RESEARCH PROTOCOL

DOCUMENT NO.	01	**VERSION NO.**	2.0	**DATE**	18-1-2024
PROTOCOL NAME	Intravenous ferric carboxymaltose versus oral ferrous sulphate for the treatment of moderate to severe postpartum anemia in Nigerian women (IVON-PP): an open label randomized controlled trial alongside an implementation study				
FUNDING ORGANIZATION	Bill & Melinda Gates Foundation				
CHIEF INVESTIGATOR **Name and contact information**	Professor Bosede Bukola Afolabi College of Medicine, University of Lagos. +2348023154064 bbafolabi@unilag.edu.ng				
Chairman DSMC **Name and contact information**	Professor Morenike Ukpong Obafemi Awolowo University, Ile-Ife, Nigeria +2347062920394 toyinukpong@oauife.edu.ng				
COORDINATING CENTER (If applicable)	College of Medicine, University of Lagos Nigeria.				

APPROVED BY:

Professor Bosede B Afolabi	18/1/2024
Principal Investigator (Title, Name & Signature)	Date

Protocol development and Sign off

Protocol Contributors	
The following people have contributed to the development of this protocol:	
Name:	Affiliation and role:
Bosede B Afolabi	Professor of Obstetrics and Gynecology, College of Medicine, University of Lagos. Chief Investigator
Mobolanle Balogun	Consultant Public Health Physician & Senior Lecturer, Department of Community Health & Primary Care, College of Medicine, University of Lagos. Co-investigator
Kate F Walker	Clinical Associate Professor of Obstetrics, University of Nottingham. Co-investigator
Eleanor J Mitchell	Associate Professor of Clinical Trials, University of Nottingham. Co-investigator.
Ochuwah Babah	Senior Lecturer & Honorary Consultant, Department of Obstetrics & Gynecology, College of Medicine, University of Lagos/ Lagos University Teaching Hospital, Idi-araba, Lagos. Co-investigator
Yewande Oshodi	Associate Professor & Honorary Consultant Psychiatrist. Department of Psychiatry. College of Medicine, University of Lagos. Co-Investigator
Ibrahim Abioye	Director, Afya Technologies, Lagos. Co-investigator.
Aduragbemi Banke-Thomas	Associate Professor in Maternal Health, London School of Hygiene and Tropical Medicine. Co-investigator.
Ejemai Eboreime	Research Associate, Department of Psychiatry, University of Alberta. Co-investigator
Titilope A. Adeyemo	Professor & Consultant Hematologist, Department of Hematology & Blood Transf. College of Medicine, University of Lagos/Lagos University Teaching Hospital. Co-Investigator
Folashade Ogunsola	Professor & Consultant Clinical Microbiologist, Department of Microbiology, College of Medicine, University of Lagos/Lagos University Teaching Hospital. Co-Investigator

PROTOCOL AGREEMENT

I have read and understood the protocol below.

In my capacity as Principal Investigator/Site coordinator, my duties include ensuring the safety of the study participants, supervising their care, and providing **Prof. Bosede Afolabi** with complete and timely information. This information will be provided as outlined in this study protocol. All the information relating to this study will be held in strict confidence and these confidentiality requirements apply to all staff at this study site or involved with this study.

I agree to maintain the procedures required to perform this study in accordance with principles of Good Clinical Practice and to abide by the terms of this protocol.

Site Coordinator **(Title, Name, Signature & Date)**	
Contact Information **(Address & mobile No)**	

ATTESTATIONS

I have read and understood the protocol below in my capacity as a study staff.

	Study Staff Name	Designation/Role	Signature	Date
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12				

PROTOCOL SYNOPSIS

Study title	Intravenous ferric carboxymaltose versus oral ferrous sulphate for the treatment of moderate to severe postpartum anemia in Nigerian women (IVON-PP): an open label randomized controlled trial and alongside implementation study
Funding organization	Bill & Melinda Gates Foundation
Number of study sites	20
Rationale	Postpartum anemia occurs at an estimated prevalence of 50 – 80% of women in low- and middle-income countries (LMICs). It increases the risk of maternal complications such as infection, poor wound healing, fatigue, and depression which adversely impact her ability to care for her newborn and increase the risk of maternal death. Prompt treatment of postpartum anemia is critical. Oral iron is used routinely for treatment of mild to moderate postnatal anemia, while blood transfusion is offered for severe anemia or symptomatic women with moderate anemia. Adherence to oral iron is reportedly low due to side effects and forgetfulness. Intravenous iron such as ferric carboxymaltose which can be given as a single dose might help overcome some issues relating to adherence but its benefit, cost, and ease of implementing its use in Nigeria needs evaluation.
Study design	A multicenter parallel, open label, superiority randomized controlled trial, with an alongside implementation study.
Aims	To determine the clinical effectiveness, tolerability, and safety of intravenous ferric carboxymaltose (intervention) versus oral ferrous sulphate (control) for treating iron deficiency anemia in postpartum women. To evaluate the implementation outcomes (acceptability and feasibility) of using intravenous ferric carboxymaltose in treating postpartum anemia in Nigeria.
Objective(s)	• To determine the clinical effectiveness of intravenous ferric carboxymaltose versus oral ferrous sulphate in postpartum women with moderate to severe iron deficiency anemia. • 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 will measure Vitamin D, alkaline phosphatase, total procollagen type 1 N-terminal propeptide (P1NP), fibroblast growth factor 23 (FGF23), calcium (Ca), phosphate (PO_4), which are biomarkers of phosphorus homeostasis and bone turnover. • To determine the acceptability of Intravenous Ferric carboxymaltose to women and health care professionals

	• To determine the feasibility and organizational readiness for implementing the use of intravenous ferric carboxymaltose in treating postpartum anemia in Nigeria.
Number of participants	1,400 women
Participant selection criteria	• Women aged 15 to 49 years. • Between six and 48 hours after birth. • Baseline (enrolment) moderate or severe anemia (Hb < 10g/dl). • Able and willing to give written informed consent
Intervention product, dose, and route of administration	Ferric carboxymaltose, single dose of 20mg/kg (not exceeding 1000mg), Intravenous route
(Control) product, dose, and route of administration	Ferrous sulphate, 200mg (65mg elemental iron) two times daily. Oral route.
Duration of each woman's participation	6 months
Follow-up	2 weeks (±3 days), 6 (±1) weeks, 12 (±2) weeks and 6(±1) months postpartum.
Study duration	36-months

Participant Flow Diagram

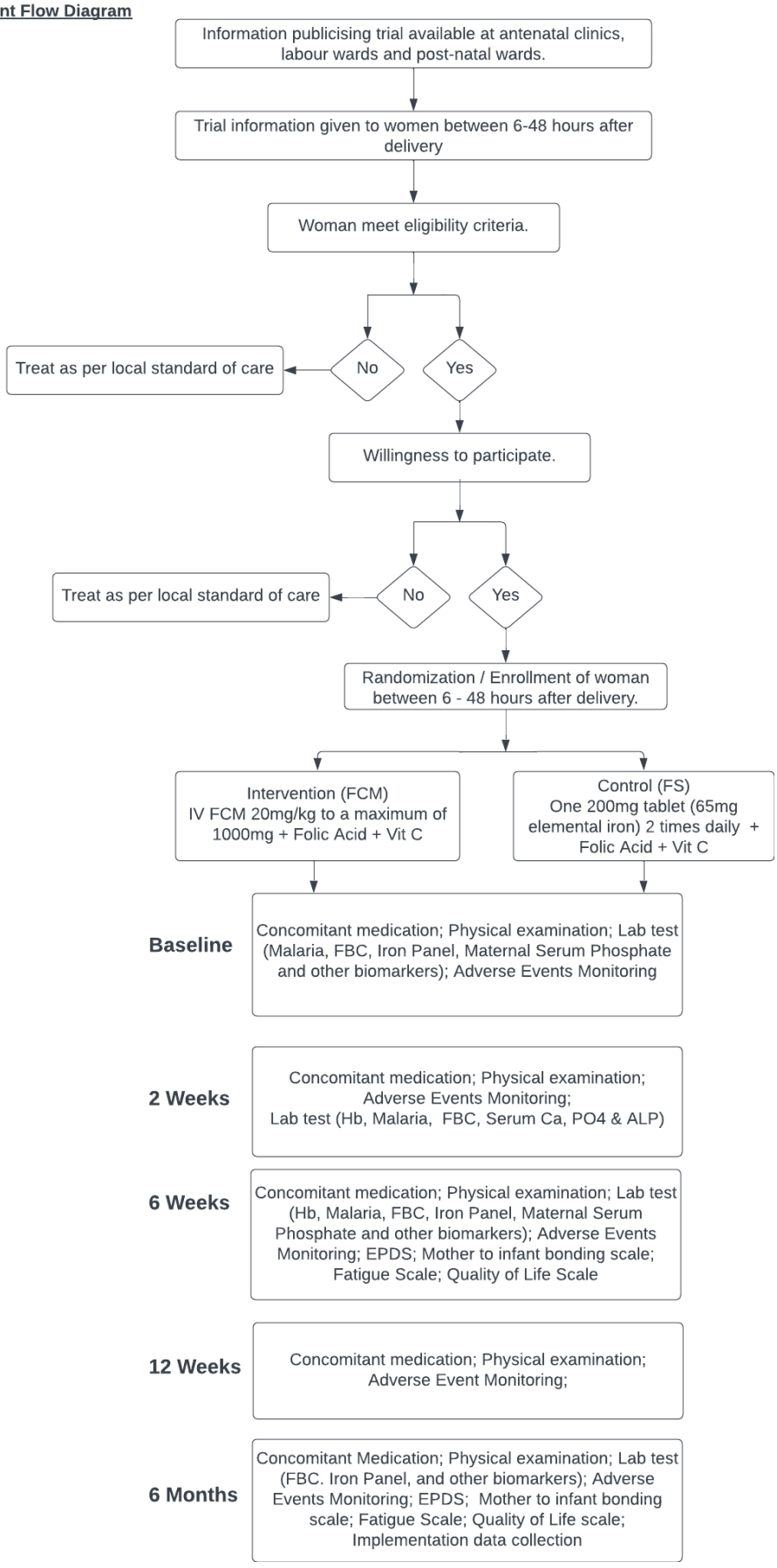


TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	Adverse event
AE(s)	Adverse Event(s)
AIM	Acceptability of intervention measure
AIP	Anemia in pregnancy
AKTH	Aminu Kano Teaching Hospital
ALP	Alkaline phosphatase
CA	Calcium
CFIR	Consolidated framework of Implementation Research
CI	Confidence interval
CMUL	College of Medicine, University of Lagos
CRA	Clinical research associate
CRF	Case report form
DSMC	Data and Safety Monitoring Committee
FGF23	Fibroblast growth factor 23 (FGF23)
FGD	Focus group discussion
FIM	Feasibility of intervention measure
GCP	Good Clinical Practice
Hb	Hemoglobin
IDA	Iron deficiency anemia
IRB	Institutional Review Board
KII	Key informant interview
LBW	Low birth weight
LMIC	Low- and middle-income countries
LUTH	Lagos University Teaching Hospital
P1NP	Procollagen type 1 N-terminal propeptide (P1NP)
POCT	Point of care test
PO_4	Phosphate (PO_4)
PPD	Postpartum depression
RCT	Randomized controlled trial.
RNA	Research Nurse Assistant

SAE Serious adverse event

SOP Standard Operating Procedure

GLOSSARY OF TERMS

Assessment	A procedure used to generate data required by the study
Chief Investigator	The Chief Investigator (CI) is the overall lead researcher for the project and takes overall responsibility within the team of researchers for the design, conduct and reporting of the study.
Control drug	The study drug (oral ferrous sulphate) used as a comparator to reduce assessment bias, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Enrolment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug (ferric carboxymaltose) whose properties is being tested in the study.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued, and no further assessments are planned
Principal Investigator	The Principal Investigator (PI) is the individual responsible for the conduct of the research at the state level and have coordinating and oversight responsibilities for all study site in their state.
Site Coordinator (Clinician)	The site coordinator (clinician), SC is the person at each study site responsible for the day to day running of the research project.
Source Document	A source document is a document in which data collected for a clinical trial is first recorded e.g patient's clinical note/file, registers, logs etc. This data is usually later entered in the case report form.
Study drug	Any drug (control or investigational) administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal

Study ID	A number assigned to each patient that is enrolled into the study. When combined with the center number, a unique identifier for each patient in the study is created. This is done automatically during the randomization process.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

INTRODUCTION

1.1 Background

Anemia in pregnancy is a major public health burden with a high 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). Postnatal anemia may result from untreated antenatal anemia or as a result of blood loss that occurs during birth. (3), and its prevalence 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 affects the neonates adversely (6). Specifically, postnatal anemia increases the risk of infection, leads to poor wound healing, and causes fatigue and depression in the mother (7). It also adversely affects breastfeeding, due to insufficient milk production, can reduce bonding between women and their newborn 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 postnatal period, while blood transfusion is offered for severe anemia or symptomatic women with moderate anemia (3). Oral iron, though inexpensive, causes significant gastrointestinal adverse effects such as vomiting, constipation, diarrhea, and abdominal pain (9), limiting adherence to this vital intervention which may pose a challenge in achieving optimum correction of anemia by the end of the postnatal period. 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 and moderately anemic women that require more rapid iron replacement for symptom control (3). Intravenous iron corrects anemia faster and in fewer doses than oral iron, 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 in Tanzania (230 women) found intravenous ferric carboxymaltose to be more effective than oral iron

for treating postpartum anemia and iron deficiency anemia with an almost five times greater odds of normalized hemoglobin level and a significantly higher ferritin level (12).

