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)

NIHR-funded research programme

Caring Expert Quality

Why do the research? The problem

- Around 1/3 women develop anaemia during pregnancy
- Anaemia is associated with adverse outcomes:
  - haemorrhage
  - prematurity
  - stillbirth
  - maternal and neonatal mortality
  - infant neurocognitive development in the early years of life

Multicenter Study > Br J Haematol. 2017 Dec;179(5):829-837. doi: 10.1111/bjh.14961. Epub 2017 Oct 26.

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

Manisha Nair [1], David Churchill [2], Susan Robinson [3], Cathy Nelson-Piercy [3 4], Simon J Stanworth [5 6 7], Marian Knight [1]

We have guidelines with an emphasis on treatment but burden of anaemia remains as shown in audits

bjh guideline

UK guidelines on the management of iron deficiency in pregnancy

Sue Pavord,[1] Jan Daru,[2] Nita Prasannan,[3] Susan Robinson,[4] Simon Stanworth[5] and Joanna Girling[6] on behalf of the BSH Committee

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY
British Society for Haematology
Listening • Learning • Leading

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: 3

Alternatively, what about prevention of anaemia?

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

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Why not just run a single RCT?

- Oral iron is commonly prescribed but women often report side effects
  - this could impact adherence
- Higher doses of iron may hinder intestinal absorption
  - what is the best dose to use?
- Women do not always want to take medication during pregnancy

Preliminary work is required before a large efficacy trial (n>11k)

The five workstreams in PANDA research programme

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

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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

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

WS4: Process evaluation
Assessing the fidelity of intervention delivery

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

CI Stanworth, Knight

The PANDA Workstream 2

A pilot, multicentre, 3-arm, open-label randomised trial

Aims: identify the **optimal iron dose**, **pilot behavioural intervention**, and finalise definitive trial protocol

300 women randomised to take iron (at ~12-week gestation until 28-weeks) :

- single-daily dose;
- alternate-daily; or
- three times/week (e.g. Monday, Wednesday and Friday)

First participant recruited: 17 January 2022

Last participant recruited: 7 October 2022

The WS2 outcomes

Outcomes included

- adherence
- tolerability
- changes in haemoglobin concentration
- acceptability and feasibility of the behavioural intervention

Measurement of these key outcomes is challenging

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- adherence – three measures
- tolerability
- changes in haemoglobin concentration
- acceptability and feasibility of the behavioural intervention

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Measuring Adherence

Tablet counts

- Mean (SD) of the percentage of tablets taken as expected:

