PROTOCOL

The value of iron treatment for postoperative obstetric patients with anemia: a randomized double blind controlled trial

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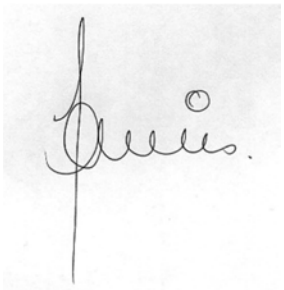
Sponsor or legal representative: Prof. dr. J.G. Nijhuis, Maastricht UMC		09APRIL 2016
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List of abbreviations and relevant definitions

CCMO	Central Committee on Research Involving Human Subjects
COV	Close out visit
CTCM	Clinical Trial Center Maastricht
CV	Curriculum Vitae
(e)CRF	(Electronic) case report form
Euro-HRQoL	Euro-health related quality of life
Fe	Iron
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Hemoglobin
IC	Informed Consent
ICH	International conference on harmonisation
IMV	Interim monitoring visit
IV	Intravenous therapy
MEMS	Medication Event Monitoring System
METC	Medical Ethics Committee
MFI	Multidimensional Fatigue Inventory
MUMC	Maastricht University Medical Centre
NaCl	Sodium Chloride
OMC	Orbis Medical Centre
(S) AE	(Serious) Adverse Event
SIV	Site initiation visit
SUSAR	Suspected Unexpected Serious Adverse Reaction
WMO	Act Medical Research on Humans

Summary

Rationale

Anemia after caesarean section is often treated with iron therapy to ensure that the hemoglobin will return to normal more rapidly. Scientific evidence for this action is limited. Several studies, in which iron therapy was given after orthopaedic or cardiac surgery, show that after 6 to 10 weeks the hemoglobin was not significantly different between patients treated with oral preparations and patients treated with a placebo. These studies have not examined the hemoglobin level during the first few weeks after surgery including the quality of life analysis.
The purpose of this double blind randomized controlled trial therefore is to examine the effect of both oral iron therapy and intravenous iron therapy on hemoglobin level and on the quality of life during the first few weeks postcaesarean in patients with a moderate anemia.

Study design

Double blind randomized controlled trial

Study population

Patients fulfilling the in- and exclusion criteria with a hemoglobin level between 5.0 and 7.0 mmol/L after caesarean sections.

Intervention

Patients will be randomized into three groups:

1. Treatment with ferrous fumarate 200 mg 2dd 1 capsule during 30 days. These patients also get once a placebo intravenously.
2. Treatment with Ferinject®. These patients also obtain 60 placebo capsules for 30 days.
3. Placebo treatment: both a placebo intravenously and 60 placebo capsules for 30 days.

Main study parameters

Primary objective: Hemoglobin levels after 3 and 6 weeks

Secondary objectives:

- Quality of life after 1, 3 and 6 weeks
- Side effects of the medication
- Predictive value of other parameters such as CRP, transferrin, ferritin and hepcidin
- Cost analysis

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

The patient will have 3 extra blood tests to determine hemoglobin, CRP, ferritin and transferrin. In addition, 4 times the patient has to fill in a questionnaire about the quality of life. One time, fluid will be administered to the patient; this may be sodium chloride 0.9% or Ferinject®. The needle for the infusion does not have to be inserted another time as this has already been done before every operation. In addition, the patient must take capsules for one month (ferrous fumarate vs. placebo). Not treating a patient (the group that gets an oral and intravenous placebo) will not entail significant risks, but may cause a longer time of fatigue and dizziness. Literature also shows that not treating a patient with a hemoglobin around 5 mmol/L is justified. The group treated with oral or intravenous iron preparations may have gastrointestinal side effects or skin reactions. No serious adverse events have been described. The occurrence of a serious allergic reaction to Ferinject® is extremely rare.
The advantage of treating a patient may be that the hemoglobin level during the first 6 weeks normalizes more rapidly, which may affect the quality of life during the first 6 weeks postoperatively.

1. INTRODUCTION AND RATIONALE

Anemia due to surgery is often treated with iron therapy to ensure that the hemoglobin will return to a normal value more rapidly. Several studies in orthopaedic and cardiac surgery, in which iron therapy was given postoperatively, show that after 6 to 10 weeks the hemoglobin was not significantly different between patients treated with oral preparations and patients treated with a placebo.[1-5] Therefore, the scientific evidence for this treatment, especially in case of a moderate anemia (Hb 5.0 – 7.0 mmol/L), is limited.

Annually there are also thousands of patients treated with either oral iron therapy or intravenous iron therapy after a caesarean section. Hospital wide protocols are available for the diagnosis and treatment of postpartum anemia, but not specifically for post caesarean anemia. The reason for giving iron preparations for a postoperative anemia is both patient and doctor-dependent. A patient with a hemoglobin level of 6.5 mmol / L without symptoms is less likely to receive iron supplementation than a patient with a hemoglobin level of 6.5 mmol / L with complaints (eg weakness, fatigue). In addition, one doctor will prescribe iron preparation more easily than another doctor does. In other words, there is no clear national or international guideline for the treatment of post caesarean anemia through iron suppletion. Giving iron supplements to patients can lead to side effects, and because of the fact that it is prescribed very frequently it leads also to high costs for medical care. Given the absence of good evidence, is giving iron post caesarean really necessary? And if so, which patients with a post caesarean anemia should get iron supplementation? Is the intravenous form superior to the oral form? Is measuring the hemoglobin level only enough to start therapy or should other blood values be determined for this decision?

