Intravenous ferric carboxymaltose versus oral ferrous sulphate for the treatment of postpartum anemia in Nigerian women (IVON-PP): an open-label, randomized controlled trial: Statistical Analysis Plan

SAP Signatures

I give my approval for the attached SAP entitled "Intravenous ferric carboxymaltose veruss oral ferrous sulphate for the treatment of postpartum anemia in Nigerian women (IVON-PP): an open-label, randomized controlled trial".

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Abbreviations and Definitions

AE	Adverse Event
AE(s)	Adverse Event(s)
CRF	Case Report Form
IDA	Iron deficiency anemia
SAP	Statistical Analysis Plan

1 Introduction

1.1 Preface

Anemia in pregnancy is a major public health burden with a higher incidence in low- and middle-income countries (LMICs) such as Nigeria(1). It is most commonly caused by iron deficiency, which accounts for 50–75%(2). As a result of the blood loss that occurs during birth, anemia is particularly prevalent in the puerperium(3) and the prevalence of postpartum anemia in LMICs has been estimated to range from 50 to 80%(4). A study in Eastern Nigeria found anemia at 48 hours and six weeks postpartum to be 73% and 48% respectively, in a cohort of 202 women followed from late pregnancy until six weeks postpartum(5).

Anemia and iron deficiency anemia in pregnancy lead to increased morbidity and mortality for the mother and neonate(6). Postnatal anemia increases the risk of infection, poor wound healing, fatigue and depression in the mother(7). It also adversely affects breastfeeding, as it is linked to insufficient milk syndrome, can reduce mother-infant bonding as a result of weakness and fatigue (3,4,8).

Oral iron is used routinely for the treatment of mild to moderate anemia in the puerperium, while blood transfusion is offered for severe cases or symptomatic women with moderate anemia(3). Oral iron, though cheap, causes significant gastrointestinal adverse effects such as vomiting, constipation, diarrhea and abdominal pain(9), thereby limiting adherence to this vital intervention which may pose a challenge in achieving optimum correction of anemia by the end of the puerperium. Adherence to oral iron is reportedly low, with only 16% of women fully compliant with their treatment in a study among pregnant women in Cameroon, one of Nigeria's neighboring countries(10).

Intravenous iron can be given as a single dose and is suitable for patients who respond poorly to oral iron or has moderate anemia that require more rapid iron replacement(3). Intravenous iron corrects anemia faster and in fewer doses than oral, requiring less patient-provider interaction, a situation that is ideal in LMICs where loss to follow up is common for various reasons especially in the postpartum period. Froessler et al. reported on 214 women with iron deficiency anemia, 107 of whom were recruited postpartum, and found a more rapid increase in serum ferritin with administration of intravenous iron sucrose compared with oral ferrous sulphate in the treatment of postpartum anemia(11). A randomized controlled trial by Vanobberghen et al. conducted among 230 women in Tanzania also found intravenous ferric carboxymaltose to be nearly five times more effective than oral iron for treating postpartum anemia and iron deficiency anemia at 6 weeks postpartum(12).

Although clinicians are aware of intravenous iron, its use is not widespread in most obstetric units in Nigeria. An equivalence randomized controlled trial performed in south eastern Nigeria found total dose infusion of high molecular weight iron dextran to be as effective as oral iron (III) hydroxide polymaltose tablets in correcting anemia by six weeks postpartum, when administered to postpartum women 48 hours or later after birth(13). In most health facilities in Nigeria, women are often discharged home after birth on oral hematinics(5) without strict monitoring of compliance to the medication. The uptake of postnatal care in Nigerian women is approximately 40%(14,15), with one survey showing 37% of women receiving postnatal care within 2 days of birth, 3% between 3 days and 6 weeks postpartum, while 60% did not receive any postpartum care(15). Most of the women discharged on oral hematinics will therefore not have the chance to have their hemoglobin levels or clinical states re-examined in order to determine whether their anemia has resolved.

There are many safe parenteral iron preparations, such as iron sucrose, iron polymaltose, ferric carboxymaltose and iron isomaltoside, with few adverse effects (16). Ferric carboxymaltose is safe and effective but was recently found to reduce serum phosphate levels (17). However, the associated reduction in serum phosphate concentration has not been shown to be clinically relevant in pregnancy, probably because it is given in just a few doses(17). In studies conducted in pregnant women, the serum phosphate has been found to return to normal within a short period of time(18–20). The main disadvantage with intravenous iron preparations is that they are relatively expensive(16) but as they offer the potential to avoid blood transfusion and its complications, this cost might be mitigated.

As postpartum anemia is highly prevalent in Nigeria, and in the context of its effects on the physical and mental health of women and their newborn, we conducted a randomized controlled trial examining the clinical effectiveness and cost-effectiveness of intravenous ferric carboxymaltose versus oral ferrous sulphate in postpartum Nigerian women. Recognizing the volatility of introducing such treatment in Nigeria, we also propose alongside an implementation study to better understand the implementation climate and assess key implementation outcomes of intravenous ferric carboxymaltose uptake in treating postpartum anemia in Nigeria.

