PREVENTT
Preoperative intravenous iron to treat anaemia in major surgery

Full title of trial	A randomised double-blind controlled phase III study to compare the efficacy and safety of intravenous ferric carboxymaltose with placebo in patients with anaemia undergoing major open abdominal surgery
Short title	**PREVENTT** (Preoperative intravenous iron to treat anaemia in major surgery)
Version and date of protocol	Final Version 4, 16/12/2013
Sponsor:	University College London (UCL)
Sponsor protocol number	12/0246
Funder (s) :	NIHR HTA (10/104/06)
EudraCT no.	2012-002786-35
ISRCTN no.	ISRCTN67322816
ACTIVE IMP(s):	Ferric carboxymaltose (Ferinject®)
PLACEBO IMP(s):	Normal saline
Phase of trial	Phase III
Sites(s)	Multi-site

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Signatures

The Chief Investigator and the JRO have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol.

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005' 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

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List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
AP	Alkaline phospatase
AR	Adverse Reaction
AST	Aspartate aminotransferase
CI	Chief Investigator
95% CI	95% confidence interval
CRF	Case Report Form
CRP	C-reactive protein
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DSMC	Data Safety and Monitoring Committee
DSUR	Development Safety Update Report
e-GFR	Estimated glomerular filtration rate
EPO	Erythropoetin
EQ-5D-5L	European quality of Life – 5 dimensions – 5 levels
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FBC	Full Blood Count
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin
Hct	Haematocrit
HRQoL	Health-related quality of life
HRU	Health Resources Used
ID	Iron deficiency
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
i.v.	Intravenous
LDL	Low density lipoproteins

LFT	Liver Function Tests
LOS	Length of stay
LSHTM	London School of Hygiene & Tropical Medicine
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MDT	Multi-Disciplinary Team
MFI	Multi-Fatigue Inventory
MHRA	Medicines and Healthcare products Regulatory Agency
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
OPA	Out-Patient Appointment
PAC	Pre Assessment Clinic
PAV	Planned Assessment Visit
PI	Principal Investigator
PIS	Participant Information Sheet
PMG	Project Management Group
POMS	Post-Operative Morbidity Survey
PREVENTT	Preoperative intravenous iron to treat anaemia in major surgery
QALY	Quality-Adjusted Life Year
RBC	Red blood cell count
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Document Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SQOM	Single Question Outcome Measure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIBC	Total Iron Binding Capacity
TSAT	Transferrin saturation
TSC	Trial Steering Committee
UE	Urea and Electrolytes

1 Trial personnel

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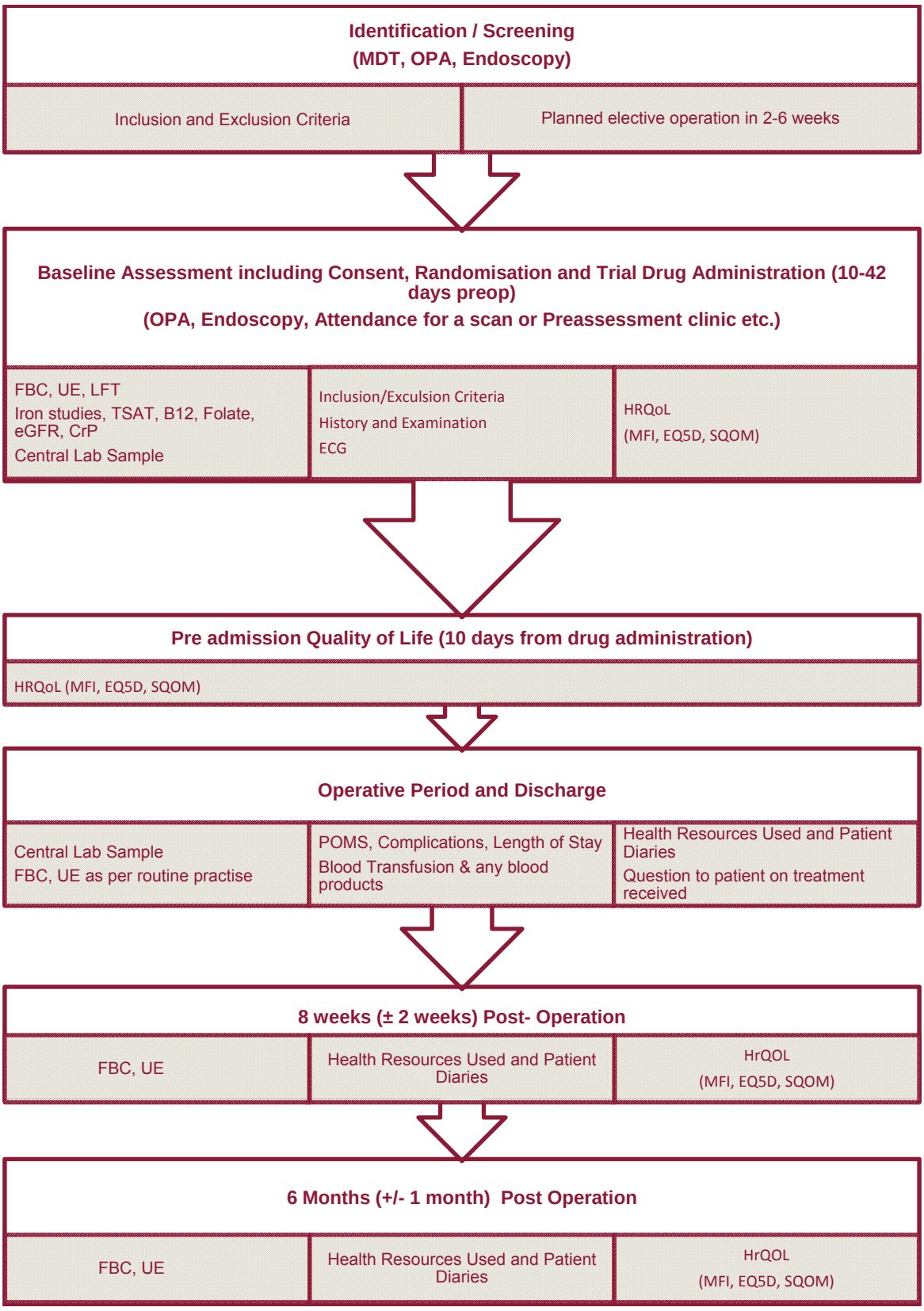
2 Summary

Title:	A randomised double-blind controlled phase III study to compare the efficacy and safety of intravenous ferric carboxymaltose with placebo in patients with anaemia undergoing major open abdominal surgery
Short title:	**PREVENTT** (**PRE**operative intra**VEN**ous iron **T**o **T**reat anaemia in major surgery)
Trial medication:	*Active treatment*: Ferric carboxymaltose solution (Ferinject®) for parenteral application, 50 mg/mL iron. Medication will be given as an intravenous (i.v.) infusion of 1000mg in normal saline over 15 minutes. *Placebo*: Normal saline (0.9% weight/volume (w/v) NaCl) administered in analogy to active treatment procedures.
Phase of trial:	III
Objectives:	Primary: To determine if a single dose of intravenous iron administered to patients with anaemia prior to major surgery reduces the need for peri-operative blood transfusion. Secondary: To evaluate the effect of intravenous ferric iron compared with placebo on health related quality of life, post-operative morbidity, safety and length of hospital stay
Type of trial:	Phase III double-blind controlled, randomised multi-centre trial
Trial design and methods:	A phase III randomised controlled trial in patients with anaemia undergoing major surgery, investigating the effects of a pre-operative single dose of intravenous iron compared with placebo. Participants will be randomised 1:1 to either treatment (1000mg Iron Carboxymaltose in 100ml of normal saline) or placebo (100ml 0.9% normal saline). Outcome assessments will occur following trial treatment administration, on admission for surgery and at 8 weeks and 6 months post operation. In-hospital outcome measurements include requirement for blood transfusion, post-operative morbidity (Post-Operative Morbidity Survey (POMS)) and health related quality of life (EQ-5D-5L and multi-fatigue inventory (MFI)). Follow-up outcome measurements include health-related quality of life measurement.
Trial duration per participant:	8 months
Estimated total trial duration:	Five years
Planned trial sites:	Multi-site: Approximately 20 mainly in England

Total number of participants planned:	500 (250 active treatment; 250 placebo)
Main inclusion/exclusion criteria:	Patients undergoing elective major open abdominal surgery at least 18 years of age, with a screening haemoglobin concentration 90-120g/L, 10-42 days before planned operation will be eligible to participate. Exclusion criteria includes a known history of acquired iron overload or a family history of haemochromatosis or thalassemia (TSAT>50%), a known hypersensitivity to ferric carboxymaltose (Ferinject®), chronic liver disease and/or screening alanine transaminase (ALT) or aspartate transaminase (AST) above three times the upper limit of normal range, renal dialysis (planned or within the next 12 months), on non-prophylactic antibiotics, temperature >37.5^{o}C, or received erythropoietin, i.v. iron therapy or blood transfusion in the previous 12 weeks.
Statistical methodology and analysis:	The co-primary endpoints are (i) risk of blood transfusion or death from randomisation to 30-days post-operation and (ii) blood transfusion rates from randomisation to 30-days post-operation adjusting for death. For the first co-primary outcome a risk ratio and 95% confidence interval will be estimated. For the second co-primary outcome a rate ratio and 95% confidence interval will be estimated using a Negative Binomial regression model. For both outcomes analysis will be by intention-to-treat using the full analysis dataset.


Identification / Screening
(MDT, OPA, Endoscopy)
Inclusion and Exclusion Criteria
Planned elective operation in 2-6 weeks
Baseline Assessment including Consent, Randomisation and Trial Drug Administration (10-42 days preop)
(OPA, Endoscopy, Attendance for a scan or Preassessment clinic etc.)
FBC, UE, LFT
Iron studies, TSAT, B12, Folate, eGFR, CrP
Central Lab Sample
Inclusion/Exculsion Criteria
History and Examination
ECG
HRQoL
(MFI, EQ5D, SQOM)
Pre admission Quality of Life (10 days from drug administration)
HRQoL (MFI, EQ5D, SQOM)
Operative Period and Discharge
Central Lab Sample
FBC, UE as per routine practise
POMS, Complications, Length of Stay
Blood Transfusion & any blood products
Health Resources Used and Patient Diaries
Question to patient on treatment received
8 weeks (± 2 weeks) Post- Operation
FBC, UE
Health Resources Used and Patient Diaries
HrQOL
(MFI, EQ5D, SQOM)
6 Months (+/- 1 month) Post Operation
FBC, UE
Health Resources Used and Patient Diaries
HrQOL
(MFI, EQ5D, SQOM)

3 Introduction

3.1 Background

Anaemia is commonly detected in patients undergoing an operation often as a consequence of the disease for which they need surgery. Current standard of care is peri-operative blood transfusion. However, data suggest that both anaemia and blood transfusion may be associated with worsened outcomes following surgery. Intravenous iron can produce a rapid rise in haemoglobin, if applied in the pre-operative setting many patients could have their anaemia corrected by the time of surgery. This may reduce the need for blood transfusion and improve patient outcomes.

The problem of anaemia and surgery

The World Health Organisation defines anaemia as insufficient Red Blood Cell (RBC) mass circulating in the blood <13g/dL for men and <12g/dL for women (1). Anaemia is associated with impaired physical function, reduced quality of life, infection, patient morbidity and mortality (2). Pre-operative anaemia is common, affecting 30-60% of all patients undergoing major elective surgery (3). In the surgical setting anaemia compounds the stress of operation; anaemia is an independent risk factor for blood transfusion, in-patient complications, delayed hospital discharge and poorer recovery (4). The cause for anaemia in this patient group is often multifactorial; due to blood losses, nutritional deficiency (iron-deficiency anaemia), anaemia of chronic disease (cancer and/or inflammatory disease) or a combination of these aetiologies. Two main types of anaemia affect surgical patients, iron deficiency anaemia (IDA) and anaemia of chronic disease (ACD), the latter is more common in chronically ill and hospitalised patients (6). ACD can be difficult to diagnose, often being regarded as a diagnosis of exclusion, key feature is a disruption of normal iron homeostasis initiated by a cytokine mediated immune response, such as in chronic inflammatory disease, during infection or following surgery (6, 7).

