END OF STUDY REPORT

19 Apr. 18

A pilot study to assess the efficacy of intravenous iron isomaltoside 1000 (Monofer®) in the management of anaemia associated with the palliative management of upper gastrointestinal adenocarcinoma

Protocol Number	9th May 2017, Version 4.1
Chief Investigator	Austin G Acheson
EudraCT Number	2013-000209-22
REC Reference Number	13/EM/0069
Sponsor Reference Number	12GA029
Study Start Date	23rd September 2013
Study End Date	28th August 2017
Funder(s)	University of Nottingham
Sponsor(s)	Nottingham University Hospitals NHS Trust

Name of Test Drug/Investigational Product	Iron isomaltoside (Monofer®)
Indication Studied	Anaemia during palliative chemotherapy for oesophagogastric adenocarcinoma

Report Author: Date:

Signature

Mr Oliver Ng DD-MMM-YYYY

Sponsor Authorisation: Signature Date:

Maria Koufali 20 APRIL 2018 DD-MMM-YYYY

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 National Research Ethics Service (previously known as 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 Trials Safety Group
WHO World Health Organisation

1. Summary of Study

This study assessed the feasibility and efficacy of intravenous iron isomaltoside to improve anaemia, quality of life and prevent blood transfusions in patients diagnosed with oesophagogastric adenocarcinoma receiving palliative chemotherapy. An open-label prospective randomised control trial comparing intravenous iron isomaltoside to standard care for anaemia during palliative chemotherapy for oesophagogastric cancer. The study was conducted at two recruiting sites in the UK (Nottingham University Hospitals NHS Trust and the Royal Wolverhampton NHS trust). Anaemic patients (<12 g/dL in women and <13 g/dL in men) with histologically proven oesophagogastric adenocarcinoma were recruited before initiation of palliative chemotherapy. Patients were randomised to receive standard care or intravenous iron isomaltoside. Post-chemotherapy changes in haemoglobin, ferritin, transferrin saturations, blood transfusions and quality of life were recorded for three cycles of chemotherapy. 27 patients participated in the trial. This did not meet our target of 40 patients due to factors that include the high decline rate of palliative chemotherapy, poor prognosis and poor acceptability within this palliative care group.

2. Objectives

Primary Objective

- To determine the feasibility of the current study design and aid design of a larger definitive study

Secondary Objectives

- To investigate whether the use of intravenous IIM (Monofer®) improves the quality of life of patients undergoing palliation of upper gastrointestinal (UGI) adenocarcinoma.
- To determine the change in haemoglobin in response to treatment with intravenous IIM compared to standard therapies.
- To review if the use of intravenous IIM can reduce the need for allogeneic blood transfusion compared to standard treatment regimens.
- To compare the outcomes of patients receiving IIM in comparison to standard therapies.

All of the objectives of the study were achieved.

3. Ethical Review

The study was conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

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

The protocol, informed consent form, participant information sheet and all substantial amendments to the original approved documents were submitted to the Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) and received formal written approval.

The study was conducted in accordance with GCP principles and NUH processes.

4. Investigational Plan

Study synopsis:

Study Title	A pilot study to assess the efficacy of intravenous iron isomaltoside 1000 (Monofer®) in the management of anaemia associated with the palliative management of oesophagogastric adenocarcinoma.
Clinical Phase	Phase IV
Trial Design	Open label randomised control pilot study
Study centre(s)	Nottingham University Hospitals NHS Trust (Nottingham City Hospital campus) and Royal Wolverhampton NHS Trust
Trial Participants	Patients with oesophageal, gastric or gastroesophageal junctional adenocarcinoma undergoing palliative management who have been identified as anaemic at the start of treatment.
Planned Sample Size	30 patients

Follow-up duration	From diagnosis for up to 15 weeks
Planned Trial Period	48 months
Primary Objective	To determine the feasibility of the current study design and aid design of larger, definitive study
Secondary Objectives	1. To determine whether the use of intravenous iron isomaltoside 1000 (Monofer®) can improve the quality of life of anaemic patients undergoing palliation of upper gastrointestinal adenocarcinoma when compared to standard treatments. 2. To compare the haemoglobin responses between therapies. 3. To compare changes in haematinics between groups. 4. To review differences in allogenic red blood cell transfusion rates between groups 5. To assess the safety of the use of intravenous iron isomaltoside 1000 in this patient group.
Primary Endpoint	Assessment of feasibility of study design (eg patient uptake to trial, assessment of patient pathway and logistical setup), and to aid determination of sample size for larger study.
Secondary Endpoints	1. Quality of life scores as governed by the EQ-5D and FACT-An questionnaires. 2. Change in the level of haemoglobin and haematinic markers following treatment with intravenous iron or standard therapies. 3. Allogenic blood transfusion number. 4. Total number of allogenic blood transfusions in each group. 5. Comparison of outcomes in patients in both groups over the course of treatment in terms of complications, and successful cycles of chemotherapy completed
IMP	Intravenous iron isomaltoside 1000 (Monofer®)
Form	Solution
Dose	As calculated by Cumulative Iron deficit (according to manufacturer's guidance)
Route	Intravenous

Enrolment

Patients were identified from the oesophagogastric MDT meetings. Included were adult patients with a proven histological diagnosis of oesophagogastric adenocarcinoma, anaemia (<12 g/dL in women and <13 g/dL in men) and a treatment decision for palliative chemotherapy.

