CONFIDENTIAL DOCUMENT

Clinical Trial Protocol

Title:

Daily vs. every other day oral iron supplementation in patients with absolute iron deficiency anemia (DEODO): a multi-centered, pilot randomized controlled trial

Protocol Number: *1534*

Principal Investigator/Institution:	Yulia Lin, MD, Hematology, Sunnybrook Health Sciences Centre
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Funding Agency	Alexandra Yeo Grant, University of Toronto
Investigational Product	Oral Ferrous Sulfate (60mg of elemental iron)

SPONSOR STATEMENT OF COMPLIANCE

This study will comply with the International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants, as well as applicable regulatory and institutional requirements.

Personnel listed below are authorized to sign the protocol and any subsequent protocol amendments on behalf of the sponsor:

Name: *(Print)*	Yulia Lin
Title: *(Print)*	Principal Investigator
Signature:	
Date of Approval: *(yyyy-mmm-dd)*	

PROTOCOL SIGNATURE PAGE

I have read this protocol in its entirety and its appendices. I agree to comply with the requirements of the study protocol and procedures for data recording/reporting and acknowledge my responsibility for the well-being of each research participant, and to ensure that all persons involved in study activities are adequately informed about the protocol, the investigational product, and their trial-related duties. The signature below constitutes the agreement to conduct this study in accordance with the REB approved protocol, GCP and applicable regulatory requirements, including confidentiality, ethical guidelines and regulations regarding the conduct of research in humans.

Qualified Investigator:

Name: *(Print)*	Yulia Lin
Title & Institution: *(Print)*	Principal Investigator, Sunnybrook Health Sciences Centre
Signature:	
Date of signature: *(yyyy-mmm-dd)*	

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LIST OF ABBREVIATIONS

The following abbreviations describe terms, documents and study personnel used in the conduct of this study protocol.

AE	Adverse Event
CBC	Complete Blood Count
CNS	Central Nervous System
CRP	C Reactive Protein
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
DEODO	Daily vs. every other day oral iron supplementation in patients with absolute iron deficiency anemia
eCRF	Electronic case report form
FACIT	Functional Assessment of Chronic Illness Therapy
FACT	Functional Assessment of Cancer Therapy
GI	Gastrointestinal
Hb	Hemoglobin
Hg	Mercury
ID	Iron Deficiency
IDA	Iron Deficiency Anemia
LR	Likelihood Ratio
MCV	Mean Cell Volume
MRP	Most Responsible Physician
NCI	National Cancer Institute
PBAC	Pictorial Blood Assessment Chart
PM	Product Monograph
PO	Oral Administration
PI	Principal Investigator
QI	Qualified Investigator
RBC	Red Blood Cell
RCT	Randomized Controlled Trial
REB	Research Ethics Board
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SD	Standard Deviation
SHSC	Sunnybrook Health Sciences Centre
SUADR	Serious Unexpected Adverse Drug Reaction
TSAT	Transferrin Saturation
WHO	World Health Organization

PROTOCOL SUMMARY

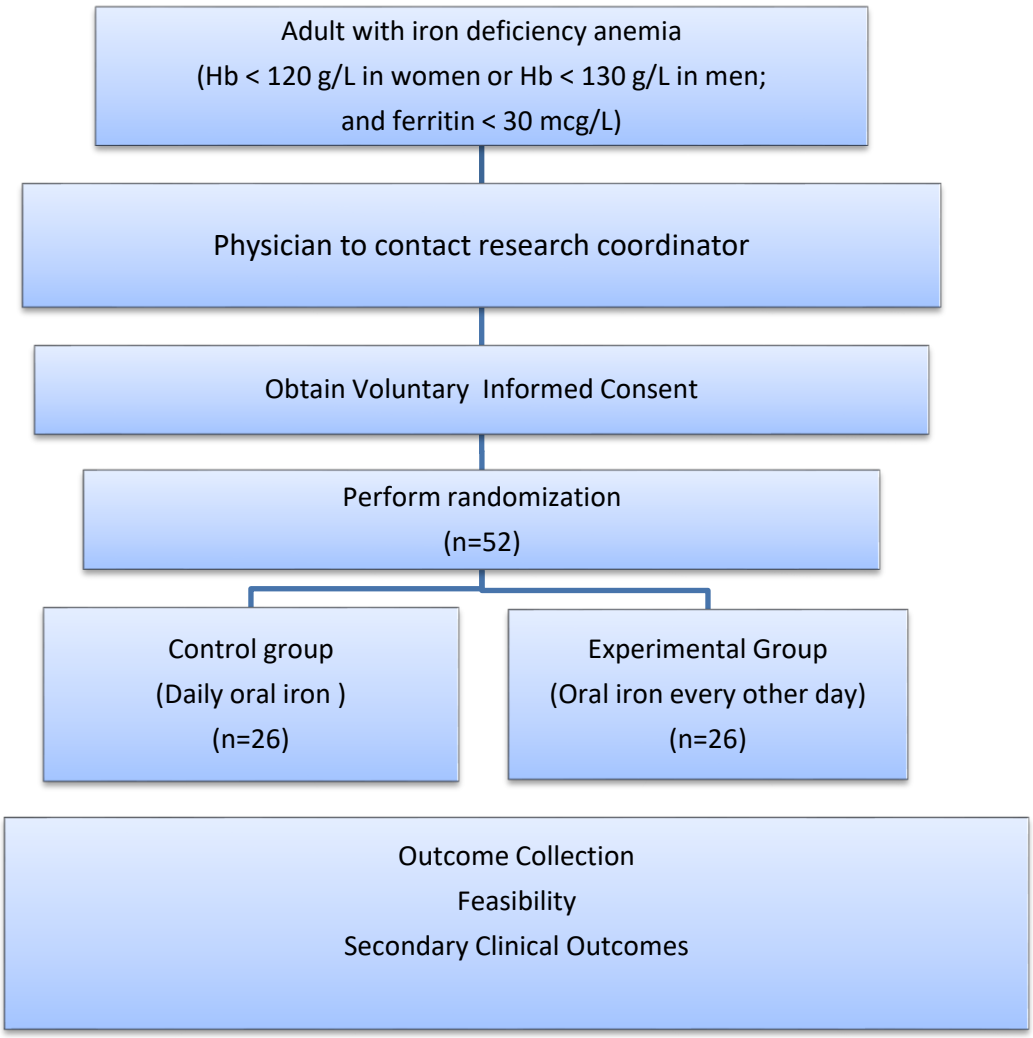
PRINCIPAL INVESTIGATOR	Yulia Lin, MD
PROTOCOL TITLE	Daily vs. every other day oral iron supplementation in patients with absolute iron deficiency anemia (DEODO): a multi-centered, pilot randomized controlled trial
PROTOCOL NUMBER	1534
PHASE	lll
INVESTIGATIONAL PRODUCT AND PLANNED USE	To evaluate the effectiveness of oral ferrous sulfate (oral iron), 300mg oral tablets and vitamin C 500mg, once daily versus every other day to improve hemoglobin 12 weeks post-initiation
STUDY DESIGN	A phase lll, multi-centered, randomized, pragmatic, open-label, controlled pilot trial
DURATION OF FOLLOW-UP	From first dose of study drug to final study visit = 12 weeks
TREATMENT ALLOCATIONS	Experimental arm: Ferrous sulfate 300mg oral and vitamin C 500mg every other day x 12 weeks Control arm: Ferrous sulfate 300mg oral and vitamin C 500mg every day x 12 weeks
PATIENT POPULATION	Patients with iron deficiency anemia defined as hemoglobin less than 120 g/L in women or less than 130 g/L in men; AND ferritin less than 30 mcg/L
SETTING	A multi-centre study, outpatient clinical setting
PLANNED SAMPLE SIZE	52 patients The anticipated duration for this study's recruitment period is 2 years.
PATIENT INCLUSION/EXCLUSION	Inclusion criteria: • Age ≥ 16 years; • Outpatients with iron deficiency anemia defined as Hb less than 120 g/L in women or 130g/L in men; AND ferritin less than 30 mcg/L Exclusion criteria: • Pregnancy • Currently breastfeeding • Known history of inflammatory bowel disease • Known history of celiac disease • Known history of thalassemia or thalassemia trait • Known inherited bleeding disorder • Known intolerance or lack of response to oral ferrous gluconate, sulfate or fumarate in the last 12 weeks • Multivitamin and mineral supplements (35 mg or more of elemental iron per day) in the 2 weeks prior to randomization • Allergy to oral iron • Allergy to any of the following medicinal and non-medicinal ingredients in ferrous sulfate: ferrous sulphate, calcium citrate, crospovidone, FD&C Red #40-Aluminum lake, FD&C Yellow #6-Aluminum Lake, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, purified water, talc titanium dioxide • Allergy to any of the following medicinal and non-medicinal ingredients in vitamin C: Ascorbic acid, Colloidal silicon dioxide,

	croscarmellose sodium, magnesium stearate, microcrystalline cellulose and stearic acid • Intravenous iron therapy in the past 12 weeks • On new anticoagulant therapy initiated in the past 6-months (e.g. warfarin, apixaban, dabigatran, edoxaban, rivaroxaban) • Surgery planned in upcoming 12 weeks • Chemotherapy planned in upcoming 12 weeks • Blood donation planned in upcoming 12 weeks • Previously enrolled in the study • Creatinine clearance less than 30 mL/min • Hemoglobin less than 80 g/L with active bleeding (defined as WHO grade 2 bleeding or higher in the past week)
RANDOMIZATION	Computer generated allocation sequence; stratified in two groups: hemoglobin ≥ 100 g/L and hemoglobin < 100 g/L
STUDY OUTCOMES	Primary Feasibility Outcome: Time to enroll 52 patients Secondary Feasibility Outcomes • Feasibility: proportion consenting to participate; proportion receiving allocated treatment; proportion completing laboratory tests, FACIT-fatigue scale, side effects questionnaire; adherence Secondary Clinical Outcomes • Mean hemoglobin increment at 4 and 12 weeks • Proportion with complete hemoglobin response at 4 and 12 weeks • Change in ferritin, serum iron and TSAT at 12 weeks • Quality of life (FACIT-fatigue scale) at 4, 8 and 12 weeks • Gastrointestinal adverse effects at 4, 8 and 12 weeks • Need for escalation in therapy • Proportion with a drop in hemoglobin of 10 g/L or more at 4 and 12 weeks
STATISTICAL ANALYSIS	The results of this pilot trial will be used to assess the feasibility and inform the design of the definitive trial. We will present point estimates of feasibility outcomes with 95% confidence intervals. An intention-to-treat analysis will be performed on all patients randomized for the secondary clinical outcomes. A per protocol analysis will be conducted for patients who have taken at least 90% of the prescribed doses.