((number dispensed - number returned)/number expected to be taken)*100

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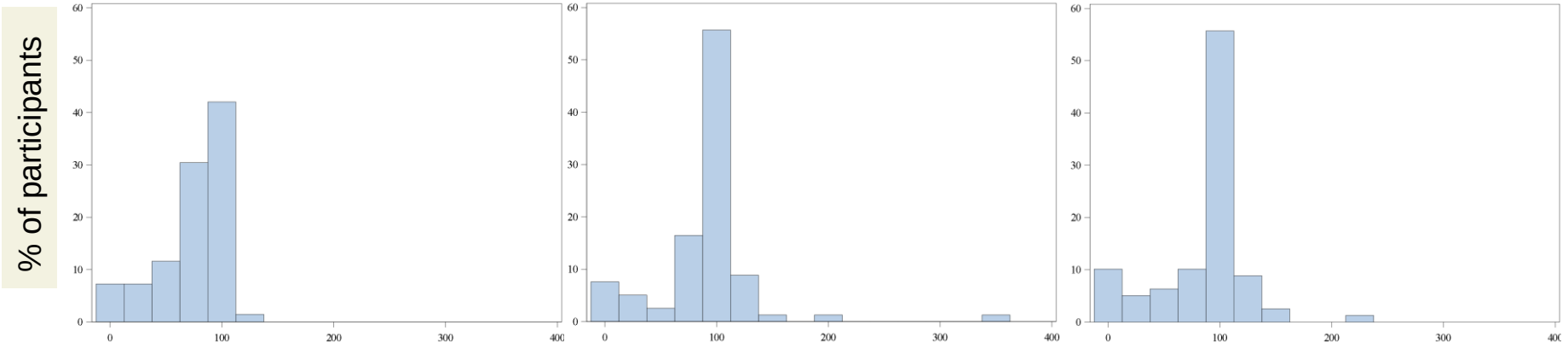
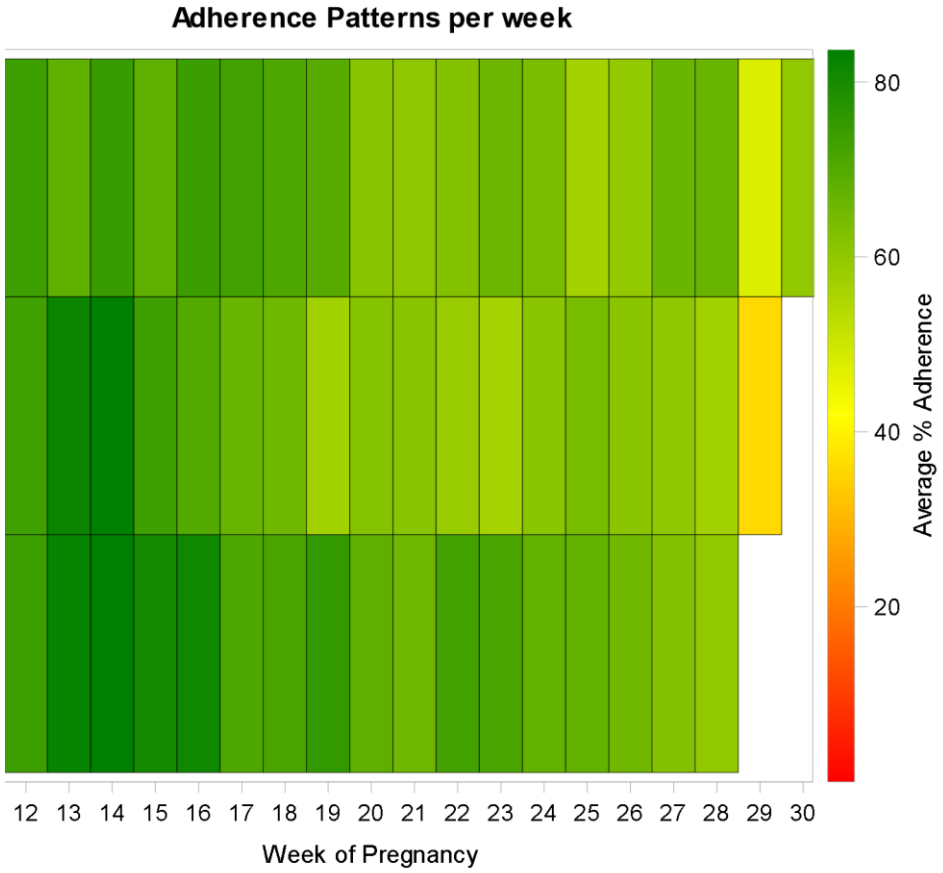


