

Prevention of Iron Deficiency Anemia Post-delivery (PRIORITY Trial)

A Randomized Controlled Trial of the Global Network for Women's and Children's Health Research

Study Protocol

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Acronyms

AE	adverse event
AGP	alpha 1 acid glycoprotein
CI	confidence interval
BMGF	Bill & Melinda Gates Foundation
CI	confidence interval
CRP	C-reactive protein
DCC	Data Coordinating Center
DMS	Data Management System
DRC	Democratic Republic of Congo
DSMB	Data and Safety Monitoring Board
EPDS	Edinburgh Postnatal Depression Scale
ERC	Ethical review Committee
FCM	ferric carboxymaltose
FDA	Food and Drug Administration
FSS-5R	5-item version of the Maternal Fatigue Severity Scale
GA	gestational age
GLMM	generalized linear mixed-effects model
GMP	Good Manufacturing Practices
Hb	hemoglobin
IDA	iron deficiency anemia
iPI	international Principal Investigator
IRB	Institutional Review Board
ITT-Asian	Intention-To-Treat population in Asian sites
ITT-African	Intention-To-Treat population in sub-Saharan African sites
ITT-LMIC	Intention-To-Treat population in LMIC aggregate
IV	intravenous
LMICs	low and lower-middle income countries
MIBS	Mother-to-Infant Bonding Scale
MOP	Manual of Procedures
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
PI	Principal Investigator
PRIORITY	Prevention of Iron Deficiency Anemia Post-delivery
RDT	rapid diagnostic test
RTI	Research Triangle Institute International
SAE	serious adverse event
Safety-Asian	safety population in Asian sites
Safety-African	safety population in sub-Saharan African sites
Safety-LMIC	safety population in LMIC aggregate
SAP	statistical analysis plan
SOP	Standard Operating Procedure
sTfR	soluble transferrin receptor
TJU	Thomas Jefferson University
US	United States of America
WHA	World Health Assembly
WHO	World Health Organization
WHO	World Health Organization Quality of Life

Abstract

Background: Anemia remains a major contributor to maternal morbidity and mortality and, despite numerous efforts, rates of anemia have not decreased, especially in low- and middle-income countries. The most common cause of anemia worldwide is iron deficiency, and anemia due to this cause will be referred to as iron deficiency anemia (IDA). While IDA during pregnancy increases the risk of adverse maternal, fetal, and neonatal outcomes, it is important to address other periods, particularly immediately after delivery when maternal hemoglobin (Hb) values often drop precipitously. An intravenous (IV) iron infusion has been demonstrated to be a safe, effective intervention to reduce anemia during pregnancy but has not been adequately assessed during the postpartum period. To reduce anemia among women of reproductive age, new, effective interventions are needed. Thus, this trial, *Postpartum IV Iron to Treat Iron-Deficiency Anemia (PRIORITY Trial),* will determine if a single-dose infusion of IV iron is a more effective means of increasing prevalence of non-anemia than standard of care of oral iron among postpartum women with moderate anemia defined as Hb 7-9.9 g/dL (folic acid will be given to all participants as per WHO guidelines).

Primary Hypothesis: At 6 weeks postpartum, the incidence of achieving a non-anemic state (defined as Hb ≥11 g/dL) will be greater among women receiving a single-dose infusion of IV iron than among women receiving standard care with oral iron. This hypothesis will be tested separately in all maternal participants as well as in the south Asian cohort and sub-Saharan African cohort.

Study Design: Two-arm, prospective, randomized trial.

Population: Women (n=4,800, in total) with moderate Hb concentrations (7-9.9 g/dL) immediately at post-delivery (6-48 hours), who deliver at study hospitals or birthing facilities in Global Network sites (Bangladesh, India [2 sites], Pakistan, Democratic Republic of Congo, Kenya, Zambia and Guatemala).

Treatment Arms:

- ***IV iron (Arm 1):*** Single-dose infusion of IV iron 6-48 hours post-delivery and folic acid
- ***Oral iron (Arm 2):*** Standard care (oral iron and folic acid)

Primary Endpoint:

- Maternal non-anemic state (Hb ≥11 g/dL) at 6 weeks postpartum

Key Secondary Endpoints:

- Change from baseline in serum Hb concentration at 6 weeks postpartum
- Maternal depression, as measured by Edinburgh Postnatal Depression Scale score > 10, at 6 weeks postpartum
- Change from baseline in serum Hb concentration at 6 months postpartum
- Maternal depression, as measured by Edinburgh Postnatal Depression Scale score > 10, at 6 months postpartum

Other Secondary Endpoints:

Maternal

- Functional outcomes

    - Maternal Fatigue Severity Scale score > 4 (6 weeks postpartum, 6 months postpartum)
    - Mother-to-Infant Bonding Scale score ≥ 4 at 6 weeks postpartum
    - World Health Organization Quality of Life score (6 weeks postpartum, 6 months postpartum)
- Anemia outcomes
    - Change from baseline in serum ferritin concentration (6 weeks postpartum, 6 months postpartum)
    - Change from baseline in serum soluble transferrin receptor concentration (6 weeks postpartum, 6 months postpartum)
    - Maternal non-anemic state (Hb ≥11.5 g/dL) (6 weeks postpartum, 6 months postpartum)
    - Maternal non-anemic state (Hb ≥12.0 g/dL) (6 weeks postpartum, 6 months postpartum)
    - Severe/moderate/mild anemia (6 weeks postpartum, 6 months postpartum)
    - Change from baseline in anemic state (6 weeks postpartum, 6 months postpartum)
- Clinical outcomes
    - Maternal mortality (randomization to 6 months postpartum)
    - Post-discharge blood transfusion through 6 months postpartum
    - Postpartum hemorrhage requiring blood transfusion or major surgery (randomization to 6 weeks postpartum)
    - Post-discharge maternal hospitalization (as an indicator to capture infection) through 6 months postpartum
- Safety
    - Hypophosphatemia (as measured by serum phosphate concentration <2.5 mg/dL) (6 weeks postpartum, 6 months postpartum if hypophosphatemia at 6 weeks postpartum)
    - Short-term safety outcomes: Serious adverse events (randomization to 6 weeks postpartum)
    - All safety outcomes: Serious adverse events (randomization to 6 months postpartum)

Infant

- Neonatal/infant mortality (randomization to 6 months postpartum)
- Post-discharge neonatal/infant hospitalization through 6 months postpartum
- Exclusive breastfeeding (6 weeks postpartum, 3 months postpartum, 6 months postpartum), based on WHO/UNICEF definition that measure exclusive feeding with breast milk during the previous day

1 Background

In 2012, the World Health Assembly (WHA) passed a resolution, WHA 65.6, which expresses a set of six global nutrition objectives to be achieved by 2025, including a 50% reduction in anemia among women of reproductive age.[1] With only a few years remaining to achieve this objective, it is clear that many countries, especially those characterized as low and lower-middle income countries (LMICs), will not achieve the targeted reduction in their anemia prevalence rates for women aged 15-49 years without a significant change in treatment approaches.

The most common cause of anemia worldwide is iron deficiency. And while it is increasingly being reported that iron deficiency anemia (IDA) during pregnancy increases the risk of adverse maternal, fetal, and neonatal outcomes, it is important to address other critical time points during a woman's life, particularly immediately after delivery when hemoglobin (Hb) concentrations often drop precipitously.

Sultan et al in a systematic review and meta-analysis, has also provided data indicating that the burden of IDA among postpartum women is under-appreciated.[2] Although the purpose of the referenced review was to compare oral versus singe-dose intravenous (IV) iron to treat postpartum anemia, the randomized clinical trials included in this review provided data that associated postpartum anemia with maternal depression, fatigue, and impaired cognition – health-related conditions that not only affect mothers, but can also affect the quality of infant care and negatively impact mother-child bonding.[3,4]

2 Study Overview

This study, **Prevention of Iron Deficiency Anemia Post-delivery (PRIORITY)**, is designed as a 2-arm randomized-controlled trial focused on postpartum women. If successful, its application can contribute to a reduction in anemia prevalence rates among women of reproductive age consistent with the resolution of the WHA. The trial will recruit women who are diagnosed with moderate anemia based on a blood sample taken 6-48 hours after childbirth. A total of 4,800 eligible women, or 600 women per research site, will be consented and enrolled in the trial by the research teams of eight international sites that, together with their United States of America (US) partners, participate in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development's (NICHD's) Global Network for Women's and Children's Health Research.

Following informed consent, women with moderate anemia, defined as Hb concentration 7-9.9 g/dL at enrollment, will be randomized to one of two study arms and subsequently receive a single-dose infusion of IV iron within 6-48 hours of delivery and prior to discharge or be given standard care consisting of the provision of tablets containing 60 mg of elemental iron to be taken twice daily for 6 weeks postpartum. Folic acid (400 mcg) will be given daily for 6 weeks postpartum to all participants as per WHO guidelines.[5] The trial's primary endpoint is maternal non-anemic state (Hb ≥11 g/dL) at 6 weeks postpartum. Oral iron treatment with folic acid to 6 months postpartum will be dependent on maternal anemic state at 6 weeks postpartum.

Secondary endpoints include maternal functional outcomes and hematological/biochemical measures of iron status, and maternal and neonatal/infant clinical outcomes. Hb, as well as markers of iron status and inflammatory markers, will be measured at 6 weeks and 6 months postpartum. Other secondary endpoints of interest include intrapartum complications, post-discharge blood transfusions, maternal and neonatal/infant hospitalizations, and maternal and

neonatal/infant mortality through 6 months postpartum, as well as rates of exclusive breastfeeding at 6 weeks, 3 months, and 6 months postpartum.

Validated instruments will be used to explore the possible impact of IV iron versus oral iron treatment for IDA on maternal functional outcomes at 6 weeks and 6 months postpartum. Maternal depression, based on the score on the Edinburgh Postnatal Depression Scale (EPDS)[6-8], will be assessed at 6 weeks and 6 months postpartum. We anticipate that some participants will continue to have symptoms of depression at 6 months postpartum after having symptoms at 6 weeks, while others may have signs of depression only at 6 months postpartum. Fatigue is one of the most common symptoms of anemia and will be assessed at 6 weeks and 6 months postpartum using the modified 5-item version of the Maternal Fatigue Severity Scale (FSS-5R). Maternal quality of life will be measured at 6 weeks and 6 months postpartum with the World Health Organization Quality of Life (WHOQOL) score, an assessment tool developed to be applicable cross culturally.[9] Maternal-infant bonding will be measured at 6 weeks postpartum using the Mother-to-Infant Bonding Scale (MIBS).[3,4]

3 Statement of the Problem

This trial is designed to determine if a single-dose infusion of IV iron is a more effective means of reducing anemia than standard of care oral iron in postpartum women, a subgroup of women of reproductive age. The following three tables summarize the magnitude of the anemia problem in LMICs where the Global Network research centers are located. The definition of anemia used in the tables is Hb concentration <11.0 g/dL for pregnant women, adjusted for altitude and smoking; the definition for non-pregnant and lactating women is <12.0 g/dL. Generally, the WHO data for anemia is based upon population-representative data surveys conducted in the listed countries.[10-14]

Table 1 presents data indicating that four countries in the Global Network had minimal decreases in anemia prevalence among reproductive age women for 2019 compared to 2012, while three countries had increased prevalence rates. Only Guatemala had a sufficient difference between the 2012 and 2019 reported rates to suggest that achieving a 50% reduction in anemia among reproductive age women may be possible by 2025 (based on the required reduction of the 2012 prevalence rate provided in the WHO data). However, the prospective data collected through the Global Network's registry (see Table 3) suggest that maternal anemia remains a substantial burden in Guatemala.[15]

Table 1: Anemia Prevalence Rates in Global Network Countries for Women of Reproductive Age (15-49 years), 2012 versus 2019

Global Network Country	Anemia Prevalence Rate (%) Among Women of Reproductive Age (15-49 years)	
	2012	2019 (latest available)
Bangladesh	35.7	36.7
Democratic Republic of Congo	46.4	42.4
Guatemala	11.0	7.4
India (2 sites)	53.2	53.0
Kenya	28.4	28.7
Pakistan	42.7	41.3
Zambia	30.5	31.5

Source: World Health Organization[10]

WHO data presented in Table 2 for both pregnant women and non-pregnant women 15-49 years of age from Global Network countries suggest that anemia reduction efforts for both groups of women should be escalated and be more effective compared to past efforts if these countries are to achieve the WHA 2025 target of a 50% reduction in anemia prevalence among reproductive age women.

WHO considers that a defined geographic area has a "severe" problem when its anemia prevalence rate for women 15-49 years of age is ≥40%. Table 2 indicates that five Global Network countries had severe prevalence rates for anemia in pregnant women and three countries in non-pregnant women.