1.2 Scope of the analyses

These analyses will assess the effectiveness and safety of intravenous ferric carboxymaltose in comparison to oral ferrous sulphate (control) to treat postpartum anaemia.

2 Study Objectives and Outcomes

2.1 Study Objectives

1. To determine the clinical effectiveness of intravenous ferric carboxymaltose versus oral ferrous sulphate in postpartum women with anemia.

2. To determine the incidence of adverse drug events including the incidence of hypophosphatemia in the mother and adherence with the use of intravenous ferric

carboxymaltose and oral ferrous sulphate for treatment of postpartum anemia. We are measuring Vitamin D, alkaline phosphatase, P1NP, FGF23, Ca, PO4, which are biomarkers of phosphorus homeostasis and bone turnover.

Outcomes

Primary

1. Proportion of participants who are anaemic at six weeks' postpartum.

Anemia is defined as haemoglobin <11 g/dL at six weeks' postpartum. Haemoglobin measurement nearest to 6 weeks postpartum will be used, of all the tests between 4 weeks and 8 weeks.

Secondary

1. Proportion of women with probable postpartum depression after treatment, measured using the Edinburgh Postnatal Depression Scale(21) at six weeks and six months postpartum
2. Change in mean postpartum hemoglobin levels at two weeks and six weeks postpartum.
3. Prevalence of anemia (Hb < 11g/dl) at six months postpartum
4. Prevalence of moderate/severe anemia at six weeks and six months postpartum. Moderate anemia is defined as hemoglobin level 7.0-9.9g/dl and severe anemia as hemoglobin level <7.0g/dl.
5. Change in mean serum ferritin, serum transferrin, serum iron and % transferrin saturation at two and six weeks postpartum
6. Need for blood transfusion after iron treatment during the first 6 weeks postpartum
7. Prevalence of fatigue at six weeks and six months postpartum, using the Fatigue Severity Scale (revised FSS-5R version), which is a brief, specific, reliable, and valid measure of postpartum fatigue(22).
8. Proportion of women with secondary postpartum hemorrhage after treatment. This will be defined as excessive bleeding requiring surgical intervention or blood transfusion from 24 hours after delivery till 12 weeks postpartum(23)
9. Proportion of infants being breastfed at six weeks and six months postpartum. We will measure any and exclusive breastfeeding at six weeks, and any breastfeeding at six months.
10. Prevalence of impaired maternal-infant bonding at six weeks and six months postpartum measured using the Mother-to-Infant Bonding Scale (MIBS) (24)
11. Incidence of confirmed or suspected maternal infections within six weeks of birth, defined by a new prescription of antibiotics for presumed perineal wound-related infection, endometritis or uterine infection, urinary tract infection or other systemic infection (clinical sepsis).
12. Incidence of hypophosphatemia at two weeks and six weeks postpartum. We will measure Vitamin D, alkaline phosphatase, P1NP, FGF23, Ca, PO_4, which are biomarkers of phosphorus homeostasis and bone turnover. Hypophosphatemia is defined as serum phosphate level <2.5 mg/dL (0.81 mmol/L). Mild hypophosphatemia as 2 – 2.5 mg/dL (0.65 – 0.81 mmol/L), moderate as 1 – 2 mg/dL (0.32 – 0.65 mmol/L), and severe as <1 mg/dL (0.32 mmol/L).
13. Incidence of early neonatal death, defined as death of newborn from enrolment of the mother to before seven completed days

14. Incidence of late neonatal death, defined as death of the newborn from enrolment of the mother top before 28 completed days
15. Incidence of infant death, defined as death from enrolment before the age of six months.
16. Incidence of post-natal maternal death from enrolment up to six weeks and at six months postpartum.
17. Incidence of other adverse drug events
18. Quality of life using the WHOQOL-BREF

Analysis will be by intention to treat, using log-binomial models, linear regression models with robust variance, and Poisson regression models (or its variants) with 95% confidence intervals and two-tailed p-values. No covariate adjustment will be considered. Missing values will be ignored.

3 Study Methods

3.1 General Study Design and Plan

Multicentre, parallel, open label individually randomized controlled trial, with 1,400 women allocated in a 1:1 ratio in conjunction with a cost-effectiveness analysis.

Single dose of 20mg/kg IV ferric carboxymaltose (not exceeding 1000mg). Intravenous route was compared with daily administration of oral 200mg ferrous sulphate (65mg elemental iron) 2 times daily..

Participants was seen in clinic at 2 weeks', 6 weeks', 3 months and 6 months postpartum.

