Title: Reducing Anemia in Pregnancy in India: the RAPIDIRON Trial
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RESEARCH PROTOCOL: Reducing Anemia in Pregnancy in India: the RAPIDIRON Trial

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Technical Advisory Group (TAG):
A 12-15-member multi-disciplinary Technical Advisory Group will provide study input at pre-determined times—preceding initiation and through the duration of the *RAPIDIRON Trial*. The TAG composition will include content experts, from India and elsewhere, researchers from the World Health Organization (WHO), the International Federation of Gynecology and Obstetrics (FIGO), the Bill & Melinda Gates Foundation, and other individuals having specific expertise in the broad area of anemia in pregnancy

Data and Safety Monitoring Board (DSMB):
The Data and Safety Monitoring Board (DSMB) is comprised of a Chair and at least three supporting members, all with expertise in the conduct of global, multi-site clinical trials. The disciplines associated with DSMB members include high-risk obstetrics/global health, neonatology, biostatistics and clinical management of anemia

Version Tracking:

Version	Date	Authors	Comment
Version 1.0	July 30, 2020	RAPIDIRON Working Group	Original Version
Version 1.1	November 19, 2020	RAPIDIRON Working Group	Added community health centers (CHCs)as participating recruitment facilities; minor re-wording/edits to accommodate this addition
Version 1.2	March 8, 2021	RAPIDIRON PI	Minor changes to permit an addition (of 1 person) to the Data and Safety Monitoring Board
Version 1.3	November 18 2021	RAPIDIRON Working Group	Addition of new sites (Bagalkot District in Karnataka and urban primary health centers in Jaipur) Modification of study procedures for final eligibility confirmation
Version 1.4	January 10, 2022	RAPIDIRON Working Group	Addition of new sites (Raichur district in Karnataka); modification of statistical section for addition of sites

Abstract

Anemia is a worldwide problem with iron deficiency being the most common cause. When occurring in pregnancy, anemia increases the risk of adverse maternal, fetal and neonatal outcomes, including maternal mortality, preterm and low birth weight (LBW) deliveries, perinatal and neonatal deaths, and long-term developmental sequelae in the surviving offspring. Anemia rates are among the highest in south Asia, and India's latest National Family Health Survey (NFHS-4) for 2015-16 indicates that anemia with hemoglobin (Hb) <11.0 g/dL affects over 50% of pregnant women.[1] For close to 40 years, India's first-level treatment for anemia in pregnancy has been oral iron; however, side effects, poor adherence to tablet ingestion and low therapeutic impact are among reasons for consideration of a new paradigm for treatment of pregnant women with iron deficiency anemia. The Government of India has given high priority to reducing the prevalence of anemia in India, and several initiatives have been directed at this objective. The latest anemia strategy, built on prior strategies and supported by the Ministry of Health and Family Welfare, was presented in a 2018 publication, *Anemia Mukt Bharat-Intensified National Iron Plus Initiative*.[2] The same overall strategy remains in effect, but a few changes have been made to specific intervention guidelines. The updated guidelines can be viewed online.[3] Notably, this research focuses on pregnant women, one of the population groups targeted by *Anemia Mukt Bharat* which has the goal of reducing prevalence of anemia among children, adolescents and women in the reproductive age group by 3% a year. The current anemia strategy, supported by the *RAPIDIRON Trial*, can help facilitate India's efforts to achieve a 2025 Global World Health Assembly target of a 50% reduction of anemia among women of reproductive age.

This study, a 3-arm, randomized-controlled trial has two primary outcomes of interest. The research is designed to assess if a single dose of an intravenous (IV) iron formulation (ferric carboxymaltose in intervention arm 1 or iron isomaltoside, also known by the international non-proprietary name of ferric derisomaltose, in intervention arm 2), administered early in the second trimester of pregnancy for treatment of moderate iron deficiency anemia (IDA), will result in a greater percentage of pregnant participants in the IV iron arms achieving a normal for pregnancy Hb concentration of $\geq$11 g/dL in the third trimester at either a 30-34 week antenatal visit or based on blood collected prior to delivery when compared to the percentage of participants randomized to an active, comparator arm (arm 3) provided oral iron. Low birth weight (< 2500 grams), one of several adverse pregnancy outcomes associated with IDA, is the other primary outcome. The hypothesis for this clinical outcome is that the LBW delivery rates for participants randomized to the IV iron arms will be significantly lower when compared to the LBW delivery rate of participants randomly assigned to the oral iron arm.

Comparison of differences between arms are proposed for the following secondary outcomes of interest: changes in hemoglobin concentration by moderate anemia subgroups (i.e., 7 - 7.9, 8 - 8.9, and 9 - 9.9 g/dL), other participant iron indices (serum transferrin saturation and ferritin levels), Hb and other iron indices of cord blood, weight gain of participants by trimester of pregnancy, mode of delivery/C-section, antepartum and severe postpartum hemorrhage, hypertensive disorders (pre-eclampsia and eclampsia), maternal or neonatal infection including documented COVID-19 infection, maternal and neonatal mortality, preterm and small for gestational age births, pregnancy loss and stillbirths, birth weight and length of live born babies (measured within 72 hours post-delivery), the need for neonatal resuscitation, neonatal admissions to an intensive care unit, time from delivery to cord clamping, unanticipated or extended hospitalizations, breastfeeding practices including self-reported exclusive breastfeeding, and maternal well-being (quality of life). Due to consideration of current *Anemia Mukt Bharat* interventional guidelines for anemia treatment in pregnant women,[3] two additional secondary outcomes will be assessed: participant need for "rescue therapy" when Hb concentration drops to <7 g/dL at any time after treatment; and referral to a higher level of care for evaluation because hemoglobin improvement is <1 g/dL based upon analysis of blood collected at 26-30 weeks of pregnancy.

Transferrin saturation (TSAT) and ferritin level will be used in the study to establish that a pregnant woman has anemia and iron deficiency, and these indices will be monitored during the study. At defined study visits when a complete blood count is performed, reticulocyte hemoglobin (Ret-He) and immature reticulocyte fraction (IRF) will also be calculated (to support exploratory analyses) since reticulocyte indices are markers for iron deficiency and potential tools for assessing response after iron therapy. Other tests to better understand the problem of anemia among pregnant women in India will also be performed. Adverse reactions to oral or IV iron will be carefully monitored, documented and assessed by independent adjudicators with expertise in the use of IV iron. The research will additionally explore factors necessary for India-wide scale-up and identify obstacles to change as well as approaches for removing such obstacles.

The study will be carried out in India in primary and community health centers (PHCs, CHCs), hospitals and birthing facilities located in four research areas in the states of Karnataka and Rajasthan. Approximately 4,320 pregnant women who meet eligibility criteria and have hemoglobin (Hb) concentrations of 7 to 9.9 g/dL (the WHO definition of moderate anemia) and confirmed IDA will be randomized 1:1:1 to one of two IV iron intervention arms or to the arm that will be given oral iron. This study supports the overall goals of the Ministry of Health and Family Welfare (MOHFW) for pregnancy care; thus, all study participants will be followed according to the Ministry's antenatal care guidelines, and data will be collected through 42 days post-delivery.

A. Study Hypothesis and Specific Aims

Hypotheses: 1) Singleton pregnant participants with moderate iron deficiency anemia who are randomly assigned to an IV iron arm and receive, early in the second trimester of pregnancy, a single dose of IV iron for treatment of anemia and the currently recommended daily dose of folic acid will have a higher conversion rate to non-anemic status (or Hb $\geq$11 g/dL) in the last trimester of pregnancy at either a 30-34 week antenatal visit or prior to delivery than pregnant women assigned to an oral iron arm and provided iron and folic acid tablets for anemia treatment; and 2) The pregnant participants assigned to an IV iron treatment group will have a lower rate of LBW deliveries (or a 20% relative reduction) compared to the pregnant women in the oral iron group.

The specific aims of the study are:

- To provide evidence that each formulation of single-dose IV iron (ferric carboxymaltose or iron isomaltoside) when compared to oral iron will prove more effective for the treatment of iron deficiency anemia in pregnancy;
- To assess if women in either of the IV iron groups have a decreased risk of delivering a low birth weight (LBW) infant compared to women in the oral iron group;
- To determine if administration of either of the two IV iron formulations used in the study will have a more favorable impact on other maternal and neonatal outcomes than oral iron by assessing differences between arms at specified timepoints for secondary outcomes including: changes in hemoglobin concentration by moderate anemia subgroups (7 - 7.9, 8 - 8.9, and 9 - 9.9 g/dL), other participant iron indices, Hb and other iron indices of cord blood, weight gain of participants by trimester of pregnancy, mode of delivery and C-section, antepartum and severe postpartum hemorrhage, hypertensive disorders (pre-eclampsia, eclampsia), maternal or neonatal infection including documented COVID-19 infection, maternal and neonatal mortality, preterm and small for gestational age births, pregnancy loss and stillbirths, birth weight and length of live born babies (measured within 72 hours post-delivery), the need for neonatal resuscitation, neonatal admissions to an intensive care unit, time from delivery to cord clamping, unanticipated or extended hospitalizations, self-reported breastfeeding practices, maternal well-being (quality of life), participant need for "rescue therapy" due to a drop in Hb level to < 7 g/dL at any time after randomization and treatment, and referral of a study participant to a First Referral Unit or District Hospital with specialized services for thorough assessment of the causes of

anemia and possible change in treatment due to <1 g/dL improvement in Hb based upon analysis of blood collected at 26-30 weeks of pregnancy;
- To demonstrate an approach for screening pregnant women to identify IDA and optimizing antenatal care by applying a scientific, evidence-based IDA treatment within a timeframe that will maximize the outcomes;
- To address rate-limiting steps to broad implementation of single-dose IV iron as a first-level approach for treatment of IDA in pregnancy and to determine best practices to facilitate scale-up;
- To conduct an independent economic/cost-effectiveness analysis comparing costs and effects of administration of each single-dose IV iron formulation used in this study versus oral iron therapy for treatment of moderate iron deficiency anemia in pregnant women, taking into consideration costs associated with clinical outcomes of IDA in pregnancy such as low birth weight, small for gestational age (SGA) and preterm infants, need for maternal or neonatal transfusion and incremental days of maternal or neonatal hospitalization.

Long Term Objectives: The research has the long-term objective of demonstrating cost-effectiveness and the feasibility of scale-up of single-dose IV iron for treatment of IDA in pregnant women in low- and middle-income countries with constrained resources. Attention will focus on what can be done within India's public health system for reasonable costs to ensure greater success in identifying and more effectively treating IDA in pregnancy, thereby reducing risks to pregnant women, developing fetuses and live-born offspring. For example, the study will provide the opportunity to focus on facility requirements and training needs of providers to ensure competent and safe administration of IV iron; and an assessment will be made of how those associated with the public health system and with academic institutions can best facilitate education among pregnant women about IDA.

Research partners have expressed interest in the conduct of future studies to determine differences in offspring of women receiving IDA treatment. It would be highly beneficial to assess differences, associated with growth, neuro-cognitive development and other relevant health indicators of offspring at a specified age, ideally between the neonatal period and 3 years of age. Another outcome of interest is the iron status of *RAPIDIRON Trial* participants as they enter a subsequent pregnancy. Although funding would be required for the conduct of such future studies, the consent form for the study associated with this protocol will contain wording that allows determination of the willingness of the consenting participant to be contacted for a future related study. For participants responding favorably, contact information and the participant code used on data forms and in the data management system for this study will be retained (under conditions to ensure confidentiality) to enable future contact and matching of data sets if future studies are initiated.

