END OF STUDY REPORT

17 AUG 2016

IVICA - An open label study to determine the efficacy of ferric carboxymaltose in preoperative colorectal cancer related anaemia, and to develop biomarkers to predict response to this treatment strategy

Protocol Number	6 May 2015, Version 7.0
Chief Investigator	Austin Acheson
EudraCT Number	2011-002185-21
REC Reference Number	11/EM/0237
Sponsor Reference #	11GS005
Study Start Date	16th May 2012
Study End Date	3rd Dec 2014
Funder(s)	National Institute of Health Research RfPB Grant No: PB-PG-0110-21041
Sponsor(s)	Nottingham University Hospitals NHS Trust

Name of Test Drug/ Investigational Product	Ferric carboxymaltose (Ferinject®)
Indication Studied	Pre-operative colorectal cancer related anaemia

Report Author: Mr Oliver Ng — Date: 18 Aug 16

Chief Investigator Authorisation: Mr Austin Acheson — Date: 18TH AUG 2016.

Sponsor Authorisation: Maria Koufali — Date: 19th August 2016

This study was carried out in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) and Nottingham University Hospitals NHS Trust (NUH) Research and Innovation (R&I) Procedures

Contents

List of Abbreviations and Definition of Terms

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRC	Colorectal cancer
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
EC	Ethics Committee (see REC)
GCP	Good Clinical Practice
GP	General Practitioner
Hb	Haemoglobin
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Products
IRB	Independent Review Board
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NRES known as	National Research Ethics Service (previously COREC)
OXTREC	Oxford Tropical Research Ethics Committee
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
QoL	Quality of Life
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC/SPC	Summary of Products Characteristics
SOP	Standard Operating Procedure

SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSat	Transferrin saturation
TSG Oxford	Oxford Radcliffe Hospitals Trust / University of Trials Safety Group
WHO	World Health Organisation

1. Summary of Study

Background

Treatment of preoperative anaemia is recommended as part of Patient Blood Management aiming to minimise perioperative allogeneic red blood transfusion. No clear evidence exists outlining which treatment modality should be used. The study aimed to compare the efficacy of preoperative intravenous (IVI) and oral iron (OI) in reducing blood transfusion use in anaemic patients undergoing elective colorectal cancer surgery.

Methods

116 anaemic adult patients (haemoglobin <12 g/dL males and <11 g/dL females) with non-metastatic colorectal adenocarcinoma were recruited from eight UK centres at least 2 weeks preoperatively and randomised to receive OI (ferrous sulphate) or IVI (ferric carboxymaltose). Perioperative changes in Haemoglobin (HB), ferritin, transferrin saturation and blood transfusion use were recorded until postoperative outpatient review.

Results

The study reached its target for recruitment. There was no difference in blood transfusion use from recruitment to trial completion both in terms of volume of blood administered (P=0.841) and patients transfused (P=0.470). Despite this, treatment rises in HB were highest with IVI (1.55g/dL[0.9-2.6]; OI 0.5g/dL[-0.1-1.3], P<0.01), which was associated with fewer anaemic IVI patients at surgery (75% versus 90%, P<0.05). HB levels were thus higher at surgery with IVI (11.9g/dL[11.5-12.3]; OI 11g/dL[10.6-11.4], P<0.01) as were ferritin (P<0.01) and transferrin saturation levels (P<0.01).

Conclusions

IVI did not minimise blood transfusion requirement across the study but was more effective than OI at treating preoperative anaemia and iron deficiency in patients undergoing colorectal cancer surgery.

2. Objectives

The primary objective for the IVICA study was to examine the efficacy of intravenous iron (Monofer) in the reduction of rate and volume of blood transfusions. All clinical objectives were met. Research examining iron transport proteins and C-myc, NKD1 is still being analysed. Outcomes are listed as follows:

Primary Outcomes

1. Rate of allogeneic blood transfusion in participants with colorectal adenocarcinoma related pre-operative anaemia
2. Number of participants transfused
3. Total number of units of blood transfused

Secondary Outcomes

1. Levels of haemoglobin and haematinic markers (full blood count, ferritin, iron, transferrin, transferrin saturation, erythropoietin). These will be measured at a point before administration of intravenous iron or oral ferrous sulphate (at least two weeks pre-operatively), immediately pre-operatively, day two post-operatively and six to twelve weeks post-operatively.
2. Side-effects and reactions to intravenous ferric carboxymaltose administration
3. Peri- and post-operative morbidity and mortality
4. Post-operative length of stay
5. Quality of life as determined by the SF36, EQ-5D and FACT-An questionnaires.
6. Levels of hepcidin
7. Levels of iron transport proteins on colonic mucosal cells (DMT1, TFR1, Ferroportin, Ferritin)
8. Levels of C-myc and NKD1 on colonic mucosal cells

3. Ethical Review

We have conducted this study in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material was submitted to the Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval. We obtained initial approval from the above parties for the study. Some issues arose surrounding version control and amendment approval (see Section 9; protocol deviations). These were resolved and all substantial amendments were ratified in version 7 of the protocol.

Participant Confidentiality

The trial staff ensured that the participants' anonymity was maintained. The participants were identified only by initials and a participants ID number on the CRF and the electronic database. All documents were stored securely and only accessible by trial staff and authorised personnel. The study complied with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

Other Ethical Considerations

In this trial, both the intervention and control group received iron in order to treat the anaemia pre-operatively. Therefore, there was no non-treatment of the participants.

There were clear guidelines that the clinicians should adhere to when considering transfusion for the participants in this trial. However, the guidelines could be overruled in any situation where the clinician feels that the clinical situation requires a different management from that detailed in the guidelines.

This study did not involve any vulnerable participants and all participants had to be able to give valid, informed consent to be enrolled in this trial.

4. Investigational Plan

This study was a multi-centre, open labelled, randomised controlled trial comparing the effect of intravenous ferric carboxymaltose to the control, oral ferrous sulphate, in patients with colorectal adenocarcinoma related pre-operative anaemia. Each patient participated for a period of 10 to 20 weeks, depending on the time between their diagnosis and the planned operation date (see Figure 1 participant pathway). The participant was recruited after the MDT meeting confirming the diagnosis of colorectal adenocarcinoma and after ensuring that the patient was suitable for operative management (see Figure 2 for pathway). The participants were required to make one extra visit to the hospital apart from their normal routine surgical outpatient appointments. Participants were recruited at six sites and the whole study including randomisation, administration of drugs and follow-up was conducted at the respective sites.

Trial participants

116 participants with histologically confirmed colorectal adenocarcinoma who were awaiting surgery and had pre-operative anaemia as defined by a haemoglobin 1g/dL below the World Health Organisation threshold for normal haemoglobin (12g/dL for males and 11g/dL for females) were recruited.