Table 2: Anemia Prevalence Rates in Global Network Countries for Pregnant and Non-Pregnant Women (15-49 years), 2012 versus 2019

Global Network Country	Anemia Prevalence Rate (%) Among Women, Ages 15-49 years			
	Pregnant Women		Non-Pregnant Women	
	2012	2019	2012	2019
Bangladesh	44.2	42.2	35.3	36.5
Democratic Republic of Congo	50.7	46.5	45.8	41.9
Guatemala	17.0	12.7	10.6	7.0
India (2 sites)	51.4	50.1	53.3	53.1
Kenya	40.7	40.3	27.2	27.9
Pakistan	47.1	44.0	42.4	41.1
Zambia	38.9	39.3	29.5	30.7

Source: World Health Organization[11,12]

Table 3 provides data for Global Network countries pertinent to the number of pregnant and non-pregnant women affected by anemia in 2019 (the latest year for which WHO data are available). The numbers are especially notable for pregnant women. From prospectively collected Hb concentrations obtained at or prior to the first trimester in the Global Network, approximately three-quarters of women meet the criteria for anemia, ranging from rates of >90% in the South Asian sites to about one-third in the Guatemala site. These rates have also been documented in

several Global Network (GN) studies demonstrating the adverse impact of low Hb concentrations on birth outcomes.[16-19]

Table 3: Number of Anemic Pregnant and Non-Pregnant Women (15-49 years) in Global Network Countries, 2019

Global Network Country	Number of Anemic Pregnant and Non-Pregnant Women (Ages 15-49 years), 2019*		Global Network Site**
	Pregnant Women	Non-Pregnant Women	Anemia (Hb ≤11g/dL) among Pregnant Women (%)
Bangladesh	771,300	16,031,000	76.6%
Democratic Republic of Congo	1,036,000	7,166,000	Not Available
Guatemala	33,530	316,000	32.7%
India (2 sites)	7,582,000	179,743,000	93.4%
Kenya	378,000	3,542,000	63.1%
Pakistan	1,702,000	20,707,000	98.5%
Zambia	157,900	1,214,000	42.8%
Total, Global Network Countries	11,660,730	227,505,000	73.1%

Sources: *World Health Organization[10-14] and **RTI International[15]

Unless a pregnant woman with anemia receives treatment to bring Hb concentration to an acceptable concentration prior to delivery, the blood loss associated with childbirth will likely increase the severity of anemia as well as the need for effective treatment to diminish poor maternal outcomes, including mortality. Other symptoms of postpartum anemia can include fatigue, weakness, dizziness, lightheadedness, shortness of breath, irregular heartbeat, lack of productivity, and a diagnosis of depression. When a mother experiences symptoms of anemia, this may compromise her ability to provide optimal care to her baby. For example, there is evidence that anemic women are less likely to comply with recommended breastfeeding practices.[20]

3.1 Study Hypothesis and Objectives

3.1.1 Primary Hypothesis

At 6 weeks postpartum, the incidence of achieving a non-anemic state will be greater in women receiving a single-dose infusion of IV iron (Arm 1) than among women receiving standard care with oral iron (Arm 2). This hypothesis will be tested separately in all women as well as in the South Asian cohort and sub-Saharan African cohort.

3.1.2 Primary Objectives

1. To compare maternal anemia at 6 weeks postpartum between women who are randomized to receive a single-dose infusion of IV iron or standard care with oral iron after delivery.

2. To compare maternal anemia at 6 weeks postpartum between South Asian women who are randomized to receive a single-dose infusion of IV iron or standard care with oral iron after delivery.
3. To compare maternal anemia at 6 weeks postpartum between sub-Saharan African women who are randomized to receive a single-dose infusion of IV iron or standard care with oral iron after delivery.

3.1.3 Key Secondary Objectives

1. To compare the change from baseline in serum hemoglobin concentration at 6 weeks postpartum between women who are randomized to receive a single-dose infusion of IV iron or standard care with oral iron after delivery.
2. To compare maternal depression measured at 6 weeks postpartum between women who are randomized to receive a single-dose infusion of IV iron or standard care with oral iron after delivery.
3. To compare the change from baseline in serum hemoglobin concentration at 6 months postpartum between women who are randomized to receive a single-dose infusion of IV iron or standard care with oral iron after delivery.
4. To compare maternal depression measured at 6 months postpartum between women who are randomized to receive a single-dose infusion of IV iron or standard care with oral iron after delivery.

As with the primary objective, all key secondary objectives will also be separately addressed in South Asian cohort and sub-Saharan African cohort.

3.1.4 Other Secondary Objectives

5. To compare maternal functional outcomes measured up to 6 months postpartum between women who are randomized to receive a single-dose infusion of IV iron or standard care with oral iron after delivery.
6. To compare maternal anemia measured up to 6 months postpartum between women who are randomized to receive a single-dose infusion of IV iron or standard care with oral iron after delivery.
7. To compare maternal clinical outcomes measured up to 6 months postpartum between women who are randomized to receive a single-dose infusion of IV iron or standard care with oral iron after delivery.
8. To compare infant outcomes measured up to 6 months postpartum between women who are randomized to receive a single-dose infusion of IV iron or standard care with oral iron after delivery.
9. To assess safety in women who are randomized to receive a single-dose infusion of IV iron or standard care with oral iron after delivery.

As with the primary objective, all secondary objectives will also be separately addressed in South Asian cohort and sub-Saharan African cohort.

3.1.5 Exploratory Objectives

1. To determine if the effect of a single-dose infusion of IV iron on maternal functional outcomes are modified by maternal markers of iron status.

2. To determine if the effect of a single-dose infusion of IV iron on infant outcomes are modified by maternal markers of iron status measured immediately at post-delivery.
3. To determine if the effect of a single-dose infusion of IV iron on maternal clinical outcomes are modified by maternal markers of iron status.
4. To determine if the effect of a single-dose infusion of IV iron on infant outcomes are modified by maternal anemia at 6 weeks postpartum.

As with the primary objective, all exploratory objectives will also be separately addressed in South Asian cohort and sub-Saharan African cohort.

4 Summary of Relevant Literature

The WHO lists excessive blood loss as one of the most common direct causes of maternal mortality.[21] In a 2014 WHO systematic analysis, hemorrhage along with other direct obstetric causes of maternal mortality, hypertensive disorders, and sepsis, caused 73% (1,771,000 of 2,443,000) maternal deaths occurring between 2003 and 2009; and indirect causes accounted for 27.5%. Notably, the WHO estimates that anemia in pregnancy now affects more than 40% of pregnant women worldwide.[22]

While there has been a small downward trend in rates of anemia worldwide, adolescent girls and pregnant women have shown little change in these rates, and anemia remains a significant contributor to maternal mortality.[23] Further, women in the postpartum period are expected to have even higher rates of anemia, especially if they experience excessive blood loss during childbirth, which is often associated with increasing rates of Caesarean section.[24]

There is an abundance of clinical trials that have reported on the increased risk that IDA has on pregnancy, delivery and the newborn. However, there is a paucity of studies that specifically address postpartum anemia. When Sultan et al. performed a systematic review of randomized trials to compare oral iron versus IV iron for the treatment of iron deficiency, fifteen published articles were identified that met inclusion criteria.[2] The studies included 1,001 women that took oral iron and 1,081 that received IV iron. Four of the studies provided data that addressed the review's primary endpoint of Hb concentration at 6 weeks postpartum. The authors concluded that women who had received IV iron achieved an increase in Hb concentration at 6 weeks postpartum that was nearly 1 g/dL higher than the Hb increase realized by women that received oral iron. Further, the safety profile of IV iron was reassuring. Besides having a reduced Hb response, women taking oral iron had a higher risk of gastrointestinal side-effects.[2] The findings were thus supportive of IV iron being considered as a viable treatment option. Despite the small number of published studies reviewed and their considerable heterogeneity, the data reported from the 2019 meta-analysis suggests associations between postpartum anemia with decreased rates of breastfeeding, increases in depression and fatigue, a reduction in life quality, and less than optimal mother-infant bonding.[2]

A 2015 Cochrane review examined randomized controlled trials whose participants had initiated treatment within six weeks of delivery due to Hb <12 g/dL.[25] The purpose of the review was to assess efficacy and safety of a treatment for postpartum IDA with that of a placebo, with no treatment, or with another treatment. Twenty-two trials with 2,858 participants were included in the review and 13 comparisons were performed. Of those, 10 studies with 1,553 participants compared IV iron and oral iron. Fatigue was assessed in two of the 10 studies and found to diminish among women that received IV iron in one of the two studies. There were 2 cardiac related events (one involving death), one case of arrhythmia and three allergic reactions among

women receiving IV iron although a direct association was not implied. Gastrointestinal events were less frequent in the women given IV iron compared to women taking oral iron. The authors found that the quality of evidence was low and inadequate to reach conclusions regarding efficacy of interventions for postpartum IDA.[25]

Recently published trials indicated that the use of IV iron reduces rates of anemia both during pregnancy and postpartum. A study was undertaken in Tanzania to study efficacy and safety of IV ferric carboxymaltose (FCM) compared to oral iron for the treatment of IDA in women after childbirth.[26] A total of 230 pregnant women immediately prior to delivery were enrolled. They had Hb <110 g/L and ferritin concentration <50 µg/L measured within 14 days before childbirth. As a result of randomization, 116 were assigned to the oral iron arm and 114 were assigned to an IV iron arm. Dependent on Hb concentration and body weight, women in the IV iron arm received either a single-dose infusion of 1000 mg of FCM, two doses of 1500 mg FCM given at least 7 days apart, or 2000 mg of FCM at least 7 days apart. Oral iron treatment consisted of three ferrous sulphate tablets containing 60 mg of elementary and 5 mg of folic acid every morning with the treatment continuing for 3 months after Hb normalization. The primary endpoint was Hb normalization defined as >11.5 g/dL at 6 weeks. Follow-up visits occurred at 6 weeks and 3, 6, and 12 months. At 6 weeks, 94 (82%) of the participants in the IV iron group and 92 (79%) in the oral iron were assessed. Seventy-five (80%) of participants in the IV iron group and 47 (51%) of the women in the oral iron group had normalized Hb when assessed. There were two mild to moderate infusion-related adverse events (AEs). Additionally, there were five serious adverse events (SAEs) – three in the IV iron group and two in the oral iron group; however, these five events were reported as unrelated to the study medication.

The newer formulations of single-dose infusions of IV iron have been found to be exceptionally safe and more effective in helping women increase Hb concentration and achieve non-anemic status. Inclusion of all delivering women who are diagnosed within 6-48 hours of delivery with Hb 7.0 to 9.9 g/dL (defined as moderate anemia) suggests generalizability of an IV iron intervention, should positive results be obtained. We anticipate that a sizable percentage of women to be screened for study participation are likely to be moderately anemic in the postpartum period. Given that IDA is an intergenerational problem, it may ultimately prove necessary to provide effective interventions prepartum, antenatally, and in the postpartum period if we hope to effectively change the trajectory of anemia in a meaningful way for women of reproductive age.

5 Research Design and Methods

5.1 Study Design

The formal research design is a 2-arm, randomized-controlled trial that will be implemented at 8 sites in 7 countries: Bangladesh, Democratic Republic of the Congo, Guatemala, India (Nagpur and Belagavi), Kenya, Pakistan, and Zambia with participants from three continents. Three sites will be included in the sub-Saharan African analysis, four sites in the South Asian analysis, and all eight sites are included in the LMIC aggregate. The research team for each site will be expected to enroll approximately 600 women who deliver at a hospital or other facility such as a health center with delivery services. The facilities which are identified to enroll participants must have capacity to draw blood and measure Hb using Hemacue® instrumentation. Given the high prevalence of endemic malaria in the three sub-Saharan African sites, a rapid diagnostic test (RDT) for malaria will be administered 6-48 hours post-delivery. If the test is positive, she will **not** be eligible for enrollment and will be referred for treatment of malaria.

Eligible and consenting anemic women with Hb 7-9.9 g/dL based upon a venous blood sample obtained after childbirth but before discharge from a hospital or other facility with delivery services (such as a health center) will be randomized between 6-48 hours post-delivery equally to one of two study arms. Participants randomized to **Arm 1** will receive a single-dose infusion of IV iron (maximum of 1 gram or less depending on participant weight) to be initiated 6-48 hours after delivery and those in **Arm 2** will receive standard of care defined for this study as 60-65 mg elemental iron, initiated between 6-48 hours after delivery, prior to discharge from the facility, to be taken at a treatment dose of twice daily for 6 weeks postpartum. Both arms will also receive 400 mcg folic acid daily for 6 months postpartum as per WHO guidelines.

Participants will be assessed at an appropriate health facility at 6 weeks and 6 months postpartum by providing a maternal blood sample that will be analyzed to determine Hb concentration. Based on serum Hb concentration at 6 weeks postpartum, Arm 2 participants will receive oral iron until 6 months postpartum as described in **Section 6.2**.