Although anaemia is diagnosed by low haemoglobin blood indices including Ferritin, MCV and MCH define the cause of anaemia. IDA is classically defined as microcytic hypochromic anaemia. A key feature of ACD is disruption of normal iron homeostasis initiated by a cytokine-mediated immune response, such as in chronic inflammatory disease or following surgery (6, 8, 9). This has been recognised and definitions of Absolute Iron Deficiency (AID) and Functional Iron Deficiency (FID) proposed instead of IDA or ACD, others have suggested the term anaemia of inflammation (10).

In pilot studies patients (1511) undergoing major surgery at UCH were assessed, 245 were anaemic. Microcytosis was observed only in 13% of anaemic patients. Ferritin levels below 30 ng/ml were seen in 31% and 64% had a Ferritin of <100 ng/ml. Therefore using low Ferritin and low MCV would mean that of 245 patients with anaemia only 13 would be defined as having ‘textbook’ IDA. Although low serum ferritin levels usually indicate reduced iron stores in the body. Ferritin is an acute phase protein and elevated in the presence of inflammation. In surgical patients the majority have underlying inflammation indicated by raised CrP levels, mean CrP was 23. IDA may therefore be masked by ‘abnormally’ high or normal ferritin levels in this group of patients. We found correlation between anaemia and raised CrP levels (p=0.006) suggesting FID.

In summary the exact definition of anaemia in the surgical patient is confusing. Proposals exist for IDA, FID, AID, and ACD. Consequently this inability to define 'Iron deficiency' in patients with anaemia before operation has meant that most patients are not treated with iron therapy. Blood transfusion in the peri-operative period remains the standard of care (5). This problem of definitions was addressed in a recent trial on patients with anaemia and heart failure. In the FAIR–HF study, AID was diagnosed when the serum ferritin level was less than 100 µg per liter and FID where ferritin was between 100 and 299 µg per liter and transferrin saturation was less than 20%. In this group of patients mean CrP was 7.46±5.34 (11). There was no difference in response between AID and FID to intravenous iron therapy. Those treated with intravenous iron had a significant improvement in patient quality of life, disease status and 6-minute walk test compared to placebo.

Blood transfusion may be a poor treatment option

The current standard of care for anaemia in patients undergoing surgery is blood transfusion. The demand for blood products increases every year. In 2008/9 1.86 million units of blood were transfused in the UK, cost per unit was £130, an overall cost of provision to the NHS of £247.4 million. Audits repeatedly suggest an inflation of 256% in the cost of blood-related products in nearly six years (1995-2001), whilst the increase in blood donations is of roughly 2% for the same period. Although blood transfusion is a well provided service it is predicted there is £7.2 million in waste and loss of productivity pertaining to whole blood and related blood products (5).

The cost to the NHS from NHS Blood Transfusion (NHSBT) is £130 for one unit of blood. However, the cumulative total NHS costs (e.g. nursing time, patient transport, treatment costs, etc) are over £635. In response to concerns over the impact of universal prion screening for blood products the NHSBT national commission has forecast an increase of £15-25/unit and nearly £41/unit in filtration charges from 2012 onwards (13).

Transfusion is known to exert immunologic and immunosuppressive effects which include a decrease in T- Cell production and natural killer cells and it is associated with increased inflammatory response (14). Although anaemia increases the requirement for transfusion, blood transfusion itself has been associated independently with a worse patient outcome (15, 16). Prospective observational studies suggest that allogenic blood transfusion (ABT) increases the risk of post-operative infection, respiratory complications, reduces patient's functionality and has a clear association with increased readmission rate in intensive care units and longer hospital stay (15, 16).

Transfusion has also been associated with increased relative risk of cancer recurrence. A Cochrane Review investigated the effects of ABT and recurrence of colorectal cancer in 12,127 patients. This recent systematic review, last assessed as up to date in November 2010, concluded that there is indeed a moderate association to be found between rates of ABT and colorectal cancer recurrence. The odds ratio (OR) reported as 1.42, with a statistically significant 95% confidence interval (CI) of 1.20 to 1.67. The conclusion was that ABT should be restricted in its use in patients undergoing colorectal cancer resections with a curative intent (17).

Treating Anaemia pre-operatively: why oral iron is not adequate

Oral Iron is a common cheap and effective method to replenish total body iron stores in the elective setting. Oral Iron is a treatment available in patients with Iron Deficiency Anaemia. However, oral iron is poorly absorbed; numerous factors inhibit iron absorption (proton pump inhibitors, anti-inflammatory drugs, inflammation, and gastro intestinal (GI) disease including H Pylori). Further about half of patients will have significant side effects of abdominal pain, constipation or heartburn. Compliance is also a great problem as only 20-40% of patients complete a full course of oral iron therapy.

Oral iron is absorbed in the duodenum at a rate of only 2-16mg per day. A formula based on body weight and Hb levels can be used to calculate the amount of iron needed to replenish iron stores – Ganzoni Formula (18). Ganzoni's calculations conclude that most patients will need between 1000 and 2000 mg of iron to replenish body reserves. Therefore oral iron is able to restore normal iron levels in 3-6 months; a period which is far too long in the surgical setting. Hb levels may in fact increase before the replenishment of iron stores, but the loss of an equivalent of one blood unit during surgery represents over 600mg of iron stores and may compromise this lengthy treatment.

The main problem is that in surgical patients the underlying disease process and concomitant inflammatory response evoke mediators that reduce the intestinal absorption of iron. This process occurs by both inhibition of erythroid colony growth and by suppression of endogenous erythropoetin (EPO) production. These intestinal cytokines, associated with a high production of hepcidin induce FID, which may incidentally find already depleted iron stores. Therefore, FID cannot be corrected by oral iron because intestinal iron absorption is decreased in the presence of normal iron stores (4, 19).

Treating Anaemia pre-operatively: why intravenous iron may work

Intravenous iron is the standard of care in patients with anaemia and renal failure. Its use has widened to routinely treat anaemia in patients with Inflammatory Bowel Disease, and cardiac disease where oral iron is ineffective and the disease/inflammatory pathways block iron absorption from the gut. Introduction of new intravenous iron preparations that can be administered as a single treatment in a relatively short (15 minute) time without need for test dose, or peri-infusion monitoring or risk have facilitated small trials of obstetric, gynecological, orthopaedic and obesity surgery. These have suggested intravenous iron may rapidly increase haemoglobin levels before operation and this may result in lower transfusion rates.

Intravenous iron has been used in a variety of observational trials and audits in surgical patient groups: -

- In orthopaedics Theusinger et al using iron sucrose tested the efficacy of this compound to correct anaemia in 20 patients with iron-deficiency. These were prescribed 900mg intravenously, over 10 days (4 weeks before surgery). The average Hb increase was of 1.0±0.6 g/dL (95% CI: 0.2-2.2); and the highest increase occurred 2 weeks after start of iron therapy ($p<0.0001$) (20). In 2004, Cuenca et al studied a population of 55 patients scheduled to undergo pertrochanteric hip fracture and used pre-operative i.v. iron therapy using also iron

sucrose. The authors studied the effect of 200-300 mg of iron sucrose three days before surgery and elected as endpoints ABT requirements and post-operative morbidity and mortality, comparing the results with 102 controls (21). Iron sucrose reduced the transfusion rates in patients with Hb levels greater than 12g/dL at admission and also reduced post-operative infection, although there were no differences in 30-day mortality rate or length of stay. In a further study of 83 patients, intervention with a higher iron dose (3 x 200 mg/48h) combined with EPO (40,000 IU) pre-operatively showed a significant reduction in ABT requirements (24% vs. 27.1%; P<0.01) (22). In a further series of 10 anaemic orthopaedic patients who were prescribed iron sucrose (1,000 mg, range 600-1800), Hb levels (+2.6 g/dL; p<0.01), ferritin (+198mg/L; p<0.01) and transferrin saturation (+21%; p<0.01) increased without significant side effects. The Anaemia Working Group in España (23), published data on 129 patients undergoing total replacement of the knee who received iron sucrose (2 x 200 mg per 48 h, i.v.), with or without EPO and a restrictive transfusion policy. The results of this observational study suggest that this blood-saving protocol, consisting of a restrictive transfusion trigger plus peri-operative administration of i.v. iron and EPO concomitantly is able to reduce ABT rate and to haste the recovery from post-operative anaemia after Total Knee Replacement (TKR), without causing iron reduction. In another observational study Bisbe et al. assessed 27 patients scheduled for orthopaedic surgery. Of these patients, 20 cases received i.v. iron sucrose and EPO and 7 received iron alone. The results showed an Hb increase of 1.7 g/dL in the group that received intravenous iron. As for the group that combined intravenous iron and EPO there was a similar increase and 25% rate of transfusion. The authors concluded i.v. iron alone is useful for correcting of pre-operative anaemia and the use of EPO should be restricted to cases in which correction of anaemia is refractory to the use of intravenous iron (24).

- Serrano-Trenas et al randomised 200 patients undergoing hip fracture surgery, of which one group (A= 100 patients) received standard treatment and another group (B= 100 patients) received intravenous iron sucrose (600mg i.v.). Use of iron reduced transfusion requirements (41.3% in Group A and 33.3% in Group B). For patients affected with intracapsular fractures 45.7% required transfusion in Group A, whereas 14.3% in Group B; p<0.005. Once again, the use of i.v. iron reduced the transfusion requirements and the number of concentrates transfused (26).
- Kim Yh et al compared the efficacy of intravenous versus oral iron in the management of anaemia in patients with menorrhagia. 76 anaemic patients (Hb<9.0 g/dL) who were scheduled to undergo surgical treatment were randomised. The intervention group received iron sucrose 3 times a week, beginning 3 weeks before surgery. The control group received oral iron (80mg/day). The increase in Hb was substantial in the intravenous iron compared to the oral group (3.0 vs 0.8 g/dL; p<0.0001). Ferritin levels were greater in the i.v. group (170.1 vs. 4.1 microg/L; p<0.0001) as well as the rate of patients achieving targeted Hb levels [76.1% vs. 11.5%; p<0.0001] (25).
- Diez-Lobo et al investigated the utility of pre-operative intravenous iron treatment to increase Hb levels and reduce need for transfusion in women with iron deficiency anaemia or iron deficiency in abdominal hysterectomy, in an observational prospective study. The intervention

arm consisted of women having surgery at least 1 month after pre-op assessment who received i.v. iron sucrose for 2-4 weeks (n=31). The control arm consisted of women who did not receive i.v. iron (n=44). Intervention with iron sucrose (760±290mg) resulted in an increase in pre-operative Hb (2.2±1.2 g/dL; p<0.0001), and lower transfusion rates (32% vs. 0%, respectively, p<0.001). In addition to this fewer women in the iron group were found anaemic 21 days post-operatively (23% vs 68%, p<0.01) (27).

- In general surgery, Munoz et al studied 84 anaemic patients scheduled for major elective surgery (30 colon cancer resections, 33 abdominal hysterectomies, and 21 lower limb arthroplasties). These patients received pre-operative i.v. iron during 3-5 weeks before surgery. Results concluded the administration of i.v. iron (Mean dose: 440 mg) caused an increase in Hb levels of 2.0 g/dL (p<0.001) and corrected anaemia in 68% of patients. No life-threatening adverse effect was witnessed (4).

A full search on Pubmed and clinical trials databases confirmed there are no trials on intravenous iron in major surgery (MESH terms: #iron AND #blood transfusion AND #surgery AND #anaemia). This was endorsed in two recent reviews, both of which called for an RCT on the role of intravenous iron in surgery to prevent blood transfusion (14, 28).