3.2 Eligibility Criteria and General Study Population

Inclusion criteria:

- Women aged between 15 to 49 years.
- Women within Six to 48 hours after delivery. A minimum of six hours has been chosen because we expect the initial post-delivery blood loss to have subsided and the hemoglobin concentration to be sufficiently representative of the true oxygen carrying capacity of the patient at that time; 48 hours has been chosen because women are usually discharged from hospital after 48 hours.
- Baseline (enrolment) laboratory-confirmed moderate or severe anemia (Hb < 10g/dl), confirmed by Hemocue haemoglobinometer.
- Able and willing to give written informed consent

Exclusion criteria:

Exclusion criteria:

- Having received a blood transfusion, for any indication, within the last three months.
- Symptomatic anemia and a need for urgent correction.
- Known haemoglobinopathy such as sickle cell disease, HbCC disease.
- Clinically confirmed malabsorption syndrome.
- Known hypersensitivity or contraindication to any form of iron treatment, study drug or any of its excipients.
- Self-reported pre-existing maternal depression or other psychiatric illness and as evidenced by a YES response to Any Past history of Psychiatry ward hospitalization, Psychiatry medications, behavioral changes, or past consultation with Psychiatry services.
- Severe allergic conditions such as severe asthma, eczema, or other atopic condition.
- Known autoimmune conditions e.g., systemic lupus erythematosus, rheumatoid arthritis or known severe drug allergies.
- Planning to move or reside outside the research area
  Women who have had intravenous iron administered in the last two years

*****A prospective participant with chronic medical condition (e.g HIV infection) will not be excluded unless there are contra-indication for the use of iron supplementation.***

3.3 Randomization and Blinding

Patients identified during early postpartum care (6 – 48 hours) to have moderate or severe anemia (haemoglobin <10 g/dL) , using the Hemocue® haemoglobinometer were enrolled, if they meet the eligibility criteria and provide informed consent. Eligible participants were consecutively enrolled. They were randomized to one of the two treatments groups. Individual randomization and allocation concealment was done with the use of a web-based randomization software known as 'Sealed envelope' in a 1:1 ratio in blocks.

3.4 Study Assessments

Table 1. Schedule of study assessments

Visit	Screening	Treatment (Baseline)	2 wks pp	6 wks pp	12 wks pp	24 wks pp
Socio-demographic and clinical		X	X	X	X	X
Physical exam		X	X	X	X	X
Haemoglobin	X		X	X		
FBC		X	X	X		X
Iron panel		X		X		X
Malaria			X	X		
Maternal serum PO_4 and other biomarkers		X	X	X		
EPDS		X		X		X
MIB				X		X

Visit	Screening	Treatment (Baseline)	2 wks pp	6 wks pp	12 wks pp	24 wks pp
FSS-5R		X		X		X
WHOQOL		X		X		X
Adverse events		X	X	X		X
Drug tolerability and safety			X	X	X	X

Analysis Time Windows

We will allow the inclusion of variables collected around the following time windows.

Table 2. Analysis Time Windows

Visit (target day)	Lower bound (weeks)	Upper bound (weeks)
Baseline (0)	N/A	N/A
2 weeks pp	1	3
6 weeks pp	5	7
12 weeks pp	9	15
24 weeks pp	18	30

3.5 Description of variables

The key variables used for analysis are described below;

Table 3.1 Description of variables: Clinical

Variable	Description
Secondary postpartum haemorrhage	Binary variable (0, 1). Excessive bleeding requiring surgical intervention or blood transfusion from 24 hours after delivery till 6 weeks postpartum(23,25)
Need for blood transfusion	Binary variable (0, 1). Clinician decision to transfuse patient between baseline and six weeks.
Maternal infections	Binary variable (0, 1). Incidence of confirmed or suspected maternal infections within six weeks of birth. This will be defined by a new prescription of antibiotics for presumed perineal wound-related infection, endometritis or uterine infection, urinary tract infection or other systemic infection (clinical sepsis)
Incidence of other adverse events	Count variable. Defined as the occurrence of vomiting, constipation, diarrhoea, abdominal pain, anaphylaxis, hypotension, or shock. ▪ Events occurring in >5% of the study population will be presented separately too.
Breastfed infants	Binary variable (0,1). Assessed at six weeks and six months. ▪ A secondary outcome