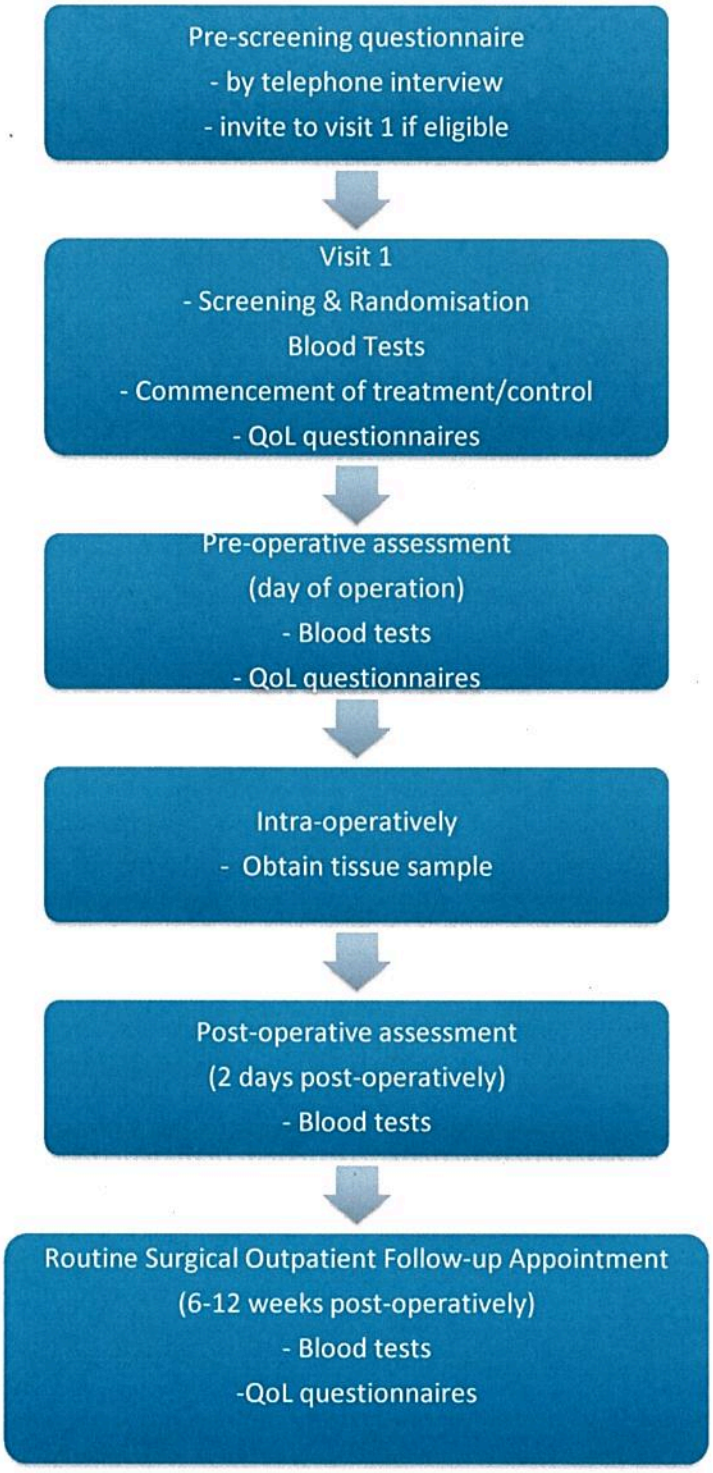

Figure 1 Flow diagram illustrating the visit pathway of a participant in the trial

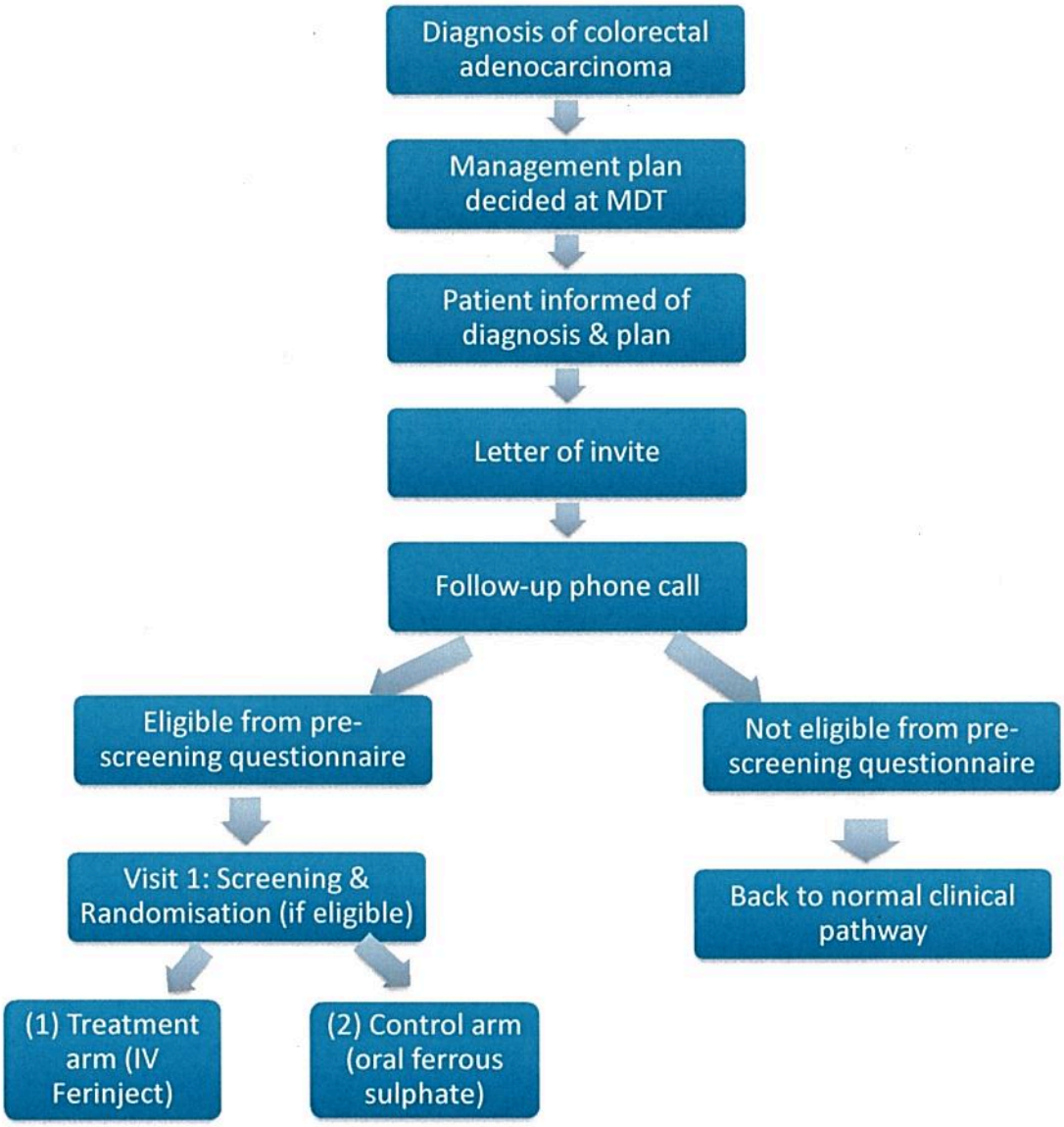

Figure 2 Flow diagram illustrating the diagnostic pathway of the patient diagnosed with colorectal cancer and the initial recruitment pathway

5. Selection of Study Population

Inclusion Criteria

- Participant was willing and able to give informed consent for participation in the study.
- Male or Female, aged 18+ years.
- Diagnosed with histologically proven colorectal adenocarcinoma.
- Anaemic at point of diagnosis of colorectal adenocarcinoma (Haemoglobin of less than 12g/dL for males and 11g/dL for females. Ferritin & MCV were measured but were not be used as an inclusion criteria)
- Medically fit for surgery.
- Date of planned surgery was ≥ 14 days from date of planned initiation of intervention (intravenous ferric carboxymaltose or oral ferrous sulphate).
- Able (in the Investigators opinion) and willing to comply with all study requirements.
- Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the study.

Exclusion Criteria

The participant could not enter the study if ANY of the following applied:

- Patients who following investigation do not have a histological diagnosis of colorectal adenocarcinoma
- Female participants who are pregnant, lactating or planning a pregnancy during the course of the study.
- Patients with evidence of iron overload or disturbances in utilisation of iron as stated in the product SPC.
- Previous gastric, small bowel or colorectal surgery (where ≥50% of stomach or terminal ileum has been resected)
- Current chemotherapeutic treatment.
- Known previous anaemia not attributable to colorectal carcinoma (i.e. anaemia in patients with well established, inflammatory disorders or chronic renal disease).
- Known haematological disease.

- Features necessitating urgent surgery (e.g. obstructive symptoms).
- Previous allergy to intravenous iron or related iron products.
- Significant symptomatic anaemia necessitating urgent transfusion (e.g. cardiovascular compromise)
- Patients who are unable to consent.
- Significant renal or hepatic impairment.
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.
- Donation of blood during the study.
- Participants who have participated in another research study involving an investigational product in the past 12 weeks
- Prisoners and minors (<18 years)
- Confirmed liver or lung metastases

