Protocol for The IronHip trial

The effects of intravenous iron on mobility in elderly patients following hip fracture surgery: a multicentre, parallel group, randomised controlled trial

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Short title:	**The IronHip trial**
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Trial Sponsor:	Region Hovedstaden, Bispebjerg Hospital Bispebjerg bakke 23

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2. Administrative

Funding

The trial is investigator initiated with a research grant (Grant no. 3165-00288A) from 'Independent research fund Denmark, which is a research fund under the Danish state. The FDI is supplied by the manufacturing company[1], without any implications in trial design, analysis, or conclusions of the study. Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital is supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL).

Time schedule and responsibility

The Trial ends at the last visit of the last participant. The trial is anticipated to begin enrolment February 2025, with the clinical trial projected to end around February 2027. Data collection ends after the last patient's follow-up, and the trial blind is not broken until after the final data analysis. Sponsor and primary investigators will be guarantors of conduction of the trial in accordance with the protocol, ICH-GCP guidelines and regulatory and legal requirements.

Monitors

The GCP Unit Copenhagen

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[1] PHARMACOSMOS A/S

3. List of abbreviations

HF	Hip Fracture (proximal femur fracture)
FDI	Ferric Derisomaltose
NMS	New Mobility Score
CRF	Case Report Form
GCP	Good Clinical Practice
DAH30	Days alive and at home up to 30
PROM	Patient Reported Outcome Measures
ICH	International Conference on Harmonisation
AE	Adverse Events
SAE	Serious adverse events
SAR	Serious adverse reactions
SUSAR	Suspected Unexpected Serious Adverse Reaction

4. Details on the investigational medicine used in trial

There will be used one active investigational medicine in the trial and given once per participant.

Name of medicinal product: Ferric derisomaltose Pharmacosmos 100 mg/ml solution for injection/infusion

Active substance: Ferric derisomaltose

Dosage form: 100 mg iron/ml for infusion

Appearance: Dark brown, non-transparent, aqueous solution

Marketing authorisation: Pharmacosmos, A/S

Marketing authorisation number: PL 18380/0001

Adress: Roervangsvej 30 DK-4300 Holbaek Denmark

Placebo drug

Name of medicinal product: Sodium chloride “Fresenius Kabi” 9mg/ml solvent for parenteral use

Dosage form: Sodium chloride 9mg/mL or 0.9% w/v

Appearance: Transparent, aqueous solution

5. Background

The burden of patients with a hip fracture (HF) has a huge impact on health care and the society. With an ageing population this patient group is expected to increase significantly worldwide from 1,3 million in 1990 to 4,5 million by 2050 (1). In Denmark there is approximately 7500 HF patients older than 65 each year(2). The majority are treated with surgery, which is associated with 16% short-term readmission, and a 30-day mortality of 10% and at the same time patients face difficulties in regaining their mobility, which is associated with increased mortality, readmission, and infection (3-10). Patients face difficulties in recovering their pre-fracture function (11). Only about 50 % regained pre-fracture mobility after one year, which is what really matters for the patients(11, 12). Thus, there is a potential for improving the treatment. There is most likely a multifactorial explanation for the poor prognosis, partly being high prevalence of frailty and serious comorbidities (13).

We will focus on anaemia and treatment with iron. Anaemia is a comorbidity that is very common after hip fractures(14), and is associated with increased mortality and impaired mobility (14, 15). Moreover, anaemia may increase the risk of postoperative infections, cardiovascular events and death. Iron deficiency may cause decreased mobility and reduced skeletal muscle function (14, 16, 17). Patients with heart failure and iron deficiency have an increased risk of recurrent hospital admission for heart failure and cardiovascular death (18). Some observational studies investigating intravenous iron in HF patients have hinted at associations with 30-day mortality, and reduced need for allogenic blood transfusion postoperatively (19-22). Randomized studies have been performed with various endpoints and mixed results (23-27) but high-quality studies on effect on functional mobility are lacking. A systematic review published in October 2024 concludes that there is a need for high-quality studies evaluating the effects of intravenous iron in patients with HF (28). In a Cochrane review from 2023 investigating ‘Interventions for reducing red blood cell transfusion in adults undergoing hip fracture surgery’ it is stated that there is lacking evidence of the effect of iron on HF patients, due to few and small studies, and due to lack of adequate inclusion of patient reported outcomes measures (29).

Rationale for the study proposal

Anaemia is prevalent in the pre-fracture stage and is exaggerated by blood and iron loss into the fracture and during surgery. Postoperatively, fatigue, anaemia, decreased muscle function and iron deficiency are all factors that potentially limit the ability of patients to participate in

rehabilitation and thereby recovering pre-fracture mobility level. Thus, the patients become less independent and more in need of care. No previous study examines the long-term effect of intravenous iron on mobility for patients with a HF. We will study the efficacy of iron in a randomized controlled trial (RCT).

6. Trial Hypothesis and objectives

Aim and hypothesis

The primary aim of this study is to investigate the effects of intravenous iron on recovery in mobility compared to the pre-fracture level in patients with a HF. We hypothesize that intravenous iron will enhance gain in mobility and hereby recovery of mobility, increase haemoglobin (Hgb), lower fatigue, have a positive effect on skeletal muscles in the weeks and months after administration.

Objectives

The primary objective is to compare the effect of a single dose of FDI (20 mg/kg body weight) relative to placebo on patients' recovery of functional mobility, measured as the change from baseline in the New Mobility Score (NMS) after 6 weeks.

Key secondary objectives are to compare the effect of a single dose of FDI (20 mg/kg body weight) relative to placebo on:

1. Assessment of haemoglobin measured post-operatively week 6
2. The amount of received red blood cell transfusion to week 6
3. Patient fatigue, measured at week 6
4. Quality of life measured with the EQ-5D-5L questionnaire measured as the change from baseline (retrograde) after 6 weeks
5. EQ VAS 0-100 measured as the change from baseline (retrograde) after 6 weeks
6. Fear of falls will be measured at week 6
7. 30 second Sit-to-Stand-Test measured as the change from baseline after 6 weeks
8. Activities of Daily Living (ADL) measured at week 6
9. Pain will be measured at week 6

10. Health Resource Use
11. Serious adverse events (SAE) measured at week 6
12. Mortality at up to 90 days

Other exploratory objectives (applicable for secondary publications)

A. To investigate the cost-effectiveness between the intervention and placebo group and the incremental cost-effectives ratio
B. The effect on 24-hour physical activity measured with SENS motion activity monitor (30) between the two groups
C. The effect on hand grip strength between the two groups
D. The effect on knee extension strength between the two groups
E. To investigate the effect on the participants cognitive abilities between the two groups
F. To investigate the effect on iron status measured with ferritin in the intervention and placebo group
G. To investigate the effect on iron status measured with transferring saturation in the intervention and placebo group

7. Trial design

Trial design and setting

The 'Iron Hip' superiority study is designed as a multicentre, parallel group, randomised, controlled trial. The trial will be stratified by centre and fracture type (Intracapsular and Extracapsular) using balanced block randomisation [1:1]. Both patients and outcome testers will be blinded to the interventions applied. We stratified by fracture type (intracapsular or extracapsular) because of different blood-loss risks (31, 32). The participating departments will be Copenhagen University Hospital Bispeberg and Frederiksberg, Odense and Svendborg University Hospital and Copenhagen University Hospital Herlev and Gentofte. These departments function administratively as three distinct entities, despite spanning multiple geographic sites.