Although clinicians are aware of intravenous iron, its use is not widespread in most obstetric units in Nigeria. An equivalence randomized controlled trial studied 284 postpartum women in southeastern Nigeria and 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 delivery (13). In most health facilities in Nigeria, women are often discharged home after delivery on oral iron (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 delivery, 3% between 3 days and 6 weeks postpartum, while 60% did not receive any postpartum care (15). Most of the women discharged on oral iron will therefore not have the chance to have their hemoglobin levels or clinical states re-examined 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 is not thought to be clinically relevant in pregnancy, probably because it is given in just a few doses. 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 and reduce maternal morbidity and mortality this cost might be mitigated.

As postpartum anemia is highly prevalent in Nigeria and has a significant detrimental impact on the physical and mental health of women and their newborns, we propose a randomized controlled trial examining the clinical effectiveness of intravenous ferric carboxymaltose versus oral ferrous sulphate for moderate to severe anemia in postpartum Nigerian women. Recognizing the volatility of introducing such treatment in Nigeria, we also propose an alongside implementation study to better understand the implementation climate and assess key implementation outcomes.

2 STUDY OBJECTIVES

2.1 Aims

a) To determine the clinical effectiveness, tolerability, and safety of intravenous ferric carboxymaltose (intervention) versus oral ferrous sulphate (control) for treating moderate to severe iron deficiency anemia in postpartum women (population).
b) To evaluate implementation of intravenous ferric carboxymaltose in treating postpartum anemia in Nigeria.

2.2 Objectives

a) To determine the clinical effectiveness of intravenous ferric carboxymaltose versus oral ferrous sulphate in postpartum women with moderate to severe iron deficiency anemia by conducting a randomized trial.
b) 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 will evaluate biomarkers of calcium and phosphate homeostasis and bone turnover and measure vitamin D, alkaline phosphatase, procollagen type 1 N-terminal propeptide (P1NP), fibroblast growth factor 23 (FGF23), calcium and Phosphate levels.
c) To evaluate the acceptability and feasibility of using intravenous ferric carboxymaltose in treating postpartum anemia in Nigeria by conducting an alongside implementation study.

3 OUTCOMES

3.1 Clinical outcomes

3.1.1 Primary outcome

Proportion of participants who are non-anemic at six weeks postpartum. Non-anemic state is defined as hemoglobin level ≥ 11.0g/dl.

3.1.2 Secondary outcomes

a) Proportion of women with postpartum depression, measured using the Edinburgh Postnatal Depression Scale at six weeks and six months postpartum.
b) Change in mean postpartum hemoglobin levels at two weeks and six weeks postpartum.
c) Achievement of a non-anemic state (Hb≥11.0g/dl) at six months postpartum.
d) 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.
e) Change in mean serum ferritin, serum transferrin, serum iron and % transferrin saturation at two weeks and six weeks postpartum.
f) Need for blood transfusion after iron treatment during the first 6 weeks postpartum.
g) Prevalence of fatigue at six weeks and six months postpartum, measured using the Fatigue Severity Scale (revised FSS-5R version) (22).
h) 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).
i) Proportion of infants being breastfed (exclusive and any) at six weeks and six months postpartum.
j) Prevalence of impaired maternal-infant bonding at six weeks and six months postpartum measured using the Mother-to-Infant Bonding Scale (MIBS) (20).
k) Incidence confirmed or suspected maternal infection within 6 weeks of birth, as 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).
l) 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 <2.5mg/dL (0.81mmol/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).
m) Incidence of early neonatal death, defined as death of newborn from enrolment of the mother to before seven completed days.
n) Incidence of late neonatal death, defined as death of the newborn from enrolment of the mother to before 28 completed days.
o) Incidence of infant death, defined as death from enrolment before the age of six months.

p) Incidence of post-natal maternal death from enrolment up to six weeks and at six months postpartum.
q) Incidence of adverse drug events.
r) Quality of life measured using the WHOQOL BREF at enrollment, six weeks, and six months post-partum.

3.2 Implementation outcomes

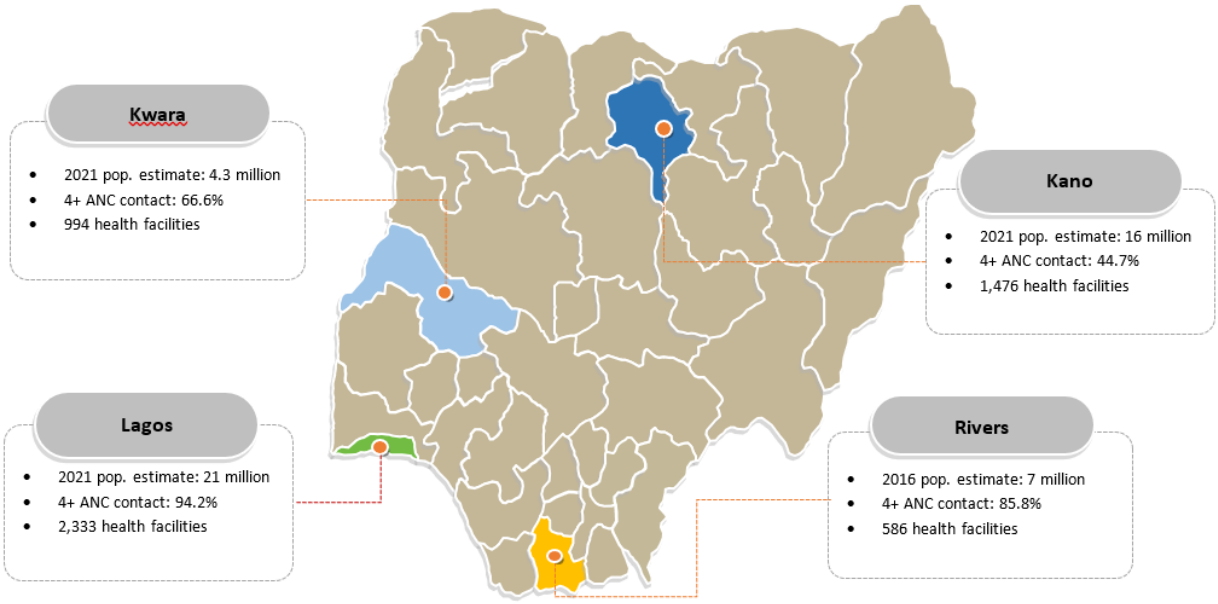
a) Acceptability of the intervention to women and health care professionals
b) Feasibility of implementing the intervention

4 STUDY DESIGN

This study is a multicenter parallel, open label, superiority randomized controlled trial, with an alongside implementation study.

4.1 Study setting and site selection

The study will be undertaken in four states in Nigeria, two states in the North - Kano and Kwara states, and two in the South - Lagos and Rivers states. North-South differentials in the use of maternal health services, and in maternal health indices, such as lower ANC attendance and poorer maternal-infant outcomes in the North (14, 24, 25) necessitated representation of both regions in this study. The variation in indices across the four states strengthens the rationale for their selection. Lagos has the highest proportion of women with 4 or more ANC contacts as per the most recent guidelines of the World Health Organization. Kano has one of the least in the country while Rivers and Kwara reflect the average number of ANC contacts for many states in Nigeria. In terms of existing infrastructure, number of health facilities range from 994 in Kwara to 2,333 in Lagos (Figure 1).



Source of data for map: 2021 projected population by the National Bureau of Statistics, 2017 demographic Statistics Bulletin by National Bureau of Statistics, 2018 Nigerian Demographic Health Survey, 2020 Nigeria Health Facility Registry

Figure 1: Map of Nigeria indicating the four selected states for the study with key population and service indices

Five (5) health facilities at the three levels of health care (primary, secondary, and tertiary health facility) will be selected from each state for this study, making a total of twenty (20) study sites for this study (one tertiary, three secondary and one primary healthcare facility). The facilities are selected with consideration for antenatal patient flow, number of deliveries and proximity of all three levels of care to facilitate an effective two-way referral system (Table 1). Each state will have a Principal investigator (PI)

and each site will have a clinician as Site Coordinator (SC) and two research nurses. Eligibility criteria applied for site selection at all the states include:

- Exclusively publicly funded primary, secondary or tertiary health facility
- Presence of an antenatal clinic that serves at least 60 pregnant women per month and a labor ward that provides deliveries for at least 20 women per month
- Presence of a labor ward that provides consistent 24-hour vaginal delivery services

Table 1: Study sites and codes

Site code	State	Name of Study Site
01	Lagos	Lagos University Teaching Hospital (LUTH), Idi-Araba, Lagos
02	Lagos	Mother and Child Centre, Amuwo-Odofin
03	Lagos	Mother and Child Centre, Gbaja (Maternity unit of Randle General Hospital, Surulere), Lagos
04	Lagos	General Hospital, Ifako Ijaiye
05	Lagos	Ipaja Primary Health Centre, Alimosho L.G.A., Lagos
06	Rivers	University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt
07	Rivers	Okrika General Hospital, Okrika
08	Rivers	Bori General Hospital, Bori
09	Rivers	Ahoada General Hospital, Ahoada
10	Rivers	Model Primary Health Centre, Orogbum
11	Kano	Aminu Kano Teaching Hospital (AKTH), Kano
12	Kano	Waziri Gidado GH
13	Kano	Nuhu Bammali GH
14	Kano	Sheik Jeddah GH
15	Kano	Kabuga PHC
16	Kwara	University of Ilorin Teaching Hospital (UITH), Ilorin, Kwara
17	Kwara	General Hospital Ilorin
18	Kwara	Adewole Cottage Hospital, Ilorin
19	Kwara	Civil Service Hospital, Ilorin
20	Kwara	Okelele Health Centre

4.2 Study population

Postpartum women with moderate to severe iron deficiency anemia.

4.2.1 Selection of participants

Inclusion criteria:

a) Women aged between 15 and 49 years.
b) Between six and 48 hours after delivery. A minimum of six hours has been chosen because we expect the initial post-birth blood loss to have subsided and the hemoglobin concentration to be sufficiently representative of the true hemoglobin concentration at that time; 48 hours has been chosen as the upper limit for pragmatic reasons because women are usually discharged from hospital after 48 hours.
c) Baseline (enrollment) moderate or severe anemia (**Hb≤9.9g/dl**), confirmed by Hemocue haemoglobinometer.
d) Able and willing to give written informed consent.

Exclusion criteria:

a) Having received a blood transfusion, for any indication, within the last three months.
b) Symptomatic anemia and a need for urgent correction.
c) Known haemoglobinopathy such as sickle cell disease, HbCC disease.
d) Clinically confirmed malabsorption syndrome.
e) Known hypersensitivity or contraindication to any form of iron treatment, study drug or any of its excipients.
f) 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.
g) Severe allergic conditions such as severe asthma, eczema, or other atopic condition.
h) Known autoimmune conditions e.g., systemic lupus erythematosus, rheumatoid arthritis or known severe drug allergies.
i) Planning to move or reside outside the research area
j) Women who have had intravenous iron administered in the last two years (26).

*****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*.**

4.3 Sample size

We will enroll 1400 women into the trial. Power calculations assume a 1:1 randomization ratio to each of the two treatment groups.

For the primary outcome (anemia), we used data from a recent meta-analysis (28), which reported that 39% of women were anemic at six weeks postpartum. A sample size of 697 participants per arm would

provide 90% power to detect to detect a relative reduction of 20% for IV iron to reduce the event rate of anemia at six weeks postpartum to 30%, after accounting for 10% loss to follow-up.

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 (29), adjusting our final alpha level to 0.0492 (*See section 9.3 for interim rule*), which increased our final sample size to 1400 (700 per arm of the study).

4.4 Randomization

Randomization and enrolment will occur between six and 48 hours after delivery and the initial post-delivery blood loss. Postpartum women during this window (6-48 hours postpartum) will be screened, enrolled, and randomized to one of the two treatments groups. Individual randomization and allocation concealment will be done with the use of a web-based randomization software known as 'Sealed envelope' in a 1:1 ratio in blocks stratified according to study site (**Table 1**). Screening, consenting, enrolment and randomization will be done by dedicated and trained study research nurses/midwives at each participating study site.

4.5 Blinding

This study is a multicenter parallel, open label, superiority randomized controlled trial. It is impossible to blind the treatment allocation as the intervention is administered intravenously, and the control is administered orally. However, the primary outcome data will be objectively determined by laboratory evaluation and will be collected without bias. For the subjective secondary outcomes, using the Edinburgh Postpartum Depression Scale (EPDS), Quality of Life questionnaire, fatigue scale, Maternal Infant Bonding questionnaire and an adverse event form, the research nurse performing data collection for these outcomes will be blinded to group allocation. These patients' reported outcomes measures will be completed without knowledge of the group allocation except for data on treatment compliance. Data on treatment compliance will be collected only after all other outcome data for the individual's visit has been completed and submitted.