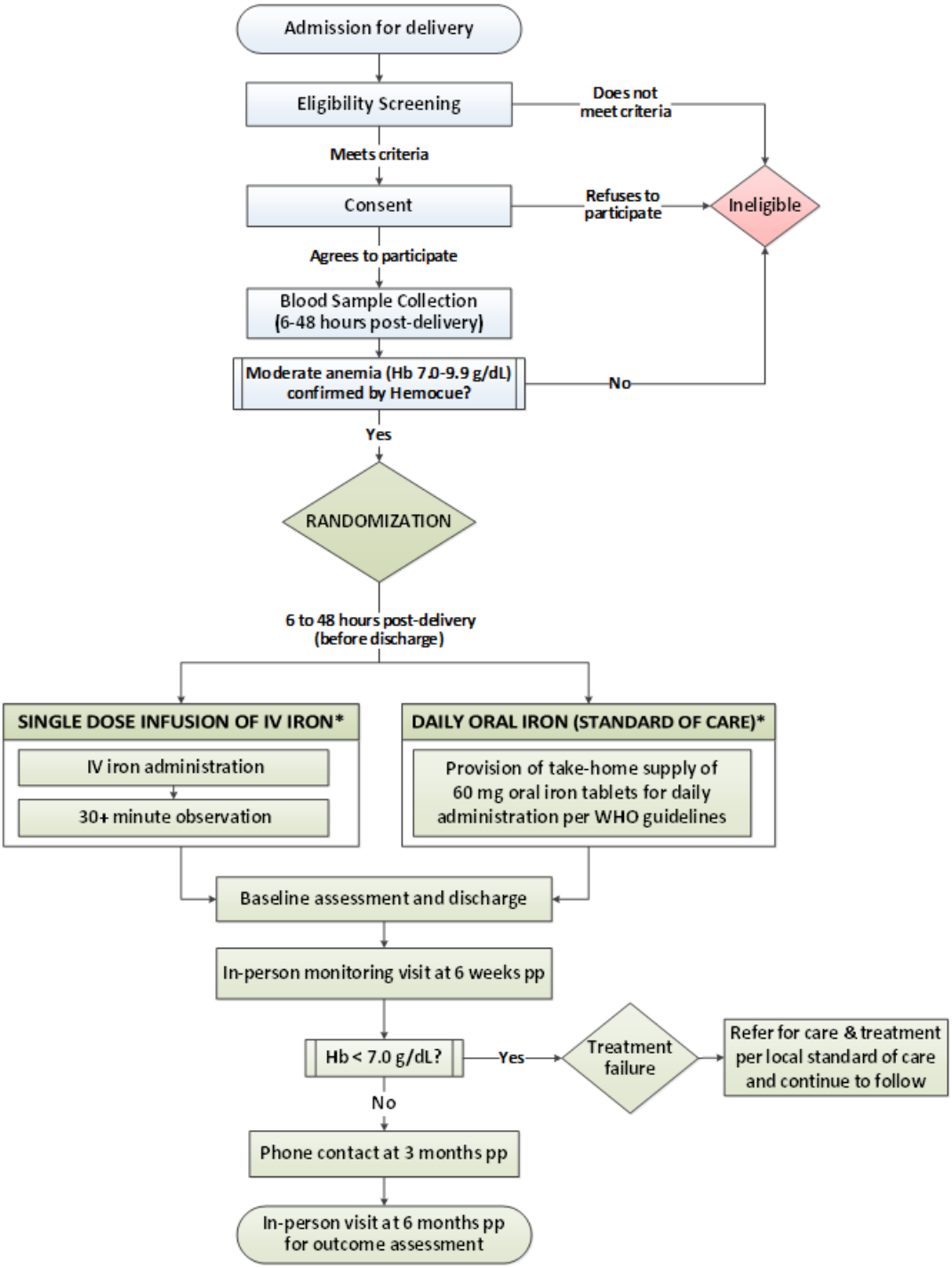
At enrollment, 6 weeks, and 6 months postpartum, serum ferritin, serum sTfR, serum C-reactive protein (CRP), and serum alpha 1 acid glycoprotein (AGP) will also be measured using the maternal blood sample. At 6 weeks postpartum, maternal serum phosphate will also be tested. If serum phosphate concentration at 6 weeks postpartum is <2.5 mg/dL, serum phosphate will be measured at 6 months postpartum as well. Additionally, in the sub-Saharan African sites, a RDT for malaria will be administered to the participant at 6 weeks and 6 months postpartum. If positive and untreated at any timepoint, the participant will be treated using local standard of care. All participants will be contacted via telephone at 3 months postpartum to assess maternal and neonatal/infant mortality as well as breastfeeding status.

The following assessment instruments will be used during the study to assess the functional outcomes:

- **Postpartum depression:** Postpartum depression at 6 weeks postpartum has been included as a key secondary endpoint based upon data from the published literature.[27,28] Postpartum depression can affect other secondary endpoints of interest including maternal quality of life, fatigue, and breastfeeding initiation and duration rates. Depression is also a risk factor for reducing infant-mother bonding. The EPDS, a validated assessment tool with a set of 10 screening questions, will be administered by trained research staff to determine whether a mother has symptoms that commonly occur with depression and anxiety during pregnancy and in the year following the birth of a child. It has several advantages over other depression-related tools, including validation in LMICs and availability in local languages used within research areas of Global Network sites.[6] For this study, the EPDS will be administered at 6 weeks and 6 months postpartum. Any woman scoring above 9 on the EPDS (cutoff for possible postpartum depression) during assessments at either time point will receive a referral for mental health support at a local facility per standard of care. Additionally, any woman answering yes to the EPDS suicidal screening question (number 10) will be referred for immediate care to a local health facility with appropriate notification of any such high-risk patient. Referrals will be documented on study forms and information about referral outcome will also be recorded at the next study visit.
- **Quality of life:** The WHOQOL score will be used to assess quality of life at 6 weeks and 6 months postpartum.[9,29,30]
- **Fatigue:** The FSS-5R will be assessed at 6 weeks and 6 months postpartum.[31]
- **Maternal infant bonding:** MIBS will be used to measure maternal-infant bonding at 6 weeks postpartum only.[4]

Figure 1 summarizes the participant enrollment and study visits. A detailed schedule of events is provided in **Appendix A.**

Figure 1: PRIORITY trial enrollment flowchart



* Both treatment arms will also receive a take-home supply of daily folic acid tablets (400 mcg per day) through 6 months pp.

5.2 Consent

Before a woman participates in the trial, the research staff must obtain her informed consent to voluntarily take part in the study. Consent will be obtained from women ≥18 years of age or minors in countries where married or pregnant minors (or their authorized representatives) are legally permitted to give consent. When enrolling minors, we will follow the in-country policies for human research protection and the guidelines approved by the local ethical review committees (ERCs). In the case of pregnant minors, this may require that written consent is obtained from her parents/guardians or husband, with written assent from the minor.

Potential participants will be screened and enrolled in the study after delivery. Consent should be obtained as early as possible after 6 hours post-delivery. Consent must be obtained for the blood draw for hemoglobin.

Potential participants can consider participation with family/friends if desired before deciding on participation. If the participant cannot read, the form will be read aloud to her by a person unaffiliated with the study. Alternatively, the Research Coordinator or a designate may read the consent, but in the presence of a witness who is unaffiliated with the research study. Potential participants will be given an opportunity to discuss the study procedures and ask questions. Additional details are provided in the study Manual of Procedures.

Fair balance will be maintained while describing the risks and benefits of participation in the trial. No undue pressure will be placed on the potential participant to enroll in the trial. It will further be explained that lack of participation will not affect the usual and anticipated standard of care. As the literacy levels will vary and may be a challenge, the consent process will include a verbal review of the consent form.

After the potential participant has read the consent form, but before she signs, the research staff will explain that she will either be given IV iron or by oral pills. Only if she is willing to commit to either option will she be enrolled; otherwise, this will be recorded as a refusal of consent. Following review of the consent, the potential participant (or parent/guardian) will be asked to sign the form. If the potential participant (or parent/guardian) is unable to sign her name, she will be asked to use her thumbprint to indicate written approval. In both cases, the unaffiliated person will also sign the consent form. Both the research staff and the study participant retain signed copies of the form.

An eligible woman may refuse to participate in the trial at the time of recruitment. This will be recorded on the study form. She may also choose to withdraw from the study at any time after enrollment. This will be recorded on the Withdrawal/Termination Form.

All research staff responsible for obtaining consent will be trained and certified in the protection of human subjects and the study-specific consent procedures. A model written informed consent form, developed according to the requirements of the U.S. Office of Research Protections (OHRP), is found in **Appendix B**. Each site may modify the model consent to conform to local standards, but the OHRP required elements must be maintained. The research sites will also be responsible for translating the consent form into the appropriate language(s) for their local context.

5.3 Selection of Health Facilities and Participants

5.3.1 Selection Criteria for Health Facilities

Health facilities which meet all of the following criteria may enroll study patients:

- Ability to collect required blood specimens and measure Hb using Hemocue®
- Capacity to administer IV iron and monitor participant for 30 minutes post-infusion
- Ability to enroll an ~600 participants at each of the sites
- Staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities are available (consistent with recommendations for IV iron administration)

5.3.2 Participant Inclusion Criteria

Women who meet all the following criteria are eligible for enrollment as study participants:

- Established pregnancy ≥28 weeks gestational age (GA) by last menstrual period and/or clinical assessment and/or ultrasonography
- Age: 18 years (or lower limit age eligible*) to 49 years
    * Some sites will be able to include women giving birth regardless of age if she is considered an adult or an emancipated minor. However, other sites will require women to be at least 18 years of age. We will adhere to local regulations.
- Confirmed moderate anemia (Hb 7.0 to 9.9 g/dL, 6-48 hours after delivery based on a venous blood sample on Hemocue®)
- Deliver in participating study hospital or health facility
- Able to provide informed consent
- Plans to remain in study area for at least 6 months postpartum

5.3.3 Participant Exclusion Criteria

Women who meet any of the following criteria are not eligible for enrollment as study participants:

- IV iron infusion already received in past 3 weeks
- Prior reaction to IV iron or oral iron or folic acid
- Contraindication to iron supplementation (some examples may include severe allergic states including asthma, hemolytic anemia, allergy, or severe infection)
- Blood transfusion already received or scheduled in the current hospital admission
- Known diagnosis of pre-existing depression or other psychiatric illness
- Major congenital anomaly prior to randomization
- Stillbirth or neonatal loss prior to randomization
- Presenting with symptomatic anemia with dyspnea or fatigue and need for immediate correction
- Known hemoglobinopathy (sickle cell disease or thalassemia)
- Positive malaria RDT prior to randomization (sub-Saharan African sites only)
- Any illness/condition requiring immediate medical care per physician's assessment

5.4 Primary Endpoint

- Maternal non-anemic state (Hb ≥11 g/dL) at 6 weeks postpartum

5.5 Key Secondary Endpoints

Maternal

- Change from baseline in serum Hb concentration at 6 weeks postpartum
- Maternal depression (as measured by EPDS score > 10) at 6 weeks postpartum
- Change from baseline in serum Hb concentration at 6 months postpartum
- Maternal depression (as measured by EPDS score > 10) at 6 months postpartum

5.6 Other Secondary Endpoints

Maternal

- Functional outcomes
    - FSS-5R score > 4 (6 weeks postpartum, 6 months postpartum)
    - MIBS score ≥ 4 at 6 weeks postpartum
    - WHOQOL score (6 weeks postpartum, 6 months postpartum)

- Anemia outcomes
    - Change from baseline in serum ferritin concentration (6 weeks postpartum, 6 months postpartum)
    - Change from baseline in serum sTfR concentration (6 weeks postpartum, 6 months postpartum)
    - Maternal non-anemic state (Hb ≥11.5 g/dL) (6 weeks postpartum, 6 months postpartum)
    - Maternal non-anemic state (Hb ≥12.0 g/dL) (6 weeks postpartum, 6 months postpartum)
    - Severe/moderate/mild anemia (6 weeks postpartum, 6 months postpartum)
    - Change from baseline in anemic state (6 weeks postpartum, 6 months postpartum)

- Clinical outcomes
    - Maternal mortality (randomization to 6 months postpartum)
    - Post-discharge blood transfusion through 6 months postpartum
    - Postpartum hemorrhage requiring blood transfusion or major surgery (randomization to 6 weeks postpartum)
    - Post-discharge maternal hospitalization (as an indicator to capture infection) through 6 months postpartum

- Safety
    - Hypophosphatemia (as measured by serum phosphate concentration <2.5 mg/dL) (6 weeks postpartum, 6 months postpartum if hypophosphatemia at 6 weeks postpartum)
    - Short-term safety outcomes: SAEs (randomization to 6 weeks postpartum)
    - All safety outcomes: SAEs (randomization to 6 months postpartum)

Infant

- Neonatal/infant mortality (randomization to 6 months postpartum)
- Post-discharge neonatal/infant hospitalization through 6 months postpartum

- Exclusive breastfeeding (6 weeks postpartum, 3 months postpartum, 6 months postpartum), based on WHO/UNICEF definition[32] that measure exclusive feeding with breast milk during the previous day

5.7 Exploratory Endpoints

Secondary endpoints will also be used as endpoints for exploratory objectives.