Reporting guidelines and checklists help researchers meet the reporting standards by providing rules and principles for specific research areas (33). Our study protocol was prepared following the guidance provided in the PREPARE statement (34); the reporting follows 'Standard protocol items: recommendations for interventional trials' (SPIRIT)

statement (35). The Trial will be monitored by the Danish GCP (Good clinical practice) unit and published prior to inclusion at Clinicaltrials.Gov. The main trial findings will be prepared according to the guidance provided in the REPORT trial guide for effective and transparent research reporting (36), while the reporting will follow the CONSORT statement (37).

General treatment plan and standard care

Patients included in the trial will follow standard procedures for surgery and the standard perioperative care as described. Patients with a HF is one of the patient groups in Denmark with a quite extensive reference program for treatment and care described by the Danish Orthopaedic Association (38). The program is very similar to NICE guidelines for HF management in the UK (39). 'The Danish Clinical Quality Program – National Clinical Registries' set specific objective goals to reach for HF patients and make reports so each department can see if the goals have been achieved.

In addition to this, each department has specific guidelines to treat this patient group and these guidelines are aligned. This means that the overall standard care for patients with HF is quite aligned throughout Denmark. Each participating department has specified accelerated regimes and strive to get patients operated within 24 hours from admission. They have regimes for pain medication, intravenous fluids, oxygen and observation of the patient vital values. As standard, all patients are given one dose of perioperative antibiotics. If patients are in anticoagulants this is paused. Low molecular weight heparin is given daily as thrombosis prophylaxis to patients without contraindications. As anaesthesia the patients all get a spinal or epidural, if there are no contraindications. After surgery, patients are planned for early mobilization and physiotherapy and more than 95% get a plan for further community-based rehabilitation when discharged from the acute hospital. HF patients' treatment is multifaceted and during hospitalisation HF are treated by a team from different specialities and professions, including orthopaedic surgeons, physiotherapists, nurses, geriatricians and anaesthesiologists.

All the participating centres follow the same transfusion regime: Patients with controlled bleeding and no anaemia symptoms get erythrocyte transfusion at 6,0 mmol/L (9.7 g/dL) pre-operatively and 5.0 mmol/L (8.1 g/dL) post-operatively. All the 3 departments administer 1 gram of tranexamic acid per-operatively to counter bleeding during surgery.

At Bispebjerg hospital the HF patients with a clinical frailty scale between 3 and 7 are offered an early follow up at day 2 and 9 where a dedicated staff visits the patient in their home and asses their level of function and takes blood tests including infection parameters. This follow up is unique to Bispebjerg Hospital.

At Odense University Hospital patients discharged to a temporary health care institution the department have an extended responsibility for the patients. For a minimum of three days patients is assed with a tool for 'Early detection of critical illnesses' and after that a nurse assess the patient and takes a blood test to screen for infection. This follow up is unique for Odense University Hospital.

At Herlev Hospital they use an antero-lateral surgical approach for hemiarthroplasty and at Odense and Bispebjerg they use a posterior approach with a piriformis sparring technique. A randomized controlled trial found that there were no differences in functional outcomes for these two surgical approaches (40).

Each centre/department determines whether the 6- and 12-week follow-up assessments are conducted in the participant's home or within an ambulatory setting, but it will be in-person. In this configuration, any site-specific differences will be accounted for at the site level.

Selection, recruitment, and withdrawal of subjects

Potential participants will be identified by screening acute proximal femur fracture (HF) patients who have undergone surgery at the three participating departments. Screening will occur postoperatively from day 1 to 5 to determine eligibility. Dedicated staff assigned to the project at each department will identify patients using electronic medical records.

Table 1
Inclusion 1. 65 years of age or older 2. Acute proximal femur fracture surgery 3. A haemoglobin measurement ≤6,5 mmol/L (10.5 g/dL) on day 1 to 5 postoperatively 4. Independent prefracture indoor walking ability, indoor NMS ≥ 2 5. Ability to speak and understand Danish

6. Able to provide informed consent on their own behalf

Exclusion

1. Known allergy to intravenous iron
2. Residing permanently at a nursing home
3. Haematological conditions with a risk of iron overload e.g. haemochromatosis, hemosiderosis, or where alternative treatments are necessary e.g. haematological malignancies
4. Other contraindication to iron treatment, e.g. severe liver cirrhosis and hepatitis
5. Severe uncontrolled infection as assessed by the responsible clinician (e.g. bacteraemia or sepsis)
6. Plasma sodium levels below 125 or above 150 mmol/L on the day of inclusion
7. Renal replacement therapy
8. Severe dementia assessed by physician
9. Recent intravenous iron injection, 4 weeks prior to surgery
10. Patient declared terminal ill
11. Pathologic Fracture

Patients will be informed about the trial verbally and provided with written participant information, covering the trial's purpose, procedures, potential benefits, risks associated with treatment using ferric derisomaltose, and details regarding trial participation. The dedicated staff will hand over the information material and talk with the patient about the trial. Following this, a delegated physician will inform the patient about the trial and insure the information is understood. It will be emphasized that participation is voluntary and withdrawal from the trial can occur at any time without consequence. All written materials and consent forms will adhere to ICH-GCP (41).

If they consent to participation, they will sign a written informed consent form and be enrolled in the project by a physician from one of the three participating departments. Written consent will be secured only after the patient demonstrates understanding. After signing the consent form the physician makes a final assessment if the patient is eligible following the in- and exclusion criteria. After enrolment, but before intervention, the local dedicated staff obtains all baseline measures.

If the haemoglobin 'inclusion criteria' is meet on any day from 1-5 a patient may be enrolled and receive the intervention on day 1-5.

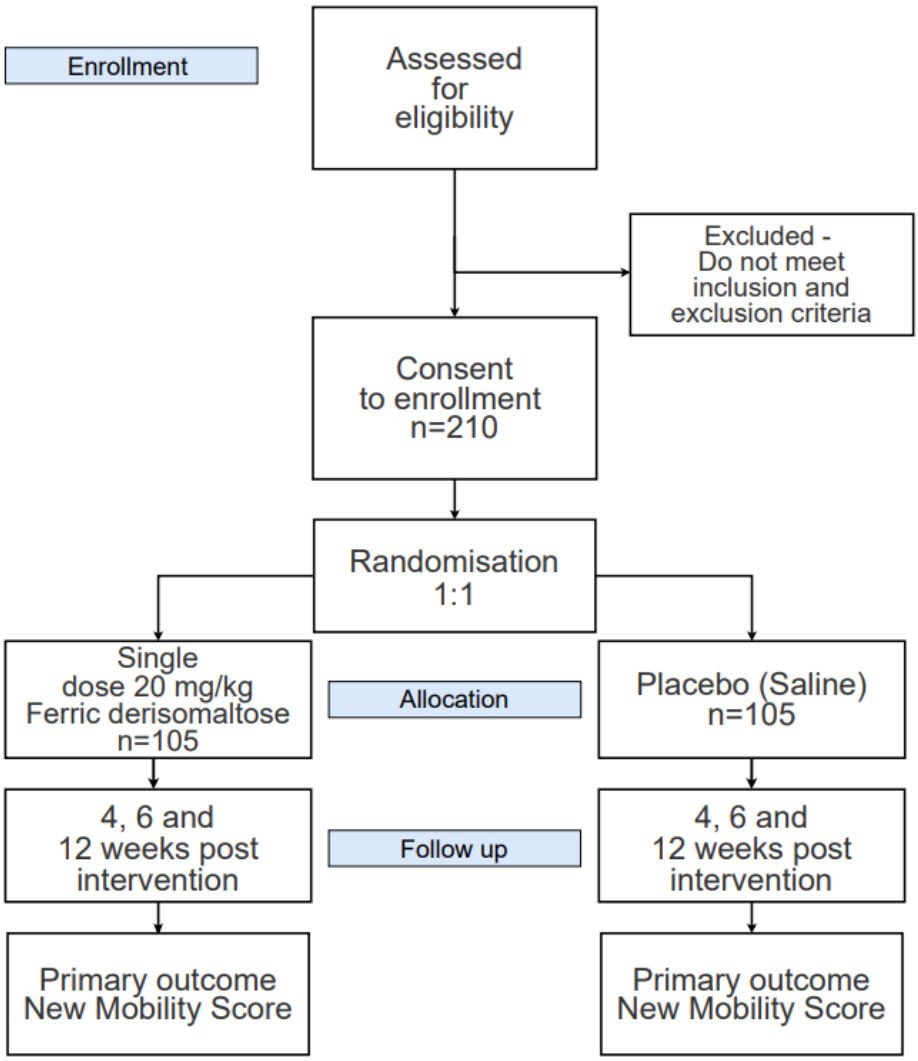
Oral iron supplement during trial

Oral iron medication to participants during hospitalization will not be administered. Patients on an oral iron medication at the time of admission will not be excluded; but their oral iron treatment will be paused for two weeks after inclusion in the trial. Standard care will otherwise continue unchanged. For instance, if any physician deems it necessary to initiate oral iron therapy during the follow-up period, these subjects will not be excluded from the trial.