4.6 Study intervention

4.6.1 Administration of study drugs

Administration of ferric carboxymaltose (FCM): Eligible women randomized to the intervention arm (FCM) will be observed at the dedicated ward or daycare room for treatment initiation and will be given **intravenous ferric carboxymaltose (FCM)** in a single dose of 20mg/kg up to a maximum of 1000mg. This dose will be administered as an infusion diluted in 200 ml 0.9% sodium chloride and **infused over a minimum of 15 - 20 minutes** (**Table 2**). Thereafter, they will be **observed closely for a minimum of 30 minutes** after infusion. [***Refer to IVON-PP Trial - Protocol for the administration of Intravenous Ferric***

Carboxymaltose and the Emergency Treatment of Hypersensitivity Reaction Type 1 (Anaphylaxis); Protocol no 2].

Administration of Ferrous Sulphate (FS): The women randomized to the control arm (FS) will be given for take home, one **200mg tablet of study drug, ferrous sulphate** which contains 65mg of elemental iron, to be taken two times daily and 1 hour before meals or 2 hours after meals with a full glass of water till 6 weeks postpartum (**Table 2**). The study drug for the control arm (FS) will be prepared in sachets, dispensed, and packaged in 2-week, 4-week and 6-week doses for the appropriate visit schedule. The women will be sent daily reminders by text messages and asked to bring in their empty sachets for sighting and for a pill count and evaluation of compliance at each study visit.

Table 2: Oral and intravenous Iron dosing for intervention and control arms

Study arm	Study medications	Dose	Comments
Intervention	Drug: intravenous ferric carboxymaltose	Single dose of 20mg/kg (to a maximum of 1000mg)	A dose of 20mg/kg body weight (but not exceeding a max of 1,000mg) of ferric carboxymaltose will be given in 200mls of normal saline as a single dose infusion administered over 15 – 20 minutes
Control	Drug: oral ferrous sulphate	One 200mg tablet (65 mg elemental iron) 2 times daily	Treat with 2 times daily regimen till six weeks postpartum.[a, b]

a. All patients will also receive 5mg folic acid daily and 400mg Vitamin C daily.

b. After six weeks, any women with Hb still less than 11g/dl will be treated with oral iron or further investigated for the cause of the anemia and treated appropriately.

In addition, all study participants in both arms of the study; FCM and FS will receive 5mg folic acid daily, Vitamin C 200mg two times daily unless in known cases of allergy or intolerance to vitamin c and/or folic acid and followed from enrollment till 6 months post-partum. They will be seen on the postnatal wards from six hours after delivery, and then followed up at the health facility or home at two, six and 12 weeks, and six months postpartum.

4.6.2 Malaria treatment and prevention

All participants will be screened at baseline (enrollment), two and six weeks postpartum for malaria parasitemia with SD BIOLINE Malaria Ag P.f and treated with artemisinin-based combination therapy or any other tolerated alternative if positive for malaria parasites.

4.7 Participant Identification

Each participant will be uniquely identified in the study by a combination of the study site code and a four-digit number to make a study ID number e.g., 01-0001, 01-0002 etc. The study site codes are pre-assigned

and logged into the sealed envelope by the Chief Investigator as shown in **Table 1.** After signing the informed consent form, the patient will be assigned a Study ID automatically generated as she is randomized on the web-based randomization form.

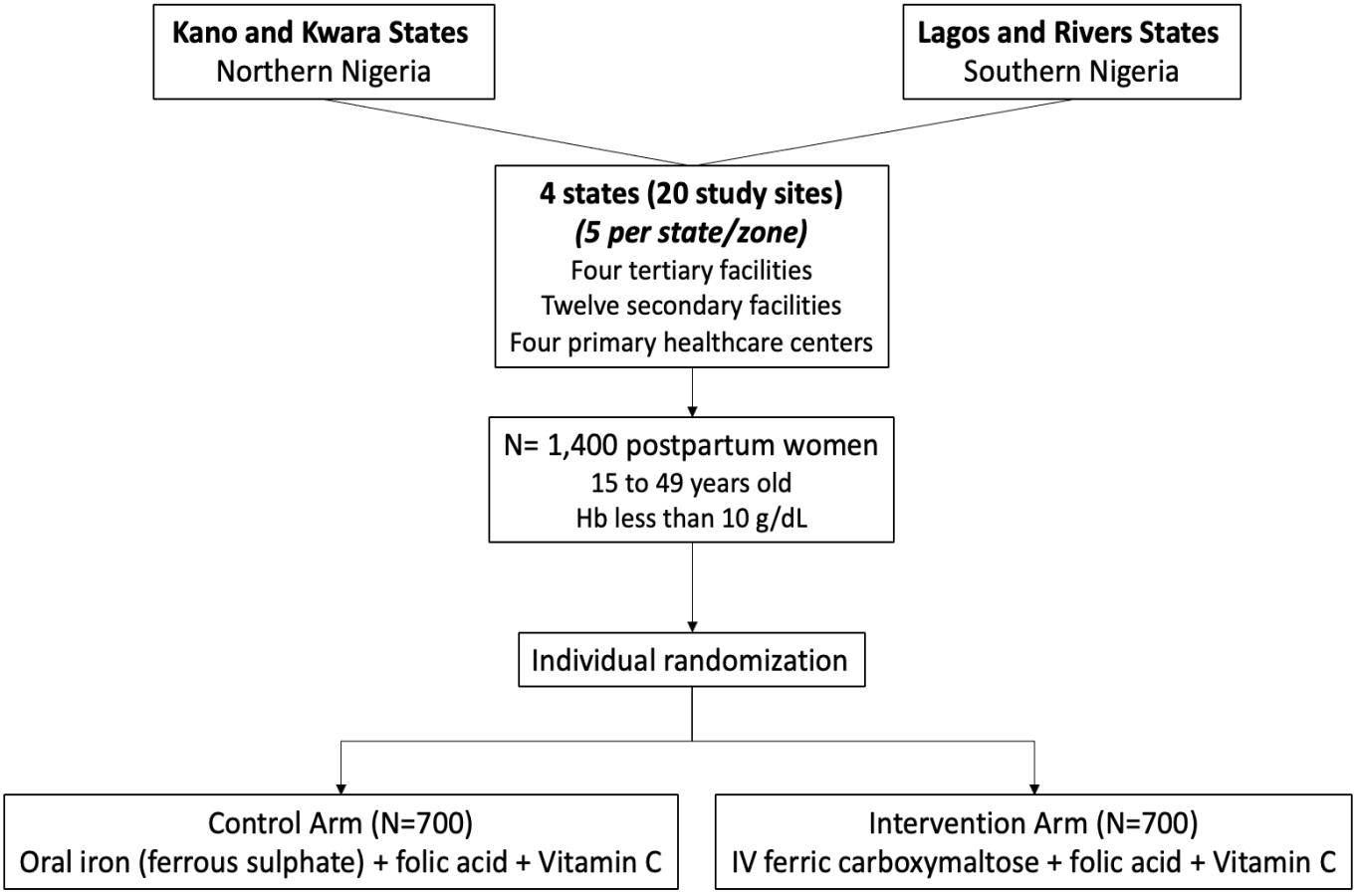


Figure 2: Prospective (clinical trial) study design flowchart

4.8 Physical examination

Full physical examinations will be performed at baseline, and at each visit. Examination will include measurement of the patient's weight and blood pressure, body temperature. An abdominal palpation will be performed to ensure the uterus is well contracted in all women; a physical examination of the perineum will be performed at baseline to ensure any perineal trauma has been identified. A physical examination of the breasts/perineum/abdomen will be performed if clinically indicated during follow up visits.

Information about the physical examination must be entered into the patients' clinical case notes/files at the study sites. Significant findings such as abnormal swelling, skin lesions, signs of inflammation/infection that are present prior to receiving study medication must be included in the relevant medical history/current medical conditions in the source document and the electronic Case Report Forms (CRFs).

4.9 Laboratory evaluations

Standard clinical laboratory evaluations will be performed as follows:

- Hemoglobin concentration with the Hemocue haemoglobinometer at screening, two and six weeks and six months postpartum. Complete the ***Hb check worksheet*** as appropriate *(Appendix i).*
- Malaria rapid diagnostic test (RDT) with SD BIOLINE Malaria Ag P.f at enrollment, two and six weeks postpartum and if symptomatic for malaria at any time. Complete the ***Malaria POCT worksheet*** as appropriate *(Appendix ii).*
- Full blood count at baseline (enrollment), two weeks, six weeks, and six months postpartum. At each visit, 4mls of blood will be collected in an EDTA vacutainer. ***Complete blood sample collection log for study visits on REDCap*** *(Appendix iii).*
- Iron profile: comprises serum iron, serum ferritin, serum transferrin and percentage transferrin saturation will be done at baseline (enrollment), six weeks and six months postpartum. At each visit, 4mls of blood will be collected into a Serum separating tubes (SST) tube. ***Complete blood sample collection log for study visits on REDCap***
- Maternal serum phosphate and other biomarkers: The biomarkers of phosphate homeostasis and bone turnover to be measured are Vitamin D, alkaline phosphatase, total procollagen type 1 N-terminal propeptide (P1NP), fibroblast growth factor 23 (FGF23), calcium (Ca) and phosphate (PO4) at baseline (enrollment), 2 weeks (Ca, PO4 and ALP only) and at 6 weeks postpartum. Two (2) SST tubes will be used for sample collection and 4mls of blood will be collected in each tube. ***Complete blood sample collection log for study visits on REDCap.***

All samples aside the point of care tests (POCT) will be analyzed at Synlab (an internationally accredited medical laboratory). As a third-party, a contract is in place between the University of Lagos and Synlab. The following steps will be taken at blood sampling:

- Research nurse assistants will collect blood sample as indicated for study visit using an appropriate vacutainer system.
- Complete the ***laboratory tests request form*** *(Appendix iv)* with participant's study ID, study site code and visit type (PP-1 to PP-4) to accompany the samples to the lab.
- Document date and time samples were taken and type of test in blood sample collection log on REDCap for study visit.
- Call the dispatch rider for samples pick up within 2-3 hours of sample collection.
- Store samples at 4-8^{0}C (refrigeration) immediately after collection before pickup; for not more than 12 hours.

The result in CSV format will be entered into the e-CRF by the data management team as soon as received from the laboratory. Test results will be reviewed at the back end by the investigators and if any results

are of clinical concern, the site coordinator will be contacted to schedule a study visit, and a repeat sample will be collected at the earliest visit.

4.10 VISIT SCHEDULES AND ASSESSMENTS

Participants will be seen at the postnatal wards between 6 and 48 hours after delivery at study sites for enrolment then at two, six and 12 weeks postpartum and at the end of study (EOS) visit at six months postpartum. Aside the baseline visits for enrolment, all other visits will be done at the participants' home or at the healthcare facility depending on the participants' preference.

4.10.1 Screening &and consent (visit 0)

- The required information from this visit will be completed for all prospective participants in the ***screening log*** *(Appendix v).*
- All prospective participants are women who are within six and 48 hours after delivery.
- These women will be assessed using the study eligibility criteria (inclusion and exclusion)
- Those that meets the eligibility criteria will then have their hemoglobin concentration determined using the POCT haemoglobinometer. Complete the ***Hb check worksheet*** as appropriate.
- Participants with ***Hb ≤9.9g/dL*** who have been determined to meet other study eligibility criteria are then consented for participation in the study.
- Informed consent must be obtained at this visit when the prospective participant meets **ALL** study eligibility criteria.

  The **informed consent process** is described below:

  - The research nurse assistant will provide the full participant's information sheet to the prospective participant. Information will be disclosed to the prospective participant, and it will be ensured she comprehends the nature and purpose of the study, duration of participation, procedures to be done, community tracking as necessary including home visitations and laboratory investigations to be performed. She should also be made aware of any foreseeable risk and discomfort, other study requirements and visits schedule, participants' responsibility and be willing to freely participate.

  - Acceptance/rejection to participate

  - Agreement to participate (Consent) must be recorded (written) and witnessed where necessary. Each participant will be asked to sign (or provide other mark such as thump print if need be) ***three copies*** of an ***informed consent document*** (*Appendix vi*)**,** in English or translated into Yoruba/Hausa/Igbo as appropriate. The participant will be given a signed copy to take home. If the participant cannot read, a witness must be present at the time of the information disclosure and consent process and will witness the signature or mark of the participant.

If a prospective participant is screened but does not get enrolled, the reason for not being enrolled must be documented in the screening log.

4.10.2 Enrollment and randomization visit (Visit 1)

Enrollment (visit-1) will preferably take place during the same visit/time as the screening (visit-0) or very shortly after within 6-48 hours after delivery.

- Once the participant has been screened and determined to meet study eligibility criteria and complete the informed consent document,

The following additional steps will be taken:

1. **Go to *Sealed Envelope* and randomize the participant into a study arm.**
   - The participant will be assigned a study ID which will be used to identify the participant throughout the study.
   - **Complete the enrollment log sheet** (*Appendix vii)* with the participant's assigned study ID and treatment arm.
   - The study ID only will also be written on her clinical case-notes (source document).

2. **Go to REDCap**
   - **Complete participant's biodata and locator form** (*Appendix viii*)**:** For each participant, the research nurse (RN) will obtain contact information, which will include the participant's phone number, her partner's phone number, her home address, major landmark to her home, occupation, and other necessary information as provided by the participant. The RN should determine the best way to collect this information for each study participant and complete it in the participant's biodata and locator form. If a participant misses a scheduled appointment (follow-up or end of study visit), the research staff will try to establish communication with the participant through authorized possible means (e.g., phone, emails or visiting the participant's home or workplace). The need to complete all scheduled follow up visits must be emphasized to all study participants at enrolment and at every visit.
   - Take relevant medical history and concomitant medication information.
   - Do a physical examination
   - Evaluate for the presence of any symptom and sign (adverse event(s) AEs)) and if any**, complete and submit the adverse event e-form** *(Appendix ix).*

   - **Complete enrollment e-CRF (***Appendix x***)** and relevant source document (SD) to document relevant baseline observation.
   - Take blood samples for laboratory tests **complete the blood sample collection log.**
   - Administer study drug (intervention or control) according to randomization and protocol for study drug administration (section 4.6.1)

4.10.3 Follow-up visits (2, 6, and 12 weeks postpartum)

- Each participant will have follow-up visits at home or healthcare facility whichever is preferred except the 6 weeks visit which as routine should be at the health care facility.