The use of POMS to assess morbidity

The POMS was originally developed as a measure of clinically significant post-operative short term harm at Duke University Medical Centre (DUMC, NC, USA) in the late 1990s (29). It was anticipated to have potential utility in clinical decision making, in clinical governance activities and in quality of care, prognostic, and effectiveness research. The original publication describing the POMS was an epidemiological description of patients undergoing elective major surgery at DUMC (29). The POMS was subsequently shown to be a valid and reliable measure of short-term post-operative harm in 438 patients in UK studies from University College London Hospitals (30). It is now in use in registries of peri-operative care, in outcomes research (31-34) and in effectiveness research (35). The POMS is currently being used as a primary and secondary outcome measure in NIHR and MRC funded randomised controlled trials of peri-operative interventions.

The POMS is an 18-item tool that addresses nine domains of morbidity relevant to the post surgical patient: pulmonary, infection, renal, gastrointestinal, cardiovascular, neurological, wound complications, haematological and pain. For each domain either presence or absence of morbidity is recorded on the basis of precisely defined clinical criteria. The POMS was designed with three guiding principles. First, that it should describe morbidity from the perspective of the patient as well as care-givers. Second, it should only identify morbidity of a type and severity that could delay discharge from hospital. Third, the data collection process should be as simple as possible so that large numbers of patients can be routinely screened.

Item generation was achieved through a three-stage patient centred process (29). First, investigators collected information directly from patients, nurses, and doctors using open questions to identify reasons why the patients remained in hospital after surgery. Second, the responses obtained were

categorised into domains of morbidity type. Thresholds were set for individual domains to achieve the primary goal of identifying morbidity of a type and severity that could delay discharge from hospital. Finally, the derived survey was reviewed and amended by an international consensus panel of anaesthesiologists and surgeons.

From this process a measure was produced that focused on easily collectable indicators of clinically important dysfunction in key organ systems. These indicators are readily obtainable from routinely available sources and do not require special investigations. These sources include observation charts, medication charts, patient notes, routine blood test results, and direct questioning and observation of the patient. Crucially, the indicators define morbidity in terms of clinically important consequences, rather than traditional diagnostic categories. For example, a patient with a clinically significant chest infection would register POMS defined morbidity in the pulmonary (requirement for supplemental oxygen or other respiratory support) and infection (currently on antibiotics or temperature >38°C in the last 24 hours) domains, rather than meeting specific diagnostic criteria for a chest infection.

3.2 Rationale and risks/benefits

Rationale

The problem of anaemia in patients undergoing major surgery is increasingly recognised (37). Anaemia and iron deficiency are common co-morbid conditions in surgical patients. No major clinical trial has been conducted yet, addressing the correction of iron deficiency and anaemia by use of parentral iron in patients undergoing major surgery. The NHS Enhanced Recovery Partnership Programme (ERPP) (38) has highlighted the need to address anaemia in surgical patients as a correctable condition, but no specific recommendations or guidelines for the evaluation or treatment of anaemia in these patients has been proposed.

PREVENTT is designed as a randomised, double-blind, parallel-group, placebo-controlled, multi-centre study to investigate the efficacy and safety of intravenous iron compared to that of placebo in a patient population with anaemia undergoing major surgery. The dosing is based on the maximum dose of intravenous iron that can be safely given in a reasonable time period. The reason for using Iron Carboxymaltose is its safety profile with lack of risk of anaphalaxis and ease of use.

The aim is that the proposed protocol can be incorporated into the current existing patient pathways for patients admitted for elective surgery. Pilot studies have confirmed key findings in existing research and feasibility of conducting PREVENTT within the structure of current NHS timelines for surgery. Patients could potentially be identified for PREVENTT at several points from referral to hospital including; outpatients, attendance at a diagnostic test (endoscopy) or radiology (CT, MRI), at multi-disciplinary team (MDT) meeting and also Pre Assessment Clinic (PAC). Attendance for purposes of the PREVENTT trial assessment and administration of the trial drug could be incorporated into current normal hospital practice, such as; in outpatients at endoscopy or as part of PAC visits. It is anticipated that different centres may incorporate PREVENTT into their own patient pathways as feasible.

As anaemia treatment is not standard care in these patients it was deemed acceptable to use a placebo control group for the supplemental i.v. iron therapy. The trial methodology is based on the FAIR-HF trial (11). In FAIR-HF patients with heart failure and anaemia were randomised to receive ferric carboxymaltose or placebo.

The trial design is pragmatic and aims to include the proposed intervention within current NHS timelines. The normal protocol before surgery is for patients to attend PAC 10 days to six weeks prior to operation. This is the same time period required for intravenous iron to produce an effective rise in Hb levels. Therefore anticipated surgery in 10 days to six weeks was defined in the inclusion criteria.

3.3 Assessment and management of risk

Using the MHRA guidelines this trial has been categorised as: Type A = No higher than the risk of standard medical care. The reasons being that Ferinject® is indicated for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. And in this trial, the IMP will be used broadly within the licensed indication and as per the SmPC (Summary of Product Characteristics), therefore no higher than the risk of standard medical care.

As with all iron preparations, overdosing with respect to the total amount administered will be avoided. Therefore the dose to be used for intervention in PREVENTT is within the current licensed instructions for use; 1000 mg iron carboxymaltose for a patient over 50kg. A recent phase III study demonstrated the safety and efficacy of Ferinject® at this dose (36).

Potential benefits to the patients include correction of anaemia and restoration of iron levels with potential improvements in fatigue symptoms. In order to ensure patients with iron overload are not included in the study, patients with Transferrin saturations > 50% will be excluded as this will reliably screen those patients with previously undiagnosed haemochromatosis.

The side effects for Ferinject® are listed in the Safety Reporting SOP (and can also be found in the summary of product characteristics, see section 10.2).

Caution should be exercised to avoid paravenous leakage when administering Ferinject®. Paravenous leakage of Ferinject® at the injection site may lead to brown discolouration and irritation of the skin. In case of paravenous leakage, the administration of Ferinject® must be stopped immediately.

Pregnant or lactating patients and patients with renal or liver disease will be excluded from the trial therefore any risks associated with such patients will be avoided. With intravenous iron the risk of hypersensitivity is increased in patients with a history of severe asthma, or severe allergies, but as such patients will be excluded from the trial these risks will be avoided.

4 Objectives

Primary:

To determine if a single dose of intravenous iron (ferric carboxymaltose; 1000mg) given to patients with anaemia prior to major open abdominal surgery reduces the need for peri-operative blood transfusion. For the purpose of this trial the peri-operative period is defined as from randomisation to until 30 days following operation.

Secondary:

- To evaluate the effect of intravenous ferric carboxymaltose (Ferinject®) compared with placebo on change in haemoglobin levels.
- To evaluate the effect of intravenous ferric carboxymaltose (Ferinject®) compared with placebo on post-operative morbidity, length of hospital stay and mortality.
- To evaluate the effect of intravenous ferric carboxymaltose (Ferinject®) compared with placebo on health related quality of life.
- To evaluate resource use and costs associated with the treatment with intravenous ferric carboxymaltose (Ferinject®) compared with placebo.
- To evaluate the tolerability and safety of Ferinject® compared with placebo from randomisation till study termination.
- To evaluate the effect of intravenous ferric carboxymaltose (Ferinject®) compared with placebo on:
    - Complications of the intervention itself.
    - Complications from blood transfusion or blood products.

5 Trial design

5.1 Overall design

This is a randomised, double-blind, parallel group, placebo-controlled, multi-centre, phase III study with 1:1 randomisation to either iron therapy or placebo. All patients started on investigational drug will be treated according to protocol, and will receive double-blind i.v. iron therapy or placebo. All patients will be followed for six months from date of operation. As active and placebo infusion fluid cannot be matched in appearance, unblinded study personnel, not otherwise involved in the study or in patient management, will be responsible for investigational drug administration (see section 8.4).

It is anticipated that the enrolment period will be approximately 36 months. The maximum study duration for all patients enrolled is six months following index operation. Study closure is expected to occur approximately four years after the randomisation of the first patient.

6 Selection of Subjects

6.1 Inclusion criteria

Patients who meet the following criteria at the start of treatment are eligible for the study:

1. At least 18 years of age and signed written informed consent.
2. Patients undergoing elective major open abdominal surgery.
   a. The Indication for operation may be for benign or malignant disease.
   b. Major Surgery is defined as an operation of anticipated duration more than one hour where all or part of an abdominal organ is to be removed (hepatectomy, pancreatectomy procedure, gastrectomy, oesophagectomy, colectomy (total/partial), nephrectomy, cystectomy, hysterectomy).
3. Screening haemoglobin (Hb) greater than or equal to 90 g/L (9.0 g/dL) but below or equal to 120 g/L (12.0 g/dL) within four weeks of randomisation.
4. Randomisation and administration of study infusion a minimum of 10 days and maximum 42 days before planned operation.
5. Negative pregnancy test for women of childbearing potential (within last 7 days), and agree to use effective form of contraception until 6 weeks post treatment.
6. Laboratory data used for determination of eligibility at the baseline visit must not be older than four weeks.

6.2 Exclusion criteria

Patients who, at the start of treatment, meet any of the following criteria are not eligible for the study:

1. Patients undergoing laparoscopic surgery.
2. Body weight under 50kg.
3. Known history of acquired iron overload, or family history of haemochromatosis or thalassemia or TSAT >50%.
4. Known reason for anaemia (e.g. B12 or folate deficiency or haemoglobinopathy).
5. Known hypersensitivity to ferric carboxymaltose (Ferinject®) or its excipients.
6. Temperature > 37.5°C or patient on non-prophylactic antibiotics
7. Chronic liver disease and/or screening alanine transaminase (ALT) or aspartate transaminase (AST) above three times the upper limit of the normal range.
8. Received erythropoietin, i.v. iron therapy or blood transfusion in the previous 12 weeks.
9. Immunosuppressive therapy (for organ transplantation) or renal dialysis (current or planned within the next 12 months).
10. Patients with severe asthma or severe allergy.
11. Unfit for elective surgery.
12. Pregnancy or lactation.
13. Inability to fully comprehend and/or perform study procedures in the investigator's opinion.
14. Patient involvement in another IMP trial within the previous 4 weeks, prior to randomisation. Involvement in another IMP trial, following randomisation, that may impact on the results of the PREVENTT trial.

7 Recruitment

Potential study patients will be identified from outpatients' clinics, multidisciplinary meetings and outpatient therapy visits (such as endoscopy). To aid meeting the recruitment target, 20 different sites across the UK will be participating to maximise identifying potential study patients. Wherever possible, patients will be screened for inclusion into the trial at a normal routine hospital attendance such as; outpatients or attendance for tests as part of their evaluation for surgery (radiological such as CT scan, MRI or endoscopy).

8 Study procedures and schedule of assessments

8.1 Screening Period

The aim is that the proposed protocol can be incorporated into the current existing patient pathways of patient care and assessment before operation. Pilot studies confirmed key findings in existing research and feasibility of conducting PREVENTT within the structure of current NHS timelines for surgery. Pilot studies also suggest that patient attendance for the purposes of the PREVENTT trial can be incorporated into current normal hospital practice. All identified patients will be allocated a screening number and entered onto the screening log. Details of this process are in the Screening SOP.

The patients will undergo the following during screening:

- Conformance with inclusion/exclusion criteria (including checking medication history to ensure medications are in conformance with the eligibility for the trial).
- Laboratory values for inclusion and exclusion criteria (see section 8.9.1) taken within four weeks of baseline assessment.
- Pregnancy test, for women of childbearing potential (to be done within 7 days prior to randomisation).

8.2 Informed consent procedure

Before inclusion to the study, patients must be given written and verbal information about the aims, methods, anticipated benefits and potential hazards, and given sufficient time (offered a minimum of 24 hours) to consider whether they wish to participate. If they wish a site may contact potential patients in advance by telephone before they attend a hospital appointment to explain about the trial. If the patient is interested the site can then post them the PIS to read prior to their appointment and follow this up with a further phone call within a reasonable timeframe.