Several studies examined the effect of intravenous iron versus oral iron therapy for postpartum anemia in general. Breymann et al. concluded that iron carboxymaltose was not inferior to ferrous sulfate in terms of change in mean Hb from baseline to week 12.[6] Van Wyck et al. found that ferritin was significantly higher in the i.v. iron treatment group compared to the oral iron treatment group ($p = 0.004$) two weeks after delivery, while Hb values did not differ between the groups.[7] Seid et al., however, found that ferric carboxymaltose-treated subjects were significantly more likely to: (1) achieve a hemoglobin greater than 12 g/dL in a shorter time period with a sustained hemoglobin greater than 12 g/dL at day 42, (2) achieve hemoglobin rise 3 g/dL or greater more quickly, and (3)

attain higher serum transferrin saturation and ferritin levels. Drug-related adverse events occurred less frequently with ferric carboxymaltose.[8] Also Froessler et al concluded that intravenous iron sucrose, restores iron stores faster than with oral ferrous sulfate.[9] The major limitation of all these studies is that they also included vaginal births (this group was even dominant) and not caesarean sections alone. The treatment of a postsection anemia is potentially different from a postpartum anemia after vaginal birth and especially the way of administration.

Some researchers believe that the characteristics of an anemia occurring after surgery probably fit better with an anemia due to chronic disease than an iron deficiency anemia.[10,11] The anemia associated with a chronic disease is characterized by a low content of iron and transferrin in the plasma, resulting in a reduction in the erythropoiesis.[12-14] Possible acute phase protein plays a role.[15-19] This would explain why, in contrast to intravenous therapy, oral iron therapy is not effective in a postsurgery (so also post caesarean) anemia.

In a prospective study, Iperen et al. examined the effects of larger and smaller surgery on erythropoiesis, iron metabolism and the acute phase response proteins.[20] They found that both major and minor surgery induce a state of hypoferremia despite adequate iron stores. They conclude that giving oral iron in the first weeks after surgery is not effective (if iron stores are normal before surgery). Also Cutress et al. drew this conclusion after examining the importance of oral iron therapy in patients undergoing surgery for breast cancer.[21] They concluded that because of the operation and the associated inflammatory response a disturbance occurs in the serum iron indices which may lead to inadequate supply of iron to the bone marrow and thus a disturbance in the red blood cell synthesis. This phenomenon does not appear to be related to the amount of bloodloss but to the inflammatory response, causing a blockage of iron mobilization. That's why no effect is to be expected of giving postoperative oral iron. Giving intravenous iron circumvents this problem.

Bisbe et al. compared ferric carboxymaltose with ferrous oral glycine sulphate for postoperative anaemia after total knee arthroplasty. They found that postoperative IV ferric carboxymaltose provided significant benefit over oral ferrous glycine sulphate, particularly in patients with preoperative iron deficiency, severe postoperative anemia, or both.[22]

As mentioned earlier, in Dutch hospitals oral and intravenous iron preparations are often prescribed for post caesarean patients with moderately low hemoglobin levels, although

this is not scientifically well-fetched. The purpose of this randomized controlled trial is to get an answer to these questions in patients with post caesarean anemia.

1. What is the effect of oral iron therapy on hemoglobin levels in the first weeks postoperatively?
2. What is the effect of intravenous iron therapy on hemoglobin level in the first weeks postoperatively?
3. What is the effect of oral iron therapy on quality of life in the first weeks postoperatively?
4. What is the effect of intravenous iron therapy on quality of life function in the first weeks postoperatively?

In addition, some of the iron-metabolism related parameters that may be of value in predicting the effect of iron supplementation will be determined (transferrin, CRP, ferritin, hepcidin). It will also be taken into consideration whether or not this is proportionate to the side effects of medication including the inconvenience of taking medication, and the associated costs.

2. OBJECTIVES

Primary objective:

Comparison of the hemoglobin level 3 and 6 weeks postoperatively between the different groups

Secondary objectives:

- Comparison of quality of life after 1, 3 and 6 weeks postoperatively between the different groups
- Comparison of the side-effects of various drugs
- Is there a “subgroup” of patients who have the greatest effect of the medication used (eg patients with low ferritin)
- Is there a “subgroup” of patients who respond better to ferinject than ferrous fumarate and vice versa (eg patients with elevated CRP).
- What are the costs of taking oral iron or intravenous iron

