Is untargeted iron supplementation harmful when iron deficiency is not the major cause of anaemia? A double-blind, randomized controlled trial in Cambodia

SUBJECT INFORMATION AND CONSENT FORM

Is untargeted iron supplementation harmful when iron deficiency is not the major cause of anaemia? A double-blind, randomized controlled trial in Cambodia

1. Invitation:

Principal Investigator
Dr. Crystal Karakochuk, PhD, RD
Food, Nutrition, and Health, University of British Columbia
Telephone: [redacted]
Email: [redacted]

Co-investigators
Mr. Hou Kroeun
Deputy Country Director, Helen Keller International
Telephone: [redacted]
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Director of Nutrition, Ministry of Health Cambodia
Telephone: [redacted]
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Ms. Jordie Fischer, BAS
Food, Nutrition, and Health, University of British Columbia
Telephone: [redacted]
Email: [redacted]

Research location: Kampong Thom Province, Cambodia
Granting Agency: Canadian Institutes of Health Research
Contact Numbers: If you have any concerns about your rights as a research subject and/or your experiences while participating in this study, you may contact the Research Participant Complaint Line in the University of British Columbia Office of Research Ethics at [redacted], or if long distance e-mail [redacted], or call toll free [redacted].

For emergencies only: In the event of an emergency, women in Cambodia may call Hou Kroeun at [redacted].

Fischer JAJ, *et al. BMJ Open* 2020; 10:e037232. doi: 10.1136/bmjopen-2020-037232

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Hello, my name is _____ and I am working for Helen Keller International as a Data Collector. You are being invited to participate in a research study about the effects of iron supplements for women in Cambodia.

2. Your participation is voluntary

Your participation in this study is entirely voluntary, so it is up to you to decide whether you would like to take part. Before you decide it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what participation in the study will look like, and the possible benefits, risks, and discomforts.

If you wish to take part in the study, you will be asked to provide verbal consent to the trained interviewer and sign this consent form. If you do decide to take part in this study, you are still free to withdraw at any time and without giving any reasons for your decision. If you do not wish to take part, you do not have to provide any reason for your decision not to participate.

Please take time to read the following information carefully and to discuss it with your family, friends, health staff at the community health center, and Community Leaders before you decide.

3. Who is conducting the study?

Researchers from Food, Nutrition, and Health in the Faculty of Land and Food Systems at the University of British Columbia in Canada are conducting this study with collaboration with Helen Keller International, UNICEF and the Cambodian Ministry of Health. You are entitled to request further details from the investigators.

The Principal Investigator (Crystal Karakochuk) has received financial compensation from the sponsor (Canadian Institutes of Health Research) for the work required in doing this clinical research and/or for providing advice on the design of the study/travel expenses/etc. Financial compensation to researchers for conducting the research is associated with obligations defined in a signed contractual agreement between the researchers and the sponsor. Researchers must serve the interests of the participant and also abide by their contractual obligations. For some, the payment of financial compensation to the researchers can raise the possibility of a conflict of interest. You are entitled to request any details concerning this compensation from the Principal Investigator.

This study is receiving supplements from an industry-sponsor (Natural Factors). This company is based in Canada and produces nutrition supplements. They will provide some money for the study and the nutrition supplements (for free) but they will NOT be involved in the study design, data collection, data interpretation, writing or sharing of the research findings.

4. Background

This is a research study about the safety and best and safest dose to give to all women in Cambodia, where a lot of women have anemia. Anemia is a serious health problem when you do not have enough oxygen in your blood and you feel tired. It can be due to having low amounts of iron in your diet (an important nutrient found in meat and other foods), infection or disease, or

blood disorders such as thalassemia. If you have anemia and you become pregnant, it puts you and your baby at higher risk of becoming sick. To prevent anemia, the Ministry of Health provides iron supplements to all women, but they may not be helpful or hurt your stomach if the dose is too high or if you already have enough iron in your body. This is an important study to determine the right kind and dose of iron supplements for Cambodian women to improve the health of women and their future babies. It could help to change current policies and programs about the kinds of nutrition supplements that are recommended for all Cambodian women.
The aim of this study is to evaluate the potential harm of iron supplementation in women (in accordance with the 2016 WHO global policy) compared to the placebo (no iron) group. It is also to explore the use of a better absorbed form of iron (ferrous bisglycinate), with the aim to inform the safety of the dose and/or form of iron for women. This will help the Ministry of Health and UNICEF make recommendations about what nutrition supplements Cambodian women need.