Furthermore, the patients must be notified that participation is voluntary, and that they are free to discontinue treatment or revoke consent from the study at any time without any disadvantages for their subsequent care. Although a patient is not obliged to give her/his reason(s) for discontinuing in the study prematurely, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights. Freely given written informed consent must be obtained by a physician (or other suitably qualified personnel) prior to admission. The person who takes consent will be trained in GCP (Good Clinical Practice), and if they are not the Principal Investigator (PI) then the PI will have delegated them this responsibility.

No clinical trial procedures will be conducted prior to taking consent and patient consent does not automatically mean they are enrolled onto the study. Enrolment into the study is defined as following randomisation.

The patient must be informed of and consent in writing that personal data relating to the study may be scrutinised during monitoring and during audits by authorised representatives of health authorities, by the sponsor or sponsor designees; however, personal data will be kept strictly confidential and are not made publicly available. The patient will be given a copy of the signed consent form and the original will be kept in the Investigator Site File (ISF).

If any new safety information results in significant changes in the risk/benefit assessment, or there is other new information then the PIS and consent form will be reviewed and updated as necessary. This new information will be relayed back to the patients and they will be re-consented.

8.3 Randomisation procedures

Before randomisation the patients will be confirmed to be eligible for the trial and have a haemoglobin level measured within the preceding four weeks. Randomisation will be done on a secure web-based service through the Clinical Trials Unit at the London School of Hygiene and Tropical Medicine (LSHTM), this service will be provided by Sealed Envelope. With this web-based service sites will be able to randomise 24 hours a day, 7 days a week.

Randomisation will be using minimisation taking into account baseline haemoglobin (<100/100+ g/L), age (<70/70+ years), centre and operation type (major/major +/complex). Patients will be randomised to either receive the active treatment (ferric carboxymaltose) or the placebo. The web based database will allocate the participant a unique trial identification number and their identification details will be entered onto the trial patient identification log, which is kept in the Investigator Site File (ISF). Once this number is assigned to a patient, it will not be re-used even in the event the participant withdraws from the study. If the patient fails to be randomised, the details for the screen failure will be documented in the screening log.

Randomising will be done only by the unblinded member of staff whom has been delegated this responsibility by the principal investigator as evidenced by documentation in the delegation log. The

blinded staff will not have access to the randomisation system, and will therefore remain blinded to the treatment allocated.

Each unblinded member of staff will be trained in the use of the web-based randomisation service at the site initiation visit, and will then be provided with their own individual password and pin code to access the service.

The randomisation allocation will be set up by Sealed Envelope (an internet randomisation service provider), using minimisation as described above.

8.4 Blinding and Unblinding

Blinding:
The Iron Carboxymaltose solution is dark brown in appearance; blinding will be obtained by shielding the patients from seeing preparation of the study drug and having unblinded study personnel not involved in any study assessments (efficacy or safety) responsible for preparing and administering the study treatment. This unblinded member of staff will be present throughout the trial drug administration. This will be achieved by preparing and administering the study drug behind a screen or curtain. The drug will then be shielded from vision (Opabag light protection bags for Ecoflac bottles) and administered through black tubing (Intrafix Air P with black pipe).

The unblinded person will also dispose of the administration kit in a concealed way. All patients will be monitored during the trial drug administration as per normal clinical practice; any adverse events will be documented.

Unblinding:
The blinding to the patients or other medical staff may be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for a treating health care professional to know which treatment the patient has received. Subject always to clinical need, where possible, other members of the research team should remain blinded.

Further management is at the investigator's discretion but, clinical status permitting, all remaining clinical assessments must be completed unless the patient refuses further follow-up.

In general there should be no need to unblind the allocated treatment. If some contraindication to ferric carboxymaltose (Ferinject®) develops then the treatment should be simply stopped and all usual standard care given. Unblinding should be done only in those rare cases where the clinician believes that clinical management depends importantly upon knowledge of whether the patient received ferric carboxymaltose (Ferinject®) or placebo. Unblinding will also be done in the event of a SUSAR as described in section 11.4.2. In those few cases when urgent unblinding is considered necessary, a 24-hour secure online service will be available and details provided in the Investigator's Study File.

Patients will also be provided with small cards containing all the relevant contact details, which they will be instructed to present to any treating clinician if admitted to a site not involved in the trial.

If a treating clinician believes they need to be unblinded to the patient's treatment arm they will contact the PREVENTT office at UCL to discuss the reasons for the unblinding request. They will need to provide details of the patient's date of birth and trial identification number (as provided on the patient contact card). If after discussing with PREVENTT office the patients treating clinician final decision is that the patients safety will be compromised if they remain blinded to the treatment, then unblinding will take place. The authorised personnel will use the online randomisation system to request unblinding, and will need to enter the reason for unblinding. The treating clinician will be notified of the patient's allocated treatment, but the PREVENTT office will remain blinded.

The unblinding will be recorded within the randomisation system, and an unblinding report will be produced from this for reporting unblinding to the sponsor and the Data Safety and Monitoring Committee (DSMC). All unblinding will be mentioned in the final trial report.

8.5 Baseline assessments

Wherever possible these should coincide with the routine hospital schedule such as outpatients, endoscopy or Pre Assessment Clinic (PAC) attendance. The 'baseline assessments' including laboratory tests for the purposes of the PREVENTT trial are the same as those for routine clinical care in pre-assessment before major surgery. It would be reasonable to combine this with routine clinical practise and surgical/anaesthetic pathways where possible. The screening and baseline period will not exceed 4 weeks. Any assessments that are in excess of this 4 week period will not be used to assess eligibility. Patients that do not meet the eligibility criteria will not be re-screened. Similarly patients could undergo 'baseline' assessments, randomisation and trial drug administrations at the same attendance. Assessments will include:

- Check conformance with inclusion/exclusion criteria, including laboratory tests taken within four weeks (FBC, UE, LFT, iron studies, eGFR, CRP, thyroid function tests, B12, folate).
- Documentation of past medical history
- Vital signs (blood pressure, pulse rate, body weight, height, temperature)
- 12-lead ECG
- Additional blood samples for central laboratory analysis (FBC, iron studies, TSAT, TIBC)
- HRQoL questionnaires (see Section 8.12)
- Documentation of Health Resources Used (HRU): patient diary issued

8.6 Treatment procedures

Patients who conform to all eligibility criteria and have provided written informed consent will be randomised to receive either ferric carboxymaltose or placebo as described in section 10.

Administration of the IMP will be given in a hospital setting with appropriate resuscitation facility and staff available in the event of an emergency. Patients will be administered the study medication by the

unblinded person. For the drug administration the patient will have an i.v. line sited. Following this it is advised that the skin along the donor vein will be wiped using an iodine swab to help maintain the blind. The patient is to be shielded from seeing preparation of the study drug, drug administration, disconnection and removal of the i.v. line as described in section 8.4. Patients should be closely monitored for signs of hypersensitivity during and for at least 30 minutes following the administration of the treatment.

Ferinject® group: 1000 mg of ferric carboxymaltose will be administered as an i.v. infusion (100ml n/saline) over a minimum of 15 minutes using a black infusion kit.

Placebo group: Normal saline will be administered as an i.v. infusion (100ml n/saline) over a minimum of 15 minutes using a black infusion kit.

Adverse events occurring in connection with the administration of study medication will be recorded. In the event of a patient having an allergic reaction or signs of intolerance during study drug administration, the investigator must immediately stop the study treatment and notify the PREVENTT office at UCL and submit a completed SAE form to LSHTM within 24 hours of the event (refer to section 11.4 for SAE reporting).

If the treatment is stopped for other reasons and the patient is willing, then treatment can be restarted where possible (as per local practise).

8.7 Subsequent assessments

Preoperative HRQoL

The patient will be given the HRQoL questionnaires at their baseline visit and asked to complete in 10 days (+/- 2 days), then they should return these questionnaires to the research nurse when they are admitted. These must be completed prior to admission to hospital so the stress of the admission does not impact on their answers.

Admission to Hospital

- Blood samples for central laboratory analysis (FBC, iron studies, TSAT, TIBC)
- Question to patient on randomisation process and medication received
- Blood Pressure
- Documentation of any AEs since the last visit
- Documentation of Health Resources Used (HRU): patient diary collected at admission, and issued at discharge
- Documentation of hospital admissions
- Check transfusion use

Hospital Stay

- POMS (Post-Operative Morbidity Survey) will be performed on days 3, 5, 7 and 14 after surgery, if the patient remains in hospital (see appendix B for details)
- Documentation of post operative complications (using the Clavien system)
- Check transfusion use
- FBC, UE, eGFR and CRP (if collected as part of routine care)
- On discharge to hand out documentation of health resources used (HRU) diaries

Follow-up visit (8 weeks (±2 weeks) after operation)

- Documentation of hospital admissions
- Check transfusion use
- Vital signs (blood pressure, pulse rate, body weight)
- FBC, UE, eGFR, CRP
- HRQoL questionnaires
- Documentation of HRU: diary collected and reissued

Follow-up visit 2 (6 months (+/- 1 month) after operation)

- Documentation of hospital admissions
- Check transfusion use
- Vital signs (blood pressure, pulse rate, body weight)
- FBC, UE, eGFR, CRP
- HRQoL questionnaires
- Collection of documentation of HRU (patient diary)

8.8 Flowchart of study assessments

	Screening	Baseline (randomisation/ trial drug admin)	Pre-op HRQoL	Admission	Peri-op phase	Discharge	8 weeks post-op (+/- 2 wks)	6 months post-op (+/- 1 mth)
Transfusion use				x	x	x	x	x
Full Blood Count (FBC)	x	x			Local practise		x	x
Hb	x	x					x	x
Wcc	x	x					x	x
Plts	x	x					x	x
MCV	x	x					x	x
MCH	x	x					x	x
RDW	x	x					x	x
Urea & Electrolytes (UE)	x	x			Local practise		x	x
Na	x	x					x	x
K	x	x					x	x
Ur	x	x					x	x
Cr	x	x					x	x
eGFr		x			Local practise		x	x
C-reactive Protein		x			Local practise		x	x
Liver Function Tests (LFT)	x	x						
Thyroid Function Tests		x						
B12		x						
Folate		x						
Iron studies		x						
Fe		x						
Ferritin		x						
TSAT		x						
TIBC		x						
Blood to Central Lab		x		x				

	Screening	Baseline (randomisation/ trial drug admin)	Pre-op HRQoL	Admission	Peri-op phase	Discharge	8 weeks post-op (+/- 2 wks)	6 months post-op (+/- 1 mth)
History and vital signs (including temperature, blood pressure, pulse, weight & height)		x						
Blood Pressure, pulse & weight				x			x	x
ECG		x						
HRQoL								
SQOM		x	x				x	x
MFI		x	x				x	x
EQ-5D-5L		x	x				x	x
POMS					x (Days 3, 5, 7, 14)			
Post operative complications (Clavien system)					x			
HRU patient diaries (including concomitant medications)		Issued		Collected		Issued	Issued & collected	Collected
Pregnancy test (for women of childbearing potential)	x [1]							

[1] Within 7 days prior to randomisation

8.9 Methods

8.9.1 Laboratory procedures

All tests as detailed above will be processed at the Local Laboratories: FBC, U&E, LFT, Iron Studies, B12, Folate, CRP, eGFR and TFT.

The following samples, as listed in the assessments, will be processed at the Central Laboratory: FBC, Iron studies, TSAT and TIBC (further details can be found in the blood sampling SOP). This way the site will remain blinded to any change in haemoglobin post randomisation.

8.10 Definition of end of trial

The end of the study is defined as the date that the last patient has completed his/her last study visit, or one year following randomisation of this last patient.

Premature termination of the entire study

The sponsor has the right to terminate the study at any time. Reasons which may require termination include the following:

- Recommendation from the DSMC.
- New toxicological or pharmacological findings or serious adverse events invalidate the earlier positive risk-benefit-assessment.
- The incidence and/or severity of adverse events in the study indicate a potential health hazard caused by treatment with the study medication.

8.11 Withdrawal of participants

A patient may decide to withdraw from the study at any time without prejudice to their future care.