1.0 KEY ROLES AND CONTACT INFORMATION

Regulatory Sponsor:	Sunnybrook Research Institute 2075 Bayview Avenue Toronto, ON Canada M4N 3M5
Principal Investigator:	Dr. Yulia Lin
Academic Research Organization:	Sunnybrook Health Sciences Centre 2075 Bayview Avenue Toronto, ON Canada M4N 3M5

Figure 1: Pilot Trial Schema



2.0 INTRODUCTION

This study document is the protocol for research involving human participants. This study is to be conducted according to Canadian and international standards, and in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice E6 (ICH-GCP), World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants, as well as applicable regulatory and institutional requirements and research policies.

2.1 Background

2.1.1 Prevalence of iron deficiency anemia (IDA)

Iron deficiency anemia is a global health problem and the most common cause of anemia worldwide.[1] There is significant variation based on geographical location and population studies. In North America and Europe, its prevalence ranges from 1-2% in men[2] to 2-5% in women[2-5] to 9-11% in adolescent females[6] and 17-31%[3,7] in pregnant women.

2.1.2 Consequences of IDA

Iron is an important nutrient for the production of red blood cells but also many biologic functions including energy production, DNA synthesis and cell proliferation.[8] Patients with iron deficiency (ID) and IDA can present with a multitude of symptoms including fatigue, restless legs syndrome[9] and pica.[10] In addition, ID can also lead to impacts on physical function. Adverse effects include aerobic capacity (reduced VO2 max), work intolerance and fatigue[11]; diminished exercise capacity[12,13]; cognitive impairment specifically in attention, memory, speed and executive planning function[14-16]; and higher risk of depression[17]. There may be additional negative manifestations of IDA that have not yet been fully recognized. In one study, even after excluding patients with restless legs and accounting for the presence of depression and anxiety, IDA was still associated with worse sleep quality.[18] In another retrospective cohort study of over 300,000 patients, iron deficiency was associated with combined and sensorineural hearing loss in US adults.[19] Thus ID and IDA have significant consequences which may potentially benefit from treatment.

2.1.3 Definition of IDA

The World Health Organization (WHO) defines anemia as a hemoglobin of less than 120 g/L for females and less than 130 g/L for males.[20] Although the definition of anemia is well accepted, the definition of ID is less standardized. Based on a systematic review conducted by Guyatt et al to determine the diagnostic value of laboratory tests in the diagnosis of IDA, serum ferritin was found to be the most predictive and a better diagnostic test than mean cell volume (MCV) and transferrin saturation (TSAT).[21] Serum ferritin values between 15-25 mcg/L were associated with a likelihood ratio (LR) of 8.83 for ID. Goodnough et al found that a serum ferritin of less than 30 mcg/L was associated with a sensitivity of 92% for IDA and a positive predictive value of 83%.[22]

The issue becomes more complicated when considering ID in the setting of coexisting conditions where serum ferritin may be elevated as an acute phase reactant. The most recent preoperative anemia guidelines from the British Committee on Standards in Hematology state that a serum ferritin of less than 30 mcg/L is a sensitive marker of iron deficiency; however, iron therapy may be indicated for non-anemic patients with low iron stores defined as ferritin less than 100 mcg/L and TSAT less than 20%, scheduled to undergo surgery.[23] Studies in the setting of congestive heart failure have defined ID as a ferritin less than 100 mcg/L or a ferritin less than 300 mcg/L AND a TSAT less than 20%.[24] In the setting of chemotherapy-induced anemia, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology have defined absolute ID as ferritin less than 30 mcg/L AND TSAT less than 20%,

but functional iron deficiency in patients receiving erythropoiesis stimulating agents as a ferritin of 30-500 mcg/L AND TSAT less than 50%.[25]

For the purposes of this study to ensure a population with a high likelihood of iron deficiency anemia, we have defined ID as a serum ferritin of less than 30 mcg/L.[8,26,27]

2.1.4 Oral iron preclinical studies to date

This section is not applicable.

2.1.5 Oral iron clinical studies to date

The most common oral iron supplements currently used are ferrous gluconate, sulfate and fumarate each containing increasing doses of elemental iron (35, 60 and 100 mg elemental iron per 300mg tablet, respectively).[8] Ferrous formulations have greater bioavailability than ferric preparations as it is in the ferrous form that iron is absorbed by the enterocyte. These supplements are inexpensive and often covered by provincial health plans. Although intravenous iron is also available, intravenous iron has been associated with rare serious infusion side effects including anaphylaxis, is hampered by a lack of resources for infusion facilities and nursing and thus, oral iron supplementation should be the first line of therapy when time permits.[26,28,29]

Oral iron supplementation is associated with increasing hemoglobin in multiple studies in women, pregnant women and elderly patients.[30-32] However, the optimal dose and frequency of oral iron supplementation for treatment remains unclear. A recent systematic review of 21 studies in 10,258 women between menarche and menopause compared intermittent oral iron dosing (three times or less per week) compared with no intervention (or placebo) or daily oral iron dosing. When compared with intervention (or placebo), intermittent dosing reduced the risk of anemia (RR 0.73, 95% CI 0.56 to 0.95) and improved the concentration of hemoglobin (MD 4.58 g/L; 95% CI 2.56 to 6.59). When compared with daily supplementation, women on intermittent oral iron dosing presented more often with anemia (RR 1.26; 95% CI 1.04 to 1.51, six trials) although hemoglobin concentrations were similar (MD -0.15 g/L; 95% CI -2.20 to 1.91, eight trials). The review also found no difference in diarrhea, any side effects or adherence between intermittent and daily dosing, although very few trials reported on these outcomes.

Two more recent studies showed that dosing iron on alternate days may optimize iron absorption and may be preferable.[33,34] The first study by Moretti et al sought to determine how the iron-induced increase in hepcidin influenced iron absorption for increasing doses of daily iron or twice-daily iron.[33] They found that doses of ferrous sulfate 60mg or higher resulted in an increase in hepcidin at 24 hours and resulted in a decrease of fractional iron absorption of 35-45%. Absolute iron absorption increased; however, with a six fold increase in dose, there was only a 3 fold increase in absorption. They also found that 3 doses given morning, afternoon then the following morning had the same total iron absorption as 2 morning doses. These findings suggested that alternate day dosing of oral iron at lower dosages (40-80mg) may maximize fractional iron absorption, increase dosage efficacy and improve tolerance of iron supplements.

Stoffel et al investigated two different dosing regimens in women aged 18 to 45 years with a serum ferritin less than 25 mcg/L who did not have anemia. [34] In the first study, they compared consecutive daily oral ferrous sulfate 60mg for 14 days (N=21) with alternate day dosing for 28 days (N=19). At the end of treatment, the fractional absorption was 16.3% vs. 21.8% (p=0.0013) and the total iron absorption was 131.0 mg vs. 175.3 mg (p=0.0010), favouring the alternate day dosing schedule. In the second study, they compared 120mg of elemental iron in the morning (N=10) with two split doses of 60mg given in the morning and evening for 3 consecutive days (N=10); then 14 days later, the groups

crossed-over. There was no difference in fractional absorption or total iron absorption between the two groups. The twice-daily divided dose had higher serum hepcidin concentrations. As a result, they concluded that oral iron supplements on alternate days, and as single doses might be a preferred dosing regimen and suggested confirming these findings in iron deficient anemic patients. The current proposed study attempts to address this gap in the literature.

2.1.6 Potential Risks

Side effects of oral iron supplementation include constipation, nausea, diarrhea, abdominal pain, vomiting, heartburn, flatulence and dark stools.[8,35] When compared to placebo in randomized controlled trials, ferrous sulfate had an increased incidence of gastrointestinal (GI) side effects with an OR 2.32 (95% CI 1.74-3.08). The proportion of patients with GI side effects was 35% (range 10-90%) in the ferrous sulfate arms compared with 22 % (range 0-69%) in the placebo arms. The most common side effects were constipation, nausea and diarrhea with pooled estimates of incidence of 12%, 11% and 8% respectively.[35] Additional side effects included abdominal pain, vomiting, heartburn, flatulence and dark stools. There did not appear to be a significant association between dose and GI side effects. These side effects can have a significant impact on adherence with studies reporting up to 40% non-adherence and need to be carefully documented. [36] A recent study specifically developed a one page side effect questionnaire in patients on oral iron supplementation and was able to distinguish GI symptoms between participants on oral ferrous sulfate and placebo.[37] A modification of this questionnaire will be used in the current study.

2.1.7 Quality of Life Measures in IDA

Given the impacts of IDA extend beyond anemia and can affect an individual's physical, emotional and social well-being, quality of life measures are important to incorporate in the current study. The Functional Asessment of Chronic Illness Therapy (FACIT)-fatigue scale, previously the Functional Assessment of Cancer Therapy (FACT)-Fatigue scale, was developed and validated to assess cancer-related fatigue. More recently it has also been validated in other chronic conditions such as systemic lupus erythematosus, rheumatoid arthritis and chronic immune thrombocytopenia. To date, there has been one study that has examined the effects of IDA on fatigue severity and life measures, the results of which validated the use of the FACIT-fatigue scale.[38] The scale consists of 13 patient reported items as a measure of fatigue with a 7 day recall period. Items are scored from 0 (Not at all) to 4 (Very much so). Items are summed to a single fatigue score with a range of 0 to 52. Items can be reversed score to provide a scale in which higher scores represent better functioning or less fatigue. In this study, the internal consistency reliability was good (Cronbach's $\alpha = 0.93$). Known group analysis using the FACIT-fatigue scale, using reverse scores, showed that there was a mean difference of 5.51 between the high hemoglobin group (hemoglobin > 120 g/L = mean 35.96 (SD 10.82)) and the low hemoglobin group (hemoglobin ≤ 90 g/L = mean 30.45 (SD 11.64)). The wide-spread use of the FACIT-fatigue scale and demonstrated appropriateness in IDA validates the choice of the FACIT-fatigue scale for use in the current study.