Allocation

Patients were randomised 1:1 to each group using random allocations concealed in opaque envelopes. Patients in the control arm had their anaemia managed by traditional regimens as decided by the clinical oncology team. The patients in the intravenous iron group received intravenous iron isomaltoside 1000 (Monofer ®). Doses were calculated using the Ganzoni equation of cumulative iron deficit. Iron isomaltoside was diluted in 250ml 0.9% sodium chloride and infused over a period of 60 minutes. All subsequent treatment of anaemia was at the discretion of the clinical oncology team.

Follow up

Three follow up visits were performed at the start of each cycle of chemotherapy. At each visit, blood analyses (haemoglobin, ferritin, transferrin saturations) and quality of life questionnaires, FACT-An and EuroQol EQ-5D were conducted. Adverse events, complications, blood transfusions and additional iron administration by the clinical oncology team were also recorded.

Analysis

The feasibility outcomes measured included number of eligible patients, study exclusion (screen failure rates), willingness to be recruited and randomised to the study (acceptability), withdrawal of patients (non-concordance) and study retention rates.

Clinical outcomes included haemoglobin, ferritin, TSAT, blood transfusion rate, number of units transfused, mortality, FACT-An and EQ-5D quality of life scores.

5. Selection of Study Population

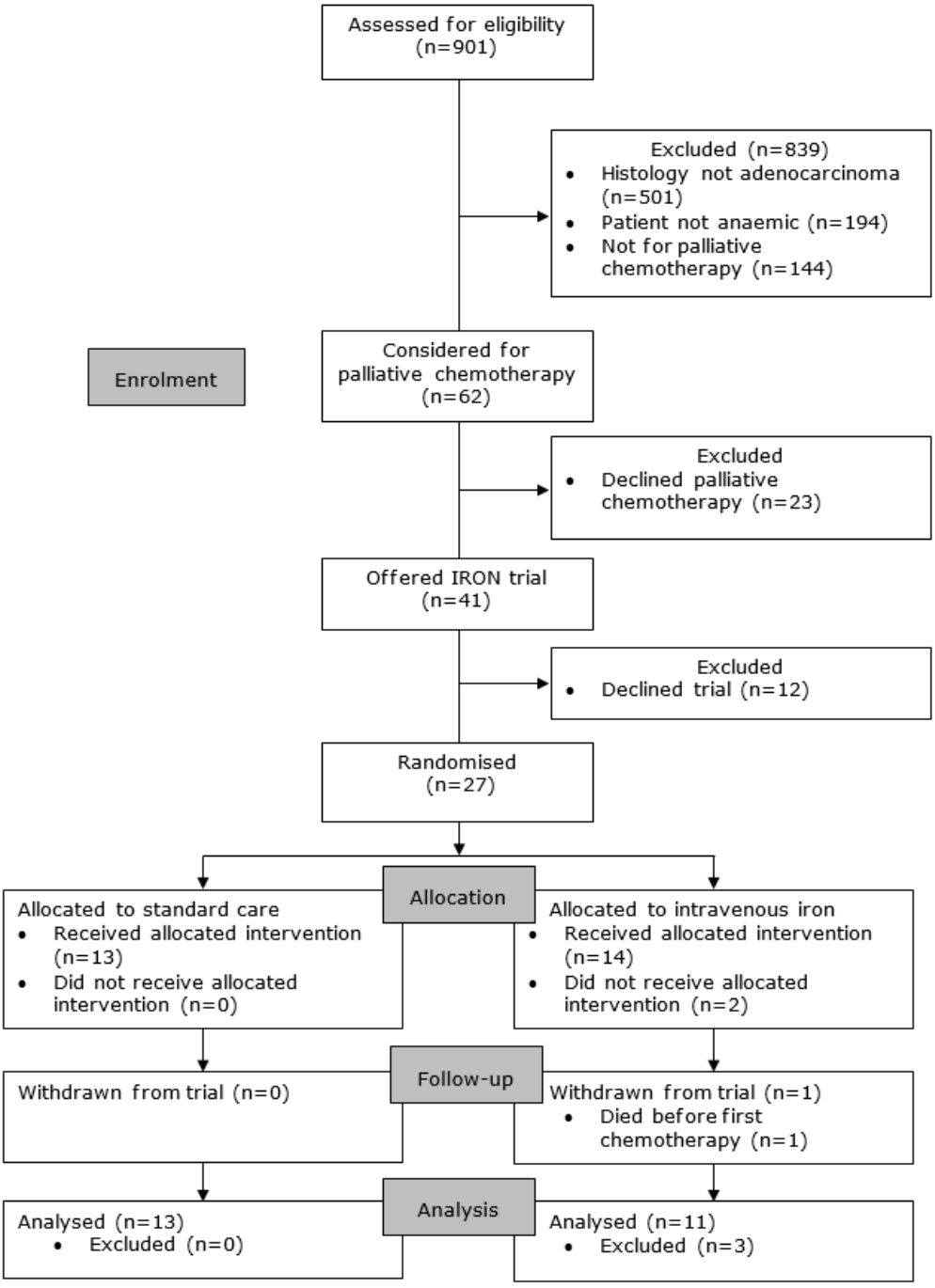
Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or Female, aged 18+
- Anaemic with haemoglobin values of <13 g/dL for males, and < 12 g/dL for females.
- Diagnosed with histologically proven oesophageal, gastric or GOJ adenocarcinoma.
- Treatment selected is palliative chemotherapy
- Medically fit for initiation of palliative chemotherapy.
- 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 may not enter the study if ANY of the following apply:
- Patients who following investigation do not have a histological diagnosis of upper GI 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.
- Known haematological disease that, in the investigators opinion would confound any changes in blood results.
- Features necessitating urgent surgery.
- Previous allergy to intravenous iron or related iron products.
- Patients who are unable to consent.
- 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.
- Prisoners and minors (<18 years)
- Non-iron deficiency anaemia (e.g. haemolytic anaemia)
- Hypersensitivity to the active substance or to any of the excipients.

