







# The use of iron administered as an infusion into a vein compared to the use of iron tablets taken by mouth for treating Nigerian women with iron deficiency anaemia during pregnancy

<b>Submission date</b> 08/12/2020	<b>Recruitment status</b> No longer recruiting	 Prospectively registered
<b>Registration date</b> 10/12/2020	<b>Overall study status</b> Completed	 Protocol added
<b>Last Edited</b> 13/02/2024	<b>Condition category</b> Pregnancy and Childbirth	 SAP not yet added
		 Results not yet added and study completed for 1-2 years
		 Raw data not yet added
		 Study completed

## Plain English Summary

### Background and study aims

Iron deficiency anaemia is a condition where a lack of iron in the body leads to fewer red blood cells. Anaemia in pregnancy is a public health burden with a high incidence in Africa. Currently pregnant women who are anaemic are treated with high-dose iron tablets taken by mouth if it is mild or moderate in severity. Those who have severe anaemia are given blood. Some women do not tolerate the tablets well as they may develop side effects like constipation, stomach pain, nausea or vomiting. There are iron preparations in existence that can be given in infusion (drip) form and have been found to be safe, and their use for the treatment of iron deficiency anaemia in pregnancy is currently being evaluated. The aim of this study is to compare the effectiveness of ferric carboxymaltose given as an infusion through a vein versus oral ferrous sulphate taken by mouth for treating iron-deficiency anaemia in pregnancy, and to compare the acceptability, safety and the cost-effectiveness of these two forms of iron preparation in pregnant Nigerian women with moderate and severe iron deficiency anaemia at 20 – 32 weeks (5 - 7 months) of pregnancy.

### Who can participate?

Pregnant women aged between 15 and 49 who are anaemic at the time they are registering for antenatal care in the hospital.

### What does the study involve?

Information is collected about the participants' health and pregnancy and a blood sample is taken. Participants are randomly allocated to one of two drug treatments. The drug may be a preparation that will be added to an infusion (drip) for administration only once and over 30 minutes, or it may be in tablet form which will be taken by mouth three times a day until delivery. During pregnancy, their blood will be checked regularly and they will be asked questions at each visit and assessed for depression using a questionnaire on three occasions in

the course of the study. Participants will be monitored all through pregnancy, through delivery and until 6 weeks after they have delivered. Their babies will also be examined after delivery to get some information such as the birth weight and will also be followed up to collect information on their immunization status.

What are the possible benefits and risks of participating?

Though the drugs to be used in this study have been found to be relatively safe in pregnancy, it is still possible to suffer some side effects from any of the medications. Participants will be monitored closely to identify any side effect early and treat at no cost. All the trial drugs will be given free of charge and all the tests relating to this research will also be done for free. Participants will be given contacts of their caregivers and will be sent regular reminders about their appointments. The findings of this study will improve the knowledge about treatment of anaemia in pregnancy and enable existing treatments to be changed if need be in order to improve the well being of pregnant women and the outcome of their pregnancy.

Where is the study run from?

University of Lagos/Lagos University Teaching Hospital (LUTH) (Nigeria)

When is the study starting and how long is it expected to run for?

November 2020 to June 2023

Who is funding the study?

Bill and Melinda Gates Foundation (USA)

Who is the main contact?

Prof. Bosede B. Afolabi

bbafolabi@unilag.edu.ng

**Study website**

<https://ivontrial.com>

## Contact information

**Type(s)**

Scientific

**Contact name**

Prof Bosede Afolabi

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**Contact details**

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### **Type(s)**

Public

### **Contact name**

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## **Additional identifiers**

### **EudraCT/CTIS number**

2021-002867-23

### **IRAS number**

### **ClinicalTrials.gov number**

NCT04976179

### **Protocol/serial number**

PACTR202012843695208

## **Study information**

### **Scientific Title**

Intravenous versus oral iron for iron deficiency anaemia in pregnant Nigerian women (IVON): an open label, randomized controlled trial

### **Acronym**

IVON

### **Study hypothesis**

Current hypothesis as of 27/06/2022:

Hypothesis 1: The researchers expect a lower prevalence of anaemia at 36 weeks' gestation, a reduction in incidence of preterm delivery, and improvement in other maternal and perinatal outcomes among the intravenous iron, compared with the oral iron group.