5. What is the purpose of the study?

This is a study of an approved supplementation treatment (iron supplements) which will be conducted to learn new information regarding the benefits of taking nutritional supplements, and the best dose and form for women. Both forms of iron supplements (ferrous sulfate and ferrous bisglycinate) are approved for use in Canada and are available for purchase in Canada at daily doses of 60mg and 18mg a day.

The purpose of this study is to understand more about the potential harm of iron supplementation in women, based upon the currently recommended amounts and doses suggested by the Cambodian Ministry of Health. This study also wants to learn more about using a more bioavailable form (greater amount of iron reaching your blood to be absorbed and used in the body) of iron (ferrous bisglycinate), which is different than the iron used commonly in Cambodia today. From this knowledge, the study will help us to understand the safety of the dose and/or the best form of iron for women in Cambodia.

The two questions this study is asking are:

1) Does 60mg daily oral iron as ferrous sulfate (as per the 2016 WHO global policy) increase bodily signs (biomarker) of potential harm in women, as compared to a placebo (tablet looks the same but is only made with sugar and without iron) or 18mg ferrous bisglycinate?
2) Does providing a more bioavailable form of iron effectively increase ferritin concentrations and reduce signs of potential harm, as compared to the standard iron form?

6. Who can participate in this study?

To participate in this study, you must:
(1) be a woman between 19-45 years in Kampong Thom province;
(2) be apparently healthy;
(3) be willing to provide consent to participate in the study and provide blood and flocked swab fecal samples;
(4) not be pregnant;
(5) not be taking medications, including antibiotics, dietary supplements, or vitamin and mineral supplements in the previous 12 weeks.

7. Who should not participate in this study?

You should not participate in this study if you do not meet the criteria above, or if you are unable to provide informed consent. If you become pregnant during the time of the study, we will stop the intervention.

8. What does the study involve?

Overall design of the study:

Women involved in this study will be randomized to one of three study groups for 12 weeks:

1) Take one capsule every day that contains 60mg of iron in the form of ferrous sulfate;
2) Take one capsule every day that contains 18mg of iron in the form of ferrous bisglycinate;
3) Take one capsule every day that contains a placebo (rice flour).

In each village women will be randomized by a computer-generated random list to one of the three study groups. This randomization process is like flipping a coin; there is an equal chance of being in any of the three groups.

This study will be double-blinded, meaning neither the study researcher/ trial investigators/ data collectors or participant know which group anyone is in. Even though the research team does not know what group participants are in, if there is an emergency the Trial Safety Officer, in Cambodia, can break the code and will know what study group everyone is in to address the problem.

If you decide to join this study: Specific Procedures

If you agree to participate, you will be asked to dedicate a total of **2.75 hours** for the study, over a total of 6 visits.

Visit 1 (Day 0): You will be asked to answer some questions about yourself (e.g. age, education), food consumption habits (e.g. types of foods you eat), water consumption habits (e.g. do you use a filter), etc. You do not have to answer questions that make you feel uncomfortable. Then we will give you a swab for you to take a rectal swab of yourself that will be collected at the next home visit. You do not need to take the rectal swab now but at any time before Visit 2. This visit will take **about 30 minutes**.

Visit 2 (Day 1): You cannot eat any food or drink anything (but water is okay) for 8 hours before your visit. We will collect a blood sample from your arm and we will pick up the rectal swab sample that you did yourself. You will be provided with tablets to take every day. This visit will take **about 15 minutes**.

Visits 3 (Day 7): We will ask you questions about how you are feeling and record everything in your symptom's diary, and we will check how many capsules are left in your container. We will also answer any questions you may have. This visit will take **about 15 minutes**.

Visit 4 (Day 35): We will ask you questions about how you are feeling and record everything in your symptom's diary, we will check how many capsules are left in your container and give you

all the rest of the tablets for the remaining days. We will also answer any questions that you may have. Then we will give you a swab for you to take a rectal swab of yourself that will be collected at the next home visit. You do not need to take the rectal swab now, but it will be collected 1-2 days before visit 5. This visit will take **about 15 minutes**.

Visit 5 (Day 91): You cannot eat any food or drink anything (but water is okay) for 8 hours before your visit. We will ask you questions about how you are feeling and record everything in your symptom's diary, we will check how many capsules are left in your container and ask you to consume your final capsule. 2 hours after ingesting the final dose a fasting blood sample will be collected from your arm. We will make sure your rectal swab was collected and will also answer any questions you may have. We will also invite you to an upcoming education session on nutrition and health. This visit will take **about 30 minutes** and will conclude the study.