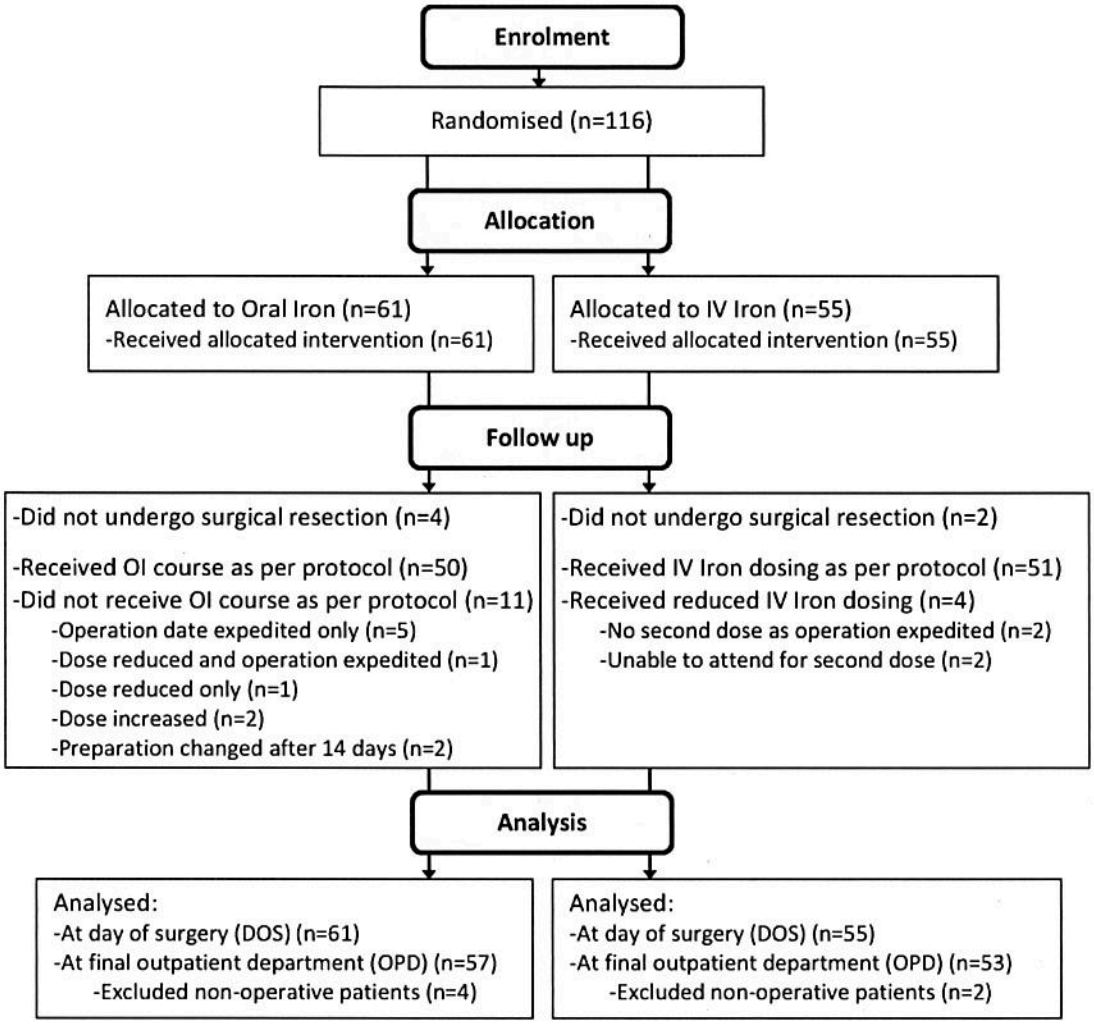

Figure 3 CONSORT diagram for IVICA study

6. Study Settings

The study was conducted at seven sites across the UK; Nottingham University Hospitals, Royal Wolverhampton Hospital, University Hospital Birmingham, Royal Derby Hospital, St James University Hospitals Leeds, University Hospitals of Leicester, Yeovil District Hospital and University Hospitals Bristol. St James University Hospitals Leeds did not recruit any patients. The investigators for this study are listed below:

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7. Interventions

Description of Study Treatment

The study intervention treatment was intravenous ferric carboxymaltose (Ferinject®). It was dosed using a fixed regime (see Table 1). A maximum of 1000 mg ferric carboxymaltose was given at one time. It was diluted with 250ml normal saline and infused over a minimum of 15 minutes. It was administered by a trained nurse or a trained doctor with constant supervision throughout the infusion. The control treatment was oral ferrous sulphate that was prescribed with a dosage of 200 mg twice a day for two weeks. The study treatments were randomly allocated but there was no blinding of the treatment.

Table 1 Fixed FCM dosing regimen (total iron dose)

Hb (g/dL)	BW<70kg	BW>70kg
>10	1000 mg	1500 mg
7-10	1500 mg	2000 mg

Compliance with Study Treatment

Compliance with the intervention (ferric carboxymaltose) was directly observed by the nurse or doctor administering the infusion. Participants self-administered the oral ferrous sulphate tablets. The participants were instructed to return all unused tablets of ferrous sulphate, when they attend the hospital for their operation. If there is a high level of non-compliance (<70%), the patient will be included in the trial under the intention-to-treat-analysis. The reasons for non-compliance were documented in the CRF.

Accountability of the Study Treatment

The study medication was partly supplied by Vifor© to each site's trials pharmacy and retrieved (any unused medication and used vials/packaging were returned to pharmacy) at the end of the study. All movements of study medication between Vifor© and the trials pharmacies was documented. The Investigator used a standard prescription form and a

member of the Investigator team collected the medication immediately after randomisation has been carried out over the phone.

Randomisation took place on visit 1 which was also the screening visit in order to minimise any inconvenience to patients who had to attend the hospital repeatedly. A small stock of both intervention and control treatment was kept at the trials pharmacy to allow immediate dispensing of the study treatment as necessary.

The participants were asked to bring all unused medication and used packaging back to the hospital when they came in for their operation, and this was returned to pharmacy.

Concomitant Medication

Throughout the study, Investigators prescribed any concomitant medications or treatments deemed necessary to provide adequate supportive care. Any medication, other than the study medication taken during the study was recorded in the CRF.

Participants who were on oral iron supplementation at time of recruitment to the trial continued taking this as prescribed to the point of randomisation.

For participants who were on oral iron supplementation at time of recruitment into the trial, if they are randomised into the intervention arm, stopped the iron tablets and were given intravenous iron. If they were randomised into the control arm, they stopped the previous oral iron supplementation and were prescribed with the form and dose of oral iron supplementation prescribed for the control group.

8. Changes in the Protocol from Initial Approval

A summary of changes in the study from that outlined in the original protocol is provided in Table 2.

Table 2 Amendment history

Amendment No.	Protocol Version No.	Date issued	Details of Changes made
Minor Amendment 1	V 3.0	06/09/11	Add exclusion criteria re: iron overload as per SPC
Minor Amendment 2	V 3.1	01/03/12	Update of dosing guidelines
Substantial Amendment 3 (a-g)	V3.2	05/03/2012	See a-g below:
(a) Value specified for definition of anaemia (b) Electrocardiogram assessment will not be performed. (c) Patients will be followed up at 6-12 weeks to coincide with routine clinical follow-up. (d) Addition of second quality of life questionnaire which will be retested at final review (e) IBC, IL-1 and IL-6 will no longer be measured (f) All females will have a pregnancy test (g) Hepcidin/erythropoietin level to be retested as part of planned blood tests at final review.			
Minor Amendment 4	V3.3	12/04/12	Extend age criteria from 18-75yr to 18+yrs

Minor Amendment 5	V 3.4	22/05/12	See a/b below
a) Page 22- clinical team will be made aware of any patient whom has failed to have had a recent FBC for retesting. b) Page 29- Vifor drug supply will be distributed between multiple sites.			
Minor Amend 6	V3.4	25/05/12	Sponsor request for PIS to be updated to reflect changes in protocol V3.4
Sub Amend 7	V4.0	09/10/2012	-Addition of a new site (Derby) -Additional QoL Questionnaire (FACT-An)
Major Amend (a-f)	V5	13/03/13	See a- below
a) Addition of new site: St James University Hospitals Leeds b) Addition of new site: University Hospitals of Leicester NHS Trust c) Addition of new site: Yeovil District Hospital NHS Foundation Trust d) Addition of new site: University Hospitals Bristol Foundation NHS Trust e) Page 17 - Clarification that tumour specimen will only be collected at Nottingham site f) Page 25 -Clarification of pregnancy testing - only to be performed in females under 55 years of age or currently menstruating			
Major Amendment (a-d)	Version 6	1/11/2013	

