

Iron Fatigue Study Information Sheet

An examination into the effects of oral iron supplementation in the presence of vitamin C in non-anaemic women of childbearing age with low iron stores and self-reported fatigue: a randomised, double-blind, placebo-controlled trial

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Background

Research suggests that approximately 20% of adults experience fatigue-related problems, with a higher prevalence in women compared to men. Although there are many causes of fatigue, low iron stores may be a contributing factor, as up to 41% of Australian women experience low iron levels.

The primary aim of this study is to investigate the anti-fatigue effects of iron supplementation. Two forms of iron supplements will be investigated in this study: microencapsulated iron pyrophosphate (MIP) and ferrous bisglycinate (FB). These iron supplements will also contain vitamin C, as this has been shown to enhance iron absorption in the body. We will examine the effects of these iron supplements on fatigue (primary objective), blood iron levels, cognitive performance, mood, brain fog, and general well-being. Furthermore, we will investigate how well these iron forms are tolerated.

This study will be conducted by Dr Adrian Lopresti and Dr Stephen Smith (Clinical Research Australia).

Information about the funding source and declaration of interests

This study is funded by Lipotec S.A.U, the company that produces the iron supplement used in this study. However, this study is being independently managed by Clinical Research Australia (CRA) without external influence from the study sponsor.

What does participation involve? (see study flow chart on page 3)

This study will comprise several steps as outlined below:

Step 1: Completion of initial online screening

This questionnaire takes approximately 10 minutes to complete. It provides us with information relating to the eligibility criteria. If, based on the screening questionnaire results, you are assessed as 'likely' eligible, you will be contacted for a phone interview. Ineligible volunteers will be informed by email that they do not fulfil the eligibility criteria.

Step 2: Phone Interview for an assessment of eligibility

If you are potentially eligible to participate in the study, you will be interviewed by a researcher. The interview will be conducted over the phone (approx. 20 minutes). The purpose of this interview is to obtain relevant background information (e.g., medication use, current treatments, fatigue symptoms, general health, etc.) and assess other relevant eligibility criteria. We will also provide you with further details about the study. If you meet our eligibility criteria and agree to participate in the study, you will proceed to the next step.

Step 3: Complete Consent Form

You will be sent an electronic version of the informed consent form. This consent form must be electronically signed and returned to us before proceeding further in the study.



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Step 4: First Blood Collection

After you have electronically signed the consent form, a second email will be sent to you with an attached blood collection referral form for Western Diagnostics Pathology (WDP). You will be required to have a blood sample collected at your nearest WDP clinic. No fasting is required, and no appointment is necessary.

Step 5: Receipt of blood results, confirmation of eligibility, and visit 1 appointment

One to two working days after your blood sample has been collected, your results will be forwarded to us. To be eligible to participate in the study, you must meet our established blood concentration cut-offs.

- a. If you do meet these criteria, you will be contacted by phone to arrange your visit 1 appointment (approximately 1 to 14 days later).
- b. If you do not meet these criteria, you will be contacted by email informing you that you are ineligible to participate. You will be sent a \$30 gift voucher.

Step 6: VISIT 1 (Day 0, Baseline): Face-to-face assessment (total time approx. 70 mins)

The face-to-face assessment will comprise the following:

- a. Measurement of vital signs and anatomical measurements: A researcher will measure your sitting blood pressure, height, weight, heart rate, and body composition. Your body composition will be measured by having you stand on a bioimpedance scale.
- b. Cognitive assessments: You will complete several tasks to measure your cognitive performance.
- c. Completion of self-report questionnaires: You will complete a series of questionnaires.
- d. Provision of 12 weeks of IP: You will be given one carton containing capsules with either MIP, FB, or a placebo.
- e. Provision of Gift Voucher. You will be given a \$30 gift voucher.
- f. 4-week re-assessment appointment: An appointment scheduled 4 weeks after this assessment date will be made.

Step 7: DAY 1: Start taking your capsules

In this study, we will be using a randomised, double-blind, placebo-controlled design. This means one-third of participants will be placed on placebo capsules, one-third on capsules containing microencapsulated iron pyrophosphate (MIP) with vitamin C, and one-third on capsules containing ferrous bisglycinate (FB) with vitamin C.