3. STUDY DESIGN

The study will be a double blind randomized controlled trial.
Patients undergoing a primary caesarean section in the Maastricht University Medical Centre and the Orbis Medical Centre in Sittard will be informed about the study, both in writing and orally. A schematic overview of assessments is given in the schedule at the end of the protocol (annex 1).
If the patient has signed the informed consent the patient data will be entered in a database and then the pre-operative blood will be taken (standard and extra). If the postoperative hemoglobin level is between 5-7 mmol/L the patient will be randomized and two extra blood tubes will be taken. Randomization will be done by the computer and the first questionnaire will be completed. The patient characteristics will be copied from the electronic patient record. Subsequently, each patient will receive an infusion with a placebo or with Ferinject® (depending on which group the patient ended up). The patients will not know the actual treatment, because the infusion line and the flask with NaCl or Ferinject® will be packed. Also the venflon will be covered by a gauze. So both the patient and the doctor will not know if a placebo or the Ferinject® itself is given. The patient will receive 60 capsules to take home, which need to be taken two times daily. This can be ferrous fumarate or a placebo. To verify compliance, patients will use a dispenser which count how often it is opened. Postoperatively, the hemoglobin will be determined another two times: after 3 and 6 weeks. At 3 weeks the research nurse will do this at the patient's home and the second time this will be obtained in the hospital where it can be combined with the regular control. The research nurse will call the patient after 1 week to ask how things are going and whether the second questionnaire has been completed. If the nurse visits the patient after 3 weeks, she will ensure that the questionnaires about the quality of life after 1 and 3 weeks were completed. The day the patient will come for the regular check at 6 weeks, she will also be seen by the research nurse who will check whether the last questionnaire was also completed. At this appointment the hemoglobin and other blood-values will also be determined.
During the pre-operative visit the informed consent will be signed. Normally this will be at the time of admission. The maximum time period between the pre-operative visit and the actual surgery may be 72 hours. In case the scheduled surgery is postponed to a time

point outside the allowed time window, the first pre-operative hemoglobin of the patient will be determined again.

4. STUDY POPULATION

4.1 Population

The study will be performed in the Maastricht University Medical Centre and the Zuyderland Hospital, Heerlen, the Netherlands. Patients fulfilling the below mentioned in- and exclusion criteria will be asked to participate in the study.

4.2 Inclusion criteria

- Postoperative hemoglobin is between 5-7 mmol / L after a terme (>37 weeks) primary Caesarean section

4.3 Exclusion criteria

- Pre-eclampsia / HELLP syndrome
- Malignancy during pregnancy or during the first six weeks postpartum
- Infections
- Per of posteroperative blood transfusion
- Hematologic disorder (hemoglobinopathy; hemochromatosis)
- Erythropoiesis-stimulating agents < 3months ago
- Myelosuppressive therapy in history
- Hepatitis
- HIV
- Alcohol abuses
- Legal incapacity
- Not understanding Dutch
- Previous allergic reaction to oral or intravenous iron

4.4 Sample size calculation

This study will examine whether intravenous iron gives an improvement of the hemoglobin content 3 weeks postoperatively in patients with a hemoglobin between 5-7 mmol / L after caesarean sections, compared with giving oral iron, as well as placebo.

Based on the assumption that a minimum of 0,5 mmol/L difference in the hemoglobin level is thought to be of clinical importance and a standard deviation of 0,7 mmol/L (based on a retrospective analysis and a comparable study [4]) it was determined that, with an alpha of 5% and a power of 80%, for each group 32 patients are needed. For 3 groups this means 96 patients. Allowing for patients lost to follow-up, the study number was set on 120 patients to guarantee adequate numbers of patients in each group.

A retrospective analysis performed at the Maastricht University Medical Centre between 1 January 2015 and June 30 2015, showed that 66 patients had a primary caesarean section. If we exclude the patients that had an operation on Friday (because during the weekends the study-medication cannot be prepared) the remaining number were 46 patients. Of these 46 patients, 31 people had a hemoglobin level between 5.0 and 7.0 mmol / L. If we assume that 70% of patients want to participate in the study, this will lead to 44 patients per year to randomize at the MUMC^{+}. The other participating hospital (Zuyderland Sittard-Heerlen) has a double amount of deliveries including Caesarean sections which means that we need at maximum 1,5 year to complete the study.

5. TREATMENT OF SUBJECTS

5.1 Investigational products

Ferinject®, an intravenous iron, will be used as one of the investigational products. Also ferrous fumarate, an oral iron, will be used. There will be two placebos: NaCl and placebo capsules.
Information about these products is given in chapter 6.
Each patient will receive an infusion with a placebo or with Ferinject® (depending on which group the patient ended up). All patients receive 60 capsules to take home, which need to be taken two times daily. This can be ferrous fumarate or a placebo.
All interventions that has to be done (blood, questionnaires etc) are given in chapter 7.3

6. INVESTIGATIONAL PRODUCTS

6.1 Name and description of investigational products

The following research products will be used.