Table 3.2 Description of biomarker variables

Variable	Description
Haemoglobin	Continuous variable, measured in g/dL. Usually, the lower limit of the measured range is 3 g/dL and the upper limit is 20 g/dL.
Anaemia	Calculated from haemoglobin variable, <11g/dL ▪ The primary outcome is anaemia at 6 weeks' postpartum. ▪ Anaemia at 6 months is a secondary outcome.
Moderate/severe anaemia	Calculated from haemoglobin variable, <10g/dL
Ferritin	Continuous variable, measured in µg/L. The lower limit of the measured range will depend on the detectable limit of the test. The lower limit will be imputed if measured value is below the detectable limit. The upper limit is set at 10,000 µg/L.
Serum ferritin categories	Categorical variable, calculated from serum ferritin(26). • Iron deficiency is defined using <15 µg/L. • Inflammation-corrected iron deficiency is based on either of two categories: i) Ferritin < 30 µg/L ii) Ferritin 30 – 100 µg/L and TSAT <20% • Elevated iron status is defined using >150 µg/L
Serum transferrin	Continuous variable, measured in mg/dL. The lower limit of the measured range will depend on the detectable limit of the test. The lower limit will be imputed if measured value is below the detectable limit.
Serum transferrin categories	Categorical variable, calculated from serum transferrin(27). • The reference range is 204 – 360 mg/dL. • Categories will be <204, 204 – 360, >360.
Serum iron	Continuous variable, measured in µg/L. The lower limit of the measured range will depend on the detectable limit of the test. Impute lower limit if measured value is below the detectable limit.
Transferrin saturation	Continuous variable, measured in percent. Usually between 20 and 45%.
Serum phosphate	Continuous variable, measured in mmol/L. Assessed at 2 and 6 weeks postpartum.
Hypophosphatemia	Measured from serum phosphate ▪ Binary variable (0, 1). ▪ Defined as serum phosphate <2.5 mg/dL (0.81 mmol/L)
Vitamin D	Continuous variable, measured in mmol/L. Assessed at 2 and 6 weeks postpartum.
Vitamin D excess	Measured from 25-hydroxyvitamin D 25(OH)D • Binary variable (0, 1). • Defined as levels >150 ng/mL (375 nmol/L)(28)
Serum alkaline phosphatase	Continuous variable, measured in mmol/L. Assessed at 2 and 6 weeks postpartum.
Serum ALP level	Measured from serum ALP • Binary variable (0,1). • Defined as alkaline phosphatase >140 IU/L(29)
P1NP	Continuous variable, measured in mmol/L. Assessed at 2 and 6 weeks postpartum.

Variable	Description
P1NP categories	The reference level of P1NP is from 15 – 70 ug/L(30). • Binary variable (0,1) • Defined as values above the upper limit of the reference range
FGF23	Continuous variable, measured in mmol/L. Assessed at 2 and 6 weeks postpartum.
FGF23 categories	The reference level of FGF23 is from 19.9 – 52.9 pg/mL(31). • Binary variable (0,1) Defined as values above the upper limit of the reference range
Corrected calcium	Continuous variable, measured in mmol/L. Assessed at 2 and 6 weeks postpartum.
Hypocalcemia	Categorical variable, calculated from corrected serum calcium. Defined as <2.12 mmol/L(32) • Binary variable (0,1)

Table 3.3 Description of patient reported outcome variables

Variable	Description
EPDS score	Continuous variable.
Depression	Binary variable (0,1). Calculated from the EPDS score. Depression will be defined as EPDS score >10 any time after birth. Given the EPDS is assessed multiple times, the highest score will be used. Any woman who commits or attempts suicide will be regarded as depressed, regardless of her score.
FSS-5R score	Continuous variable, at baseline, six weeks and six months postpartum. Calculated as the mean of the score for each item(22). • The scale is composed of 5 items and each item is assigned a score of 1 - 7 with a low score indicating that the statement is not very appropriate and a high score indicating agreement. Responses were summed and scaled to range from 1 - 7.
Fatigue	Categorical variable. Calculated from the FSS-5R score. • Defined as mean ≥4(33)
MIB score	Continuous variable, at six weeks and six months postpartum. • Maternal infant bonding was measured using the Maternal Infant Bonding Scale (MIBS). The scale is composed of nine items assessing: “loving”, “disappointed”, “neutral or felt nothing”, “possessive”, “resentful”, “dislike”, “protective”, “joyful”, and “aggressive”. Each item is rated on a four-point Likert scale (from 0, “very much” to 3, “not at all”), with the scale of some items reversed. Total scores range from 0 to 27. A high score indicates worse mother to infant bonding
Maternal-infant bonding	Categorical variable. • In addition, specific domains include *impaired bonding, reject path anger, infant focus anxiety and incipient abuse*
QoL score	Continuous variable, at baseline, six weeks and six months postpartum, from the WHOQOL-BREF.

Variable	Description
	• The scale has 26 items - two items that assess perceived quality of life and satisfaction with health, and 24 questions that assess four domains: physical, psychological, social relationships and environment. Each item was scored on a Likert scale from very poor to very good, with scores from 1 - 5(34). • Transformed from a denominator of 130 to 100
Impaired QoL	Categorical variable. Calculated from WHOQOL-BREF score • Defined as WHOQOL-BREF score <60 (34)

4 Sample Size

We calculated a sample size of 678 (339 in each study arm) study participants by assuming a power of 90% at a significance level of 5%, to detect a difference of 30% (relative risk of 0.7) as recently reported from a study (12) based on an event rate of 39% obtained from pooled estimates of anemia from the control arm of studies examining oral versus intravenous iron in postpartum women in a meta-analysis(35), assuming a two-sided test of hypothesis. When an allowance of 20% loss to follow-up was made, we calculated a sample size of 814 women with 407 in each study arm.