5.8 Stratification, Randomization, and Blinding

Postpartum women found eligible who provide consent to study participation will be individually randomized between 6-48 hours post-delivery and allocated 1:1 to one of two arms (Arm 1: IV iron; Arm 2: oral iron). A computer algorithm generated by the Global Network Data Coordinating Center (DCC) will create the random assignment to one of the treatment arms based on randomly permuted block design with randomly varied block sizes. Randomization will be stratified by site. The block sizes will be known only by the DCC personnel.

Due to the nature of the study intervention, the protocol study team, international principal investigator (iPI), site staff and participants will be unmasked to the assigned study intervention. Lab personnel will be masked to the assigned study intervention until assays for samples collected after randomization are complete.

5.9 Data Collection Procedures

Data will be collected at baseline, 6-week, and 6-month visits using a combination of participant questionnaires completed with the participant via interviewer face-to-face interviews as well as hospital record review by trained study staff. In addition to the above planned in-person study visits, one 3-month postpartum telephone follow-up will take place to complete a check-in with participants to minimize loss to follow-up at the 6-month visit. Participants will be considered lost to follow-up if they are unresponsive to study staff follow-up during a 6-month window. Windows for these study visits are detailed in the study Manual of Procedures (MOP).

5.10 Study Duration

The length of the study being proposed is approximately 30 months, based on the time required for the various study activities described below.

- After funding notification, a preparatory period of up to 6 months will be used by Global Network partners to provide community sensitization of the project and to obtain ethical and regulatory approvals required before study recruitment can begin. All financial agreements will be established during this time. Sites will also obtain needed supplies – e.g., the oral and IV iron interventions (plus folic acid supplements), supplies for IV infusions and sample collections, and Hemocue® instrumentation.
- The DCC will work with each site to obtain the IV iron formulation to be administered to women in the IV iron arm, oral iron tablets to be provided to the women in the oral iron arm, and folic acid to be given to all women as per WHO guidelines. The products will be procured in India and shipped to each site except Pakistan who will source them from local manufacturers/distributors which have a Good Manufacturing Practices (GMP) designation by the FDA.

- Time will be devoted to refining data collection and developing case report forms to support the various analyses planned for this study. The DCC will be responsible for developing an electronic data system for data entry and storage. Data collection and research procedures will be detailed in a comprehensive Manual of Operations. Intensive training of IV iron infusion teams during centralized training, as well as training of research teams from each site in all study procedures will also occur.
- Once an international site has obtained all needed ethical and regulatory approvals, procured necessary supplies, completed necessary training, and met specified readiness criteria, a site can initiate recruitment. Considering that every Global Network international partner has identified a research area with close to or over 3,000 deliveries per year, the sites should take no more than one year to recruit, randomize and treat eligible women per the protocol. Some variation in the pace of recruitment is to be expected due to variable anemia rates among the sites.
- Since each participant will be followed and assessed at 6 weeks and at 6 months postpartum, a 6-month period will be required after the last participant is recruited to complete data collection. The primary endpoint will be available 6 weeks after the last participant is randomized and treated. Validation and data quality checks will begin during this follow up period, as will planning for publications and other forms of dissemination.
- It is estimated that up to 6 months will be needed to complete validation and quality checks of the data, analyze data, issue findings, and prepare the manuscript for reporting on the primary endpoint. Study closure will occur once all essential research tasks are completed. However, the preparation of secondary manuscripts and dissemination of findings by other means could continue beyond study closure.

6 Study Drugs

6.1 Ferric carboxymaltose (FCM)

Participants randomized to the IV iron arm will receive a single-dose infusion of IV FCM, to be initiated between 6-48 hours after delivery. Following completion of the intravenous administration, all participants receiving the IV iron must be monitored for at least 30 minutes for any potential reaction to the infusion.

At 6 weeks postpartum, serum Hb will be assessed. Participants with serum Hb <7.0 g/dL at 6 weeks postpartum will be defined as treatment failures and referred to their physician for additional care.

6.1.1 Dosage, Preparation, and Administration

Ferric carboxymaltose (FCM) 50 mg iron/mL will be in a solution of 20 mL vials for infusion, using a dosage of 20 mg elemental iron per kg body weight, up to a maximum of 1 g, in a single IV infusion over 20-30 minutes. The study Standard Operating Procedures (SOPs) include details regarding FCM preparation based on the participant's body weight.

6.1.2 Study Drug Procurement

The DCC will work with the Belagavi site to procure the IV iron formulation to be administered and shipped to all sites except Pakistan. The non-generic product is produced in Europe and will be sourced from manufacturers/distributors which have a Good Manufacturing Practices (GMP)

designation by the US Food and Drug Administration (FDA). The Pakistan site will procure the IV iron formulation in-country from a GMP-certified manufacturer, per study specifications.

Guidelines for discontinuing IV infusion will be provided in the study MOP and SOPs. Participants will not be required to withdraw from study if the IV infusion is discontinued.

6.2 Oral Iron

Participants randomized to the oral iron arm will receive 60 mg elemental iron twice daily. Treatment will be initiated between 6-48 hours after delivery and prior to discharge from the facility. After discharge, each participant will take a treatment dose of twice daily for 6 weeks postpartum.

At 6 weeks postpartum, serum Hb will be assessed.

- Participants with serum Hb <7.0 g/dL at 6 weeks postpartum will be defined as treatment failures and referred to their physician for additional care.
- Participants with serum Hb 7.0-11.9 g/dL at 6 weeks postpartum will receive two 60 mg oral iron tablets daily until 6 months postpartum.
- Participants with serum Hb >11.9 g/dL at 6 weeks postpartum will receive one 60 mg oral iron tablet.

The DCC will work with each site to procure the oral iron tablets to be provided to participants. The products will be sourced from manufacturers/distributors which have a GMP designation by the FDA.

6.3 Folic Acid

All randomized participants will receive 400 mcg of folic acid daily for 6 months postpartum.

The DCC will work with each site to procure the folic acid tablets to be provided to all randomized participants. The products will be sourced from manufacturers/distributors which have a GMP designation by the FDA.

6.4 Drug Adherence and Quality Assurance Monitoring

Participant adherence to postpartum use of oral iron and folic acid will be supported and monitored utilizing a three-pronged approach. Research personnel will impress upon the maternal participants (and family members as appropriate) the importance of taking the full course of oral iron supplements (and folic acid) as instructed using standardized education messages. Secondly, study staff will monitor the number of oral iron and folic acid pills remaining (and calculate number of pills presumably taken) at the 6-week and 6-month postpartum visits. Participants will not be withdrawn from the study regardless of adherence to oral iron or folic acid.

Under Title 21 of the Code of Federal Regulations (21CFR §312.62), the iPI will maintain adequate records of the disposition of the study drugs, including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed. Records for receipt,

storage, use, and disposition will be maintained by the site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed. All records regarding the disposition of the study drugs will be available for inspection.

Manufacturers of IV iron formulation to be employed for each site will have a GMP designation by the US FDA and a certificate of authenticity provided. Each site will adapt best practice guidelines for drug shipment and storage to the needs and infrastructure of their local environment. Study staff will be trained on the drug shipment and storage plan to ensure that best practices are maintained at all times. Drug stability information will be maintained throughout the study.

For quality assurance, a sample of IV iron and oral iron from each site will be randomly selected and tested for bioavailability at multiple time points during the study period at the DCC. A sample from each batch will be tested.

7 Statistical Considerations and Analytical Plans

This section briefly describes the statistical considerations and analytical plans that will be followed for this study. A statistical analysis plan (SAP) will also be developed and finalized prior to database lock. The SAP will include a detailed description of each analysis and will precede any analyses described in the section.

7.1 Analysis Populations

The following analysis populations will be used:

- Intention-to-Treat (ITT-LMIC) Population: All participants enrolled in the LMIC aggregate and who were randomized. All participant infants will also be included in this population. Analyses of this cohort will be conducted based on randomized treatment.
- Intention-to-Treat (ITT-Asian) Population: All participants enrolled in the South Asian sites and who were randomized. All participant infants will also be included in this population. Analyses of this cohort will be conducted based on randomized treatment.
- Intention-to-Treat (ITT-African) Population: All participants enrolled in the sub-Saharan African sites and who were randomized. All participant infants will also be included in this population. Analyses of this cohort will be conducted based on randomized treatment.
- Safety-LMIC Population: All participants included in the ITT-LMIC Population that receive any study drug during the study. All participant infants will also be included in this population. Analyses of this cohort will be conducted based on treatment received.
- Safety-Asian Population: All participants included in the ITT-Asian Population that receive any study drug during the study. All participant infants will also be included in this population. Analyses of this cohort will be conducted based on treatment received.
- Safety-African Population: All participants included in the ITT-African Population that receive any study drug during the study. All participant infants will also be included in this population. Analyses of this cohort will be conducted based on treatment received.

7.2 Statistical Hypotheses

All objectives in this trial will be addressed using two-sided hypothesis tests applied to the relevant analysis population and endpoint. For example, the null (H_0) and alternative (H_A) statistical hypotheses for the primary objective are as follows:

- H_0: The incidence of achieving a non-anemic state in women randomized to a single-dose infusion of IV iron is equal to women randomized to standard care with oral iron.
- H_A: The incidence of achieving a non-anemic state in women randomized to a single-dose infusion of IV iron is not equal to women randomized to standard care with oral iron.

This hypothesis will be separately tested in the ITT-LMIC Population, ITT-Asian Population, and ITT-African Population.

7.3 Analytical Plan

All statistical analyses will be performed by DCC biostatisticians. Data will be monitored for accuracy and completeness throughout the study. Analyses will only be performed after the database has been locked.

For descriptive summaries of study data, the following will be presented:

- Nominal/categorical measures will be summarized using frequencies and percentages.
- Interval or ratio scale measures will be summarized using means, standard deviations, medians, 95% confidence intervals (CIs), 25^{th} and 75^{th} percentiles, and ranges.
- Ordinal measures will be summarized depending on the number of levels. An ordinal measure with five levels or fewer will be summarized as a nominal measure. An ordinal measure with more than five levels will be summarized as an interval or ratio scale measure.

Unless otherwise specified, each objective will be addressed by fitting separate statistical models to each endpoint in the ITT-LMIC Population, ITT-Asian Population, and ITT-African Population. To account for multiple comparisons arising from performing hypothesis tests in 3 analysis populations for each endpoint, a Bonferroni-corrected significance level of 0.05/3=0.0167 will be used for hypothesis testing to preserve an overall family-wise Type I error rate of 0.05. To ensure a joint CI of 95%, 98.33% simultaneous CIs will also be constructed.

Unless otherwise specified, each objective that will be assessed using an endpoint measured at one timepoint only will be addressed using a generalized linear model specified with a distribution (e.g., Normal, multinomial, etc.) and link function (e.g., identify, log, etc.) appropriate to each outcome. Each model will include a fixed effect for treatment arm and site.

Unless otherwise specified, each objective that will be assessed using an endpoint measured at multiple timepoints will be addressed using a generalized linear mixed-effects model (GLMM) specified with a distribution (e.g., Normal, multinomial, etc.) and link function (e.g., identify, log, etc.) appropriate to each outcome. Each model will include a fixed effect for treatment arm, site, timepoint (treated categorically), a two-way interaction between treatment arm and timepoint as well as a random effect for participant to allow estimation of the intervention effect at each timepoint. Various covariance structures (e.g., unstructured, compound symmetry, etc.) will be

evaluated by comparing information criteria across the models with different covariance structures and selecting the covariance structure that produces the best fit.

7.3.1 Primary Analyses of Primary Objective

As described previously, the primary hypothesis will be tested in all participants with an evaluable primary endpoint in each of the three populations using a Bonferroni-corrected two-sided significance level of 0.0167: 1) ITT-LMIC Population; 2) ITT-Asian Population; and 3) ITT-African Population. In each analysis, the incidence of non-anemia at 6 weeks will be compared between the two treatment arms using a generalized linear model with a Poisson distribution and log link. The model will include fixed effects for treatment arm and site. Such a model will allow estimation of the adjusted incidence risk ratio of non-anemia at 6 weeks between the IV iron arm and the oral iron arm, as well as the associated 98.33% CIs and p-values.