Hypothesis 2: The researchers expect intravenous ferric carboxymaltose to be more acceptable, feasible and cost-effective than oral ferrous sulphate in the treatment of moderate to severe IDA in pregnancy

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Previous hypothesis as of 15/12/2020:

Hypothesis 1: The researchers expect a lower prevalence of anaemia at 36 weeks' gestation, a higher increase in maternal haemoglobin concentration levels at 4 weeks post treatment initiation, and improvement in other maternal and perinatal outcomes among the intravenous iron, compared with the oral iron group

Hypothesis 2: The researchers expect intravenous ferric carboxymaltose to be more acceptable, feasible and cost-effective than oral ferrous sulphate in the treatment of moderate to severe IDA in pregnancy

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Previous hypothesis:

Hypothesis 1: The researchers expect a 14% lower prevalence of anaemia at 36 weeks' gestation and a 1g/dl increase in maternal haemoglobin concentration levels at 4 weeks post treatment initiation among the intervention group, compared with the control group.

Hypothesis 2: The researchers expect intravenous isomaltoside to be more cost-effective than oral ferrous sulphate in the treatment of moderate to severe IDA in pregnancy.

### **Ethics approval required**

Old ethics approval format

### **Ethics approval(s)**

1. Approved 02/12/2020, Lagos University Teaching Hospital Health Research and Ethics Committee (P.M.B. 12003, Surulere, Lagos, Nigeria; +234 (0)15850737, +234 (0)15852187, +234 (0)15852209; luthethics@yahoo.com), ref: ADM/DCST/HREC/APP/3971
2. Approved 17/01/2021, National Health Research and Ethics Committee (chairman@nhrec.net, +234-09-523-8367), ref: NHREC/01/01/2007
3. Approved 23/04/2021, National Agency for Food Drug Administration and Control (NAFDAC) (der.headquarters@nafdac.gov.ng, +234-09-523-8367), ref: NAFDAC/DER/VCTD/IVON/VOL.2

### **Study design**

Multicenter interventional parallel open-label individually randomized controlled trial with a cost-effectiveness analysis

### **Primary study design**

Interventional

### **Secondary study design**

Randomised controlled trial

**Study setting(s)**

Hospital

**Study type(s)**

Treatment

**Participant information sheet**

See study output table

**Condition**

Iron deficiency anaemia in pregnant women

**Interventions**

Current interventions as of 27/06/2022:

Eligible women will be admitted on a day case basis into the dedicated ward or day room for treatment initiation. They will be individually randomized in a 1:1 ratio to receive either intravenous ferric carboxymaltose or oral iron. "Sealed envelope" will generate the randomisation code list, shared ONLY with the unblinded pharmacist by email, who will then label each drug kit with a code according to the randomisation list and send to the appropriate study site. As each new patient is recruited in a particular site, her details will be entered into an electronic tablet and a code is generated that corresponds to the codes on a particular drug kit. She is then given a labelled drug kit that corresponds to her assigned code. The intervention group will receive intravenous ferric carboxymaltose will be 20 mg/kg body weight (but not exceeding 1000mg) given in 200 ml of normal saline as a single-dose infusion administered over 15 – 20minutes. The control group will receive oral ferrous sulphate 200 mg (65 mg elemental iron) three times daily from enrolment till delivery.

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Previous interventions as of 12/04/2021:

Eligible women will be admitted on a day case basis into the dedicated ward or day room for treatment initiation. They will be individually randomized in a 1:1 ratio to receive either intravenous ferric carboxymaltose or oral iron. "Sealed envelope" will generate the randomisation code list, shared ONLY with the unblinded pharmacist by email, who will then label each drug kit with a code according to the randomisation list and send to the appropriate study site. As each new patient is recruited in a particular site, her details will be entered into an electronic tablet and a code is generated that corresponds to the codes on a particular drug kit. She is then given a labelled drug kit that corresponds to her assigned code. The intervention group will receive intravenous ferric carboxymaltose will be 20 mg/kg body weight (but not exceeding 1000mg) given in 250 ml of normal saline as a single-dose infusion administered over 15 minutes. The control group will receive oral ferrous sulphate 200 mg (65 mg elemental iron) three times daily from enrolment till delivery.