			(a) Page 22 Age limit re-submitted for MHRA review. This was reviewed by ethics committee in amendment 4 but was erroneously not submitted to MHRA at that point. (b) Page 23 - Clarification that patients with confirmed liver and lung metastases will be excluded. (c) Page 29 - Patients who are lost to follow up or who fail to undergo surgery will still have data to review in line with an intention to treat basis. (d) Page 37 - Clarification of composition of the Trial Management Group
Minor Amendment	V 6.1	10/4/2014	Page 28 Recording of preoperative urea value and intraoperative findings for calculation of operative risk
Major amendment	V 6.1/ 6.2	12 Aug 14	Oliver Ng added to investigators* *REC approved the addition of Oliver Ng on 08/Jan/2015 but without approving the associated study documentation. In addition there was a discrepancy with the version control of the protocol which read v6.1 (but should have been v6.2). REC approved the incorrect v6.1 of the protocol on 05/Jun/2015.
Major amendment (a-b)	V 7.0	6 May 15	
			(a) Correct version control of addition of Oliver Ng as an investigator. (b) Page 16 - Addition of P selectin test

9. Protocol Deviations

In total 71 protocol deviations were reported during this study. The most common deviations reported were bloods not taken or not processed by the hospital laboratories (24) and QoL questionnaires not being completed (11). No deviations affected data integrity and missing data were considered and described in the analysis. A number of deviations related to SAEs were reported (9), due to reporting of SAE outside of the 24 hour timeline (6) or on an out of date version of the SAE proforma (3). Of these, one was related to the IMP, a rash and mild swelling around eyes during Ferinject infusion due to allergic reaction. It resolved the same day and patient went home approximately 1 hour later. This was categorised as related and expected. No serious breach occurred requiring reporting to the MHRA. One deviation related to the approval of amendments and documents whereby REC approval was granted for amendments but subsequent NHS permissions was not granted. This was rectified and risk assessed. No risk to patient safety or the scientific value of the study were identified. Finally, monitoring queries from Birmingham were not addressed after the final close out visit due to no staff. PI and CI concluded that this did not affect patient safety or data integrity.

Site	No of deviations	Details
Nottingham	25	SAE reporting (7) Bloods not taken/processed (7) Surgery cancelled/delayed (2) Follow up not complete (5) QoL questionnaires incomplete (3) Amendment approvals (1)
Leeds	0	
Wolverhampton	12	QoL questionnaires incomplete (5) Bloods not taken/processed (5)

		Drug administration (1) Inclusion criteria (1)
Bristol	4	Clinical exam not performed (1) Bloods not taken/processed (2) Follow up timing (1)
Yeovil	4	Drug administration (1) Bloods not taken/processed (1) Drug administration (2)
Derby	19	QoL questionnaires incomplete (3) Bloods not taken/processed (9) Clinical exam not performed (2) Baseline height and weight (1) Vital signs not recorded (1) Follow up timing (1) SAE reporting >24h (1) GP letter (1)
Birmingham	7	Bloods not taken/processed (5) SAE report >24h (1) Monitoring queries (1)

10. Patient Information & Consent

Informed Consent

A named member of the research team took consent from the participant once they had ascertained that the patient fits the eligibility and inclusion criteria.

The participant personally signed and dated the latest approved version of the informed consent form before any study specific procedures were performed.

Written versions of the participant information and Informed consent (see appendix) were presented to the participants detailing the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It was clearly stated that the participant was free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant was allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they would participate in the study. Written Informed Consent was then obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent was suitably qualified and experienced, and had been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent was given to the participants. The original signed form was retained at the study site. A copy of the signed Informed Consent was placed in the participant's medical notes.

11. Randomisation

Randomisation and Codebreaking

Randomisation was carried out on eligible patients at the time of the screening visit (Visit 1). Randomisation was based on an online randomisation service that was provided by the Clinical Trials Unit, University of Nottingham. Patients were randomised on a 1:1 ratio between (i) oral ferrous sulphate, or (ii) intravenous ferric carboxymaltose, using computer generated variable blocked randomisation methods prepared by the trial statistician. This study was an open label study and as such there was no formal blinding of the agents used. However, bias was minimised between the two groups by the randomisation process. The corresponding information was recorded on the CRF by the investigator.

12. Safety Reporting

The laboratory tests conducted, their schedule, the methods for measuring them are described below (Table 3). 55 patients (35 male) received IV iron and 61 patients (37 male) received oral iron. Mean age was 73.8 years (67.4-78.6 IQR) for the IV iron group and 74.7 (67.9-80.8 IQR) for the oral iron group. Patients in the IV iron group received ferric carboxymaltose 1000 mg (n=10), 1500 mg (n=30) or 2000 mg (n=15), in one dose (1000 mg group) or two doses (1000 mg plus 500 mg or 1000 mg). Those in the oral iron treatment group received oral ferrous sulphate 200mg twice daily and adherence to treatment was 90% of patients (n=50) who did not have the date of surgery moved (n=55). Two patients (3%) reduced the dose due to drug side effects (dyspepsia and constipation), one of whom also had their operation date moved forward. Two patients increased the dose to three times daily on clinician request and two changed the drug oral formulation to ferrous fumarate 210 mg after 14 days. No patients randomised to oral iron went on to receive IVI.

Table 3 Assessment schedule

Visit	Location & Time	Assessments
Visit 1	Screening >2 weeks before operation date NUH clinic	Eligibility check Informed consent taken Recording of medical & drug history, height, weight and blood pressure Baseline blood tests (Full blood count (FBC), CRP, erythropoietin, iron, transferrin, transferrin saturation, hepcidin) Randomisation & dispensing of trial medication Quality of life questionnaires.
Pre-op	Morning of operation date Pre-op clinic	Repeat quality of life questionnaires Blood tests (FBC, CRP, erythropoietin, iron, ferritin, transferrin, transferrin saturation, hepcidin) Assessment of compliance with medication (if in control arm)
Intra-op	Operating theatre	Obtain sample of tissue from resection specimen

Post-op day 2	Day 2 post-op Inpatient ward	Blood tests (FBC, CRP, erythropoietin, iron, ferritin, , transferrin, transferrin saturation) Identification of any peri-operative blood transfusion
Post-op	Week 12 post-op NUH clinic	Blood tests (FBC, CRP, erythropoietin, iron, ferritin, transferrin, transferrin saturation, Hepcidin) Final Quality of life questionnaires Identification of any post-operative complications

Reporting Procedures for All Adverse Events

All AEs occurring during the study observed by the investigator or reported by the participant, whether or not attributed to study medication, were recorded on the CRF. The following information was recorded: description, date of onset and end date, severity, assessment of relatedness to study medication, other suspect drug or device and action taken. Follow-up information was provided as necessary.

AEs considered related to the study medication as judged by a medically qualified investigator or the sponsor were followed until resolution or the event was considered stable. All related AEs that resulted in a participant's withdrawal from the study or were present at the end of the study, were followed up until a satisfactory resolution occurred.

It was left to the investigator's clinical judgment whether or not an AE was of sufficient severity to require the participant's removal from treatment. A participant could also voluntarily withdraw from treatment due to what he or she perceived as an intolerable AE. If either of these occurred, the participant underwent an end of study assessment and was given appropriate care under medical supervision until symptoms ceased or the condition became stable.

The relationship of AEs to the study medication was assessed by a medically qualified investigator. No pregnancy occurred during the clinical study.

Reporting Procedures for Serious Adverse Events

The Nottingham University Hospitals Trust undertook an immediate review of reported SAEs for the study. All SAEs were to be reported to R&I within one working day of discovery or notification of the event (see Protocol Deviations for exceptions). No SUSARs required reporting to the Competent Authorities MHRA and the Research Ethics Committee concerned. No fatal or life-threatening SUSARs occurred. In addition to the expedited reporting above, the CI submitted throughout the clinical trial a safety report to the Competent Authority (MHRA in the UK and Ethics Committee).

Serious adverse events

During the study there were 34 reported serious adverse events resulting in 5 deaths, all unrelated to the IMP. One adverse event was related to the IMP and resulted in a <24 hour self-limiting allergic reaction during Ferinject administration that did not require hospitalisation, did not result in any long term disability and was not life threatening. This is a recognised side effect of the IMP described in the manufacturers SmPC.

The most common SAEs reported were gastrointestinal (15), respiratory (7) and wound infections (3) and were all recognised complications of either bowel cancer or the surgical treatment of bowel cancer.

In summary, no new safety issues regarding the IMP have been identified in this study.