The following steps will be taken at the follow up visits:

1. **Go to REDCap, using the participant's study ID-**

    - **Complete and submit the Edinburgh Postnatal Depression Scale (EPDS) e-form** *(Appendix xi)* at 6 weeks visit.
    - **Complete and submit the Maternal infant bonding scale e-form** *(Appendix xii)* at 6 weeks visit.
    - **Complete and submit the fatigue scale e-form (***Appendix xiii)* at 6-week visit.
    - **Complete and submit the quality of life (WHOQOL BREF) scale e-forms** *(Appendix xiv)* at 6 weeks visit.
    - Evaluate for the presence of any symptom and sign (adverse event(s) AEs)) and if any, **complete and submit the adverse event e-form for all follow up visit.**

The visit e-CRF will be available to you ONLY after completing and submitting the above steps on REDCap.

- Evaluate compliance to study drug and document in the e-CRF.
- **Complete follow-up visits e-CRF** (*Appendix xv)* and relevant source documents
- Re- supply study drug (control arm) in an amount sufficient to last until the next follow up visit up to the 6th week visit.
- Counsel and necessary referral (e.g., family planning clinic, psychosocial support etc.).

2. **Additional steps**

    - Perform malaria rapid diagnostic test (RDT) with SD BIOLINE Malaria Ag P.f and complete the *Malaria POCT worksheet* as appropriate (2- and 6-week postpartum visits).
    - Do hemoglobin concentration check with the haemoglobinometer at every follow up visit. And complete Hb check worksheet as appropriate.
    - Take blood samples for laboratory tests as indicated for visit type and complete the blood sample collection log on REDCap. This sample can also be used for the hemoglobin concentration check.
    - Counsel as appropriate based on any queries they might have about their health or that of their newborn/baby.

The research team at site will be responsible for the visits and attending to the participant and re-supplying the participants with the study drugs at two weeks.

4.10.4 Interim contacts and unscheduled visits

- The participant or the site clinician may request an interim contact or an unscheduled visit at any time during the study.
- Interim or unscheduled visits are usually adverse event (AE)-related visits in which health-related events, adverse drug effects, or abnormalities are reported.
- Other reasons for an interim or unscheduled visit not in response to an AE may include:
    - To get more trial drugs in cases of loss or misplacement.
    - To ask questions and discuss problems with study compliance
    - Interim examination - examination requested but no complaints or symptoms
- All interim contacts and unscheduled visits will be documented in the participants study records and visit e-CRFs.

4.10.5 End of study (EOS at six months post-partum)- visit

- All participants will complete the study at six months postpartum and all relevant data will be captured into all the appropriate study visit e-CRF.

These steps will be taken at the participant's end of study visit: -

1. **Go to REDCap, using the participant's study ID-**
    - **Complete the Edinburgh Postnatal Depression Scale (EPDS) e-form for six months visit**
    - **Complete the Maternal infant bonding scale e-form for six months visit**
    - **Complete the fatigue Scale e-form for six months visit**
    - **Complete the quality-of-life scale (WHOQOL BREF) e-forms for six months**
    - Evaluate for the presence of any symptom and sign (adverse event(s) AEs)) and if any**,** complete and submit the adverse event e-form*.*

The visit e-CRF will be available to you ONLY after completing and submitting the above steps on REDCap.

- **Complete follow-up visits e-CRF for six months** and relevant source documents.
    - **Take blood samples for laboratory tests** as indicated for visit type and complete the blood sample collection log on REDCap.
    - Counsel as appropriate based on any queries they might have about their health or that of their newborn. Counsel and necessary referral (e.g., family planning clinic, psychosocial support etc.)
    - Thank participant for their participation and inform them of plans for dissemination of research findings.

2. **Additional steps**

- Site coordinators will complete **end of study e-CRF** *(Appendix xvi)* at completion of all study visits and data entry and other relevant source documents.

4.10.6 Community tracking and home visits for follow up

Postnatal care attendance is very low amongst Nigerian women (NDHS 2018). It can therefore be difficult to retain them within a clinical trial during the postnatal period. To avoid loss to follow up, participants will be followed up to the communities and their homes.

The following steps ***MUST*** be taken to avoid loss to follow up and to track those who fail to keep scheduled visits:

- Continuous interaction with participants at every visit to reaffirm comprehension of the nature and purpose of the study, duration of participation, procedures to be done.
- Re-affirm permission to track and for home visit when necessary, including the possibility to collect information and blood samples for laboratory tests during the home visits.
- Reconfirm participant's phone numbers and information on participants locator form at every visit and discuss possible physical location of participant for the next scheduled visit and document it in the locator form.
- All participants visit schedules must be closely monitored.
- Reminders for next scheduled visit must be sent by test message, WhatsApp, or email as convenient at least 1 week to the scheduled visit.
- A phone call should be made a day prior to scheduled visit.
- Offer to cover transport cost/other compensation for the visit.
- In the event that a participant fails to keep a scheduled appointment, community tracking of the participant must be activated using the participant's locator form and a home visit made within 48 hours.
- Participants will be continuously engaged in the trial by sending text messages about study progress.

The tables below list all the assessments and indicates with an "X" the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation and the e-CRFs. The Table also indicates which data are entered into the database (D) or remain in source documents only (S) or both (S, D).

- Assessments that generate data for database entry and which are recorded on CRFs are listed using the CRF name (Enrollment, follow up visits, and end of study).
- Assessments that are transferred to the database electronically (e.g., laboratory data) are listed by test name.

Table 3: Assessment and schedule for study participants

Phase / Activity		Baseline (Screen &enroll)	Follow up visits (postpartum)			End of study (EOS)
Study visits no			2 weeks	6weeks	12weeks	6months
Inclusion/exclusion criteria (S,D)		X				
Written informed consent (S)		X				
Socio-demographics/PMH (S,D)		X				
Concomitant medication (S,D)		X	X	X	X	X
Clinical symptoms (S,D)		X	X	X	X	X
Physical examination (S,D)		X	X	X	X	X
Lab Tests (S,D)	Hb	X	X	X	X	X
	Malaria	X	X	X		
	FBC	X	X	X		X
	Iron panel	X		X		X
	Maternal Serum P04 and other markers	X	X (Ca, PO4 & ALP only)	X		
Intervention drug (FCM); S, D		X				
Control drug (FS); S, D		X	X	X		
Adverse Events (S, D)		X	X	X	X	X
Edinburgh Postnatal Depression Scale (EPDS) (D)				X		X
Mother to infant bonding scale (D)				X		X
Fatigue scale (D)				X		X
Quality of life scale (D)				X		X
Implementation data collection (D)						X
End of study (D)						X

Note: All Participants will be recruited from the postnatal wards from 6 hours after delivery, followed up at home or hospital two weeks later, seen again at six weeks, 12 weeks, and six months postpartum.

* Iron panel comprises serum iron, serum ferritin, transferrin saturation and percentage transferrin saturation. FCM: Ferric carboxymaltose. FS: Ferrous sulphate. S: Source document. D: Database (REDCap e-forms).

5 PARTICIPANTS WITHDRAWAL AND STUDY DISCONTINUATION

5.1 Premature participant withdrawal from the trial

A participant must be withdrawn from the study for any of the following reasons:

- Voluntary withdrawal of informed consent
- Participant could also be withdrawn at any time if the investigator concludes that it would be in the participant's best interest for any reason.

Protocol violations should not lead to patient withdrawal unless they indicate a significant risk to the participant's safety.

Participant may voluntarily withdraw from the study for any reason at any time during the study. If premature withdrawal occurs for any reason, the investigator must determine the primary reason for the premature withdrawal from the study and record this information on the study completion CRF. Participants who are prematurely withdrawn from the study will not be replaced by newly enrolled participants.

5.2 Alternate/Further treatment and evaluation

Where any participant fails to respond adequately to study treatment and moderate-severe anemia persists despite iron therapy, such participants will be further evaluated for other forms of anemia and/or referred to specialist hematologist for further evaluation of other causes of anemia at any point during follow up. Relevant information on alternate or additional treatment must completed in the source document and the e-CRF and the participants must be followed up to the end of the study.

5.3 Loss to follow up

If a participant fails to appear for a scheduled visit, at least three attempts to contact her will be made over the subsequent 30 days. These attempts will be documented in the participant study file. Her file will remain open until by calculation, she would have completed 6+1-month post-partum.

For participants who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the RN should show "due diligence" by documenting in the source documents (visitation and call logs; *Appendix xvii*) steps taken to contact the participant, e.g., dates and numbers of phone calls, home visit, etc.

If the participant does not return to the study before she had completed 6+1-month post-partum, the end of study form will only be completed at her completed 7 months post-partum. The form will indicate that the participant was lost to follow up. The "lost to follow up" designation cannot be made for any participant until the natural end of her study visits which is 6+1-month post-partum.

6 STUDY PRODUCTS, INVENTORY & TREATMENT

6.1 Study Drugs

- IV ferric carboxymaltose
- Oral ferrous sulphate

6.2 Study drug supply and resupply, storage, and tracking

- Study drugs will be received by a designated person at the study site, handled and stored safely and appropriately, and kept in a secured location to which only the investigator and designated assistants have access.
- Upon receipt, all study drugs should be stored according to the instructions specified on the drug labels.
- Study drugs and all clinical supplies are to be dispensed only in accordance with the protocol.
- The site coordinator and research nurses must maintain an accurate record of supplies and dispensing of study drugs in the ***drug accountability ledgers*** *(Appendix xviii)*.
- Monitoring of drug accountability will be performed by the clinical monitor during site visits and at the completion of the trial.
- Participants may be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

6.3 Dispensing the study drug and labeling

- Each study site will be supplied with the study drugs by the trial pharmacist.
- Once a patient at a particular site is randomized. The site coordinator or research nurse assistant will identify the study drug to dispense to the patient based on the randomization arm.
- Immediately before dispensing the study drug to the patient, site coordinator/RN will document into all required the source documents (**enrollment log, patients case notes and *drug accountability ledger) and e-CRF*** with the participant's unique Study ID.

6.4 Other concomitant treatment and medication

Use of any other drug unprescribed and herbal medications are strongly discouraged. However, if taken, the information should be collected in the e-forms under co-medications. Participants will be specifically requested not to take any other iron containing medication.

6.5 Study drug discontinuation

- Study drug must be discontinued for a given participant if the investigator determines that continuing it would result in a significant safety risk for that patient. This should only be done after discussion with and approval from the chief investigator/PI.
- The following circumstances require study drug discontinuation:
  - Emergence of severe adverse reactions such as severe nausea/vomiting, allergy, severe pruritus, anaphylaxis, and other life-threatening symptoms
  - Abnormal laboratory values: Hb <6g/dl

Participants who discontinue study drug for adverse effects (AE) or any reason other than an AE will be followed to study completion at 6 months postpartum at which times all the assessments as listed for the visits will be performed. Reasons for study drug discontinuation should be completed, giving the date and primary reason for stopping the study drug under the relevant section of the CRF.

6.6 Treatment exposure and compliance

- All medication (other than study drug) and significant non-drug therapies administered after the patient starts treatment with study drug will be documented under concomitant medications/significant non-drug therapies in the e-CRF after start of study drug.
- Records of study medications used, and exact dosage administration and compliance will be kept during the study.
- Drug accountability will be noted by the clinical monitor during site visits and at the completion of the study.

7 ADVERSE EVENTS AND REPORTING REQUIREMENTS

7.1 Adverse Events

- An adverse event (AE) is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drugs include the investigational drug/ control drug under evaluation that is given during the treatment phase of the study.
- Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug.
- Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or are considered clinically significant, or require therapy. E.g., hypophosphatemia requiring treatment.
- Clinical signs and symptoms will be assessed at baseline, before dosing and at all follow-up visits, and recorded in the e-CRF. Any symptom that worsens or starts after baseline will be recorded as a new adverse event on the e-CRF.
- The occurrence of adverse events, such as fever, weakness, chills/rigors, headache, myalgia, dizziness, epigastric pain, abdominal pain, anorexia, nausea, vomiting, diarrhea, palpitations, insomnia, pruritus, coughing, tinnitus, abnormal gait, tremor, clonus, or dyskinesia, will be sought by the investigator (or designee) at each study visit and recorded in the e-CRF.
- Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

7.2 Reporting Adverse Events (AEs)

- All adverse events that occur from the point of enrollment and throughout study duration will be collected non-systematically from each participant. Participants will be routinely asked at every study visit “do you have any symptoms now or noticed any since your last visit?”
- If a participant reports an AE at enrollment but before the administration of study intervention, the AE will be reported as not related to study drug. All other adverse events reported after enrollment into the study and until the end of study will be defined and graded for severity using the **National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0**
- Study site coordinators/clinician will document on the appropriate study e-CRF, and clinical case notes all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product.
- The study clinician must provide on the AE e-form information on symptoms, time of onset, severity, frequency, product-relatedness, actions taken and participant outcome.
- The causality of AE to trial drugs will be determined by the principal investigator and documented along with the interventions given, and the outcome.
- The PI may request additional information from the site if it is needed to further evaluate the AE.