Study End: The next time we visit you (in the following 4-8 weeks), it will be to share the findings of the research and to tell you about your health status, including whether or not you have anemia and iron deficiency and this meeting will take about **1 hour**.

Mandatory Blood or Tissue Collection and/or Biobanking

Providing blood samples and flocked fecal swab at Visits 2 and 5 are mandatory for participation. Blood collection will be limited to what is required for the current study. We will measure:

- Serum NTBI: a biomarker of iron overload which can increase the risk of oxidative damage to cells and DNA.
- Serum ferritin: a biomarker of iron status
- DNA single-strand breaks: used to assess DNA damage
- Gut pathogen abundance: a marker of gut pathogen growth
- Gut calprotectin: a biomarker of intestinal inflammation
- α-1 acid glycoprotein: a biomarker of chronic inflammation.
- C-reactive protein: a biomarker of acute inflammation.
- Hemoglobin: a biomarker of anemic status
- Serum folate: reflects folate intake and levels
- Serum B12: vitamins that work closely with folate in the body

Samples will be identified by each participant's study ID. All blood samples will be temporarily stored in freezers at the National Institute of Public Health Laboratory (NIPHL) in Phnom Penh, Cambodia, until they are shipped to either Canada or Germany for further processing. Samples will be kept in a secure, locked place in Dr. Karakochuk's lab at the University of British Columbia. The blood analysis results will have personal identifiers de-linked. The samples and data will only be accessible by the Principal Investigator (Karakochuk) and co-investigator (graduate student, Jordie Fischer). The blood analysis results will not be put in your health records. Samples will be stored for approximately 5 years after collection. They will be kept for potential future research purposes and reconsent will not be obtained. After 5 years, the samples will be destroyed following UBC biological safety protocols. For blood samples that are sent to Germany for processing, any remaining blood will be immediately destroyed after processing is completed. Samples will not be sold.

9. What are my responsibilities?

If you choose to be enrolled in this study, we request that:

- You avoid becoming pregnant
- You take your supplement every day
- You do not begin taking antibiotics, non-steroidal anti-inflammatory drugs, dietary supplements, or vitamin and mineral supplements during the trial without informing a worker

10. What are the possible harms and discomforts?

There is a very low risk to you in this study. Many women take iron supplements around the world. There are some mild and rare effects of iron supplements, including: constipation (difficulty to go to the toilet), cramping, nausea (feeling dizzy or sick) or other discomforts. Your stool may change color or become darker due to the contents of the supplement. This is normal and you should not be concerned. You will be informed of these possible effects and provided with information about how to reduce and/or avoid these symptoms, in order to more comfortable. The blood collection procedure has a slight risk of causing discomfort, slight bruising, and in very rare cases, an infection at the site of the prick.

There is a moderate risk to very few women with severe genetic blood disorders (a disorder in the bloods proteins). However, the prevalence of severe genetic blood disorders in Cambodia has been shown to be low (less than 1%) and the duration of supplementation in our study is short (12 weeks), thus we do not expect this to be a major concern. If we determine that you have a severe blood disorder you will be referred to a health facility for further follow up (transport and doctor visit will be paid).

In addition to the risks of physical harms outlined in this consent form, there are also possible non-physical risks associated with taking part in this study. For example, disclosure of genetic or tissue marker research data could result in discrimination by employers or insurance providers toward you or your biological (blood) relatives. The chance that research data would be released is estimated to be small.

11. What are the potential benefits of participating?

If you agree to take part in this study, there may or may not be a direct benefit to you. If you are in one of the three group receiving nutrition micronutrients, you may see health benefits from increased dietary nutrient intake. Although you may not be receiving iron, nutrition education will be provided by trained local research staff. At the end of the study we will return to your village to inform you of your anemia and iron status.

If we find out that your blood is low in iron at the end of the trial, you will receive 12 weeks of free iron supplements, which will help you feel better.

We understand this survey will take some time away from your work and family. If you are required to travel to the local health center for blood collection, you will be provided with $2

USD to reimburse travel expenses. You will also receive a soap, sarong or can of fish (your choice) for your time.

We hope that the information learned from this study can be used in the future to benefit other women with anemia.

12. What are the alternatives to the study treatment?

As of 2016, the World Health Organization recommends a daily dose of 60mg of oral iron supplementation for 12 weeks in women and adolescents where anemia prevalence is more than 40%, which includes Cambodia. Our study is giving this recommended dose so there are no recommended alternative treatments for anemia.

