting of SAEs

What to report:

- 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 must be reported using the eSAE form 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 a final outcome has been reached.

Recording and reporting of SAEs

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

- Hospitalisation for routine treatment or monitoring, or general care.
- Hospitalisation due to any elective surgical procedure that was planned and scheduled prior to trial entry,
- Hospitalisation for birth/delivery or management of pregnancy loss
- Birth defect/congenital anomaly

The above events should still be recorded in the medical notes

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Monitoring & Audits

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Monitoring schedule and type

PANDA-Prevention study is a Type A low risk study;

Monitoring carried out by the central research team will be:

1) Remote monitoring once per year, the first of which will occur 6 months after activation.

2) On-site monitoring will occur only if triggered as a result of safety concerns, poor protocol compliance, lack of site communication etc.

Close out visit

- Close out visit will be performed remotely

Monitoring schedule and type

- Investigator Site File review – to ensure ISF is kept up to date
- Source data review and verification
- Pharmacy review – pharmacy file review for completeness, review of prescriptions, accountability log and reconciliation of returns.
- Discussion with the site team on any issues, provide additional training if required, ensure compliance to the protocol/GCP.

- If the visit is triggered, the focus of the visit will be on the cause of the trigger, e.g. due to protocol breach, SAE reporting etc.

- Monitoring feedback letter will be sent to the site, citing any outstanding issues that needs to be resolved by the site.

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NHS Blood and Transplant

Trial team responsibilities

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Protocol Deviations

- Sites must notify NHSBT CTU of any deviations from or breach of the protocol or GCP immediately.
- CTU team may detect a deviation at site during monitoring.
- Sites should contact NHSBT CTU if in any doubt as to whether a certain situation constitutes a deviation.
- All breaches reported to the CTU will be assessed by our Quality Assurance Team.
- All breaches will be assessed to check that they do not meet the definition of a serious breach.

Protocol Deviations

A **serious breach** of GCP or the protocol is defined as:

"a deviation from a trial protocol or the principles of GCP which is likely to affect to a significant degree either:

a) The safety or physical or mental integrity of the subjects of the trial; or

b) The scientific value of the trial."

If a deviation is classified as a serious breach, this should be reported to the NHSBT CTU immediately.

The NHSBT CTU Team will report to the REC and MHRA as per required timelines.

Document management

- It is the responsibility of the site to maintain the essential documents in the ISF and pharmacy file:
  - Maintain and update delegation and training logs (send to PANDA@nhsbt.nhs.uk).
  - CVs and GCP certificates for all team members on the delegation log.
  - All updated documents sent by the central trial team should be filed in the corresponding section of the ISF and all previous versions marked as superseded.
    - Confirmation of receipt will be required for an audit trail.

What's next?

Site will not be activated until the following are in place:

- All approvals (R&D permissions/contract execution).
- All essential documents are received (e.g. lab accreditation).
- Signed and dated CVs and evidence of GCP training.
- Completed site delegation log, with all trial staff approved by the PI.
- Localised documentation received (e.g., PIS, ICF etc.).
- OpenClinica database training is completed.
- Site activation email received to begin recruitment (green light).

PANDA
Primary prevention of maternal ANaemia to avoid preterm Delivery and other Adverse outcomes

NHS Blood and Transplant

Thank you for listening

Any questions?

Contacts:

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