A patient may withdraw from the follow-up visits or they may withdraw their consent for any data collected to be used. Patients will be encouraged to allow data and samples that have been collected before withdrawal to be used in the analyses. However, if consent to use data/samples is also withdrawn, then these will be discarded. Patients withdrawing from the study will continue to be followed-up by their local team.

Patients who do not end up receiving the IMP or the planned index operation will stay on the study and will be followed up as in line with this protocol, unless consent is withdrawn (refer to section 14.3.2).

If a patient's treatment was stopped before being fully given for any reason the patient will be followed up as in line with this protocol unless consent is withdrawn.

The patient withdrawal will be recorded in the eCRF, including the reason for withdrawal if known.

Patients who withdraw from the trial will not be replaced, but their data will be included based on the intention-to treat principle (unless they withdraw consent for their data to be used). A 5% loss to follow-up has been allowed for.

8.12 Clinical Methods

The time schedule for the assessments and the time windows allowed are provided in the flow chart in section 2. The endpoints for statistical analysis are defined in section 14. The trial treatment should be administered as soon as possible after randomisation (preferably on the same day). All patients must be followed according to protocol, clinical status permitting, whether they receive their allocated trial treatment or not (unless the patient withdraws their consent for follow-up).

Assessments

Evaluation of efficacy is based on the following parameters

- Blood transfusion
- Change in haemoglobin
- Post Operative Morbidity Score (POMS)
- HRQoL questionnaires (EQ-5D-5L, MFI, and SQOM scores)

Post-Operative Morbidity Survey (POMS)

The POMS is an 18-item tool that addresses nine domains of morbidity relevant to the post-surgical patient: pulmonary, infection, renal, gastrointestinal, cardiovascular, neurological, wound complications, haematological and pain. For each domain either presence or absence of morbidity is recorded on the basis of precisely defined clinical criteria on days 3, 5, 7 and 14 after surgery (if the patient remains in hospital). See appendix B for details

Health Related Quality of Life Questionnaires (HRQoL)

(i) Single Question Outcome Measure (SQOM)

The single question outcome measure (SQOM) is scheduled to take place at baseline, pre-operatively, at eight weeks and six months after operation. See appendix A for details.

(ii) Multidimensional Fatigue Inventory (MFI-20)

The Multidimensional Fatigue Inventory is a self-report instrument. The current version contains 20 statements which cover different aspects of fatigue. The MFI-20 is scheduled to take place at baseline, pre-operatively, at eight weeks and six months after operation. See appendix C for details.

(iii) European Quality of Life – 5 Dimensions – 5 Levels (EQ-5D-5L)

The European Quality of Life – 5 Dimensions – 5 Levels questionnaire is a brief, utility-based HRQoL instrument. It consists of a health descriptive system and a visual analogue scale (EQ-VAS) for respondents to self-classify and rate their health on the day of administration of the instrument The EQ-5D-5L is scheduled to take place at baseline, pre-operatively, at eight weeks and six months after operation. See appendix D for details.

Health Economics Assessments

Data collected in the health related quality of life questionnaires (e.g. SQOM, MFI-20, EQ-5D-5L) will be considered as source data, i.e. additional source data verification will not be performed. These data will be handled as integral parts of the clinical trial.

Health resource utilisation

For all patients, resource utilisation in the study from baseline to end of their follow up will be documented prospectively using a mixture of CRF and patient diaries; the former will cover the period during which patients are admitted to hospital for their surgery; the latter will be completed by patients before and after their admission for surgery.

In the CRF we will collect data related to the treatment of anaemia or iron deficiency, related to the intake of study medication, and related to adverse events with a suspected relationship to the study drug. In addition we will collect data on length of stay in different settings (e.g. intensive care unit).

The patient diaries will cover three time periods: from study infusion until being admitted for surgery; from discharge from hospital after surgery until eight weeks post-surgery; and, from eight weeks post-surgery until six months post-surgery. Patients will be asked to record all types of health care use, irrespective of the underlying cause.

During each time period we will collect resource use data on hospital contacts, primary care and community care contacts, other NHS contacts, medications, and days off work. More specifically, we will collect the following information on hospital contacts:

- Inpatient stays
- Day cases
- Hospital clinic appointment not to have a scan
- Hospital clinic appointment to have a scan
- Accident and Emergency Department attendances

We will ask patients to record the dates of each contact and the hospital contacted.

We will collect the following information on primary care and community care contacts:

- GP visits at practice or health centre
- GP visits at home
- GP telephone contacts

- Nurse visits at practice or health centre
- Nurse visits at home
- Nurse telephone contacts

We will ask patients to record the dates of each contact.

We will ask patients to record other NHS contacts, listing the type of contact or the health care professional contacted, where the contact took place and the date of the contact.

We will ask patients to record the medications taken, including the name of the medication, the dosage taken each time, the number of doses taken each day, the number of days the medication is taken and whether the medication was prescribed by a doctor or nurse, or bought over the counter.

We will also ask patients to record:

- Whether or not they are working (in paid employment or self-employed)
- If they are working, how many days off work they have had to take due to their health.
- How many days friends and family have had to take off work as a result of the patient's health.

Safety assessments

Evaluation of safety is based on the following parameters

- Haemoglobin level change
- Duration of hospital stay and any readmission in the six month follow up period
- Any reaction or side effect from trial therapy
- Any reaction or side effect from whole blood or blood product, transfusion reaction
- Mortality
- e-GFR
- AEs: type, nature, incidence and outcome
- Vital signs (blood pressure, pulse rate and body weight)
- Physical examination
- Clinical laboratory panels (haematology, clinical chemistry, iron status, urinalysis)

Hospitalisation and mortality

The duration of hospital stay for the index operation will be documented in detail including pre-operative, intensive care and post-operative length of stay. Any other hospitalisations, operations or rehabilitation admissions as well as deaths during the study will be documented in detail, including reasons, and dates. The duration of stays will also be documented in the CRF.

Estimated glomerular filtration rate (e-GFR)

The Modification of Diet in Renal Disease trial (MDRD) formula will be used to determine e-GFR

$$\text{e-GFR} = 170 \times [P_{cr}]^{-0.999} \times [\text{Age}]^{-0.176} \times [0.762 \text{ if patient is female}] \times [1.180 \text{ if patient is black}] \times [\text{BUN}]^{-0.170} \times [\text{Alb}]^{+0.318}$$

Alb = serum albumin concentration (g/dL); P_{cr} = serum creatinine concentration (mg/dL); BUN = blood urea nitrogen concentration (mg/dL).

The e-GFR will be calculated by the local laboratory for each of the visits with clinical chemistry analyses.

Laboratory measurements

Haematological, clinical chemical and urinalysis parameters will be analysed at the local laboratory.

Blood for clinical chemistry and haematology does not have to be drawn under fasting conditions. Blood samples are to be handled and stored according to the instructions provided by the laboratory. A urine or serum pregnancy test (according to local practice) for females of childbearing potential will be performed on site, using validated standard methods, at screening.

Clinically relevant abnormalities detected by laboratory assessments are to be documented and followed up as adverse events. Definition of clinical relevance is up to the investigator's opinion.

Vital signs and 12-lead ECG

Vital signs include pulse rate, blood pressure and body weight at screening. Pulse rate and blood pressure must be measured with the patient in sitting position after at least 10 minutes of rest. The diastolic blood pressure must be read at the disappearance of sounds (Korotkoff phase V). If the disappearance of sound is not detectable, Korotkoff phase i.v. should be used for manual measurements; care must be taken not to miss a ‘silent gap’.

Body weight must be measured in underwear or light clothing without shoes. The same calibrated scale must be used throughout the study.

The ECG should be recorded as a standard 12-lead as per hospital protocol.

9 Name and description of all drugs used in the trial

9.1 Treatment of subjects

Investigational product/treatment

Active study medication

Medication name:	Ferinject®
Active ingredient:	Ferric carboxymaltose
Dosage form:	50 mg iron/ml solution for injection/infusion.
Appearance:	Dark brown, non-transparent aqueous solution

Excipients:	Sodium hydroxide, hydrochloric acid and water for injection
Strength/Packaging:	Each 2 ml vial contains 100 mg of iron as ferric carboxymaltose.
	Each 10 ml vial contains 500 mg of iron as ferric carboxymaltose.
Manufacturer:	Vifor Pharma UK Limited

Placebo – medication in control group

Medication name:	NaCl (normal saline)
Trade name:	NaCl
Active ingredient:	NaCl (normal saline)
Dosage form:	0.9% w/v NaCl as sterile solution in water for injection
Excipients:	Water
Strength/Packaging:	100 ml container with 100 ml normal saline
Manufacturer:	As per local hospital supplier

9.2 Concomitant medication

All medications being continued by a patient on enrolment and all medications given in addition to the study medication during the study are regarded as concomitant medications and will be documented by the patients in the patient diaries (these details will be transcribed into the eCRF), and in the patient's medical records. All changes to concomitant medication taken from enrolment until completion of the study will also be recorded (including changes in dose, change in formulation, starting or stopping medication).

If required, oral iron therapy should not be started for at least 5 days after an injection of Ferinject®.

Immunosuppressive therapy for organ transplant or renal dialysis are not allowed prior to the study. The same applies to erythropoietin and i.v. iron therapy, and patients taking these should be excluded from the study. However, should a patient receive these therapies or require Chemotherapy or Radiotherapy post IMP administration a gap of 24 hours is recommended, the PREVENTT trial office at UCL should be notified, and the patient will remain in the trial and followed up as per protocol.

10 Investigational Medicinal Product

10.1 Name and description of investigational medicinal product(s)

See section 9.1 for details.

10.2 Summary of known and potential risks and benefits

The side effects of the investigational medicinal product (ferric carboxymaltose) are minimal: the common side effects (>=1/100, <1/10) are headache, dizziness, hypertension, nausea, alanine

aminotransferase increased, hypophosphataemia and injection site reactions, as detailed in the summary of product characteristics: http://beta.medicines.org.uk/emc/, then search for Ferinject®. Please see the Safety Reporting SOP for the full list of side effects.

10.3 Description and justification of route of administration and dosage

The intervention patients will receive is an i.v. infusion, this will be shielded from vision (Opabag light protection bags for Ecoflac bottles) and administered through black tubing (Intrafix Air P with black pipe). Each injection will have a volume of 100ml N/saline with 1000mg iron. Placebo patients will receive an i.v. infusion, performed with the same method of blinding as described. Each injection will have a volume of 100ml N/saline.

Please see section 3.1 for reasons why intravenous iron and not oral iron is being used for this trial.

10.4 Dosages, dosage modifications and method of administration

The PREVENTT trial is comparing a one off infusion of intravenous iron with placebo.

Ferinject® group:
For all patients the total iron dose will be 1000mg as a one off infusion in 100ml n/saline administered over a minimum of 15 minutes.

Placebo group:
Placebo patients will receive the same volume of normal saline without the trial drug; 100ml n/saline administered over a minimum of 15 minutes.

10.5 Preparation and labelling of Investigational Medicinal Product

Packaging and labelling for study medication will be performed according to Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines. The study medication will be labelled in accordance with local study site regulations for investigational agents and with the provision contained in the Medicine Act 1968 (as current). The local pharmacy will be responsible for sourcing the trial products; the unblinded authorised person will be responsible for the preparation of the trial products and to maintain accountability in a blinded fashion as described in section 8.4. In instances however, where the reconstitution of the trial IMP occurs at a distant location to administration (for example at pharmacy) the prepared IMP will be labelled with the approved template provided by the sponsor.

No trial specific labelling will be used because the drug will be taken from general commercial stock for use in the trial and will not be segregated as clinical trial supply before use. Ferric carboxymaltose

(Ferinject®) is a marketed product and the trial will be using it broadly within its authorisation. There will be a blinded trial specific prescription form to be completed and signed by the Investigator. The unblinded staff (as delegated by local principal investigator) will complete with the concealed treatment allocation and collect the IMP ready for preparation and administration.

10.6 Drug accountability

A drug inventory/dispensing record will be maintained and updated by the authorised unblinded personnel for all drugs provided and dispensed at each study site. At the end of the study, one copy of the drug inventory/dispensing record should be sent to the sponsor, one kept in the central study file and one in the site files. An unblinded person at each study site is responsible for all drug supplies. Written documentation is mandatory.