- Capsulated Ferrous fumarate: 200 mg ferrous fumarate contains 65 mg Fe + + Features: Iron is necessary for the synthesis of haem in hemoglobin.
- Placebo capsules. The placebo will be made by Basic Pharma and are capsules filled with starch.
- Ferinject®: Solution for injection/infusion 50 mg Fe ^{3}/ml, vial of 2 ml, 10 ml or 20 ml. Properties: In iron (III) carboxymaltose the iron is present in a complex with a carbohydrate polymer, which releases the iron at the iron transport and storage proteins in the body (ferritin, transferrin).
- Flask of NaCl 0.9%

6.2 Summary of findings from clinical and non-clinical studies

The use of ferrous fumarate and Ferinject® is indicated for an iron deficiency anemia. For these indications, the used drugs in this study, are therefore registered in the Netherlands. Whether the use of ferrous fumarate is also indicated with postoperative anemia, is not evident. An overview of clinical and non-clinical studies on the use of ferrous fumarate and Ferinject® postoperatively is given in the introduction of this protocol.

6.3 Summary of known and potentional risks and benefits

Ferrous fumarate

Side effects

Gastrointestinal complaints such as nausea, stomach-ache, constipation and diarrhea. These effects are dose dependent. Iron solutions may cause discoloration of the teeth.

Potential risks

None

Benefits

Faster growth of hemoglobin level in iron deficiency

Placebo Capsules

Side effects

No known side effects

Potential risks

None

Benefits

No known benefits

Ferinject®

Side effects

Common (1-10%): headache, dizziness, rash, nausea, abdominal pain, constipation, diarrhea. Injection site reactions. Transient decrease in the concentration of phosphorus in the blood, increased ALAT. Uncommon (0.1-1%): myalgia, arthralgia, paresthesia, hypotension, redness, taste disturbance, vomiting, dyspepsia, flatulence, itching, urticarial, pyrexia, fatigue, chest pain, rigors, malaise and peripheral edema. Increased aspartate aminotransferase, γ-GT and lactate dehydrogenase

Potential risks

Anaphylactic shock, this occurs very rarely

Benefits

Faster increase in hemoglobin levels in iron deficiency anemia when oral iron therapy has proved to be ineffective or cannot be used

NaCl 0.9%

Side effects

With 250 ml NaCl 0.9%, one need not worry about side effects, below, side effects are described after larger amounts of NaCl

Fluid retention in the arms and legs (peripheral edema), pulmonary congestion (when excessive therapy)

Potential risks

Too much sodium in the blood is sometimes accompanied by restlessness, muscle weakness, dullness, convulsions and possible unconsciousness (hypernatremia)

Benefits

As far as known, the use of NaCl in an iron deficiency anemia has no advantages

6.4 Description and justification of route of administration and dosage

Ferrous fumarate is available in suspension form and in tablet form. In this study the tablet form will be used, also because this form is used in the current setting standard and we want to precisely examine the current situation. The tablets are capsulated to match placebo capsules used in this study.
Ferinject® is only available as intravenous administration.

6.5 Dosages, dosage modifications and method of administration

Capsulated Ferrous fumarate

200 mg ferrous fumarate contains 65 mg Fe + +
Features: Iron is necessary for the synthesis of haem in hemoglobin
Way of administration: oral
Dosage: 200 mg 2x daily

Placebo capsules

Placebo capsule is a 200 mg capsule filled with starch.
Features: None
Way of administration: oral
Dosage: 200 mg 2x daily

Ferinject®

Solution for injection / infusion ³ 50 mg Fe / ml, vial of 2 ml, 10 ml or 20 ml.
Features: In iron (III) carboxymaltose the iron is present in a complex with a carbohydrate polymer, which releases the iron at the iron transport and storage proteins in the body (ferritin, transferrin).
Way of administration: intravenous
Dose: single dose of 1000 mg

0.9% NaCl

1 flask containing 250 ml of fluid (each 500 ml of solution contains 4.5 g Sodium Chloride)
Features: Used for the treatment of isotonic extracellular dehydration; the treatment of sodium deficit, as a medium or solvent of compatible drugs for parenteral administration
Way of administration: intravenous
Dosage: 250 ml

6.6 Preparation and labelling of Investigational Medicinal Product

The capsulated ferrous fumarate and placebo capsules will be supplied by Basic Pharma. This company provides randomized double-blind study medication, labeled according to the study protocol. The company provides a controlled distribution to the pharmacy of the participating hospitals. Ferinject® will be supplied by Vifor Pharma.

6.7 Drug accountability

Capsulated ferrous fumarate and matching placebo will be provided in bottles, packaged in cartons by Basic Pharma to the MUMC and OMC pharmacy. Basic Pharma has a GMP license, so all these things are recorded and traceable. Ferinject® will be provided by Vifor Pharma, also packaged in cartons. Three packages will be arranged by the MUMC and OMC pharmacy: package 1: NaCl, ferrous fumarate; package 2: NaCl, placebo capsules; package 3: Ferinject®, placebo capsules. Remaining Ferinject® will be returned to Vifor Pharma. Excess placebo and ferrous fumarate will be destroyed by the MUMC and OMC pharmacy.

7. METHODS

7.1 Study parameters

7.1.1 Main study parameter

Hemoglobin level after 3 and 6 weeks.