- Site coordinators will report serious adverse events (SAEs; see section 7.2.5) to the principal Investigator and the local Ethics committee as soon as possible and in accordance with the local ethics committee requirements.
- Discontinuation of study drug may be considered if a participant experiences a severe adverse drug event of Grade 3 or higher. Decision for discontinuation will be made by the PI and or the study participant. Study personnel will document the circumstances and data leading to discontinuation.

All adverse events must be recorded on the e-CRF with the following information:

1. Event (nomenclature/description) (**See section 7.2.1**)
2. The severity grade (mild, moderate, severe, life threatening or death) (**see section 7.2.2)**
3. Its relationship to the study drug(s) **(see section 7.2.3)**
4. Its duration (start and end dates or if continuing at final physical exam)
5. Whether it constitutes a serious adverse event (SAE)
6. Action taken (Treatment)
7. Outcome

7.2.1 Nomenclature/description

Terminology used to describe an adverse event is very important. Preferred terms to be used to describe any observed/identified AE(s) are defined as in the abridged version of the **NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5** (38) *(Appendix xix).* The preferred terms are descriptive terminology which should be utilized for AE reporting in the CRF. A grading (severity) scale is also provided for each AE term. Inaccurate or inconsistent coding of events may lead to missed safety signals.

7.2.2 Severity (Grade)

Grade refers to the severity of the AE. The study abridged version of **NCI CTCAE** displays Grades 1 -5 with unique clinical descriptions of severity for each AE

Table 4: Adverse effects grading with unique clinical descriptions of severity

Severity	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences: urgent intervention indicated
Grade 5	Related to death

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.2.3 Relationship of AE to study product

The Chief Investigator or designated Principal Investigator must determine the relationship of the AE to the product under investigation and document in the appropriate section of the e-CRF. For each AE, an assessment of the relatedness to the study drugs should be made using the following scale:

- **Unrelated:** Onset of the AE had no reasonable temporal relationship to administration of the study product or a causal relationship to administration of the study product is biologically implausible or the event is attributed to an alternative etiology.
- **Unlikely-related**: Onset of the AE has an inconceivable possibility that the event was related to, or caused by the investigational intervention?
- **Possibly related:** Onset of the AE has a reasonable temporal relationship to study product administration and a causal relationship is not biologically implausible.
- **Probably related:** Onset of the AE has a strong temporal relationship to administration of the study product that cannot be explained by the participant's clinical state or other factors and a causal relationship is not biologically implausible.
- **Definitely related:** Onset of the AE shows a distinct temporal relationship to administration of the study product that cannot be explained by the participant's clinical state or other factors, or the AE occurs on re-challenge, or the AE is a known reaction to the product or chemical group or can be predicted by the product's pharmacology.
- These criteria in addition to good clinical judgement should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

7.2.4 Duration of AE

Start and Stop date of AE must be reported in the e-forms. This may be unknown or ongoing even at final physical examination. The study clinician must make effort to document the best estimates of duration of AE or if it is still ongoing

7.2.5 Serious Adverse Events

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

Note: Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements as shown below.

7.2.6 Suspected Unexpected Serious Adverse Reactions (SUSARs)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as an untoward and unintended response to a study drug, which is not listed is the product information, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. Investigators will determine whether an AE is a SUSAR given the participants clinical course, previous medical conditions, and concomitant medications. SUSARs are assessed by the sponsor and or study investigator as being unexpected, serious, and as having a reasonable possibility of a causal relationship with the study drug. Reports of these reactions are subject to expedited submission to health regulatory authorities.

Reporting SAEs and SUSARs

- All SAEs and SUSARs must be reported by the site clinician to the Principal Investigator and in turn to Chief Investigator as soon as possible after the SAE or SUSAR is identified.
- Site clinician must report SAEs and SUSARs to the PI who should report to the CI within 24 hours of the study site becoming aware of the problem. The investigator may report the SAE via telephone or email; however, a SAE report form must be completed as soon as possible after the informal report.
- The *Principal Investigator* will complete ***SAE report form (****Appendix xx****)*** and forward to the CI for reporting to the Steering committee (TSC), DSMC and using the pharmacovigilance form (*Appendix* xxi) to NAFDAC.
- A SUSAR that meets the seriousness criteria of life-threatening and/or results in death must be reported by the CI to the TSC within seven (7) calendar days. A SUSAR that is not life-threatening or does not result in death must be submitted to the regulatory authorities within fifteen (15) calendar days.

7.2.7 Treatment of adverse events

All adverse events should be treated appropriately. Treatment may include one or more of the following:

- No action taken (i.e., further observation only).
- Study drug dosage adjusted/temporarily interrupted.
- Study drug permanently discontinued due to this adverse event.
- Concomitant medication given.
- Non-drug therapy given.
- Patient hospitalized/patient's hospitalization prolonged.

The action taken to treat the adverse event should be recorded on the adverse event e-CRF.

- Once an adverse event is detected, it should be followed up until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.
- Information about common side effects already known about the investigational drug will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.2.8 Outcome of SAEs

The outcome of a SAE should be reported as follows:

- Resolved
- Ongoing
- Resolved with minor sequelae
- Resolved with major sequelae

This reporting is required in the end of study form.

7.3 Safety

Adverse events will be monitored throughout the study to assess the general safety and tolerability of the two treatment groups.

Safety assessments will consist of:

- monitoring and recording all adverse events
- the monitoring of laboratory tests results
- regular measurement of vital signs
- physical examinations as indicated.

7.3.1 Safety issues with ferric carboxymaltose

7.3.1.1 Hypersensitivity reactions (HSRs)

Parenterally administered iron preparations including FCM can cause hypersensitivity reactions including *serious and potentially fatal anaphylactic/anaphylactoid reactions* (39). The risk is enhanced for patients with known allergies including *drug allergies*, patients with a history of *severe asthma, eczema, or other atopic allergies*. There is also an increased risk of hypersensitivity reactions in patients with *immune or inflammatory conditions (e.g., systemic lupus erythematosus, rheumatoid arthritis*). ***These conditions with increased risk for HSRs are excluded from this study.***

Other risk factors for hypersensitivity reaction are previous reaction to intravenous iron, *fast iron infusion rate and staff or patient anxiety.*

- FCM should only be administered when study staff that are trained to evaluate and manage anaphylactic reactions are immediately available and, in an environment, where full resuscitation facilities can be assured.
- Each patient should be observed for adverse effects for at least 30 minutes following FCM administration. If hypersensitivity reactions or signs of intolerance occur during administration, the infusion must be stopped immediately, and the resuscitation protocol activated (***Refer to IVON Trial - Protocol No: 02; Administration of Intravenous Ferric Carboxymaltose and the Emergency Treatment of Hypersensitivity Reaction Type 1 (Anaphylaxis).***
- Facilities for cardiorespiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

CAUTION:

- Acute hypersensitivity reactions during iron infusions are very rare but can be life-threatening and so these special precautions must be always considered.

- Every administration of FCM:
    - Must be preceded by a recheck for risk factors for an HSR, the general condition of the patient and base-line observations including pulse rate, blood pressure and respiratory rate.
    - The infusion should be prepared as stated in the manufacturer's instructions.
    - Infusion should be initiated slowly and not increased until it is clear that it is being well-tolerated (usually after 5-10 min).
    - Observation/monitoring every 15 min and for 30 min after the infusion finishes.
    - A test dose is not appropriate or necessary as it may give false reassurance.
    - Patients should be closely monitored for signs of hypersensitivity during and for at least 30 min after administration.

7.3.1.2 Extravasation

Caution should be exercised to avoid para-venous leakage when administering FCM. Para-venous leakage of FCM at the administration site may lead to irritation of the skin and potentially long-lasting brown discoloration at the site of administration. In case of para-venous leakage, the administration of FCM must be stopped immediately and another good venous access must be sought.

7.3.2 Safety issues with Ferrous Sulphate

7.3.2.1 Immune system disorders

Allergic reactions to FS have been reported. Ask patient to report any unusual effect promptly.

7.3.2.2 Gastro-intestinal disorders

Abdominal discomfort and anorexia, abdominal pain, nausea, and vomiting (these are usually dose related), constipation, diarrhea, and dark stools. Contact irritation can occur with ferrous sulphate tablets resulting in erosion or ulceration, particularly if they become lodged in the upper gastrointestinal tract.

Caution:

- Ask patients to keep medication out of the sight and reach of children, as overdose may be fatal.
- Ask about previous allergy to iron formulations.
- Administer oral FS with caution in patients with existing gastrointestinal disease like difficulty in swallowing and inflammatory bowel diseases.
- Due to the risk of mouth ulcerations and tooth discoloration, tablets should not be sucked, chewed, or kept in the mouth but swallowed whole with water.
- Advise to take FS 1 hour before meals or 2 hours after meals with a full glass of water

7.4 Data analysis plan for adverse events (Harm)

Using intention to treat analysis, the absolute risk, the frequency/incident rate and severity grade of anticipated adverse drug reactions such as abdominal pain, nausea and vomiting, hypotension and hypophosphatemia for participants in each study arm, the incident rate of any Serious Adverse Reactions (SAR) which are SAEs that are thought to be causally linked to the trial drug and Suspected Unexpected Serious Adverse Reaction (SUSAR) which are unexpected occurrence of a SAR for each arm of the study will be collated and analyzed. The mean and SDs or median and interquartile range for serum phosphate level will be calculated as appropriate, while extreme values will be stated if observed.

7.5 Validation of the Patient Reporting Outcome (PRO) Tool

7.5.1 Objective

To evaluate the test-retest reliability of the Edinburgh Postnatal Depression Scale (EPDS), Modified 5-item Fatigue Severity Scale (FSS-5R), Mother to Infant Bonding (MIB), and WHO quality of life brief version (QOL-BREF) in Nigerian languages among participants in the IVON-PP trial.

7.5.2 Study population

A sample of women with an upcoming six-week visit will be selected for the sub-study. Consent into the validation sub-study will take place at enrolment into IVON-PP trial or at the two weeks' visit. All women enrolled in the study in November 2023 and onwards will be considered for inclusion in the validation sub-study.

To be eligible for the sub-study, participants must be:

1) Eligible for and enrolled in the IVON-PP trial.
2) Willing to attend one extra visit around the time of the six weeks' visit.

Participants' health status or randomization arm will not, otherwise, be a basis for inclusion or exclusion. Participants' informed verbal consent will be sought.

7.5.3 Study design

Participants will be invited to attend an extra postpartum visit, one to four weeks before or after their scheduled 6 weeks' postpartum visit, at the participants' convenience. The study team will follow the regular study visit schedule (2 weeks and 6 weeks post-partum) to the extent possible, and schedule additional visits as necessary.

All consecutive study participants will be invited to participate until the minimum sample size for the chosen language is reached.

To the extent possible, the extra visit will be conducted in the same manner as the scheduled six weeks' visit. That is, if the scheduled six weeks' visit occurs as a physical in- hospital or at the participant's home, then the extra visit will take place at the same site as the study schedule visit. The same will apply for visits completed virtually.

7.5.4 Visit and instrument schedule

The following schedule of visits will be followed:

Tools	6 weeks visit	Extra visit
EPDS	In chosen language	In same language
MIB	In chosen language	In same language
FSS-5R	In chosen language	In same language
WHOQOL-BREF	In chosen language	In same language

7.5.5 Data collection

Data will be collected electronically using REDCap. Surveys will not be anonymous as it will be necessary to link the two visits for each participant.

The preferred language selected by the participant for the main study will be the preferred language for this sub-study. All participants will complete the instrument in the same preferred language on the date of the 6 weeks' visit, as well as at an extra study visit.

7.5.6 Ethical considerations

Verbal consent will be sought from each individual participant for inclusion in the sub-study. All participants will have their transportation cost for the extra clinic visit reimbursed.

7.5.7 Sample size

The sample size required was determined to be 118 per language based on a median of the sample sizes that have worked well for previous studies among patients(40). For the EPDS, the sample size for some published translation and validation studies have been 87(41), 100(42), 118(43), 123(44), and 451(45). For the MIB, sample sizes that have worked well include 63(46) and 554(47). For the FSS, the sample size for published translation and validation studies have included 23(48), 83(49), 113(50), 123(51), and 427(52). For the WHOQOL-BREF, sample sizes that have worked well include 228(53) and 538(44).

7.5.8 Data analysis

All analyses will be completed using R and RStudio. Test-retest reliability will be assessed using Pearson correlation.