The unblinded persons at the sites will keep adequate records of the receipt, preparation, administration and return or destruction of the study medication. They will conceal the accountability forms to blinded personnel. All data regarding the study medication must be recorded on the relevant forms provided by the sponsor. Any unused materials will be returned to site pharmacy and destroyed locally in line with site pharmacy procedures. A record of this destruction will be kept to document that return and destruction of materials is conducted by the unblinded persons at site.

10.7 Source of IMPs including placebo

The IMP and the placebo will be sourced from routine hospital stock and their handling, management and storage will be subject to standard procedures of the pharmacy.

10.8 Post-trial IMP arrangements

There will be no post-trial IMP arrangements as the treatment is a single dose. Therefore after the trial standard care will resume.

11 Recording and reporting of adverse events and reactions

11.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response in a subject to an investigational medicinal product which **is related** to any dose administered to that subject. *This includes medication errors, uses outside of protocol*

	(including misuse and abuse of product)
Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious adverse reaction **	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death • is life-threatening • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
Important Medical Event	These events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'.
Unexpected adverse reaction	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product set out: (a) in the case of a product with a marketing authorisation, in the summary of product characteristics for that product, (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
SUSAR	Suspected Unexpected Serious Adverse Reaction

** Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

11.2 Recording adverse events

All adverse events (AEs) will be recorded in the medical records following consent. Any AEs which occur within 30 days of the trial treatment will be noted in the CRF, recorded onto an AE form and reported to the LSHTM CTU.

If the investigator suspects that the subjects' disease has progressed faster due to the administration of ferric carboxymaltose, then he will record and report this as an unexpected adverse event.

Clinically significant abnormalities in the results of objective tests (e.g. laboratory variables, Xray, ECG) will also be recorded as adverse events, and if are not expected as part of disease or IMP, these will be recorded as unexpected.

All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

11.3 Assessments of Adverse Events

Each adverse event will be assessed for the following criteria:

11.3.1 Causality

The assessment of relationship of adverse events to the administration of ferric carboxymaltose is a clinical decision based on all available information at the time of the completion of the case report form.

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. In the case of discrepant views on causality between the local investigator and others, all parties will discuss the case to achieve a consensus opinion. In the event that no agreement is made, the MHRA will be informed of both points of view.

Category	**Definition**
Suspected	There is at least some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication).
Not suspected	There is little or no evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).

11.3.2 Expectedness

Category	Definition
Expected	An adverse event that is classed in nature as serious and which is consistent with the information about ferric carboxymaltose listed in the SmPC
Unexpected	An adverse event that is classed in nature as serious and which is not consistent with the information about ferric carboxymaltose listed in the SmPC

The reference document to be used to assess expectedness against the IMP is the SmPC (Summary of Product Characteristics) which can be found at http://beta.medicines.org.uk/emc/, then search for Ferinject®. The protocol will be used as the reference document to assess disease related and/or procedural expected events.

11.3.3 Seriousness

Seriousness as defined for an SAE in section 11.1.

Collection, recording and reporting of adverse events (including serious and non-serious events and reactions) to LSHTM CTU will be completed according to the Safety Reporting SOP.

11.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the hospital notes, noted in the CRF, and recorded in the LSHTM CTU's AE form. The AE's will be reported to the sponsor at least once per year.

The responsible investigator will complete the serious adverse event form and the form will be faxed to LSHTM CTU on 020 7927 2189, **within 24 hours** of his/her becoming aware of the event. The responsible investigator will respond to any SAE queries raised by LSHTM CTU as soon as possible.

All serious adverse events (SAEs) will be reportable to the LSHTM CTU (as delegated by the sponsor) up to 30 days post the trial treatment.

LSHTM CTU will notify the sponsor immediately (within 24 hours) of all SUSARs which are reported.

11.4.1 Notification of deaths

All deaths will be reported to LSHTM CTU (who will then inform the sponsor) irrespective of whether the death is related to disease progression, the trial treatment, or an unrelated event.

11.4.2 Reporting SUSARs

The LSHTM CTU will notify the main REC and MHRA of all SUSARs. SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after the LSHTM CTU has learned of them. Other SUSARs must be reported to the REC and MHRA within 15 days after the LSHTM CTU has learned of them.

Any SUSAR related to the IMP will need to be reported to the LSHTM CTU irrespective of how long after IMP administration the reaction has occurred (the CTU will forward all such reports to the sponsor).

In the event of a SUSAR the LSHTM CTU will be unblinded to the trial treatment the patient is receiving, as they are responsible for reporting SUSARs to the MHRA and ethics.

If the patient was receiving the active IMP then the unblinded SUSAR report will be submitted to ethics, and to the MHRA (via the eSUSAR website). The blinded SUSAR report will be forwarded to the CI and the local investigators.

Please see section 8.4 for further details of unblinding.

11.4.3 Development Safety Update Reports

The sponsor will provide the main REC and the MHRA with Development Safety Update Reports (DSUR) which will be written in conjunction with the chief investigator, LSHTM CTU and the Sponsor's office. The report will be submitted within 60 days of the Developmental International Birth Date (11th October) of the trial each year until the trial is declared ended. This will be done in accordance with the Safety Reporting SOP.

11.4.4 Annual progress reports

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given (5th November), and annually until the trial is declared ended.
The chief investigator in collaboration with LSHTM CTU will prepare the APR.

11.4.5 Pregnancy

Should a study participant become pregnant whilst undertaking the PREVENTT Trial, or aid in the conception of a child (i.e. fathering a child) whilst they are participating in the trial, the pregnancy and resulting child will be followed up for a period of no less than 18 months to verify whether a congenital anomaly or birth defect is present. See the Safety Reporting SOP for details.

11.4.6 Overdose

If a treatment overdose occurs (for example a prescribing error > 1000mg of Iron Carboxymaltose) this will be treated as a protocol violation and reported to LSHTM CTU by the unblinded staff. Treatment, if necessary, would be at the discretion of the treating physician. The LSHTM CTU would then inform the sponsor of any suspected overdoses, which would be an observation by the unblinded staff allocated to administer the treatment.

If an overdose results in a serious adverse event (SAE) then the overdose will need to be fully described on the SAE form.

Any patient who receives an overdose will not be withdrawn from the trial (unless they specifically ask to be) and will be included in the intention-to-treat analysis.

11.4.7 Reporting Urgent Safety Measures

If an urgent safety measure needs to be taken, the PI/LSHTM CTU shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA, the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

The guidance for urgent safety measures are on the MHRA website and these details will be followed: (http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARsandASRs/index.htm).

11.4.8 Notification of Serious Breaches

A “serious breach” is a breach which is likely to effect to a significant degree:
a) the safety or physical or mental integrity of the subjects of the trial;
Or
b) the scientific value of the trial.

The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of –
(a) the conditions and principles of GCP in connection with that trial;
or
(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The PI will notify LSHTM CTU immediately of any case where the above definition applies during the trial conduct phase. The CTU will then inform the CI and the sponsor immediately and will follow the Protocol Deviations and Violations SOP.

12 Data management and quality assurance

12.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.

The Case Report Forms (CRFs) will not bear the subject’s name or other personal identifiable data. The subject’s date of birth and trial identification number will be used for identification.

12.2 Data collection tools and source document identification

Trial data will be collected electronically at each participating centre and transferred electronically to a secure server at the trial coordinating centre at the London School of Hygiene & Tropical Medicine (LSHTM) via a secure web based system. Data collection and entry will be by trained investigators or research nurses at each site. Designated investigator staff will enter the information required by the protocol onto the eCRFs from the source documents. The following documents will be used as source documents:

- Medical Notes
- Drug charts
- Anaesthetic records
- Electronic hospital systems for laboratory results
- Patient diaries
- Validated Questionnaires (patients will complete paper copies and these will be the source documents, and delegated members of staff will transcribe the data into the eCRFs), e.g. EQ-5D-5L

Details of all study staff involved in data processing are contained in the site specific delegation log for each centre. Copies of these are held in the LSHTM PREVENTT trial master file. Paper Case Report Forms (CRFs) will be available for use by sites should they wish to use these in addition to the electronic version. The eCRF data will be used for the final analysis.

It will be the responsibility of each local investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

12.3 Data handling and analysis

The PREVENTT database application will be built on the popular open source web platform commonly referred to as LAMP (Linux, Apache, MySQL and PHP). It will be hosted on a centralised application server at LSHTM and accessed by users through a normal web browser (e.g. Internet Explorer or Firefox). Online forms (eCRFs) with built in validation checks are used by investigators or research nurses at participating centres to enter data. The system is blinded so that treatment groups are not revealed to users of the database application.

Data will be extracted from the system by exporting the database tables as CSV text files or other suitable format. Analyses will be conducted by the trial statistician in a statistical package (such as Stata) after importing the database tables. For unblinded analyses these files may be combined with the CSV file exported from the unblinded randomisation system.

eCRF requirements

Data will be entered at each local site using an electronic data capture (EDC) system and will be managed at the LSHTM CTU by the data manager or assistant trial manager. The data analysis will be performed by the trial statistician based at LSHTM CTU.

Electronic data will not be double entered but will be monitored by regular site visits and central statistical monitoring. Control checks will be programmed into the system before data entry begins and the EDC system will be capable of automatically flagging data points that are erroneous using range checks and validators (e.g. date of death occurs before date of birth), as well as flagging data points entered that are likely to be inaccurate or from a typing error (e.g. blood pressure of 80/120 instead of 120/80). The eCRF will also be set up so that data cannot be missed out or left blank. Any changes made to the electronic data are tracked to maintain an edit trail.

Patients will be expected to complete the HRQoL questionnaires at their hospital assessment visits. However if patients do not attend these appointments then blinded research staff will be responsible for contacting them and encouraging them to complete these, and also the patient diaries.

The data will be transmitted securely to the trial coordination centre, via password/PIN protected online data entry over an encrypted internet connection (SSL). This transfer will be in accordance with the Data Protection Act 1998, the UCL Information Security Policy and the Trust Information Governance Policy.

13 Record keeping and archiving

Archiving will be authorised by the sponsor following submission of the end of study report.

The Principal Investigators are responsible for the secure archiving of site specific essential trial documents. The Clinical Trials Unit at the LSHTM and the Chief Investigator will be responsible for the secure archiving of all other essential documents and trial database. All essential documents will be archived for a minimum of 5 years after completion of trial. The use of the data from the study will be controlled by the Chief Investigator and the Clinical Trials Unit at the LSHTM.

Destruction of essential documents will require authorisation from the sponsor.

14 Statistical Considerations

Timothy Collier (Medical Statistics Department, London School of Hygiene & Tropical Medicine) is the trial statistician who will be responsible for all statistical aspects of the trial from design through to analysis and dissemination.

14.1 Outcomes

14.1.1 Primary outcomes

The co-primary outcomes are:

- Risk of blood transfusion or death from randomisation until 30-days following the index operation.
- Blood transfusion rate (including repeat transfusions) from randomisation until 30-days following the index operation.

A blood transfusion event is defined as receiving any volume of one unit or more than one unit of packed red cells or any other blood product. Where more than one unit of packed red cells or any other blood product is intended to be received contiguously this is regarded as a single blood transfusion.

The blood transfusion rate is defined as the number of blood transfusions divided by the total patient time at risk.

14.1.2 Secondary outcomes

- Change in haemoglobin levels from randomisation to (i) day of index operation, (ii) 8-weeks post index operation and (iii) 6 months post index operation.

- Total number of units of blood or blood products cross matched, total number of packed red cells and any blood products transfused from randomisation to 30 days post index operation.

- Post Operative Morbidity Survey outcome at days 3, 5, 7 and 14 following the index operation. Outcomes will be presence of morbidity defined by the domains of the POMS e.g. gastrointestinal, cardiovascular.