Site	No of SAEs	Details
Nottingham	19 (0 related to IMP, 4 deaths)	Gastrointestinal (9) - perforation/leak 4, ileus/obstruction 3, bleed 1, disease progression 1 Respiratory (4) - pneumonia/LRTI 4 Sepsis (1) - generalised sepsis Cardiovascular (2) - MI x 2 Wound (1) - wound infection Vascular (1) - ruptured AAA Genito-urinary (1) - UTI
Leeds	0	
Wolverhampton	3 (0 related to IMP, 1 death)	Gastrointestinal (2) - diarrhoea, bowel obstruction. Cardiovascular (1) - cardiac arrest following epidural leading to death.
Bristol	0	
Yeovil	0	

Derby	9 (0 related to IMP)	Gastrointestinal (4) - enterocutaneous fistula, ileus x 2, anastomotic leak Respiratory (1) - lower respiratory tract infection Wound (2) - surgical site infections x 2 Renal (1) - acute kidney injury Vascular (1) - Left brachiocephalic pseudoaneurysm
Birmingham	3 (1 related to IMP)	Respiratory (2) - hospital acquired pneumonia x 2 Allergic (1) - rash and swelling around eyes following administration of IMP.

13. Laboratory Evaluations

Not applicable.

14. Statistical Analysis

Hypothesis

The primary hypothesis tested was that intravenous iron will decrease transfusion rates. The mean change in transfusion rates was reported. Paired non-parametrically distributed data was compared with Wilcoxon signed rank test. Non- parametrically distributed independent data was compared with Mann-U Whitney test. Parametrically distributed data and mean transfusion volume administered were assessed with Students-T test. Two-tailed Chi-squared test was used to assess differences in categorical data. Statistical analysis was performed using SPSS® version 22 (SPSS, Chicago, Illinois, USA).

An analysis of the factors and covariates which influenced response including baseline demographic and clinical factors was investigated using logistic regression analyses. Baseline (serum iron parameters) covariates were included in this analysis to assess their influence in predicting response. The underlying assumption of linearity between baseline continuous covariates (including serum iron parameters) and response was assessed and if required appropriate non-linear transformations applied to the covariate data.

Quality of life was analysed using longitudinal statistical methods comparing treatment groups with appropriate consideration given to missing data due to dropout and death. Questionnaire responses were combined and transformed into dimension scores. Standardised area under the curve analysis was used to assess mean observed symptomatic and functional QoL over a period of 8 weeks from randomisation whilst minimising multiple testing.

Power calculation

The primary hypothesis to be tested is that intravenous iron will decrease transfusion rates. To detect an effect size of one unit (SD 1.6) of blood transfused, a 90% power (alpha 0.05), 58 patients will be required in each arm of the study. This would be considered a clinically significant effect and is consistent with previously published data [25]

Level of Statistical Significance

The level of statistical significance to be used was $p<0.05$.

Procedure for Accounting for Missing, Unused, and Spurious Data.

All attempts were made to avoid and to recover any missing data. In the event of missing data being unrecoverable, a repeat sample was taken in the case of a blood test. If this was not possible (e.g. due to interventions being commenced), the participant was excluded from the trial. Any unused or spurious data was recorded in the CRF in the section for additional information.

Inclusion in Analysis

All randomised patients were included in the analysis on an intention-to-treat basis.

15. Main Findings of the Study

General

There were no demonstrable differences between the two groups in demographic variables as summarised in Study OI treatment protocol was adhered to by over 90% of patients (n=50) who did not have the date of surgery moved (n=55). Two patients (3%) reduced the dose due to drug side effects (dyspepsia and constipation), one of whom also had their operation date moved forward. Two patients increased the dose to three times daily on clinician request and two changed the drug oral formulation to ferrous fumarate after 14 days. No patients randomised to OI went on to receive IVI.

In the IVI group, 82% of patients received two doses of IVI (n=45). The total dose administered was thus 2000mg in 27% (n=15), 1500mg in 55% (n=30) and 1000mg in 18% (n=10). Of those receiving 1000mg, four were calculated as needing a second dose but either had their operation date moved forward (n=2) or were unable to attend the required appointment (n=2).

Post-infusion (<24 hours) headache was the most frequent complication of IVI reported (n=3). Only one significant adverse drug reaction (ADR) was experienced; a rash which required intervention in the form of oral antihistamine medication.

Four patients had their operation cancelled on the day of surgery due to deterioration in their clinical condition, one patient died during induction of anaesthesia and the operation was abandoned at initial laparotomy in one patient due to finding inoperable disease. Consequently 110 patients underwent resectional surgery. Study operative details are illustrated in Table 4.

Table 4. Median duration of study iron treatment was 21 days in both groups (OI, IQR 15-33; IVI IQR 15-34, P=0.748), although eleven patients failed to meet the desired fourteen day treatment period. Of these patients (OI, n=6; IVI, n=5, P=0.891), three had their date of operation moved due to a change in clinical condition, and eight due to an earlier date becoming available after recruitment to the study. Median time to outpatient department was comparable between groups, at 97 days (IQR 56-135) for OI and 87 days (IQR 53-145) for IVI (P=0.849).

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Table 4 Patient demographics

	Oral Iron	IV iron
n	61	55
General Demographics		
Males	37	35
Females	24	20
Age years (IQR)	74.7 (67.9-80.8)	73.8 (67.4-78.6)
Height m (95%CI)	1.67 (1.64-1.7)	1.68 (1.66-1.71)
Weight kg (95%CI)	72.78 (68.7-76.9)	79.01 (74.9-83.2)
Screening details:		
Patients receiving oral iron at recruitment	30	25
Median number of days of iron pre-treatment if applicable (IQR)	20 (6-34)	26.5 (13-37)
Pre-operative Risk Assessment:		
ASA □2	43	30
ASA □3	18	25
Median CR Possum mortality score at Recruitment % (IQR)	3.58 (2.58-9.29)	3.48 (2.58-6.62)
Tumour Details:		
Tumour T Stage: T□ 2	5	8
Tumour T Stage:T3 & 4	52	45
Median Tumour size mm (IQR)	45 (35-60)	41 (34-55)

Outcome Data

Two patients received a total of 3 units of blood preoperatively, both within the OI group. Six patients were transfused blood in each group on the day of surgery (P=0.894), with no difference in mean volume transfused (P=0.863). From recruitment until the end of the study, there was no difference in mean transfused volume (OI, 0.632u [95%CI 0.258-1.006]; IVI, 0.698u [95%CI 0.151-1.246]; P=0.841) or number of patients transfused (OI, n=14; IVI, n=10; P=0.470).

Haemoglobin levels at recruitment were comparable between groups, yet were significantly higher in the IVI group at surgery (Figure 4). This equated to a significantly greater median treatment rise in haemoglobin (P<0.01) for IVI (1.55g/dL [IQR 0.9-2.6], P<0.01) compared to OI (0.5g/dL [IQR -0.125-1.325], P<0.01). At surgery, 55 patients (90%) in OI remained anaemic, which was significantly higher compared to the 41 patients (75%) in IVI (P<0.05). Furthermore, 30 patients within the OI group required post-operative iron supplementation which was significantly higher than the IVI group (n=4, P<0.01).

Ferritin levels were significantly higher in the IVI group at surgery (OI, 27.5µg/L [IQR 17-51.5]; IVI, 558 µg/L [IQR 330-1085]; P<0.001), despite parity in recruitment ferritin levels (P=0.224). This same relationship was evident with TSAT levels at surgery (OI, 9% [IQR 5-14]; IVI, 19% [IQR 16-29]; P<0.001), despite TSAT levels being significantly lower in the IVI group at recruitment (P<0.05).

Post-operative length of stay was 6 days for both groups (OI, 6 days [IQR 4-9]; IVI [IQR 5-10], P=0.95). There were 9 deaths in the entire cohort over the duration of the study period (OI n=4; IVI n=5) which was not statistically different between groups (P=0.87). The same was true of 90 day mortality (OI n= 2; IVI n=3; P=0.91). There was no difference in grade of complication severity between groups from recruitment to outpatients (P=0.995) or in complication rate over the same period (P=0.30). The same was true for infective complication grade (P=0.083) and rate (P=0.09).