Proportion of tablets taken as expected

Measuring Adherence

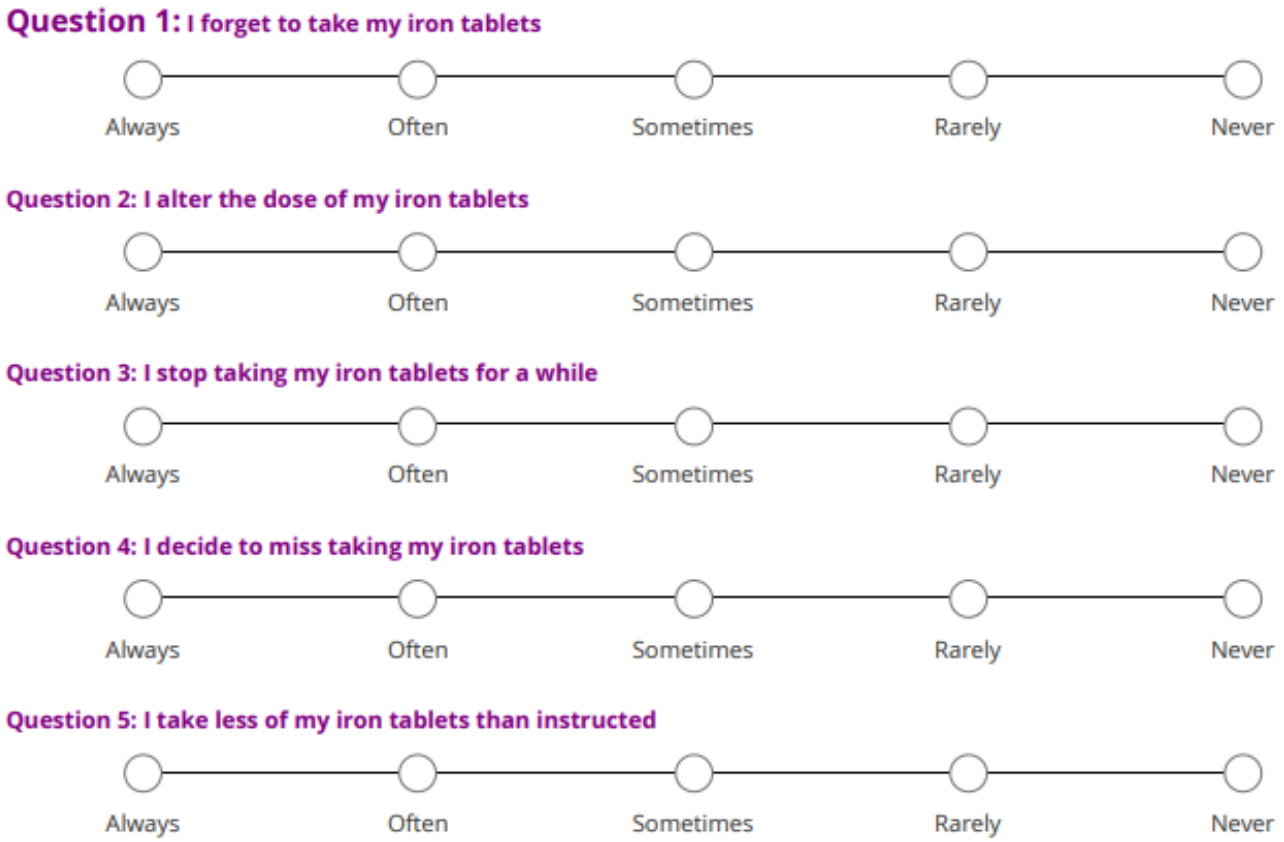
MEMS data

- Each day categorised as adherent or not

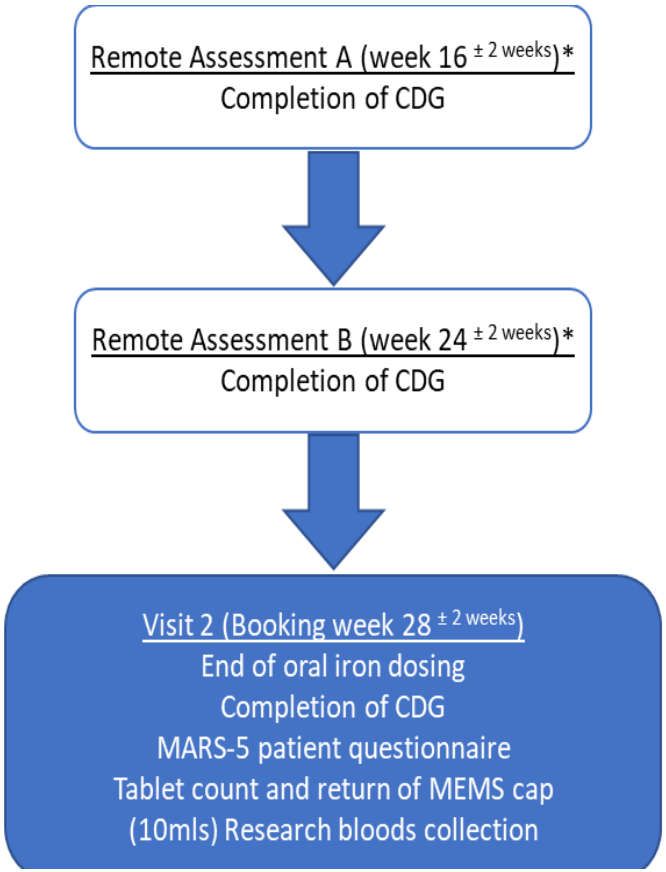


Measuring Adherence

Participant-reporting: MARS-5 questionnaire (Medication Adherence Report Scale)



Measuring tolerability: Side Effects



Participant ID:

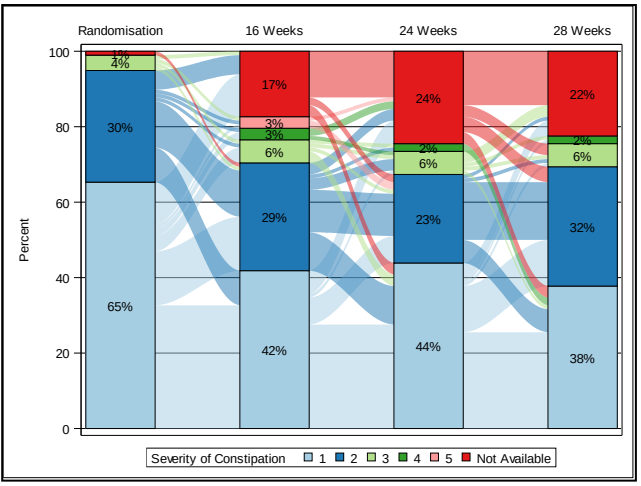
Visit Date:

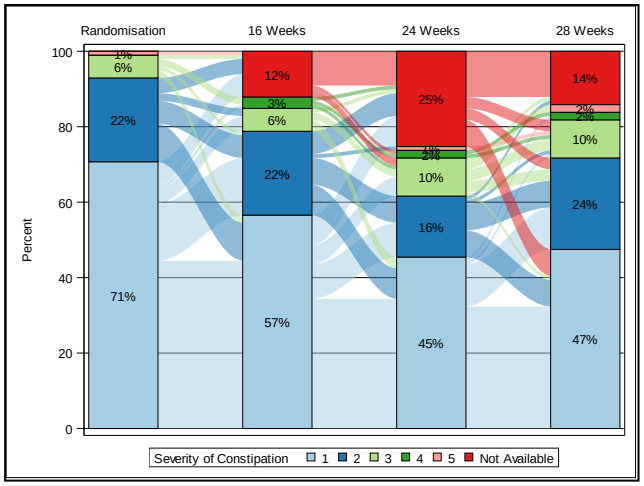
Gestation (week):

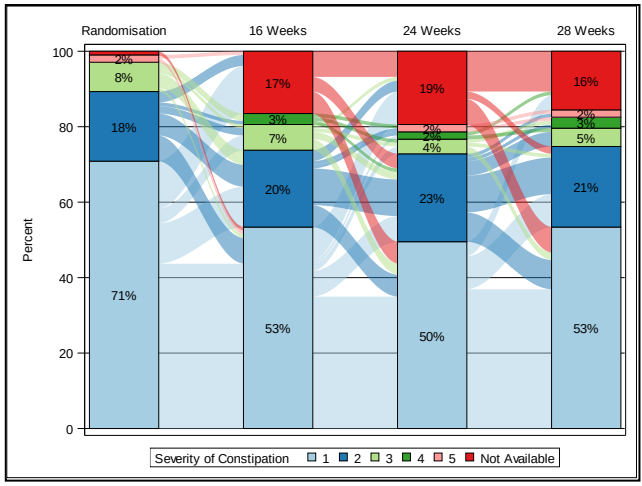
No symptom → Severe symptoms

	Scale				
Symptoms	1	2	3	4	5
Nausea					
Heartburn					
Vomiting					
Indigestion					
Constipation					
Other, please specify and provide a grade if applicable:					
Black stools	Yes / No				