2.2 Current Proposal and Rationale

We propose a pilot, pragmatic, non-inferiority, open label randomized controlled trial (RCT) in outpatients with iron deficiency anemia to evaluate the effectiveness of oral ferrous sulfate 300mg (60mg elemental iron) once daily versus every other day to improve hemoglobin at 12 weeks post-initiation. The rationale for this study includes: (1) IDA is a common and prevalent condition with potential adverse consequences if left untreated; (2) optimizing effectiveness of oral iron supplementation while minimizing side effects will improve treatment for patients. We will enroll 52

patients in this pilot study at 2 centres. If this pilot trial is deemed to be feasible, we will plan a definitive multicentre trial.

2.3 Study Impact and Benefit

Because IDA is a global health problem, common in clinical practice and treatable, this study, although simple in its question and design, will have a significant practical impact on how clinicians treat outpatients with iron deficiency anemia and how patients tolerate therapy.

For the patient, the expected benefit from taking part in this study for the participant is the potential to improve and treat iron deficiency anemia. These potential changes may lead to improved symptoms associated with iron deficiency anemia, such as cognitive and physical functioning, and fatigue.

3.0 OBJECTIVES AND SCIENTIFIC AIMS

3.1 Primary Objective

The primary purpose of this trial is to determine the feasibility of performing a pilot pragmatic, open-label, randomized controlled trial to evaluate effectiveness of oral ferrous sulfate 300mg (60 mg elemental iron) once daily versus every other day to improve hemoglobin at 12 weeks post-initiation.

3.2 Trial Secondary Objective

The secondary purpose of this trial is to determine the effectiveness of alternative oral iron supplementation dosing regimens on iron deficiency anemia, including hemoglobin, while minimizing side effects to improve patient treatment.

3.3 Primary Outcome Measure

Feasibility: Time to enroll 52 patients

3.4 Secondary Outcome Measures

Feasibility

1. Proportion of eligible patients consenting to participate
2. Proportion of consenting patients receiving the allocated treatment
3. Proportion of treated patients completing 4 week and 12 week laboratory tests
4. Proportion of treated patients completing 4 week, 8 week and 12 week FACIT-fatigue scale
5. Proportion of treated patients completing 4 week, 8 week and 12 week side effect questionnaire
6. Proportion of treatment doses taken as per protocol (adherence)
7. Proportion of treated patients taking at least 90% of their prescribed doses
8. Proportion of treated patients requiring a step down in therapy due to adverse side effects

Clinical/Safety

9. Mean hemoglobin increment at 4 and 12 weeks
10. Proportion with complete hemoglobin response defined as hemoglobin greater than or equal to 120 g/L at 4 weeks and 12 weeks for women and greater than or equal to 130 g/L at 4 weeks and 12 weeks for men.

11. Change in reticulocyte count at 4 and 12 weeks
12. Change in ferritin, serum iron, TSAT at 12 weeks
13. Quality of life (FACIT-fatigue scale) at 4, 8 and 12 weeks
14. Proportion with side effects and type of side effects at 4, 8 and 12 weeks
15. Proportion of patients who stop taking oral iron due to side effects at 4 and 12 weeks
16. Need for escalation in therapy (need for alternative oral iron therapy (including if a participant in the every other day group escalates to daily iron), need for intravenous iron, need for transfusion, visit to emergency department related to anemia) at 12 weeks
17. Proportion of patients with a drop in hemoglobin of 10 g/L or more from baseline at weeks 4 and 12

4.0 HYPOTHESES

We hypothesize that 52 patients will complete the trial within a 2-year period. This includes an expected drop out rate of 30% leaving 36 patients for analysis.

5.0 STUDY METHODS

5.1 Study Design

This is a pilot pragmatic, non-inferiority, open label randomized controlled trial (RCT) in outpatients with iron deficiency anemia to evaluate the effectiveness of oral ferrous sulfate 300mg (60mg elemental iron) once daily versus every other day to improve hemoglobin at 12 weeks post-initiation. Patients will be randomized according to a computer-generated allocation sequence to receive either once daily dosing or every other day dosing. Randomization will be stratified by centre and baseline hemoglobin (hemoglobin ≥ 100 g/L OR < 100 g/L). Following randomization, patients will receive oral iron tablets for a period of 12 weeks, with clinical and subjective data collection occurring 1, 4, 8 and 12 weeks following the commencement of oral iron. The study will aim to recruit 52 patients in total, randomizing 26 patients to each study arm. This sample size includes an anticipated 30% drop out rate (see section 8.1).

5.2 Study Population

We propose broad eligibility criteria to increase the generalizability and feasibility of the proposed trial. The exclusion criteria are predominantly conditions where oral iron has already been shown to be ineffective. There are no exclusions based on sex, race or ethnicity in this trial.

5.2.1 Inclusion Criteria

- Age ≥ 16 years;
- Outpatients with iron deficiency anemia defined as hemoglobin less than 120 g/L in women or less than 130 g/L in men; AND ferritin less than 30 mcg/L.

5.2.2 Exclusion Criteria

- Pregnancy
- Currently breastfeeding
- Known history of inflammatory bowel disease
- Known history of celiac disease
- Known history of thalassemia or thalassemia trait
- Known inherited bleeding disorder

- Known intolerance or lack of response to oral ferrous gluconate, sulfate or fumarate in the last 12 weeks
- Multivitamin and mineral supplements (35 mg or more of elemental iron per day) in the 2 weeks prior to randomization
- Allergy to oral iron
- Allergy to any of the following medicinal and non-medicinal ingredients in ferrous sulfate: ferrous sulphate, calcium citrate, crospovidone, FD&C Red #40-Aluminum lake, FD&C Yellow #6-Aluminum Lake, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, purified water, talc titanium dioxide
- Allergy to any of the following medicinal and non-medicinal ingredients in vitamin C: Ascorbic acid, Colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and stearic acid
- Intravenous iron therapy in the past 12 weeks
- On new anticoagulant therapy initiated in the past 6 months (e.g. warfarin, apixaban, dabigatran, edoxaban, rivaroxaban)
- Surgery planned in upcoming 12 weeks
- Chemotherapy planned in upcoming 12 weeks
- Blood donation planned in upcoming 12 weeks
- Previously enrolled in the study
- Creatinine clearance less than 30 mL/min
- Hemoglobin less than 80 g/L with active bleeding (defined as WHO grade 2 bleeding or higher in the past week)

5.3 Study Activities

5.3.1 Patient recruitment, consent, screening and enrolment

Patients meeting inclusion criteria will be identified through referring clinician offices (hematology and primary care physicians). Initial contact about the study will be made by a health care provider from the patient's clinical team. Study personnel will approach the MRP for permission to approach the patient or ask that they introduce the study to the patient. With permission to enter the patient's circle of care, the research coordinator will then approach potentially eligible patients. The research coordinator will introduce the trial, confirm eligibility and conduct the informed consent discussion. The study personnel will screen patients for exclusion criteria by asking about the patient's medical history and reviewing their bloodwork that will be taken as a standard of care when visiting the MRP. Patients interested in participating and meeting both inclusion and no exclusion criteria will be given an Informed Consent Form. This discussion will include the rationale for the study, the anticipated risks and benefits of participation, and their rights as a study participant (including withdrawal at any time). Capable participants will be offered an opportunity to ask questions and consult with their family and/or their physician before enrollment. If the patient is deemed incapable of providing informed consent for the study, study personnel will approach the patient's physician to determine if it is safe to delay treatment while a substitute decision maker is identified and approached. As the initiation of oral iron is not urgent, there will be enough time to assess the patient for inclusion in the study before initiating treatment. The subject will be invited to participate and must provide informed consent prior to any study related procedures. One signed copy of the informed consent will be placed in the participant's medical record, another copy given to the participant and the original kept in the study file with the research coordinator. Once the subject is enrolled, his/her family physician will be informed about

his/her participation in the study. If the participant does not wish to participate, the reason for declining will be documented. Patients will be identified by initials only on the screening log.

Another potential recruitment site will be through Canadian Blood Services. Blood donors that have been deferred due to low hemoglobin levels (within the local Toronto area close to hospital study sites) will be provided with a letter (see Supporting Documents) which explains that the donor was deferred and for the donor to see visit their family physician for further investigation. In addition, a letter to the family physician will explain key points about the study purpose, rationale, procedures and detailed information about the DEODO trial. If the patient is interested in participating in the study, after visiting their family physician, the family physician can refer the patient to one of the study sites. The letter contains contact information for the Principal Investigator and Research Coordinator if the patient or their family physician has any questions. It is also acceptable for the patient to contact the study site directly in which case permission from the MRP is not required. Once the patient is referred to or has contacted a study site, then consent will occur as outlined in the previous paragraph.

Once the patient has consented, bloodwork will be performed at the participating institution's laboratory or at a local lab, if it has not been performed in the past 2 weeks. Eligibility of the patient will be determined. If the eligibility is confirmed, then the patient will be enrolled (assigned a study ID) and randomized. Any additional bloodwork required within the pre-specified time frame (see 5.4.1.2) can be drawn or added on to the bloodwork already completed.

All sites will obtain Research Ethics Board (REB) approval of the protocol and the informed consent form. A recruitment log of eligible and ineligible patients as well as reasons for non-consent will be kept at each participating centre. We anticipate that this study will take 2 years to complete.

5.3.2 Randomization and stratification

Randomization allocation will be performed by Clinical Trial Services at Sunnybrook Health Sciences Centre using a computer generated allocation sequence. The randomization code will be generated in random blocks of 4 to 6, stratified by centre, and hemoglobin at time of randomization (hemoglobin greater or equal to 100 g/L or less than 100 g/L). Randomization will be provided to the sites in opaque numbered envelopes. The study is an open-label study. The research coordinator/assistant will enroll participants for this study.

5.3.3 Interventions

A schematic representation of the protocol summary is shown in Figure 1.

5.3.3.1 Investigational Products

Oral ferrous sulfate is the natural health product used throughout this study, and will be provided to patients in 300mg (60mg of elemental iron) tablets.