Study population and recruitment plan

We estimate that there will be approximately 1600 HF patients above 65 years per year at the 3 participating departments combined (2). Of these approximately 75% will have a Hgb <6,5 mmol/L (10,5 g/dL) on day 1 to 5 following surgery, based on data from Bispebjerg Hospital in 2021. Approximately half of the 75% will be eligible following the listed criteria. We conservatively estimate to enrol 20 % of the remaining group. 1600*0.75*0.5*0.2= 120 patients enrolled per year. This corresponds to recruitment period of 1.75 years (210/120).

Each department has appointed a local primary investigator (a physician), and before enrolment each department have appointed a dedicated project staff. Each department will enrol 70 patients. The local investigator is responsible for adherence to the recruitment plan.



Informed Consent

Patients who are candidates and deemed by physician as able to give consent for themselves will be asked to provide written informed consent.

Patients are informed of their right to take 24 hours for consideration and to have a companion present during the consultation. The discussion about the trial will take place in a quiet, undisturbed environment. Participants will be informed of their right to withdraw consent at any time without any impact on their standard medical care. This will be communicated during the consent process and reiterated throughout the trial. Participants will also be informed that the investigators reserve the right to withdraw them from the trial if it is determined that such action is necessary to safeguard their best interests in accordance with their treatment plan.

The informed consent form will be stored at each department together with the trial master file. See subject information and informed consent form in the separate document attached (In part II) with subject information and informed consent form.

Randomization: Sequence generation and Allocation concealment

Sequence Generation: Among the eligible patients, 210 individuals who sign the informed consent form will undergo baseline measures before being randomly assigned to receive either FDI or placebo. Randomization will be performed in permuted blocks of 2, 4, and 6, using computer-generated random numbers (SAS Proc Plan [420 potential envelopes]). Each site will have 140 "digital envelopes" (70 for each of the two fracture types), in the eCRF (REDCap), totalling 420 across all three sites (70×2×3). The anticipated 70 participants per centre randomly allocated, will be stratified by fracture type (intracapsular or extracapsular). The database manager will generate the allocation sequence and incorporate it in REDCap.
Allocation concealment: To ensure concealment of the assigned intervention, the local dedicated staff will be able to access REDCap and perform the “randomisation” per participant. This will generate a participant identification number (randomization number) corresponding to a number on a package available at each centre. The local trained healthcare professional from the department is given the participant identification number (the randomization number) from which they can find the corresponding package containing the allocated trial drug. The unblinded local trained healthcare professional will gain access to the participant’s specific assignment only after this disclosure, where the label inside the package (and obvious colour difference) will reveal what will be administered.

Intervention

Depending on allocation for intervention, patients will get single dose 20mg/kg body weight (Maximum of 2000 mg) of FDI on the same day as enrolment. Body weight will be weighed or patient-reported, as obtaining an exact measurement may be challenging following hip fracture surgery. This approach aligns with standard every day clinical practice for weight dependent drugs. The patient allocated for intervention will receive FDI diluted in 100 mL isotonic sodium chloride 0.9% and the patient allocated to placebo will receive 100 mL isotonic sodium chloride 0.9% solution, both infused over minimum 30 min. A trained healthcare professional in the department will give the intervention on the same day as inclusion, if possible. Before the infusion, a set of vital parameters is recorded, including

blood pressure, pulse rate, blood oxygen level, and body temperature. The healthcare professional remains with the patient for the first five minutes of the infusion. After this initial period, the healthcare professional provides the patient with a "call bell" to request assistance if they experience any discomfort.
During the 30-minute infusion and the 30 minutes following it, the healthcare professional observes the patient regularly, for signs of allergic reactions, changes in consciousness, or cardiopulmonary symptoms.
If no symptomatic reactions are observed, no further monitoring is required after one hour. However, if symptoms are detected, appropriate measures are taken to address them.

Before recruitment start the health care professionals from each department will receive education in how to handle FDI.

Safety conditions concerning dosing

The IMP vials are limited to a maximum volume of 10 ml (100 mg/ml) which reduces the risk of incorrect dose dispensing leading to severe toxicity. Furthermore, the SmPC states "The active substance in Ferric derisomaltose has a low toxicity. The preparation is well tolerated and has a minimal risk of accidental overdosing."
The practical safety measures described in section 'IMP accountability' together with the abovementioned safety procedure will reduce the risk of incorrect dosing and severe toxicity to an minimum.

Allergic reaction

In case of an allergic reaction there will always be clinical personal staff present to handle the acute reaction following local guidelines. Since the patient is admitted in the orthopaedic ward during administration there will always be doctors and nurse nearby and medication and equipment to treat acute anaphylactic will be immediately available in the ward. If the investigational medicine is discontinued due to an allergic reaction, the participant will continue to be followed according to the intention-to-treat principles. The staff will be informed about the distinctions between recognizing and managing hypersensitivity reactions and anaphylactic reactions.

Co-enrolments

Patients who are already participating in a trial may be approached for enrolment in this study. Based on experience and former evidence this process can be conducted with sensitivity. Both patients and research teams are generally capable of making informed decisions regarding if it is appropriate to participate in both trials. The primary investigator will discuss with sponsor to determine the acceptability of co-enrolment.

Placebo

The placebo group is given 100 ml isotonic saline/sodium chloride 0.9%. This is such a small amount that it is considered placebo.

Blinding

The FDI solution is a non-transparent brown liquid, while the placebo is saline, a transparent aqueous solution. A trained healthcare professional from the department, assigned a participant identification number, will open the corresponding package, with either FDI or placebo and the treatment will be revealed. Following accountability procedures, both the solution bag (FDI or saline) and the intravenous (IV) line will be covered with specially designed infusion bag covers and sleeves to ensure the solution remains unidentifiable. Once covered, the solution is suspended on an IV drip stand and transported to the participant's room. The IMP is then connected to the participant's peripheral venous catheter, with the connection secured and concealed using a small piece of tape. After administration, the IV tubing will be flushed with saline to prevent the participant from observing any residual solution.

Trained healthcare professional responsible for administering the IMP will undergo specific training in blinding procedures. Prior to participant enrolment, adherence to these procedures will be emphasized at each centre to ensure participants remain blinded to their treatment allocation. Additionally, it will be reinforced that the trained healthcare professional must not disclose treatment allocation to others. Any accidental breaches of the blinding protocol will be documented in eCRF. Prior to patient enrolment the local project personnel and central project manager ensures that all materials for the blinding procedure is available.

Due to the visible differences between the FDI solution and placebo, the trained healthcare professional administering the treatment will not be blinded. However, all other project staff

and scientific personnel involved in the study will remain blinded to the participant's treatment allocation. This will be achieved through the treatment allocation not being visible in the eCRF, only the randomisation number. The following individuals and groups will remain blinded to treatment allocation until the study database is locked and all analyses specified in the statistical analysis plan have been completed.

Group	**Blinding status**
Participant	Blinded
Primary Investigators	Blinded
Coordinating investigator	Blinded
Project Manager	Blinded
Database manager	Not Blinded
Obtaining baseline values (dedicated staff)	Blinded
Department health care prof. (giving intervention)	Not blinded
Outcome tester (dedicated staff)	Blinded
IronHip steering committee	Blinded
Sponsor	Blinded
Statistician	Blinded

Emergency unblinding

The blinding may need to be broken if the patient's continued treatment requires knowledge of the assigned intervention for safety reasons. The department nurse that gives the intervention is not blinded to which treatment the participant is receiving and can therefore break the blind, during infusion, if it is necessary for any safety reasons.

If it is deemed necessary to break the blind for safety reasons the coordinating investigator, project manager or local primary investigator can be contacted and do so. Breaking of the code can be done through the sealed randomisation envelopes. In case of emergency unblinding, being planned or by accident the following documentation is recorded: the reason for unblinding, when it occurred, who requested the unblinding, who had access to the unblinded data, in cases where unblinding occurred by mistake: the consequences of the unblinding and any preventive actions taken. The investigators will ensure that necessary procedures and expertise is available to handle any emergency situations that may arise because of the trial.

Demographic, baseline and follow up data

All demographic and baseline data will be obtained by project staff and reported in the CRF. Following data will be obtained at inclusion by the project tester: sex, age, height, weight, residential status, current medication (including anti-coagulants, anti-platelets, iron supplements), ASA classification, clinical frailty score, type of anaesthesia, blood tests from admission, current infection, type of infection, comorbidities from admission, time to surgery from admission, blood loss during surgery, fracture type, operative method and duration of surgery. Baseline values for primary and key secondary outcomes with a baseline value described in section on outcome measures is also attained after consent, but before randomisation. Follow up data is acquired on post operative infections (surgical and others that demand readmission), length of stay, complications (re-operations, thromboembolic events, others that demand hospital admission), number of falls, discharged to where (home, rehabilitation, nursing home), readmissions, hospital bed days, acute and outpatient visits will be attained from electronic patient records. Socioeconomic data (work, sick leave, salary, education) is acquired at 12 week follow up.

Primary outcome measure, time points and endpoint

All participants will report their pre-fracture (baseline) NMS. A dedicated staff member will measure NMS at baseline by asking patients about their capabilities regarding NMS during the week leading up to their fracture (refer to Table 2 and separate attached document 'patient facing documents'). NMS will be assessed by phone during week 4 after the intervention. At weeks 6 and 12 after the intervention, a project staff member will attain NMS in-person. When obtaining the primary and secondary outcomes at 4, 6, and 12 weeks from intervention, there will be a margin of +7/- 3 days from these time points to collect the data.

The recovery of mobility, from pre-fracture, will be compared using repeated measures mixed linear models, with primary endpoint NMS after 6 weeks estimated based on the difference in least squares means. NMS is a validated patient reported outcome measurement 0–9-point score for HF patients, with 9 point equal to a fully independent indoor, outdoor and during walking ability and 0 point indicating no walking ability at all (42, 43). Each of the 3 activities is scored as: 0 = not able to, 1 = able to with help from another person, 2 = able to with a walking aid, and 3 = able to with no difficulty and no aid(44).

Table 2				
Mobility	No difficulty and no aid	With a walking aid	With help from another person	Not at all
Able to get about the house (indoor walking)	3	2	1	0
Able to get out of the house (outdoor walking)	3	2	1	0
Able to go shopping (walking during shopping)	3	2	1	0

The New Mobility Score (0-9 points)
Kristensen MT, Hvidovre Hospital. Updated Parker and Palmer following personal communication with Dr. Martyn Parker, Peterborough, England, December 2009

Key secondary outcomes measures, time points, and endpoints

1. **Haemoglobin**

   Blood test will be obtained, and haemoglobin analysed at baseline and following the 6- and 12-week patient visit. The baseline haemoglobin is the earliest usable value possible to include the participant in the trial with.

2. **Red blood cell transfusion requirement**

   This will be measured by the proportion of patients who receive at least one red blood cell unit and the amounts of units per patient on postoperative day (POD) 7 and POD 30 attained from electronic patient records. A red blood cell unit is standardized and has a volume of 250 ml with a haematocrit value of 0,59 and haemoglobin concentration of 3.0 mmol/portion.

3. **Fatigue**

   Fatigue will be measured with 'Verbal rating scale – Fatigue' from 0, 4 where 0 indicates no fatigue and 4 represents extreme fatigue. Measured at baseline, 4, 6 and 12 weeks after intervention.

4. **Quality of life** with EuroQol EQ-5D-5L

This will be measured by project staff using the questionnaire EQ-5D-5L, on inclusion as a retrograde baseline the weeks prior to admission and at 6 and 12 weeks after intervention. EQ-5D-5L questionnaire measures health-related quality of life across five dimensions, with scores ranging from 1 (no problems) to 5 (extreme problems). Higher scores indicate worse outcomes, reflecting greater health issues

5. EuroQol Visual Analogue Scale (EQ VAS 0-100)
   The EQ VAS 0-100 (range) is a visual analogue scale where 0 represents the worst imaginable health state and 100 represents the best. Higher scores on the EQ VAS indicate a better health outcome. Measured as a retrograde baseline the weeks prior to admission and at 6 and 12 weeks after intervention

6. **Fear of falls**
   Short Falls efficacy scale International (Short-FES-I) for assessment of concern for falling during different activities measured at baseline and at 6 and 12 weeks after intervention. Short-FES-I scores ranging from 7 (no concern about falling) to 28 (severe concern about falling). Higher scores indicate greater concern about falling.

7. **30 second Sit-to-Stand-Test (STS)**
   The test uses a chair placed against a wall, with the participant seated in the middle and arms crossed at the chest. Participants are encouraged to stand and fully sit as many times as possible within 30 seconds, with correct form monitored by the tester. If a participant uses their arms, they score a 0, and only correctly executed stands are counted. This test assesses a wide range of ability levels, from those unable to stand to those completing over 20 stands. Lower score indicates worse outcome. Measured at baseline, 6 and 12 weeks.

8. **Activity of daily living**
   Barthel Index 20 Barthel measured at baseline (as retrograde pre-fracture) and at 6 and 12 weeks after intervention. Barthel 20 Index measures a patient's level of independence in daily activities, with scores ranging from 0 (complete dependence) to 20 (complete independence). Higher scores indicate a better outcome, reflecting greater independence.

9. **Pain**

   Hip fracture-related pain during activity will be evaluated with the verbal rating scale, 0-4 points, at baseline and at 6 and 12 weeks after intervention. A score of 0 indicates no pain, while a score of 4 represents unbearable or the worst imaginable pain.

10. **Days alive and at home up to 30 (DAH30)**

    The DAH30 is determined using a combination of electronic medical records (obtaining length of stay) and direct participant inquiries at the 6 week follow up. DAH30 ranges from 0 to 30, representing the number of days within the 30-day period following intervention that a participant remains alive and at home. "Home" refers to the participant's usual place of residence, which can include facilities like care homes or assisted living arrangements.

    To calculate DAH30, 30 is reduced by the participant's initial length of stay after the operation and by any additional days spent in a hospital or other facility due to readmissions within the first 30 days. Days not spent at home, except for holidays, are also subtracted—this includes time spent in more dependent living arrangements with relatives for example. If a participant never returns home or dies within the first 30 days, their DAH30 score is 0.

11. **Serious adverse event (SAE)**

    SAE defined following the ICH – GCP guidelines. Will be assessed at the 6 weeks follow up.

12. **Mortality**

    90 days following enrolment it is obtained if patients are alive from patient electronic medical records and from this survival, 30 and 90 mortality is calculated.

All PROM forms used in the trial, along with references, can be found in the separate attached document 'Patient facing Documents'.

Explorative outcomes

A. Cost-effectiveness analysis

Cost-effectiveness analysis will be made from a societal perspective including cost of FDI, hospital bed days, readmissions, outpatient visits and costs related to lost productivity of the patients (production loss). The analysis will be done according to the guidelines for health economic evaluation (45). The analysis will be based on data from the electronic patient records and data on the duration of patient's sick leave and absence from work from patient surveys. The main results from the analysis will be a comparison of the mean costs per patient in the intervention and the control group, the mean change in Quality Adjusted Life Years gained in the two groups (based on EQ5D) and the incremental cost-effectives ratio.

B. Physical activity measured with activity sensor

We plan to measure the effect of intravenous iron on 24-hour physical activity measured with SENS motion activity monitor(30). All the patients that are enrolled at Bispebjerg Hospital, consisting of 70 participants will be equipped with a SENS motion monitor at the 6 weeks follow up. The monitors measure the amount of time spent on lying, sitting (sedentary), standing, walking, and transitions. 10 days after the monitor is affixed, they will be collected, and data pulled. The average amount of time they are standing and walking per day is determined and the two groups compared.

C. Hand Grip Strength

Hand grip strength measured with a dynamometer will be measured at baseline and after 6 and 12 weeks, on the 70 participants enrolled at Bispebjerg Hospital (46). It will be assessed using a dynamometer measured in kilograms with a higher score representing better hand grip strength. This outcome aims to determine how intravenous iron therapy influences hand grip strength, comparing the changes between the two groups.

D. Knee Extension Strength

Knee extension strength will be measured using a dynamometer, measured in Nm/Kg with a higher score representing better Knee extension strength. Measured on participants enrolled at Bispebjerg Hospital. The goal is to examine the effect of

intravenous iron therapy on knee extension strength between the two groups at these key points. Knee extension strength will be measured at baseline and at 6- and 12-week follow-ups.

E. Cognition

Cognition will be measured with the PROM; Orientation-Memory-Concentration test (OMC) at baseline, week 6 and 12 post-intervention, to examine if there are any differences in the groups. This PROM form can be found in the separate attached document 'Patient facing Documents'. The OMC test range from 0-28 points, with a score of 25-27 indicating no or minimal cognitive impairment, and a score of 0-7 indicating severe impairment.

F. Ferritin Levels as a Measure of Iron Status

This outcome focuses on assessing the ferritin levels in both the intervention and placebo groups. Ferritin will be measured in ng/mL. The aim is to determine how intravenous iron therapy affects ferritin levels in comparison to the placebo group. Measured at baseline and week 6 and 12 post intervention.

G. Transferrin Saturation as a Measure of Iron Status

Transferrin saturation, measured as a percentage, will be assessed in both the intervention and placebo groups. This outcome will evaluate how transferrin saturation is affected by intravenous iron therapy compared with placebo. Transferrin saturation will be measured at baseline, and at the 6- and 12-week follow-ups.

8. Trial management and organisation

At each department there will be a dedicated staff that is responsible for recruitment and follow up. Besides this there will be a project manager at the coordinating department that will oversee that the recruitment plan is followed and assist the local dedicated staff. For each step-in recruitment, intervention and follow up there will be created a Standard of Operation Procedure (SOP) with a step-to-step guide on how to execute the tasks.

The primary investigators and coordinating investigator are responsible for the day-to-day execution of the trial. At least once a month the coordinating investigator will meet with the sponsor.

Each year following recruitment start the coordinating investigator will create a year report following criteria from GCP.

Steering committee consists of sponsor, all investigators, the project manager, all collaborated stated in this document. Additional members may be added from each site.

Patient Timeline and Follow-up

Subjects will be screened, enrolled, and receive the intervention from days 1 to 5 postoperatively. The follow-up period after the intervention lasts for 90 days, with active participation concluding 12 weeks post-intervention.

After enrolment dedicated staff will record all baseline data linked to the unique ID number in the case report form (CRF). Following the intervention, patients will receive standard care and be discharged according to usual protocols.

A follow-up phone call will be conducted in week 4 post-surgery to obtain the New Mobility Score (NMS). Prior to the follow-up visits at weeks 6 and 12, dedicated staff personnel will contact the participants to schedule visits. Each participating centre has predetermined whether follow-up assessments will be conducted in the patient's home or in an ambulatory setting. Participants will always have the option to complete the follow-up visit in an ambulatory setting rather than in their home.

During the week 6 follow-up, dedicated staff will collect a blood sample, assess the 6-week outcome measures. This process will be repeated at the 12-week follow-up. After both visits, the collected data will be entered into the eCRF. All original questionnaires will be stored in each department together with the Trial Master File.

Blood samples will be analysed by the local laboratories at each department and results will be recorded in the electronic patient records. Shortly after 90 days post-intervention, dedicated project staff will collect the final follow-up data from the patient's electronic medical records.

Table 3

Outcome measures and timepoints					
	Baseline	**4 weeks**	**6 weeks**	**12 weeks**	**90 days***
Primary outcome:					
New Mobility Score	x	x	x	x	
Key secondary outcomes:					
Haemoglobin	x		x	x	
Red blood cell transfusion					x
Fatigue	x	x	x	x	
Quality of life -EQ 5D 5L	x		x	x	
Quality of life – EQ VAS 0-100	x		x	x	
Fear of falls	x		x	x	
30 second Sit-to-Stand-Test	x		x	x	
Activity of daily living	x		x	x	
Pain	x		x	x	
DAH30			x		
Serious Adverse Events			x		
Mortality					x

*The outcomes are measured there; refer to outcomes section for details on the corresponding period they reflect

Criteria and procedures for discontinuing trial treatment and participation

The individual patient's trial participation is discontinued if the patient withdraws his/her consent, and that either the trial treatment or trial participation is discontinued if the investigator finds it necessary for the safety of the participant.

If a participant decides to withdraw, they will be asked to state the reason for withdrawal, though it is emphasized that this is not mandatory to disclose. This is documented in the eCRF.

If a participant withdraws from the trial but consents to limited follow-up, permission will be asked to continue to obtain all possible outcomes per phone and monitor for serious adverse events (SAEs) during hospitalisation and with a phone call 6 weeks after intervention.

Additionally, the patient will follow standard treatment for HF and regular postoperative visit.

Intervention period and Time schedule

The primary, secondary and exploratory outcomes will all be attainable 90 days after the last intervention. 90 days after last enrolment occurs the recruitment faze of the trial ends.

Criteria for discontinuation

We do not plan any interim analysis. The sponsor reserves the rights to discontinue the trial for any safety or administrative reasons. Sponsor will take in considerations from the steering committee on the matter.

9. Statistical methods

Sample size and Power considerations

Assuming that the intravenous iron will result in an at least 1.00 NMS points better than that of the placebo administration, with an SD of 2 points, we calculated that we would need 172 elderly HF patients in the intention-to-treat (ITT) population to test a 2-sided hypothesis with 90% power at a 5% level of statistical significance. Since we aim to enrol equally many patients from each of the three centres, anticipating some attrition and missing data during outcome assessments, we aim to enrol at least 200 individuals (16% added to the formal sample size estimation), with the explicit target being 210 individuals (i.e., corresponding to 70 patients per centre; i.e., 22% added to the formal sample size estimation). We chose the target difference (47) corresponding to a Minimal Important Difference (MID) of 1 NMS unit (48), based on previous related studies (49, 50).

Statistical methods

The primary analyses will be based on the Intention to Treat (ITT) population, i.e., based on the Full Analysis Set (All randomized individuals with an available baseline measure). The ITT principle asserts the effect of a treatment policy (that is, the planned treatment regimen), rather than the actual treatment given (i.e., it is independent of treatment adherence). Accordingly, participants allocated to a treatment group (FDI and Placebo, respectively) will be followed up, assessed and analysed as members of that group, irrespective of their

adherence to the planned course of treatment (i.e., independent of withdrawals and cross-over phenomena). Missing data in the ITT population will be handled indirectly and statistically modelled using repeated-measures linear mixed models (for continuous outcome measures). These models are considered valid if data are 'Missing at Random' (MAR).

All 95% confidence intervals and *P* values will be two sided. We will not apply explicit adjustments for multiplicity, rather we will analyse the secondary outcomes in a prioritized order.

In this study, participants will be randomly assigned to two treatment groups (FDI vs Placebo), and observations will be made at 4 time points for the primary outcome measure (i.e., at baseline [t=0] and 4, 6, and 12 weeks from baseline). Contrasts between groups will be estimated based on repeated-measures analysis of covariance applied in mixed linear models (i.e., 6 weeks from baseline being the primary endpoint assessment). The primary endpoint is defined as the difference in Least Squares Means for change from baseline in the New Mobility Score (NMS) after 6 weeks. The primary statistical model will consist of fixed effects (Strata, Group, Time, and Group×Time) and random effects (Participant ID). Fixed effects define the expected values of the observations, and random effects define the variance and covariances of the observations. Accordingly, we will analyse continuous outcome measures (including NMS) as change from baseline using repeated measures mixed linear models, incorporating participants as random effects. These models will feature fixed effect factors for randomization group, week, and their corresponding interaction (Group × Week), while adjusting for baseline values and the stratification factors. Data from all available time points will be utilized. Results will be reported as least square means with standard errors (SEs), and differences between least square means will be reported with two-sided 95% confidence intervals (95%CIs). The between-group difference in the primary endpoint will be confirmed by a two-sided test with a significance level (α) of 0·05. Dichotomous responder analyses and harms will be estimated and presented as categorical data (as counts [%]) and groups compared using odds ratio (OR) with 95%CIs.

To explore the presence of important contextual factors, we will perform subgroup analyses with comparison between subgroups and a P value for interaction (51). We will according to the following pre-exposure covariates:

- Fracture type
- Participants that receive massive transfusion with erythrocytes within 24 hours of surgery

- Participants with a transferrin-saturation below 20 % at baseline
- Participants with anaemia at admission to the hospital

10.Investigational medicine

FDI is a parenteral iron therapy that replenishes iron depots and promotes higher levels of haemoglobin. FDI is composed of iron and a carbohydrate shell, which allows for controlled release of iron. It is utilized in the treatment of iron deficiency anaemia. Monofer is an intravenous formulation of ferric derisomaltose. Following intravenous administration, the compound is rapidly taken up by the reticuloendothelial system, particularly in the liver and spleen and slowly releases iron for use in the body. Plasma half-life range from 1-4 days. It is broken down into iron and derisomaltose. The iron binds to protein, forming hemosiderin or ferritin, and to a lesser extent, transferrin. Small amounts of iron are excreted through urine and feces. Derisomaltose is either metabolized or excreted unchanged.

Drug selection and dose choice: Risks and benefits

To evaluate the effect of intravenous iron, the investigational medicine FDI was selected due to its ability to be administered in a single high dose, which is advantageous both in a trial context and for potential future clinical use. FDI has a low reporting frequency of ADRs and very few severe reactions. The choice is further supported by FDI's lower risk of inducing hypophosphatemia compared to other intravenous iron products (52, 53).

In this trial, FDI will be administered once at a dose of 20 mg/kg body weight (Maximum of 2,000 mg), which is the maximum permissible single infusion dose per week according to the manufacturer's guidelines SmPC (54). This dosing strategy is chosen to avoid underdosing and is considered safe, as serious adverse reactions (SARs) are uncommon or rare, as indicated in Table 3. The dosing regimen aligns with the protocol used in a major recent trial involving the same patient group, the HiFIT Trial (23). The same dose regime was used in an observational Danish study in 2021 and on the same patient group (19).

FDI is an established therapeutic agent with a well-documented safety profile(55-57). It is routinely administered to the relevant patient population in Danish hospitals. Numerous clinical trials have evaluated FDI in this group, with additional studies involving other

intravenous iron formulations providing further evidence. These trials describe the treatment as safe (24-27). See Appendix 1 for an overview of FDI use in studies specifically targeting orthopaedic patients.

In alignment with the Danish Medicines Agency's guidelines, this trial adopts a risk-adapted approach to clinical trial management and is classified as low-risk. The potential benefits of this intervention are detailed in the rationale for study section and our hypothesis. Patients will receive standard care in addition to the intervention and the scheduled follow-ups. During these follow-ups, there is a possibility that project personnel may incidentally detect critical health conditions in participants, leading to enhanced treatment. This potential benefit applies to both the intervention and placebo group.

The risks for the intervention group include the known side effects of FDI, as listed in Table 3 of the Summary of Product Characteristics (SmPC), section 4.8.

Table 3 - **Adverse drug reactions observed during clinical trials and post-marketing experience**

MedDRA System Organ Class	**Common (≥ 1/100 to <1/10)**	**Uncommon (≥ 1/1000 to <1/100)**	**Rare (≥ 1/10000 to <1/1000)**	**Not known**
Immune system disorders		Hypersensitivity, including severe reactions	Anaphylactoid/ anaphylactic reactions	
Nervous system disorders		Headache, paraesthesia, dysgeusia, blurred vision, loss of consciousness, dizziness, fatigue	Dysphonia, seizure, tremor, altered mental status	
Cardiac disorders		Tachycardia	Arrhythmia	Kounis syndrome
Vascular disorders		Hypotension, hypertension		
Respiratory, thoracic and mediastinal disorders		Chest pain, dyspnoea, bronchospasm		
Gastrointestinal disorders	Nausea	Abdominal pain, vomiting, dyspepsia, constipation, diarrhoea		
Skin and subcutaneous tissue disorders	Rash	Pruritus, urticaria, flushing, sweating, dermatitis	Angioedema	Distant skin discolouration

Metabolism and nutritional disorders		Hypophosphataemia		
Musculoskeletal and connective tissue disorders		Back pain, myalgia, arthralgia, muscle spasms		
General disorders and administration site conditions	Injection site reactions*	Pyrexia, chills/shivering, infection, local phlebitic reaction, skin exfoliation	Malaise, influenza like illness**	
Investigations		Hepatic enzyme increased		

* Includes the following preferred terms, i.e. injection site erythema, -swelling, - burning, -pain, -bruising, -discolouration, -extravasation, -irritation, -reaction.

** Influenza like illness whose onset may vary from a few hours to several days.

Packaging, labelling and storage

The FDI and placebo for the trial will be supplied by the hospital pharmacy in the Capital Region. The pharmacy will not modify the IMP or placebo. They will assign labels and numbers to all blinded packages before distribution to the trial sites. The numbering will correspond to the generated randomization list. The FDI and placebo will be labelled inside the blinded packages. Details of the labelling content are provided in a separate attached document.

It will be stored under the conditions specified by the pharmacy and dispensed from the medicine cabinet at each department. An authorized and trained personal will be responsible for preparation and administration of IMP according to the SmPC or relevant local procedures.