Visualising the side effect rates: Sankey diagrams



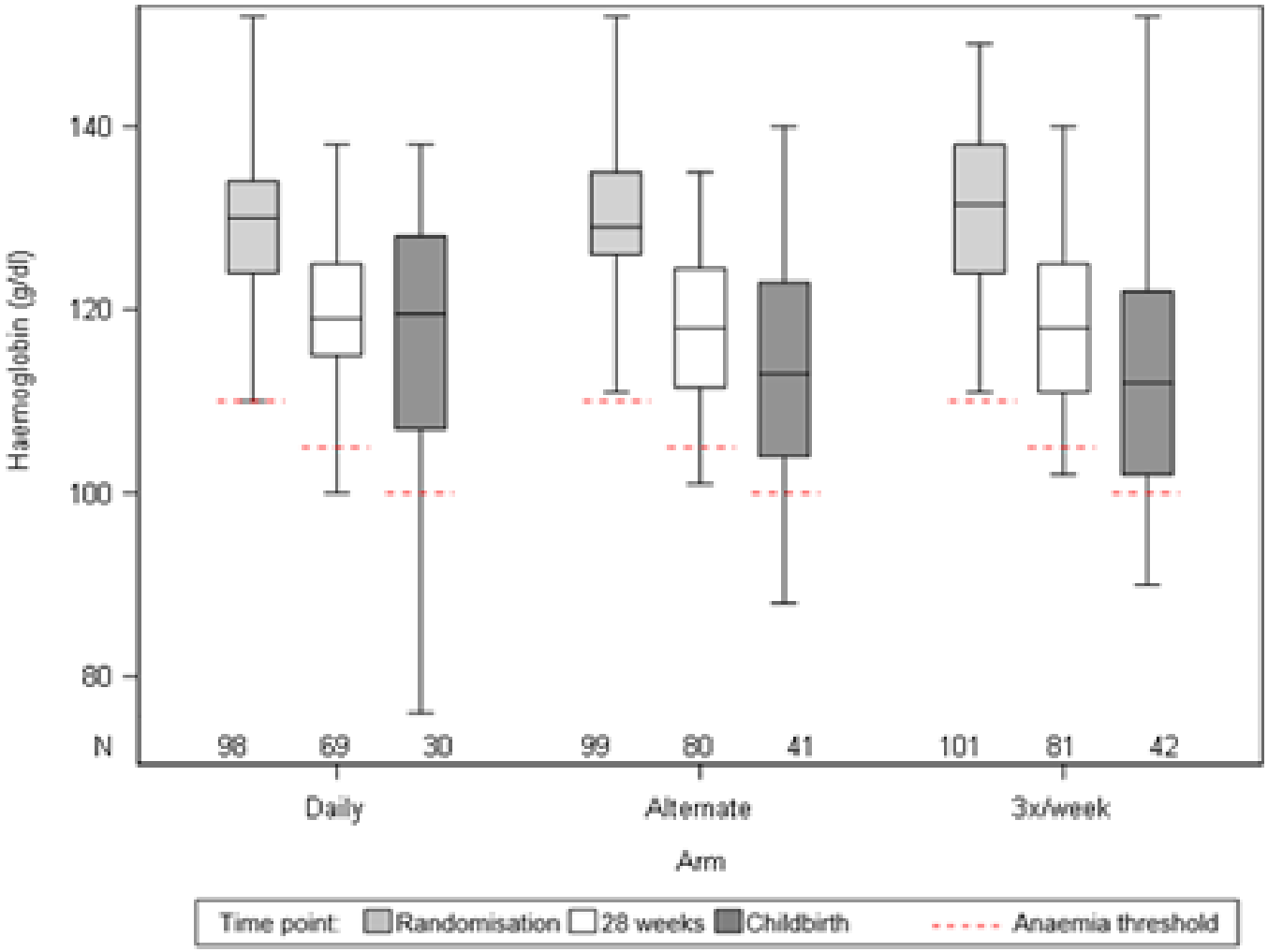




Increasing severity

We can visualise and compare severity of symptoms at different time points for the three arms