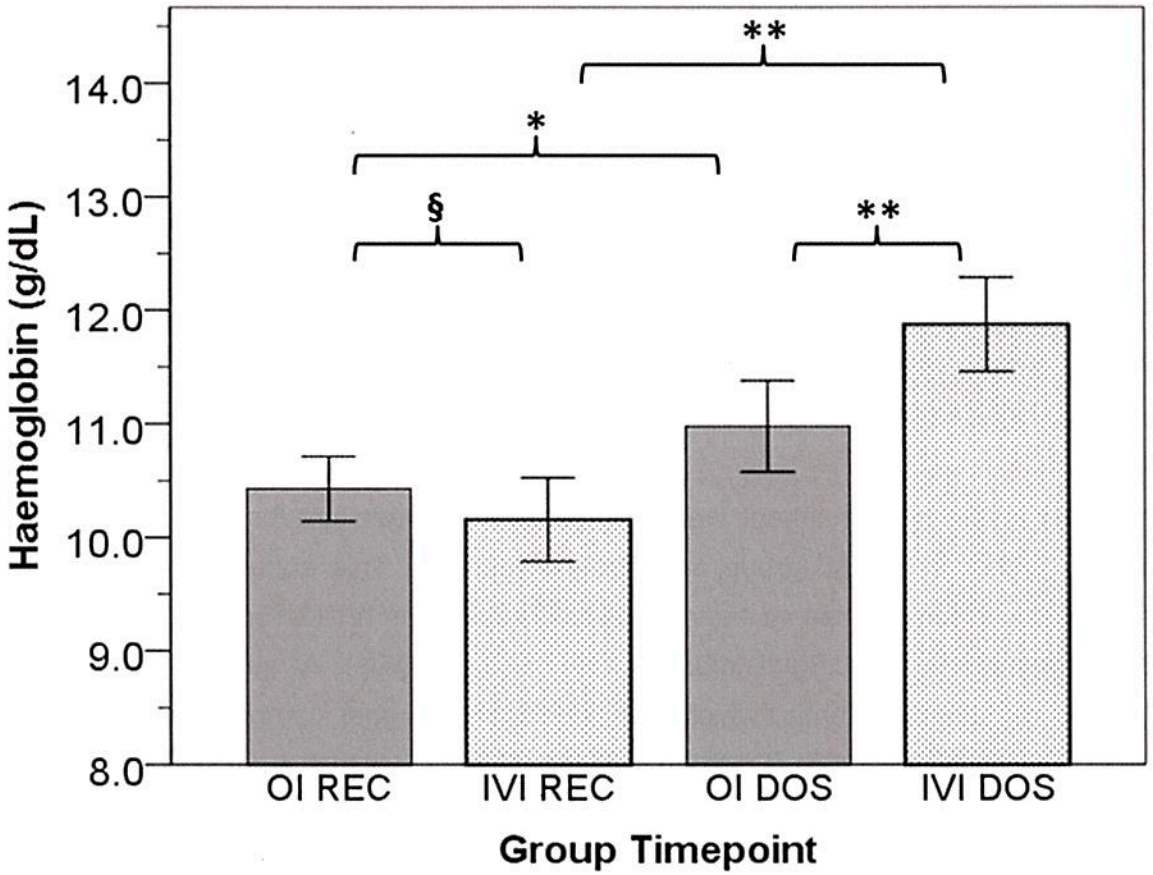

Figure 4 Changes in haemoglobin by time point and treatment group

The overall safety evaluation of any test drugs or IMP should be discussed with particular attention being paid to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal and death.

Safety

The known risks of the drugs used (ferric carboxymaltose and ferrous sulphate) have not changed with the current findings of this study. They continue to appear safe and efficacious in this setting.

16. Conclusions

Patient Blood Management aims to improve patient outcome by minimisation of allogeneic red blood cell transfusion use, the requirement of which is directly linked to preoperative anaemia. The primary aim of this study was to review if IVI would reduce blood transfusion use as a consequence of a more efficacious treatment of anaemia. Although the current data did indicate that IVI was more efficacious at treating preoperative anaemia in this patient group, this did not translate to a significant difference in blood transfusion use.

It was also of interest that no differences were evident in postoperative patient outcomes. Severity of preoperative anaemia has previously been linked with direct increases in mortality, morbidity and length of stay following surgery. It would thus be expected that the more efficacious treatment of anaemia with IVI may confer greater benefits on those outcomes measures. The non-inferiority of IVI in this context must also be noted. The current study demonstrated that IVI can be safely administered to this patient cohort, and did not identify any severe ADR historically associated with older preparations. Furthermore, infective complication rates were comparable which has been identified as a potential limitation to IVI use.

This is the first study to randomise anaemic colorectal cancer patients to receive either oral or intravenous iron in the preoperative phase, and is currently the largest clinical trial to prospectively evaluate OI and IVI in surgical patients. One key limitation of the study was that overall transfusion use was lower than anticipated which may render the study vulnerable to Type II error. Previous studies have identified perioperative transfusion rates in untreated anaemic colorectal cancer patients in the order of 50%, with similar figures for those treated with oral iron. The lower number in the current study may be reflective of a higher uptake of laparoscopic surgery than previous trials indicating the key role that blood loss has in the need for perioperative transfusion.

Although IVI was demonstrated as a superior treatment for iron deficiency in the current study, it is possible that the duration of preoperative therapy was insufficient to allow IVI to have maximal effect on haemoglobin levels which could have impacted on blood transfusion use. Preclinical and clinical studies have indicated that maximal IVI utilisation takes longer than the 21 day treatment period used in the present study. If IVI could be administered earlier in clinical practice, for example as soon as anaemia is identified, a greater rise in haemoglobin may become apparent with potential further reductions in blood transfusion use. In contrast, it could be argued that the effect of oral iron within this study is the maximal which may be seen in clinical practice. The adherence rate was higher than is generally expected and would be expected to decline with longer treatment periods.

In summary, no overall benefit was seen with IVI compared to OI in reducing allogeneic red cell blood transfusion use. However, IVI appears more effective than OI at treating anaemia and iron deficiency in anaemic patients with CRC. This may not have had clinical effect on transfusion use due to the duration of study treatment, but given the significant cost differences between these treatments and simplicity of OI administration, further study may be required before IVI is used as first line treatment in this setting.

17. Future Research

The main aim of this trial was to compare the efficacy of IVI and OI in the preoperative management of anaemia in patients with CRC using mean volume of ARBT administered as the primary endpoint. The current data failed to identify any difference between groups in this measure, or the number of patients transfused, when considered at key time points from surgery to outpatient follow-up.

It is important to recognise that despite the IVI and OI groups being very similar (Table 4), a notable difference was seen in the number of patients with significant cardiac or respiratory comorbidity. This is a major factor frequently used in the clinical decision to administer ARBT, hence it is possible that the patients in the IVI group were more likely to receive ARBT.

Furthermore, although the mean HB levels at REC were comparable between groups, the number of patients with more severe anaemia was higher in the IVI group. This may further indicate that there were more patients at high risk of requiring ARBT in the IVI group.

It is also of importance that subgroup analysis did identify transfusion differences between groups. The mean transfusion volume and number of patients transfused from REC to the end of the 7th postoperative day was lower in the IVI group when reviewing operative patients who experienced less than 1.5L intraoperative blood loss.

It is of note that certain subgroups of patient also benefitted from IVI over this period. There was a reduction in the transfusion rate of patients with moderate and severe anaemia at REC in the IVI group. Previous studies have indicated that the lower the HB is on the DOS, the higher the likelihood of ARBT requirement. It is possible that IVI is more effective at reducing the severity of anaemia, and thereby placing patients into an HB range that carries a "standard" risk of ARBT use which is comparable to non-anaemic patients.

HB levels at surgery of those transfused within the study were lower than those patients not transfused irrespective of study treatment. If IVI is more efficacious at raising HB levels preoperatively, it would indicate that the risk of transfusion requirement could be reduced to a greater degree with this treatment.

It is possible that the study failed to identify transfusion differences over a longer period due to the randomisation of more patients to the OI group. The study had been powered to recruit a minimum of 55 patients to each arm which was achieved at recruitment. However, when considering patients undergoing surgery, the IVI group did fall below this threshold by 2 patients due to cancellation of operations. Consequently, the IVI group was potentially underpowered for the primary endpoint. This vulnerability is exemplified by the fact that over half the units of ARBT transfused to this group were to just 2 patients with postoperative complications.

It is also possible that the duration of preoperative therapy was insufficient to allow IVI an optimal time period to take effect. Although, the current study identified a significant improvement with IVI in the treatment of iron deficiency measured in terms of TSAT and ferritin, it is possible that the median 21 day treatment period was insufficient for a maximal effect.

In the current study, the use of laparoscopic surgery (LS) was high reflecting changes in trend within CRC surgery. It is relevant, that although the use of LS was comparable between groups, the overall blood loss was lower across the study in patients undergoing LS, as was the use of ARBT. Such findings are consistent with previous trials (Kiran et al., 2004), hence it is possible that the high LS uptake reduced overall ARBT use rendering any inter-group differences less evident.