At each site there will be a designated box labelled 'Iron Hip Trial'. A designated healthcare professional from each department will be responsible for monitoring the stock, that none of the stock is expired. Durability of IMP is 3 years, so it is expected to last throughout the trial inclusion faze.

It is the responsibility of the hospital pharmacy to ensure that drugs are stored in accordance with the manufacturer’s storage instructions as detailed in the applicable Summary of Product Characteristics (SmPC).

IMP Accountability

Upon receipt of the IMP, the investigators or delegated project staff will conduct a receipt check to ensure that all necessary documentation accompanying the shipment is complete and accurate.

Accountability for the IMP will be ensured and documented. The IMP will be double-checked by trained healthcare professional before administration and then recorded in the eCRF form.

The records will include:

- Initials of the responsible personnel
- Batch/lot number
- Date and time of dispensing
- Amount of IMP dosed.

Account for any medication that is lost, damaged, or otherwise unaccounted for, including documentation of the circumstances and corrective actions taken.

11. Patient and public involvement

We have discussed the project with a few HF patients. We talked with them at the clinical follow up in geriatric ambulatory. When asking them what is important following a hip fracture in general and what we can improve they say that mobility and the independence in daily life functions are most important. They found the primary patient reported outcome, to improve mobility, relevant for them. This corelates with a qualitative study that found that mobility was a prominent theme when they were interviewed about what HF patients considered most important in their recovery (12, 58).

We also consulted two HF patients to gather their feedback on our patient information materials. We spoke with them a few days after their surgery, while they were still in the orthopaedic ward—timing that aligns with our planned participant enrolment. Both patients found the information to be clear and easy to understand.

12. Assessment of safety

Definition of adverse events and reactions

In the trial, adverse events and reactions are defined as follows:

Adverse Event (AE): Any unfavourable medical occurrence in a patient or trial participant following administration of a pharmaceutical product, which does not necessarily have a

causal relationship with the treatment. **Adverse Reaction (AR):** Any harmful and unintended response to an experimental medicine at any dose, indicating a causal relationship between the medicine and the reaction.

Serious Adverse Event (SAE) or Serious (Suspected) Adverse Reaction (SAR): A serious adverse event or suspected adverse reaction that, at any dose, results in death, is life-threatening, requires hospitalization or prolongation of hospitalization, or leads to significant or permanent disability or incapacity.

Suspected Unexpected Serious Adverse Reaction (SUSAR): A serious adverse reaction where the nature or severity is inconsistent with the known product information.

SAE related to the trial will be recorded up until the week 6 visit, starting from intervention and ending at week 6. After the week 6 visit the dedicated project staff will report events in the eCRF. We expect the trial drug, FDI to be eliminated from the body by this time.

Safety measures

When needed the causality between the events and the trial medication, as well as the severity, will be assessed by a primary investigator at one of the 3 departments who are trained in the protocol.

The Summary of Product Characteristics section 4.8 for FDI will be used as a reference when assessing whether a serious adverse reaction is unexpected or expected.

Risk adapted recording and reporting

This trial is categorized as a "low-risk" trial because it involves the use of authorized medical products with well-documented safety profiles and standard dosing regimens commonly used in clinical practice, trials, and for the patient group in question. The trial design is non-complex, and risks are further minimized by excluding patients at risk due to secondary conditions.

In accordance with the Danish Medicines Agency's Guideline (59) on risk-adapted recording and reporting of events, adverse events (AEs) are exempt from recording in this trial. All participants are hospitalized during the intervention, and any serious adverse events (SAEs) that occur during this time are recorded in the eCRF. From discharge until the six-week

follow-up, SAEs are recorded and reported in the eCRF when brought to the attention of the dedicated staff by the participants who are informed to report them. In the participant information there is contact information on coordinating investigator, project manager and sponsor. At the six-week follow-up, SAEs are specifically reviewed, recorded, and reported. The following variables connected to the SAE's must be recorded: description of event, onset and end of event, relation to intervention product and action taken.
This approach, based on the plasma half-life of the medical products, their safety profiles as outlined in the Summary of Product Characteristics, and the "low-risk" classification, is considered safe and appropriate for participants.

The local investigator and coordinating investigators are responsible for ensuring that SAE are recorded in the electronic CRF according to ICH guidelines. The project staff will handle this responsibility during hospitalisation and follow up.

Patients experiencing SAE will undergo appropriate clinical assessments and if relevant laboratory tests acquired. SAE is reported to the local or primary investigator and sponsor immediately or within 24 hours of becoming aware of them. The sponsor will report SAR annually to the Danish Medicines Agency and the Research Ethics Committee, including a safety report for trial patients. All reported events will be followed up until resolved or as clinically required.

An annual safety report will be submitted through the CTIS-system, with a report on the safety of all investigational medicinal products used in the clinical trial, in accordance with Art 43 in regulation 563/2014.

Suspected Unexpecte d Serious Adverse Reactions (SUSARs) will be reported by the sponsor in the EudraVigilance system in accordance with the Clinical Trial Regulation (CTR). The reporting will be done via the capital hospital pharmacy. . Sponsor will be registered in the EudraVigilance system prior to the commencement of the trial. Fatal and life-threatening SUSARs will be reported as fast as possible, within 7 days, while all other SUSARs will be reported within 15 days. Prior to reporting a SUSAR, an emergency unblinding must occur for the individual patient.

All reports will include comments on any consequences that may impact the trial. The final report will include a description of all SAE.

Ongoing monitoring and audit

The sponsor is responsible for ongoing monitoring of the trial's risk and benefit ratio and will maintain oversight of the trial. The coordinating primary investigator will oversee the local sites. Any situations that may affect the safety of trial participants or the trial's performance must be immediately reported to the Danish Medicines Agency. Additionally, these reports should be communicated to all investigators and Research Ethics Committees involved.

13.Data handling and quality control

Direct access to source data/documentation

The trial will be conducted in accordance with applicable regulations governing clinical trials involving human participants, ensuring adherence to quality control and quality management standards, and following Good Clinical Practice (GCP) guidelines. The primary investigator and local investigators at the hospital are responsible for managing and archiving data in compliance with current regulations. Data collected through worksheets and records will only be made available to third parties in accordance with Danish law. This includes access for monitoring by GCP units and inspections by authorized representatives of relevant authorities.

Protection of participant data

All information related to this trial will be treated with strict confidentiality, and those responsible for the trial are bound by confidentiality agreements. Patients will be anonymized in all reported test results. Data handling will comply with the General Data Protection Regulation (GDPR), the Danish Data Protection Act and Danish Health Care Act and be correctly reported authorities. Trial data is archived for at least 25 years after the end of the trial. The trial summary results will be uploaded to CTIS within one year after the "end of trial," with duly justified reasons provided if the summary of the clinical trial results is submitted after more than one year.

Investigators will ensure compliance with the protocol, Good Clinical Practice (GCP) guidelines and by the regulation (EU) No 536/2014. Data collected in worksheets and records

will only be made available to third parties in accordance with the Act on Processing of Personal Data, specifically for monitoring by GCP units or inspections by authorized representatives of relevant authorities.

Participants will receive information detailing the following:

- Results will be stored and analysed on a computer.
- All information will be treated confidentially.
- Patients will be anonymized in the reporting of trial results.
- There is a possibility of review by public authorities if they require access to relevant information.
- GCP units will have access to trial information.
- The study will comply with the General Data Protection Regulation (GDPR) and the Danish Data Protection Act.
- Patients have the right to request access to, and rectification or erasure of, their personal data, or to request a restriction of processing or object to processing.
- Patients have the right to lodge a complaint with a supervisory authority.

Quality control and quality assurance

The trial will be monitored according to Danish law and ICH-GCP-guidelines by Copenhagen University Hospital's GCP Unit. The investigators will see to that all staff involved in the trial will be adequately trained for their role, following the GCP guidelines. All delegated tasks and training will be logged in the TMF.