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Previous interventions:

Eligible women will be admitted on a day case basis into the dedicated ward or day room for treatment initiation. They will be individually randomized in a 1:1 ratio to receive either

intravenous iron isomaltoside or oral iron. "Sealed envelope" will generate the randomisation code list, shared ONLY with the unblinded pharmacist by email, who will then label each drug kit with a code according to the randomisation list and send to the appropriate study site. As each new patient is recruited in a particular site, her details will be entered into an electronic tablet and a code is generated that corresponds to the codes on a particular drug kit. She is then given a labelled drug kit that corresponds to her assigned code. The intervention group will receive iron isomaltoside 20 mg/kg single dose, maximum 1500 mg diluted in 100 ml 0.9% Normal Saline infusion and given over 30 minutes. The control group will receive oral ferrous sulphate 200 mg (65 mg elemental iron) three times daily from enrolment till delivery.

## **Intervention Type**

Drug

## **Phase**

Phase III

## **Drug/device/biological/vaccine name(s)**

Intravenous ferric carboxymaltose, oral ferrous sulphate

## **Primary outcome measure**

Current primary outcome measure as of 14/03/2022:

1. Prevalence of maternal anaemia (diagnosed as haemoglobin less than 11g/dl), at 36 weeks' gestation, measured with a haematological auto-analyser.
2. Incidence of preterm birth, measured at delivery.

Previous primary outcome measure:

1. Prevalence of maternal anaemia (diagnosed as haemoglobin less than 11g/dl), at 36 weeks' gestation, measured with a haematological auto-analyser
2. Maternal haemoglobin levels measured using HemoCue at 4 weeks post-initiation of treatment and at delivery measured with a haematological auto-analyser

## **Secondary outcome measures**

Current secondary outcome measures as of 20/07/2023:

1. Safety and tolerability, including the incidence of hypophosphatemia and severity of maternal adverse effects measured using medical records at Day 1 and 4 weeks post enrolment, at 36 weeks gestational age and at 6 weeks post delivery; added 12/04/2021: serum phosphate concentration measured with laboratory assays using maternal blood and cord blood taken at delivery
2. Severe maternal events, specifically, haemorrhage, sepsis, shock and the need for blood transfusion measured using medical records at delivery
3. The incidence of low infant birth weight (<2.5 kg), prematurity (<37 weeks' gestation as dated from the last menstrual period or a first-trimester ultrasound scan), stillbirth and neonatal mortality (birth till 28 days of life), the proportion of infants being breastfed at 1, 2 and 4 weeks of life, and receiving BCG, oral polio and hepatitis vaccination in the same time period, measured using medical records
4. Depression linked to the emotional well-being of mothers measured using the validated Edinburgh Postnatal Depression Scale at enrolment, 36 weeks gestational age and 7 days post delivery
5. Maternal haemoglobin levels measured using HemoCue at 4 weeks post-initiation of

treatment and at delivery measured with a haematological auto-analyser

6. Prevalence of maternal iron deficiency (diagnosed by serum ferritin level less than 30 ng/ml) at 36 weeks' gestation measured using laboratory assay

Previous secondary outcome measures from 14/03/2022 to 20/07/2023:

1. Safety and tolerability, including the incidence of hypophosphatemia and severity of maternal adverse effects measured using medical records at Day 1 and 4 weeks post enrolment, at 36 weeks gestational age and at 6 weeks post delivery; added 12/04/2021: serum phosphate concentration measured with laboratory assays using maternal blood and cord blood taken at delivery

2. Severe maternal events, specifically, haemorrhage, sepsis, shock and the need for blood transfusion measured using medical records at delivery