7.3.2 Supportive Analyses of Primary Objective

Separate subgroup analyses of the primary endpoint will also be performed in each of the three populations by including an interaction between treatment arm and the following variables:

- Region
- Mode of delivery (cesarean versus vaginal)
- Baseline hemoglobin (g/dL)
- Baseline serum ferritin concentration (mg/dL)
- Baseline in serum sTfR concentration (mg/dL)

For categorical variables, each analysis will allow estimation of the adjusted incidence risk ratio (and 98.33% CI) of non-anemia at 6 weeks between the IV iron arm and the oral iron arm within each sub-group. For continuous variables, each analysis will allow estimation of the adjusted incidence risk ratio (and 98.33% CI) of non-anemia at 6 weeks between the IV iron arm and the oral iron arm at the 25^{th}, 50^{th}, and 75^{th} percentile. Evidence of effect modification will only be concluded if the two-way interaction is statistically significant at the 0.0167 level..

Because use of antenatal care may differ by site, it is also possible that the primary endpoint is highly correlated amongst participants randomized at the same site. To further explore this, a sensitivity analysis of the primary endpoint in each of the 3 populations will be conducted that accounts for correlation amongst participants at the same site. In this case, a generalized linear mixed model will be fit to the primary endpoint that includes a fixed effect for treatment arm and a random effect for site.

To assess the impact of loss to follow-up, a sensitivity analysis will also be conducted using multiple imputation to include all randomized participants (regardless of whether or not each participant has an evaluable primary endpoint) in the analysis. Further details regarding the strategy for multiple imputation will be provided in the SAP.

To assess the impact of the change in WHO guidelines for adjustment of Hb adjustments for altitude in Guatemala, a sensitivity analyses will be conducted that use the WHO 2011 adjustment of -0.5 g/dL across all measurements and the WHO 2024 adjustment of -1.1 g/dL across all measurements.

7.3.3 Analyses of the Key Secondary Objectives

As described previously, Key Secondary Objectives #1-#4 will be tested in all participants with a corresponding evaluable secondary endpoint in each of the three populations using a Bonferroni-corrected two-sided significance level of 0.0167: 1) ITT-LMIC Population; 2) ITT-Asian Population; and 3) ITT-African Population.

To control the overall family-wise Type I error rate of 0.05 across the primary and set of key secondary objectives, a fixed sequence hierarchical testing strategy will be applied. Specifically:

- If there is evidence of statistical significance of the Primary Objective for at least one of the three populations, then Key Secondary Objective #1 will be formally tested in each of the three populations using a Bonferroni corrected two-sided significance level of 0.0167.
- If there is no evidence of statistical significance of the Primary Objective for at least one of the three populations, then no further analyses of the remaining key secondary objectives evaluated in each of the three populations will be performed.

A similar strategy will be applied to Key Secondary Objectives #2, #3 and #4 (in this order) until there is either no evidence of statistical significance or all hypothesis tests associated with Key Secondary Objectives #1, #2, #3, and #4 are performed.

Table 4 provides a summary of the endpoints that will be used to address each key secondary objective as well as the corresponding model and estimates that will be obtained from each model. While corresponding 98.33% CIs will always be reported, p-values will only be reported if formal hypothesis testing can be conducted as outlined in the hierarchical testing procedure described previously.

Table 4: Key Secondary Objectives and Endpoints

Objective	Endpoint	Model	Estimate
Key Secondary Objective #1	Change from baseline in serum Hb concentration (g/dL) at 6 weeks postpartum	GLMM[1,4] • Distribution: Normal • Link: Identity	Adjusted mean difference in the change from baseline in serum Hb concentration at 6 weeks postpartum between participants randomized to IV iron and participants randomized to oral iron
Key Secondary Objective #2	Maternal depression (as measured by EPDS score > 10) at 6 weeks postpartum	Generalized linear model[2,3] • Distribution: Poisson • Link: Log	Adjusted incidence risk ratio of maternal depression at 6 weeks postpartum between participants randomized to IV iron and participants randomized to oral iron
Key Secondary Objective #3	Change from baseline in serum Hb concentration (g/dL) at 6 months postpartum	GLMM[1,4] • Distribution: Normal • Link: Identity	Adjusted mean difference in the change from baseline in serum Hb concentration at 6 months postpartum between participants randomized to IV iron and participants randomized to oral iron
Key Secondary Objective #4	Maternal depression (as measured by EPDS score > 10) at 6 months postpartum	Generalized linear model[2,3] • Distribution: Poisson • Link: Log	Adjusted incidence risk ratio of maternal depression at 6 months postpartum between participants randomized to IV iron and participants randomized to oral iron

1. Model will include fixed effects for treatment arm, site, timepoint (treated categorically), a two-way interaction between treatment arm and timepoint as well as a random effect for participant.
2. As referrals from the screening assessment at 6 weeks postpartum could introduce bias into the intervention effect estimation at 6 months, maternal depression (as measured by EPDS score > 10) at 6 weeks postpartum and 6 months postpartum will be analyzed separately. To adjust the effect of IV iron on maternal depression at 6 months postpartum by maternal depression at 6 weeks postpartum, a marginal structural model will be fit using inverse probability weighting to allow estimation of the causal effect of IV iron on maternal depression at 6 months postpartum. Additional details of this approach will be provided in the SAP.
3. Model will include fixed effects for treatment arm and site.
4. Secondary analyses will be conducted that include serum CRP and AGP at 6 weeks postpartum and 6 months postpartum as covariates.

7.3.4 Analyses of the Other Secondary Objectives

As described previously, Secondary Objectives #5-#9 will be tested in all participants with a corresponding evaluable secondary endpoint in each of the three populations using a Bonferroni-corrected two-sided significance level of 0.0167: 1) ITT-LMIC Population; 2) ITT-Asian Population; and 3) ITT-African Population. Secondary Objective #9 will be tested in all participants in each of the following populations: 1) Safety-LMIC Population; 2) Safety-Asian Population; and 3) Safety-African Population.

Table 5 provides a summary of the endpoints that will be used to address each secondary objective as well as the corresponding model and estimates that will be obtained from each model. While corresponding 98.33% CIs will be reported, no approach to account for multiple endpoints addressing each objective will be made and so no p-values will be reported.

Table 5: Other Secondary Objectives and Endpoints

Objective	Endpoint	Model	Estimate
Secondary Objective #5	FSS-5R score > 4 at 6 weeks postpartum and 6 months postpartum	GLMM[2] • Distribution: Poisson • Link: Log	Adjusted risk ratio of the FSS-5R score > 4 at 6 weeks postpartum and 6 months postpartum between participants randomized to IV iron and participants randomized to oral iron
	MIBS score ≥ 4 at 6 weeks postpartum	Generalized linear model[1] • Distribution: Poisson • Link: Log	Adjusted risk ratio pf the MIBS score ≥ 4 at 6 weeks postpartum between participants randomized to IV iron and participants randomized to oral iron
	WHOQOL-BREF Overall Perception of Quality of Life score at 6 weeks postpartum and 6 months postpartum	GLMM[2] • Distribution: Normal • Link: Identity	Adjusted mean difference in the WHOQOL-BREF score at 6 weeks postpartum and 6 months postpartum between participants randomized to IV iron and participants randomized to oral iron
	WHOQOL-BREF Overall Perception of Health score at 6 weeks postpartum and 6 months postpartum		
	WHOQOL-BREF Physical Domain Score at 6 weeks postpartum and 6 months postpartum		
	WHOQOL-BREF Psychological Domain Score at 6 weeks postpartum and 6 months postpartum		
	WHOQOL-BREF Social Relationships Domain Score at 6 weeks postpartum and 6 months postpartum		
	WHOQOL-BREF Environment Domain Score at 6 weeks postpartum and 6 months postpartum		
Secondary Objective #6	Change from baseline in serum ferritin concentration (mg/dL) at 6 weeks postpartum and 6 months postpartum	GLMM[2,3] • Distribution: Normal • Link: Identity	Adjusted mean difference in the change from baseline in serum ferritin concentration at 6 weeks postpartum and 6 months postpartum between participants randomized to IV iron and participants randomized to oral iron
	Change from baseline in serum sTfR concentration (mg/dL) at 6 weeks postpartum and 6 months postpartum	GLMM[2,3] • Distribution: Normal • Link: Identity	Adjusted mean difference in the change from baseline in serum sTfR concentration at 6 weeks postpartum and 6 months postpartum between participants randomized to IV iron and participants randomized to oral iron

Objective	Endpoint	Model	Estimate
	Non-anemic state (Hb ≥11.5 g/dL) at 6 weeks postpartum and 6 months postpartum	GLMM[2] • Distribution: Poisson • Link: Log	Adjusted incidence risk ratio of non-anemia at 6 weeks postpartum and 6 months postpartum between participants randomized to IV iron and participants randomized to oral iron
	Non-anemic state (Hb ≥12.0 g/dL) at 6 weeks postpartum and 6 months postpartum	GLMM[2] • Distribution: Poisson • Link: Log	Adjusted incidence risk ratio of non-anemia at 6 weeks postpartum and 6 months postpartum between participants randomized to IV iron and participants randomized to oral iron
	Anemic state at 6 weeks postpartum • No anemia: Hb ≥11 g/dL • Mild anemia: Hb >9.9 g/dL and <11 g/dL • Moderate anemia: Hb 7.0-9.9 g/dL • Severe anemia: Hb <7.0 g/dL Anemic state at 6 months postpartum • No anemia: Hb ≥12 g/dL • Mild anemia: Hb >9.9 g/dL and <12 g/dL • Moderate anemia: Hb 7.0-9.9 g/dL • Severe anemia: Hb <7.0 g/dL	GLMM[2] • Distribution: Multinomial • Link: Cumulative logit	Adjusted odds ratio of achieving a less severe anemic state at 6 weeks postpartum and 6 months postpartum between participants randomized to IV iron and participants randomized to oral iron
	Change from baseline in anemic state at 6 weeks postpartum and 6 months postpartum • Better: Hb >9.9 g/dL • No change: Hb 7.0-9.9 g/dL • Worse: Hb <7.0 g/dL	GLMM[2] • Distribution: Multinomial • Link: Cumulative logit	Adjusted odds ratio of improvement in anemia at 6 weeks postpartum and 6 months postpartum between participants randomized to IV iron and participants randomized to oral iron
Secondary Objective #7	Maternal mortality between randomization and 6 months postpartum (yes/no)	Generalized linear model[1] • Distribution: Poisson • Link: Log	Adjusted relative risk of maternal mortality between participants randomized to IV iron and participants randomized to oral iron
	Post-discharge blood transfusion through 6 months postpartum (yes/no)	Generalized linear model[1] • Distribution: Poisson • Link: Log	Adjusted relative risk of post-discharge blood transfusion between participants randomized to IV iron and participants randomized to oral iron
	Postpartum hemorrhage requiring blood transfusion or major surgery between randomization and 6 weeks postpartum (yes/no)	Generalized linear model[1] • Distribution: Poisson • Link: Log	Adjusted relative risk of postpartum hemorrhage between participants randomized to IV iron and participants randomized to oral iron
	Post-discharge maternal hospitalization though 6 months postpartum (yes/no)	Generalized linear model[1] • Distribution: Poisson • Link: Log	Adjusted relative risk of post-discharge maternal hospitalization between participants randomized to IV iron and participants randomized to oral iron
Secondary Objective #8	Neonatal/infant mortality between randomization and 6 months postpartum (yes/no)	Generalized linear model[1] • Distribution: Poisson • Link: Log	Adjusted relative risk of neonatal/infant mortality between participants randomized to IV iron and participants randomized to oral iron
	Post-discharge neonatal/infant hospitalization through 6 months postpartum (yes/no)	Generalized linear model[1] • Distribution: Poisson • Link: Log	Adjusted relative risk of post-discharge neonatal/infant hospitalization between participants randomized to IV iron and participants randomized to oral iron
	Exclusive breastfeeding (yes/no) at 6 weeks postpartum, 3 months postpartum, and 6 months postpartum	GLMM[2] • Distribution: Poisson	Adjusted relative risk of exclusive breastfeeding at 6 weeks postpartum, 3 months postpartum,

Objective	Endpoint	Model	Estimate
		• Link: Log	and 6 months postpartum between participants randomized to IV iron and participants randomized to oral iron
Secondary Objective #9	Hypophosphatemia (as measured by serum phosphate concentration <2.5 mg/dL) at 6 weeks postpartum	Generalized linear model[1] • Distribution: Poisson • Link: Log	Adjusted relative risk of hypophosphatemia at 6 weeks postpartum between participants randomized to IV iron and participants randomized to oral iron
	Hypophosphatemia (as measured by serum phosphate concentration <2.5 mg/dL) at 6 months postpartum (if hypophosphatemia at 6 weeks postpartum)	Generalized linear model[1] • Distribution: Poisson • Link: Log	Adjusted relative risk of hypophosphatemia at 6 months postpartum between participants randomized to IV iron and participants randomized to oral iron (amongst those with hypophosphatemia at 6 weeks postpartum)
	Short-term safety outcomes: Pre-defined groupings of SAEs that occur between randomization and 6 weeks postpartum will be defined in the SAP. Using these pre-defined groups, separate short-term safety endpoints will be defined for each participant by the occurrence of at least 1 short SAE group.	Generalized linear model (per endpoint)[1] • Distribution: Poisson • Link: Log	Adjusted relative risk of the occurrence of at least 1 short-term SAE group between participants randomized to IV iron and participants randomized to oral iron
	All safety outcomes: Pre-defined groupings of SAEs that occur between randomization and 6 months postpartum will be defined in the SAP. Using these pre-defined groups, separate safety endpoints will be defined for each participant by the occurrence of at least 1 SAE group.	Generalized linear model (per endpoint)[1] • Distribution: Poisson • Link: Log	Adjusted relative risk of the occurrence of at least 1 SAE group between participants randomized to IV iron and participants randomized to oral iron

1. Model will include fixed effects for treatment arm and site.
2. Model will include fixed effects for treatment arm, site, timepoint (treated categorically), a two-way interaction between treatment arm and timepoint as well as a random effect for participant.
3. Secondary analyses will be conducted that include serum CRP and AGP at 6 weeks postpartum and 6 months postpartum as covariates.