B. Background and Significance

Well over half of the pregnant women in India are anemic, and this is a major contributing factor to the high rate, nearly 60%, of children 6-59 months of age, who are also classified as anemic[1] (using the same World Health Organization-recommended hemoglobin level of <11 g/dL that is relevant to pregnant women). Optimal fetal, neonatal and childhood brain growth and development require adequate iron. However, women with moderate to severe anemia during the late 2nd and early 3rd trimesters of pregnancy are often unable to make up their iron deficit. Thus, despite active transport via the placenta, insufficient iron may be transmitted to the developing fetus with consequent negative sequelae, including long-term neurodevelopmental impairment of the newborn. A study of Chinese pregnant women found that daily oral iron, initiated at or prior to 20 weeks gestation and continued until delivery, improved maternal iron parameters; however, 45% of the babies born to these women were iron deficient suggesting that oral iron supplementation may not optimally reach the developing fetus.[4] Published evidence confirms that

iron deficiency in infancy is associated with a statistically significant increase in cognitive and behavioral abnormalities which may persist for decades despite iron repletion.[5] While one of the primary outcomes for this study is the rate of LBW delivery (a leading cause of under-5 mortality and an independent risk for poorer neurodevelopment), anemia in pregnancy is associated with other adverse pregnancy outcomes such as increased preterm birth and perinatal and neonatal mortality.[6]

The Cochrane Collaboration reported a paucity of quality trials that assessed clinical maternal and neonatal effects of iron administration to anemic, pregnant women.[7] The Cochrane reviewers indicated the need for large, high quality trials that assess clinical outcomes and treatment effects. This need has not been adequately met, especially in terms of assessing the efficacy of newer treatment approaches, specifically the use of single-dose IV iron during pregnancy. Implementing the proposed study will address this identified but unmet need and increase the likelihood that India's guidelines and recommendations of respected health organizations will continue to undergo refinement and thereby better meet criteria for convenience, cost-effectiveness, and feasibility to enable broader and more rapid implementation and scale-up.

C. Research Team Information and Preliminary Studies

Since 2001, Dr. Richard Derman has been a Principal Investigator (PI) for the Global Network for Women's and Children's Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), in partnership with Jawaharlal Nehru Medical College (JNMC), Belagavi, Karnataka, India. The first collaborative study was a single-site, randomized, placebo controlled, community-based trial of oral misoprostol for prevention of postpartum hemorrhage (PPH). This study was implemented in the Belagavi District of Karnataka. Its findings were published in the *Lancet* in 2006 and indicated a reduction in PPH of nearly 50%; severe PPH showed an 80% reduction.[8] Importantly, the study resulted in world-wide scale-up of misoprostol use for PPH prevention.

Eleven additional Global Network studies have been completed, including the multi-site study known as *Aspirin Supplementation for Pregnancy Indicated Risk Reduction in Nulliparas (ASPIRIN) Trial*, which was implemented by Dr. Derman as Global Network PI in collaboration with US colleagues (including Dr. Matthew K. Hoffman as Lead Co-Investigator and Dr. Robert M. Silvers as expert consultant), and the JNMC research team. The findings for this trial, published in *The Lancet,*[9] indicates that a daily, low-dose aspirin tablet initiated early in pregnancy and continued to 36 weeks gestation can significantly reduce preterm births (the leading cause of under-five mortality). The Belagavi Women's and Children's Health Research Unit (or Global Network Site 8) has also completed, or is participating in, more than 20 other studies funded by various private and public sources—e.g., the Bill & Melinda Gates Foundation, the Thrasher Research Fund, the Children's Investment Fund Foundation, and the World Health Organization which recently named JNMC a WHO Collaborating Centre for Research in Maternal and Perinatal Health.

The *RAPIDIRON Trial* will involve oversight from a research support team at Thomas Jefferson University, collaboration with researchers from JNMC Women and Children's Health Research Unit,, SNMC Bagalkot, RIMS Raichur, researchers, and a Rajasthan research partner, Sawai Man Singh Medical College, Jaipur.. Key personnel of the JNMC research team include: Global Network Senior Foreign Investigator and Director of the Women's and Children's Health Research Unit, Dr. Shivaprasad S. Goudar; the Belagavi site Principal Investigator for *RAPIDIRON*, Dr. Mrutyunjay B. Bellad (a JNMC faculty member and practicing obstetrician/gynecologist); the key study pharmacist, Dr. M.S. Ganachari and other Research Unit personnel, including Dr. Manjunath S. Somannavar, Dr. Yogesh Kumar S, and Dr. Umesh S. Charantimath. The key personnel from SNMC, Bagalkot include Dr. Ashalata A. Mallapur and Dr. Umesh Ramdurg. For RIMS and MRHRU Raichur, the key personnel are Dr. Basavaraj V. Peerapur, Dr. Radha Sangvi,

Dr. Praveen S. Patil, Dr. Subarna Roy, and Dr. Phaniraj Vastrad. The Rajasthan Co-Investigators associated with Sawai Man Singh Medical College, Jaipur, include: Dr. Sudhir Bhandari, Principal and Controller, and Senior Professor in the Department of Medicine; Dr. Sudhir Mehta, Hematologist and Senior Professor, Department of Medicine, and Unit Head; Dr. Seema Mehta, Senior Professor, Department of Obstetrics and Gynecology; Dr. Amarjeet Mehta, Professor, Department of Pediatric Medicine; Dr. Kusum Lata Gaur, Senior Professor, and Dr. Dharmesh Kumar Sharma, Associate Professor--both from the Department of Preventive and Social Medicine.

Critical input into the design of the *RAPIDIRON Trial* has been provided by Co-Investigators who are recognized experts in hematology, neonatology, obstetrics, maternal-fetal medicine, epidemiology, biostatistics, implementation science, evaluation and health economics. Dr. Michael Auerbach, a global leader with vast experience in the use of IV iron within his academic practice (of hematology and oncology) conducted the first US prospective study of IV iron use in pregnancy. Study findings, published in 2017, indicated that IV iron was safe (with no serious adverse events), less toxic and more effective than oral iron.[10] Dr. Auerbach, often with Dr. Derman and/or others contributing to *RAPIDIRON,* has authored relevant articles on iron deficiency anemia (IDA), treatment approaches, and the need for iron deficiency screening of all pregnant women.[11,12,13,14,15] Dr. Michael Georgieff, Executive Vice Chair and Professor, Department of Pediatrics at the University of Minnesota School of Medicine, is an internationally known researcher whose laboratory studies focus on the biological basis for the negative neurodevelopmental effects of fetal/neonatal iron deficiency and anemia. His work has contributed to an understanding of the neurological effects of iron deficiency prior to birth and the mechanisms by which long-term effects can be carried into adulthood.[16,17]

Dr. Stephen T. Mennemeyer, Emeritus Professor, Department of Health Care Organization and Policy, School of Public Health, University of Alabama at Birmingham has a rich background which includes teaching and research on health economics and the cost-effectiveness of health care interventions. He will be responsible for the economic/cost-effectiveness analysis incorporated into The *RAPIDIRON Trial.*

Dr. Dennis Wallace, who will serve as Senior Biostatistical Consultant and Chief Quality and Safety Officer for the *RAPIDIRON Trial*, provides statistical design and analysis support for clinical trials and observational studies; and he serves as a member of Data and Safety Monitoring Boards for clinical trials in women's and children's health and type I diabetes mellitus. Prior to his retirement as a Senior Research Statistician from RTI International in 2019, he spent 25 years as a study statistician or principal investigator for Data Coordinating Centers for clinical trials supported by the U.S. National Institutes of Health and the Bill & Melinda Gates Foundation across broad therapeutic areas including women's and children's health, neonatology, substance abuse, infectious diseases, cardiovascular disease, and autoimmune diseases. In that role, he participated in the design and analysis of more than 30 phase II-IV clinical trials that included both individually- and cluster-randomized studies.

The work of several practitioners and researchers with expertise in anemia and its consequences has been considered during the development of this protocol. Dr Sandra (Sunny) Juul, Chief of Neonatology at the University of Washington School of Medicine developed an internationally recognized research program funded by the National Institutes of Health that is devoted to improving neonatal neurodevelopmental outcomes. She is the lead author, along with Drs. Auerbach and Derman, of a recent publication on perinatal iron deficiency and implications for mothers and newborns.[12] Early in her career, Dr. Juul identified clinical practices for decreasing the severity of anemia in preterm newborns that could decrease the need for transfusions or erythropoietin treatment.[18] Dr. Nancy Krebs provided leadership to a Global Network-sponsored study, funded by the Bill & Melinda Gates Foundation, which confirms the benefit on fetal growth-related birth outcomes of nutritional supplements commenced before conception or by late in the

first trimester of pregnancy as compared to standard of care.[19] She is an author, together with Dr. Georgieff, of a review of the benefits and risks of iron supplementation in iron-deficient, iron-sufficient, and iron-overloaded pregnant women and children.[20] Dr. Jane Sandall, a Professor of Social Science and Women's Health at King's College, London is recognized as both an academic and research leader with a global reputation for expertise in implementation science and prerequisites essential for ensuring scale-up of positive research findings.

In addition to utilizing experts for the formulation of the *RAPIDIRON* study design, the creation of a Technical Advisory Group (TAG) represents a means for ensuring continued involvement of experts as well as stakeholders who can influence adoption of more effective approaches for reducing anemia in pregnancy, especially in low- and lower middle-income countries. The composition of the TAG includes representatives from India that serve in various leadership roles, researchers from the World Health Organization (WHO), the International Federation of Gynecology and Obstetrics (FIGO), the Bill & Melinda Gates Foundation, and other individuals having specific expertise in the broad area of anemia in pregnancy

D. Research Design and Methods

To understand current practices, baseline information will be collected from providers and administrators of participating primary and community health centers. Consumers of PHC and CHC services—women who have reached at least 20 weeks of pregnancy--will also be questioned. Findings from this initiative will guide the economic analysis and help inform scale-up of anemia therapy. Examples of information to be obtained during the preparatory phase of this overall project include:

- Availability of iron and folic acid tablets and the protocol used for tablet distribution;
- Techniques used for monitoring adherence to instructions for appropriate ingestion of tablets;
- Timing for measurement of Hb levels in pregnant women and referral patterns for low hemoglobin;
- Compliance with the recommended anthelmintic regimen;
- Availability, use, timing, and dosing of IV iron sucrose or other approved IV iron formulations;
- Level of adherence to the prenatal care visit schedule;
- Number/percent of women who return for a visit approximately 6 weeks postpartum; and
- Baseline cost estimates for provision of the anemia bundle and costs associated with adverse clinical outcomes.

The formal research design is a 3-arm, randomized, controlled trial that will be implemented within geographic clusters in Belagavi, Bagalkot, and Raichur districts of Karnataka as well as clusters in Jaipur, Rajasthan. Prior to initiation of participant recruitment, community sensitization will have occurred in the villages located in the clusters. Accredited Social Health Activists (ASHAs) who live in and provide services to the villages will help identify potential study participants early in their pregnancies and accompany them to screening visits. ASHAs will also be available to accompany participants to subsequent study-related visits. Additionally, mobile teams, generally comprised of a study nurse and a laboratory technician, will respond to a call to go to a participant's delivery facility to ensure study-related tasks are performed and delivery data are collected and entered into data forms on a timely basis. Members of these teams can also be used to go to a participant's home or current location for other study related activities.