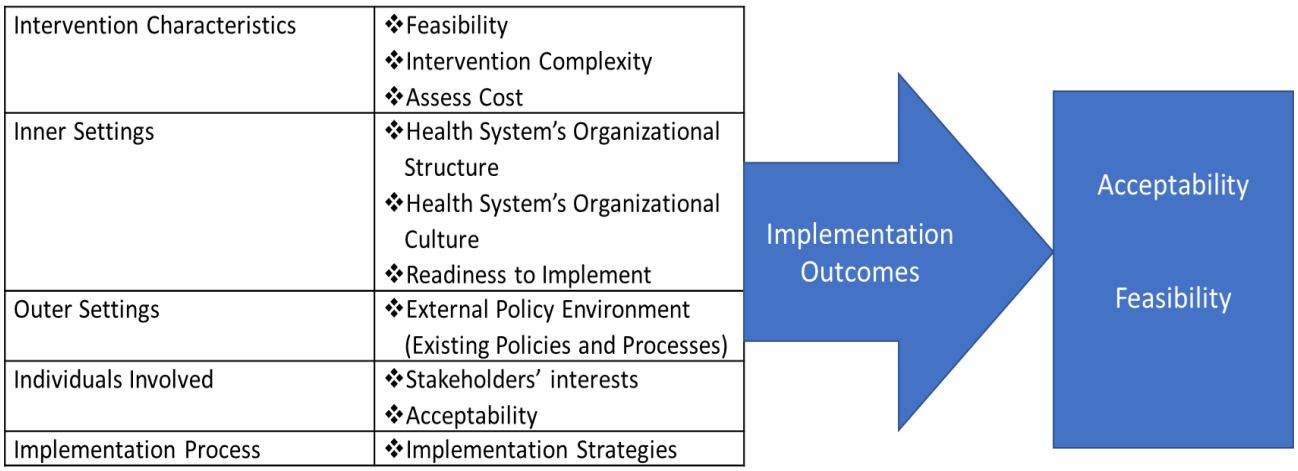
8 Implementation research

8.1 Theoretical framework for implementation research

New innovations (and existing innovations introduced into new contexts) commonly fail due to challenges with adoption, adaptation, and implementation (30, 31). This is particularly common in LMICs. Determinants of successful implementation of an innovation range across systemic, economic, policy and individual factors. These determinants could either facilitate or impede the observed effectiveness and sustainability of efficacious interventions. Thus, hybrid trials seek to evaluate the effectiveness of interventions as well as understand strategies and contexts suitable for optimal and sustained implementation (32). Implementation science has evolved theories, models, and frameworks to guide the understanding of the implementation climate, and to improve implementation of outcomes (33). Implementation climate has been defined as "targeted employees' shared summary perceptions of the extent to which their use of a specific innovation is rewarded, supported, and expected within an organization" (34). Whereas outcomes of implementation are considered as the direct effects of deliberate and purposive actions to implement innovations (35). These outcomes include acceptability and feasibility.

This study will be guided by the Consolidated Framework for Implementation Research (CFIR) (36) and the Reach-Effectiveness-Adoption-Implementation-Maintenance (RE-AIM) framework (37) to understand how contextual determinants and implementation climate impact on implementation outcomes. The CFIR will explore five major domains, each of which may affect implementation of ferric carboxymaltose in Nigeria. There are the intervention characteristics (e.g., stakeholders' perceptions about the relative advantage of implementing the intervention, intervention complexity), inner setting (e.g., implementation climate, leadership engagement), outer setting (e.g., external policies and incentives), characteristics of individuals involved in implementation (e.g., knowledge and beliefs about the intervention), and the implementation process (Figure 3).

Figure 3: Implementation evaluation guided by the Consolidated Framework for Implementation Research (CFIR)



8.2 Study population

We plan to work with multiple stakeholders for the implementation research. They will include:

- Postpartum women with and without anemia (between two to six weeks postpartum)
- Postpartum women with past or current anemia treatment (between two to six weeks postpartum)
- Male partners of postpartum women
- Healthcare workers: doctors, nurses/midwives, pharmacists, laboratory technologists, community health officers
- Health facility managers
- Community leaders
- Policy makers

The sampling of respondents will be purposive but will cut across various categories of stakeholders in the three levels of the health system in the various states.

8.3 Data collection methods

8.3.1 Qualitative data collection

We plan to conduct focus group discussions (FGDs) and key informant interviews (KIIs) with the identified stakeholders in each state. Interview guides will be developed using CFIR. The implementation climate and outcomes will be explored, as well as barriers and facilitators to successful implementation. The implementation research questions include:

- What are the perspectives of patients, health workers and other key stakeholders regarding the administration of intravenous iron infusion for the treatment of post-partum anemia?
- How feasible is it to implement intravenous iron as a new management strategy for post-partum anemia?
- What factors could prevent or obstruct the adoption and routine administration of intravenous iron infusion for the treatment of post-partum anemia?
- What is the acceptability of the administration of intravenous iron infusion for the treatment of post-partum anemia to health workers, patients, and other key stakeholders in the health system?

While FGDs were chosen because the interaction of members within stakeholder groups will be essential to providing the most robust description of stakeholder's perception of implementation outcomes, KIIs provide an opportunity to have one-on-one in-depth discussions and are more practical to set up for the identified stakeholders.

Table 5 details the target stakeholders and their numbers for each type of stakeholder and across each state.

Table 5: Target stakeholders for qualitative data collection

Target stakeholders	Data collection method	Number per state	Number overall
Postpartum women	FGD	1	4
Healthcare workers	FGD	1	4
Male partners	FGD	1	4
Total FGDs		**3**	**12**
Postpartum women with past or current anemia treatment	KII	3	12
Apex healthcare workers	KII	5	20
Health facility managers	KII	1	4
Community leaders	KII	1	4
State policy makers	KII	2	8
Total KIIs		**12**	**48**

The final sample size will depend on achieving data saturation (a point in data collection when no additional issues or insights are identified from interviewing additional participants).

8.3.1.1 **Conduct of FGDs**

A convenience sample of 8 to 12 participants will be invited to participate in each FGD. Verbal consent using a script designed for the study will be sought and received from the participants before commencement. At the beginning of the FGD, socio-demographic data will be collected from participants using a socio-demographic form designed for the study and they will be given identification numbers or nicknames. The sessions will be audio-recorded with consent. One note taker will observe the participants' interaction, body language and the environment in general. The moderator will be a trained research assistant with prior experience facilitating FGDs and with bilingual capacity in English language and any of the local dialects dominantly spoken in the four states (Yoruba, Hausa, or Pidgin English). All interviews will be conducted with the FGD guides purposefully designed for the different categories of stakeholders and encourage active discussion, participation and interaction among the individuals taking part in the FGD. They will be initially written in English and forward translated into the local dialects. During the FGDs, participants will be asked open-ended questions and allowed to provide their perspectives on each issue. Further probing and follow-up questions will be done to provide clarity and lucidity. The sessions will be held in a comfortable, convenient, and accessible place. Each session will last between 60 to 90 minutes.

8.3.1.2 Conduct of KIIs

The KIIs will be conducted by a trained research assistant with prior experience conducting KIIs in a setting that will be convenient for the participants. Most interviews will be face to face except where not feasible, for example with policy makers. In such cases, virtual interviews will be conducted. Verbal consent using a script designed for the study will be sought and received from the participants before commencement. Socio-demographic data will be collected from participants using a socio-demographic form designed for the study. All interviews will be audio recorded. The KIIs will be moderated by the same trained research assistants using KII guides designed for the different stakeholders.

8.3.2 Quantitative data collection

Quantitative data on acceptability and feasibility will be collected from among all healthcare workers who are working on IVON-PP trial across all sites. We will use the Acceptability of Intervention Measure (AIM) and Feasibility of Intervention Measure (FIM) tools developed by Weiner et al. Data will be collected electronically using RedCap to generate a link to the self-administered survey tools that will be send to study participants. survey.

8.4 Ethical issues and protection

We expect that participating in interviews in this study will expose participants to minimal risk (considering that the topic in question is not of a sensitive issue) and are therefore proposing verbal consent for all FGDs and KIIs. This will also provide ease of consenting illiterate participants and groups for the FGDs. Consent script will be translated to participant's language of choice and will be administered by study staff who speak the local language within the sites and communities. Study staff will ask participants to summarize the study activities to ensure that all activities are well understood. During the consent process, any misunderstandings regarding procedures, risks, or benefits will be clarified. Individuals will be provided with information on how to contact the study staff for further clarifications. Study staff have been trained extensively on how to ensure that individuals provide voluntary informed verbal consent.

For quantitative data collection, an electronic informed consent form will accompany the tools to be filled online by willing participants (healthcare workers) before completing the survey.

8.5 Data analysis

Data obtained through audio recordings will be transcribed then analyzed using thematic analysis aided by NVivo software (QSR International, Melbourne, Australia). Data analysis will be both deductive and inductive. Deductive analysis will be guided by the CFIR. Two researchers will independently conduct the initial coding after familiarization with the transcripts, thereafter subsequent and final coding criteria will be agreed by both researchers following iterative review of emerging themes as informed by the research questions. The final sets of themes and sub-themes relevant to the overall research goals will be reported and supported with verbatim quotes.

8.5.1 Framework for triangulating methods

The RE-AIM will serve as an overarching framework for triangulating methods and findings from the clinical effectiveness trial and the implementation research (Table 6).

Table 6: Framework for triangulating methods

RE-AIM Domain	Outcomes	Measures	Data sources
Reach	Dose delivered	The proportion of targeted women who are approached/informed about the new treatment	Trial implementation data
	Dose received	The proportion of approached/ informed women who accept the treatment	Trial implementation data
Effectiveness	Clinical effectiveness	Primary outcomes • Anemia prevalence at six weeks Secondary outcomes • Depression prevalence at six weeks and six months • Fatigue • Need for blood transfusion • Secondary PPH • Infections • Prevalence of breastfeeding • Maternal-infant bonding	Surveys and clinical records
Adoption	Acceptability	Barriers and facilitators to adoption	FGDs/KIIs guided by the CFIR
Implementation	Feasibility	Implementation drivers/ climate (Barriers and facilitators)	Qualitative focus group discussions/ key informant interviews guided by the CFIR

8.6 Timeline of data collection for implementation research

Data collection will be collected at baseline and endline of the trial. This approach will provide pre-implementation perspectives as well as collect data on potential change in perspective as the trial progresses. The timeline for both qualitative and quantitative data collection is detailed in table 7.

Table 7: Timeline of data collection

Implementation outcome	Data collection Timepoint(s)			Target stakeholders	Mode of data collection
	Baseline	During	End of study		
Acceptability (includes facilitators and barriers)	X		X	Healthcare workers, pregnant women and their partners, health facility managers, state government health officials, policymakers	FGDs, KIIs AIM survey
Feasibility	X		X	Healthcare workers	FGDs, KIIs FIM survey

9 DATA MANAGEMENT PLAN

9.1 Data collection

IVON-PP will adopt REDCap, a secure web-based application to collect all relevant study data. Electronic case report forms, surveys and other data collection instruments have been developed and refined in the REDCap to collect information at enrolment, follow-up, end of study visits and for adverse events. Other study instruments in the REDCap are the EPDS, fatigue scale, MIB scale and quality of life scale e-forms. Designated investigators and study staff will enter the information in real time as required by the protocol into these electronic forms on the REDCap and source documents as indicated. REDCap page will be accessed at: http://live.ivonpptrial.com/

A data management team consisting of a data manager, a data officer and data entry clerks will coordinate data collection and management. They will ensure real-time collection of complete, accurate and reliable data by the study staff as sites. Clinical monitors will review the e-CRFs and other tools and cross reference with source documents for completeness and accuracy and instruct site personnel to make any required corrections or additions as necessary.

9.2 Data management plan and quality control

The data management team will follow the data management plan (DMP) for the trial that specifies the methods for ***data handling*****, data collection, data entry, and transmission, data compilation and management, data quality and security and data analysis.** (See data management plan (DMP))

The team will submit regular weekly/monthly report to the chief investigator or designee.

9.3 Data Management and analysis

The assignment of participants into analysis populations will be performed prior to database lock and any data analysis.

- *Randomized* – all participant who receive a randomization number.
- *Intention-to-treat (ITT)* – all randomized patients with at least one relevant post-baseline efficacy assessment, and who had at least one dose of study drug. Following the intention-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.
- *Primary Analysis (PA)* – all ITT patients that completed 2- and 6-weeks postpartum visit.
- *Per Protocol (PP)* – all PP patients that meet all the following:
    - Took at least 80% of scheduled study drug
- *Safety* – all patients that received at least one dose of study drug and had at least one post-baseline safety assessment. Patients will be analyzed according to treatment received.

9.4 Data analysis plan

Primary analysis will be conducted by the intention to treat principle. Categorical variables will be expressed as frequencies and percentages. For continuous variables, a Shapiro–Wilk test of normality will be performed, and normally distributed data will be presented as means ± SD, while non-normally distributed data will be presented as median and interquartile range (IQR). However, the literature will be reviewed to ensure that variables are handled in their natural form. The effect of IV iron (vs. oral iron) on the primary endpoint (anemia at six weeks post-partum) would be analyzed using log-binomial regression models to obtain relative risks, 95% confidence intervals and p-values. The extent to which inclusion of baseline covariates modifies the precision of estimates would be explored. Generalized linear mixed models will be used to estimate the effect of treatment arm on repeated measures of hemoglobin and iron status biomarkers. The proportions of participants in the treatment arms who are anemic or iron deficient, and the proportions of participants who achieve anemia correction at 6 weeks and 6 months follow-up with be compared. Kaplan Meir plots and log-rank test will be used to explore the time to anemia correction. Subgroup analysis will be conducted to compare study findings by mode of delivery (caesarean vs vaginal delivery), and by the occurrence of primary post-partum hemorrhage. Two tailed test of hypothesis and 95% confidence interval is assumed as statistical level of significance. Stata version 17 (Stata Corp, Texas, USA) statistical software will be utilized for analysis. The variance estimator with cluster option (clustering on site of study) will be utilized.