To adjust for the prevalence of iron deficiency anemia at baseline, we assumed a proportion of 70% of anaemic women will have IDA, based on recent estimates from Lagos. Assuming a power of 90% at a significance level of 5%, with two-sided test of hypothesis, we calculated a sample size of 1,114 women with 557 participants in each study arm. When a loss to follow up of 20% was added, the required sample size became 1,338 (669 participants in each arm) participants.

Bearing in mind the proposed one-time interim analysis to be conducted by the Data and Safety Monitoring Board (DSMB) at mid recruitment, we applied the O'Brien-Fleming rule(36), adjusting our final alpha level to 0.0492 (See interim rule section), which increased our final sample size to 1,380 (690 per arm of the study).

A total of 1400 postpartum women were randomized into the IVON-PP study.

5 General Analysis Considerations and Specific Statistical Analysis Plans

5.1 Timing of Analyses

The final analysis will be performed on the final unblinded dataset, after data cleaning is completed and database is locked.

5.2 Analysis Populations

5.2.1 Intention to Treat (ITT) population

- The intention to treat population refers to all participants who were randomized. Following the intention-to-treat principle, participants will be analyzed according to the treatment they were assigned to at randomization.

5.2.2 Per-protocol or on-treatment population

- Individuals who received the treatment for the arm to which they were randomized will be included in a per-protocol or on-treatment population, as part of sensitivity analysis. This analysis could potential be biased as it deviates from the intention-to-treat analysis and will be interpreted cautiously(37).

5.3 Covariates and Subgroups

The following table is a list of covariates to be presented in Table 1.

Table 5.3.1

Variable	Description
Age	Continuous variable, measured in years
Age categories	Categorical variable
Parity	
Gestational age	Continuous variable, measured in weeks
Educational attainment	
State	Categorical variable
Ethnicity	Categorical variable
Haemoglobin at baseline	Continuous variable
Anemia categories at baseline	Categorical variable, <11 g/dL
Ferritin at baseline	Continuous variable
Iron deficiency	Categorical variable, definition in Table 3.2

Additional baseline variables to be considered.

Table shell 1. Participant characteristics

Variables	IV iron	Oral iron	Overall
Age			
Mean (SD)			
Median [Min, Max, IQR]			
Age Categories (years)			

Variables	IV iron	Oral iron	Overall
<20			
20 - <30			
30 - <40			
40 and above			
Parity			
0			
1 or 2			
3 or 4			
5 or more			
Educational attainment			
No formal education			
Completed primary			
Completed Secondary			
Completed Tertiary			
Region			
Kano			
Kwara			
Lagos			
Rivers			
Enrollment Haemoglobin			
Mean (SD)			
Median [Min, Max,IQR]			
Anaemia Grade			
Moderate			
Severe			
Enrollment Ferritin			
Mean (SD)			
Median [Min, Max,IQR]			
Iron deficiency			
<15 µg/L			
Corrected for inflammation			

Values are n(%) for categorical variables and mean (SD) or median (min, max) for continuous variables. The decision to report the mean (SD) or median (IQR, min, max) may be guided by the distribution of the variable.

5.4 Multiple Testing

All p-values will be presented to the third decimal place. There is a single primary outcome in this trial and no adjustment for multiple testing will be done(38). However, one-time interim analysis was conducted with a stopping alpha of 0.0054 based on the O'Brien-Fleming rule. Thus, the alpha level for statistical inference in our analysis will be **0.0492**(36).

P-values will be reported per convention. They will not be used by themselves to interpret the findings of the study. In line with the American Statistical Association's guidance(39), we will consider the statistical methods used, the magnitude of any effects observed and the importance of the findings.

5.5 Handling of missing data

As previously stated, analyses will be by intention-to-treat principle. Throughout, the denominator for each analysis will be reported so as to be transparent wherever there is missing data. For outcomes missing in <5%, missing data will be ignored as imputation is unlikely to improve the precision or prevent bias(40). This approach is known as a *complete-case intention-to-treat* approach(41).

For outcomes missing in ≥5% of participants for whom it is expected, supplementary tables comparing baseline characteristics in those with and without the missing outcome will be reported. In addition, multiple imputation or inverse probability of treatment weighting may be considered, and results compared with the complete case analysis.

6 Summary of Study Data

For the ITT populations, baseline covariates will be summarized to describe the population. Continuous variables will be summarized using, n, mean, standard deviation (SD), medians, interquartile ranges (IQR), minimum and maximum as appropriate. Distribution of the continuous variables will be tested for normality graphically and using the Shapiro-Wilk test. The frequency and percentages of observed levels will be reported for all categorical measures. Summary tables will be presented for each treatment arm, and will be annotated with the total population size relevant to that table/treatment. The number of missing observations will be presented in the footnote of each table. Example of the summary Table is as shown in Table 1 above. Appropriate graphs will be produced especially for longitudinal data to graphically compare the trends between the two arms of the study