Study participants will be recruited from among pregnant women who obtain antenatal care at participating PHCs and CHCs at about 12 weeks of pregnancy or early in the second trimester. Standard of care for this visit is analysis of a blood sample to determine Hb level. Consistent with MOHFW guidelines, pregnant women who are identified with a Hb level under 7 g/dL will be

ineligible for participation in *RAPIDIRON;* they will instead be referred to a facility where they can be evaluated to determine the etiology of the anemia and receive appropriate care. Pregnant women with Hb 7 - 10.4 g/dL will be screened for consistency with initial eligibility criteria, including 18-40 years of age and intent to remain in the research area throughout delivery and the postpartum period. If no exclusionary criteria are known to apply, pregnant women with Hb in the specified range will be educated about the study and given the opportunity to consent. If initial eligibility criteria are met and consent is provided, blood will be drawn and transported to respective study hospitals to confirm moderate anaemia of 7.0 - 9.9 g/dL and iron deficiency status (Serum ferritin < 30 ng/ml and/or TSAT < 20%) along with CBC and reticulocyte indices. The results for Hb and the other two iron indices will be provided to the clinical staff at the participant's PHC or CHC prior to the subsequent study visit (#2) to allow determination of eligibility for a participant's continuation in the study. Dependent on their state of residence, the women eligible on laboratory parameters will be referred for a visit to either the JNMC affiliated KLE Dr. Prabhakar Kore Hospital and Medical Research Center (Belagavi), an associated hospital of S.N. Medical College, Bagalkot, Raichur Institute of Medical Sciences, or the hospital associated with SMSMC (Jaipur, Rajasthan) for a pregnancy-dating ultrasound to confirm a singleton pregnancy with live fetus that has not advanced beyond the timepoint for randomization to a study arm. This second, study-related visit should occur at about 12-16 weeks of pregnancy. Consistent with regulations governing ultrasounds, no information about sex of the fetus will be provided. Those eligible after dating ultrasound will be considered for randomization between 14-17 weeks. As an exploratory component of this study, the blood drawn at the first visit will be used to determine complete blood count (CBC) and reticulocyte indices--specifically reticulocyte hemoglobin (Ret-He) and immature reticulocyte fraction (IRF). Additionally, a sub-sample of 200 participants from each of the 4 sites will be tested for B12 and folate levels, and a sub-sample of 120 women from each of two sites: Belagavi and Jaipur, will be tested to determine baseline serum phosphate levels.

Except for blood samples obtained from pregnant women and analyzed onsite at the initial screening visit to determine Hb level, blood collected subsequently for study-related purposes will be sent to the central laboratory designated for each of the four research sites. Use of the specified central laboratories will ensure greater standardization of laboratory procedures, access to appropriate and dependable laboratory equipment, compliance with laboratory quality control measures, and confidence in test results. The central laboratories of the four participating study hospitals will ensure availability of results for entry into the *RAPIDIRON* database. Medical Officers (or designated clinical staff) of PHCs or CHCs will be provided test results when needed. Hemoglobin values will be sent throughout the course of the study. TSAT and ferritin indices will be forwarded to PHCs and CHCs to enable eligibility screening for randomization at the third visit. Glucose levels will be provided subsequent to screening for gestational diabetes; and out-of-range serum phosphate results for blood collected twice post-treatment from women in the IV arms will be provided for review by PHC or CHC clinical staff.

All pregnant women completing visit #2 will return to the PHC to complete eligibility screening for randomization. When a woman's dating ultrasound indicates a singleton pregnancy of less than 14 weeks, unless medically indicated, she will not be scheduled to go to the PHC or CHC until she reaches the 14th week of pregnancy. Visit #3 is intentionally designed to occur between the interval of 14-17 weeks of pregnancy to coincide with antenatal care recommendations of the Ministry of Health and Family Welfare. Further, the visit is timed to ensure that anemia treatment for randomized participants will be initiated early in the second trimester, up to 17 weeks 0 days, as there is no safety data relative to use of IV iron in the first trimester.

During visit #3, the inclusion and exclusion criteria (found on page 17) will be applied to determine if a pregnant woman is eligible for continued study participation and randomization. Data from the Maternal Newborn Health Registry, funded by NICHD in association with its Global Network for Women's and Children's Health Research, were used to assess the impact of various levels of

anemia among pregnant women and their newborns.[6] Among a cohort of 92,247 Indian and Pakistani pregnant women, 87.8% were anemic. When classified as normal or by anemia severity (that is, mild, moderate, or severe), the highest percentage of pregnant women, or 49.2%, were in the moderate group (Hb 7 - 9.9 g/dL); and this secondary analysis found that these moderately anemic women had higher rates of poor pregnancy outcomes than pregnant women having higher Hb concentratons.[6] This is a finding consistent with the published evidence from small, interventional studies. For pregnant women residing in under-resourced countries and having mild anemia (Hb between 10 – 10.9 g/dL), research findings have not shown a consistent relationship between anemia and poor pregnancy outcomes.[21] Thus, for this research, only anemic pregnant women consenting to study participation will have the opportunity for randomization to a study arm if blood drawn at the second visit indicates that they have moderate anemia (that is, hemoglobin concentration of 7 - 9.9 g/dL) as well as evidence of iron deficiency defined for this study as transferrin saturation (TSAT) < 20% and/or ferritin <30 ng/mL.

At visit #3, randomization of eligible pregnant women will be conducted to obtain a 1:1:1 allocation ratio among the three treatment arms consisting of an oral iron arm and two IV iron arms (a ferric carboxymaltose arm and an iron isomaltoside arm). Randomization will be stratified by enrollment by research area (located in either Rajasthan or within each of the three districts in Karnataka), with the four Indian research areas comprising the four randomization strata. Randomization sequences will be generated for each stratum using a computer-generated algorithm based upon a randomly permuted block design with randomly varied block sizes. The block sizes will be known only to personnel responsible for the randomization algorithm. Details of the randomization algorithm and the randomization process will be included in a Randomization Plan developed during the preparatory phase of the study.

All randomized participants will be given a single dose of deworming medication which government guidelines specify should be taken in the second trimester of pregnancy.[2,3] Women assigned to the oral iron arm will receive iron and folic acid tablets consistent with the most recent *Anemia Mukt Bharat* treatment guideline for dosage and frequency as found online.[3] That guideline specifies that the tablets are to be taken twice daily for anemia treatment; but if Hb reaches a normal level for pregnancy ($\geq$11 g/dL), the tablets are to be taken at a prophylactic frequency of once daily.[3] The women randomized to an IV iron arm will be provided folic acid tablets to enable compliance with the recommended daily dosage. The IV iron infusions will be performed, preferably on the same day, at a participating community health center (CHC). On a case-by-case basis, the infusion may be delayed a short time conditional upon IV iron being administered by 17 weeks 0 days of pregnancy. The visit for an IV infusion is labeled #3a in Appendix B.

Pregnant women randomly assigned to an IV iron arm, if weighing 50 kg or more, will receive the assigned single-dose formulation with 1000 mg of iron. However, women under 50 kg will receive a lower dose of iron as determined by a formula that has been used by both manufacturers of the IV iron formulations to be used in the study—that is, 20 mg iron/kg body weight.[22,23] Both IV iron formulations (described in Appendix C) are approved and available commercially in India, and both are proposed for use in this study for the following reasons: 1) they allow single-dose infusions of up to 1 gram of iron; 2) they have proven efficacy and availability in many countries of the world; 3) they are associated with very low rates of adverse events; 4) high quality studies show no difference in severe side effects among available IV iron formulations, and 5) there is greater probability that multiple studies of various single-dose formulations will be instrumental in driving down market prices and lead to public sector pricing and greater utilization.

JNMC, SNMC, RIMS, and SMSMC investigators will identify a pharmacist who will be assigned to the research team in their respective state to assure compliance with the specified randomization process and receipt of the correct iron supplementation modality by participants. Oral iron use will not be masked. However, blinding will occur for the two IV iron arms since IV

iron participants will know only that they have been randomly assigned to receive an IV iron infusion without knowing the specific arm and the formulation that will be used. Further, neither the PHC staff nor the CHC infusion team will know which IV iron formulation was assigned. Rather, a pharmacist associated with each CHC performing IV iron infusions for the trial will be designated to prepare the randomly assigned IV iron formulation, per participant weight and manufacturer instructions, on the day of treatment. When a participant is to be provided an infusion at the CHC, the pharmacist will collect an infusion order from the participant. The form will have a randomization number and the participant's weight, which is needed for correct dosing. The pharmacist will match the number to randomization tables that have been provided and then prepare the correct formulation. Those who are involved with the administration of IV iron infusions for this trial will be thoroughly trained to ensure appropriate performance of their clinical and research responsibilities; this includes CHC Medical Officers and nurses who will be trained as coordinators/infusion nurses. Notably, those who will administer an IV iron infusion will be trained to ensure that it is given over an equivalent period of time consistent with package labeling for both the formulations; training will also provide instructions pertinent to an observational period recommended by both formulation manufacturers subsequent to infusion completion (of at least 30 minutes).[22,23] This time should be sufficient for recognizing and appropriately addressing drug-related reactions should any occur as well as accurately recording data in the infusion data form.

Although the *Anemia Mukt Bharat* national guidelines[2,3] indicate that IV iron sucrose or ferric carboxymaltose (FCM) may be considered as a first-level treatment when anemia has been detected late in pregnancy or when compliance to an oral iron regimen is likely to be low, the *RAPIDIRON Trial* will use ferric carboxymaltose in addition to iron isomaltoside (also known as. ferric derisomaltose). However, IV iron sucrose will not be used for study-related infusions, primarily because clinical trials have not shown that it has advantages over single-dose IV iron.[24,25] Further, the package insert for iron sucrose indicates the need for five individual and staggered infusions, which results in greater potential for non-compliance of iron sucrose compared to newer single-dose IV iron formulations. A 2018 article in the Journal of the Indian Society of Hematology and Blood Transfusions states that the problem of multiple infusions "has been circumvented by the newer preparations like iron isomaltoside and ferric carboxymaltose which allow larger infusion doses."[26] Faculty of the All India Institute of Medical Sciences recently completed a study that provided evidence that more convenient single-dosing of IV iron resulted in a significantly higher rise in Hb over 12 weeks compared to iron sucrose. Those receiving IV iron also had greater improvement in fatigue scores and required fewer facility visits for treatment. No serious adverse events occurred in either study group.[24]

Two weeks following an IV iron treatment, only IV iron participants will visit the PHC or CHC (Visit #4 in Appendix B). A blood sample will be collected and analyzed to determine serum phosphate levels. Recent published reports have associated intravenous ferric carboxymaltose with a significant reduction in serum phosphate level in some patients[27] although the clinical significance is unclear.

Blood samples will be obtained for determination of hemoglobin, TSAT, and ferritin during the antenatal care visit to a PHC or CHC at 20-24 weeks of pregnancy (#5). At the 26-30-week visit (#6), blood samples will be used to assess hemoglobin, TSAT, ferritin, CBC and reticulocyte indices. These visits are consistent with the MOHFW antenatal visit schedule, and they will allow collection of blood to assess changes in hemoglobin levels and iron deficiency status as appropriately measured by TSAT and ferritin levels. Consistent with governmental guidelines, the screening test for gestational diabetes will be done at the PHC or CHC visit #6, which is scheduled to occur at 26-30 weeks of pregnancy. Recognizing that gestational diabetes can affect birth

weight and neonatal iron status,[28,29] data will be analyzed by study arm and presented for the subset of gestational diabetic women.

Once pregnant women are enrolled and randomized to a study arm and treated, a plan for "rescue therapy" will be implemented should a participant's hemoglobin level drop below 7 g/dL. Current *Anemia Mukt Bharat* guidelines indicate that when a pregnant woman has severe anemia (< 7 g/dL) a referral should be made to a First Referral Unit (FRU) or District Hospital (a facility with tertiary care services) for further investigation of causes of anemia and possible consideration of treatment with either IV iron sucrose or ferric carboxymaltose[3] (unless evaluation of causes of anemia uncover a diagnosis that contraindicates such treatments). Another updated treatment guideline[3] calls for pregnant women identified with moderate anemia before the third trimester and prescribed iron/folic acid tablets to be similarly referred for further investigation and consideration of an alternate therapeutic approach if improvement in Hb level is <1 g/dL after at least 2 months since initiation of oral iron treatment. Thus, it is considered appropriate that *RAPIDIRON* participants, regardless of study arm, also be referred if blood drawn at PHC or CHC visit #6 (at 26-30 weeks of pregnancy) indicates that hemoglobin improvement is <1 g/dL. Data will be captured to enable comparison between study arms of occurrences of rescue plan implementation as well as the need for referral due to insufficient treatment response. Results of hematologic assessments will be obtained, when appropriate, as such reports could identify reasons for non-response to the randomly assigned treatment. Participants referred for either specified reason will be expected to continue in the study and participate in remaining monitoring visits.