Interim analysis will be conducted after achieving half of the sample size. Based on O'Brien-Fleming method (29), the threshold for significance of the primary endpoint at the interim analysis will be alpha = 0.0054. The clinical trial is terminated if the null hypothesis is rejected. The alpha level for the analysis at the end of the study will be adjusted to 0.0492 based on alpha adjustment based on O'Brien-Fleming method.

Interim analysis will also be performed to adjust the sample size, if necessary, as part of an adaptive study design. This will be a blinded analysis and its aim is to determine the actual effect size of the primary outcome in order to adjust the sample size if required. This will be performed by an independent body, and not the study co-investigators.

10 STUDY MONITORING PLAN

10.1 Monitoring and evaluation (M & E) mechanism

The Project monitoring and evaluation mechanism will help to determine progress being made towards achievement of study outcomes and will provide constructive recommendations to address key problems identified. It will review the effectiveness, efficiency, and timeliness of project implementation; analyze effectiveness of implementation and partnership arrangements; identify issues requiring decisions and remedial actions; analyze whether the project is on track with respect to achieving the expected results; and propose any mid-course corrections and/or adjustments to the Work Plan as necessary.

The project M&E mechanism will include

- An Administrative Core- this will be the essential infrastructure that will enable synergy and coordination of the project, scientific core, and the collaborating sites of IVON-PP. The administrative core will consist of the Chief Investigator, a project manager, a project officer, other administrative staff. They will provide administrative oversight and management of the research study and coordinate all internal and external meetings of investigators, staff, and monitors.
- The full research team consisting of the CI, Co-Is, State PIs and administrative core will hold a biweekly meeting via zoom platform.
- The Trial Steering Committee (TSC) will meet (in person ideally) prior to commencement of the accrual and then at a minimum of once yearly (in person or remotely) and will provide independent oversight of the trial and associated studies on behalf of the trial sponsor.
- The Data Safety and Monitoring Board (DSMB) will meet (in person ideally) prior to commencement of the accrual and then at a minimum of once yearly (in person or remotely) to independently assess safety, effectiveness and futility of the trial and will report to the TSC. Full details of both the TSC and DMC will be outlined in a charter.
- The DSMB will review the prevalence of serious adverse events with the possibility of either continuing or stopping the trial. The details for the operation and responsibilities of the DSMB will be provided in the DSMB operational protocol/charter.
- Clinical Trial Monitors – Independent clinical research associates/monitors will be responsible for trial monitoring. To verify that: (a) the rights and well-being of human subjects are protected. (b) The reported trial data are accurate, complete, and verifiable from source documents. (c) The conduct of the trial follows the currently approved protocol/amendment(s), with Good Clinical Practice (GCP), and with the applicable regulatory requirement(s). Clinical trial monitors will conduct:
    I. Pre-Trial Monitoring visit: to ensure feasibility of the trial at the selected center and interest of the site investigator.
    II. Trial Initiation visit: to deliver study material, documents, products and make sure the investigational team understands the protocol and GCP requirements.

III. Routine Monitoring visit: Make sure the study is conducted according to the protocol and GCP and help the investigational team in solving problems. These will be conducted online and onsite as necessary every 2 weeks.
IV. Close-out visit: Make sure the investigator file is archived properly and collect back all unused material, documents, or products.

10.2 Clinical monitoring plan

Site visits by the clinical monitor will be made in accordance with SOPs for IVON-PP clinical monitoring. The purpose of the monitoring is to ensure the quality and accuracy of data collected on the e-CRF and entered in the database and to determine that all regulatory requirements surrounding clinical trials are met.

The site investigators will allow the clinical monitors and designated persons to inspect study documents (e.g., consent forms, drug distribution forms, CRF and pertinent clinic records for confirmation of the study data).

Various authorized individuals may visit the study site to audit the progress of this study (e.g., NAFDAC, state board, HREC). ***A site monitoring visit log (****Appendix xxi****)*** will be maintained at the study site in which all visits made by authorized individuals are recorded. All clinical records and the e-CRFs for all the participants enrolled in this study will be made available for review to authorized individuals.

Clinical monitors' visits will include

i. Before the study begins, the clinical monitors will conduct an evaluation visit at each site (***Pre-trial site assessment & selection visit***) using a checklist (*Appendix xxii*) to determine the suitability of the site for the clinical trial.
ii. Trial initiation visit (study start-up) using ***study initiation checklist*** (*Appendix xxiii*)
iii. Site monitoring visits - 2 weekly/monthly monitoring visits (to track study progress) using the ***site monitoring visit checklist*** (*Appendix xxiv*). The main task for the clinical monitor during site monitoring visits is to conduct source document verification such as consent form checking and data verification. The overall responsibility of the monitors is to ensure that the study is being conducted according to the protocol, SOPs, GCP and applicable regulatory requirements. A detailed monitoring plan will be developed for this study and will be used by the clinical monitors. This plan will specify responsibilities and qualifications of the identified clinical monitors, back-up provisions, in house monitoring procedure and site monitoring visit procedures. All monitoring visits will be documented.
iv. Close-out visit: the monitors will ensure the investigator's file and all other study documents are properly archived and will collect back all unused material, documents, or products for destruction as appropriate.

11 PROTOCOL VIOLATIONS AND DEVIATIONS

11.1 Protocol violations

Any deviation that may affect the subject's rights, safety, or welfare, and/or the completeness, accuracy, and integrity of the study data. This is considered a major, more serious, variance from an approved protocol than a deviation.

Examples of protocol violations

- Omission or inadequate administration of informed consent.
- Inclusion/exclusion errors
- Treatment errors: no treatment or incorrect treatment (including dose or regimen, expired product), participant compliance problems.
- Forcing a participant to enter or remain in the study, failure to withdraw a subject meeting withdrawal criterion.
- Inadvertent loss of samples or data.
- Participants who should have been discontinued from the study due to protocol criteria, but were not
- Working under an expired professional license/certification, debarred or disqualified status

The investigator will notify the Ethics committee in writing as soon as possible and document on the Protocol Deviation/Violation Form (*Appendix* xxv) the reasons for protocol violation and ensuing events. Protocol violations may also be identified by the clinical monitors during the periodic and closeout monitoring visits as well as during in house monitoring.

11.2 Protocol deviation

Any change, divergence, or departure from the approved study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB, and ***does not affect*** the participant's safety, rights, or welfare and/or the completeness, accuracy, and integrity of the study data.

Examples of Protocol deviation

- implementation of unapproved recruitment procedures.
- use of an incorrect informed consent version.
- Missing original signed and dated consent form or missing pages from executed consent form.
- Inappropriate documentation of consent, including missing signatures
- Individual obtaining consent not listed on IRB approved application
- Subject visit/procedure falls outside of the window of time indicated by the protocol, or is not done per protocol, and there is no increased potential for risk to the subject or any damage to the integrity or completeness of the data.

11.3 Serious noncompliance

Failure to comply with federal regulations, state laws, institutional policies, requirements, or determinations of the Ethics committee, and/or provisions of the approved research study, where the occurrence involves substantive potential or actual increased risk to the safety, rights, and welfare of participants.

11.4 Reporting protocol violation and deviations

- The Trial clinical monitors must report violations may affect the subject's rights, safety, or welfare, and/or the completeness, accuracy, and integrity of the study data to the State *Principal Investigator* and the *Chief Investigator.*
- It is the *Chief Investigator's* responsibility to report protocol violations to the steering committee upon discovery. Protocol violations which may be considered serious noncompliance are to be reported to the ethics committee within 5 business days on the Protocol Violation Report. The *Chief/Principal Investigator* must develop a corrective action plan to present to the committee for review and approval. This corrective action plan will outline what steps the investigators has taken or will take to resolve the event and to prevent such events from occurring in the future.

11.5 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Ethics committee. Only amendments that are required for patient safety may be implemented prior to ethics committee approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the ethics committee at the study site should be informed within 10 working days.

12 STUDY DOCUMENTS

12.1 Study initiation

The following documents will be in place and monitored by a clinical monitor at the study site before any potential participants are contacted.

1. Investigator's Site file with Signed Study protocol, screening log, enrollment log, informed consent form, protocol violation form, SAE report form, Sample CRFs, drug accountability form, delegation log.
2. Information given to participants: consent form, other written information, advertisements
3. Financial records
4. Signed agreement between involved parties (Chief Investigators, State PIs, and site coordinators)
5. Ethics committee approval
6. CV for investigator, Co-Investigator and Site coordinators, research nurses and other staff
7. Laboratory test normal values
8. Instructions for handling investigational product and trial related materials, drug label form
9. Site Monitoring visit log

12.2 Study conduct

During the study the following documents will be in place and periodically monitored by a clinical monitor at the study site. Revision of documents will be made if relevant and made available at study sites.

1. Revisions to the investigators file
2. Revisions to protocol and amendments
3. Revisions to the CRFs
4. Revisions of information given to participants: consent form, other written information, advertisements
5. Ethics committee updated approvals
6. Ethics committee composition changes
7. Updated CV for investigator, Co-Investigator and Site coordinator
8. Update on laboratory test normal values
9. Documentation of investigational product and trial related materials
10. Relevant communication other than site visits
11. Signed consent forms.
12. Sample of e-CRFs
13. Copies of documentation of CRF corrections
14. Notification of *Principal Investigator* on SAEs
15. Notification on SAE, protocol; violations by investigator to local Ethics committee
16. Interim or annual report to ethics committees
17. Participant screening log
18. Participant randomization code list

19. Investigational products accountability documents
20. Staff signature list
21. Site Monitoring visit logs
22. Progress reports

12.3 Study completion

After completion of the study, all the documents in 12.1 and 12.2 should be in the file together with the following:

1. Investigational products accountability documents
2. Documentation of product destruction (if destroyed at site)
3. Complete participant ID code list
4. Final report by investigators to IRB.

12.4 Record maintenance and retention

The investigators will maintain records in accordance with Good Clinical Practice guidelines.

The signed original informed consent documents for each participant, original and copies of CRFs and original copies of study documentation (e.g., drug inventory forms, participant clinic records, original laboratory reports, etc.) will be kept in a locked area at all times to be accessed only by personnel involved in the study. Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords. Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information, whenever feasible, identifiers will be removed from study-related information, precautions are in place to ensure the data is secure by using passwords and encryption.

At study completion at various study sites, all study documents will be moved and stored at the College of Medicine, University of Lagos and retained by the Chief Investigator for a minimum of 10 years.

The investigators may be subject to a field audit by the sponsor to validate the participation of study participants and to verify the data reported on the CRFs. This audit could occur while the study is in progress or several years after the study is completed. All the participants' records and other study documentation must be filed and accessible on short notice (3-5 days) during the study and subsequent retention period.

13 LABORATORY QUALITY ASSURANCE

- All study laboratory tests will be conducted by Synlab Nigeria.
- The study team will put in place a QA plan and transportation logistics before initiation of the study. The detailed QA plan will be finalized when the sites and the reference laboratories have finalized logistics.
- Synlab Nig laboratory services has been chosen based on the international accreditation and recognition, experience and facilities which comply with Good Laboratory practices (GLP) and ISO certification.

14 ETHICS AND RESEARCH INTEGRITY

14.1 Administrative procedures: Ethical and environmental considerations

- This trial will be registered with the International Standard Randomized Controlled Trial Number (ISRCTN) Registry.
- Ethical approvals will be obtained from the National Health Research and Ethics Committee of Nigeria (NHREC), Health Research and Ethics committees of the Lagos University Teaching Hospital, Idi-Araba, Aminu Kano Teaching Hospital, Lagos state Health Service commission, Lagos State Primary Healthcare Board, Kano State Ministry of Health, Kwara State Ministry of Health, and Rivers State Ministry of Health
- All study investigators and site coordinators are trained and certified in Good Clinical Practice (GCP) and Responsible conduct of biomedical research (RCR).
- The purpose of the study will be duly explained to all eligible participants prior to recruitment. They will be informed of their right to withdraw or refuse to partake in the study without prejudice to the usual standard of care given to them at the health facility.
- All participating women will sign the study's informed consent form prior to entry into the study and be given a copy.
- The personal information of each participant will be kept strictly confidential.
- Study data will be stored securely in a central electronic database. Only authorized personnel will have access to the data of all participants collated centrally.
- The statistician will be granted access to the electronic database during statistical analysis or at any other time the *Chief Investigator* might require her to review the data.
- Study participants will not pay for study related drugs or tests as the medication for the research will be given at no cost all through the study period. All investigations pertaining to this research will also be conducted at no cost to the participants.
- This proposed research poses minimal or no risk to both mother and baby. Blood specimen collection might cause minimal discomfort in form of pain. For this reason, all the blood sample collection will be made as comfortable as possible for the women. The intervention drug ferric carboxymaltose is known to be safe and is not expected to have significant adverse effects on participants.
- All research staff will be adequately trained to monitor, recognize, and manage any significant AEs. In the rare instance of any moderate/severe AEs such as hypophosphatemia and anaphylaxis, trained research staff will effectively resuscitate and transfer care to higher level health facility for adequate care at no cost to the participant.
- Participants can voluntarily withdraw from the study for any reason at any time and could also be withdrawn at any time if the investigator concludes that it would be in the patient's best interest for any reason.
- All participants will receive folic acid and vitamin C supplementation as normally prescribed.
- The participants will enjoy equal rights and quality care all through the duration of the research.
- Environmental issues are not applicable to this study.