Neither you nor the investigator will know which group you have been placed in. This random allocation is important for us to assess the true effects of the iron supplements.

You will be required to take **ONE** capsule, **ONCE** daily, in the morning on an empty stomach. It is extremely important that you take these capsules every day

* Placebo involves providing a substance with no known treatment effects. In this case, the placebo will contain corn starch.

Step 8: WEEK 4: Second Blood collection

Approximately 4 weeks after your first visit, you will need to visit your nearest WDP clinic to have another blood sample collected. Blood collection can occur on the same day as visit 2 or up to 3 days prior.

Step 9: VISIT 2 (WEEK 4): Face-to-face assessment (total time approx. 30min)

The face-to-face assessment will comprise the following:

- a. Measurement of vital signs and anatomical measurements: A researcher will measure your sitting blood pressure, height, weight, and body composition.
- b. Completion of self-report questionnaires: You will complete a series of questionnaires.
- c. Provision of Gift Voucher. You will be given a \$30 gift voucher.
- d. Week 12 re-assessment appointment: An appointment scheduled 8 weeks after this assessment date will be made.

Step 10: WEEK 8: questionnaires (online): You will complete questionnaires online, which will take approximately 10 to 15 minutes

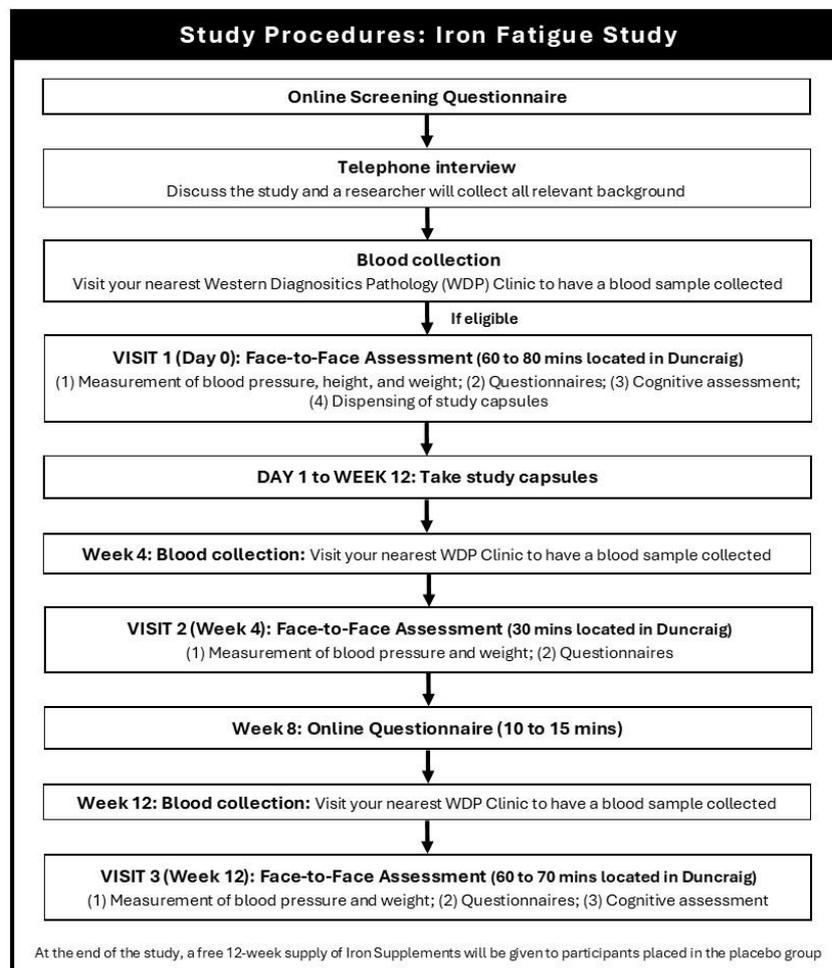
Step 11: WEEK 12: Third Blood collection:

Approximately 12 weeks after your first visit, you will need to visit your nearest WDP clinic to have a final blood sample collected. Blood collection can occur on the same day as visit 3 or up to 3 days prior.