A blood sample will be collected at the PHC or CHC at visit #7, which is designed to occur at 30-34 weeks of pregnancy. Hemoglobin test results will be used to determine if a participant's hemoglobin has improved enough to be considered normal for pregnancy, that is $\geq$11 g/dL. When a study participant presents for delivery (visit #8), blood will be drawn to determine if maternal hemoglobin level has reached $\geq$11 g/dL. If a study participant is found not to be in true labor and is discharged before a blood sample can be obtained, every effort will be made to obtain a pre-delivery blood sample at a subsequent visit whey delivery actually occurs.

Visit #8 is intended to be the source for other valuable information related to anemia. The time that intervenes between birth of a baby and umbilical cord clamping will be observed and recorded to allow a better understanding of cord clamping practices, which can affect rates of vaginal bleeding and newborn iron stores. Data collection will facilitate comparison of practices between the four research sites with the guidelines of the World Health Organization. Notably, it is a recommended strategy of *Anemia Mukt Bharat* to promote "practice of delayed cord clamping (by at least 3 minutes or until cord pulsations cease) in all health facility deliveries followed by early initiation of breastfeeding within 1 hour."[3] Following delivery, cord blood samples will be obtained and analyzed to determine hemoglobin, TSAT, ferritin and reticulocyte indices; samples will also be bio-banked for possible future analyses.

It is expected that many of the randomized participants will deliver at the study PHCs and CHCs, but others may utilize other birthing facilities in the research sites of Karnataka and Rajasthan. Community sensitization activities will be designed to reach as many delivery service providers as feasible to promote support for the study. However, for purposes of *RAPIDIRON,* study participants or someone accompanying them to birthing facility will be asked to inform a trained mobile team (including a nurse and laboratory technician) that will be expected to report to the facility to ensure performance of data collection tasks essential for this study including: collection of blood from the participant prior to delivery; collection of cord blood; measuring weight and length of the newborn; recording the time between a baby's birth and clamping of the umbilical cord; capturing delivery details relative to the primary and secondary outcomes of the study; and ensuring timely transport of samples to the designated central laboratory. If a mobile team is unable to arrive at a facility prior to delivery, the team will be expected to visit the facility within 72

hours of the participant's delivery and obtain as much study data as feasible by talking to the participant and the facility provider and reviewing the medical record. When a participant elects to deliver at a study PHC or CHC, the facility will have trained staff familiar with the study; and dependent on the resources of the facility, it may be possible to collect a pre-delivery maternal blood sample as well as a sample of cord blood and store it until the arrival of the mobile team.

The last study visit, #9, will occur at about 42-days post-delivery. An ASHA will accompany the mother and her baby to the participant's PHC or CHC where blood will be collected to determine the mother's hemoglobin, TSAT, ferritin level and reticulocyte indices. Mothers in the IV iron arms will also be tested a second time for serum phosphate levels. All mothers will be administered a validated quality of life questionnaire and asked about breast feeding practices. The data generated as a result of this visit may be useful if a study is done to assess growth and neurodevelopmental status of the offspring at defined timepoints to 3 years of age.

See Appendix B for a visual presentation of participant milestones and the plan for study visits.

E. Statistical Methods

1. Sample Size Justification

For this 3-arm trial, recruitment and randomization of participants will continue until there is confidence that there will be a minimum of 1,332 randomized participants with adequate data sets in each arm. The two primary outcomes are conversion to non-anemic state (Hb $\geq$11 g/dL) prior to delivery at either of two specified timepoints in the last trimester of pregnancy and LBW delivery (under 2500 grams). Four primary hypothesis tests will be performed: two tests comparing each IV iron arm to the oral arm with respect to the rate of conversion to non-anemic status prior to delivery and two tests comparing each IV iron arm to the oral arm with respect to the rate of LBW. In all cases, the null hypothesis is that the rate in the IV arm is the same as that in the oral iron arm. To control the type-I error rate across both outcomes and all tests, the alpha level for the comparison of rates of non-anemic patients will be 0.001, divided evenly between the two comparisons, and the alpha level for the comparison of LBW rates will be 0.049, divided evenly between the two outcomes. That is, each IV iron arm will be compared with the oral iron arm with respect to rates of conversion to non-anemia at the 0.0005 level, and each IV iron arm will be compared with the oral iron arm with respect to rates of LBW at the 0.0245 level.

The sample size for *RAPIDIRON* is primarily driven by the comparison of LBW rates. A rate of 25% LBW is assumed in the oral iron arm. The assumption for the LBW rate in this arm is considered reasonable based upon a rate for LBW of 21% found in a Parks et al. paper of anemic study participants with a Hb level at delivery of 7 - 9.9 g/dL[6] and our inclusion of more rural sites for participant selection. The referenced article used data from the NICHD Global Network's Maternal Newborn Health Registry for JNMC's geographic clusters participating in the Registry as well as data from other Global Network clusters located around Nagpur, India and in Pakistan.

Assuming a true LBW rate of 25% in the oral iron group, a final sample of 1,332 per group gives 80% power to detect a 20% relative reduction (relative risk of 0.8; 20% LBW rate in a particular IV iron group) at the alpha=0.0245 level allowing for one interim analysis when 1/3 of the information on LBW is available. With p-value boundaries of 0.000026 at the interim analysis and 0.02449 at the final analysis, based on 10,000 simulations, with complete data on 1,332 subjects per arm (444 per arm at the interim analysis), if both IV iron arms have true risk of LBW of 20%, there is a 1.6% probability of stopping early for efficacy, approximately 80% probability of concluding a particular IV arm has lower LBW risk than the oral arm, and greater than 90% probability of concluding at least one of the IV arms is better than the oral iron arm. It is projected that approximately 4,320 pregnant women will need to be randomized 1:1:1 to each of the three study arms based on assuming 7.5% missing birth weight data (due to stillbirth and other

reasons). Any one of the four research teams (based in Belagavi, Bagalkot, Raichur, or Jaipur) will enroll and randomize no more than 60% of all study participants.

With 1,332 study participants per group, we have greater than 95% power to detect differences in rates of non-anemia of at least 10% at the alpha=0.0005 level although differential rates approaching 30% are anticipated.

2. Primary Data Analysis

The primary analysis for anemia will compare each IV iron arm to the oral iron arm with respect to the percentage of participants who achieve Hb of ≥11 g/dL at either a 30-34 week antenatal visit or at a birthing facility based on blood collected prior to delivery using a Cochran-Mantel-Haenszel (CMH) chi-square test stratified by enrollment site (randomization stratum) at the 0.0005 level. The CMH-adjusted risk ratio and associated 99.95% confidence interval will be calculated for both comparisons. No interim efficacy analysis is planned for the anemia outcome.

Each IV arm will be compared to the oral iron arm with respect to risk of LBW using a CMH chi-square test stratified by enrollment site at the 0.000026 level when data are available on at least 444 subjects per group (1/3 of expected information). The study will stop for efficacy if either IV arm shows significantly lower risk of LBW at the interim analysis. If the study is not stopped early, the final tests will be performed at the 0.02449 level. Stopping boundaries were calculated using a Lan-Demets spending-function approach with O'Brien-Fleming bounds. The CMH-adjusted risk ratio and associated 97.55% confidence interval will similarly be calculated for both comparisons.

The primary analysis will be performed using the intent to treat (ITT) cohort. Missing anemia and LBW data will be imputed using multiple imputation. The exact method of imputation will be specified in the statistical analysis plan prior to analysis. Fifty data sets will be imputed and the Wilson-Hilferty transformation[30,31] will be applied to the CMH statistics fit to each data set. Results will be pooled using the method of Rubin[32] to calculate the overall test of significance. The log (relative risk) estimates of each imputed data set will similarly be combined.

3. Secondary Analyses
   A. Additional Analyses of Primary Outcomes:
      i. IV iron arms will be descriptively compared with respect to the rate of LBW births and rates of non-anemic patients by estimating the CMH-adjusted risk ratio and associated 95% confidence interval.
      ii. An additional analysis comparing IV iron to oral iron will be performed on the per protocol cohort.
      iii. An exploratory Hb-based subgroup analysis will be performed to estimate the effect of treatment on conversion to non-anemia status and the risk of LBW solely by level of Hb measured prior to randomization (between the beginning of week 14 and 17 weeks 0 days of pregnancy). Hb-based subgroups will be defined based on clinical considerations but may be collapsed depending on the sample sizes within each group.
   B. Analyses for Secondary Outcomes:
      i. Included among secondary outcomes to be used for characterizing participant experiences and assessing differences among study arms are changes in hemoglobin concentration by subgroups (i.e., 7 – 7.9, 8 – 8.9, and 9 – 9.9 g/dL), variation in participant iron indices at specified timepoints, the need for "rescue therapy" if a participant's Hb drops below 7 g/dL, referral for evaluation due to less than 1 g/dL improvement in Hb at 26-30 weeks of pregnancy, Hb and other iron indices of cord blood, weight gain of participants by trimester of pregnancy, mode of delivery/C-section, antepartum and severe postpartum hemorrhage, hypertensive disorders, maternal or neonatal infections including documented COVID-19,

maternal and neonatal mortality, preterm and small for gestational age births, pregnancy loss and stillbirths, birth weight of live born babies, newborn length, the need for neonatal resuscitation, neonatal admissions to an intensive care unit, time from delivery to cord clamping, unanticipated or extended hospitalizations, breastfeeding practices, and maternal well-being (quality of life). Missing secondary outcome data will not be imputed.

ii. Analysis of categorical secondary outcomes with respect to treatment arm differences will use generalized linear models to estimate relative risks and associated confidence intervals.

iii. Analysis of continuous, longitudinally-measured, secondary outcomes with respect to treatment arm differences will use mixed effects linear regression, accounting for correlation among repeated measurements over time and adjusting for site as a random effect. Mean differences between randomization groups will be estimated from the model results at each measurement time along with appropriate confidence intervals.

iv. Association of hemoglobin levels at delivery with LBW delivery will be evaluated using logistic regression. For this analysis hemoglobin levels will be categorized using the WHO definitions for severity: < 7 g/dL (severe); 7 - 9.9 g/dL (moderate); 10 - 10.9 g/dL (mild); and $\geq$11 g/dL (non-anemic or normal).

v. If one or both of the IV iron formulations are demonstrated to be effective in transitioning women to non-anemic status (Hb $\geq$11g/dL) in the third trimester of pregnancy at either or both of two timepoints prior to delivery, or if one or both IV iron formulations are effective in reducing the risk of LBW deliveries, a series of secondary exploratory analyses will be performed to identify baseline factors that are predictive of treatment success. The objective of these analyses will be to support future implementation of the treatment regimen in broad populations by identifying subpopulations most likely to benefit from the treatment regimen. Separate logistic regression models will be constructed for the anemia and LBW outcomes, with predictors to include Hb levels at the time of randomization as well as TSAT and ferritin levels and other baseline characteristics identified in the Statistical Analysis Plan.

4. Interim Analysis

An interim analysis for efficacy for the LBW outcome will be performed when data are available on at least 444 subjects per group (1/3 of expected information). Using stopping boundaries from a Lan-Demets spending function with O'Brien-Fleming bounds, we set α_1=0.000026 so that the study would stop if the comparison of either IV arm to the oral arm had p<0.000026 at the interim analysis. Assuming the observed risk of LBW is 25% in the oral arm, this would occur if the observed risk of LBW in a particular iron arm were 13.7% or less. To maintain an overall type-I error rate of 0.0245 for each IV vs. oral comparison, if the null hypothesis is not rejected at the interim analysis, the final comparisons for LBW will be completed at the 0.02449 level.

Assuming the study is not stopped for efficacy, one formal interim analysis for futility will be completed based on a data snapshot taken when the anemia outcome is available for 666 subjects per group (1/2 of expected information). The interim analysis for futility will involve the conditional power associated with two hypothesis tests: the two-degree of freedom CMH test of differences in prevalence of anemia prior to delivery across the three treatment arms and the two-degree of freedom test of differences in risk of LBW across the three treatment arms. If analyses for both primary efficacy outcomes show a conditional power of less than 0.2 based on the observed data at the time of the interim analysis and the assumed effect for the study design, the Data and Safety Monitoring Board (DSMB) may consider recommending that the study be stopped.

The analysis for safety will have two components. First, point and 97.5% confidence interval estimates of the risk of mortality and incidence of at least one SAE will be developed for each of the three treatment arms. If the interval estimates provide evidence that either of the active IV iron treatment arms has significantly higher risk of either mortality or adjudicated SAE incidence than the active comparator arm (oral iron), the DSMB will consider recommending stopping enrollment on that active IV iron treatment arm. In making the recommendation, the DSMB can consider the overall risk profile of the treatment arms and any evidence of efficacy that has been accumulated at the time of the interim analysis.

Additional details of the planned interim analysis will be developed in collaboration with the DSMB and the details will be included in a formal Interim Analysis Plan that will be approved by the DSMB prior to enrollment.

5. Safety Analyses

All safety analyses will be descriptive based on the safety cohort with no planned formal inference for safety. All adverse events will be summarized by system organ class by arm with point and interval estimates of the risk of each of these events estimated by either exact binomial methods or normal approximations to the binomial as appropriate for the incidence of the event. Descriptive statistics will also be generated for maternal and infant mortality and for incidence of SAEs.

6. Analysis Cohorts
   A. Intent-to-treat (ITT) cohort: All randomized study participants will be included using group assignments as randomized.
   B. Per-protocol cohort: All study participants who receive the complete, recommended dosage of the randomly assigned IV iron formulation between the beginning of the 14th week and 17 weeks 0 days of pregnancy will be included in this cohort as will all study participants assigned to oral iron therapy who take equal to or greater than 75% of prescribed pills (as each woman given oral iron will be asked to maintain a diary indicating her pattern of use). However, use of any non-study-provided iron preparation post-randomization will represent an exclusion for the purpose of the per protocol analysis. Additionally, a participant assigned to an IV iron arm that receives only a portion of the recommended dosage for the randomly-assigned IV iron formulation will also be excluded.
   C. Safety cohort: All study participants who are randomized and receive either the provided oral iron tablets or at least some portion of the one-time, recommended dosage of the assigned IV iron formulation and who provide any safety data subsequent to treatment will be included in this cohort. For all safety analyses, these participants will be included in the analysis based on treatment actually received, not by randomization arm.

Assignment of patients into the various cohorts and treatment arms will be determined based on a masked data review prior to initiation of analyses.

F. Gender/Minority/Pediatric Inclusion for Research

Since this study is designed to assess benefits of single-dose IV iron administration to pregnant women with iron deficiency anemia, such women will necessarily constitute the participants to be randomized for this trial.

The study is to be carried out in two states of India; thus, participants will be classified as adult female Asians. Pregnant women utilizing facilities classified in the Indian public health system as primary or community health centers will have the opportunity to participate if they meet specified eligibility criteria. No pregnant woman will be excluded because of socio-economic status or other

personal characteristic that could be considered to qualify such women as minorities. Anemia in pregnancy can have detrimental outcomes for both a pregnant woman and her offspring. When a pregnant woman lacks sufficient iron stores to meet her needs and transfer adequate iron to the developing fetus, there may be higher risks for adverse consequences including fetal and neonatal death, preterm and low birth weight babies. The study includes cord blood collection after delivery to allow determination of Hb level and other iron indices and to provide comparative data useful for study purposes. Participation in the study will end for mothers and babies at about 42 days post-delivery.

G. Human Participants (Subjects)

1. Participant Characteristics and Inclusion and Exclusion Criteria

It is estimated that approximately 16,000 pregnant women will be screened for low hemoglobin at a visit during the first trimester of pregnancy or early in the second trimester. This should provide an adequate number of pregnant women who are subsequently determined eligible to be randomized equally to each of the three study arms. In India, adulthood begins at age 18 and marriage is discouraged prior to this age. Research involving children is permitted, but generally discouraged if the research can achieve its objective without the involvement of children. Thus, those approached for study participation at a first antenatal visit to a PHC or CHC should be in the age range of 18-40 and capable of providing informed consent on their own (although potential participants can obtain consultation from family members to help them reach a decision about study participation). Inclusion criteria follow for both initial participation in the study and for continued participation and randomization at a subsequent study visit (which is identified as #3 in Appendix B).

Inclusion Criteria for Study Consent for Initial Participation

- Pregnant women between 18–40 years of age at time of consent that received education about the study and were capable of giving informed consent;
- Hemoglobin concentration of 7 – 10.4 g/dL;
- Expressed intent and expectation of remaining in the designated research area during the pregnancy and delivering at a facility in or near the research area and remaining in the area to enable study participation and data collection consistent with the research protocol;
- Expressed willingness that specifically includes agreement to randomization to the standard care study arm (of oral iron) or to one of the two arms involving treatment with single-dose IV iron.

Additional Inclusion Criteria for Randomization and Continued Study Participation

For randomization to a study arm:

- Iron deficiency anemia defined for this study as moderate anemia with hemoglobin concentration level between 7 - 9.9 g/dL, serum transferrin saturation (TSAT) <20%, and/or ferritin <30 ng/mL;
- Presence of a live singleton, intrauterine fetus and dating ultrasound (at visit #2) that indicates a pregnancy that, at randomization, would be between the beginning of week 14 and prior to 17 weeks 0 days.

Exclusion Criteria

- Fetal anomaly if detectable when an initial ultrasound is done to date the pregnancy (subsequent discovery of a fetal anomaly is not viewed as an exclusion criterion);
- History of cardiovascular disease, hemoglobinopathy, or other disease or condition considered a contraindication for treatment, including conditions recommended for exclusion by the manufacturers of oral or IV iron to be used in this study;
- Any condition that in the opinion of the consenting physician warrants study exclusion.

Termination by a physician may occur at any time during the study for documented medical cause.

2. Sources of Research Material

At the first antenatal visit, a blood sample will be collected and analyzed onsite at a PHC or CHC to determine Hb level as this is standard of care. Blood collected from the consented participants at the initial visit will also be analyzed in the central laboratories to determine Hb concentration and determine if TSAT and ferritin values are indicative of iron deficiency anemia amenable to iron therapy. For safety monitoring purposes, at the second visit, a sub-sample of 200 participants from each of the four research sites will be tested to determine baseline B12 and folate levels; and a sub-sample of 120 pregnant women from two research sites (Belagavi and Jaipur) will be tested for baseline serum phosphate levels. Also, during some monitoring visits post-treatment, blood samples will be obtained to determine Hb concentration as well as other iron indices, CBC and reticulocyte indices. Glucose testing will occur at a study visit scheduled between 26-30 weeks of pregnancy. After participants arrive at a birthing facility but pre-delivery, blood will be collected to determine Hb level. Subsequent to delivery, cord blood will be obtained to assess Hb, TSAT and ferritin, and reticulocyte indices. Participants that received IV iron will be tested to determine serum phosphate level after about 2 weeks post-treatment and again at the last study visit scheduled to occur at the 6-week post-delivery visit. Other than collection of blood samples from all randomized study participants for analysis of Hb, TSAT, ferritin, CBC and reticulocyte indices, these participants will also be administered a validated quality of life questionnaire.

While results of blood tests will result in much of the data needed for the research, observations (for example, during the delivery), querying participants, and review of medical records when necessary to obtain required data also represent sources of study data. Forms will be used for recording data, and appropriate forms will be available at participating PHCs, CHCs, the designated central laboratories and facilities where participants are expected to deliver. To protect participant rights to confidentiality and privacy only a study identification number will be recorded on these forms rather than personal, identifying data.

3. Description of Plans for Recruitment and Consent Procedures

Community sensitization will occur in those communities that are typically served by the PHCs and CHCs that have agreed to participate in this study. Sensitization generally consists of research staff holding meetings with community leaders, health officials that supervise participating facilities, and others such as married couples who may consider study participation Accredited Social Health Activists (ASHAs) who live within the communities of recruiting PHCs or CHCs will participate in the study (with authorization of the supervising health officials) and be trained to help identify women early in pregnancy who are potential study enrollees. They will also be available to accompany potential participants to facilities for screening, dating of the pregnancy (by ultrasound), randomization followed by treatment, antenatal monitoring and delivery, phosphate testing only of IV iron participants (2 weeks post-treatment), and the 42-day post-delivery visit.. ASHAs receive incentive-based fees for their work associated with government-defined responsibilities which include identifying pregnant women and encouraging antennal care, preferably starting in the first trimester of pregnancy; periodically visiting pregnant and postpartum women and newborns; and transporting mothers and children to health facilities for needed care.

ASHAs who have received education on IDA can be an additional source of information about the study. However, consent will be obtained by a trained facility health care provider or research staff member who is a physician or other health care provider who has adequate health-related training to educate and answer questions from a potential participant about IDA and the nature of the study.

4. Description of Risks and Assessment of Likelihood and Seriousness

Side effects of IV iron are rarely associated with serious consequences. Most adverse drug reactions resulting from use of ferric carboxymaltose or iron isomaltoside, as reported during use in clinical trials or post-marketing experience, appear in the uncommon column of adverse event tables found on the Website of the Electronic Medicines Compendium (eMC).[22,23] Risk of uncommon events, based upon event to drug administrations, was reported as ≥1/1,000 to <1/100), while common events occur in ≥1/100 to <1/10 administrations. The list of either uncommon or common drug reactions for the formulations to be used in *RAPIDIRON* includes flushing, sweating, blurred vision, nausea, injection/infusion site reactions headache, hypophosphataemia, dizziness, fatigue, tachycardia, hypotension, hypertension, abdominal pain, vomiting, dyspepsia, constipation, diarrhoea, dyspnoea, pruitus, urticaria, dermatitis, myalgia, arthralgia, muscle spasms, pain in extremity, back pain, arthraigia, pyrexia, chills/shivering, chest pain, oedema peripheral, infection, local phlebitis reaction, and skin exfoliation.[22,23] Anaphylaxis, a severe hypersensitivity 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 considered a rare adverse drug reaction with risk of occurrence, as reported in the tables on the eMC Website, as ≥1/10,000 to <1/1,000. Examples of other drug reactions characterized as rare are loss of consciousness, anxiety, phlebitis, syncope, presyncope, bronchospasm, flatulence, arrhythmia, angioedema, pallor, face oedema, malaise and influenza like illness.

A complete list of adverse drug reactions associated with the study IV iron formulations will be included in *RAPIDIRON's* Manual of Operations. An article published in 2006 indicated that reported adverse drug events (ADEs) for the single-dose IV iron formulations had been decreasing over time and that the overall rate was "extremely low" at about 38 events per million.[33] 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 side effects are quite common and can affect up to 70% of those prescribed the oral iron formulation most often recommended in India (ferrous sulfate).[35] 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 most serious problems with oral iron is that it's not taken as prescribed. Additionally, a large portion of those that take oral iron per instructions experience side effects and simply cannot tolerate taking the drug; consequently, such symptoms may cause dietary changes that result in less than ideal weight gain during pregnancy.