6.1 Participant Disposition

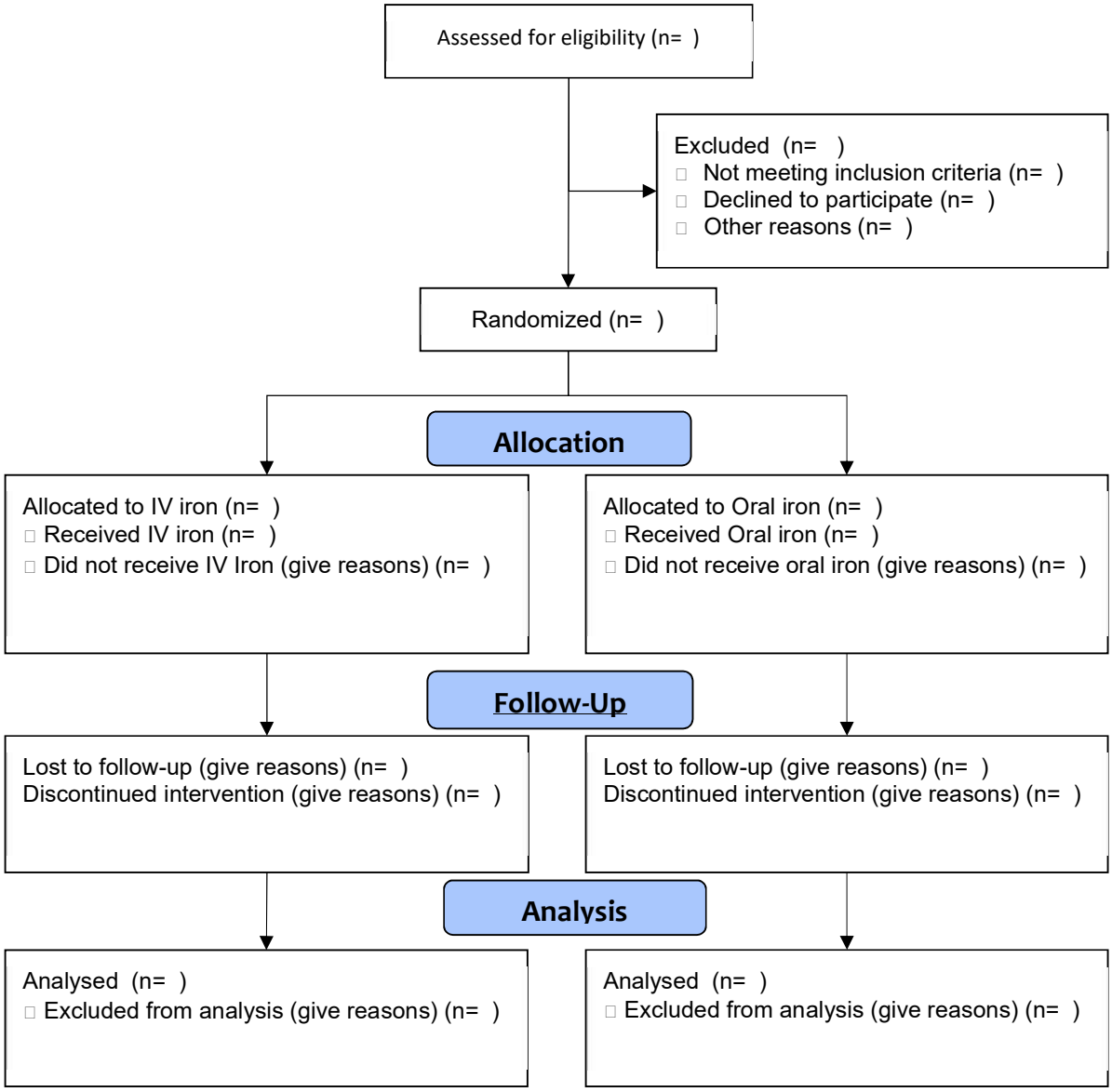
The following CRFs will be used to determine which participants reached the following stages.

Visit (target day)	CRF
Baseline (0)	Enrolment form
2 wks pp	2-weeks post-partum form
6 wks pp	6-weeks postpartum form
12 wks pp	12-weeks postpartum form
24 wks pp	24-weeks postpartum form

The time-dependent rates of recruitment will be provided in graphical format.

A flow diagram of participant selection will be included.

Figure. Flow diagram



6.2 Protocol Deviations

Given that analysis will be by ITT, no specific protocol deviations will impact the approach to analysis. The summary statistics will be produced in accordance with section 5 (General Analysis Considerations).

6.3 Concurrent Illnesses and Medical Conditions

The summary statistics of any concurrent illnesses and medical conditions will be produced in accordance with section 5 (General Analysis Considerations).

6.4 Treatment Compliance

Treatment compliance will be assessed for the oral iron arm using the remaining pill count and diary records. Each participant's average compliance rate will be estimated thus:

$$\frac{Number\ of\ pills\ absent\ from\ returned\ regimen\ sachet}{Number\ of\ pills\ ever\ dispensed\ to\ participant}\%$$

If pill count information is missing, participant will be assumed to have not taken the regimen on those days. The summary statistics will be produced in accordance with section 9.