The transfusion rate and mean volume of ARBT administered to both groups was lower than control data and previously published studies. This raises 2 possibilities. Firstly, it is possible that both OI and IVI are effective at reducing ARBT requirement compared to no

treatment. Secondly, as the overall mean transfusion for both OI and IVI in the open surgery subgroup was similar to previously published data, it may indicate that the high utilisation of LS in the current trial has indeed minimised the potential effect of iron supplementation by reducing blood loss. This emphasises a need to further investigate potential biomarkers which may predict response to iron treatment and thus improve patient selection for treatment.

Future research should focus on the administration of iron therapy at the earliest time point to optimise efficacy of this treatment and should be appropriately powered to reflected reductions in blood transfusion requirements that have results from the increased utilisation of laparoscopic surgery. Randomisation should also take into account severity of anaemia and existing cardiorespiratory disease, two key confounders of blood transfusion utilisation. Long term follow up over 5 years should also be incorporated to capture the potential reduction in disease recurrence and long term morbidity and mortality associated with correcting anaemia and reducing blood transfusions.

18. Arrangements for Disseminating Findings

The results will be published in a scientific journal that is peer-reviewed and the paper will be reviewed and approved by all the investigators prior to submission for publication. Any publication will adhere to the University of Nottingham publication policy. Participants will be informed of the results by correspondence and information will be made available to the general population through publication in open access peer-review scientific journals.

19. Appendices

Patient information sheet

Informed consent form

A Multicentre Randomised Controlled Trial Comparing The Efficacy Of Intravenous And Oral Iron In The Preoperative Management Of Colorectal Cancer Anaemia: The Ivica Trial (BJS under review)

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Nottingham University Hospitals NHS
NHS Trust

PATIENT INFORMATION SHEET

IVICA Trial: Intravenous iron in colorectal adenocarcinoma associated anaemia

Name of investigators:

Mr A.G. Acheson	Dr M.J. Brookes	Mr O Ng
Mr J.A.D. Simpson	Mr T Pinkney	Mr J Lund
Dr C Tselepis	Dr T Iqbal	Mr R Longman
Mr D Miskovic	Mr N Francis	Mr B Singh

Invitation
You have been invited to take part in a research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish to. Ask us if there is anything that is not clear or if you would like more information. Please take the time to decide whether you wish to take part or not. If you decide to take part, you may keep this leaflet. Thank you for reading this.

What is the purpose of the study?
To examine the efficacy of intravenous iron (Ferinject®) when used to treat colon cancer related anaemia.

Background
Doctors at the Department of Surgery are interested in helping people who are suffering from anaemia. Anaemia is a condition in which the patient suffers from a reduced level of haemoglobin that is responsible for carrying oxygen in the blood stream. It is a common condition in patients diagnosed with cancer. There are different types of anaemia and it is important to identify the correct type because the treatments may be different.

Anaemia that occurs at the same time as cancer can be treated by giving the patient extra iron. Iron can be given in the form of a tablet or more recently by injection and in some cases it is treated with a blood transfusion. Iron tablets are considered standard treatment but iron injections are a relatively new treatment. This study will help us to correctly identify the type of anaemia and assess whether iron injections are an effective treatment method.

Why have I been chosen?
You have been chosen because you have been diagnosed with colorectal cancer and have associated anaemia.

This decision is based upon recent blood tests taken by your clinical team. If these are not available, then you will be contacted directly to ensure that all blood tests are up to date in preparation for your surgery.

Do I have to take part?
It is up to you to decide whether or not to take part. Your participation is entirely voluntary. If you do decide to take part, you will be given this information sheet to keep and be asked to

sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. This will not affect your treatment or prevent you from participating in future studies provided you are eligible.

What do I have to do?
You will be asked to complete three quality of life questionnaires, known as the SF36, the EQ-5D and FACT-An on your first visit (Screening visit), again at your pre-operative review (on the day of the operation) and finally at your last appointment which will take place 6-12 weeks after your surgery.

You will undergo a health check to make sure there are no reasons why you cannot participate in the study and this will include medical history and a blood pressure check.

As part of this study, you will receive either an injection of iron a minimum of two weeks before your surgery or be started on iron tablets at least two weeks before your surgery.

Four blood tests will be taken to assess if your anaemia is improving with treatment and to check your anaemia has resolved after the operation .These blood tests will be on the day treatment starts, just before your operation, two days after your operation and 6-12 weeks after your operation.

If the blood test before the operation does not demonstrate an improvement in the anaemia, you may be considered for an alternative treatment but this will be discussed with you and your surgical consultant.

During the operation, part of the tissue that is removed together with the cancer specimen will be retained by the research team and analysed. Any excess tissue may be stored in the tissue bank within the University of Nottingham for use in future studies. No extra tissue will be removed other than what is necessary, as determined by your surgical consultant.

During the study, you will be asked not to take part in any other studies before discussing it with one of the members of the research team. You will be able to drive home after the study visits and continue with your normal daily activities. You will be expected to make one to two extra visits to the hospital for the purposes of the study. All other visits will coincide with the normal clinical visits that are arranged as part of your cancer treatment.

A diagram has been included at the end of this sheet which should explain clearly what will happen if you agree to take part in the study.

What is the drug or procedure that is being tested?
The drugs being tested are iron tablets called ferrous sulphate and an iron injection, called Ferinject® (Syner-Med). The injection is also known by the scientific name, iron carboxymaltose. These medications have undergone rigorous safety testing and are considered safe for use. Similar drugs have been used to treat anaemia caused by other types of illness for many years.

What are the side effects of any treatment or procedures received when taking part?
Recognised side effects of Ferinject include headache, dizziness, nausea, abdominal pain, constipation, diarrhoea and rash. The majority of these side effects only tend to affect 1 in 100 patients. Side effect that can occur with ferrous sulphate include constipation, stomach upset and your stools may become dark (this is a harmless side effect).

What are the possible disadvantages and risks of taking part?
A small minority of people may have an allergy to iron injections. If you feel unwell after your treatment, let your study doctors know. You may require further medical treatment.

Some people may experience a local reaction to the iron injection. This is nothing to worry about and should settle down shortly after the injection is given.

In some patients, the iron treatments may not be effective in treating the anaemia. These patients may require further treatment for anaemia prior to surgery.

It is possible that if the treatment is given to a pregnant woman, it will harm the unborn child. Therefore, pregnant women must not take part in this study; neither should women who plan to become pregnant during the study. Women must have a pregnancy test before taking part and prior to each dosing to exclude the possibility of pregnancy. Women who could become pregnant must use an effective form of contraception during the course of this study. Any woman who finds that she has become pregnant whilst taking part in this study should immediately tell her study doctor. Additionally, women who are breastfeeding are also excluded as no research has been carried out to determine what the potential effects on the baby may be.

Are there any benefits related to taking part?
Correcting anaemia prior to surgery has been shown to improve patient recovery after the operation. Therefore, by receiving an iron supplement, you may reduce your risk of complications before, during and after surgery. You will also be providing information that may improve the treatment of future patients undergoing surgery.

Exclusion criteria
There are certain conditions that will prevent you from taking part in the study. These include, but are not limited to:

- Patients with a history of allergy to intravenous iron or iron products
- Patients under the age of 18 years
- Patients unable to give consent
- Pregnant Women
- Women who are breastfeeding

What if relevant new information becomes available?
Sometimes during the course of a research project, new information becomes available about the treatment or drug that is being studied. If this happens, your study doctors will tell you about it and discuss whether you want to or whether you should continue in the study. If you decide not to carry on, your study doctor will make arrangements for your care to continue. If you decide to continue in the study, you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the study. He/She will explain the reasons and arrange for your usual care to continue. If the study is stopped for any other reasons, you will be informed and your continuing care will be arranged.

What if something goes wrong?
If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for, legal action for compensation but you may have to pay your legal costs. Regardless of this, if you wish to complain, or have any concerns about any aspect of this study, you should ask to speak to one of the researchers who will do their best to answer your questions.
In case you have a complaint regarding your treatment by a member of staff or anything to do with the study, you can initially approach the lead investigator, Mr A. Acheson (contact details are provided at the end of this information sheet). If this achieves no satisfactory

outcome, the normal National Health Service complaints procedure should be available to you.