The participating centres, sponsor, project manager, and investigators involved in the trial will permit monitoring, audits, and inspections by authorities, including providing direct access to source data and documents.

Case report form and data Management

For each patient included in the trial, an electronic CRF will be completed in the electronic REDCap database. Data input will be stored on a secure server utilizing REDCap within The Capital Region of Denmark. Data entry occurs through an encrypted connection, complying with the demands for data security. All data entries and modifications are meticulously logged in REDCap. The database is capable of storing social security numbers and adheres to GCP requirements for the use of electronic CRF Forms in clinical trials. Obtaining the NMS

on week 4 by phone, will be registered directly in the eCRF. Upon completion of the study, all data will be pseudonymized.

All data on main outcomes initially recorded on a sheet, before being entered into the eCRF, will be signed by the project staff who collected it and stores at each trial unit.

At each department there will be a Trial Master File that contains documents following the ICH GCP guidelines. Sponsor, investigators, project nurses and project managers will have access to the REDCap database.
Socioeconomic data, besides what is described in follow up data, will be obtained from pertinent registers, including sources such as "Statistics Denmark," with requisite permissions secured in advance.

Data on screened patients

Screened patients who are not eligible or does not wish to participate is recorded according to the CONSORT statement and GCP guidelines. Screening will involve retrieving data from the electronic medical record before obtaining patient consent. This data, entered into the electronic Case Report Form (eCRF), will include details on age, sex, inclusion and exclusion criteria to assess trial eligibility but will not contain any personally identifiable information. Information regarding screening will be used for the rate of inclusion and be part of a flow-chart of inclusion of participants. Screening information will contribute to enrolment rates.

Trial management and organisation

At each department there will be dedicated staff that enrols patients and handle follow up. Besides this there will be a project manager at the coordinating department that will oversee that the recruitment plan is followed and assist the project staff. For each step-in recruitment, intervention and follow up there will be created a Standard of Operation Procedure (SOP) with a step-to-step guide on how to execute the tasks.

The local primary investigators is responsible for the day-to-day execution of the trial. At least once a month the coordinating investigator will meet with the sponsor.
Each year following recruitment start the coordinating investigator will create a year report following criteria from GCP. The IronHip trial group (steering committee) consist of sponsor, investigators, project manager and all collaborators listed in the top of the protocol.

Roles in the trial

- Nicolas T. Jones: coordinating primary investigator
- Søren Overgaard: initiator, sponsor, primary supervisor for NJ
- Robin Christensen: Senior biostatistician
- GCP-units: monitor.
- Copenhagen Pharmacy: labelling, packing of trial medication.

14.Ethical considerations and dissemination

This study is of international importance as the challenges faced by patients with a HF are similar in Western countries. Moreover, the NICE guidelines in the UK closely align with the Danish guidelines, suggesting that the findings from this trial could be broadly applicable and accepted. Furthermore, the implementation of a relatively inexpensive and easy-to-administer drug, such as intravenous iron, should be feasible across different healthcare settings.

FDI is widely used and several trials and studies examining the use of intravenous iron (FDI) in similar contexts have found it to be safe and well-tolerated, which supports the justification for its use in this study. Participants will be informed about the purpose, methods, potential benefits, and risks of the study, and informed consent will be obtained from all patients.

The study aims to improve patient outcomes, particularly functional mobility, which is crucial for the quality of life in elderly HF patients. By potentially enhancing recovery, the trial could contribute significantly to better healthcare practices.

The trial will be conducted in line with the ethical principles established in the Declaration of Helsinki – The World Medical Association (2024) and the principles of Good Clinical Practice. Monitoring for adverse effects will adhere to CGP guidelines and the safety of the participants will be a primary concern throughout the trial.

The ethical considerations extend to the dissemination of the findings, ensuring that the results are reported transparently and shared widely to benefit global healthcare communities. Deidentified data might be shared upon request.

The potential influence of this study on clinical guidelines and patient care practices underscores the necessity of strict adherence to the highest ethical standards. The findings will be submitted for publication in peer-reviewed, high-impact journals, ensuring compliance with the authorship criteria established by the International Committee of Medical Journal Editors (ICMJE). Nicolas T. Jones will serve as the first author, with Søren Overgaard as the senior (last) author.

15.Appendix

Appendix 1Overview of FDI utilization in studies with orthopaedic patients

Appendix 1 Overview of FDI utilization in studies with orthopaedic patients

Author, year	Lasocki S. et al. 2023	Kwon JH. et al. 2022	Clemmensen SZ. et al. 2021	Hansen LT., 2023	Yoo S. et al. 2021
Title	Ferric derisomaltose and tranexamic acid, combined or alone, for reducing blood transfusion in patients with hip fracture (the HiFIT trial): a multicentre, 2 x 2 factorial, randomised, double-blind, controlled trial.	Effect of intraoperative intravenous ferric derisomaltose supplementation on reduction of postoperative anemia and transfusion in chronic kidney disease patients after total knee replacement	Association between intravenous iron therapy and short-term mortality risk in older patients undergoing hip fracture surgery: an observational study	Impact of postoperative intravenous iron therapy on postoperative infections in older patients with severe anaemia after hip fracture surgery	Efficacy of intra-operative administration of iron isomaltoside for preventing postoperative anaemia after total knee arthroplasty: A randomised controlled trial
Design	Multicenter, 2×2 factorial, randomized, double-blind, controlled trial	Retrospectively observational study looking at patient undergoing total knee replacement, grouping them in with/with out Chronic Kidney Disease and FDI/Non FDI	Retrospectively single centre observational study, looking before and after implementation of FDI	Retrospectively single centre observational study, looking before and after implementation of FDI	Single centre, randomised, controlled, double-blind, parallel-group study
Type of surgery	Hip fracture	Total knee replacement	Hip Fracture	Hip Fracture	Total knee arthroplasty
Total N	413	191	210	198	89
Hemoglobin criteria FDI	9.5 g/dl (5.6mmol/l) to 13.0 g/dl (8.1mmol/l)	Patients with hemoglobin level <10 mg/dL (6.2mmol/l) preoperative were excluded	<6.5 mmol/l (10.5 g/dl)	<6.5 mmol/l (10.5 g/dl)	FDI dose depending on Hgb >/< 10 g/dl and >/< 70 kg body weight
Primary	Percent of patients transfused during hospitalisation (or by day 30)	The postoperative hemoglobin level for each postoperative day	Primary outcome was 30-day mortality post-surgery	The initiation of systemic antibiotic treatment defined the occurrence of a postoperative infection	Incidence of anaemia at 30 days after TKA
Secondary outcomes	Haemoglobin, iron deficiency, mortality, Alive and home 90 days. Ability to walk 3 m or across a room, Quality of life and Activities of Daily Living.	Patient transfusion rate, volume of transfusion and length of hospital stay	Impact on hemoglobin level 14–30 days postoperatively	In hospital/out of hospital	Hgb level, iron panels, postoperative red blood cell transfusion requirements, hospital length of stay, the incidence of surgical site infection, and quality of life at 30 days
Dose	20mg/kg body weight	400 mg	20 mg/kg	20 mg/kg body weight	FDI dose depending on Hgb >/< 10 g/dl and >/< 70 kg body weight
Control	Placebo: 60 ml saline	No FDI	No FDI	No FDI	Placebo:100 ml 0.9% sodium chloride
Intervention	FDI and/or tranexamic acid, with placebo.	Observational study	Observational study	Observational study	FDI or placebo
Follow up primary outcome	Discharge or up to 30 days	Postoperative day 1-14	30 days postoperatively	30 days from the day of surgery or until first occurrence	30 days after TKA

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