7.1.2 Secondary study parameters

- Quality of life after 1, 3 and 6 weeks
- Side effects of medication
- Predictive value of other parameters such as CRP, transferrin, ferritin and hepcidin
- Cost analysis

7.2 Randomization, blinding and treatment allocation

Randomisation is performed by the ALEA Screening and Enrollment Application Software of Formsmsvision BV (Abcoude). Minimisation with stratification factor Hemoglobin (5.0-6.0 or 6.1-7.0), age (<60 years or >=60 years), ASA (1-2 or 3-5), type of surgery (laprotomic, laproscopic or vaginal and other) and amount of blood loss (<500 mL or >=500 mL) will be performed. The minimization method supported by ALEA is based on the minimization principles published in a paper by Pocock & Simon[23].

With the kit-number the pharmacy knows which package the patient should receive. It will be ensured that the infusion line and the flask with NaCl or Ferinject® will be packed. Also the venflon will be covered by a gauze. The placebo capsules will exactly resemble the capsulated ferrous fumarate tablets.

7.3 Study procedures

Interventions

Blood

Postoperative determination of the hemoglobin level is part of the regular care and will be performed on the first day after the operation.
In this study we want to examine the blood three times more than in the regular care, namely 1 day and 3 and 6 weeks postoperatively. At 1 day (after randomization and before treatment) it will be taken in the hospital. At 3 weeks the research nurse will visit the patient at home. At 6 weeks the patient will visit the hospital for the regular follow up.

Determination of other parameters in the blood will not lead to more discomfort of the patient.

The lab results will be saved using an anonymous survey number.

Administration of an infusion

Each patient has postoperative IV, so no extra IV is needed for the study. The patient will receive either a flask NaCl (placebo) or a single dose of Ferinject® on the first or second day after the operation (24-48 hours postoperatively).

Capsules

The patient will start using capsules (either a placebo or ferrous fumarate) on the first or second day after the operation (24-48 hours postoperatively).

Each patient is given 60 capsules to take home, where she has to take 1 capsule 2 times a day.

Questionnaire

Each patient will be asked to complete a questionnaire four times: after informed consent before starting treatment, and 1, 3 and 6 weeks postoperatively. This questionnaire is a combination of the EuroHRQoL and MFI questionnaires. Completing the questionnaire takes about 10-20 minutes and can be filled in via computer or on paper.

This will be conducted as follows: the first questionnaire will be completed in the hospital the first day postoperatively before the study-medication is started. After 1 week the research nurse will call the patient at home to ask how things are going and whether the second questionnaire has been completed. After 3 weeks the nurse visits the patient and will ensure that the questionnaires about the quality of life after 1 and 3 weeks are completed. The day the patient will come for the regular check at 6 weeks, she will also be seen by the research nurse who will check whether the last questionnaire has also been completed.

Data collection

Patient characteristics. The following information will recorded:

• Age

• Morbidity

• Race
• ASA score
• Use of iron therapy preoperative (doses and duration of iron therapy)
• Amount of blood loss during surgery

7.4 Withdrawal of subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Participation in the study is entirely voluntarily.
When necessary, the code of the administered medication can be broken to know with which medication the patient is treated.

7.5 Replacement of subjects in case of withdrawal

A dropout of 10-20% is taken into account. Results will still be included, unless the patient withdraws consent. Assessments that will be done at the withdrawal visit are adverse events, drug accountability and collect not-used study medication.

7.6 Premature termination of the study

Premature termination of the study may occur:
a. if no positive decision is obtained with regard to the research or if the judgement of the competent medical research ethics committee that has assessed the research is irrevocably revoked;
b. if a reasonable case can be made for terminating the research in the interests of the subjects' health.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending further review by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 Aes, SAEs and SUSARs

8.2.1 Adverse events (AE)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

In the current study design, there is no expectation that the treatment will lead to Serious Adverse Events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:

- Summary of Product Characteristics (SPC) for an authorised medicinal product;
- Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the

main points of concern. The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

The research coordinator at the corresponding centre will report the incident within 24 hours to the principal investigator followed by a written notification within 48 hours.

8.3 Annual safety report

A report of events, adverse events and serious adverse events will be combined with the annual progress report and be sent to the METC.

8.4 Follow up of adverse events

All adverse events will be continued until they disappear completely, or until a stable situation has been reached. Depending on the event, additional tests or medical procedures for followup can be required.

9. STATISTICAL ANALYSIS

9.1 Primary study parameter

Primary study parameter is change in hemoglobin level (mmol/L) between baseline and either 3 or 6 weeks postoperatively. Differences in change between the two experimental groups, and between each experimental group and the control group will be tested by use of the
Student’s T-test.

9.2 Baseline differences

Differences in baseline characteristics are not expected in view of randomization. In order to check for any imbalances, values of variables measured at baseline (including hemoglobin) will be compared between groups (means for continuous variables, percentages for categorical variables). No statistical testing of baseline differences will be done since all differences will be due to chance.9.3 Multivariable analysis. In case of prognostically important baseline differences between groups, multivariable linear regression analysis will be carried out instead of the Student's T-test.

9.3 Multivariable analysis

In case of prognostically important baseline differences between groups, multivariable linear regression analysis will be carried out instead of the Student's T-test.