Step 12: VISIT 3 (WEEK 12): Face-to-face assessment (total time approx. 60min)

The face-to-face assessment will comprise the following:

- a. Measurement of vital signs and anatomical measurements: A researcher will measure your sitting blood pressure, weight, heart rate, and body composition.
- b. Capsule count and return of IP cartons: You will now stop taking your capsules and will need to return all remaining capsules and IP cartons.
- c. Cognitive assessments: You will complete several tasks to measure your cognitive performance.
- d. Completion of self-report questionnaires: You will complete a series of questionnaires.
- e. Provision of Gift Voucher. You will be given a \$100 gift voucher for your travel costs and time.



Compensation for participating in this study

To compensate participants for travel costs and time associated with participating in this study, the following gift vouchers will be provided:

1. Participants who are judged ineligible after the 1st blood test will be given a \$30 gift voucher
2. Eligible participants will be given the following:
 - i. Visit 1: \$30 gift voucher
 - ii. Visit 2: \$30 gift voucher

- iii. Visit 3: \$100 gift voucher
3. Eligible participants will undergo a bioimpedance measurement at each visit. This measures your body fat, muscle mass, metabolic age, etc. At the end of the study, if you would like a copy, we can provide you with a report of your measurements (normally valued at \$80 to \$100)
4. At the end of the study, volunteers in the placebo group will also be offered a complimentary 12-week supply of microencapsulated iron pyrophosphate to try.

Criteria for inclusion/ exclusion in this study

To be included in the study, the following inclusion criteria must be met:

1. You are a menstruating woman
2. You are aged 18 to 50 years
3. Your blood ferritin levels are below the established cut-off
4. You have self-reported fatigue/ low energy
5. You are a non-smoker
6. You have a BMI between 18 and 35 kg/m²
7. You understand and are willing and able to comply with all study procedures
8. You are willing to provide a personally signed and dated informed consent form detailing all pertinent aspects of the trial.

If any of the exclusion criteria below are met, you will not be suitable for participation in this study:

1. Your blood haemoglobin levels are above the established cut-off (indicating anaemia)
2. You are suffering from a recently diagnosed or uncontrolled medical condition including but not limited to: severe menstrual problems including heavy bleeding or lengthy periods; unmanaged gastrointestinal disease; history of gastric surgery; cardiovascular disease; cancer/malignancy; liver disease; iron overload condition (e.g., hemochromatosis, hemosiderosis, hemoglobinopathies); stomach ulcers; diabetes; hyper/hypotension, gallbladder disease/gallstones/biliary disease, autoimmune disease, or endocrine disease.
3. You are planning to provide blood donation during the study period
4. You have been diagnosed with a severe psychiatric disorder (other than mild-to-moderate depression or anxiety) or neurological disease, including but not limited to Parkinson's disease, Alzheimer's disease, and uncontrolled epilepsy.
5. You regularly take medications, including but not limited to proton pump inhibitors, antacids, histamine-2 receptor antagonists, nonsteroidal anti-inflammatory drugs, and antibiotics.
6. You have changed medication in the last 3 months or have an expectation to change during the study duration
7. You are taking iron supplements or vitamins, herbal, or other nutritional supplements reasonably expected to influence study outcomes.
8. You have a current or 12-month history of regular illicit drug use
9. You have an alcohol intake greater than 14 standard drinks per week
10. You are pregnant, breastfeeding, or intend to fall pregnant in the next 3 months
11. You plan to make major lifestyle or dietary changes, or have a planned surgery during the study period

Voluntary participation and withdrawal from the study

It is important that you understand that your involvement in this study is voluntary. While we are grateful to have you participate, we respect your right to decline. There will be no consequences to you if you decide not to participate, and this will not affect any future treatment/service. If you decide to discontinue participation at any time, you may do so without providing an explanation. If you withdraw, any assessments already conducted may continue to be used for analysis.

Please note that if you choose to commence a treatment to reduce your fatigue, or you require medical treatment for any other condition during the study, this may result in withdrawal from the study. Your health is the utmost priority, and your choice/need to commence new treatment before completing this study is respected and supported.