7.3.5 Analyses of Exploratory Objectives

Analyses of the exploratory objectives will be described in data analysis plans that are separate from the SAP that will be used to describe the analyses of the primary and secondary objectives.

7.3.6 Descriptive Analyses

Baseline characteristics will be compared between treatment arms in each of the analysis populations (ITT-LMIC, ITT-Asian, ITT-African, Safety-LMIC, Safety-Asian, Safety-African) using descriptive statistics. Each nominal/categorical variable will be summarized within each treatment arm and overall using a frequency and a percentage. The distribution of each nominal/categorical variable will be compared between the arms using a Pearson's chi-squared test or Fisher's exact test (as appropriate). Interval or ratio scale variables will be summarized within each arm and overall using a mean, standard deviation, median, and inter-quartile range. The distribution of each interval or ratio scale variable will be compared between treatment arms using a Wilcoxon Rank Sum Test. To preserve an overall family-wise Type I error rate of 0.05, a Bonferroni corrected significance level of 0.05/3=0.0167 will be used.

7.4 Sample Size Considerations

Sample size was determined based on the primary objective using the following assumptions:

- Because the primary objective will be addressed by separately testing the intervention effect on the incidence of non-anemia in three populations (ITT-LMIC, ITT-Asian, and ITT-African Populations), the sample size must be large enough within each of the 3 populations to ensure at least 90% power in detecting the intervention effect in each population based on a two-sided Bonferroni-corrected significance level of 0.0167. Additionally, to maximize the generalizability of the study, an approximately equal number of participants must be enrolled at each site. Under these assumptions, because the ITT-African Population has the least number of sites (3) compared to the other two populations (ITT-LMIC Population has 8 sites, ITT-Asian Population has 4 sites), the primary driver of the site-specific sample size is the hypothesis test that will be conducted in the ITT-African Population.
- In the Tanzania study (see Section 4), 51% of participants in the oral iron arm had Hb >11.5 g/dL at 6 weeks postpartum. Because the primary endpoint for this trial uses a cutoff of ≥11 g/dL, we will assume that in participants randomized to the oral iron arm, the percentage of participants with non-anemia at 6 weeks postpartum will be 60%.
- A clinically meaningful effect size is given by an incidence risk ratio of achieving a non-anemic state between the IV iron arm and oral iron arm of approximately 1.15. Assuming that 60% of participants randomized to the oral iron arm achieve a non-anemic state at 6 weeks postpartum, such an effect size is equivalent to 69% of participants randomized to the IV iron arm achieving a non-anemic state at 6 weeks postpartum.
- Software: PASS 2023 (Version 23.0.1)
    - Procedure: Tests for Two Proportions with the following options specified:
        - Power Calculation Method: Normal Approximation
        - Alternative Hypothesis: Two-Sided
        - Test Type: Z-Test C.C. (Pooled)
        - Group Allocation: Equal (N1=N2)

Under the above assumptions, a sample size of 784 participants per arm (i.e., total sample size of 1,568 participants with an evaluable primary endpoint) in the ITT-African Population is needed to detect an incidence risk ratio of achieving a non-anemic state between the IV iron arm and oral iron arm of 1.15 with at least 90% power. Given that there are 3 sites in the ITT-African Population, a total of 523 participants with an evaluable primary endpoint will be required in each of the 8 sites. Note that this sample size will be sufficient to detect an incidence risk ratio of at least 1.10 in the ITT-LMIC Population (equivalent to at least 66% of participants randomized to the IV iron arm achieving a non-anemic state at 6 weeks postpartum) and an incidence risk ratio of at least 1.13 in the ITT-Asian Population (equivalent to at least 68% of participants randomized to the IV iron arm achieving a non-anemic state at 6 weeks postpartum) with 90% power.

While the ability to retain participants for a period of 6 weeks has been well established in previous Global Network common protocols implemented in these sites (i.e., <5% loss to follow-up), we will conservatively assume an approximately 12-13% loss to follow-up, resulting in a total of 600 participants to be randomized per site. Consequently, 4,800 women will be enrolled in the study with each of eight participating sites responsible for enrolling and following 600 women to 6 months postpartum.

7.5 Interim Analyses

An interim analysis will not be performed to assess efficacy or futility because stopping this trial early in any of the 3 analysis populations (ITT-LMIC, ITT-Asian, ITT-African) due to evidence of efficacy or futility in the corresponding populations will substantially limit our ability to assess regional differences, which is of primary interest in this trial.

8 Human Subjects

8.1 Potential Risks and Benefits

Side effects of IV iron are rarely associated with serious consequences. Most adverse drug reactions resulting from use of the available IV iron formulations, either during clinical trials or post-marketing experience, appear in the uncommon column of AE tables that are typically found on Websites providing information on the specific drug formulation (the US FDA, the Website of the Electronic Medicines Compendium, and others).[32,33] Risk of uncommon events, based upon event to drug administrations, for two of the newer formulations to be used in this trial was reported as ≥1/1,000 to <1/100), while common events occurred in ≥1/100 to <1/10 administrations. For the two formulations used in two states in India for a trial which began in March 2020, the list of either uncommon or common drug reactions for the formulations being used included flushing, sweating, blurred vision, nausea, injection/infusion site reactions headache, hypophosphatasemia, dizziness, fatigue, tachycardia, hypotension, hypertension, abdominal pain, vomiting, dyspepsia, constipation, diarrhea, dyspnea, pruritus, urticaria, dermatitis, myalgia, arthralgia, muscle spasms, pain in extremity, back pain, pyrexia, chills/shivering, chest pain, edema peripheral, infection, local phlebitis reaction, and skin exfoliation.[34-40] Anaphylaxis, a severe hypersensitivity (allergic) reaction that may include difficult breathing, itching, or a rash over the entire body, may occur with all parenteral iron preparations. However, this event is generally considered a rare adverse drug reaction with risk of occurrence. Examples of other drug reactions characterized as rare are loss of consciousness, anxiety, phlebitis, syncope, presyncope, bronchospasm (including wheezing), flatulence, arrhythmia, angioedema, pallor, face edema, malaise and influenza like illness.

A complete list of adverse drug reactions associated with the study IV iron formulation will be included in the Manual of Operations for this study. An article published in 2006 indicated that reported adverse drug events for the single-dose infusions of IV iron formulations had been decreasing over time and that the overall rate was “extremely low” at about 38 events per million.[36] Further, over 100 published papers confirm the rarity of major complications associated with IV iron use.

A recent UpToDate article, *Treatment of Iron Deficiency Anemia in Adults*, reviews treatment options, discusses the advantage of modern IV iron products and provides practical tips for reducing the risks of allergic and infusion reactions.[34]

Side effects typically listed for oral iron include the following: nausea or upset stomach, diarrhea, faintness, vomiting, constipation, and black stools. These side effects may not be considered serious if occurring only periodically, but many studies indicate that some of these are quite common and can affect up to 70% of those for whom oral iron is prescribed. The oral iron formulation most often recommended is ferrous sulfate.[40] Side effects are often cited as the reason for a high percentage of those prescribed oral iron failing to adhere to instructions for taking the recommended tablets or not taking them for the recommended period of time. Thus,

perhaps one of the more concerning issues with oral iron is that it is not taken as prescribed. Additionally, a portion of those that take oral iron per instructions experience side effects and don't tolerate the drug well; consequently, such symptoms may cause dietary changes that result in less-than-ideal weight gain during pregnancy or decreased compliance of the supplement regimen. Further, there is insufficient data to determine whether provision of oral iron given to moderately anemic women in the postpartum period results in improved outcomes.

While the follow-up period for study oversight will generally assume that most women will return for postpartum and follow-up care, it is recognized that women, in non-study situations, often do not return for such visits despite their importance in reducing and identifying postpartum complications and subsequent health risks.

8.2 Procedures for Protecting Against or Minimizing Potential Risks

A study consultant and member of the Thomas Jefferson University (TJU) research team, Dr. Michael Auerbach, has authored several articles comparing IV iron formulations. In one of these articles, he commented that newer formulations with carbohydrate shells which bind elemental iron more tightly and allow slower release are much safer than older formulations; consequently, SAEs have been marginal to absent in prospective trials. Minor reactions (such as mild arthralgia/myalgia of the chest or flank or facial flushing) abate without the need for therapy.[41] In a 2017 article, he stated that evidence indicates that single-dose infusion formulations currently available in the US are "all safe and effective and there are no major, clinically important differences.[36] The preponderance of recent reviews on the use of IV iron indicate that SAEs are rare, and that infusion reactions are not common when the newer single-dose infusion formulations are used. However, the very low risk of severe infusion reaction should not be ignored. A remedy for minimizing risk has been proposed by Gomez-Ramirez, Shander, Spanh, Auerbach, et al: "As preventive measures, prior to the infusion, staff should inform all patients about infusion reactions and identify those patients with increased risk of hypersensitivity or contraindications for IV iron. Infusion should be initiated at a low rate for a few minutes. In the event of a reaction, if required, the very first step should be the immediate cessation of the infusion, followed by evaluation of severity and treatment. Rampton, et al. have also developed recommendations for management and prevention of hypersensitivity reactions to IV iron that include meticulous observation, prompt recognition and appropriate response based upon accurate estimate of severity.[37]

Prior to the provision of IV iron treatments, those administering infusions will receive comprehensive training that will include information on how to recognize signs, treat a minor infusion reaction as well as those related to a rare severe or anaphylactic event. It is important that the nature of a reaction be understood so the most appropriate action will be taken. IV iron, for purposes of the study, will be administered at the hospital/facility where childbirth occurs, and the infusion team will be specifically trained for the study and determined competent to fulfill responsibilities before study recruitment begins.

The facilities must have all appropriate supplies for resuscitation (consistent with recommendations for product use). Prior to an infusion of IV iron, an explanation of risks and benefits as has previously described during the consent process and in the consent form (Appendix B) will be given to the participant. Despite being randomized, any study participant has a right to refuse treatment, withdraw from the trial, and nevertheless receive standard care. Additionally, a participant's physician may elect to withdraw a participant from the study for any medical concern.

Given the high prevalence of endemic malaria in the three sub-Saharan African sites, a RDT for malaria will be administered 6-48 hours post-delivery, and at 6 weeks and 6 months postpartum. If the test is positive at consent, the woman will not be eligible for enrollment but will be referred for treatment using local standard of care. If positive and untreated at either of the other timepoints, she will be referred for treatment using local standard of care and results documented.

8.3 Study Safety Monitoring

8.3.1 Reporting Adverse Events

Infant deaths as well as side effects (mild, expected) and other dosing reactions to study drug that occur after randomization and on or before 6 months postpartum will be recorded and reported to the DSMB bi-annually. However, no events will be reported in this trial as AEs other than those events that satisfy the criteria for SAE reporting (see Section 8.3.2).

8.3.2 Reporting Serious Adverse Events

SAEs will be monitored continuously using a form that will be required for any event that occurs in maternal participants after randomization and on or before 6 months postpartum and meets the following criteria:

- Results in maternal death;
- Is life-threatening;
- Requires hospitalization or prolongs existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Any other serious or unexpected AE that the study investigator(s) feels should be reported.

The occurrence of any of these events will trigger completion of the SAE Form.

8.3.3 Method and Timing for Reporting Serious Adverse Events

The International Principal Investigator (iPI) must report the following SAEs by emailing or transmitting a copy of the form to the DCC as follows:

<u>Within 48 hours of iPI's notification of the event:</u>

- All deaths;
- All SAEs with a definite or probable relationship to the intervention.