9.4 Secondary study parameters

Quality of life

Each patient will be asked to complete three questionnaires at four times: at baseline after informed consent before starting iron treatment, and 1, 3 and 6 weeks postoperatively. The questionnaires are: 1) the EuroQoL, a generic health related quality of life questionnaire. In this questionnaire patients indicate their current health in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression 2) the Multi-Dimensional Fatigue Questionnaire which is a 20-item self-reported instrument to measure fatigue. At baseline (first day postoperatively in the hospital but before the study-medication is started) patients will be asked to complete the questionnaires. At 1 week after start of the treatment, the research nurse will call the patient at home to ask whether the second questionnaire has been completed. After 3 weeks the nurse visits the patient and will ensure that the questionnaires about the quality of life after 1 and 3 weeks are completed. At 6 weeks, the patient will visit the outpatient clinic and will also be seen by the research nurse who will check whether the last questionnaire has also been completed.

Quality of life data between the groups will be analysed using Repeated Measurement

ANOVA.

Side effects of the medication

The next side effects will be registered: headache, constipation, diarrhea, nausea, dizziness, rash and stomach-ache. On questionnaire B, C, and D the patients can indicate whether there is any of these side effects.

For each potential side effect, the percentage of patients reporting it will be compared between groups. Groups will be compared using the Chi-square test.

Predictive value of other parameters

We will determine for number of parameters whether they predict patients' sensitivity to iron supplementation. These parameters are: CRP, transferrin, ferritin and hepcidin. The significance of these parameters will be determined by doing subgroup analyses among patients with either high or low values of the parameters (i.e. the similar analyses as in 9.1 but within subgroups).

Cost-analysis

Resource use and costs of the intravenous and oral iron therapy will be measured. If relevant and appropriate, a cost-minimisation or a cost-effectiveness analysis will be performed. In that case, the analysis will include a time-horizon of 6 weeks and be performed from a health care perspective.

9.5 Alpha

We will employ an alpha of 5% (2-sided testing).

9.6 Handling of missing values

Missing values in the primary outcome parameter (hemoglobin) will be imputed by means of the last known observation. Missing values in baseline characteristics will be imputed by means of a multiple imputation procedure.

9.7 Statistical analysis package

Statistical analysis will be carried out using either SPSS or SAS.

9.8 Interim analysis (if applicable)

Not applicable

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki, version Fortaleza 2013 and in accordance with the Medical Research Involving Human Subjects Act (WMO).

10.2 Recruitment and consent

All patients who are scheduled for a primary caesarean section will be informed about the study by the physician who is arranging the procedure. A copy of the patient information and consent form will be given to the patient. About one week later the research nurse will call the patient, and ask her if there are any questions and if she likes to participate. When the patient likes to participate, the informed consent form will be signed on the day the patient visits the hospital for the scheduled operation by both the patient and one of the members of the research team. The ultimate responsibility will always lie with the investigator(s), but they can delegate this specific task. Who is authorized to obtain the informed consent will be noted in a delegation log. A standard operating procedure informs the members of the research team in which case (i.e. specific questions) they should contact the investigators or one of the doctors before the patient signs the informed consent. Medical responsibility will hereby be ensured. After signing, the patient will get a screening number and pre-operatively blood will be taken and stored. If the patient meets all inclusion criteria including post-operative Hb 5-7 mmol/L, she can be randomized and hepcidin, transferrin, ferritin and CRP will be determined. If the patient does not meet all inclusion criteria including of post-operative Hb 5-7 mmol/L, she will not be randomized and the preoperatively stored blood will be destroyed.

10.3 Benefits and risks assessment

The expected risk of complications by treatment with Ferinject® or ferrous fumarate seem very low, but could improve quality of life.

10.4 Compensation for injury

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

Online patient questionnaires

Patient-reported outcomes will be captured with electronic online questionnaires using Select Survey. This will reduce the percentage of missing data and errors in the collected data.

Randomization

Randomization will be performed online in ALEA.

Data management

Data will be captured by means of an electronic CRF, called MACRO, provided by CTCM. With MACRO, the data will be captured and analyzed in a GCP compliant manner, including queries and audit trails. The database will be digitally archived for 15 years after study closure.

Before study start, all individuals that are authorized by the Principal Investigator to perform Data Entry will be trained on the eCRF. For every subject enrolled in this trial, the eCRF must be completed within a reasonable time period after data collection. All clinically significant results must be recorded on the eCRF.

11.2 Monitoring and quality assurance

Monitoring will be performed by trained and qualified monitors of the CTCM. According to Good Clinical Practice (GCP) guidelines, the main task of the monitor is ensuring that:

- The rights and well-being of human subjects are protected
- Reported trial data are accurate, complete and verifiable from source documents
- The conduct of the trial is in compliance with the currently approved protocol, GCP and applicable regulatory requirements. Prior to the study start, a monitoring plan will be assembled, specifying the Source Document Verification Plan, the Drug Accountability Plan, the frequency of monitoring visits and frequency of checking the Trial Master Files/Investigator Site Files. Monitoring will be performed remotely (using the eCRF) and on site.