Your privacy

Your privacy is very important to us. Your participation in this study and any information provided will be treated in a confidential manner. Your name and identifying details will not be used in any publication arising out of the research. Following the study, the data will be stored in a de-identified format in a locked cabinet in the

Investigator's office and will be retained for statistical analysis and potential future publication. Re-identified codes will be retained for 6 months in case they are needed and will then be destroyed.

Possible benefits

Many women of childbearing age experience problems with fatigue, and research shows that low iron can be a potential cause. Although there are many iron supplements on the market, many have not undergone investigation of their anti-fatigue effects in well-controlled clinical trials. Furthermore, some iron supplements are associated with side effects that can lead to their discontinuation. Therefore, identifying iron supplements that are well-tolerated and can reduce fatigue is important. If these iron supplements are found to be effective and are well-tolerated, they provide women with low iron stores a natural, clinically trialled option to help reduce fatigue.

Possible risks

Participation in this study carries minimal risk, and numerous measures will be in place to minimise the likelihood of potential risks. The oral intake of iron supplements in generally healthy women of childbearing age with low iron is considered safe. However, gastrointestinal side effects, which are often influenced by the form of iron, can occur. Gastrointestinal side effects can include nausea, constipation, flatulence, a metallic taste, or abdominal pain/distress. Change in stool form and colour (to green or tarry black) can also occur.

In this study, we will collect a blood sample from your vein (venepuncture). Although venepunctures are very safe, there is a possibility of bruising at the site of the needle puncture. This usually appears within 24 hours and may range in size from a small spot to a large purple bruise. While bruising can be unsightly, it is not dangerous and typically disappears over a few days. Very rarely, a small artery that contains blood at a much higher pressure than in veins will lie unusually close to, or underneath, a vein. In this situation, the artery may be accidentally punctured during venepuncture. Bruising on the lower arm may develop over the next 2 to 3 days. Again, this is not dangerous and will gradually disappear over a couple of weeks. Although extremely rare, some people may have a small branch of one of the sensory nerves in the arm running over the surface of a vein. Rarely, the needle will hit this tiny nerve on the way into the vein. This may cause a sharp, electric-shock-type pain. This may be all that occurs, but in some cases, a tingling type of pain may persist for 1 to 4 weeks as the nerve heals. This is inconvenient and may be unpleasant, but it eventually subsides. Another rare complication is the formation of a small clot (or thrombus) in the vein at the site of the venepuncture. This is noticed as a small firm lump just under the skin at the venepuncture site. The lump may be tender, and it will typically subside over a couple of weeks. Finally, although extremely rare, an infection can occur at the site of puncture. Please notify us immediately if this occurs. To minimise all these risks, blood collections will be collected by a qualified and experienced phlebotomist using current best practices.

What to do if you experience significant side effects

If you experience any significant illness, injury, or side effect that has commenced since starting your capsules, please contact Dr Adrian Lopresti or Dr Stephen Smith immediately (contact details are below). You may be asked to stop participating in the study and to seek medical advice.

Dr Stephen Smith: Ph: 9448 7376 | Mob: 0412 813 518 | Email: steve@clinicalresearch.com.au

Dr Adrian Lopresti: Ph: 9448 7376 | Mob: 0411 969 797 | Email: adrian@clinicalresearch.com.au

Feedback on study results

It is estimated that the results of this study will be finalised in late 2026. A summary of the results obtained from all participants in this study will be emailed to you when they have been published in a peer-reviewed journal (usually 6 to 12 months after the completion of the study).

Questions

If you would like to discuss any aspect of this study, please contact the principal investigator, Dr Adrian Lopresti, on 08 9448 7376 or email adrian@clinicalresearch.com.au

This study has been approved by the National Institute of Integrative Medicine (NIIM) Human Research Ethics Committee (HREC) (Trial Reference Number: 0161E_2025). If you have any reservations or complaints about the ethical conduct of this research and wish to talk with an independent person, you may contact the NIIM Research Ethics Office (Tel. 03 9804 0646) or email hrec@niim.com.au. Any issues you raise will be treated in confidence and investigated fully, and you will be informed of the outcome.