<u>Within 7 days of iPI's notification of the event:</u>

- All life-threatening events;
- All SAEs with a possible relationship to the intervention;

- All emailed or faxed forms should also be entered into the Data Management System (DMS) and transmitted within 7 days as a back-up to ensure no SAE is missed.

Additional reporting procedures include:

- The DCC will forward all SAEs to the US-based PI and NICHD for further assessment of relationship to study intervention. The PI and iPI will be responsible for reporting to their respective Institutional Review Board and other regulatory authorities per their institutional policy.
- The DCC will be responsible for reporting SAEs to the DSMB bi-annually at a minimum. The frequency of reporting to the DSMB may be increased if the reported events or interim data reviews by the DSMB indicate that more frequent safety monitoring is needed.
- Any SAE considered unrelated to the intervention is not required to be reported in an expedited manner. These events should be entered into the DMS and transmitted per routine procedures.

In addition, study forms will document infant deaths as well as side effects and other dosing reactions that occur after randomization and on or before 6 months postpartum as documented in the study MOP.

8.4 Data Monitoring Plan and Stopping Rules

8.4.1 Data Monitoring

All the sites will report data to the DCC, located at Research Triangle Institute International (RTI). The data will be used to evaluate protocol adherence and site performance (e.g., recruitment, loss to follow-up, data quality). The DCC will provide standardized progress reports to NICHD and the site investigators on a monthly basis to monitor outcome variables, side effects and other dosing reactions, and SAEs.

Oversight of the trial will be handled by two principal groups with different focuses:

1) **Data and Safety Monitoring Board (DSMB):** This trial will utilize the Global Network DSMB, an independent group which has been appointed by NICHD and is comprised of experts in statistics, ethics, perinatal and obstetric care in LMICs. For the purpose of this trial, an additional expert may be appointed, as needed.

   The DSMB will meet at a minimum twice per year to review study progress as well as safety measures, with additional meetings held as determined by DSMB members. Reports generated by the DSMB, including SAE and other safety or data concerns, will be provided to the Foundation as they are available. The Data Safety Monitoring Plan will be fully developed, reviewed, and approved prior to the launch of the trial. Additionally, it is anticipated that adjudicators from within the Global Network with appropriate expertise will review SAEs to assess relationship to the study drug.

   As outlined previously, an interim analysis will also be performed by the DCC and the results of the analysis will be reviewed by the DSMB. Based upon their review, the DSMB will either

recommend stopping the study early due to evidence of efficacy or futility of the primary objective or to continue the study as planned. This recommendation may either be accepted or rejected by the PRIORITY Trial Working Group and NICHD.

2) **PRIORITY Trial Working Group:** The study will be overseen by the PI, Dr. Richard Derman, Associate Provost for Global Affairs at TJU, along with other faculty and TJU consultants having relevant content expertise. The PRIORITY Trial Working Group will be organized to include representatives from TJU, RTI, and the PIs and iPIs associated with the Global Network for Women's and Children's Health Research (see Appendix B).

8.4.2 Participant Stopping Rules and Withdrawal Criteria

Participants may be prematurely terminated from the study for the following reasons:

- The participant elects to withdraw consent/assent from all future study activities, including follow-up.
- The participant is "lost to follow-up" as defined in the study MOP (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
- The participant dies.
- The participant experiences recurrent symptoms that may or may not require medical intervention but prevent the participant from tolerating the study therapy regimen.
- The participant's continued participation in the study is assessed by the iPI to no longer be in the best interest of the participant or to jeopardize the safe conduct of the study.

Participants who withdraw or are withdrawn will not be replaced.

8.4.3 Study Stopping Rules

No formal study stopping rules will be used in this trial.

9 Trial Implementation

9.1 Trial Coordination

RTI International will serve as the DCC for this study and perform in a similar capacity as it does for the NICHD Global Network for Women's and Children's Health Research. RTI will provide statistical leadership in terms of study design, analyses, and quality assurance and facilitating DSMB oversight. RTI will also be responsible for study drug procurement, and randomization scheme. In addition, RTI will develop and harmonize study data collection procedures and develop and manage the electronic DMS, including an operational plan that details the data-related duties of the study partners and discusses the interface with the DMS.

9.2 Study Implementation and Community Sensitization

Given historically well-developed community engagement, the iPIs will oversee implementation of the trial at their site per Global Network procedures. Global Network sites often engage community health workers to assist in the implementation of a study. Such community health workers will be incorporated into this study as they often accompany women to delivery and will help to ensure adherence to the subsequent study visits. Given the community engagement,

historically, the sites have all had high (>95%) follow-up rates for long-term follow-up for other Global Network studies. Each site will put into place strategies to ensure maximum follow-up rates which will be closely monitored both at the site and by the central team.

Sites have additionally engaged in community sensitization activities to ensure that leaders and residents associated with communities in a Global Network research area are aware of a study to be implemented and its purpose. It is beneficial that such activities are a component of this study so that women have access to study information before they are admitted to a facility for delivery. Advance knowledge about the study may increase the probability that a woman, if eligible, will consent to study participation.

10 Publications and Dissemination

It is a goal of the study to disseminate the findings from this trial as efficiently and widely as possible so that the results may inform public health efforts both in each of the sites as well as globally. The primary paper will be led by the study PI, with authorship from the participating sites and the DCC, in accordance with the policy and procedures of the Global Network. Secondary papers may be proposed by co-investigators and following review and approval from the PRIORITY Steering Committee analyses supported by the DCC. It is also expected that co-investigators will present the trial's design, methods and findings to Ministry of Health, professional groups, and other public venues. All presentations of trial results will be reviewed according to Global Network policies.

11 Concluding Remark

This is a relatively large trial to assess a new approach for reverting to a non-anemic state in the postpartum period (primary endpoint) and through 6 months postpartum. It has the advantage of involving experienced research partners strategically located in three continents, including sub-Saharan Africa and south Asia, allowing for assessment of regional differences. The Global Network partners have a strong track record of conducting large, complex trials with high quality data and study adherence. In addition, the Global Network partnership which leverages an existing research infrastructure allows for an efficient timeline to complete this important trial. Leveraging the Global Network partnerships for other major research efforts has impacted WHO policy and led to changes in the standard of care for women and infants in LMICs. Thus, there is high probability that this study can influence policy and ultimately lead to improved outcomes for delivering women.

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Appendix A Schedule of Events

	Labor & delivery	6 wk pp visit[1]	3 mo pp telephone call	6 mo pp visit	As needed
Screening	X				
• *Eligibility confirmation*[2]	X				
Consent	X				
Randomization	X				
IV Fe Administration	X				
Oral Fe BID	X	X			
Oral Folic Acid for 6 mo pp[3]	X	X			
Data Collection					
• *Medical history*	X				
• *Maternal serum Hb*	X	X		X	
• *Mode of delivery*	X				
• *Maternal hospital admissions*		X		X	
• *Maternal complications*		X		X	X
• *Maternal serum ferritin, sTfR, and inflammatory markers (CRP and AGP)*	X	X		X	
• *Maternal serum phosphate*		X		X[4]	
• *Malaria RDT (sub-Saharan African sites)*	X	X		X	
• *Oral Fe drug and folic acid compliance*		X		X	
• *Maternal Fatigue Severity Scale*		X		X	
• *Edinburgh Postnatal Depression Scale*		X		X	
• *WHO Quality of Life*		X		X	
• *Mother-to-Infant Bonding Scale*		X			
• *Maternal death*	X[5]	X	X	X	X
• *Neonatal/infant weight*	X	X		X	
• *Neonatal/infant breastfeeding*		X	X	X	
• *Neonatal/infant hospital admissions*		X		X	
• *Neonatal/infant death*	X[5]	X	X	X	X
SAE Assessment	X	X		X	X

1. pp, postpartum
2. Includes malaria rapid diagnostic test (RDT) in sub-Saharan African sites
3. All randomized participants will receive folic acid for 6 months pp as per WHO guidelines.
4. Maternal serum phosphate concentration will only be measured at 6 months pp if serum phosphate concentration at 6 weeks postpartum is <2.5 mg/dL.
5. Maternal or neonatal/infant death should only be captured after consent is obtained.

Appendix B Sample Consent Form

Study Title:	**Global Network for Women's & Children's Health Research Prevention of Iron Deficiency Anemia Post-delivery (PRIORITY Trial)**
Principal Investigator:	**Shivaprasad Goudar, MD**
USA Lead Principal Investigator:	**Richard Derman, MD, MPH**
IRB number (*if applicable*):	
Version Date:	**13 September 2022; 22 February 2023**
Version No:	**1.1; updated 2.0**

SPONSORS: Foundation for the National Institutes of Health and the National Institute of Child Health and Human Development (NICHD)

You are being asked to be in a research study for women with moderate anemia (low amounts of iron in the body) who have just had a baby. This form provides you with information about the study so that you can decide if you would like to participate. A member of the research team will describe the study to you and answer all your questions. Please read the information below and ask questions about anything you don't understand before deciding whether to take part. You may also request that the research staff read the form to you.

Why is this study being done?

Anemia is a serious problem worldwide. During the period immediately after birth and through the next 6 weeks, anemia is associated with problems such as excessive bleeding after delivery. Anemia can also be the cause for feeling tired or being less productive at work or at home and reduced breastfeeding.

What is the purpose of the study?

The purpose of this study is to learn the best way to treat women who have moderate anemia immediately after giving birth. If you have anemia, it may be due to iron deficiency. Measuring hemoglobin in your blood is a way to detect anemia. Taking iron supplements helps to correct anemia. We want to compare iron status at 6 weeks and at 6 months after birth in women that receive an IV iron supplement OR an oral iron supplement (usual standard of care) after delivery. We also want to compare how well the two ways of supplementation prevent other health issues such as maternal or infant death, maternal depression, hospitalization, hemorrhage, and other postpartum complications.

Participants will be randomly assigned to receive up to one gram of IV iron supplement between 6 and 48 hours after giving birth or 60 mg iron supplements by mouth two times a day for 6 weeks. All women will be asked to take folic acid for 6 months.

Who can participate?

You are being asked to be in this research study because you have just had a baby in this health facility, may have moderate anemia, are **18**-49 years and plan to stay in this community for at least the next 6 months.

Eight sites i.e., Bangladesh, the Democratic Republic of Congo, Guatemala, India (Nagpur and Belagavi), Kenya, Pakistan, and Zambia will recruit women who have just had a baby (or pregnant women about to give birth) for the study. Up to 600 women in your community will participate in the study. A total of 4,800 women from the 8 research sites will participate in the study.

What will happen if I join this study?

You are being provided with information about the *PRIORITY* study procedures. First, we will ask you some simple questions to see if you are eligible for the study. If you are eligible after these questions, we will collect a small amount of blood (1/2 teaspoon or 2-3 mL) from the vein in your arm between 6 and 48 hours after you have your baby to measure the amount of hemoglobin in your blood. If your hemoglobin is moderately low, you will be eligible to participate in the study. If your hemoglobin is extremely low, you will not be included in the study and instead will be referred to an appropriate health care provider for follow up and treatment. If your hemoglobin is normal or high, you will not be able to participate in the study. You are encouraged to ask questions at any time.

If you are eligible and want to join the study, you will be randomly assigned (by chance) to receive either IV iron within 6-48 hours of giving birth OR to take oral iron supplement two times each day for 6 weeks as described above. If you are in the oral iron supplement group, you will continue to take the oral iron supplement either once or twice a day until your baby is 6 months old. The amount you take will depend on your hemoglobin concentration at the 6-week visit. Both groups will also receive oral folic acid supplements for 6 months.

While you are at the health facility to deliver your baby, the study team will do the following after delivery:

- Collect half of a teaspoon 2 mL (*or 1 tsp, 4 mL in India*) of blood from a vein in your arm to measure the amount of iron and inflammation in your body
- Collect information about your health and well-being during labor, at the time of delivery, and after delivery
- Weigh your baby
- Receive a single infusion of IV iron (up to 1 gram) if you are assigned to the IV group OR be given oral iron supplements to take every day at home
- Receive folic acid tablets to take every day at home for 6 months

These activities will take about 60 minutes to collect the samples, ask you some questions, and give you your supplements.

Follow up visits at 6 weeks and 6 months after delivery. At these two times, you and your baby will return to the facility for the following activities:

- If you are assigned to the oral iron group, we will ask you about how often you are taking the oral iron tablets provided. At the 6 week visit, we will also give you additional tablets (either one or two per day) that you will need to take from 6 weeks until 6 months after delivery.
- Collect about 1.5 teaspoons (up to 4 mL) of blood from a vein in your arm to measure the amount of iron and inflammation in your body. Part of this sample will be sent to a laboratory [in Germany] for some of the blood tests and some will be analyzed here. At six weeks, we will also measure the amount of phosphate in your blood here. If it is low, we will measure it again 6 months after delivery. We will also test to see if you have malaria [*include for African sites*].
- Ask you questions about your health and well-being. We will also ask you about what your baby is eating and your relationship with your baby
- Weigh your baby
- Refer you for further care at six weeks if you have severe anemia (hemoglobin is very low)
- Ask if you have had any unexpected hospital visits. We want to learn if you have had more hospital or clinic visits than is normally expected as a result of study participation. We will also

collect information about the reason for any unexpected visit(s) from your clinical record. We may contact you during this period to see if you have more information to share with us

These activities will take between 1-2 hours to complete at each visit. To ensure that we have accurate and complete information about the health of you and your baby, we will look at and collect information from the medical records at the health facilities where you and your baby have received care after being randomized. By agreeing to participate in this study, you are also agreeing to give permission for the study staff to look at your medical records. We will take precautions to protect the information that is collected from your medical records. Only study staff will have access to this information. To further protect you and your baby, study data recorded on data forms will be coded with a number in place of your name. However, if there is a need to release study information about your treatment to ensure you get appropriate emergency care, an authorized staff person can obtain access to a protected record of study participant names and the assigned code.

Follow up telephone call 3 months after delivery

A member of the research team will call you to ask you a couple of questions about how you are feeding your baby and to confirm your contact information for the 6-month visit.

What are the possible risks and discomforts of participating?

The collection of blood from your arm may cause some discomfort, light-headedness, bleeding, swelling, or bruising where the needle enters the body, and in rare cases, fainting, or infection. To minimize this, we will ensure research staff are well trained in the procedure.

Consumption of oral iron tablets may cause nausea, vomiting, loose stools, feeling faint, hard or dry stools, or black colored stools.

Side effects of intravenous iron are usually minimal. A severe allergic reaction that may include difficulty breathing, itching, or a rash over the entire body may occur with an IV iron infusion but it is very rare (between 1 in 10,000 to 1 in 1,000 infusions). Examples of other rare reactions that have been reported for IV iron study formulations include feeling faint, temporary reddening of the skin usually of the face and neck, anxiety, swelling of blood vessels, irregular heartbeat, accumulation of gas in the abdomen, swelling of the skin or mucous membrane, paleness, tiredness, and common cold or flu-like illness. Uncommon reactions that occur between 1 in 1,000 to 1 in 100 infusions are abdominal pain, vomiting, diarrhea, constipation, sweating, blurred vision, high or low blood pressure, muscle spasms, back or pain in your arms or legs. Common reactions occurring between 1 in 100 to 1 in 10 reported for at least one of the study formulations are headache, dizziness, decreased blood phosphate, rash, redness of the skin, nausea, and a reaction where iron is infused into a vein. The research staff have been trained and will make all efforts to avoid these problems and to provide medical assistance as necessary.

While the chance of you having a reaction is low, the local research staff have been selected because of their skills, knowledge, and familiarity with your community. The research staff are here to support you during the study and should be contacted between visits if you have any questions or concerns.

Another possible risk of participating in this study is that your name and personal information may be seen by persons who are not part of the project. To prevent this, you will be given an identification number that will be used in place of your name on all study documents. We will do all that we can to protect your information, but it cannot be guaranteed.

You may become embarrassed, anxious, or worried when we ask personal questions about your pregnancy or medical history. You do not have to answer any question if you do not want to.

There may be other uncommon or previously unknown risks. Please tell us about any problems you may have.

De-identified information from this research study will be kept by the research team. De-identified means that you and your baby will not be individually identified by name or other personal identifiers in the database. Your full name, address, medical record, date of birth or other personal details will not be included. Information released from this study will not identify you or your baby's participation in this research study.

What are the possible benefits of participating?

Aside from the immediate possibility of quality-of-life benefits from iron supplementation, information gained from this trial may lead to the development of new guidelines and standards of care that might help a large number of women who are having babies in the future.

If new information about the benefits or risks of intravenous iron use after pregnancy becomes available during this study, this information will be given to you by study staff.

Will I have to pay for anything?

It will not cost you anything to be in the study. You will not have to pay for any of the supplements, medical examinations, procedures, or laboratory tests that are needed for this trial.

Will I be paid to be in the study?

You will not be paid to be in the study.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to refuse to participate or to withdraw your participation at any time. If you refuse or decide to withdraw, you will not lose any benefits or rights to which you are entitled. These actions will not have any negative effect on the health care that you will receive from your local health providers. You will still continue to receive your usual medical care.

Can I be removed from this study?

You will be removed from the study if the research staff think that your participation may cause you harm. The research staff may also remove you from the study for other reasons at their discretion. The Sponsor, Regulatory Authorities, or the Ethics Committee may stop the study at any time whenever there is good reason to do so.

What happens if I am injured or hurt during the study?

In order to protect your health and keep you safe during your participation in the study, it is very important that you follow the study doctor's instructions and medical advice and notify the study doctor if any injury during your participation in the study happens. In case of an injury occurring to you during the clinical trial, free medical management shall be given as long as required or until such time it is

established that the injury is not related to the clinical trial, whichever is earlier. In case of trial-related injury or death, study sites shall provide financial compensation for the injury or death.

The above stated compensation will be determined as per the relevant law and regulations.

Who has reviewed the study?

All research studies are reviewed by an independent group of people, called a research Ethics Committee to protect your safety, rights, well-being and dignity. This study has been reviewed and given approval by **[insert name here]**.

Will your participation in this study be kept confidential? How will your personal information be used?

The study doctor and research team will collect, record and use personal information about you for the study purposes. Your personal information collected during the study may include sensitive information about your physical or mental health or condition and you and your baby's health information from medical records if relevant to this study. This also includes your non-health related personal information to be collected for the study, including education and economic status. Your privacy and your personal information will be protected using measures which follow the requirements applicable for the protection of your personal information. Any information about you that is collected during this study will remain confidential. During the study, your collected personal information including your medical files may be disclosed to the Sponsor, its affiliates, research partners, designees and its representatives assisting with the research (such as the contract research organization, study monitors, and auditors), central laboratory and regulatory authorities and health insurers. Your medical files will be reviewed only at the hospital or study doctor's office in order to check the information and verify the clinical study procedures, without violating your right to privacy and confidentiality.

All information which is collected about you in records that leave the study centre for the purposes of medical, laboratory, statistical or regulatory activities related to the study will be identified by your study subject number. Your full name or any address details will not be included in these records. Data that have been modified to remove information that may directly or indirectly identify you from the study may be published or sent to regulatory authorities or health insurers.

Data Sharing

Both regulatory bodies and journal editors now require that patient-level study data from clinical trials be made available to other researchers. Sharing your information for future research will not directly benefit you. It is hoped that allowing other researchers to use the data from this study will lead to a greater understanding of how treatment of anemia postpartum can improve outcomes for mothers and infants. Data that have been modified to remove information that may directly or indirectly identify you from this study may be shared with other researchers and may be included in a de- identified public use database managed by NICHD Data and Specimen Hub (DASH) in compliance with the U.S. National Institutes of Health (NIH) Public Access Policy. Any data or blood samples that are shared with other researchers will be constructed or labelled to ensure that the identity and medical information of each study participant will remain strictly confidential.

What should you do if you have additional questions?

If you have questions about this study or a project-related injury, you should contact **[insert name(s) and phone here]**.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time. Your personal information will not be made available on the site.

Future research participation

You may be contacted to participate in other studies if you consent to this study. You may be contacted again after you finish the study if we need to clarify any of the information you previously provided.

Informed Consent Form

Study Title: **Prevention of Iron Deficiency Anemia Post-delivery (PRIORITY Trial)**

Participant's initials: _____ Participant's Name: _____

Date of Birth / Age: (optional): _____

Address (in full) of the Participant: (optional) _____

Name and address of the nominee(s) and his/her relation to the Participant (optional)

_____

(For the purpose of compensation in case of trial related death (optional)

Participants ID: <ID number> (NOTE: the following should be included as appropriate in each site)

Please initial box

(Subject)

(i) I confirm that I have read and understood the Information sheet dated **[insert date here]** for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Institutional Ethics Committees and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

(NOTE: THE FOLLOWING IS MANDATORY FOR EACH SITE TO INCLUDE)

Participant Name (print): _____

Signature (or Thumb impression) of the Participant

_____ __ Date: _____

Name of Person Obtaining Informed Consent (print): _____

Signature of Person Obtaining Informed Consent

_____ Date: _____

(*If a patient has limited ability to read and write, an impartial witness should be present during the entire informed consent discussion and her legally acceptable representative should sign on patient's behalf). In these instances, the patient places her left thumb impression in the place of the signature.

Patient's Legally Acceptable Representative's Statement: NA

I, as the patient's legally acceptable representative, was present during the consenting procedure and understand the preceding information describing this study. All of the questions regarding the study and the patient's participation in it have been answered to my satisfaction and that of the patient. I state that all aspects of the study were clearly presented during the consent procedure. The patient is willing to participate in the study and I sign below on his/her behalf testifying to this effect.

Name of the Participant: _____

Name of the Legally Acceptable Representative: _____

Relationship to the Participant: _____

Signature of the Legally Acceptable Representative: _____

Date: _____

Impartial Witness Declaration of Participant's Informed Consent NA

By signing the consent form I attest that the information was accurately explained to and apparently understood by the patient and the legally acceptable representative (if applicable) and that informed consent was freely given by the patient.

Name of the Impartial Witness: _____

Signature of the Impartial Witness: _____ Date: _____

Address of the Impartial Witness: _____

Future Contact

We may wish to contact you in the future about participating in other related research studies. Please indicate below if you are willing to be contacted.

Yes, I agree to be contacted No, I do not agree to be contacted

(Copy of the duly filled ICF shall be handed over to the participant or his/her attendant)

Appendix C Protocol Changes

Version	Authors	Main changes
1.0	RJD, EMM, JW, DW	First version circulated; submitted to IRBs and ERCs
2.0	EMM, DCB, JW, RJD	• Clarified primary, key secondary, other secondary, and exploratory objectives and endpoints • Added section describing selection criteria for health facilities • Changed inclusion criteria to ≥28 weeks gestation (from >20 weeks) • Added prior reaction to IV iron or oral iron or folic acid to exclusion criteria • Added positive malaria RDT test immediately at post-delivery (prior to randomization) for sub-Saharan Africa sites to exclusion criteria • Removed stratified randomization by mode of delivery (cesarean versus vaginal) • Added serum phosphate measurement at 6 weeks and 6 months postpartum (if serum phosphate concentration at 6 weeks postpartum is <2.5 mg/dL) • *For those receiving infusion*, clarified that infusion must be **initiated** within 6-48 hours post-delivery • *For those receiving oral iron*, clarified that dose must be **initiated** within 6-48 hours post-delivery • Added section on consent • Added section on study drugs • Further developed statistical analyses section • Added section study safety monitoring • Added section on participant and study stopping rules • Modified criteria for oral iron dosing after 6 weeks postpartum • Removed serum collection in first trimester in those with an intercurrent pregnancy • Added anemic state at 6 weeks postpartum to list of other secondary endpoints in Section 5.6 and revised analysis plan in Section 7.3.4 accordingly • Revised footnotes in Appendix A
3.0	DW	• Removed reference to Ferinject and clarified language describing dosage, preparation, and administration of FCM in Section 6. • Updated that FCM is non-generic and produced in Europe in Section 6.
3.1	DW, JM	• Changed serum ferritin concentration at 6 weeks postpartum and 6 months postpartum from a key

		secondary endpoint to the list of other secondary endpoints measuring anemia • Changed serum sTfR concentration at 6 weeks postpartum and 6 months postpartum from a key secondary endpoint to the list of other secondary endpoints measuring anemia • Changed the order of the remaining key secondary objectives/endpoints to better reflect clinical importance • Based on a literature review, EPDS score is highly skewed and so a cutpoint of > 10 will be used to define this endpoint at 6 weeks postpartum and 6 months postpartum • Based on a literature review, Maternal Fatigue Severity Scale score is highly skewed and so a cutpoint of > 4 will be used to define this endpoint at 6 weeks postpartum and 6 months postpartum • Based on a literature review, Mother-to-Infant Bonding Scale score is highly skewed and so a cutpoint of ≥ 4 will be used to define this endpoint at 6 weeks postpartum and 6 months postpartum • Clarified the statistical model that will be used to analyze the primary endpoint • Modified the description of the subgroup analyses of the primary endpoint to include additional modifiers and clarify analytic approach • Added sensitivity analysis of primary endpoint to assess the impact of the change in WHO guidelines for adjustment of Hb adjustments for altitude in Guatemala • Clarified analysis of key secondary endpoints • Revised analytic approach for other secondary endpoints to reflect changes to objectives/endpoints • Included justification regarding the decision to not perform an interim analysis of efficacy or futility of the primary endpoint