There are several kinds ***of monitoring visits:***

- Site initiation visit (SIV): The SIV will be performed after all approvals have been obtained and prior to enrolling the first subject. There will be 1 SIV per site.
- Interim monitoring visit (IMV): Several IMV's will be performed during the trial. Frequency of visits is determined in the monitoring plan.
- Close out visit (COV): The COV will be performed at the end of the trial, after collection of all data. There will be 1 COV per site.

Monitoring visits will be planned in accordance with the study site personnel. According to the ICH GCP guidelines, the investigator must enable the monitor during visits, providing him/her with all necessary information and documents. Furthermore, the investigator is obliged to answer all queries raised by the monitor in the eCRF in a timely manner.
After each monitoring visit, a follow-up email with all action points will be sent to the site.
These action points will be addressed at the beginning of the next monitoring visit.

11.3 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trials, serious adverse events/ serious adverse reactions, other problems and amendments.

11.4 End of study report

The principal investigator will inform the evaluative committee within 90 days after discontinuation of the study. The end of the study is defined as the day when the hemoglobin level of the last patient 6 weeks postoperatively is determined and the questionnaire has been filled out. After this, the analysis will take place. If the investigation is terminated earlier, the principal investigator will inform the METC with the reasons for the premature termination. Within one year after completion of the investigation, the investigator will send a research report with the results of the investigation to the METC, including abstracts or publications related to the investigation.

11.5 Public disclosure and publication policy

The data and conclusions that emerge from the study will be described in one or more articles for publication and submission to an international peer reviewed journal.

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

Ferinject

a. Level of knowledge about mechanism of action
Ferinject provides usable iron transport-and-storage proteins.
Research showed that Fe from ferinject was very quickly eliminated from the blood and transferred to the bone marrow and deposited in the liver and spleen.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism
The efficacy and safety of Ferinject has been studied in different therapeutic areas necessitating intravenous iron to correct iron deficiency. See also SPC.

c. Pharmacokinetic considerations
Positron emission tomography demonstrated that ^{59}Fe and ^{52}Fe from Ferinject was rapidly eliminated from the blood, transferred to the bone marrow, and deposited in the liver and spleen.
After administration of a single dose of Ferinject of 100 to 1,000 mg of iron in ID patients, maximum total serum iron levels of 37 µg/mL up to 333 µg/mL are obtained after 15 minutes to 1.21 hours respectively. The volume of the central compartment corresponds well to the volume of the plasma (approximately 3 litres).
The iron injected or infused was rapidly cleared from the plasma, the terminal half-life ranged from 7 to 12 hours, the mean residence time (MRT) from 11 to 18 hours. Renal elimination of iron was negligible.

d. Study population
Patients have had a primary caesarean section and have a postoperative hemoglobin between 5-7 mmol / L. Infections, disease during pregnancies will be excluded. See also chapter 4.3

e. Interaction with other products

As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly. Therefore, if required, oral iron therapy should not be started for at least 5 days after the last injection of Ferinject.

f. Can effects be managed?
Administration of Ferinject in quantities exceeding the amount needed to correct iron deficit at the time of administration may lead to accumulation of iron in storage sites eventually leading to haemosiderosis. Monitoring of iron parameters such as serum ferritin and transferrin saturation may assist in recognising iron accumulation. If iron accumulation has occurred, treat according to standard medical practice, e.g. consider the use of an iron chelator.

Capsulated ferrous fumarate

Capsules (European Pharmacopoeia standard) are filled with 2 tablets of 100 mg ferrous fumarate and starch 1500. The use of a capsule around the ferrous fumarate will not change the effect of ferrous fumarate. See also the IMPD for the capsulated ferrous fumarate.

a. Level of knowledge about mechanism of action
Ferrous fumarate provides usable for iron transport-and-storage proteins.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism
The efficacy and safety of ferrous fumarate has been studied in different therapeutic areas necessitating oral iron to correct iron deficiency. See also SPC

c. Pharmacokinetic considerations
In the acid conditions of the gastric contents, ferrous fumarate is dissociated and ferrous ions are liberated. These irons are absorbed in the proximal portion of the duodenum.

The ferrous iron absorbed by the mucosal cells of the duodenum is oxidised to the ferric form, and this is bound to a protein to form ferritin. Ferritin in the mucosal cells releases iron into the blood, where it is bound to transferrin and passed into the iron stores - liver, spleen, and bone marrow. These stores are a reserve of iron for synthesis of haemoglobin, myoglobin, and iron containing enzymes. Iron is lost from the body through loss of cells in urine, faeces, hair, skin, sputum, nails, and mucosal cells, and through blood loss. Ferrous fumarate has the same pattern of absorption and excretion as dietary iron.