5. Description of Procedures for Protecting Against or Minimizing Potential Risks

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, serious adverse events are 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.[36] In a 2017 article, he stated that evidence indicates that single-dose formulations currently available in the US are "all safe and effective and there are no major, clinically important differences."[37] The literature on both ferric carboxymaltose and iron isomaltoside supports this claim. The preponderance of recent reviews on the use of IV iron indicate that serious adverse events are rare, and that infusion reactions are not common when the newer single-dose 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 and others: "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 intravenous iron. Infusion should be started 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."[38] 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.[39] Prior to the provision of IV iron treatments, those administering treatment will receive comprehensive training that will include how to recognize signs of 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 community health centers. Further, IV iron will only be administered at participating CHCs when the facilities are confirmed as having capability and appropriate supplies for resuscitation (consistent with recommendations for product use). Such guidelines are already in place at facilities that provide infusion of iron sucrose or ferric carboxymaltose. Prior to an IV iron infusion, the pregnant woman to be treated will be given an explanation of risks and benefits as included in the consent form. Despite being randomized, any study participant has a right to refuse treatment, withdraw from the trial, and nevertheless receive standard antenatal care.

6. Description of Potential Benefits and Importance to the Study Participants and Others

A woman starting a pregnancy with iron deficiency anemia will likely become more anemic as the pregnancy progresses, as a result of physiologic hemodilution, unless she is treated for this problem. As noted, IDA has undesirable consequences not only for the pregnant woman but also for the developing fetus. Oral iron, as the typical approach for mild and moderate IDA treatment in pregnancy, is often limited by inadequate absorption or poor patient compliance that may be attributable to adverse side effects, particularly those gastrointestinal in nature, and the extended period of time during which oral iron should be taken.

With the use of a single infusion of IV iron, the risk of a serious adverse event is now considered marginal. Further, the newer formulations can significantly raise hemoglobin levels, replenish iron stores, and diminish IDA symptoms in the pregnant woman. And importantly, IV iron improves the pregnant woman's ability to transmit iron to the fetus who requires an adequate supply of iron for normal growth and development.

7. Discussion of Why Risks Are Reasonable in Relation to Benefits

Pregnant women with IDA can suffer a range of consequences including low energy, fainting, breathing difficulties, palpitations, sleep difficulties, and greater susceptibility to more serious complications that can lead to death or disability. When a pregnant woman has untreated IDA, there can be serious consequences for a fetus, including intrauterine death. A live-born offspring may be born preterm, small for gestational age, or with a low birth weight. Such a newborn is at much higher risk of neonatal death. Babies that survive can experience IDA and be at higher risk for cognitive and behavioral, delays or disabilities that remain throughout life, likely due to having a low birth weight combined or independently associated with iron deficiency. Provision of IV iron to a pregnant woman with IDA has been shown to reduce the risk of these maternal, fetal and newborn consequences. Although risk for the recipient of IV iron cannot be considered to be zero, the risk of a serious adverse event is supported by evidence to be extremely low. Further, a prospective study of Chinese pregnant women provided oral iron/folate supplementation or placebo/folic acid found that prenatal iron supplementation reduced anemia, iron deficiency, and iron deficiency anemia for some pregnant women, but results were suboptimal as most women and >45% of neonates had iron deficiency regardless of supplementation.[40]

A large randomized trial is urgently needed to compare the conversion rate to non-anemic status and the rate of deliveries of low birth weight babies and other meaningful outcomes in pregnant women receiving a single dose of IV iron for IDA compared to a group of pregnant women provided oral iron. Small studies utilizing IV iron formulations have shown promise, but confusing

guidelines, inconsistent implementation, and the need for multiple dosing are rate-limiting steps preventing generalizability. It is clear that single-dose IV iron infusions hold great promise for maximizing clinical outcomes in mothers and neonates. This study will provide both the data and an implementation platform upon which scale-up can occur.

H. Data and Safety Monitoring Board and Data and Safety Monitoring Plan

1. Data and Safety Monitoring Board (DSMB)

The multi-disciplinary Data and Safety Monitoring Board has five individuals. The Board Chair has expertise in high-risk obstetrics and global health research. The other members have expertise that spans obstetrics and gynecology, neonatology, biostatistics, clinical trials design and implementation, and clinical management of anemia. All members of the DSMB are free of significant conflicts of interest (i.e., financial, intellectual, professional, or regulatory) to enable performance of their duties in an unbiased manner.

The duties to be performed by the DSMB include:

- Review and approve a charter to address the committee's scope of work;
- Agree on a mutually acceptable schedule for meetings (given that DSMB participants reside in three different continents);
- Review serious adverse events (SAEs) and adverse events (AEs) and unanticipated problems posing risks to study participants or their fetuses/offspring;
- Assure that the research is conducted in a manner to minimize risk and promote safety;
- Assess data quality, participant recruitment, accrual and retention; and
- Prepare reports that outline DSMB recommendations and provide them to the study Principal Investigator, the Senior Foreign Investigator, and the Chief Quality and Safety Officer.

The DSMB met remotely to provide input into this protocol; and they are scheduled to meet again to approve the DSMB charter and ensure adequacy of the informed consent form. The DSMB will review the Data and Safety Monitoring Plan and give specific instruction if it determines the list of items to be reported and forwarded for review should be expanded. The DSMB will meet again approximately 3 months after initiation of recruitment. Thereafter, the DSMB will meet approximately every 6 months until all study participants have completed all study visits and data have been collected for outcomes through 42 days post-delivery. The DSMB may revise the meeting schedule if workload justifies this. If a scheduled meeting is considered too remote to review an SAE and determine relevant action, information may be distributed to DSMB members via email and input sent to the DSMB Chair who can communicate a recommendation representing consensus among DSMB members to senior key personnel of the study. The Chief Quality and Safety Officer will be the intermediary in supplying appropriate data to the DSMB for review.

2. Description of the Data and Safety Monitoring Plan (DSMP)

For this research, a serious adverse event (SAE) involves a randomized participant that initiated treatment OR the fetus or newborn of such a participant. To qualify as an SAE, at least one criterion below will apply to the event--

- Results in a maternal or neonatal death, or a fetal death greater than 20 weeks gestation;
- Is life-threatening;
- Requires an unanticipated hospitalization or prolongs an existing hospitalization;
- Results in persistent or significant disability or incapacity; and
- Represents other serious or unexpected adverse events that a study investigator feels should be reported, including need for resuscitation.

Study drug reactions will be reported as an SAE if meeting an SAE criterion above; such reactions will be reported as a study-related SAE if they are so confirmed by adjudication. Specified adverse

events, other unexpected adverse drug reactions (not qualifying as an SAE by adjudication), and minor side effects reported by study participants will be reported to and monitored by the DSMB. Specific instructions will be provided for reporting an infusion reaction so that it can be determined how quickly the reaction resolved and what was done to facilitate resolution. Minor side effects of oral iron or IV iron will be collected during the study. If data indicate that any of the side effects are long-lasting and interfere with the pregnant woman's/mother's daily routine, researchers may file the effect(s) as an adverse event. Side effects that meet a criterion for an SAE should be reported with the reason noted.

In addition to serious adverse events (SAEs), adverse events will be captured and reported on a regular basis. Such events will include those noted as secondary outcomes, exclusive of those conditions that, by definition, must be reported as an SAE or an unexpected drug reaction by the regulatory authorities. The DSMB may additionally request information on other events it believes may pose relevant risk.

Specific forms will be utilized to report an SAE or an AE. For an SAE, the reporting form should be sent to the person designated to receive it within 7 days of the notification of the event to the study team. Reportable adverse and serious adverse events will be shared with the Data and Safety Monitoring Board as will the determination made by two independent adjudicators (with expertise in iron infusion) about whether the SAE is associated or not with the IDA treatment approaches used in this study. Adjudicator reports will also be provided to the Principal Investigator, Senior Foreign Investigator and the Chief Quality and Safety Officer.

If there is an unanticipated problem recognized as posing a risk to participants or others and it is likely to reoccur within one or multipe research sites, a designated researcher associated with the site should obtain additional information on the unanticipated event and compile a report to forward to the study Principal Investigator, Chief Quality and Safety Officer and the Chair of the DSMB. The Chair will review the report and determine significance of the event to the study and the need for action to avoid harm to participants. The Chair may put the report on the agenda of the next DSMB meeting or communicate with members to address the unanticipated problem sooner.

At each DSMB scheduled meeting after initiation of study recruitment, SAE/AE data and a report summarizing recruitment and participant status will be prepared for review and discussion. Following its deliberations, the DSMB will issue any recommendations it may have and specify that the study should continue based upon absence of safety concerns.

After the DSMB meeting that will occur approximately nine months after participant recruitment begins, the DSMB will provide a communication summarizing SAE/AE data as well as any pertinent DSMB recommendations that may be required by the Thomas Jefferson University Institutional Review Board (IRB) or the Ethics Committees of the Indian research partners.

I. Database Management System (DMS)

Jawaharlal Nehru Medical College (JNMC) will have the responsibility for the development of an independent data management unit and utilization of the database system for the *RAPIDIRON Trial.* Data will be collected primarily with the use of paper-based forms. JNMC has successfully used the Research Electronic Data Capture (REDCap) system for numerous research projects. This system is a secure web application for building and managing online surveys and databases, and it offers a secure, privacy compliant web-based electronic data capture and maintenance system. The data are stored in a centralized system. REDCap software requires each user to have their own account and user privileges are applied to ensure that users have access only to data and information they need and are authorized to have. REDCap can be accessed from

multiple sites from any computer or mobile device, including PCs, Macs, tablets, and mobile phones.

The REDCap Website[41] notes that there is a REDCap consortium which is essentially a vast support network of collaborators associated with thousands of active institutional partners in over one hundred countries. Consortium members both utilize REDCap and offer support.
The Manual of Operations for the *RAPIDIRON Trial* will discuss REDCap's important features for this research—for example, authentication procedures, data export and de-identification, data storage, security provisions and quality control measures.

J. Other Components of the Program to be Funded Independently by the Children's Investment Fund Foundation (CIFF)

A timetable for the *RAPIDIRON Trial* clinical research project is found in Appendix A. In addition to activities associated with the clinical trial discussed in this protocol, the timetable indicates that activities will be planned and data collected for related project activities that are proposed for additional funding by the *Children's Investment Fund Foundation* (CIFF) based in the United Kingdom. The activities relate to:

- A process evaluation of the research to be performed by a contracted research organization (aka Clinical Research Organization) based in India and funded externally by the Children's Investment Fund Foundation; and
- A complete medical and hematologic assessment of all study participants who require "rescue" intervention or those who are non-responders to iron supplementation.

Co-Investigator, Dr. Stephen T. Mennemeyer, will have primary responsibility for the economic/cost-effectiveness analysis. It was determined that such an analysis could be useful for promoting scale-up of singe-dose IV iron infusions of formulations being used in the study if hypotheses for the primary outcomes are proven true.

Given the importance of distinguishing serious adverse drug reactions specifically related to intravenous iron infusions from non-serous reactions that commonly occur with the use of any intravenous medication, two experts familiar with the use of IV iron have been designated as adjudicators. Professor/Dr. Anat Gafter-Gvili, an expert in internal medicine and hematology who works as head of a Department of Medicine and senior physician of the hemato-oncologic clinic associated with Rabin Medical Center, Beilinson in Israel, will serve as one of the adjudicators. The second adjudicator will be Dr. Hema Divakar, former President of the Federation of Obstetric and Gynaecological Societies of India (FOGSI) and currently Vice President of the Non-communicable Diseases Division of the International Federation of Gynecology and Obstetrics (FIGO). Dr. Divakar is based at Divarkar's Specialty Hospital, Bengaluru, Karnataka, India. She is an obstetrician and women's health advocate who has 20 years of experience as a researcher. She also serves as a member of the Government of India's Anemia Committee. These two adjudicators will conduct timely reviews and provide case by case validation of all SAEs. These reports will immediately be shared with the study PI, the Chief Quality and Safety Officer, and the DSMB.

The highly qualified experts selected for the Technical Advisory Group (TAG) participated in the first official TAG meeting in June 2020. TAG members were oriented to the proposed research and provided the opportunity for discussion of the protocol prior to final refinement and issuance of the official version to be submitted for review and approval by governmental, regulatory and ethical review entities. Recommendations from TAG members have been incorporated into this protocol.

CONCLUDING STATEMENT: This research has a positive up-side without incurring significant

risk. It is designed to support and fine-tune guidelines of the Ministry of Health and Family Welfare, Government of India, to answer key questions related to clinical outcomes, and to validate the use of single-dose IV iron therapy. Further, it sets the stage for stakeholders to rapidly import and implement cost-effective programs that have enormous potential for reducing mortality and morbidity and improving the quality of life for women and children.

APPENDIX A

Timetable for ***Reducing Anemia in Pregnancy in India with Iron: the RAPIDIRON Trial:*** Clinical Research and Other Project Tasks

I. Year 1, Preparatory Phase (occurs prior to recruitment of study participants)**:**

A. Obtain all necessary ethical and human participants approvals as well as approvals from other review and regulatory bodies--
   1. Institutional Ethics Committee (IEC) of KLE Academy of Higher Education and Research, Belagavi (review entity for Jawaharlal Nehru Medical College)
   2. Institutional Ethics Committee for Sawai Man Singh (SMS) Medical College, Jaipur
   3. Thomas Jefferson University Institutional Review Board (IRB)
   4. Ethics Committee of Department of Health and Family Welfare, Government of Karnataka
   5. Ethics Committee of Medical, Health and Family Welfare Department, Government of Rajasthan
   6. Health Ministry's Screening Committee (HMSC), with the Indian Council of Medical Research (ICMR) acting as its Secretariat: the review process can vary in length from approximately 3-6 months, but it cannot begin until there is a commitment of funds See https://www.icmr.nic.in/content/guidelines
   7. Drug Controller General of India (DCGI): for an academic research study, notification to DCGI by the Institutional Ethics Committee of the primary research partner in India is required and an in-person meeting may be requested for presentation of the research; the study is deemed to be approved in the absence of receipt of comments/queries within 30 days of notification by the IEC.

B. Develop the data forms for use in the study as well as a Manual of Operations

C. Conduct additional pre-research meetings with various national and state governmental stakeholders (e.g., National and State Ministries of Health and Family Welfare), and convene appropriate meetings with other stakeholders, including a meeting of the Technical Advisory Group
   Note: Periodic reports on the status of the *RAPIDIRON Trial* research will be shared with stakeholders to maintain both interest and support.

D. Prepare facilities in both Karnataka and Rajasthan that will participate in the research and conduct community sensitization activities in clusters served by recruiting facilities (primary and community health centers) and area delivery facilities to inform and educate public health system representatives (Medical Officers, physicians, nurses, accredited social health activists or ASHAs, and others) and community leaders of the purpose of the planned *RAPIDIRON Trial* research and to enlist their support and assistance in the research.

E. Design and conduct a baseline survey for collection of data from providers and administrators at participating PHCs and CHCs that will administer IV iron to enable appreciation of the context in which the research will be conducted; also design and conduct a PHC or CHC consumer tool for administration to a sample of pregnant women that have reached at least 20 weeks of gestation.

F. Orient individuals/organizations that will have a role in process evaluation of the research (e.g., a Contract Research Organization also known as a Clinical Research Organization), develop the plan for a cost-effectiveness analysis to assess financial feasibility and scale-up costs of an IV iron intervention should the research achieve its objectives; plan the evaluation and analyses to ensure collection of needed data and define specific timetables

G. Develop the independent *data management system* (DMS) and finalize and print data collection forms for the *RAPIDIRON Trial* research; detail the arrangement for data collection and management and system maintenance throughout the research process

H. Orient members of the Data and Safety Monitoring Board (DSMB) that will oversee the study primarily for monitoring and safety purposes, and hold the first meeting for orientation to the research [Completed]
I. For sponsoring colleges in India (JNMC, RIMS, and SNMC in Karnataka and SMS Medical College in Rajasthan), organize the research teams, identifying and hiring or otherwise making arrangements for involvement with those that will serve as *RAPIDIRON Trial* research personnel (employed, contracted personnel and volunteers), including those in the public health system, such as accredited social health activities (ASHAs) that will have roles in research implementation (to be done consistent with the approved, detailed budget for the *RAPIDIRON Trial*)
J. With leadership from the Women's and Children's Health Research Unit of Jawaharlal Nehru Medical College (JNMC), in cooperation with SMS Medical College (Jaipur), establish a program management unit (PMU) in Jaipur for the clinical research component to be implemented in Rajasthan
K. Conduct an implementation meeting in Spring 2020 (via Zoom) and include key research investigators and consultants, and adjudicators; and subsequent to the implementation meeting, conduct a first meeting (via audio-video conferencing) of the Technical Advisory (TAG) [Completed]
L. Ensure that all key research and finance personnel to be involved in this CIFF-funded initiative are aware of and committed to following all applicable CIFF reporting requirements—financial as well as program-related
Note: Principal Investigator/Project Director, Dr. Richard J. Derman, will ensure timely submission of reports and invoices/financial documents to meet CIFF requirements.
M. Plan for the use of US Co-Investigators and Consultants that will be utilized during the training of those that will administer IV iron in community health centers (or CHCs) and provide oversight of research implementation phases of the project
Note: A timetable will be developed to ensure availability of Co-Investigators and Consultants as required during this CIFF-funded project.
N. Conduct focused, multi-day training of research personnel, including the providers that will distribute oral iron/folic acid tablets to oral iron participants and the physicians and infusion nurses that will administer intravenous iron; ensure understanding of the Manual of operations and the policies/procedures relevant to this research
O. Confirm that facilities participating in the research are ready to begin recruitment and especially confirm that the community health centers (CHCs) to be used for IV iron infusions meet criteria for IV iron service delivery
P. Orient the independent adjudicators about the mechanism for determination of whether a serious adverse event occurred

II. <u>Year 1, Initial Participant Recruitment and Engagement</u>

A. Initiate screening and recruitment of participants
B. Engage in research activities involving study participants and move them through study visits and milestones
See Appendix B for a Gantt chart (Progression of a *RAPIDIRON Trial* Participant through Milestones and Visits) which includes details related to participant visits and milestones.
C. Once recruitment begins, enter data into the data management system and continue data entry until all participants complete involvement in the study
D. Address any issues that may arise during the early phase of participant recruitment and clarify any components of the manual of operations as may be necessary
E. Compile the primarily process-related data for inclusion in the first quarterly Data Monitoring Report to be distributed to the *RAPIDIRON* research teams and shared with representatives of the Children's Investment Fund Foundation

F. Prepare and submit a funding application to allow follow-up of offspring born to study participants to 3 years of age to enable assessment of growth and neurodevelopment status at key points during infancy/early childhood.

III. Twenty-four Month Period of Active Participant Recruitment/Randomization, Treatment and Follow-up

A. Continue recruitment of participants until targeted sample size has been reached and engage participants in research activities, moving them through study visits and milestones and entering associated data in the data management system
B. Implement the plan for the provision of assistance and support from the Technical Advisory Group (TAG); hold the second and third-year TAG meetings as well as a general, annual meeting in year 2 (and year 3 if funds are sufficient); and inform meeting attendees about all aspects of the research as conducted to-date
C. Arrange site visits to the research sites in India by US research staff and consultants
D. Convene the DSMB approximately every 6 months until study closure
E. Ensure Children's Investment Fund Foundation receives information and process-related data required for an 18-month evaluation of this *RAPIDIROM Trial*
F. Throughout the period of active involvement of participants in the *RAPIDIRON Trial*, ensure distribution of reports with findings for all suspected SAEs reviewed by adjudicators on an emergent basis
   Note: Infusion team members will render an opinion about the relationship of an adverse event that may be related to administration of an IV iron formulation.

IV. Last Period (Approximately Five Months) for Data Validation and Analysis, Issuance of Findings and Dissemination of Results

A. Following completion of activities in section III, validate data in the DMS and compile data to enable analysis of study results and preparation of research findings
B. Complete study closure, finalize a manuscript with findings for the primary outcomes (low birth weight and conversion to non-anemic state) and the discussion of secondary outcomes and research impact as well as the implication of the economic analysis; plan for widespread dissemination of study results
C. Convene the Technical Advisory Group to help support the development of a dissemination plan and to provide input into evaluation of the *RAPIDIRON Trial* research project
D. Communicate with stakeholders to translate research findings and discuss appropriate actions/responses that are appropriate to the study findings and recommendations
E. Based on research findings, detail a plan for dissemination and operationalization of findings and advocacy initiatives, including publication of study-related manuscripts
F. Assuming positive study findings, seek resources for a dissemination meeting, international in scope and designed to share study results with key India officials. Global health organizations, and representatives of low- and middle-income countries where anemia in pregnancy remains a significant threat to the health of pregnant women and their offspring
G. Dependent on the identification of resources for an offspring follow-up study, generate a tracking and communication plan that can be implemented to enable determination and comparison of offspring growth and neurodevelopmental status to 3 years of age

APPENDIX B: Progression of a *RAPIDIRON Trial* Participants through Milestones and Visits

Week of Pregnancy (P)
12P 13P 14P 15P 16P 17P 18P 19P 20P 21P 22P 23P 24P 25P 26P 27P 28P 29P 30P……..

Visit #1: At a participating PHC or CHC at approximately 12 weeks of pregnancy or early in the second trimester of pregnancy

Provide education about the study
Record and review Hb results obtained at the PHC or CHC (as part of routine antenatal care)
Pre-screen a pregnant woman for initial eligibility, consent and arrange for a second visit per the protocol
Complete data forms to be obtained at this visit (contact, pre-screening/pregnancy information, and consent information)

- If Hb is under 7 g/dL, the pregnant woman is ineligible for study participation but is referred to a higher-level facility for evaluation
- If Hb concentration is 7 – 10.4 g/dL, a pregnant woman is considered initially eligible for the study and consented.
    - Blood will be collected and transported to designated study laboratories to determine Hb, TSAT, ferritin, complete blood count (CBC) and reticulocyte indices. Each laboratory sends specified test results to the appropriate PHC or CHC for use at visit #2. The transported blood will be used to determine baseline serum phosphate levels for a sub-sample of 120 pregnant women at two of the sites (Belagavi and Jaipur; total 240) and to measure baseline B12 and folate levels for a sub-sample of 200 pregnant women at each hospital (total 800).
- If Hb is higher than 10.4 g/dL, the pregnant woman is ineligible for the study but is encouraged to receive standard antenatal care.

Visit #2: At the KLE Dr. Prabhakar Kore Hospital and Medical Research Center (Belagavi), a hospital affiliated with SNMC, Bagalkot, RIMS, Raichur, or the hospital affiliated with SMSMC (Jaipur) at approximately 12-16 estimated weeks of pregnancy

Provide an ultrasound to date pregnancy and provide results to the PHC or CHC health care provider for use at visit #3

- Each pregnant woman completing this visit returns to the PHC or CHC for visit #3 to determine eligibility for continued study participation and randomization

Visit #3: At the participant's PHC or CHC, within the interval for randomization (start of week 14 and no later than 17 weeks 0 days)

Share results of the dating ultrasound with the participant.
Assess eligibility for randomization, including:
- Singleton, second-trimester pregnancy between 14 weeks and no more than 17 weeks 0 days
- Hb 7 – 9.9 g/dL, TSAT <20% and/or ferritin < 30 ng/mL as determined by the analysis of blood drawn at visit #1

Randomize an eligible woman; inform participant of randomization to the oral iron arm or an IV iron infusion arm (but not which one)
Collect socioeconomic status data, dietary information, height and weight, blood pressure, other data specific to this visit for a woman determined eligible for continued study participation and randomization, and complete study data form

- A participant randomized to the oral iron arm receives deworming medication, tablets that will provide the recommended daily doses of iron and folic acid along with instructions consistent with Ministry of Health and Family Welfare (MOHFW) guidelines
- A participant randomized to an IV iron arm receives deworming medication and folic acid consistent with the daily dosage guideline; the IV iron infusion is arranged at a CHC—on the same day (or, based upon case-by-case consideration, on a day not later in the pregnancy than 17 weeks 0 days)

Progression of *RAPIDIRON Trial* Participants through Milestones and Visits, continued

Week of Pregnancy (P)
14P 15P 16P 17P 18P 19P 20P 21P 22P 23P 24P 25P 26P 27P 28P 29P 30P 31P 32P 33P 34P……

Visit #3a: At a CHC for an IV iron arm pregnant woman, between 14 weeks and 17 weeks 0 days of pregnancy

Counsel the pregnant woman about the infusion procedure, risks and benefits and confirm willingness to receive the infusion
Provide the IV iron infusion using the correct formulation prepared by the CHC pharmacist (using randomization number and body weight)
Monitor the participant for the recommended time after infusion
Complete the study data form, including information relevant to the infusion

Visit #4: At an IV iron arm participant's PHC or CHC, 2 weeks post receipt of an IV iron infusion

Draw a blood sample from an IV iron arm participant and send it to the designated central laboratory for analysis of serum phosphate level (**See Note 1**)

Visit #5: At participant's PHC or CHC, 20-24 weeks of pregnancy

Monitor the participant's pregnancy per guidelines
Draw blood samples to determine Hb, TSAT, and ferritin (**See Note 1**)
Collect data specific for this visit (participant weight, blood pressure, etc.), complete study data form
Send blood samples to the central laboratory for analysis and distribution of results

Visit #6: At participant's PHC or CHC, 26-30 weeks

Monitor the participant's pregnancy per guidelines
Draw blood samples to determine Hb, TSAT and ferritin, CBC, reticulocyte indices, glucose level (**See Note 1)**
Collect data specific for this visit (participant weight, blood pressure, etc.), complete study data form
Send blood samples to the central laboratory for analysis and distribution of results

- If the blood sample drawn at visit #6 does not show improvement in Hb of at least 1 g/dL, referral is arranged to a First Referral Unit or District Hospital for further investigation of anemia causes and possible consideration of an alternate therapeutic approach

Note 1: Except for the first visit when hemoglobin level will be determined onsite at the PHC or CHC, subsequent blood samples will be sent to a designated central laboratory in each of the four research areas (three located in Karnataka, and one in Rajasthan). Hb results will be sent to appropriate PHC or CHC clinical staff throughout the study; additionally, TSAT and ferritin values will be shared for use in eligibility screening for randomization at visit #3. The test results from blood drawn at visit #6 to identify gestational diabetes will also be sent to the PHC or CHC clinical staff.

Progression of *RAPIDIRON Trial* Participants through Milestones and Visits, continued

Week of Pregnancy (P) to Delivery (D)
30P 31P 32P 33P 34P 35P 36P 37P 38P 39D* 40D*… (D = Delivery)

Visit #7: At the participant's PHC or CHC, 30-34 weeks of pregnancy

Monitor the participant's pregnancy per guidelines
Review the result of diabetes testing and Hb level
Obtain blood sample and send it to the central laboratory to enable determination of Hb level for this visit (**See Note 1)**
Collect visit-specific data (e.g., participant weight, blood pressure) and complete study data form

- This PHC or CHC visit is the first of two timepoints when Hb level will be used to determine if a participant has achieved non-anemic status in the last trimester of pregnancy prior to delivery – that is, Hb ≥11 g/dL

Visit #8: At participant's birthing facility
Involves the mobile team called prior to delivery; if not at the delivery, the mobile team will visit the facility within 72 hours and obtain and record data

Collect pre-delivery blood sample from participant to determine Hb level
Post-delivery, collect cord blood to determine Hb, TSAT and ferritin, and reticulocyte indices
Record mode of delivery
Weigh and record baby's birth weight
Record time between a baby's birth and clamping of the umbilical cord
Record the need for neonatal resuscitation or referral of mother or baby for specialized services
Complete study data form, including relevant mother/baby outcomes
Arrange timely transport of Hb and cord blood samples to the designated laboratory for analysis and distribution of lab results (**See Note 1**)

- This visit is the second timepoint when Hb level will be used to determine if a participant has achieved non-anemic status for pregnancy prior to delivery. It is also the preferred time for collecting data for birth weight and newborn length

* *

Post-delivery (P-D) Week
1 P-D 2 P-D 3 P-D 4 P-D 5 P-D 6 P-D…

Visit #9: At participant's PHC or CHC approximately 42 days post-delivery (for mother and baby)

Assess health status of mother and baby
Obtain self-reported information regarding breastfeeding practices, including exclusive breastfeeding
Administer quality of life assessment tool
Draw blood samples from the mother to determine Hb, TSAT, ferritin, CBC and reticulocyte indices (**See Note 1**)
For a mother in an IV iron arm, obtain a blood sample to enable determination of serum phosphate level
Collect visit-specific study data; complete the study closure form and thank the participant for her study participation
Send blood samples to the central laboratory for analysis and distribution of lab results

APPENDIX C

Description of Intravenous Iron Drug Formulations:
Ferric Carboxymaltose (FCM) and Iron Isomaltoside

Ferric Carboxymaltose

Ferric carboxymaltose (FCM) was approved in Europe before the US. In the initial filing there were concerns about hypophosphatemia and hemodynamic events which proved to be clinically insignificant in registrational trials. A broad label was granted FCM in 2013 and a large body of clinical evidence reports its safety and efficacy. The approval for FCM differs in Europe (Ferinject) and the United States (InjectoFer). In Europe, the 500 mg and 1000 mg vial size allow a dose of 1000 mg in 15 minutes. This large dose in a short period of time is a result of a complex carbohydrate core which binds the elemental iron tightly, releasing it slowly during its time in plasma. However, in the US, the only vial size approved is 750 mg and thus a 1000 mg dose cannot easily be provided. In Europe, where the price is less than 25% of that in the US, it is less of a problem. Data from a prospective double-blind comparison of FCM and ferumoxytol, provide high quality evidence that doses greater than 1000 mg are imprudent based on findings five weeks post-treatment.

In the FIRM study,[42] 1020 mg of ferumoxytol (two vials) each administered over fifteen minutes was compared to 1500 mg (two vials) of FCM over the same time period. This paradigm was a US Food and Drug Administration (FDA) mandate. At five weeks, the hemoglobin differences were 0.24 grams which is clinically insignificant. There were no safety issues although 50% of those who received FCM had measurable phosphorus levels below the lower limit of normal compared to 0.1% of those who received ferumoxytol. No clinically relevant signs of hypophosphatemia were observed in either group.

FCM has been shown to be safe and effective in pregnancy, abnormal uterine bleeding, inflammatory bowel disease, cancer and chemotherapy induced anemia, chronic kidney disease, congestive heart failure, restless legs syndrome and a host of other conditions associated with iron lack. As with the other formulations of intravenous iron, minor infusion reactions occur while serious adverse events are extremely rare.

In a soon to be published prospective, open label study, FCM was compared to iron isomaltoside (the other formulation to be used in this trial) in patients with iron deficiency anemia primarily unrelated to pregnancy. Hypersensitivity was defined by a standardized set of Medical Dictionary for Regulatory Activities terms. Rates of serious or moderate-to-severe adverse events were low for both products and hypophosphatemia was more common with FCM. A recent study by Wolf et al.[43] implied that multiple exposures to FCM may be associated with protracted hypophosphatemia with clinically meaningful sequelae. Prospective data supporting that position are lacking. There is no outcome data in infants of women given FCM during pregnancy.

Based on dozens of clinical trials, FCM, is safe and effective across a broad group of diagnoses associated with iron lack and is widely used in the North America and Europe. In every study in which FCM was compared to oral iron it proved superior in hemoglobin increment, time to target hemoglobin and toxicity profile. FCM has been compared to iron sucrose in prospective studies and shown to have equal or improved efficacy and safety with far fewer visits increasing convenience of both patients and caregivers, decreasing the likelihood of minor infusion reactions, extravasations and costs.

Iron Isomaltoside

Isomaltoside is the newer of the two formulations and the last parenteral iron approved in Europe. Isomaltoside has been renamed ferric derisomaltose by the World Health Organization and the FDA; but for now, the more familiar nomenclature remains in use. Isomaltoside was recently approved under a broad label for iron deficiency in the US with an expected launch in the fourth quarter of 2020. Like FCM, isomaltoside can be administered as 1000 mg in 15 minutes and is actually approved for maximum single doses of 20 mg/kg. As is the case with FCM, there is no evidence that doses of greater than 1000 mg of isomaltoside are advantageous.

Isomaltoside has also been shown in multiple clinical trials to be safe and effective. Unlike FCM, the incidence of hypophosphatemia below the lower limit of normal is uncommon. Examples of the efficacy with the use of isomaltoside are dialysis and non-dialysis dependent chronic kidney disease, congestive heart failure, inflammatory bowel disease, cancer and chemotherapy induced anemia, cardiac surgery and post-partum hemorrhage. Isomaltoside is gaining popularity in Europe where it's been approved in 22 countries; and it is available in other countries, including India, through marketing collaborations.

Isomaltoside, like FCM, has a complex carbohydrate core which binds elemental iron tightly, allowing slow release during its plasma life. As a result, a large dose of 1000 mg or more can be administered in 15 minutes. Isomaltoside has also been compared with iron sucrose. In a study among chronic disease kidney patients, 351 haemodialysis patients were randomized 2:1 to isomaltoside or iron sucrose.[44] The primary endpoint was the proportion with a hemoglobin concentration in the target range of 9.5 to 12.5 grams at six weeks. Both showed similar efficacy and safety with the same benefit in increased convenience, decreased numbers of intravenous lines, fewer chances for minor infusion reactions and extravasations and decreased cost when compared to iron sucrose, similar to FCM but at a lower cost.

Consistent with the results of the study among chronic kidney disease patients, isomaltoside was compared to iron sucrose in an open label, multi-center trial in which 1,512 patients with iron deficiency across a broad spectrum of diagnoses, were enrolled.[25] Randomization was 2:1 to a single 1000 mg dose of isomaltoside or five 200 mg infusions of iron sucrose. The co-primary endpoints were adjudicated serious or severe hypersensitivity reactions and change in hemoglobin from baseline to week eight. The co-primary efficacy endpoint of non-inferiority in hemoglobin was met and isomaltoside led to a significantly more rapid hematological response in the first two weeks. In multiple clinical trials where isomaltoside was compared to oral iron, isomaltoside was superior in magnitude of hemoglobin response and time to target hemoglobin.

Supporting the safety of isomaltoside in pregnancy is a recently published series of 213 iron deficient pregnant women in the 2nd and 3rd trimester who received 1000-1500 mg of isomaltoside in a single infusion over 15-30 minutes and were compared to 213 who did not receive such infusions.[45] Consistent with the overwhelming preponderance of published evidence, the hemoglobin increment in the treatment arm was highly statistically significant compared to those not receiving infusions ($P<0.001$). Only 10 self-limited, adverse events were noted during administration of isomaltoside, and no serious adverse events were reported. There was no relationship between the occurrence of adverse events and dose of isomaltoside received. The author concluded that a single total dose infusion of isomaltoside is a safe, effective and convenient treatment for iron deficiency in pregnancy.

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