Vitamin C is a natural health product used throughout this study, and will be provided to patients in 500mg tablets.

5.3.3.2 Acquisition and Formulation

Once randomization has occurred, a prescription for the dosing regimen will be given to the patient to bring to pharmacy at the local site. Patients opting for virtual clinic visits will have their prescription filled by the study coordinator, and the pills couriered to their address on file. Patients will also have the

option to pick-up their prescription from the study site (curbside pick-up). There will be two randomization groups, one for hemoglobin ≥ 100 g/L (Mild IDA) and one for hemoglobin < 100 g/L (Moderate IDA).

5.3.3.3 Packaging

The study drug will be shipped as bulk orders of tablets that will then be distributed into individual bottles by the pharmacy at the local site. The oral ferrous sulfate tablets will be packaged in bottles containing the corresponding amount of pills depending on which treatment arm the patient has been assigned to. One patient kit will contain a bottle of oral ferrous sulfate tablets and another standard package of Vitamin C pills that are to be taken along with the study drug.

5.3.3.4 Treatment Assignment Procedures

Once enrolled, patients will be randomized to either the daily, or every other day treatment arm through the randomization procedure described in section 5.3.2.

5.3.3.5 Daily Dosing

Starting on Day 1, patients will take ferrous sulfate 300mg (60 mg elemental iron) on an empty stomach with vitamin C 500mg daily for a period of 12 weeks. Patients will be instructed to take oral iron at bedtime but can take it at another time during the day if more convenient. If patients cannot tolerate the oral iron on an empty stomach, they will be instructed to take it with a small amount of food, as long as dairy and tannins are not ingested at the same time.

5.3.3.6 Every other day dosing

Starting on Day 1, patients will take ferrous sulfate 300mg (60 mg elemental iron) on an empty stomach with vitamin C 500mg every other day for a period of 12 weeks. Patients will be instructed to take oral iron at bedtime but can take it at another time during the day if more convenient. If patients cannot tolerate the oral iron on an empty stomach, they will be instructed to take it with a small amount of food, as long as dairy and tannins are not ingested at the same time.

5.3.4 Adherence and Dose Modification

This is a pragmatic trial. Adherence will be documented by patients by providing a patient diary (see Supporting Documents) which shows the days on which they are supposed to take oral iron. This will be provided in a paper format. The research team will remind the patient to fill in their patient diary at 4 and 8 weeks. At the 12 week visit, the patient will be instructed to bring in their patient diary and pill bottle. A pill count will also be done to confirm adherence.

It is anticipated that ~ 30% of patients may not tolerate oral iron. The patient adherence diary instructions (see Supporting Documents) can be referred to for simple instructions (under point # 5) if the patient is having mild symptoms with the oral iron. Side effects may improve over the initial 1-2 weeks of oral iron. However, in some cases, patients may not be able to tolerate oral iron. Patients will be instructed to follow their planned schedule as prescribed. If they continue to have symptoms, patients will be instructed to step down in frequency (e.g. from daily to every other day; from every other day to two times per week; from two times per week to once per week) and to record how frequently they are able to take oral iron.

If patients are unable to take the oral iron at all, they will be continued to be followed as long as they are willing to continue and do not meet any criteria for withdrawal. Please refer to Section 10. Criteria for withdrawal from study.

5.3.5 Receiving, Storage, Dispensing and Return

5.3.5.1 Receipt of Investigational Product

McKesson Canada Corporation will act as the distributor for the oral ferrous sulfate supplements, and ship the tablets to Pharmacy at the local sites. The tablets will be transported under temperature controlled conditions. Once received, an inventory will be performed on the study product by study staff to ensure the correct product and amount were delivered, and the integrity of the product was not compromised during transportation. As such, any damaged or unusable product will be documented on the receipt log and the principal investigator will be notified.

5.3.5.2 Storage and Stability

Upon receipt of the product, the ferrous sulfate tablets require special handling and will be transferred to a temperature controlled area of the pharmacy, which is regularly monitored for quality assurance.

5.3.5.3 Dispensing of Investigational Product

The iron tablets will be provided in a bottle, with a child safety cap, to patients by the Pharmacy. The participants will be told how often they are to ingest the tablets, based on which treatment arm they have been randomized to, and will also be given a patient diary specific to their regimen that will be used for patient adherence. The patients will be directed to keep the study supplements at room-temperature conditions.

5.3.5.4 Return and Destruction of Investigational Product

Participants will be made aware of their responsibility to return any unused ferrous sulfate tablets at the end of the 12 week treatment duration, they will bring in the unused tablets and original study bottle back to the research team during their 12 week in-person visit to the local study site. A remote/telephone visit for the week 12 follow-up is also acceptable given the current situation with COVID-19. Virtual visits will also be an option post-COVID-19. Patients opting for a virtual 12-week clinical visit will be requested to courier their pill bottles and adherence diary back to the local site. In this case, a pre-paid return envelope will be provided. Patients will also have the option to return their pill bottles and adherence diary via curbside drop off.

5.4 Study Visits and Assessments

5.4.1 Baseline Visit and Assessment

Baseline assessment will occur according to the schedule below and may be performed in person/remotely (telephone/zoom/OTN). The following assessments will be completed at baseline:

5.4.1.1 Screening and enrollment will occur within 1 week of randomization

Case logs will be initiated for each referral meeting inclusion criteria, indicating:

- Any applicable exclusion criteria as listed in 5.2.2
- Reason for lack of consent amongst eligible patients
- Protocol violations for enrolled patients

Medical history:

- Demographics: age, sex, height, weight
- Diagnosis (reason for iron deficiency anemia, if known)
    - Example: gynecological, gastrointestinal, urologic, blood donation

- History of observed bleeding in the past 2 months: Y/N
    - Location of bleeding
    - Severity by WHO grade 1-3 (see Appendix A)
    - If menstrual bleeding, use validated tool (see Appendix B)
- Diet
    - Vegetarian
    - Vegan
- Blood Donation: Y/N
    - Number of times in past year?
    - Number of times in past 4 months?
- Comorbidities
    - Rheumatologic disorders: e.g. SLE, rheumatoid arthritis
    - Smoking
- Medication history at time of enrollment
    - Ranitidine
    - Proton pump inhibitor use
    - Medications
    - Other vitamin supplements (not including iron)
- History of oral iron use: Y/N
    - Any iron use in the past year: Y/N
    - If yes, last oral iron intake: (date)
    - Type of oral iron and tolerability
- History of IV iron use in the past year: Y/N
    - Type of IV iron

Questionnaire:

- FACIT-Fatigue scale (see Supporting Documents)

5.4.1.2 Baseline Laboratory Assessment

- Hemoglobin, reticulocyte count, ferritin, serum iron, TSAT, C reactive protein within 2 weeks of randomization (and at least 2 weeks off any oral iron supplementation)
- Creatinine within 3 months of randomization
- Screening bloodwork can be used for the baseline laboratory assessment

5.4.2 Follow-up Visits and Assessments

5.4.2.1 Week 1

Participants will be contacted by telephone or email for the following assessment at Day 7 ± 3 days

- Adherence as determined by patient diary (supporting documents)
- Side effect questionnaire (supporting documents)

5.4.2.2 Week 4

Participants will be contacted by telephone or email at Day 28 ± 7 days for the following assessment

- Adherence as determined by patient diary
- Side effect questionnaire
- FACIT-fatigue scale questionnaire
- Medication history (to confirm if any new or discontinued medications)
- Reminder to do laboratory tests (at the local site or local lab) for CBC, reticulocyte count

At the week 4 assessment, if the participant has a drop in hemoglobin of more than 10 g/L from baseline, then the patient will be referred back to the most responsible physician for management and escalation of therapy. If the patient receives escalation of therapy (need for alternative oral iron therapy including if a participant in the every other day group escalates to daily iron, need for intravenous iron, need for transfusion, visit to emergency department related to anemia), the participant will no longer complete any further study assessments and the most responsible physician will be notified. The reason for the drop in hemoglobin will be classified as: ongoing bleeding; non-compliance (defined as less than 50% of pills); other reason; or no clear reason.

5.4.2.3 Week 8

Participants will be contacted by telephone or email at Day 56 ± 7 days for the following assessment

- Adherence as determined by patient diary
- Side effect questionnaire
- FACIT-fatigue scale questionnaire
- Medication history (to confirm if any new or discontinued medications)

5.4.2.4 Week 12 Final Study Visit

Participants will be assessed in person/remotely (telephone/zoom/OTN) at Day 84 ± 7 days for the following assessment

- Adherence as determined by patient diary and pill count
- Side effect questionnaire
- FACIT-fatigue scale questionnaire
- Medication history (to confirm if any new or discontinued medications)
- Laboratory tests: CBC, reticulocyte count, ferritin, serum iron and TSAT
- Need for escalation in therapy: Y/N
    - Increase in oral iron regimen from every other day to daily
    - Intravenous iron
    - Transfusion
    - Visit to emergency department related to anemia

5.4.2.5 Week 13

Participants will be contacted by telephone or email at 7 days ± 3 days after the Week 12 final study visit for assessment of adverse and serious adverse events.

5.4.2.6 Table of Assessments and Procedures to be Performed Throughout the Study

See Appendix C.

5.4.3 Prior and Concomitant Medications

Throughout the study duration, and two weeks leading up to randomization, patients are not permitted to receive other sources of iron supplementation, including but not limited to, other oral ferrous tablets and intravenous iron therapy.

Patients should be advised not to take oral iron within 2 hours of antibiotics, bisphosphonates[39], levodopa, methyldopa[40], mycophenolate mofetil[41], or thyroid medication[42].

5.4.4 Participant Compliance Monitoring and Assessment

Throughout the study duration, patients' compliance with ingesting their oral iron tablets will be monitored through a personal patient diary, through direct contact between the patient and research coordinator/assistant at designated assessment times and a pill count following the 12 week supplementation period. Patients will have the opportunity to check-off when they have taken their tablet on the calendar pages of their patient diary, which indicate which days they should be ingesting the oral ferrous sulfate. At the first, fourth, and eighth weeks after beginning the study treatment, patients will either be called or emailed to assess patient adherence.

If a patient misses a pill, they will continue with the next dose as directed on the calendar and will be advised not to double up dosing.