13. What if new information becomes available that may affect my decision to participate?

If you choose to enter this study and at a later date a more effective treatment becomes available, it will be discussed with you. You will also be advised of any new information that becomes available that may affect your willingness to remain in this study.

14. What happens if I decide to withdraw my consent to participate?

Taking part in this study is voluntary. You may withdraw from this study at any time without giving reasons. If you choose to enter the study and then decide to withdraw at a later time, you have the right to request the withdrawal of your information and samples collected during the study. This request will be respected to the extent possible. Please note however that there may be exceptions where the data and samples will not be able to be withdrawn for example where the data and/or sample is no longer identifiable (meaning it cannot be linked in any way back to your identity) or where the data has been merged with other data. If you would like to request the withdrawal of your data [and/or samples], please let your study doctor know.

15. Can I be asked to leave the study?

If you are not able to follow the requirements of the study or for any other reason, the study doctor may withdraw you from the study and will arrange for your care to continue. On receiving new information about the treatment, your research doctor might consider it to be in your best interests to withdraw you from the study without your consent if they judge that it would be better for your health. If you are asked to leave the study, the reasons for this will be explained to you and you will have the opportunity to ask questions about this decision.

16. How will my taking part in this study be kept confidential?

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of UBC Clinical Research Ethics Board, and Cambodian National Ethics Committee for Health Research for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study number as a subject in this study. Only this number will be used on any research-related information collected about you during the course of this study, so that your identity (i.e. your name or any other information that could identify you) as a subject in this study will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. No records that identify you by name or initials will be allowed to leave the Investigators' offices. De-identified information such as blood samples and other data will be sent to the researchers at the University of British Columbia. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected. You also have the legal right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

Any study related data and/or samples, sent outside of Canadian borders may increase the risk of disclosure of information because the laws in Cambodia and Germany, dealing with protection of information may not be as strict as in Canada. However, all study related data and/or samples, that might be transferred outside of Canada will be coded (this means it will not contain your name or personal identifying information) before leaving the study site. By signing this consent form, you are consenting to the transfer of your information and/or samples, to organizations located outside of Canada.

- National Institute of Public Health Laboratory in Cambodia
- National Pediatric Hospital in Cambodia
- Erhardt laboratory in Germany

17. What happens if something goes wrong?

By signing this form, you do not give up any of your legal rights and you do not release the study doctor, participating institutions, or anyone else from their legal and professional duties. If you become ill or physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you.

In case of a serious medical event, please report to an emergency room and inform them that you are participating in a clinical study and that the following person can then be contacted for further information: Dr. Crystal Karakochuk at telephone number: [redacted]

18. What will the study cost me?

All research-related medical care and treatment and any related tests that you will receive during your participation in this study will be provided at no cost to you. Travel expenses will be paid to participants who require transport to attend the health center for any reason ($2 USD). At each visit, participants will receive an incentive for attendance. The participants will have the opportunity to choose between a sarong, a soap, or a can of fish (each $2 USD).

19. Who do I contact if I have questions about the study during my participation?

If you have any questions or desire further information about this study before or during participation, or if you experience any adverse effects, you can contact Hou Krouen at telephone number: [redacted]

20. Who do I contact if I have any questions or concerns about my rights as a participant?

If you have any concerns or complaints about your rights as a research participant and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the University of British Columbia Office of Research Ethics by e-mail at [redacted] or by phone at [redacted] (Toll Free: [redacted]).

21. After the study is finished

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

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

22. Signatures

Is iron supplementation harmful in populations where iron deficiency is not the cause of anemia? A 12 week randomized controlled trial in Cambodia

This study has been explained to you and you have been given the chance to ask questions about taking part in this study. If you have questions you can ask the interviewer or contact Hou Kroeun in Cambodia, a Khmer speaking contact ([redacted]).

Participant Consent Form

- I have listened to or read and understood this form.
- I have had enough time to consider the information provided and to ask for advice.
- I have been able to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the results of this study will only be used for scientific objectives.
- I understand that participation in this study is voluntary
- I understand that I am completely free to refuse to participate or to withdraw from this study at any time, and that this will not change the quality of care that I receive.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I understand that there is no guarantee that this study will provide any benefits to me.
- I have read this form and I freely consent to participate in this study.
- I have been told that I will receive a dated and signed copy of this form.

I consent to participating in this study.

Printed Name of Subject	**Signature or Thumbprint**	**Date**

Printed Name of Person Obtaining Consent	**Study Role**	**Signature**	**Date**