14.2 Informed consent

- No participant may be admitted into this study until the investigator has obtained her written informed consent.
- An investigator shall seek such consent only under circumstances that provide the prospective participant with sufficient opportunity to consider whether to participate in the study.
- Informed consent must be obtained without coercion, undue influence or misrepresentation of the potential benefits or risks that might associated with participation in the study
- Informed consent encompasses all oral or written information given to the participants about the study and study materials. This includes the consent from signed by the participant, recruitment advertising and any other information provided to the participant. All such information that is given to the participant will be in a language that is understandable to her. The information will not include any language in which the participant is made to waive any of her rights or which releases or appears to release the investigator or the investigators institution.
- Informed consent will be documented using a written consent form (in triplicate) that is signed by the participant (or participant's mark if she cannot sign). A copy of the signed consent form will be given to each participant while a copy will be kept at study site and a copy will be sent for archiving at the central coordinating office. The consent form includes each of the basic elements of an informed consent document and describes each of the risks or discomforts to the participant that have been identified as reasonably foreseeable.

14.3 Future use of stored data and specimens

Data collected may be stored without identifiers indefinitely at the College of Medicine, University of Lagos (CMUL) and may be shared with secondary researchers within or outside the participating sites.

Informed consent will be obtained from each participant to store some of the blood samples collected. A small portion of the blood samples will be stored indefinitely at our Biospecimen Repository at CMUL for current and future research that might include genetic research. The individual genetic results or incidental findings will not be shared with the participants as these tests will be research-related and the initial findings may need additional research before their clinical significance is understood, and appropriate actions can be determined.

Stored samples may be shared without identifiers with secondary researchers within or outside the participating sites. It is possible that some of the genomics research conducted either by the study investigators or secondary researchers could eventually lead to the development of new diagnostic tests, new drugs or other commercial products. If this should occur, there is no plan for research participants to receive any part of the profits generated from such products.

14.4 Participant confidentiality

Participants' personal data such as names with contact details, house address, phone numbers e.t.c will be collected to facilitate follow up. The confidentiality of all participants enrolled in the study will be protected as much as possible. To protect participants' confidentiality, computer-based files will be encrypted, password protected files will be used when sending information over the internet, documents e.g signed consent forms will be stored in locked file cabinets and personal identifiers will be removed from study documents as soon as possible. Study participants will not be identified by name on any report or publication resulting from data collected in this study.

14.5 Regulatory and ethical compliance

This clinical trial was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki.

14.6 Responsibilities of the investigators and IRB

This protocol and the informed consent form have been reviewed and approved by a properly constituted Independent Ethics Committee/Research Ethics Boards (IRB) before the commencement of the study. Signed and dated statements that the protocol and informed consent have been approved by the IRBs have been obtained by the Chief investigator before study initiation.

Prior to study start, all investigators are required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all the instructions and procedures found in this protocol and to give access to all relevant data and records to monitors, auditors, IRBs, and regulatory authorities as required.

15 DISSEMINATION STRATEGIES

This indicates the steps that will be taken to ensure the project outcomes are brought to the attention of stakeholders.

The study results will be presented to women at antenatal clinics and in local community groups using posters and presentations. The findings of the study will also be presented at conferences (international and local) to disseminate them to a large body of professionals in the field of Obstetrics and Gynecology, Hematology, Internal Medicine, Pediatric etc. The findings will also be published in high impact peer reviewed journals for wider dissemination of information and will be used in counselling post-partum women with anemia at the various postnatal clinics on complications associated with anemia and preventive measures that may be employed. Charts will be created to facilitate counselling at the various antenatal clinics. We will issue press releases about the findings of the study.

REFERENCES

1. Khalafallah AA, Dennis AE. Iron deficiency anaemia in pregnancy and postpartum: pathophysiology and effect of oral versus intravenous iron therapy. J Pregnancy. 2012;2012:630519.
2. Balarajan Y, Ramakrishnan U, Ozaltin E, Shankar AH, Subramanian SV. Anaemia in low-income and middle-income countries. Lancet. 2011;378(9809):2123-35.
3. Api O, Breyman C, Çetiner M, Demir C, Ecder T. Diagnosis and treatment of iron deficiency anemia during pregnancy and the postpartum period: Iron deficiency anemia working group consensus report. Turkish journal of obstetrics and gynecology. 2015;12(3):173-81.
4. Milman N. Postpartum anemia I: definition, prevalence, causes, and consequences. . Annals of Hematology. 2011;90(11):1247-53.
5. Emegoakor CF, Iyoke CA, Ezegwui HU, Umeora OU, Lawani LO, Madu AJ. Rates and determinants of peripartum and puerperal anemia in Enugu, Nigeria. Niger J Clin Pract. 2016;19(6):709-14.
6. Parks S, Hoffman MK, Goudar SS, Patel A, Saleem S, Ali SA, et al. Maternal anaemia and maternal, fetal, and neonatal outcomes in a prospective cohort study in India and Pakistan. BJOG. 2019;126(6):737-43.
7. Azami M, Badfar G, Khalighi Z, Qasemi P, Shohani M, Soleymani A, et al. The association between anemia and postpartum depression: A systematic review and meta-analysis. Caspian J Intern Med. 2019;10(2):115-24.
8. Henly SJ, Anderson CM, Avery MD, Hills-Bonczyk SG, Potter S, Duckett LJ. Anemia and insufficient milk in first-time mothers. Birth. 1995;22(2):86-92.
9. Auerbach M, Gafter-Gvili A, Macdougall IC. Intravenous iron: a framework for changing the management of iron deficiency. Lancet Haematol. 2020;7(4):e342-e50.
10. Fouelifack FY, Sama JD, Sone CE. Assessment of adherence to iron supplementation among pregnant women in the Yaounde gynaeco-obstetric and paediatric hospital. Pan Afr Med J. 2019;34:211.
11. Froessler B, Cocchiaro C, Saadat-Gilani K, Hodyl N, Dekker G. Intravenous iron sucrose versus oral iron ferrous sulfate for antenatal and postpartum iron deficiency anemia: a randomized trial. J Matern Fetal Neonatal Med. 2013;26(7):654-9.
12. Vanobberghen F, Lweno O, Kuemmerle A, Mwebi KD, Asilia P, Issa A, et al. Efficacy and safety of intravenous ferric carboxymaltose compared with oral iron for the treatment of iron deficiency anaemia in women after childbirth in Tanzania: a parallel-group, open-label, randomised controlled phase 3 trial. Lancet Glob Health. 2021;9(2):e189-e98.
13. Iyoke CA, Emegoakor FC, Ezugwu EC, Lawani LO, Ajah LO, Madu JA, et al. Effect of treatment with single total-dose intravenous iron versus daily oral iron(III)-hydroxide polymaltose on moderate puerperal iron-deficiency anemia. Ther Clin Risk Manag. 2017;13:647-53.
14. National Population Commission Nigeria. National Demographic and Health Survey Nigeria 2018 [Available from: https://dhsprogram.com/pubs/pdf/FR359/FR359.pdf.
15. Akinlo A, Adeleke B, Olapeju E. Influence of Use of Maternal Health Care on Postpartum Contraception in Nigeria. DHS Working Papers No. 92. Calverton, Maryland, USA: ICF International. DHS Working Papers [Internet]. 2013:[1-38 pp.].
16. Pollock RF, Muduma G. A budget impact analysis of parenteral iron treatments for iron deficiency anemia in the UK: reduced resource utilization with iron isomaltoside 1000. Clinicoecon Outcomes Res. 2017;9:475-83.
17. Emrich IE, Lizzi F, Siegel JD, Seiler-Mussler S, Ukena C, Kaddu-Mulindwa D, et al. Hypophosphatemia after high-dose iron repletion with ferric carboxymaltose and ferric derisomaltose-the randomized controlled HOMe aFers study. BMC Med. 2020;18(1):178.

18. Pels A, Ganzevoort W. Safety and Efficacy of Ferric Carboxymaltose in Anemic Pregnant Women: A Retrospective Case Control Study. Obstet Gynecol Int. 2015;2015:728952.
19. Shim JY, Kim MY, Kim YJ, Lee Y, Lee JJ, Jun JK, et al. Efficacy and safety of ferric carboxymaltose versus ferrous sulfate for iron deficiency anemia during pregnancy: subgroup analysis of Korean women. BMC Pregnancy Childbirth. 2018;18(1):349.
20. Jose A, Mahey R, Sharma JB, Bhatla N, Saxena R, Kalaivani M, et al. Comparison of ferric Carboxymaltose and iron sucrose complex for treatment of iron deficiency anemia in pregnancy- randomised controlled trial. BMC Pregnancy Childbirth. 2019;19(1):54.
21. WHO. The global prevalence of anaemia in 2011. Geneva: World Health Organization. 2011 [Available from: https://apps.who.int/iris/bitstream/handle/10665/177094/9789241564960_eng.pdf,accessed?sequence=1.
22. Wilson N, Wynter K, Fisher J, Bei B. Postpartum fatigue: assessing and improving the psychometric properties of the Fatigue Severity Scale. Arch Womens Ment Health. 2018;21(4):471-4.
23. Abdul-Kadir R, McLintock C, Ducloy AS, El-Refaey H, England A, Federici AB, et al. Evaluation and management of postpartum hemorrhage: consensus from an international expert panel. Transfusion. 2014;54(7):1756-68.
24. Meh C, Thind A, Ryan B, Terry A. Levels and determinants of maternal mortality in northern and southern Nigeria. BMC Pregnancy Childbirth. 2019;19(1):417.
25. Fagbamigbe AF, Olaseinde O, Setlhare V. Sub-national analysis and determinants of numbers of antenatal care contacts in Nigeria: assessing the compliance with the WHO recommended standard guidelines. BMC Pregnancy Childbirth. 2021;21(1):402.
26. Landes SJ, McBain SA, Curran GM. Reprint of: An introduction to effectiveness-implementation hybrid designs. Psychiatry Res. 2020;283:112630.
27. Power calculator for binary outcome equivalence trial [Internet]. 2012. Available from: https://www.sealedenvelope.com/power/binary-equivalence/.
28. Sultan P, Bampoe S, Shah R, Guo N, Estes J, Stave C, et al. Oral vs intravenous iron therapy for postpartum anemia: a systematic review and meta-analysis. Am J Obstet Gynecol. 2019;221(1):19-29 e3.
29. O'Brien PC, Fleming TR. A Multiple Testing Procedure for Clinical Trials. Biometrics. 1979 Sep;35(3):549
30. Uwakwe R. Affective (depressive) morbidity in puerperal Nigerian women: validation of the Edinburgh Postnatal Depression Scale. Acta Psychiatrica Scandinavica. 2003 Apr;107(4):251-9.
31. Mao F, Sun Y, Wang J, Huang Y, Lu Y, Cao F. Sensitivity to change and minimal clinically important difference of Edinburgh postnatal depression scale. Asian Journal of Psychiatry. 2021 Dec 1;66:102873.
32. Smith-Nielsen J, Matthey S, Lange T, Væver MS. Validation of the Edinburgh Postnatal Depression Scale against both DSM-5 and ICD-10 diagnostic criteria for depression. BMC Psychiatry. 2018 Dec 20;18(1):393.
33. De Bruin GP, Swartz L, Tomlinson M, Cooper PJ, Molteno C. The factor structure of the Edinburgh Postnatal Depression scale in a South African peri-urban settlement. South African Journal of Psychology. 2004 Mar;34(1):113-21.
34. Eboreime EA, Olawepo JO, Banke-Thomas A, Abejirinde IO, Abimbola S. Appraising and addressing design and implementation failure in global health: A pragmatic framework. Glob Public Health. 2021;16(7):1122-30.
35. Allen CR, Gunderson LH. Pathology and failure in the design and implementation of adaptive management. J Environ Manage. 2011;92(5):1379-84.

36. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care. 2012;50(3):217-26.
37. Nilsen P. Making sense of implementation theories, models and frameworks. Implement Sci. 2015;10:53.
38. Common terminology criteria for adverse events (CTCAE) version 5 [Internet]. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7
39. Ehlken B, Nathell L, Gohlke A, Bocuk D, Toussi M, Wohlfeil S. Evaluation of the Reported Rates of Severe Hypersensitivity Reactions Associated with Ferric Carboxymaltose and Iron (III) Isomaltoside 1000 in Europe Based on Data from EudraVigilance and VigiBase™ between 2014 and 2017. Drug Saf. 2019;42(3):463-71.

APPENDICES

I. Hb worksheet
II. Malaria POCT worksheet
III. Blood Sample Collection Log
IV. Laboratory Request form (Synlab Request form)
V. Screening Log forms
VI. Informed consent form
VII. Enrollment log sheet
VIII. Participant biodata and locator form
IX. Adverse event reporting form
X. Enrollment e-CRF
XI. Edinburgh Postnatal Depression Scale (EPDS)
XII. Maternal infant bonding scale e-form
XIII. Fatigue scale
XIV. Quality of life (WHOBREF) scale
XV. Follow-up visit e-CRF
XVI. End of study e-CRF
XVII. Call Log/Visitation Log
XVIII. Drug Accountability Form (FCM, FS, ANTI-MALARIA)
XIX. NCI Common Terminology Criteria for Adverse Events version 5 (Abridged)
XX. SAE report form
XXI. NAFDAC Pharmacovigilance form
XXII. Pre-trial site assessment and selection visit
XXIII. Study initiation checklist
XXIV. Site monitoring visit checklist
XXV. Protocol deviation/ violation form.
XXVI. Site monitoring visit log
XXVII. Referral for psychiatric consultation