3. The incidence of low infant birth weight (<2.5 kg), prematurity (<37 weeks' gestation as dated from the last menstrual period or a first-trimester ultrasound scan), stillbirth and neonatal mortality (birth till 28 days of life), the proportion of infants being breastfed at 1, 2 and 4 weeks of life, and receiving BCG, oral polio and hepatitis vaccination in the same time period, measured using medical records

4. Depression linked to the emotional well-being of mothers measured using the validated Edinburgh Postnatal Depression Scale at enrolment, 36 weeks gestational age and 7 days post delivery

5. Maternal haemoglobin levels measured using HemoCue at 4 weeks post-initiation of treatment and at delivery measured with a haematological auto-analyser

Previous secondary outcome measures:

1. Safety and tolerability, including the incidence of hypophosphatemia and severity of maternal adverse effects measured using medical records at Day 1 and 4 weeks post enrolment, at 36 weeks gestational age and at 6 weeks post delivery; added 12/04/2021: serum phosphate concentration measured with laboratory assays using maternal blood and cord blood taken at delivery

2. Severe maternal events, specifically, haemorrhage, sepsis, shock and the need for blood transfusion measured using medical records at delivery

3. The incidence of low infant birth weight (<2.5 kg), prematurity (<37 weeks' gestation as dated from the last menstrual period or a first-trimester ultrasound scan), stillbirth and neonatal mortality (birth till 28 days of life), the proportion of infants being breastfed at 1, 2 and 4 weeks of life, and receiving BCG, oral polio and hepatitis vaccination in the same time period, measured using medical records

4. Depression linked to the emotional well-being of mothers measured using the validated Edinburgh Postnatal Depression Scale at enrolment, 36 weeks gestational age and 7 days post delivery

**Overall study start date**

01/11/2020

**Overall study end date**

15/06/2023

## **Eligibility**

**Participant inclusion criteria**

1. Pregnant women aged 15 to 49 years old between 20- and 32-weeks' gestational age
2. Baseline (enrolment) laboratory-confirmed moderate or severe anemia (Hb <10 g/dl)

**Participant type(s)**

Patient

**Age group**

Mixed

**Lower age limit**

15 Years

**Upper age limit**

49 Years

**Sex**

Female

**Target number of participants**

1,056

**Total final enrolment**

1056

**Participant exclusion criteria**

Current exclusion criteria as of 27/06/2022:

1. Medically confirmed significant bleeding, major surgery or received blood transfusion within the last 3 months.
2. Severe symptomatic anemia needing urgent correction with blood transfusion.
3. Anemia of other cause besides IDA e.g., Sickle cell anemia.
4. Clinically confirmed malabsorption syndrome.
5. Hypersensitivity to any form of iron treatment.
6. History of any immune related illness e.g., SLE, Rheumatoid arthritis.
7. Preexisting maternal depression or other psychiatric illness.
8. Severe allergic reactions such as severe asthma.
9. History of severe drug allergy.

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Previous exclusion criteria:

1. Medically confirmed significant bleeding, major surgery or received a blood transfusion within the last 3 months
2. Symptomatic anaemia with dyspnea or fatigue and a need for urgent correction
3. Concurrent anaemia of another cause besides IDA
4. Clinically-confirmed malabsorption syndrome or hypersensitivity to any form of iron treatment
5. Preexisting maternal depression or other psychiatric illness