Changes in haemoglobin



Results of workstream 2

A range of different methodology and visualisations has helped the interpretation of the complex outcomes

These results have been combined with other outcome data such as changes in haemoglobin concentration

All of this information has been presented to an independent expert panel to help inform the decision on the best dose of iron for the large efficacy trial

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Summary and now planning for big trial

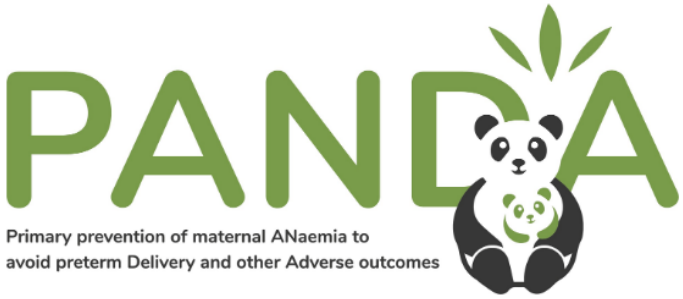
Results currently being written up for publication

WS2 has lead to many valuable insights for the main definitive trial.

WS3 will start next year, recruiting 11,020 participants to iron versus placebo

Does oral-iron supplementation prevent anaemia during pregnancy and reduce adverse maternal and infant outcomes?

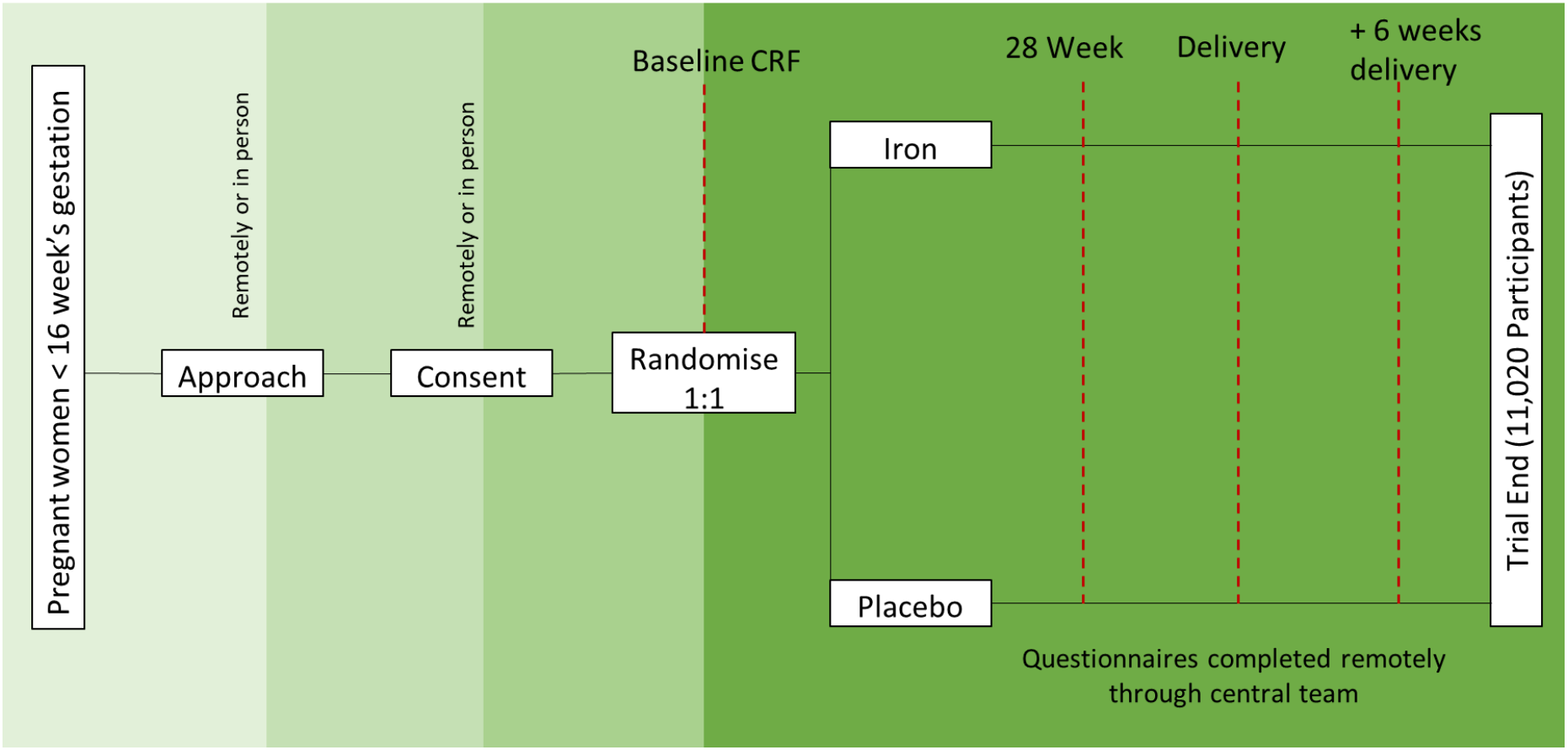
Trial Design



- Multi-centre
- Randomised
- Double-Blinded
- Two-arm

200mg ferrous sulphate vs matched placebo

Trial Schema



Target Population

Inclusion	Exclusion
Healthy non-anaemic pregnant women	Known haemoglobinopathies
Live fetus on a first trimester ultrasound scan	Anaemia of any type
15 weeks + 6 days gestation or less	Severe gastrointestinal disease
Age 18 and above	Allergies to iron
Able to give informed consent	Multiple pregnancies
	Haematological conditions that require treatment with either regular oral or intravenous iron, e.g. dyserythropoiesis or other similar condition/disease.
	Chronic renal disease
	Known haemochromatosis
	Recent red cell transfusion, within 30 days

Chosen outcomes

- The outcome measures have been chosen to comprehensively answer the questions about the prevention of anaemia in pregnancy and relevant to PPI
  - Clinical outcomes:
    - Primary - Preterm birth, small for gestational age, mortality
    - Secondary – inc; prevention of anaemia, haemorrhage, infection, mental health, maternal quality of life & infant development
  - Health Economics:
    - Quality of life, Use of resources inpatient and outpatient
  - Adherence:
    - Adherence questionnaire at 28 weeks and + 6weeks
    - Fidelity survey – 28 weeks

Schedule of assessments

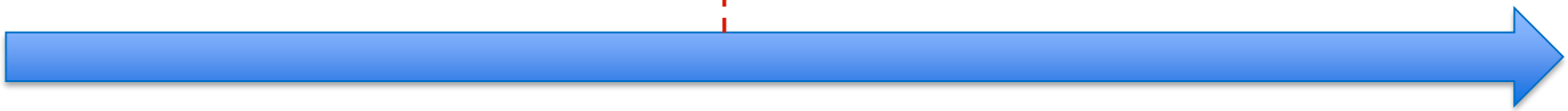
Site collection

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

28 Week's
- FBC
- Anaemia treatment
- EQ5D

Delivery
- FBC
- Mother outcomes
- Baby outcomes

+6 weeks delivery
- Mother outcomes
- Baby outcomes



Central team/remote data pull

- EQ5D
- MARS 5
- BI questionnaire

- EQ5D
- MARS 5
- Post birth questionnaire
- Interview
- Healthcare utilisation

Follow-up assessments

WS4

- Along with acceptability questionnaire, interviews will be held with participants taking the iron, Interviews also with midwives involved in recruitment.

UCL CENTRE FOR BEHAVIOUR CHANGE

WS5

- Follow up using data linkage – 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

Current progress

- Currently have 25 sites in set-up. Still open to new sites.
- Plan is to open first 10 sites in the first 1month or two and then the rest when further IMP is available to distribute.
- Recruitment targets are approx. 20 participants per month
- For enquires please email PANDA@nhsbt.nhs.uk

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