Will I get paid for taking part?
There is no payment for taking part in the study because managing anaemia is part of the normal care provided to patients being treated for colorectal cancer. Travel expenses are only considered under exceptional circumstances because the majority of study appointments will be arranged so that they coincide with the normal clinical visits you will make to receive treatment for the colorectal cancer.

Will my taking part in this study be kept confidential?
Yes. All the information that is collected about you during the course of the research will be kept strictly confidential. Your medical records will be inspected by the research team for the purposes of analysing the results. Your name however, will not be disclosed outside the hospital. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it. With your permission, we will notify your GP of your participation in the trial.

Trial records may be stored for up to 15 years. Data collected during the study may be transferred for the purpose of processing, analysis etc. to associated researchers within the European Economic Area. Some countries outside Europe may not have laws which protect your privacy to the same extent as the Data Protection Act in the UK or European Law.

What will happen to the results of the research study?
Once the research is finished, it will be presented at scientific meetings and published in a medical journal. You will not be identified in this publication. Should you wish to have a copy of this article, then it will be made available to you.

Who is organising and funding the research?
The research is organised by the Department of GI Surgery, University of Nottingham and is sponsored by Nottingham University Hospitals Trust. It is funded by the National Institute of Health Research.

Who has reviewed the study?
This study has been reviewed and given a favourable opinion by the Nottingham 2 Research Ethics Committee. In addition, the Medicines and Healthcare products Regulatory Agency (MHRA) has reviewed the study according to the established rules.

Who do I contact for further information?

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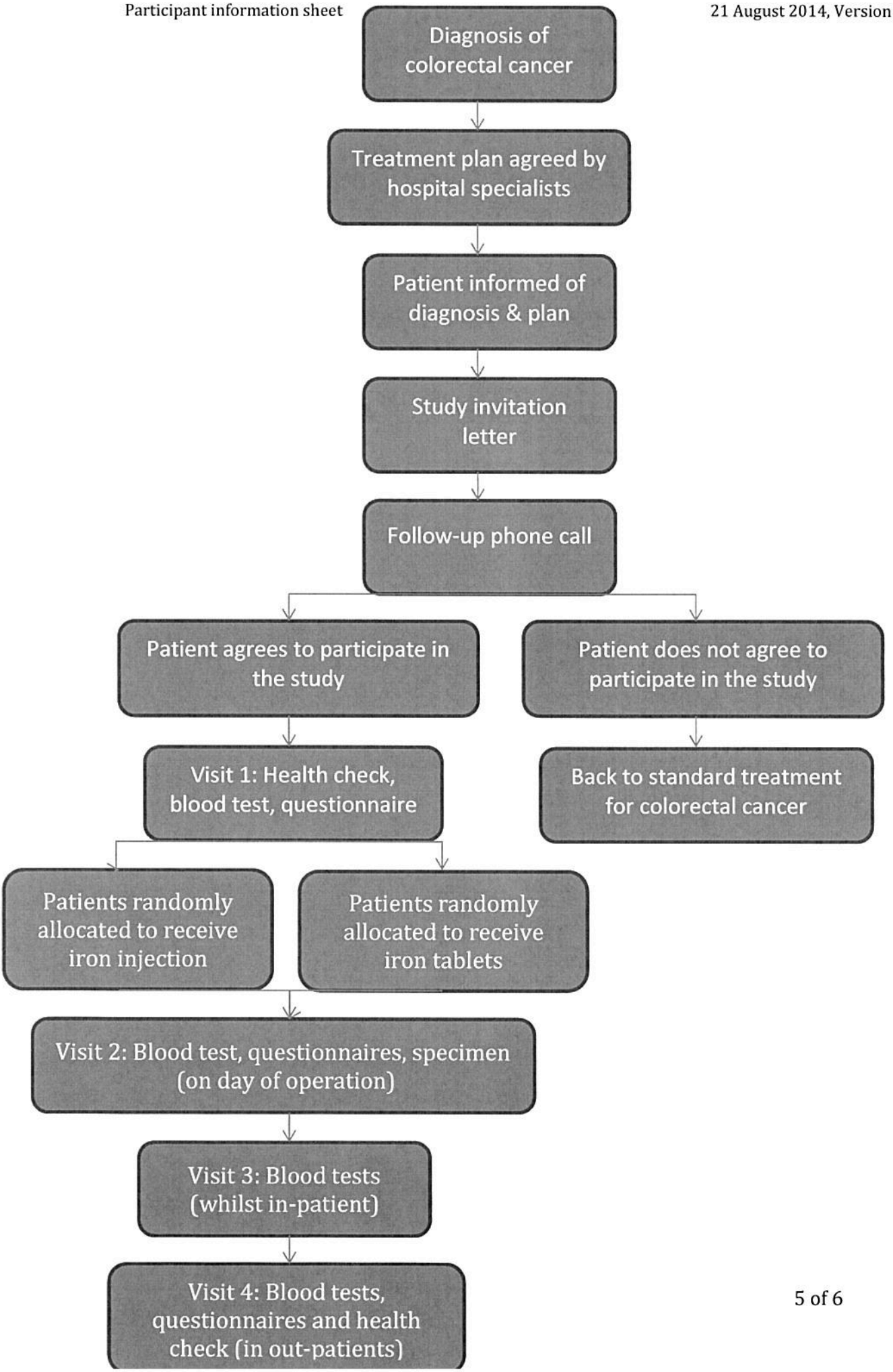
Department of GI Surgery,
Queen's Medical Centre,
Nottingham NG7 2UH

Austin.acheson@nottingham.ac.uk

Thank you for taking the time to read this information sheet and for considering participation in this study. If you participate, you will be given a copy of this information leaflet and signed consent form to keep.


Diagnosis of colorectal cancer
Treatment plan agreed by hospital specialists
Patient informed of diagnosis & plan
Study invitation letter
Follow-up phone call
Patient agrees to participate in the study
Patient does not agree to participate in the study
Visit 1: Health check, blood test, questionnaire
Back to standard treatment for colorectal cancer
Patients randomly allocated to receive iron injection
Patients randomly allocated to receive iron tablets
Visit 2: Blood test, questionnaires, specimen (on day of operation)
Visit 3: Blood tests (whilst in-patient)
Visit 4: Blood tests, questionnaires and health check (in out-patients)

Nottingham University Hospitals NHS
NHS Trust

Title: Intravenous iron in colorectal adenocarcinoma associated anaemia (IVICA Trial 2011)

Name of investigators:

Mr A G Acheson	Mr O Ng	Dr M J Brookes	Mr J A D Simpson
Mr T Pinkney	Mr J Lund	Dr T Iqbal	Dr C Tseplis
Mr D Miskovic	Mr N Francis	Mr B Singh	Mr R Longman

IVICA Study No. [ ]

Patient consent form

		Please initial Box
1	I voluntarily agree to take part in this study.	
2	I have been given an opportunity to ask questions and discuss the study with one of the above investigators or their deputies on all aspects of the study and have understood the advice and information given as a result.	
3	I confirm that I have been given a full explanation by the above named and that I have read and understand the information sheet dated **21 Aug 2014, version 6**	
4	I agree to the above investigators contacting my general practitioner and surgical consultant to make known my participation in the study where relevant.	
5	I agree to comply with reasonable instructions of the supervising investigator and will notify him immediately of any unexpected unusual symptoms or deterioration of health.	
6	I understand that information about me recorded during the study will be kept in a secure database. If data is transferred to others it will be made anonymous.	
7	I authorise the investigators to disclose to me any abnormal test results.	
8	I agree for the tissue taken during the operation to be used for research purposes and to be stored for the length of the study.	
9	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care or legal rights being affected. I understand that should I withdraw, then the examination results and information, collected so far cannot be erased and that this information may still be used in the project analysis.	
10	I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	

11	I have not been a subject in any other research study in the last three months which involved taking a drug, being paid a disturbance allowance, having an invasive procedure (e.g. venepuncture, endoscopy) or exposure to ionising radiation.	
12	I agree to give blood samples for the purpose of this research study.	
13	I agree for any excess tissue or blood samples to be stored in the University of Nottingham Tissue Bank for future research. I understand that the samples will be anonymised and will not have any identifiable information.	
14	I agree to contact a member of the research team if I am admitted to the hospital and also to inform the emergency medical staff of my participation in this study.	

Name of patient

Address

Telephone no.

Signature

Date

I confirm that I have fully explained the purpose of the study and what it is involved to:

I have given the above named a copy of this form together with the information sheet.

Name of person taking consent

Signature

Date

IVICA Study No.