Sunnybrook
HEALTH SCIENCES CENTRE

Informed Consent Form for Participation in a Research Study

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

Study Doctor: *Dr. Yulia Lin,* Transfusion Medicine & Hematology
Phone: 416-480-4042

Sponsor/Funder(s): This study is an investigator initiated study funded by the University of Toronto – Alexandra Yeo Grant.

INTRODUCTION

You are being invited to participate in a clinical trial (a type of study that involves research). You are invited to participate in this trial because you have iron deficiency anemia (low iron with low red blood cell count) and are 16 years or older. This consent form provides you with information to help you make an informed choice. Please read this document carefully and ask any questions you may have. All your questions should be answered to your satisfaction before you decide whether to participate in this research study.

Please take your time in making your decision. You may find it helpful to discuss it with your friends, family and/or your family doctor.

Taking part in this study is voluntary. Deciding not to take part or deciding to leave the study later will not result in any penalty or affect current or future health care.

As a Substitute Decision Maker, you are being asked to provide informed consent on behalf of a person who is unable to provide consent for him/herself. If the participant gains the capacity to consent for him/herself, your consent for them will end. Throughout this form, "you" means the person you are representing.

IS THERE A CONFLICT OF INTEREST?

There are no conflicts of interest to declare related to this study.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

The standard initial treatment for iron deficiency anemia is an oral iron supplement.

Oral ferrous sulfate is an oral iron supplement commonly used to treat iron deficiency anemia. Laboratory tests show that it may improve anemia, such as the hemoglobin level (measure of red blood cells in the blood) and ferritin (measure of iron stores). It is less clear if taking oral iron daily (standard treatment) compared with every other day may result in the same improvement in hemoglobin level with fewer side effects.

Health Canada, the regulatory body that oversees the use of natural health products in Canada, has not approved the use of oral ferrous sulfate tablets for the treatment of iron deficiency anemia, based on the Health Canada Product Monograph, which indicates its use as prevention

for iron deficiency anemia. Health Canada has allowed the use of oral ferrous sulfate to be used in this study to treat iron deficiency anemia.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to optimize the effectiveness of oral iron supplementation while minimizing side effects to improve patient treatment. As this study is a pilot study, another primary purpose is to test the study plan and to determine whether enough participants will join a larger study and accept the study procedures. This type of study involves a small number of participants and so it is not expected to definitively prove safety or effectiveness. The results may be used as a guide for larger studies, although there is no guarantee that they will be conducted. Participation in a pilot study does not mean that you will be eligible to participate in a future larger study.

The purpose of this study is to compare the effects of taking oral ferrous sulfate tablets with vitamin C every other day, on you and your iron deficiency anemia, compared to taking oral ferrous sulfate with vitamin C daily, which is commonly-used to treat iron deficiency anemia. Vitamin C is taken with oral iron to improve iron absorption.

WHAT OTHER CHOICES ARE THERE?

You do not have to take part in this study in order to receive treatment or care. Other options (in addition to the standard or usual treatment described above) may include, but are not limited to:

- other oral iron supplements, including, but not limited to; oral ferrous gluconate or fumarate;
- intravenous iron therapy, if oral iron is not tolerated or effective;
- other research studies may be available if you do not take part in this study;
- no therapy at this time.

Please talk to your usual doctor or the study doctor about the known benefits and risks of these other options before you decide to take part in this study. Your usual doctor or the study doctor can also discuss with you what will happen if you decide not to undertake any treatment at this time.

You do not have to take part in this study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

It is anticipated that about 52 people will take part in this study, from research sites located in Toronto, Ontario, Canada.

This study should take approximately two years to complete and the results should be known in about 1 year after completion.

WHAT WILL HAPPEN DURING THIS STUDY?

ASSIGNMENT TO A GROUP

If you decide to participate then you will be "randomized" into one of the groups described

below. Randomization means that you are put into a group by chance (like flipping a coin). There is no way to predict which group you will be assigned to. You will have a 50% chance of being placed in either group. Neither you, the study staff, nor the study doctors can choose what group you will be in. However, you will be told which group you are in.

WHAT IS THE STUDY INTERVENTION?

Group 1 (Experimental intervention): Every other day oral ferrous sulfate supplementation

If you are randomized to this group you will take a 300mg (60mg elemental iron) tablet of ferrous sulfate on an empty stomach at bedtime, with a 500mg vitamin C tablet every other day, for a period of 12 weeks.

Group 2 (Non-Experimental Intervention): Daily oral ferrous sulfate supplementation

If you are randomized to this group you will take a 300mg (60mg elemental iron) tablet of ferrous sulfate on an empty stomach at bedtime, with a 500mg vitamin C tablet daily, for a period of 12 weeks.

- Medicinal and non medicinal ingredients of 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.
- Medicinal and non medicinal ingredients of vitamin C: Ascorbic acid, Colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and stearic acid.

WHAT ELSE DO I NEED TO KNOW ABOUT THE STUDY INTERVENTION?

If you have side effects while you are on this study, the study doctor may make changes to the intervention.

Normally, as part of usual care, you would receive daily oral iron tablets with vitamin C for initial treatment of iron deficiency anemia. If you decide to take part in this study, you may not receive daily oral tablets as usual treatment.

If you opt for virtual clinic visits you will have your prescription filled by the study coordinator, and the pills couriered to your address on file. You will also have the option to pick-up your prescription from the study site (curbside pick-up). At the end of the study, we will ask you to courier back your pill bottles and adherence diary to the local study site. We will provide a pre-paid return envelope to you. You also have the option to return your pill bottles and adherence diary via curbside drop off.

WHAT ARE THE STUDY PROCEDURES?

Non-Experimental Procedures

The following tests will be done as part of this study. Some of these tests may be done as part of your standard care, in which case the results may be used. Some of these tests may be

done more frequently than if you were not taking part in this study and some may be done only for the purpose of the study. If the results show that you are not able to continue participating, the study doctor(s) will let you know.

- A complete blood count at the baseline assessment, 4 and 12 weeks after study intervention has begun, this involves drawing a blood sample and is standard of care for those who have, or are suspected to have, iron deficiency anemia.
- Ferritin measure at the baseline assessment and 12 weeks after study intervention has begun, this involves drawing a blood sample and is standard of care for those who have, or are suspected to have, iron deficiency anemia.
- Reticulocyte count at the baseline assessment, 4 and 12 weeks after study intervention has begun, this involves drawing a blood sample and is standard of care for those who have, or are suspected to have, iron deficiency anemia.
- C reactive protein measure at the baseline assessment, this involves drawing a blood sample and is not standard of care for those who have, or are suspected to have, iron deficiency anemia.
- Serum iron measure at the baseline assessment and 12 weeks after study intervention has begun, this involves drawing a blood sample and is not standard of care for those who have, or are suspected to have, iron deficiency anemia.
- Transferrin saturation measure at the baseline assessment and 12 weeks after study intervention has begun, this involves drawing a blood sample and is not standard of care for those who have, or are suspected to have, iron deficiency anemia.
- Creatinine measure at the baseline assessment, this involves drawing a blood sample and is not standard of care for those who have, or are suspected to have, iron deficiency anemia.

Questionnaires

You will be provided with questionnaires during your visits when you are enrolled, as well as 1, 4, 8 and 12 weeks following your enrollment. The purpose of the side-effect questionnaire is to account for any gastrointestinal effects resulting from the oral iron tablets. The purpose of the FACIT-fatigue scale questionnaire is to understand how the iron tablets may affect fatigue severity and life measures associated with iron deficiency anemia. Each questionnaire will take about 5 minutes to complete, and will be conducted through phone calls or emails; at the end of this consent form you will be asked for your consent to receiving phone calls and/or emails from our research team.

The information you provide is for research purposes only. Some of the questions are personal. You can choose not to answer questions if you wish.

Participant Diaries

You will be asked to keep a diary of when you take your iron tablets. A patient calendar with specific reminders will be provided to patients; please record whether you have taken your tablet, using a checkmark, on the days indicated with a blank box on the calendar. During the follow up phone-calls or emails at weeks 1, 4, 8, 13, and the in-person or virtual visit at week 12, you will be prompted by our research team to answer questions about your adherence to the study schedule.

MANDATORY SAMPLE COLLECTION

The researchers doing this study need to do tests on samples (described below) to determine the results of oral iron supplementation on biological markers.

The collection of the blood samples is a necessary part of this study and will be collected without fasting. Samples will be used only for these purposes. The samples will not be sold.

Once these tests have been completed, any leftover samples will be destroyed according to the site's policy.

Reports about research tests done with your samples will be given to the study doctor(s). If you would like to learn the results of this research, please let them know.

Blood Collection (Required)

Blood samples will be taken by inserting a needle into a vein in your arm. These will be taken at the same time as your study related visits whenever possible, at entry into the study, and at four and twelve weeks after beginning the study treatment. Throughout the entire study duration, the total amount of blood that will be drawn is 22ml (11ml at the baseline assessment, 3ml at the week 4 assessment and 8ml at the 12 week assessment), and will be used to determine the following measures; complete blood count, reticulocyte count, C reactive protein, ferritin, serum iron, transferrin saturation and creatinine clearance. These blood samples will be examined by the local laboratory where your blood is drawn.

How will samples be identified?

As these samples would already be drawn as part of your usual care, the samples will be identified with your name and medical record number. To protect your identity, the information that will be on your samples for research purposes will be limited to your assigned participant identification code. .

Despite protections being in place, there is a risk of unintentional release of information.

Can I withdraw these samples?

If you no longer want your samples to be used in this research, you should contact the Research Coordinator or Study Doctor, who will ensure the samples are retrieved and destroyed according to local hospital policy.

If tests have already been done on your sample(s) it will not be possible to withdraw those results. However, no further testing will be done.

If samples are withdrawn, participants may continue to participate in the main part of the study.

WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?

If you choose to participate in this study, you will be expected to:

- Tell the study doctor about your medical history and current medical conditions;
- Tell the study doctor about all prescription and non-prescription medications and supplements, including vitamins and herbals, and check with the study doctor before starting, stopping or changing any of these. This is for your safety as these may interact with the intervention you receive on this study.

- It is especially important to tell the study doctor if you are taking any other medications containing iron or vitamin C.
  - Tell the doctor if you are allergic 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
  - Tell the doctor if you are allergic 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.
- Tell the study doctor If you are taking any multivitamin or mineral supplements containing 35mg or more of elemental iron per day.
- Tell the study doctor if you are thinking about participating in another research study
- Tell the study doctor if you become pregnant or are breastfeeding or father a child while participating in this study
- Study participants should not become pregnant while on the study
- Avoid drinking/eating dairy products, antacids, calcium, tea and coffee for 1 hour prior to and 1 hour after ingesting the iron tablet, throughout the study duration.
- Stop taking other iron supplementations for two weeks prior to randomization, and during the study duration
- The oral iron tablets are for you alone, and must not be shared with others. If someone accidentally takes an excessive amount of the iron tablets, they should promptly seek medical attention.
- Follow a visit schedule for timely assessments as follows:

Visit	Baseline Week	Week 1	Week 4	Week 8	Week 12	Week 13
Clinic assessments (in-person/virtual)	✓				✓	
Laboratory (lab assessments)	✓		✓		✓	
Email/phone (questionnaires)		✓	✓	✓		✓

- Return the study *diary* that you take home to complete
- Return any unused study medication

HOW LONG WILL PARTICIPANTS BE IN THE STUDY?

The study intervention will last for about 12 weeks; however the total study duration for a patient may exceed this amount due to the randomization and consenting period.

There will be a follow-up visit at 12 weeks after the first dose of the study treatment.

You may be seen more often if the study doctor determines that this is necessary.

No matter which group you are randomized to, and even if you stop the study intervention early, we would like to keep track of your health for the duration of the 12 week treatment period, to capture outcomes that occur once they have discontinued study intervention to determine feasibility. We would do this by having you complete the scheduled laboratory tests and quality of life assessments.

There will be one final phone call or email at 13 weeks to check if you have had any side effects or adverse events.

CAN PARTICIPANTS CHOOSE TO LEAVE THE STUDY?

You can choose to end your participation in this research (called withdrawal) at any time without having to provide a reason. If you choose to withdraw from the study, you are encouraged to contact the study doctor or study staff.

You may withdraw your permission to use information that was collected about you for this study at any time by letting the study doctor know. However, this would also mean that you withdraw from the study.

Information that was recorded before you withdrew will be used by the researchers for the purposes of the study, but no information will be collected or sent to the sponsor after you withdraw your permission.

CAN PARTICIPATION IN THIS STUDY END EARLY?

The study doctor may stop your participation in the study early, and without your consent, for reasons such as:

- The study intervention does not work for you
- You are unable to tolerate the study intervention
- You are unable to complete all required study procedures
- The study doctor no longer feels this is the best option for you
- The Regulatory Authorities (for example, Health Canada) or research ethics board withdraw permission for this study to continue
- If you plan to become pregnant or breastfeeding

If this happens, it may mean that you would not receive the study intervention for the full period described in this consent form. If you are removed from this study, the study doctor will discuss the reasons with you and plans will be made for your continued care outside of the study.

WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?

You may experience side effects from participating in this study. Some side effects of oral iron are known and are listed below, but there may be other side effects that are not expected. There are no side effects from vitamin C. You should discuss these with the study doctor.

The study doctor will watch you closely to see if you have side effects. When possible, other medicine will be given to you to make side effects less serious and more tolerable. Many side effects go away shortly after the study intervention is stopped, but in some cases side effects can be serious, long-lasting, permanent, or may even cause death.

Risks and side effects related to the experimental intervention of oral ferrous sulfate, we are studying include:

Very likely (21% -100%):

- Gastrointestinal Distress
- Abdominal Pain
- Dark stools

Less likely (5 – 20%):

- Constipation
- Nausea
- Heartburn
- Vomiting
- Diarrhea
- Flatulence

All of the aforementioned risks may vary in severity and reversibility, but are highly likely to stop once study supplementation stops if you are experiencing these symptoms.

The risks and side effects of the standard or usual treatment will be explained to you as part of your standard care. These risks are not included in this consent form.

It is possible that other drugs (prescription and non-prescription drugs), vitamins, or herbals can interact with the study intervention. This can result in either the intervention not working as expected or result in severe side effects.

Long term effects of unmonitored oral iron intake can lead to iron overload. Although, this is very unlikely to happen in the 12 week period of the study intervention.

If you should have a side effect or any other unexpected effects from the medication, please contact the study investigator listed at the end of this form.

WHAT ARE THE REPRODUCTIVE RISKS?

There are no reproductive risks associated with this study.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

The expected benefit from taking part in this study is the potential to improve iron deficiency anemia, such as your hemoglobin levels. These potential changes may lead to improved symptoms associated with iron deficiency anemia, such as; cognitive and physical functioning, and fatigue.

If you agree to take part in this study, the experimental intervention may or may not be of direct benefit to you.

Additionally, we hope the information learned from this study will advise the optimal tablet dosing schedule for other people with iron deficiency anemia in the future.

HOW WILL PARTICIPANT INFORMATION BE KEPT CONFIDENTIAL?

If you decide to participate in this study, the study doctors and study staff will only collect the information they need for this study.

Records identifying you at this centre will be kept confidential for 25 years and, to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this consent document.

Authorized representatives of the following organizations may look at your original (identifiable) medical/clinical study records at the site where these records are held, to check that the information collected for the study is correct and follows proper laws and guidelines.

- The research ethics board who oversees the ethical conduct of this study in Ontario
- *Representatives of Sunnybrook Research Institute, who* oversee the ethical conduct of research at this location
- Health Canada (because they oversee the use of natural health products/drugs/devices in Canada)

Information that is collected about you for the study (called study data) may also be sent to the organizations listed above. Representatives of Clinical Trials Ontario, a not-for-profit organization, may see study data that is sent to the research ethics board for this study. Your name, address, or other information that may directly identify you will not be used. The records received by these organizations may contain your participant code, sex and date of birth (month, year only).

If the results of this study are published, your identity will remain confidential. It is expected that the information collected during this study will be used in analyses and will be published/ presented to the scientific community at meetings and in journals. This information may also be used as part of a submission to regulatory authorities around the world to support the approval of the study intervention.

Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated.

A copy of the consent form that you sign to enter the study may be included in your health record/hospital chart.

Data collected using your email server resides on that respective server (i.e. Google, Apple) and no assurance can be made about its confidentiality or that it will only be used for research purposes.

Upon enrolment, participants will be asked by the research team if they prefer to be contacted via email and/or telephone. Based on the participant's response, they will provide information regarding their email address or personal telephone number. Please note that the Sunnybrook email network is secure, however personal email accounts or those used by participants may not be secure and no assurance can be made about its confidentiality.

WILL FAMILY DOCTORS/HEALTH CARE PROVIDERS KNOW WHO IS PARTICIPATING IN THIS STUDY?

Your family doctor/health care provider will be informed that you are taking part in a study so that you can be provided with appropriate medical care. If you do not want your family doctor/health care provider to be informed, please discuss this with the study team.

WILL INFORMATION ABOUT THIS STUDY BE AVAILABLE ONLINE?
A description of this clinical trial will be available on https://clinicaltrials.gov/ and http://www.transfusionquest.ca/. These websites will not include information that can identify you. You can search this website at any time.

WHAT IS THE COST TO PARTICIPANTS?
The oral ferrous sulfate supplements will be supplied at no charge while you take part in this study.

You may not be able to receive the study intervention after your participation in the study is completed. There are several possible reasons for this, some of which are:

- The intervention may not turn out to be effective or safe.
- Your caregivers may not feel it is the best option for you.
- You may decide it is too expensive and insurance coverage may not be available.
- The intervention, even if approved in Canada, may not be available free of charge.

The study doctor will talk to you about your options.

Taking part in this study may result in added costs to you. For example:

- You may miss work as a result of participation in this study. However this is not unique to the study protocol as patients with iron deficiency anemia would potentially miss work as a result of standard care and attending standard appointments anyways.

ARE STUDY PARTICIPANTS PAID TO BE IN THIS STUDY?
You will not be paid for taking part in this study.

If you decide to participate in this study, you will be reimbursed up to $10 for parking, during your week 4 visit to a clinic that will obtain necessary blood samples and up to $25, for your

week 12 visit to your corresponding site. For study related expenses, specifically hospital parking, you will need to provide your receipts for parking to the research staff in order to be reimbursed. Participants attending their week 4 and 12 visits in-person are eligible for the parking reimbursement.

In the case of research-related side effects or injury, medical care will be provided by the study Doctor.

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study.

You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of the results of this study, please let the study doctor know. The results of this study will also be available on the clinical trial registry (see the "Will information about this study be available online" section for more details).

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form you do not give up any of your legal rights against the study doctor or involved institutions for compensation, nor does this form relieve the study doctor or their agents of their legal and professional responsibilities.

You will be given a copy of this signed and dated consent form prior to participating in this study.

WHAT IF RESEARCHERS DISCOVER SOMETHING ABOUT A RESEARCH PARTICIPANT?

During the study, the researchers may learn something about you that they didn't expect. For example, the researchers may find out that you have another medical condition.

If any new clinically important information about your health is obtained as a result of your participation in this study, you will be given the opportunity to decide whether you wish to be made aware of that information.

WHOM DO PARTICIPANTS CONTACT FOR QUESTIONS?

If you have questions about taking part in this study, or if you suffer a research-related injury, you can talk to your study doctor, or the doctor who is in charge of the study at this institution. That person is:

Dr. Yulia Lin 416-480-4042

Name Telephone

If you have questions about your rights as a participant or about ethical issues related to this study, you can talk to someone who is not involved in the study at all. That person is:

Chair of the Sunnybrook Research Ethics Board
Name

416-480-6100 ext. 88144
Telephone

SIGNATURES

- All of my questions have been answered,
- I understand the information within this informed consent form,
- I allow access to my medical records and specimens as explained in this consent form,
- I allow research personnel involved with this study to contact me by telephone and/or email,
- I do not give up any of my legal rights by signing this consent form,
- I understand that my family doctor/health care provider will be informed of my participation in this study
- I agree, or agree to allow the person I am responsible for, to take part in this study.

Signature of Participant/ Substitute Decision-Maker	PRINTED NAME	Date
Signature of Person Conducting the Consent Discussion	PRINTED NAME & ROLE	Date
Signature of Principal Investigator	PRINTED NAME	Date

Complete the following section only if the participant is unable to read or requires an oral translation:

- The informed consent form was accurately explained to, and apparently understood by, the participant/substitute decision maker, and
- Informed consent was freely given by the participant/substitute decision maker

Signature of Impartial Witness/Translator *(If participant were unable to read/required an oral translation)*	PRINTED NAME	Date