**Recruitment start date**

09/08/2021

**Recruitment end date**



15/12/2022

## **Locations**

### **Countries of recruitment**

Nigeria

### **Study participating centre**

#### **Lagos University Teaching Hospital**

Idi-Araba

Lagos

Nigeria

100254

### **Study participating centre**

#### **Lagos Island Maternity Hospital**

Campbell Street

Lagos Island

Lagos

Nigeria

101231

### **Study participating centre**

#### **Mother and Child Centre**

1st Avenue

1st Gate

Festac Town

Amuwo-Odofin

Lagos

Nigeria

102312

### **Study participating centre**

#### **Simpson Primary Health Centre**

Simpson Street

Ebute-Metta

Lagos

Nigeria

101212

### **Study participating centre**

**Iwaya Primary Health Centre**

Omotola street

Iwaya

Lagos

Nigeria

100213

**Study participating centre**

**Aminu Kano Teaching Hospital**

Zaria Road

Kano

Nigeria

7002333

**Study participating centre**

**Sheikh Jeddah General Hospital**

Bello Road 700224 Sabon Gari West

Kano

Nigeria

700271

**Study participating centre**

**Bammali General Hospital**

Emir Palace Road 700224 Kan Karofi

Kano

Nigeria

713261

**Study participating centre**

**Kumbotsu Comprehensive Primary Health Centre**

Kumbotsu

Kano

Nigeria

700104

**Study participating centre**

**Sharada Primary Health Centre**

Sharada

Kano

Nigeria

700234

**Study participating centre**  
**Kabuga Comprehensive Primary Health Centre**  
Gwarzo Rd, Kofar Dukayuwa  
Nigeria  
Kano  
Nigeria  
700282

## Sponsor information

**Organisation**  
University of Lagos

**Sponsor details**  
College of Medicine  
Lagos  
Nigeria  
12003  
+234 (0)8023002960  
provost@cmul.edu.ng

**Sponsor type**  
University/education

**Website**  
<http://www.unilag.edu.ng/>

**ROR**  
<https://ror.org/05rk03822>

## Funder(s)

**Funder type**  
Charity

**Funder Name**  
Bill and Melinda Gates Foundation

**Alternative Name(s)**  
Bill & Melinda Gates Foundation, Gates Foundation, BMGF, B&MGF, GF

## **Funding Body Type**

Private sector organisation

## **Funding Body Subtype**

Trusts, charities, foundations (both public and private)

## **Location**

United States of America

# **Results and Publications**

## **Publication and dissemination plan**

The researchers plan to publish the protocol in a peer-reviewed journal. The researchers plan to publish the study findings in high-impact peer-reviewed journals. The findings of the study will be presented at conferences (both international and local) so as to disseminate the findings to a large body of professionals in the field of Obstetrics and Gynaecology. The findings will be used in developing standard operating care manual/ protocol for the management of iron deficiency anaemia in pregnancy. The researchers will issue press releases about the findings of the study.

## **Intention to publish date**

30/06/2024

## **Individual participant data (IPD) sharing plan**

The datasets generated during and/or analysed during the current study will be stored in a publicly available repository. The researchers will store the data and deposit it in 'Open Science Framework' after approval is obtained from the ethics committee. The researchers will also provide metadata along with the data to describe it. No patient identifier will be included in the data shared. Potential new users may access our data including the metadata on the 'Open Science Framework'. The researchers will share the data at the time of publication of our first paper. The assigned DOI number, the OSF website details and the approach to data sharing will be included as an appendix to all publications emanating from this research to facilitate accessibility to our data and metadata. The researchers will also share these at any conference presentation both international and local, and also on the study website to facilitate access by other researchers.

The individual participant data (IPD) sharing will commence at the time of the first publication or within 6 months of completing the study. The duration of IPD sharing will be 2 years. The tentative start date for IPD sharing is 01/01/2024 and the tentative end date is 31/12/2025.

Key access criteria include:

1. The principal investigator will bear overall responsibility for this data and will be responsible for deciding whether to supply research data to a potential new user. The CMUL HREC will provide an independent oversight function.
2. Data will be made available at the time of publication, at the latest. Depending on the nature of the data itself, data may be made available earlier, either on an individual basis to interested researchers and/or potential new collaborators.
3. The researchers will ensure that the informed consent forms clearly spell out and seek consent for future data sharing. However, only de-identified data will be shared.
4. All external users will sign and be bound by our data sharing agreements and will not be

allowed to use the data for reasons other than stated in their application.

5. IPD sharing will be by open access on Open Science Framework during the period of IPD sharing.

## IPD sharing plan summary

Stored in publicly available repository

## Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Participant information sheet</a>			11/12/2020	No	Yes
<a href="#">Protocol article</a>		08/09/2022	09/09/2022	Yes	No
<a href="#">Other publications</a>	Qualitative study	13/02/2024	13/02/2024	Yes	No