Lastly, at the end of the 12 week supplementation period, patient will return the patient diary, the pill bottle provided to them and any unused tablets for a final pill count; this number is compared to the number of tablets the patient should have ingested during the 12 weeks.

5.4.5 Protocol Deviations

Planned or unplanned deviations may occur on the part of the participant, the investigator, or study research team. In resolution to a deviation, corrective/preventative actions are to be developed and implemented in a timely manner. Protocol deviations will be documented and reported as required and assessed where necessary during analysis.

6.0 STORAGE AND DISPENSATION OF FERROUS SULFATE

Pharmacy will dispense a 3 month prescription for each group (see Supporting Documents). The patient must keep the drug at room temperature.

7.0 CRITERIA FOR OUTCOME ASSESSMENT

7.1 Primary outcome assessment

Feasibility: Enrollment in the trial will be defined as documentation of informed consent for patients approached

If the study is unable to enroll 52 patients in a 2 year enrolment period, the study as it is currently designed will not be deemed feasible.

7.2 Secondary outcome assessments

Feasibility

1. Proportion of eligible patients consenting to participate

$$\frac{\text{\# meeting eligibility criteria - \# in whom consent not obtained}}{\text{\# meeting eligibility criteria}}$$

2. Proportion of consenting patients receiving the allocated treatment

$$\frac{\text{\# consenting to treatment - \# not administered allocated treatment}}{\text{\# consenting to treatment}}$$

3. Proportion of treated patients completing 4 week and 12 week laboratory tests

$$\frac{\text{\# completing 100\% of 4 week and 12 week lab tests}}{\text{\# consenting to treatment}}$$

4. Proportion of treated patients completing 4 week, 8 week and 12 week side effect questionnaire

$$\frac{\text{\# completing 100\% of 4 week, 8 week and 12 week side effect questionnaire}}{\text{\# consenting to treatment}}$$

5. Proportion of treated patients completing 4 week, 8 week and 12 week FACIT-fatigue scale

$$\frac{\text{\# completing 100\% of 4 week, 8 week and 12 FACIT-fatigue scale}}{\text{\# consenting to treatment}}$$

6. Proportion of treatment doses taken as per protocol based on pill count

$$\frac{\text{total \# of doses - \# of missed doses}}{\text{total \# of doses}}$$

7. Proportion of treated patients taking at least 90% of their prescribed doses

$$\frac{\text{\# of patients taking at least 90\% of prescribed doses}}{\text{total \# of treated patients}}$$

8. Proportion of treated patients requiring a step down in therapy

$$\frac{\text{\# of patients requiring step down in therapy}}{\text{total \# of treated patients}}$$

Clinical/Safety

9. Hemoglobin increment at 4 and 12 weeks is defined as the 4 or 12 week hemoglobin value minus the baseline hemoglobin value

10. Proportion with complete hemoglobin response defined as hemoglobin greater than or equal to 120 g/L in women; and 130 g/L in men at 4 weeks and 12 weeks

11. Change in reticulocyte count at 4 and 12 weeks defined as the 4 or 12 week reticulocyte count minus the baseline reticulocyte count

12. Change in ferritin, serum iron and TSAT at 12 weeks defined as the value at 12 weeks minus the baseline value

13. Quality of life (FACIT-fatigue scale) at 4, 8 and 12 weeks

14. Proportion with side effects and type of side effects at 4, 8 and 12 weeks as determined by the oral iron side effect questionnaire

15. Proportion of patients who stop taking oral iron due to side effects at 4 and 12 weeks

16. Need for escalation in therapy (increase in oral iron regimen from every other day to daily, need for intravenous iron, need for transfusion, visit to emergency department related to anemia) assessed at 12 weeks

17. Proportion of patients with a drop in hemoglobin of 10 g/L or more at weeks 4 and 12

8.0 STATISTICAL CONSIDERATION

8.1 Sample Size and Sample Size Justification

The required sample size for this pilot RCT is calculated based on the primary outcome of the definitive study which is the mean hemoglobin increment in each group. For the every other day oral iron group to be considered non-inferior, the mean hemoglobin increment in the every other day oral iron group should not be more than 5 g/L less than the mean hemoglobin increment in the daily oral iron group. This is based on the Cochrane review[31] of intermittent compared with daily dosing showing that the mean hemoglobin difference between intermittent and daily oral iron was -0.15 g/L (95% CI -2.2 g to 1.9 g). Looking at individual studies within the Cochrane review, the standard deviations for the baseline and end of intervention hemoglobin measurements were approximately 10 g/L. Stoffel et al[34] specifically studied the use of ferrous sulfate 300mg po daily over 14 days vs alternate day oral iron over 28 days. The baseline mean hemoglobin in each group was 128 g/L (-SD 117; + SD 140) and 132 g/L (-SD 125; +SD 140) respectively. At the end of the intervention, the hemoglobin was 132 g/L (-SD 125; +SD 140) and 136 g/L (-SD 129; +SD 144), respectively. Thus, the standard deviation for these 2 studies is closer to 10 g/L.

Table 2 below shows the sample size required to confirm non-inferiority of every other day oral iron compared with daily iron based on the true mean difference of the mean increment between the two groups, the standard deviation, the non-inferiority margin and the power of the study. The table also takes into account the adjusted sample size with a 30 % drop out considered.

Table 2: Sample size calculation

True difference of mean increment between two study groups, (g/L) [A, D]	Standard Deviation (SD) of the increment (g/L) [B]	Non-inferiority margin for the difference (g/L) [C]	Power	Total Sample size required to confirm non-inferiority	Adjusted sample size with 30% drop out considered [E]
0	5	>-5	80%	28	40
	7.5	>-5	80%	58	84
	10	>-5	80%	102	146

0	5	>-5	90%	36	52
	7.5	>-5	90%	80	116
	10	>-5	90%	140	200
-0.15	5	>-5	80%	28	40
	7.5	>-5	80%	62	90
	10	>-5	80%	108	156
-0.15	5	>-5	90%	38	56
	7.5	>-5	90%	84	120
	10	>-5	90%	148	212

A. Increment will be calculated from each subject first, and then mean increment for each study group. A difference in the mean increment will be calculated as mean increment in the every other day oral iron group minus mean increment in the daily oral iron group.
B. Standard deviation (SD) was not available for the increment. It could be estimated from SDs or the pre- and post- treatment hemoglobin level and assumed correlation between pre- and post-hemoglobin. If SDs for the pre- and post- hemoglobin are equal to 10, and correlation between them is 0.5, the estimated SD for the increment is 10. If the correlation between pre- and post- is 0.75, then the estimated SD for the increment is 7.1.
C. One sided 95% confidence interval of the difference between two groups in the hemoglobin increment will be calculated (every other day minus daily). If the bound of the confidence interval is greater than -5, then non-inferiority can be confirmed.
D. If we assume the true difference between two groups is -0.15 as reported from the meta-analysis, the sample size required could be slightly larger.
E. Total sample size was divided by 70% to account for a 30% drop out.

Given that this pilot trial is a proof-of concept study, a sample size of 52 patients was deemed appropriate. Therefore, we will aim to enroll 52 patients to determine the feasibility of the trial and to provide more accurate estimates of the numbers required for a definitive trial. The trial will be deemed feasible if we are able to enroll 52 patients over 2 years at two sites.

The trial will proceed until there are 52 enrolled patients and at least 36 patients who complete the trial to 13 weeks.

8.2 Final Analysis Plan

The results of this pilot trial will be used to assess the feasibility and inform the design of the definitive trial. We will present point estimates of feasibility events, including enrolment, adherence to protocol and accrual, as proportions with 95% confidence intervals. We will present continuous data as means and standard deviations, or medians and inter-quartile ranges, as appropriate.

An intention-to-treat analysis will be performed on all patients randomized for the secondary efficacy outcome. A per protocol analysis will be conducted for patients who have taken at least 90% of the

prescribed doses. Subgroup analysis will be performed on the stratified groups with hemoglobin 100g/L or greater and hemoglobin less than 100g/L. Additional subgroup analyses will include: patients with ongoing bleeding (WHO grade 2 or higher) vs no bleeding; and normal vs. increased CRP (based on the normal range).

8.3 Interim analysis

Safety and interim analyses will be performed after enrolling 20 patients to the study.

8.4 Stopping Rules

This study will be stopped prior to its completion if: (1) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; or (2) any new information becomes available during the trial that necessitates stopping the trial.

9.0 ASSESSMENT OF SAFETY

9.1 Definitions

9.1.1 Adverse Event

An **Adverse Event (AE)** is defined as any new event that may jeopardize the patient which the study investigator physician perceives may be directly related to the enrolment in the pilot study or to the assigned arm. Adverse events are not study related if they are related primarily to the underlying disease. All AEs are to be documented and assessed for relatedness. If related to the study drug and occurring from baseline up to one week after the final study visit, the AE will be recorded on the eCRF and coded as per the most recent edition of the Common Terminology Criteria for Adverse Events (CTCAE).

9.1.2 Expected adverse events with ferrous sulfate

Side effects of oral iron supplementation include constipation, nausea, diarrhea, abdominal pain, vomiting, heartburn, flatulence and dark stools.[8,35] When compared to placebo in randomized controlled trials, ferrous sulfate had an increased incidence of gastrointestinal (GI) side effects with an OR 2.32 (95% CI 1.74-3.08). The proportion of patients with GI side effects was 35% (range 10-90%) in the ferrous sulfate arms compared with 22 % (range 0-69%) in the placebo arms. The most common side effects were constipation, nausea and diarrhea with pooled estimates of incidence of 12%, 11% and 8% respectively.[35] Additional side effects included abdominal pain, vomiting, heartburn, flatulence and dark stools.

Overall, the risk to patients enrolled in this study is anticipated to be low, as 1) patients with IDA would normally be treated with oral iron; 2) patients with a prior history of intolerance to oral iron will be excluded; 3) exclusions include patients with baseline gastrointestinal disease such as inflammatory bowel disease; 4) patients will be monitored for side effects throughout the study; and 5) side effects stop immediately with stopping oral iron with no long term sequelae.

9.1.3 Unexpected Adverse Event

An unexpected adverse event is defined as any adverse event that is not identified in section 9.1.2 or in nature, severity or frequency in the current Health Canada Product Monograph.

9.1.4 Unexpected Adverse Drug Reaction (ADR)

An unexpected ADR is an adverse reaction, the severity of which is not consistent with the Health Canada Product Monograph. All noxious and unintended responses to a medicinal product related to any dose should be considered an ADR.

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

9.1.5 Serious Adverse Event (SAE)

A serious adverse event (SAE) in the study is defined as:

a) any event that is fatal or immediately life threatening, permanently disabling, severely incapacitating, or requires prolonged inpatient hospitalization, or
b) any event that may jeopardize the patient and requires medical or surgical intervention to prevent one of the outcomes listed above, AND
c) which the attending physician perceives may be directly related to enrolment in the study, or to the assigned arm.

SAEs will be considered to be study-related if the event follows a reasonable temporal sequence from the study intervention and could readily have been produced by the intervention. Adverse events are not study related if they are related primarily to the underlying disease.

9.2 Assessment of an Adverse Event

9.2.1 Relationship (Causality/Relatedness)

The causality assessment is the determination, according to the investigator's clinical judgment, of the existence of a reasonable possibility that the study drug (IP) caused or contributed to an adverse event.

If the investigator or delegated sub-investigator is unsure about whether or not the study drug caused or is related to the event, then the event will be handled as "related" to the study drug for reporting purposes of the trial. If the causality assessment is "unknown but not related" to the study drug, this should be clearly documented in the source documents.

9.2.2 Expectedness

Events are classified as unforeseen or unexpected if the nature, severity or frequency is not consistent with the risk information set out in Section 9.1.2 or the Product Monograph (PM) or label.

9.2.3 Seriousness

Events are classified as serious if associated with effects threatening the life or physiological functions of a participant. Refer to the definition for "Serious Adverse Events" in section 9.1.5.

9.2.4 Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (e.g. mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a

participant's life or functioning. The terms “serious” and “severe” are not synonymous. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

To assess the severity of an adverse event the investigators will use the following:

- the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

9.2.5 Adverse Event Recording

Investigations into potential adverse events should be done during each contact with a participant. Investigations may be done through specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded promptly in the source document, and assessed by an investigator in a timely manner allowing sufficient time to meet required reporting timelines for SAEs and serious unexpected adverse drug reactions (SUADRs) if needed. Adverse event CRFs should be completed using source documents by a delegated research team member in a timely manner/within 15 days of site awareness. All clearly related signs, symptoms, and abnormal diagnostic procedures should be recorded in the source document, though should be grouped under one diagnosis. Each diagnosed adverse event should then be categorized in accordance with the revised NCI Common Terminology Criteria for Adverse Events (CTCAE).

The following are not considered AEs and therefore do not require recording:

- Pre-existing diseases or conditions identified and recorded at screening/baseline unless, at the discretion of the investigator, the disease or condition worsens in severity or frequency

- At the discretion of the investigator, events considered likely manifestations of the underlying disease or that commonly occur in the study population independent of study drug exposure

- Elective medical or surgical procedures.

9.3 Procedures for Reporting a Serious Adverse Event and Unanticipated Events

9.3.1 Investigator reporting: Notifying the REB

Serious adverse events and unanticipated events should be recorded and reported to the REB in accordance with local reporting requirements and timelines.

9.3.2 Investigator reporting: Notifying the Sponsor

The investigator is responsible for reporting SAEs and SUADRs to the sponsor (Sunnybrook Research Institute) in accordance with applicable regulations and reporting requirements and timelines.

Events that are assessed to be **serious and unexpected and related or cannot be ruled out as related** to the investigational product are considered SUADRs. Reporting for SUADRs should include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. The minimum information required includes at least one identifiable participant, one identifiable reporter, one serious reaction, and one suspect product.

Additionally, for SAEs and SUADRS, a Suspect Adverse Reaction Report – CIOMS I Form (see appendix D) must be completed by the investigator and forwarded to the Sponsor within 24 hours of site awareness.

Information on other possible causes of the event, such as concomitant medications and illnesses should also be provided as soon as is made available.

9.3.3 Sponsor Reporting of SUADRs: Notifying Health Canada

The regulatory sponsor is responsible for reporting SUADRs to regulatory authorities in accordance with local expedited reporting requirements and timelines. In addition, the Sponsor will complete the ADR Expedited Reporting Summary Form and submit this form in conjunction with the completed CIOMS Form to the appropriate Health Canada directorate.

9.3.4 Sponsor Reporting of SUADRs: Notifying Sites

The regulatory sponsor is responsible for distributing expedited reports of SUADRs to each investigator for submission to local Ethics Committees within 15 days of sponsor awareness.

9.3.5 Reporting and Entry Timelines

Study investigators will report SAEs to the sponsor within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded and reported to the sponsor within 24 hours of site awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported to the sponsor within 72 hours of site awareness.

Adverse event information will be entered into the CRF in a timely manner and **no later than 15 days** from the time the investigator becomes aware of the event.

Serious adverse event information will be entered into the CRF in a timely manner/**within 72 hours** from the time the investigator becomes aware of the event.

9.4 Data and Safety Monitoring Board (DSMB)

A data and safety monitoring board is not deemed to be required because: 1) this is a pilot randomized trial to assess feasibility; 2) there are no concerns regarding unacceptable toxicity; 3) the experimental arm is the same drug but at a lower dose; 4) the primary outcome is not a “major endpoint” such as mortality; and 5) there are no ethical concerns regarding possible extreme efficacy of one arm so as to consider stopping the trial early.

10.0 CRITERIA FOR WITHDRAWAL AND DISCONTINUATION FROM STUDY

Patients will be followed until 12 weeks or until there is an escalation of therapy as defined by need for: alternative oral iron therapy (including if a participant in the every other day group escalates to daily iron), need for intravenous iron, need for transfusion, or a visit to emergency department related to anemia.

10.1 Early Termination and Reasons for Withdrawal

Patients may find that they are not able to continue in the study due to intolerable side effects from the oral iron despite simple measures to address the side effects. Patients are permitted to withdraw consent at any time if they desire and will not undergo further trial investigations if they do so. Additionally, patients who become pregnant during the course of the study will be stopped from using the study medications and withdrawn from the study. Other reasons for withdrawal include use of

intravenous iron, use of blood transfusion, any deviation from inclusion/exclusion criteria and serious adverse events (as described in section 9.3).

Participants withdrawing from the study should be contacted by the study research team requesting a final visit and to follow up with any unresolved adverse events. Once withdrawn from the study, no further study procedures or evaluations should be performed, or additional study data collected. However, every effort should be made to obtain permission to document the reason for withdrawal and to collect participant outcomes, such as survival data up to the protocol-described end of participant follow up period, where possible. Any data collected prior to the withdrawal of consent may be retained and used by the sponsor. If the patient withdraws from the study, the research team will notify the patient's referring physician.

10.2 Data Collection and Follow-up for Withdrawn Participants

Patients will be asked to continue with follow-up quality of life assessment and laboratory tests. It is important to continue to follow these patients and capture outcomes that occur once they have discontinued study intervention to determine feasibility. Through telephone calls and emails, every effort will be made to obtain permission to document the reason participants withdrew consent and to continue collecting the quality of life assessments and laboratory values previously mentioned. Patients who have completed at least 90% of the prescribed doses will be included in the per-protocol analysis.

11.0 ETHICAL ISSUES

11.1 Ethical conduct and ethical issues

Approval for patient accrual must be obtained from research ethics board (REB) at the study center before patient recruitment can begin. Any additional correspondence with REB must be maintained by the research coordinator/assistant at each participating site.

11.2 Informed Consent

Study personnel will approach the MRP for permission to approach the patient or ask that they introduce the study to the patient. With permission, the research coordinator will then approach potentially eligible patients to introduce the trial and conduct the informed consent discussion. By being invited into the patient's circle of care with the permission of the MRP, study personnel will screen patients for exclusion criteria by asking about the patient's medical history and reviewing their bloodwork that will be taken as a standard of care when visiting the MRP. Patients interested in participating and meeting both inclusion and no exclusion criteria will be given an Informed Consent Form. This discussion will include the rationale for the study, the anticipated risks and benefits of participation, and their rights as a study participant (including withdrawal at any time). Capable participants will be offered an opportunity to ask questions and consult with their family and/or their physician before enrollment. If the patient is deemed medically incapable, study personnel will approach the patient's physician to determine if it is safe to delay treatment while a substitute decision maker is identified and approached. As the initiation of oral iron is not urgent, there will be enough time to assess the patient for inclusion in the study before initiating treatment. The subject will be invited to participate and must provide informed consent prior to any study related procedures. One signed copy of the informed consent will be placed in the participant's medical record, another copy given to the participant and the original kept in the study file with the research coordinator. Once the subject is enrolled, his/her family physician will be informed about his/her participation in the study. If the participant does not wish to participate, the reason for declining will be documented and the patient will be considered a screening failure (failure to provide informed consent).

12.0 STUDY ADMINISTRATION

The coordinating site will be Sunnybrook Health Sciences Centre. The site research coordinators will be responsible for trial coordination, site training, site start-up/activation, document management, supply management, database development, data management and statistical analysis. Study data and patient surveys will be entered and maintained on a secure password protected database developed using REDCap (www.projectredcap.org) and will be accessible via the Internet for data entry purposes.

12.1 Arrangements for day-to-day management of the trial

The research coordinator will be responsible for this aspect of the study, including system checks, maintenance, and data back-up. Patient data will be collected monthly and entered into the electronic case report forms. Data queries will be generated monthly for participating sites. A bi weekly status report will include an update on the recruitment and status of all randomized patients. Monthly to bi-monthly audit and feedback meetings will be held for participating sites. Protocol violations will be audited at each site and recorded on designated Protocol Violation Forms.
Clinical research coordinators at each site will work with site investigators on start-up activities (REB applications; study contract; organizing study materials; local in-services). Thereafter, research coordinators will screen, consent and enrol patients, complete case report forms, and respond to data queries.

12.2 Quality Assurance

Study data will be maintained on a secure password protected database accessible to study centres from the world-wide-web. Each centre will enter data for the study participants enrolled at their site. Quality control will be ensured by oversight by the research coordinator at Sunnybrook Research Institute, who will review the electronic data for all participants on a regular basis for completeness and consistency.

Quality and completeness of data entry will be reviewed as soon as possible after data entry, within five business days of data entry for the first five participants randomized at each site, and within 15 days of data entry thereafter. Data queries generated by identification of incomplete or inconsistent data will be raised and should be resolved by the study coordinator or PI in a timely manner. Corrections or changes in the data management system are tracked with the retention of the original data and the corrected data with the date of data entry and submitting personnel.

13.0 SITE MONITORING, auditing and inspecting

13.1 Site Monitoring Plan

Site monitoring is conducted to ensure the safety of human study participants and the protection of their rights and well-being. Monitoring also verifies that collected study data is accurate, complete and verifiable by source documentation and that the study is conducted in accordance with the protocol and operating procedures.

Monitoring for this study is the responsibility of the sponsor, Sunnybrook Research Institute. The delegated monitor will evaluate study processes and documentation based on the approved protocol/amendment(s), of the Natural Health Product Regulations, the International Conference on Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP) and institutional policies.

The extent and nature of monitoring is outlined in the Monitoring Plan. The monitoring plan specifies the frequency of monitoring, monitoring procedures, the level of site monitoring activities, and the distribution of monitoring reports. Monitoring activities will be performed both in person and remotely.

Reports of findings identified during monitoring activities will be provided to sites detailing any required actions. Documentation of monitoring activities and findings will be provided to the site study team and the study QI. The institution and/or local REB reserves the right to conduct independent audits as necessary.

The Investigator is responsible for ensuring monitors and/or quality assurance reviewers are given access to all study-related documents noted above and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and have adequate space to conduct the monitoring visit or audit.

13.2 Monitoring Plan

The monitoring plan will consist of the following: 1) A site initiation visit for non-Sunnybrook sites will be conducted prior to the commencement of the study to ensure both sites are appropriately aware and prepared to conduct study procedures to institutional, provincial and Health Canada standards. During this initiation teleconference, any issues that may be raised will be adequately dealt with and recorded in a report for future reference. 2) A site monitoring visit will be conducted by Clinical Trial Services or its delegate. This visit will involve reviewing study procedures, participant data and Health Canada regulation compliance. A report will be generated based on the visit which addresses any changes that need to be made or considered for appropriate regulatory compliance and patient safety.

13.3 Auditing and Inspecting

The investigator will provide direct access to source data/documents for the purposes of study-related monitoring, audits, and inspections by the REB, the sponsor, and applicable regulatory bodies. The investigator will permit the review of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.) and will ensure access to applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

14.0 DATA HANDLING AND RECORD KEEPING

14.1 Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Personal Health Information Protection Act of 2004 (PHIPA) and the Research Ethics Board. PHIPA outlines the rules for the collection, use and disclosure of personal health information. The Act requires each participant to consent to the collection, use and access of personal health information (PHI), unless consent is waived by the REB. As consent is required, each participant will be informed of the following:

- What PHI will be collected during this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

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

14.2 Source Documents

Source data/documents are original documents, data and records in a clinical study that are necessary for the reconstruction and evaluation of the study. Original documents and data records in this study include, but are not limited to:

- Worksheets
- hospital records
- medical records
- memorandum
- participants' diaries or evaluation checklists
- pharmacy dispensing records
- copies or transcriptions certified after verification as being accurate and complete
- participant files and records kept at the pharmacy
- entries entered directly into the source documents

Source documents have been developed for the baseline assessment (including, medical history), week 1 contact information, week 4 contact information, , week 8 contact information, week 12 contact information, week 12 assessment, week 12 pill count, side effect questionnaire and quality of life questionnaire, and protocol deviations.

Each participating site will maintain appropriate medical and research records for this study, in addition to regulatory and institutional requirements for the protection of confidentiality of participants. If electronic source data documents are printed it should be signed and dated by the investigator to confirm content and filed with other source documents.
The investigator(s) and research team members listed on the Task Delegation Log (TDL) will have access to participant medical records and will collect only the information needed for the study.

Sponsor delegated monitors, representatives of institutional committees and regulatory authority representatives of the country in which the study is being conducted will also have access to examine records for the purposes of quality assurance reviews, audits and evaluation of study safety and progress.

14.3 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study personnel under the supervision of the investigator. All source documents and applicable laboratory reports will be reviewed as needed and used to ensure that data collected for the purposes of the study are accurate and complete. Contemporaneous review of laboratory results and the assessment of clinical significance for those results considered out of range will be documented by means of dated signature by the reviewing investigator. Study personnel, including data entry team members, should use source documents to complete case report forms (CRFs).

As part of the safety plan for this study, the investigator will review individual study participant records to ensure that appropriate mechanisms to protect the safety of study participants are being followed, that protocol requirements are being adhered to, and that data is accurate, complete, and secure. Participant records include, but are not limited to: consent forms, case report forms, data forms, laboratory specimen records, inclusion/exclusion forms, and medical charts. All study data will be collected by a member of the study research team and recorded in accordance with applicable procedures.

14.4 Data Capture

14.4.1 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for this study. Electronic/Paper case report forms (eCRFs/pCRFs) will be used to collect data for this study. CRFs will be completed by data capture personnel and signed off by the investigator in a timely manner. Good documentation practices will be implemented according to standard operating procedures. All data requested on the CRF must be recorded and verifiable by source document.

14.5 Records Retention

It is the responsibility of the REB, investigator and regulatory sponsor to retain study essential documents as per local regulatory requirements and GCP Guidelines.

Study essential documents must be maintained in a secure and confidential manner for participating Canadian sites for a period of 25 years. For the purposes of this study, the start date of the retention period is the date of the final report of the trial. Exceptions may be made for sites which close prematurely, wherein the start date for the retention period will be the date of notification to Health Canada of the sites closure. All study records are then to be destroyed according to local and national policy and requirements. It is the investigator's responsibility to request authorization for destruction at the completion of the retention period and/or for the sponsor to inform the investigator/institution when these documents may be destroyed.

14.6 Clinical Trial Registration

In accordance with Health Canada's Notice "Registration and Disclosure of Clinical Trial Information, November 30, 2007", the investigator will register this study on Clinicaltrials.gov (www.clinicaltrials.gov), a publically available registry that conforms to international standards for registries.

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APPENDIX A:

WHO Bleeding Severity Scale[43]

	Grade 1	Grade 2	Grade 3
Oral and nasal	➢ Oropharyngeal bleeding – total duration of all episodes in previous 24 hours ≤30 minutes* ➢ Petechiae of oral mucosa ➢ Epistaxis – total duration of all episodes in previous 24 hours ≤30 minutes*	➢ Oropharyngeal bleeding – total duration of all episodes in previous 24 hours >30 minutes* ➢ Epistaxis – total duration of all episodes in previous 24 hours >30 minutes*	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Skin, soft tissue, musculoskeletal	➢ Petechiae of skin ➢ Purpura ≤1 inch diameter ➢ One or more spontaneous hematomas in the soft tissue or muscle >1 inch	➢ Purpura >1 inch diameter ➢ Spontaneous hematoma in deeper tissues ➢ Joint bleeding (confirmed by aspiration, imaging study or other accepted technique)	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Gastrointestinal	➢ Positive stool occult blood test‡	➢ Melanotic stool ➢ Hematochezia – visible red blood mixed in stool, not requiring a transfusion ➢ Hematemesis – grossly visible blood in emesis or in nasogastric drainage tube (not related or secondary to swallowed blood)	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Genitourinary	➢ Any biochemical or microscopic Hb/RBCs without red urine‡ ➢ Abnormal vaginal bleeding (unexpected bleeding out of normal cycle or bleeding heavier than normal or breakthrough bleeding (patient on hormonal therapy to	➢ Gross/visible hematuria without need for transfusion ➢ Abnormal vaginal bleeding (unexpected bleeding out of normal cycle or bleeding heavier than normal or breakthrough bleeding (patient on hormonal therapy to	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†

	prevent bleeding)) with spotting	prevent bleeding)) more than spotting	
Pulmonary		➢ Hemoptysis – visible blood ➢ Blood in broncho-pulmonary lavage, or blood tinged sputum (excluding those with nose or oropharyngeal bleeding)	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Body cavity		➢ Visible blood in body cavity fluid (e.g. red cells apparent in fluid aspirate) shore of criteria for Grade 3 or 4	➢ Grossly bloody body cavity fluids and organ dysfunction with symptoms, and/or need to intervene (e.g. to aspirate), and/or need for transfusion
Central nervous system		➢ Retinal bleeding without visual impairment ➢ Lumbar puncture with blood (>5 RBC/µL in CSF on microscopic analysis and non-traumatic tap), no symptoms and no visible red color	➢ Lumbar puncture with visible red color in absence of symptoms, and non-traumatic tap
Invasive sites		➢ Bleeding at invasive sites (venipuncture sites, intravenous lines or catheter exit sites): active oozing at site for a cumulative total of >1 hour in the previous 24 hours	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Hemodynamic instability			➢ Any bleeding associated with moderate hemodynamic instability (hypotension; >30mmHg fall or >30% decrease in either systolic or diastolic blood pressure) and requiring RBC transfusion over routine transfusion needs†
Grade 4:			

- Any bleeding associated with severe hemodynamic instability (hypotension; >50mm/Hg fall or >50% decrease in either systolic or diastolic blood pressure, with associated tachycardia (heart rate increase of ≥20% for 20 minutes) and requiring RBC transfusion over routine transfusion needs
- Fatal bleeding from any source
- Retinal bleeding with visual impairment (Visual impairment is defined as a field deficit, and patients with suspected visual impairment require an ophthalmologic consult for documentation)
- CNS symptoms with non-traumatic bloody lumbar puncture
- CNS bleeding on imaging study with or without dysfunction

RBC indicates red blood cell; Hb, hemoglobin; CSF, cerebrospinal fluid; Hg, mercury; and CNS, central nervous system

*Count actual bleeding (i.e. "running out" or need for basin, Kleenex, towel, etc.) not minor bleeding

†Red cell transfusion must be specifically related to treatment of bleeding within 24 hours of onset of bleeding

‡Not assessed in PLADO

APPENDIX B:

Pictorial Blood Assessment Chart (PBAC) for menstrual bleeding[44,45]

A score of > 100 on the PBAC is defined as menorrhagia.

Pictorial Blood Loss Assessment Chart

DAY	DAY1	DAY2	DAY3	DAY4	DAY5	DAY6	DAY7	DAY8	DAY9	DAY10	TOTAL TALLIES	MULTIPLYING FACTOR	ROW TOTAL
												X1	
												X5	
												X20	
												X1	
												X5	
												X10	
Small blood clots (= Dime)												X1	
Large blood clots (≥ Quarter)												X5	
Menstrual accidents												X5	
Total Score (Sum of rows)													

How to use the Pictorial Blood Assessment Chart:

- Record the number of tampons and sanitary pads used each day during your period by placing a tally mark under the day next to the box representing the amount of bleeding noted each time you change your pads or tampon (see example at right)
- Record clots by indicating whether they are the size of a dime or a quarter coin in the small and in the large blood clot row under the relevant day.
- Record any incidences of flooding (accidents) by placing a tally mark in the menstrual accident row.

Scoring the Chart:

At the end of your period tabulate a "**Total Score**" by multiplying the total number of tallies in each row by the "**Multiplying Factor**" at the end of the row. Then sum the "**Row Totals**" to obtain the final "**Total Score**"

Example:

Ms. Smith in the first day of her period, she used 7 pads (5 lightly stained, 1 moderately and 1 heavy stained). She also used 1 moderately stained tampon and had 3 blood clots 1 small and 2 large. She also had one incidence of flooding.

Days	D1	D2	D3	D-
	𝍸			
	I			
	I			
				
	I			
				
Small blood clots (= Dime)	I			
Large blood clots (≥ Quarter)	II			
Menstrual accidents	I			
Total Score				

Completed by: _____ Date: _____

Reviewed by: _____ Date: _____

APPENDIX C:

Table 1: Flow Chart of Assessments/Procedures to be Performed Throughout the Study

Procedures	**Prior to Enrolment**	**After Enrolment**	**Week 1 (±3 days)**	**Week 4 (±7 days)**	**Week 8 (±7 days)**	**Week 12 (±7 days)**	**Week 13 (7 days ± 3 days after final study visit)**
Referring clinician offices identify potential patients as participants	X						
Patient (surrogate) informed consent	X						
Inclusion and exclusion criteria	X						
Randomization		X					
Baseline Data							
Case Logs *(reason for lack of consent, protocol violations)*	X						
Medical History		X					
Laboratory Assessments							
Hemoglobin	X			X		X	
Reticulocyte Count	X			X		X	
C reactive protein (CRP) – acute phase reactant	X						
Ferritin	X					X	
Serum Iron	X					X	
Transferrin Saturation (TSAT)	X					X	
Creatinine clearance	X						
Subjective Patient Assessments							
FACIT-Fatigue Scale Questionnaire		X		X	X	X	
Patient Diary Adherence			X reminder	X	X	X	
Side Effect Questionnaire				X	X	X	
Pill Count						X	
Adverse and Serious Adverse Events			X	X	X	X	X
Need for Therapy Escalation			X	X	X	X	

APPENDIX D:

Suspect Adverse Reaction Report

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	

Daily vs. every other day oral iron supplementation in patients with absolute iron deficiency anemia (DEODO): a multi-centered, pilot randomized controlled trial

Summary of Changes Table

Protocol Summary of Changes

Protocol V5 dated July 9, 2020 (updated from Protocol V4 dated December 6, 2020)

Section	Change	Rationale
Page 1	Added protocol number 1534	Was left blank in previous protocol version
5.3.1 Patient recruitment, consent, screening and enrolment	**Add:** Once the patient has consented, bloodwork will be performed at the participating institution's laboratory or at a local lab	Allow for patients the option to complete bloodwork at a local lab if they feel unsafe entering the hospital due to COVID-19.
5.3.3.2 Acquisition and Formulation	**Add:** Once randomization has occurred, a prescription for the dosing regimen will be given to the patient to bring to pharmacy at the local site. Patients opting for virtual clinic visits will have their prescription filled by the study coordinator, and the pills couriered to their address on file. Patients will also have the option to pick-up their prescription from the study site (curbside pick-up).	Allow for patients to pick up/drop-off their prescription without in-person contact at the hospital.
5.3.5.4 Return and Destruction of Investigational Product	**Add:** the local study site. A remote/telephone visit for the week 12 follow-up is also acceptable given the current situation with COVID-19. Virtual visits will also be an option post-COVID 19. Patients opting for a virtual 12-week clinical visit will be requested to courier their pill bottles and adherence diary back	Allow for patients the option to complete their week 12 visit virtually if they feel unsafe entering the hospital due to COVID-19. Allow for patients to pick up/drop-off their prescription and adherence diary without in-person contact at the hospital.

	to the local site. In this case, a pre-paid return envelope will be provided. Patients will also have the option to return their pill bottles and adherence diary via curbside drop off.	
5.4.1 Baseline Visit and Assessment	**Add:** Baseline assessment will occur according to the schedule below and may be performed in person/remotely (telephone/zoom/OTN).	Allow for patients the option to complete their week baseline visit virtually if they feel unsafe entering the hospital due to COVID-19.
5.4.2.2 Week 4	**Add:** Reminder to do laboratory tests (at the local site or local lab)	Allow for patients the option to complete bloodwork at a local lab if they feel unsafe entering the hospital due to COVID-19.
5.4.2.4 Week 12 Final Study Visit	**Add:** Participants will be assessed in person/remotely (telephone/zoom/OTN) at Day 84 ± 7 days for the following assessment	Allow for patients the option to complete their week 12 visit virtually if they feel unsafe entering the hospital due to COVID-19.
List of changes	Updated list of changes	Include all changes made to study documents

Protocol V4 dated Dec 6, 2019 (updated from Protocol V3 dated June 27, 2019)

Section	**Change**	**Rationale**
Protocol Summary	Revised exclusion criteria from 'on anti-coagulant therapy' to 'on new anticoagulant therapy initiated in the past 6 months'	Patients who have been on anticoagulants for longer than 6 months have had stability on their anticoagulation; thus should be eligible
5.2.2 Exclusion criteria	Revised exclusion criteria from 'on anti-coagulant therapy' to 'on new anticoagulant therapy initiated in the past 6 months'	Patients who have been on anticoagulants for longer than 6 months have had stability on their anticoagulation; thus should be eligible

5.3.1 Patient recruitment, consent, screening and enrolment	Adding the following to clarify the general process of recruitment 'with permission to enter the patient's circle of care the research coordinator will then approach potentially eligible patients For recruitment through Canadian Blood Services it has been clarified that 'It is also acceptable for the patient to contact the study site directly in which case permission from the MRP is not required'	As the Canadian Blood Services donor letter contains the Research Coordinator's contact information for both sites, it is acceptable for patients to contact study personnel directly regarding their interest.

Protocol V3 dated Jun 27, 2019 (updated from Protocol V1.2 dated Aug 31, 2018)

Section	Change	Rationale
Title page	Removed: Research Coordinator name and credentials	Since CRC keeps changing for the research study, it is best to not have this mentioned on the front page of the protocol.
Key role and contact information	Removed clinical laboratory/department contacts and address for the research coordinators	Same reason as above
5.3.1 Patient, recruitment, consent, screening and enrolment	Added "once the patient has consented, screening bloodwork will be performed at the participating institution's laboratory, if it has not been performed in the past 2 weeks. Eligibility of the patient will be determined. If the eligibility is confirmed, then the patient will be enrolled (assigned a study ID) and randomized. Once the patient has been enrolled, additional bloodwork not already performed within the pre-specified time frame (5.4.1.2) will be conducted (either drawn from the patient or added	To clarify the process of eligibility, enrolment and randomization of the study. Also clarifying the the time period of the blood-test that can be used to assess the eligibility.

	on to the bloodwork already done). Removed "once patient has been enrolled, additional bloodwork not already performed within the pre specified time frame (5.4.1.2) will be conducted (either drawn from the patient or added on to bloodwork already done). If the patient is deemed eligible, the patient will be randomized.	
5.3.3.3 packaging	Removed 120 from the sentence "standard package of 120 vitamin C pills that are to be taken along with the study drug".	Participants receive either '45' or '90' tablets in their packaging depending on their randomization schedule. Standard package does not include 120 vitamin C pills.
5.4.1.1 screening and enrollment will occur within 1 week of randomization	Removed 'response' for both IV and oral iron.	Lack of response to oral iron is already captured in the eligibility checklist. Response to IV iron does not impact this study.
5.4.1.2 Baseline laboratory assessment	Added "screening bloodwork can be used for the baseline laboratory assessment"	To clarify that the screening bloodwork can be used for baseline laboratory assessment.
5.4.2.2 week 4	Added "medication history (to confirm if any new medications or discontinued any previous medications)".	To clarify that the study team will be asking the participants if they have started any new medication at each visit during the trial.
5.4.2.3 week 8	Added "medication history (to confirm if any new medications or discontinued any previous medications)".	Same as 5.4.2.2
5.4.2.4 Week 12 Final study visit	Added "medication history (to confirm if any new medications or discontinued any previous medications)".	Same as 5.4.2.2
5.4.4 participant compliance monitoring and assessment	Added "if a patient misses a pill, they will continue with the next dose as directed on the calendar and not to double up dosing".	To specify the procedure if a participant misses a pill. Also to clarify that missing a pill is not considered a protocol violation.
8.1 sample size and sample size justification	Added "the trial will proceed until there are 52 enrolled patients and at least 36 patients who complete the trial to 13 weeks without dropping out".	To specify the number of patients needed in order for the trial to be considered complete.
Appendix B	Added "completed by, date and reviewed by and date"	To record the personnel completing and reviewing the PBAC score calculation.

Appendix C	Revised inclusion/exclusion criteria to “prior to enrolment” from “after enrolment “ Revised Medical History to “after enrolment” to “prior to enrolment” Added checkmarks for AE and SAE under week 1, week 4, week 8, week 12 Added checkmarks for need for therapy escalation under week 1, week 4, week 8	To correct the order of procedures followed for enrollment. Inclusion and exclusion criteria are always reviewed prior to enrolment versus after. Medical history are reviewed after enrolment. Additionally, the team will be assessing the patient for AE and SAE at each follow-up call and visit with the participant during the duration of the trial.