- Health-related quality of life outcome:
    - Change in The Multidimensional Fatigue Inventory (MFI) questionnaire total score from baseline to the 10 day assessment and at 8 weeks and 6 months post operatively.
    - Change in European Quality of Life: 5 Dimensions-5 Levels (EQ-5D-5L) questionnaire total score from baseline to the 10 day assessment and at 8 weeks and six months post operatively.
    - Change in Single Question Outcome Measure (SQOM).

- Health economics outcome:
    - Health care resource utilisation from baseline to 6 months post-surgery.
    - Calculated NHS and societal costs from baseline to 6 months post-surgery.

  - Quality-adjusted life years from baseline to 6 months post-surgery.
  - Cost-effectiveness, measured in terms of the incremental cost per % reduction in patients receiving blood transfusions and incremental cost per quality-adjusted life year gained, using data from baseline to six months post-surgery.

- Safety and related efficacy outcomes:
  - Any reaction or side effect from trial therapy
  - Any reaction or side effect from whole blood or blood product, transfusion reaction
  - Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)
  - Length of hospital stay
  - Mortality at 8 weeks and 6 months post-operatively.
  - Readmission within 8 weeks and within 6 months of the index operation
  - Blood transfusion from randomisation to 8 weeks and 6 months post-operatively
  - Change in e-GFR
  - Vital signs
  - Laboratory data

14.2 Sample size and recruitment

14.2.1 Sample size calculation

The sample size requirement was calculated for the composite primary endpoint of blood transfusion or death by 30-days. The assumptions for the sample size calculations were based on data from the pilot study and observational trials and audits described above in section 3.1. The anticipated risk of blood transfusion in the control group is approximately 40%. Using a type-1 error rate of 5% and allowing for a 5% loss to follow-up, recruiting 500 patients (250 in each group) will give 90% power to detect an absolute reduction in risk of 14% (equivalent to a 35% relative risk reduction, RR=0.65) in the treatment group (or approximately 80% power to detect an absolute reduction of 12% (30% relative reduction)).

14.2.2 Planned recruitment rate

We anticipate recruiting 20 patients per month into the trial across the 20 centres (i.e. an average of 1 patient per centre per month). Taking into account the time it will take for centres to open, and the fact that not all centres will open at once, we estimate that we will be able to reach the target of 500 patients in 3 years.

14.3 Statistical analysis plan

A full statistical analysis plan (SAP) will be developed by the trial statistician. The SAP will be finalised before breaking the blind, and will include details on dealing with missing data/non-compliers and

withdrawals (expected to be minimal). Withdrawal/non-compliers will be included where possible (and permission to use data has not been withdrawn). A brief summary of the SAP is provided below.

14.3.1 Summary of baseline data and flow of patients

Baseline comparisons of the two treatment groups will be made using descriptive and summary statistics only, i.e. comparisons using hypothesis tests and p-values will not be carried out. Continuous variables will be summarised using means and standard deviations or median and interquartile range as appropriate. Categorical variables will be summarised using frequencies and percentages.

A Consort flow diagram will be produced to describe the passage of patients through the trial from screening, enrolment, randomisation, treatment, index operation, discharge, follow-up, and analysis.

14.3.2 Primary outcome analysis

The primary objective of the study is to determine the efficacy of intravenous ferric carboxymaltose (Ferinject®) compared to placebo on the number of patients receiving a blood transfusion or dying from randomisation until 30 days following index operation.

The primary efficacy analysis will be carried out on the full analysis set (FAS) based on an intention-to-treat principle. The FAS will consist of all patients randomised irrespective of whether or not they undergo the planned index operation.

Patients who don't receive the infusion or don't undergo the index operation will be followed as normal (unless the patients ask to be withdrawn from follow-up). The primary outcome is 30 days following index operation, so for those patients not undergoing surgery the outcome is 30 days post planned operation date (if the date of planned surgery is known) or 30 days post the 42 days (if it is not known).

A risk ratio and 95% confidence interval for the first co-primary endpoint (occurrence of blood transfusion or death) will be calculated. Absolute risk differences will also be presented.

The second co-primary endpoint (blood transfusion rates) will be analysed using a Negative Binomial regression model. This will take into account recurrent blood transfusions and allows for different patient tendencies (frailties) for repeat transfusions. Deaths will be adjusted for in the analysis.

14.3.3 Secondary outcome analysis

Analysis of secondary outcomes will be based on the FAS. For continuous outcomes mean differences and 95% CIs will be estimated using analysis of covariance. For binary outcomes risk ratios and risk differences and their 95% CIs will be estimated using binomial regression. For time-to-

event outcomes and rates hazard ratios will be estimated using Cox proportional hazards or negative binomial regression models as appropriate.

Health-related quality of life analysis

The focus will be to compare the HRQoL of Ferinject® patients with that of placebo patients. HRQoL and levels of functioning will be assessed using the MFI and EQ-5D-5L. For each instrument, baseline visit and later study visit will be scored separately as specified in the instrument's instructions. Then, changes from baseline will be calculated and compared between patients receiving intravenous ferric carboxymaltose (Ferinject®) and patients receiving placebo.

Health economics analysis

We will estimate cost and cost-effectiveness for the 'within-trial' period, up to six months post-surgery. Costs will be assessed from the perspective of the NHS and personal social services (PSS) and also from a societal perspective. Cost components included in the analysis will be as listed in section 8.12. The volume of resource use for each cost component will be measured directly in the trial from the CRF, and prospectively completed patient diaries, as described in section 8.12; unit costs will be taken from standard published sources.

The cost-effectiveness measures will be the incremental cost per % reduction in patients receiving blood transfusions and the incremental cost per quality-adjusted life year (QALY) gained. Costs will be measured as described. The % reduction in patients receiving blood transfusions is the primary outcome in the trial. QALYs will be calculated based on the health related quality of life (HRQL) and mortality data collected during the trial. HRQL will be measured according to the EQ-5D-5L. Patient-specific utility profiles will be constructed assuming a straight line relation between each of the patients EQ-5D-5L scores at each follow-up point. The QALYs experienced by each patient from baseline to six months post-surgery will be calculated as the area underneath this profile.

Multiple imputation by chained equations will be used to deal with missing EQ-5D-5L and resource use values. Subsequent analyses of imputed data will include variance correction factors to account for additional variability introduced into parameter values as a result of the imputation process.

Cost-effectiveness will be calculated as the mean cost difference between intervention versus placebo divided by the mean difference in outcomes (% blood transfusion/QALYs) to give the incremental cost-effectiveness ratio (ICER). Non-parametric methods for calculating confidence intervals around the ICER based on bootstrapped estimates of the mean cost and QALY differences will be used. The bootstrap replications will also be used to construct a cost-effectiveness acceptability curve, which will show the probability that use of iron is cost-effective at six months post-surgery for different values of the NHS' willingness to pay for an additional QALY. We will subject the results to deterministic (one-, two- and multi-way) sensitivity analysis.

Safety analysis

The safety analysis will be based on the safety set which is defined as all randomised patients according to the treatment received.

14.3.4 Sensitivity and other planned analyses

Additional supportive sensitivity analysis will be carried out on a per-protocol analysis set. Missing data arising from loss to follow-up will be accounted for using appropriate statistical methods.

All planned analyses will be described in detail in the SAP.

14.4 Randomisation methods

Patients will be allocated to treatment or placebo in a 1:1 ratio using minimisation (with a random element incorporated) taking into account age (<70 years/70+ years), baseline haemoglobin (<100/100+ g/L), centre and type of operation (major/major +/complex).

14.5 Interim analysis

Interim analyses for safety will take place in a schedule to be agreed with the DSMC. There will be no interim efficacy analyses.

14.6 Other Statistical Considerations

Any deviations from the final SAP will be clearly documented in the final report and the relevant publications.

15 Name of Committees involved in trial

Project Management Group (PMG)

The PMG will be made up of staff from the sponsor (UCL) and the CTU and will be responsible for the day to day running of the trial. It will meet weekly during the planning stages of the study and less frequently when the study is actually recruiting.

Trial Steering Committee (TSC)

The TSC includes members of the PMG, experts in the fields of surgery and haematology, as well as two lay representatives. They will meet at regular intervals, not less than once a year. The TSC, in the development of this protocol and throughout the trial, will take responsibility for:

- major decisions such as a need to change the protocol for any reason
- monitoring and supervising the progress of the trial

- considering recommendations from the DSMC informing and advising the PMG on all aspects of the trial

Full members

Chair: Andrew Bradbury (University of Birmingham)
Stefan Anker (Charite)
Trevor Burley (lay member)
Jane Keidan (King's Lynn)
Andrew Klein (Papworth)
Iain MacDougall (King's College)
Gavin Murphy (Leicester)
Toby Richards (UCL)
Isabel Unsworth (lay member)
Shelley van Loen (lay member)

Observers

Claire Atterbury (King's Lynn)
Tim Clayton (LSHTM)
Tim Collier (LSHTM)
Rosemary Knight (LSHTM)
Rebecca Swinson (LSHTM)
Laura Van Dyck (LSHTM)

Data Safety and Monitoring Committee (DSMC)

The DSMC includes three independent members including two medical experts and a statistician. Members of the DSMC cannot be investigators in the study or participate in other committees for this study. The role of the DSMC will be to monitor independently the safety of the study participants and to suggest amendments to this protocol if deemed necessary for reasons of patient safety or feasibility of study procedures. The DSMC members will meet early in the trial to establish a DSMC Charter. The chair of the DSMC reports to the chair of the TSC. To minimise potential bias, DSMC members will not have direct contact with the study site personnel or with study subjects.

The charter will cover:- criteria for early termination, stopping/discontinuation rules and breaking of randomisation code, what documentation will be completed if part/all of the trial is discontinued, and at what intervals the safety interim analysis will take place.

Membership

Chair: Lorna Williamson (Medical and Research Director, NHS Blood and Transplant)
Angela Crook (Senior Statistician, Medical Research Council Clinical Trials Unit)
John Pepper (Consultant Cardiac Surgeon, Royal Brompton)

Unblinded statistician

Joanna Dobson (LSHTM)

16 Direct Access to Source Data

The Principal Investigator/institutions will permit the sponsor, LSHTM CTU, the UK regulatory authority (MHRA), REC and local trust R&Ds to carry out trial-related monitoring, audits, REC review and regulatory inspections, by providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion and consent to provide access to their medical records will be obtained.

17 Ethics and regulatory requirements

The sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter, and submitted supporting documents have been approved by the appropriate regulatory body (MHRA) and a main research ethics committee, prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and or regulatory approval prior to implementation.

Before a site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee must apply for NHS permission from their Trust Research & Development (R&D) and be granted written permission. It is the responsibility of the Chief Investigator/ Principal Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see the safety reporting SOP for details of reporting urgent safety measures).

Within 90 days after the end of the trial, the sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the sponsor with a summary report of the clinical trial, which will then be submitted to the MHRA and main REC within 1 year after the end of the trial.

Amendments to the protocol have to be approved and signed by Trial Steering Committee and the Chief Investigator. All substantial protocol amendments must be submitted to the ethics committee for review and approval. Small administrative amendments may be made by the trial manager with approval from the TSC.

All investigators are to conduct the study in accordance with the current protocol except when it is necessary to deviate in order to protect the safety, rights, and welfare of patients (see section 11.4.7).

In the event that an isolated, unforeseen instance occurs resulting in a protocol deviation, the principal investigator is to document this deviation and notify the trial manager as soon as possible. In no instance should this increase the patient's risk or affect the validity of the study.

The study number, the title of the study, the progressive number and the date of the amendment must be reported in the first page of the document. Exhaustive justifications that motivate the amendment to the protocol should clearly be addressed in the document.

For changes that do not modify the study protocol content, e.g. a new monitor appointed, an administrative change can be made. This document has to be approved and signed by the trial manager.

18 Monitoring requirement for the trial

The conduct of the study will be supervised by specifically trained monitors from the LSHTM CTU. A trial specific monitoring plan will be established following a risk assessment and full details will be available in the Monitoring SOP. The trial will be monitored according to this agreed plan. Local investigators shall ensure that all study data are available for trial related monitoring, audits, and research ethics committee review.