7 Effectiveness Analyses

7.1 Primary Effectiveness Analysis – anaemia at 6 weeks' postpartum

The main analysis will be conducted in the ITT population.

The frequency of occurrence of the primary outcome will be presented as N and percent of the total study population, and by treatment group (IV iron vs. oral iron). Log-binomial regression models will be performed to produce and risk ratios and confidence intervals presented. To account for possible clustering by site, the variance estimator with cluster option will be utilized.

If the log-binomial model fails to converge, the log-Poisson model which provides consistent and nearly efficient estimates of the relative risk and its confidence intervals will be used(42).

No covariate adjustment will be done in the main analysis. In sensitivity analysis, baseline covariates that are strongly prognostic of the outcome or imbalanced in the treatment arms may be included in the model if their inclusion improves the precision of the estimates(43,44). The estimates will be regarded as improved if the distance between the upper and lower confidence limits reduces by >10%.

Table shell 2: Primary outcome

Outcome	level	IV iron	Oral iron	Risk ratio	Confidence intervals	P-value
Postpartum anaemia at 6 weeks	Anaemic					
	Non-anaemic					

7.2 Secondary Effectiveness Analyses

7.2.1 Analyses of Secondary Outcomes

These analyses will be conducted in the ITT population.

The frequency of occurrence of the categorical outcomes will be presented as N and percent of the total study population, by region, and by treatment group (IV iron vs. oral iron). N, mean, standard deviation (SD), median, interquartile range, minimum and maximum will be used to summarize continuous variables as appropriate.

For binary outcomes, log-binomial regression models will be used to obtain the relative risk and 95% confidence intervals. In some cases, the log-binomial models may not converge and log-Poisson models (or its variants/extensions), which provide nearly efficient relative risk, its confidence intervals and standard errors will be used(42).

For count variables, Poisson regression models will be used to obtain rate ratios and 95% confidence intervals. The log of the number of days since treatment may be included as the offset term(45).

For continuous variables, linear regression models will be used to obtain mean differences with confidence intervals. Generalized least square models with unstructured variance-covariance structure and an interaction term for the trial arm (IV vs. oral iron) and the time point (0, 2, 6, and 24 weeks) will be used to estimate the effect of treatment arm on repeated measures of haemoglobin, iron status biomarkers and patient-reported outcome measures.

7.2.2 Table shells

Table shell 3. Secondary maternal clinical outcomes

Outcome	Level	IV iron	Oral iron	RR	CI	P-value
Blood transfusion, %	No					
	Yes					
Maternal infection, %	No					
	Yes					

Table shell 4. Secondary infant clinical outcomes

Outcome	Level	IV iron	Oral iron	RR	CI	Pvalue
Breastfeeding, %	No					
	Yes					
Early neonatal death, %	No					
	Yes					
Late neonatal death, %	No					
	Yes					
Infant death (≤6 months) , %	No					
	Yes					

Table shell 5. Secondary maternal biomarker outcomes

Outcome	Level	IV iron	Oral iron	Mean difference	CI	P-value
Haemoglobin change, delivery to 2 weeks, Mean (SD)						
Haemoglobin change, delivery to 6 weeks, Mean (SD)						
Mod/Sev mat. anaemia, 6 weeks	No					

Outcome	Level	IV iron	Oral iron	Mean difference	CI	P-value
Maternal anaemia, 6 months, %	Yes					
	No					
Ferritin, 6 weeks, Mean (SD)	Yes					
Iron deficiency, %	No					
	Yes					
Transferrin, 6 weeks, Mean (SD)						
Serum iron, 6 weeks, Mean (SD)						
TIBC, 6 weeks, Mean (SD)						

Table shell 6. Maternal patient-reported outcomes

Outcome	level	IV iron	Oral iron	ES	CI	P-value
6 weeks						
Edinburgh postnatal depression score	Mean					
Probable postnatal depression	No					
	Yes					
Fatigue severity score (FSS-5R)	Mean					
Fatigue	No					
	Yes					
Mother-infant bonding score	Mean					
Impaired bonding	No					
	Yes					
Rejection and pathological anger	No					
	Yes					
Infant-focused anxiety	No					
	Yes					
Incipient abuse	No					
	Yes					
WHO Quality of Life Score	Mean					
Suboptimal quality of life	No					
	Yes					
6 months						
Edinburgh postpartum depression score	Mean (SD)					
Probable postpartum depression	No					
Yes	Yes					
Fatigue severity score (FSS-5R)	Mean (SD)					
Fatigue	No					
	Yes					
Mother-infant bonding score	Mean (SD)					
WHO Quality of Life Score	Mean (SD)					
Suboptimal quality of life	No					

Outcome	level	IV iron	Oral iron	ES	CI	P-value
	Yes					

7.3 Subgroup Analyses

The frequency of key covariates and outcomes will be evaluated across the following subgroups:

a) regions
b) baseline anemia category
c) baseline iron status

Likelihood ratio tests will assess whether the relationship of treatment group and the outcome varies by the subgroup.