d. Study population
Patients have had a primary caesarean section and have a postoperative hemoglobin between 5-7 mmol / L. Infections, oncologic diseases during pregnancy, HELLP syndrome, pre eclampsia will be excluded. See also chapter 4.3

e. Interaction with other products
Iron reduces the absorption of penicillamine, bisphosphonates, ciprofloxacin, entacapone, levodopa, levofloxacin, levothyroxine (thyroxine) (give at least 2 hours apart), moxifloxacin, mycophenolate, norfloxacin, ofloxacin, zinc.
Absorption of both iron and antibiotic may be reduced if Fersamal is given with tetracycline.Absorption of oral iron is reduced by calcium salts, Magnesium salts (as magnesium trisilicate), Trientine.
Chloramphenicol delays plasma iron clearance, incorporation of iron into red blood cells and interferes with erythropoiesis. Some inhibition of iron absorption may occur if it is taken with cholestyramine, tea, eggs or milk.
Avoid concomitant use of iron with dimercaprol.
Oral iron antagonises hypotensive effect of methyldopa.

f. Can effects be managed?
In case of overdose
Supportive and symptomatic measures include ensuring a clear airway, monitor cardiac rhythm, BP and urine output, establishing IV access and administering sufficient fluids to ensure adequate hydration. Consider whole bowel irrigation. If metabolic acidosis persists despite correction of hypoxia and adequate fluid resuscitation, an initial dose of 50 mmol sodium bicarbonate may be given and repeated as necessary, for adults guided

by arterial blood gas monitoring (aim for a pH of 7.4). Consider the use of desferrioxamine, if /the patient is symptomatic (other than nausea), serum iron concentration is between 3-5 mg/L (55-90 micromol/L) and still rising. Haemodialysis does not remove iron effectively but should be considered on a supportive basis for acute renal failure as this will facilitate removal of the iron-desferrioxamine complex.

Ferrous fumarate placebo capsules(see also IMPD): Containing starch 1500

a. Level of knowledge about mechanism of action
Starch 1500 and the capsule has no pharmologic action

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism
Placebo capsules with starch 1500 have been used in more studies without any effects.

c. Pharmacokinetic considerations Not applicable

d. Study population
Patients have had a primary caesarean section operation and have a postoperative hemoglobin between 5-7 mmol / L. Infections, oncologic diseases during pregnancy will be excluded. See also chapter 4.3

e. Interaction with other products
No interactions

f. Can effects be managed?
Not applicable

12.2 Synthesis

The group treated with oral or intravenous iron preparations may have side effects on gastrointestinal region or skin reactions.

The use of ferrofumaraat can give the following adverse events: mild constipation in 1-10%, diarrhea in 0.1-1%. Skin reactions occur only in 0.01-0.1%. Nausea, stomach pain, vomiting and anorexia are also reported. We don't expect other risk/adverse events because it has already been used for many years. No serious adverse events have been described.For ferinject the next adverse events are described: headache, dizziness, nausea, abdominal pain, constipation, diarrhea and skin rash in 1-10%. Uncommon (0.1-1%): myalgia, arthralgia, paresthesia, hypotension, redness, taste disturbance, vomiting, dyspepsia, flatulence, itching, urticarial, pyrexia, fatigue, chest pain, rigors, malaise and peripheral edema. Increased aspartate aminotransferase, γ-GT and lactate dehydrogenase. Dyspnoe only in 0.01-0.1%.The occurrence of a severe allergic reaction to Ferinject® is extremely rare, but cardiopulmonary resuscitation will always be available. People with previous allergic reactions to oral or intravenous iron are excluded from the study. Other risks or adverse events are not to be expected because ferinject has been given for several years.

Not treating a patient (the group that only receives oral and intravenous placebo) will not entail major risks, but may cause a longer time of fatigue and dizziness. Literature also shows that not treating a patient with a hemoglobin around 5 mmol/L is justified[1,2,3]. Because not treating patients with an intense low hemoglobin level (<5 mmol/Hg) can lead to more risks, they are excluded from the study.

The patient does not have to undergo an invasive procedure: the load is relatively small and does not entail major risks, while the results of the study may lead to better use of medication for the patient, hence fewer side effects and less costs for care**.**

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Annex 1. Assessment schedule

Visits and Timepoints [1]	Pre-operative	Surgery	Post-operative	Week 1	Week 3	Week 6	Withdrawal
	Screening			Telephone call	Home visit		
Assessments	Day - 3 to -1	Day 0	Day 1, within 24-48 hours after surgery	Day 7	Day 21	Day 42	
Informed consent	X						
Inclusion/exclusion criteria	X						
Demography (age, race)	X[2]						
Relevant Medical History / Current medical conditions	X[2]						
ASA score	X[2]						
Type of surgery		X[2]					
Amount of blood loss during surgery		X[2]					
Hb	X		X		X	X	
Transferrin, Ferritin, CRP	X		X[2]		X	X	
Hepcidin	X		X[2]		X	X	
QoL questionnaires			X[2]	X	X	X	
(Serious) Adverse events			X[2]	X	X	X	X
Randomization			X[2]				
Dispense studymedication			X[2]				
Drug accountability			X[2]		X	X	X
Collect not-used study medication						X	X

1 Due to logistic reasons adjustments in timepoints can occur

2 Only if post-operative Hb is within 5 and 7 mmol/L