19 Finance

The costs for the study itself are covered by a grant from the Health Technology Assessment Programme (HTA).

20 Insurance

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in

the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

21 Publication policy

All proposed publications will be discussed with sponsor prior to publishing, other than those presented at scientific forums/meetings. We will also follow the guidelines from the funders with regards to their publication policy.

22 Statement of compliance

The trial will be conducted in compliance with the approved protocol, the UK Regulations, EU GCP and the applicable regulatory requirement(s).

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Appendices

Appendix A – Single Question Outcome Measure (SQOM)

Appendix B – Post-Operative Morbidity Survey (POMS)

Appendix C – Multidimensional Fatigue Inventory (MFI-20)

Appendix D – European Quality of Life – 5 Dimensions (EQ-5D-5L)

Appendix A

Single Question Outcome Measure

The single question outcome measure (SQOM) is scheduled to take place at baseline, pre-operatively, at eight weeks and six months after operation. Before any other assessment, interview or procedure, the patient will be given a one-sheet letter that states the following information:

You are participating in a study to determine whether iron therapy injected in your blood vessels (which you may or may not have received) has any effect on your condition. Your doctor would like to know whether your medical condition has changed since the start of this study (<date completed by study personnel>).

Please indicate your answer to the following question using a cross:
Since I started my participation in this study, my medical condition:

- □ has much improved
- □ has (moderately) improved
- □ has improved a little
- □ is unchanged
- □ is a little worse
- □ is (moderately) worse
- □ is much worse

Please take your time to think about your answer and make sure you have placed only one cross. When you are finished, please return this sheet to your doctor or study nurse.

The SQOM score will be transferred to the CRF.

For patients who are hospitalised for any reason on the planned date of the final SQOM assessment any effort will be made to obtain the SQOM assessment. If the SQOM assessment cannot be performed on a patient in a hospital, he/she will be categorised as 'hospitalised' and ranked below 'much worse'. Patients who died on or before the planned date of SQOM assessment will be categorised as 'died' and ranked below 'hospitalised'.

The SQOM will be recorded ***before*** any other assessment, interview or investigational drug administration, so that the answers will not be influenced by study procedures.

Appendix B

Post-Operative Morbidity Survey (POMS)

The POMS is an 18-item tool that addresses nine domains of morbidity relevant to the post-surgical patient: pulmonary, infection, renal, gastrointestinal, cardiovascular, neurological, wound complications, haematological and pain. For each domain either presence or absence of morbidity is recorded on the basis of precisely defined clinical criteria on days 3, 5, 7 and 14 after surgery (if the patient remains in hospital).

Post-Operative Morbidity Survey (Bennett-Guerrero et al 1999; Grocott et al 2007)

Morbidity type	Criteria
Pulmonary	The patient has developed a new requirement for oxygen or respiratory support
Infectious	Currently on antibiotics and/or has had a temperature of >38°C in the last 24 hours
Renal	Presence of oliguria < 500ml/24hours, increased serum creatinine (>30% from pre-operative level); urinary catheter in situ
Gastrointestinal	Unable to tolerate an enteral diet for any reason including nausea, vomiting and abdominal distension
Cardiovascular	Diagnostic tests or therapy within the last 24 hours for any of the following: 1) new MI or ischaemia, 2) hypotension (requiring fluid therapy >200ml/hr or pharmacological therapy), 3) atrial or ventricular arrhythmias, 4) cardiogenic pulmonary oedema, thrombotic event (requiring anticoagulation)
Neurological	New focal neurological deficit, confusion, delirium or coma
Haematological	Requirement for any of the following within the last 24 hrs: packed erythrocytes, platelets, fresh-frozen plasma, or cryoprecipitate
Wound	Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms
Pain	New postoperative pain significant enough to require parenteral opioids or regional analgesia

POST-OPERATIVE MORBIDITY SCORE

Patient Date of Birth: **Study ID:** | | | | | |

Day: 3 5 7 14 (Please circle) **Date: ____ /____ /____**

Pulmonary	**Yes**	**No**
Has the patient developed a new requirement for oxygen?	☐	☐
Has the patient developed a new requirement for respiratory support?	☐	☐

Infectious		
Is the patient currently on antibiotics?	☐	☐
Has the patient had a temperature of >38° C the last 24 hours?	☐	☐

Renal		
Does the patient have any of the following?		
Oliguria (<500ml/d)	☐	☐
Creatinine (>30% from pre-op level)	☐	☐
Urinary catheter in situ	☐	☐

Gastrointestinal		
Unable to tolerate enteral diet (oral or tube feed)?	☐	☐
Is the patient experiencing nausea, vomiting or abdominal distension?	☐	☐

Cardiovascular		
Has the patient undergone diagnostic tests or therapy within the last 24 hours for any of the following?		
New MI	☐	☐
Ischaemia or hypotension (requiring drug therapy or fluid therapy >200ml/h)	☐	☐
Atrial or ventricular arrhythmias	☐	☐
Cardiogenic pulmonary oedema/new anticoagulation (warfarin/heparin/fragmin)	☐	☐

Neurological		
Does the patient have new confusion/delirium?	☐	☐
Does the patient have a new focal deficit or coma?	☐	☐

Wound complications		
Has the patient experienced wound dehiscence requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms?	☐	☐

Haematological		
Has the patient required any of the following within the last 24 hours?		
RBC	☐	☐
Platelets, FFP, cryoprecipitate	☐	☐

Pain		
Has the patient experienced surgical wound pain significant enough to require:		
Parenteral opioids?	☐	☐
Regional analgesia?	☐	☐

Ambulation:

Wheelchair ☐ Unaided ☐ Aided ☐ Crutches ☐ Zimmer ☐ Bedbound ☐

If POMS not done please tick one or more of the following. This information is used to ascertain why the patient is still in hospital:

1. Surgical drain insitu ☐ ☐
2. Social Reasons ☐ ☐
3. Equipment needed at home ☐ ☐
4. Mobility (ongoing physio & OT needs) ☐ ☐
5. Institutional failure (transport not booked, O/P appointment/follow-up not arranged) ☐ ☐
6. Delayed discharge (Lack of rehab or other bed) ☐ ☐
7. Other reason (state)

   .....

Appendix C

Description of the MFI-20

The Multidimensional Fatigue Inventory is a self-report instrument. The current version contains 20 statements which cover different aspects of fatigue.

These 20 items are organized in five scales. Each scale contains four items. The scales are balanced to reduce the influence of response tendencies as much as possible; each scale contains two items indicative for fatigue and two items contra-indicative for fatigue. Indicative items (e.g. "I tire easily") are formulated in such a way that a high score suggests a high degree of fatigue. In case of contra-indicative items (e.g. "I feel fit") a high score indicates a low degree of fatigue.

The respondent has to compare each of the 20 statements with how he or she felt lately. The choice for this time frame was made on the basis of the considerations that a) the instrument has to measure persistent fatigue contrary to acute fatigue resulting from effort and b) the instrument has to be sensitive to changes resulting for example from treatment. Because of the latter, the time frame can not be too long.

The response-scale consists of five boxes and runs from agreement with the accompanying statement "yes, that is true" to disagreement "no, that is not true". The respondent has to mark the box which intuitively corresponds most with his or her own condition.

MFI-scales:

General Fatigue	item: 1, 5, 12, 16
Physical Fatigue	item: 2, 8, 14, 20
Reduced Activity	item: 3, 6, 10, 17
Reduced Motivation	item: 4, 9, 15, 18
Mental Fatigue	item: 7, 11, 13, 19

2. Administration

The instrument can be presented as a written questionnaire, to be completed in the absence of a researcher or interviewer. The instructions for completing the questionnaire are printed on the instrument. The respondent has to read these instructions carefully. If the instrument is used orally in an interview situation it may be recommended that the interviewer reads the instructions out loud. It has to be stressed that all questions need to be answered and that the statements refer to the situation of the last few days.

3. Scoring of items and subscales

The scores per item run from 1 to 5. A higher score indicates more fatigue. Therefore, the items indicative for fatigue need to be recoded (1=5, 2=4, 3=3, 4=2, 5=1). This concerns item: 2, 5, 9, 10, 13, 14, 16, 17, 18, 19.

For each scale a total score is calculated by summation of the scores of the individual items. Scores can range from the minimum of 4 to the maximum of 20. The use of a total score over all 20 items is not recommended. After all, when a total score obtained by summation is interpreted as a global judgement concerning the degree of fatigue, the question remains as to whether the separate dimensions contribute to a similar degree to this global judgement. If, however, one is interested in just one score as an indicator of fatigue, we advise to use the score on the scale for General Fatigue.

4. Permission for using the Multidimensional Fatigue Inventory, 20-item version

The MFI-20 is copyrighted on the names of the authors.

For academic use, the MFI is available with no charges under the condition that:

- Investigators may be requested to share their results with the authors so that reliability and validity testing can proceed appropriately.
- In publications reference is made to:

Smets EMA, Garssen B, Bonke B and Haes de JCJM (1995). The Multidimensional Fatigue Inventory (MFI); Psychometric qualities of an instrument to assess fatigue. *Journal of Psychosomatic Research*, **39**, 315-325.

Commercial institutions, including pharmaceutical companies, will be requested a fee for the use of the instrument. The height of this fee and the conditions under which the instrument can be used will be stipulated in a declaration of agreement.

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MFI® MULTIDIMENSIONAL FATIGUE INVENTORY

® E. Smets, B.Garssen, B. Bonke.

Instructions:

By means of the following statements we would like to get an idea of how you have been feeling **lately**. There is, for example, the statement:

"I FEEL RELAXED"

If you think that this is **entirely true**, that indeed you have been feeling relaxed lately, please, place an **X** in the extreme left box; like this:

yes, that is true ☒1 ❑2 ❑3 ❑4 ❑5 **no, that is not true**

The more you **disagree** with the statement, the more you can place an **X** in the direction of "no, that is not true". Please do not miss out a statement and place only one **X** in a box for each statement.

1	I feel fit.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
2	Physically, I feel only able to do a little.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
3	I feel very active.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
4	I feel like doing all sorts of nice things.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
5	I feel tired.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
6	I think I do a lot in a day.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
7	When I am doing something, I can keep my thoughts on it.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8	Physically I can take on a lot.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
9	I dread having to do things.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
10	I think I do very little in a day.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
11	I can concentrate well.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
12	I am rested.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
13	It takes a lot of effort to concentrate on things.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
14	Physically I feel I am in a bad condition.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
15	I have a lot of plans.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
16	I tire easily.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
17	I get little done.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
18	I don't feel like doing anything.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
19	My thoughts easily wander.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
20	Physically I feel I am in an excellent condition.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true

Thank you very much for your cooperation

Appendix D

The EQ-5D-5L questionnaire is a brief, utility-based HRQoL instrument. It consists of a health descriptive system and a visual analogue scale (EQ-VAS) for respondents to self-classify and rate their health on the day of administration of the instrument The EQ-5D-5L is scheduled to take place at baseline, pre-operatively, at eight weeks and six months after operation. The descriptive system has 5 items/dimensions (i.e., mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Scoring methods have been developed to assign each of the possible health states a utility score in which 1 represents full health (no problems with all 5 items) and 0 represents being dead. EQ-5D-5L utility scores can be used to calculate quality-adjusted life-years (QALYs) for cost-utility analysis of health interventions. The EQ-VAS is a vertical, graduated (0–100 points) 20 cm 'thermometer', with 100 at the top representing 'best imaginable health state' and 0 at the bottom representing 'worst imaginable health state'. The EQ-VAS score can be used as a measure of clinical outcome, using individual respondents' own judgment.

The HRQoL instruments will be self-administered, i.e. completed by the patient using a separate patient questionnaire. The patient shall complete the questionnaire ***before*** any other assessment (exception: SQOM) or interview is carried out in a quiet place, so that the answers will not be influenced by the study procedures.

The patient questionnaires will be considered as source data, i.e. additional source data verification will not be performed. They will be handled as integral parts of the clinical trial.

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =