Study Protocol

Intravenous Iron for Iron-Deficiency Anemia in Pregnancy: A Randomized Controlled Trial (IVIDA)

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Version 6.2

NCT03438227

SYNOPSIS

Objective: To assess the effectiveness and safety of treating iron-deficiency anemia in pregnant women with intravenous iron compared to oral iron.

Background: Iron deficiency is the most common cause of anemia in pregnancy worldwide, and, when severe, can have serious consequences for mothers and babies. In the U.S., anemia affects nearly 20% of pregnancies, and the majority are iron-deficiency anemia. While treatment of iron-deficiency anemia with iron supplementation is recommended, treatment strategies remain controversial. The American College of Obstetrics and Gynecology (ACOG) recommends oral iron supplementation for iron-deficiency anemia in pregnancy and postpartum, with intravenous iron reserved for the rare patient who cannot tolerate or will not take oral iron. Conversely, UK professional organizations recommend a more liberal use of intravenous iron for the treatment of iron-deficiency anemia in pregnancy and postpartum. The reason for these disparate recommendations is that few high-quality studies comparing oral to intravenous iron have been conducted in developed countries, and the potential impact of intravenous iron treatment on obstetric and perinatal outcomes remains unclear. The most recent Cochrane review—mostly of trials conducted in low-income countries—found that, although intravenous iron more effectively improved hemoglobin levels and iron stores compared to oral iron, no clinical outcomes were assessed and there were insufficient data on adverse effects. Thus, there is a need for a well-designed trial to clarify whether intravenous iron should be used more liberally for the treatment of iron-deficiency anemia in pregnancy in the U.S.

Study design: Open-label, randomized controlled trial

Primary outcome: Maternal anemia (hemoglobin (Hgb) <11mg/dl) on admission for labor & delivery

Secondary outcomes:

1. Safety (infusion reactions)
2. Maternal outcomes (Hgb, serum ferritin, blood transfusion, mode of delivery)
3. Neonatal outcomes (gestational age at delivery, infant birth weight, cord gases, umbilical artery lactate, APGAR scores, cord blood Hgb & ferritin, neonatal morbidities, postpartum disposition)

Subject selection:

Inclusion criteria

- Pregnant women
- 18 years or older
- Diagnosed with iron-deficiency anemia
  - Serum ferritin <30ug
  - Hgb <10 g/dl
- Between 24 - 34 weeks gestation
- Plan to deliver at an in-network hospital
- Able and willing to give informed consent

Exclusion criteria

- Diagnosis of non-iron-deficiency anemia
- Multiple gestation
- Known or suspected major fetal anomalies or aneuploidy
- Planned delivery at out-of-network hospital
- Unable or unwilling to give consent

Randomization and treatment: Patients who meet all inclusion criteria and no exclusion criteria will be enrolled and randomized in a 1:1 ratio using a computer-generated randomization sequence to one of two treatment protocols**:**

1. Oral Iron Supplement- Oral iron supplementation (ferrous sulfate 325mg once daily to three times daily through delivery)

2. Intravenous Iron- Intravenous iron infusion (1000mg of intravenous iron dextran; given as a single dose after enrollment as close as possible to 24 weeks gestation). If iron dextran is unavailable due to drug shortage, ferumoxytol will be substituted; 510 mg IV will be administered followed by a second dose (510 mg IV) 3 to 8 days after the initial dose.

Procedures: All patients presenting for prenatal care will have workup for anemia with repeat CBC at 24 to 28 weeks gestation per standard of care. Patients found to have iron-deficiency anemia (Hgb <10 g/dL and ferritin <30ug) at 24 – 28 weeks and who meet all other inclusion and exclusion parameters will be eligible to be approached for the study. In addition, patients who do not receive standard anemia screening but are diagnosed at 28 – 34 weeks gestation with iron-deficiency anemia (hemoglobin<10mg/dl and ferritin <30ug) will be eligible for the study. Subjects will be randomized to one of the two treatment groups (oral or intravenous iron supplementation). Study patients will have Hgb and ferritin drawn at delivery. Their neonates will have Hgb and ferritin drawn via cord blood at delivery. If a cord gas or umbilical artery lactate level is drawn out of clinical necessity, this data will be collected also. Chart abstraction will be used to assess additional maternal and neonatal outcomes. Pregnancy, labor and delivery management will be per standard obstetric practice.

Sample Size: 120 subjects over an estimated 15 - 18 months.

BACKGROUND

Iron deficiency is the most common cause of anemia in pregnancy worldwide, and, when severe, can have serious consequences for mothers and babies. In the U.S., anemia affects nearly 20% of pregnancies and the majority are iron-deficiency anemia. Patients on oral iron for iron-deficiency anemia with a Hgb<11mg/dl at the time of delivery have a 3-fold increased risk of peripartum blood transfusion (3.8% vs 1.3%, RR 2.90, 95% CI 1.97, 4.36) based on institutional data from Washington University in St. Louis. Therefore, treatment of iron-deficiency anemia with iron supplementation is recommended.[1] However, there is controversy about the treatment strategies.

The American College of Obstetrics and Gynecology recommends oral iron supplementation for iron-deficiency anemia in pregnancy, with intravenous iron reserved only for the "*rare patient who cannot tolerate or will not take oral iron*."[1] Conversely, guidelines from the U.K. are more liberal on the use of intravenous iron for the treatment of iron-deficiency anemia in pregnancy.[2] Both treatment guidelines are based on limited data regarding the risks and benefits of intravenous iron for treatment of iron-deficiency anemia in pregnancy. The majority of randomized trials were conducted in developing country settings. In fact, few high-quality studies have been conducted in developed countries, and none has been conducted in the U.S. Moreover, there is limited data from prior studies on the impact of intravenous iron treatment on perinatal outcomes. The most recent Cochrane review including mostly trials conducted in low-income countries found that, although intravenous iron improved hemoglobin levels and iron stores more than the oral route, no clinical outcomes were assessed and there were insufficient data on adverse effects. The authors concluded that "*large, good quality trials, assessing clinical outcomes including adverse effects … are required*."[3]

OBJECTIVE

This study aims to assess the effectiveness and safety of treating pregnant women with iron-deficiency anemia with a protocol including intravenous iron compared with a protocol based on oral iron. We *hypothesize* that treating iron-deficiency anemia with intravenous iron is associated with improved maternal and neonatal outcomes compared with treatment using oral iron.

STUDY DESIGN AND METHODS

Overview: We will conduct an open-label, randomized controlled trial to assess the effectiveness and safety of treating iron-deficiency anemia in pregnant women with intravenous iron compared with oral iron. We test the *hypothesis* that treating iron-deficiency anemia with intravenous iron is associated with improved maternal and neonatal outcomes compared with oral iron. We will use broad inclusion criteria and analyze data using the intention-to-treat principle to increase generalizability of the findings.

Inclusion & exclusion criteria:

Inclusion criteria:

- Pregnant women
- 18 years or older
- Diagnosed with iron-deficiency anemia
    - Serum ferritin <30ug
    - Hgb <10 g/dl
- Between 24 – 34 weeks gestation
- Plan to deliver at an in-network hospital
- Able and willing to give informed consent

Exclusion criteria:

- Diagnosis of non-iron-deficiency anemia
- Multiple gestation
- Known or suspected major fetal anomaly or aneuploidy
- Planned delivery at out-of-network hospital
- Unable or unwilling to give consent

Study outcomes:

Primary outcome: The primary outcome of the trial is maternal anemia, defined as Hgb <11mg/dl, on admission for labor and delivery.

Secondary outcomes:

1. *Safety*:
   i. Mild/moderate infusion reactions: chest tightness, itching, urticaria, flushing, nausea/vomiting, arthralgia, back or joint aches, mild shortness of breath, tachycardia, hypertension or hypotension, abdominal pain, diarrhea, peripheral edema, headache, dizziness, syncope, or numbness.
   ii. Major infusion reaction: anaphylaxis-like reaction, seizures, or non-reassuring fetal heart rate tracing.

2. *Maternal outcomes*:
   i. Hgb at admission to labor and delivery
   ii. Hgb on postpartum day 1
   iii. Ferritin at admission to labor and delivery
   iv. blood transfusion
   v. mode of delivery
   vi. postpartum disposition
   vii. readmission

3. *Neonatal outcomes*
   i. gestational age at delivery
   ii. birth weight
   iii. cord gases (if performed as SOC)
   iv. umbilical artery lactate (if performed as SOC)
   v. APGAR scores
   vi. Hgb (obtained from cord blood)
   vii. Ferritin (obtained from cord blood)
   viii. neonatal morbidities
   ix. postpartum disposition

Screening:

Pregnant women attending prenatal care will be screened for anemia with repeat CBC at 24 to 28 weeks gestation per standard of care. If the initial Hgb at this gestational age is less than 10 mg/dL, they will undergo testing for iron-deficiency anemia. Iron-deficiency anemia will be defined as anemia with serum ferritin <30ug. Any pregnant woman diagnosed with iron-deficiency anemia who meets all inclusion criteria and no exclusion criteria will be eligible for the study (**Figure 1**). In addition, patients who present for prenatal care after 28 weeks gestation who meet all inclusion criteria and no exclusion criteria will be eligible for enrollment if they are diagnosed with iron-deficiency anemia prior to 34 weeks.

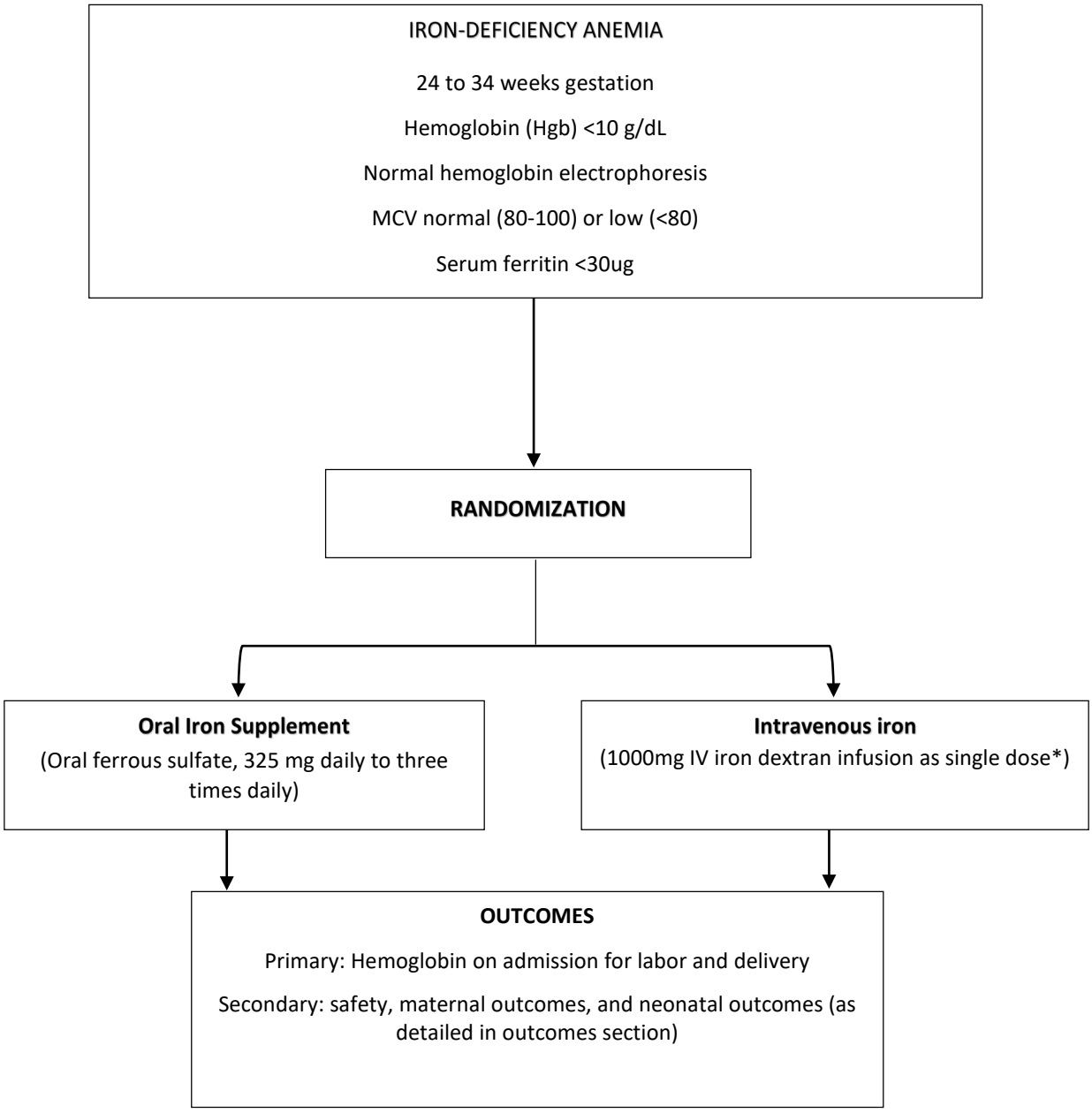
Randomization and Treatment Groups: Patients meeting all inclusion criteria and no exclusion criteria who sign informed consent will be enrolled and randomly assigned in a 1:1 ratio using a computer-generated randomization sequence to one of two treatment protocols. The two treatment protocols are:

1. Oral Iron Supplement- Oral iron supplementation will occur throughout pregnancy with ferrous sulfate at a dose range of 325mg daily to 325mg three times daily. Patients will be instructed to take on an empty stomach or with an acidic beverage like orange juice. Patients will continue oral iron supplementation through delivery, then refer to their treating physician for further postpartum consumption. Patients will be asked to report any side effects of oral iron between 2 – 4 weeks after randomization. Side effects will also be assessed at delivery along with reported compliance to the oral iron regimen.

2. Intravenous Iron- The intravenous iron infusion will occur in the form of 975mg of intravenous iron dextran diluted in 250 or 500mL of 0.9% sodium chloride given as a single dose over 1-2 hours. Prior to starting the treatment dose, participants will receive a test dose of 0.5mL (25mg) of iron dextran and will be monitored by hospital nursing staff for 20-30 minutes (or per local infusion protocol) to ensure there are no transfusion

reactions. This amounts to a cumulative dose of 1000mg IV iron dextran. If iron dextran is unavailable due to drug shortage, ferumoxytol will be substituted for this treatment group. Subjects will be given an initial 510mg IV dose in 100 ml 0.9% sodium chloride over at least 15 minutes. This dose will be followed by a second dose of the same concentration 3 to 8 days later. All iron infusions will occur on an obstetric unit equipped with continuous monitoring and emergency equipment. Patients will have continuous fetal monitoring throughout and at least 30 minutes after the infusion. Patients will be called by research staff 48 - 72 hours after infusion (second infusion if administering ferumoxytol) to assess for transfusion reactions. Women who receive intravenous iron will not receive further oral iron supplementation during pregnancy. Postpartum iron supplementation will be left to provider discretion.

Figure 1: Study protocol



*If iron dextran is unavailable due to drug shortage, ferumoxytol will be substituted. The initial dose will be 510mg ferumoxytol IV followed by a second dose of 510mg ferumoxytol IV 3 to 8 days later.

STUDY PROCEDURES

Study patients will have hemoglobin drawn at admission to labor and delivery and on postpartum day one. Neonatal hemoglobin and ferritin (and blood gases and/or lactate if performed out of clinical necessity) will be assessed via cord blood. Obstetric and neonatal outcomes will be collected by a trained research nurse. Subjects randomized to the oral iron group will be asked to report compliance with taking oral iron supplements as well as any side effects of taking the oral iron. This self-report will be assessed during their admission to labor and delivery (or via phone up to 2 days after discharge). See **Figure 2** for schedule of events. Pregnancy, labor and delivery management will be per standard obstetric practice.

Figure 2: Schedule of events

Event	Screening & Enrollment 24-34 weeks	Prenatal Period	48-72 hrs after infusion*	Delivery	Postpartum period prior to discharge
Inclusion/Exclusion	X				
Informed Consent	X				
Demographics	X				
Prenatal history	X				
Randomization to oral iron vs. IV iron	X	Oral continues Infusion occurs*			
Phone call: AEs/ outcomes of IV iron			X		
Effects & outcomes of oral iron supplementation (self-report)		X (Once 2-4 weeks after randomization)		X	
Oral iron compliance (self-report)				X	
Maternal blood draw: Hgb	SOC			X	X PPD1
Maternal blood draw: Serum ferritin	SOC			X	
Cord blood collection & processing (Hgb & ferritin; cord gas and/or lactate if performed as clinical necessity)				X	
Delivery & neonatal outcomes via chart abstraction					X

**If ferumoxytol is administered due to shortage of iron dextran, two infusions will occur in the prenatal period as outlined in the randomization section of this document. The post-infusion phone call will occur 48-72 hours after the second infusion.*

Data analysis: Analyses will follow the intention to treat principle, in which patients will be analyzed in the group to which they were randomized whether or not they received the assigned treatment. Continuous variables will be compared using the Student's *t*-test or Mann Whitney *U* test, as appropriate. Categorical variables will be compared using the χ^2 or Fisher's exact test, as appropriate. We will calculate crude and unadjusted risk estimates and differences. We will use multivariable logistic regression to adjust for potential confounders. We will estimate the number needed to treat to prevent occurrence of one primary outcome.

Sample size estimation: Based on institutional data the baseline rate of anemia (Hgb<11mg/dl) on admission to labor and delivery among women on supplemental oral iron is 38.5%. We estimate that 108 patients will provide 80% power to detect a 60% or greater relative difference in anemia (38.5% versus ≤15.4%) with intravenous iron (alpha=0.05, 2-tailed test). We will recruit **120 patients** to account for an anticipated 10% loss to follow-up (**Table 1**).

The anticipated effect size of 60% is plausible and conservative. A study by Al *et al*., the only study that reported the outcome of Hgb <11 at the time of delivery, showed an effect size of 88% (4.4% versus 37.8%, RR 0.12, 95% CI 0.03, 0.48).[4] Based on preliminary data showing that 10 pregnant women received intravenous iron in 6 weeks at the Washington University Medical Center, we anticipate that the 124 patients will be recruited within 15 months.

Table 1: Sample size estimation
(Baseline: **38.5%**, Power: 80%, alpha 0.05, loss: 10%)

Risk Estimate RR (%)	Anticipated Rate	N	N+10%
0.67 (33)	25.8%	418	460
0.60 (40)	23.1%	276	304
0.50 (50)	19.3%	168	185
0.40 (60)	**15.4%**	108	**120**
0.33 (67)	12.7%	82	90
0.30 (70)	11.6%	74	81

HUMAN SUBJECTS PROTECTION

Assessment of Risks

Potential Risks: Patients participating in this study who undergo oral or intravenous iron supplementation are at risk for the following:

- Low Risk
  - Blood draw complications:
    - Common: minor pain at site, bruising
    - Less common: fainting or dizziness
    - Rare: blood clots or infection at IV site
  - Breach of confidentiality
- Moderate/High Risk
  - Oral iron supplement side effects:
    - Common: constipation, nausea/vomiting, stomach discomfort or upset, dark stools
    - Less common: diarrhea, heartburn, urine discoloration
  - Iron dextran and ferumoxytol infusion side effects:
    - Common: discomfort and/or bruising at the IV site
    - Less common: chest tightness, itching, urticaria, flushing, nausea/vomiting, arthralgia, back or joint aches, shortness of breath, tachycardia, hypertension or hypotension, abdominal pain, diarrhea, peripheral edema, headache, dizziness, syncope, or numbness.
    - Rare: Anaphylaxis, seizures, or non-reassuring fetal status

Protections Against Risks

Subjects eligible for recruitment will be approached in a private clinic location. The informed consent process and every study visit will occur in a private location. Every follow up interview will be conducted in a private setting, or it can be conducted over the phone if the participant would prefer that option. Prior to beginning any phone interviews, study staff will ensure that the participant is in a private space.
The measures outlined below will be employed to monitor and minimize risks.

i. Patients will be counseled about the risks prior to enrollment in the study.
ii. Patient confidentiality will be protected by ensuring only research personnel have access to identifiable patient information. Study files will be kept in a secure room. Patient information will be coded and de-identified prior to analysis and publication of study results.
iii. All iron infusions will occur on an obstetrics unit equipped with emergency protocols and equipment in the rare event that a serious adverse event may occur and/or emergent delivery is necessary. All subjects will be infused with close monitoring including continuous fetal heart rate tracing. If an infusion reaction occurs at the time of infusion, treatment will be administered per the unit care team.
iv. Patients will be contacted by phone by research staff 48 - 72 hours after infusion to assess for transfusion reactions.
v. The study team will monitor, document and report to the Institutional Review Board, any adverse events among study participants per the plan detailed below.

Reportable Events

The PI at each site will oversee the safety of the study at his/her site. During the study, the investigator or study site personnel will be responsible for querying and recording adverse events (AEs) and serious adverse events (SAEs), as detailed below.

Types of Reportable Events:

Serious Adverse Events (SAE)
The site must report all SAEs to the lead site, whether or not they result from study participation, within 24 hours of learning of the event. A serious adverse event (SAE) is any adverse event occurring within the timelines specified in the protocol that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Adverse Events (AE)
An adverse event is any untoward medical occurrence in a clinical investigation subject administered an investigational product and which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

For this study, abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g., electrocardiogram, X-rays, vital signs) per se are not reported as AEs. Only the Adverse Events of Special Interest (AESI) defined below will be recorded on the CRFs and in the subject's chart.

Adverse Events of Special Interest (AESI)
Adverse events of particular clinical importance (other than SAEs mentioned above) will be classified as adverse events of special interest (AESIs). For this study, AESIs refer to:

- Mild/moderate reactions:
  - venipuncture complications (blood clot or infection)
  - bowel changes (constipation or diarrhea)
  - chest tightness
  - itching
  - urticaria
  - flushing
  - nausea/vomiting
  - abdominal pain
  - peripheral edema
  - arthralgia
  - new onset back or joint aches
  - mild shortness of breath
  - tachycardia
  - severe hypertension (For infusion group: confined to infusion timeframe only)
  - severe hypotension (For infusion group: confined to infusion timeframe only)
  - neurological changes (syncope, dizziness, headache) (For infusion group: confined to infusion timeframe only)

- Major reactions:
  - anaphylaxis-like reaction (For infusion group: confined to infusion timeframe only)
  - seizures (For infusion group: confined to infusion timeframe only)
  - non-reassuring fetal heart rate tracing (For infusion group: confined to infusion timeframe only)

Assessing and Documenting Reportable Events:
Subjects will be evaluated for adverse events in the following manner:
- Routine monitoring by infusion nurses during the IV iron treatment, with data obtained from the subject's EMR by research staff.
- Subjects will be called by research staff 48-72 hours after infusion to assess for transfusion reactions.
- Subjects on oral iron therapy will be monitored via their EMR and via contact with research staff as outlined in schedule of events

An adverse event report will be generated for each event that will include the following:
- Date of event discovery
- Severity (mild, moderate, severe, life threatening/disabling, death)
- Relationship to treatment
- Action taken
- Outcome
- Expected or not
- Date reported
- Relevant notes/chart records/supporting documentation to corroborate the event
- To whom event was reported (i.e. IRB, lead site, etc.)
  - **Non- serious AESIs will be reported to the lead site within 5 days of discovery, and to the IRB at renewal.**
  - **SAEs and SAESIs will be reported within 24 hours of discovery to the IRB and the lead site.**

Relationship of Reportable Events:
An investigator must make the determination of relationship to the drug for each SAE and/or AESI. The relationship to the drug should be assessed using the guidelines presented in the table below.

Relationship to Drug	Description
Related	• Previously known toxicity of agent; *or* • Follows a reasonable temporal sequence from administration of the drug; *or* • Follows a known or expected response pattern to the suspected intervention; *or* • Is confirmed by stopping or reducing the dosage of the drug; *and* is not explained by any other reasonable hypothesis
Probably related	• Follows a reasonable temporal sequence from the time of study intervention; *and/or* • Follows a known response pattern to the study drug; *and* • Was unlikely to have been produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy
Possibly related	• Follows a reasonable temporal sequence from the time of study intervention; *and/or* • Follows a known response pattern to the study drug; *but* • Could have been produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy
Unlikely related	• Does not follow a reasonable temporal sequence from the time of study intervention; *and* • Was likely produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy but for which relationship cannot be definitely ruled out
Not related	The adverse event can be determined with certainty to have no relationship to the study drug

Severity of Reportable Events:

The investigator will assess the severity of the AE using the following general guidelines:

Severity	Description
Mild:	An AE that is usually transient, requiring no special treatment, and does not interfere with the subject's daily activities.
Moderate:	An AE that introduces a low level of inconvenience or concern to the subject and may interfere with daily activities but is usually ameliorated by simple therapeutic measures.
Severe:	An AE that interrupts a subject's usually daily activity and typically requires systemic drug therapy or other treatment (a severe AE may not necessarily qualify as an SAE).
Life-threatening:	An AE that put the subject at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.

Outcomes of Reportable Events:

The investigator will categorize the outcome of each reportable event according to the definitions below:

Status	Description
Resolved:	The subject recovered from the SAE or AESI.
Resolved with sequelae:	A condition whereby the consequences of a disease or injury include lingering effects.
Ongoing:	At the time of the last assessment, the event is ongoing, with an undetermined outcome. Note: Ongoing SAEs and AESIs are not considered resolved as a result of death and no SAE or AESI stop date should be recorded for an AESI that is ongoing at the time of death.
Fatal:	Adverse Event directly caused death. If a subject dies during participation in the study the lead site should be provided with a copy of any post-mortem findings. Note: Death is an outcome of an adverse event and not an adverse event in itself. All reports of subject death should include an adverse event term (other than "Death") for the cause of the death.

Other Reportable Events: Promptly Reportable Study Conduct Events

The following events must be reported to the lead site and the IRB within five (5) business days of the study team becoming aware of the event.

- Conduct of research without submitting for IRB review.
- Conduct of research prior to receiving IRB notification of final approval.
- Initiation of substantive changes (i.e., changes that would affect the subjects' willingness to participate, such as changes to study procedures, risks and/or benefits) to the research protocol without prior IRB approval, including changes necessary to eliminate apparent immediate hazards to the subject. (note**:** "IRB-approved protocol" refers to all study information, including that contained in the IRB Questionnaires, formal protocol document, consents, etc.)
- Inclusion of vulnerable subject populations without specific IRB approval.
- Conduct of research when IRB approval has expired or been suspended or terminated.
- Subject interactions or review of identifiable research data by individuals who have not completed appropriate investigator requirements (e.g., COI disclosure and CITI training).
- Major protocol deviations/protocol noncompliance that occurred and may, in the opinion of the PI, (1)impact subject safety and/or (2) affect the integrity of the data, such as:
    - Dosing errors.
    - Enrolling a subject who does not meet eligibility criteria.
    - Study visits outside of the protocol-specified timeframe or missed study visits.
- Failure to obtain consent and/or authorization from subjects, including obtaining consent from someone who cannot legally consent for the subject.
- Other major deficiencies in informed consent or HIPAA authorization process or documentation (e.g., substantive outdated informed consent or HIPAA content, such as missing study procedures information, that may affect subjects' willingness to participate).

Study Conduct Events Reportable at IRB Renewal:
Events that do not meet the criteria for prompt reporting should be reported at the time of next study renewal to ensure the IRB has a full understanding of the conduct of the research. **Events that must be reported with the next study renewal submission include:**

- Protocol deviations/protocol noncompliance not previously reported to the IRB.
- Minor noncompliance (i.e., likely not serious or continuing), such as:
  - Use of a consent form that is not the most recently-approved version when the content is not substantively different from the current IRB approved consent.
  - Use of an unstamped consent form when the content is the same as the current IRB approved version.
  - Enrolling more subjects than approved by the IU IRB.
  - Conduct of research by individuals not listed on the study protocol but who have completed appropriate investigator requirements.
  - Implementing minor wording changes to IRB study documents without prior IRB approval.
  - Failure to appropriately document consent and/or authorization, if the missing information can be clearly corroborated by other documentation (e.g., research notes).

Data Monitoring and Quality Control
Periodic monitoring visits will be made at the investigational site throughout the clinical study to ensure that the investigator obligations are fulfilled, and all applicable regulations and guidelines are being followed. These visits will ensure that the facilities remain acceptable, the investigational plan is being followed, the IRB and local authorities have been notified of approved investigational plan changes as required, complete records are being maintained, appropriate and timely reports have been made to the sponsor and/or its designees and the IRB, and the investigator is carrying out all agreed upon activities.

An annual report will be generated beginning one year after the first enrollment and will include the following:

- A list and summary of adverse events;
- Whether adverse event rates are consistent with pre-study assumptions;
- A summary of recruitment and retention and reason for dropouts;
- Whether the study is on track to be completed and accomplish the stated aims.

Confidentiality:
Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigators, by regulation, retain the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

DATA COLLECTION AND MANAGEMENT

Case Report Forms

Qualified study staff at the investigational site will perform primary data collection. Electronic case report forms (eCRFs) will be used to collect all subject data during the study. The investigator is responsible for the accuracy and completeness of all data on the eCRFs. Lead site personnel will review completed eCRFs at regular intervals throughout the study.

Information on the eCRFs will be compared to information originally recorded on source documents related to the study. Information on the eCRF must match the same information on the source documents or a data query will be issued. All eCRFs will be reviewed for completeness, validity, and consistency. Queries will be generated and resolved with the sites and all protocol deviations will be recorded on the eCRF.

Source Data and Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

POTENTIAL BENEFITS AND KNOWLEDGE GAINED

The study is not designed to provide direct benefits to research participants. However, if our hypothesis that intravenous iron is superior to the standard oral iron is true, those participants randomized to intravenous iron will enjoy the benefits of reduced anemia. More importantly, results from this study have the potential to reduce anemia-related complications in pregnant women and their babies. Since the anticipated risk to participants is low, the risks-benefit ratio is very favorable.

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