Table shell 7. Subgroup analysis

Modifier	Subgroup	Level	IV iron	Oral iron	RR	CI	Pvalue
Region	Kano	Anaemic					
		Non-anaemic					
	Kwara	Anaemic					
		Non-anaemic					
	Lagos	Anaemic					
		Non-anaemic					
	Rivers	Anaemic					
		Non-anaemic					
Baseline anemia	Anemic	Anaemic					
		Non-anaemic					
	Non-anemia	Anaemic					
		Non-anaemic					
Iron status	Iron deficient	Anaemic					
		Non-anaemic					
	Not deficient	Anaemic					
		Non-anaemic					

8 Safety Analyses

8.1 Adverse Events

Adverse events will be classified using the Common Terminology Criteria for Adverse Events (CTCAE) grading. The number and proportion of participants with adverse events that occur in up to 0.5% of the study population will be presented by study arm. Adverse events categorized by the treating physician to be related to the treatment will also be listed by study arm, regardless of their

frequency.
The timing of the adverse events will be noted relative to the study visit, and unscheduled visits will be counted as occurring relative to the closest study visit.

Table shell 8. Adverse events

Adverse events	IV iron, n(%)	Oral iron, n(%)	Overall
Total			
Listed			

8.2 Serious Adverse Events (SAE)

A Serious Adverse Event (SAE) is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug.
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
    - social reasons and respite care in the absence of any deterioration in the patient's general condition.

- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

The number and proportion of participants who experience SAEs will be analysed and presented. The appropriate grading of severity of the SAEs will also be presented in counts and proportion. A listing of SAEs experienced will be included per participant.

If any serious adverse events occur in >5% of individuals who receive either intervention, the time to occurrence of the adverse event will be summarized using median (IQR) and graphically with Kaplan-Meier curves.

Table shell 9. Serious adverse events – summary

SAE	LDA, n(%)	Placebo, n(%)	Overall
Total			

SAE	LDA, n(%)	Placebo, n(%)	Overall
Listed			

Table shell 10. Serious adverse events – list

record_id	SAE	Relationship	Comments including action taken

8.3 Safety-related laboratory outcomes

The analysis will be by the intention to treat principle and based on the participants who had completed the relevant visit.

The occurrence of dichotomous outcomes will be expressed as frequencies (N) and percentages. Continuous variables will be presented as mean (SD). In addition, the proportion of individuals with missingness in each outcome will be presented by treatment arm.

The effect of either treatment on the occurrence of dichotomous outcomes will be analyzed using log-binomial regression models to obtain relative risks, 95% confidence intervals and p-values. The effect of treatment on the mean (SD) of continuous outcomes will be analyzed using linear regression models to obtain mean differences. Confidence intervals and p-values will be obtained via cluster-robust variance estimation, with clustering for site.

Table shell 11. Safety laboratory values

Outcome	Level	IV iron	Oral iron	ES	CI	p
Two weeks						
Serum phosphate, MD	Mean (SD)					
Hypophosphataemia, RR	No					
	Yes					
Alkaline Phosphatase, MD	Mean (SD)					
Elevated Alkaline Phosphatase, RR	≤140					
	>140					
Corrected Calcium, MD	Mean (SD)					
Hypocalcaemia, RR	<2.12					

Outcome	Level	IV iron	Oral iron	ES	CI	p
Two weeks						
	≥2.12					
Six weeks						
Serum phosphate, MD	Mean (SD)					
Hypophosphataemia, RR	No					
	Yes					
Alkaline Phosphatase, MD	Mean (SD)					
Elevated Alkaline Phosphatase, RR	≤140					
	>140					
Corrected Calcium, MD	Mean (SD)					
Hypocalcaemia, RR	<2.12					
	≥2.12					
Vitamin D, MD	Mean (SD)					
Total procollagen type 1 N-terminal	Mean (SD)					
Fibroblast growth factor 23 (FGF23),	Mean (SD)					

9 Reporting Conventions

P-values ≥0.001 will be reported to 4 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

10 Quality Assurance of Statistical Programming

A second review statistician will independently check the entire analyses and will explicitly check the code used to produce each table and other results.
To provide high quality code that is understandable, and allows for reproducibility of the analysis, the following details will be provided in annotation preceding code chunks.

- Population of analysis
- date and time included
- Description of desired output from analysis

R-studio will primarily be utilised for statistical analysis and review of analysis will be independently done with both R (based on the codes supplied in the primary analysis) and STATA statistical

software(Version 18).

11 Summary of Changes to the Protocol and/or SAP

Rationale for Adjustments of Statistical Analysis Plan from Protocol

Any changes from the protocol-specified definitions of aims, outcomes and statistical analytic approaches will immediately be outlined below. As much as possible, all changes will be done before database lock and unblinding of the study. In extreme cases, changes may be made after the unblinding, but the justification and detailed changes will be outlined.

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13 List of Tables, Listings and Figures