- Patients with a history of asthma, allergic eczema or other atopic allergy
- Decompensated liver cirrhosis and hepatitis
- Rheumatoid arthritis with symptoms or signs of active inflammation



6. Study Settings

The study was conducted at two sites across the UK; Nottingham University Hospitals and Royal Wolverhampton Hospital. The investigators for this study are listed below:

Chief Investigator: Mr Austin George Acheson
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Consultant Gastroenterologist and Honorary Senior Lecturer,
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Mr Barrie David Keeler (Principle Investigator)
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7. Interventions

Description of Study Treatment

The study intervention treatment is intravenous Iron Isomaltoside 1000 (Monofer ®) (IIM). It will be administered in line with the product Summary of Product Characteristics Guidelines (SPC). Doses will be calculated by the Ganzoni equation of cumulative iron deficit. To replenish iron stores by a single infusion, doses up to 20mg/kg body weight of iron may be administered per week. The IIM is diluted in 250ml 0.9% sodium chloride and infused over a period of 60 minutes. The patient will be observed by clinical staff during the administration of the drug. Following recruitment at the end of the patient's second oncology appointment (OA2), a mutually acceptable appointment will be arranged to administer the drug. The location of administration should have all the required resuscitation equipment for safe monitoring and treatment of patients during drug infusion. The dose required will be based upon the most recent haemoglobin value and the patient's weight at the recruitment visit.

Storage of Study Treatment

The study treatment is intravenous iron III isomaltoside 1000 (Monofer®) which is presented in glass vials of 1ml (100 mg iron as iron (III) isomaltoside 1000), 2 ml (200 mg iron as iron (III) isomaltoside 1000), 5 ml (500 mg iron as iron(III) isomaltoside 1000) and 10 ml (1,000 mg iron as iron(III) isomaltoside 1000). The drug will be stored in the Trials Pharmacy on B Floor, Nottingham University Hospital (Queen's Medical Centre Campus) at room temperature in a secure cabinet. At Royal Wolverhampton NHS Trust, the drug will be stored at the local Trials Pharmacy.

Compliance with Study Treatment:

Compliance with the intervention (iron III isomaltoside 1000) will be directly observed by the nurse or doctor administering the infusion. A record of the IV administration will be made in the patient's medical notes. The reasons for non-compliance will be documented in the CRF.

Accountability of the Study Treatment

The Trials Pharmacy at each site will be accountable for the medication whilst in the department. This will be dispensed upon provision of a valid prescription form.
Accountability will be monitored using drug accountability logs within the Trials Pharmacy, which will be subject to monitoring by the sponsor.

Concomitant Medication

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

Participants who are on oral iron supplementation at time of recruitment to the trial will continue taking this as prescribed if in the "control" observation arm, but discontinue this if allocated to the "treatment arm" as IIM therapy is commenced.

8. Changes in the Protocol from Initial Approval

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	3	1 March 2014	BK	Addition of RWH as a site
	3	1 March 2014	BK	Modification of patient pathway to allow patient recruitment at an earlier point if patient chooses (pages 11-14, 19)
2	3	1 March 2014	BK	Addition of the blood test EPO at recruitment (p20)
3	3.1	5 Jan 15	ON	Oliver Ng added to investigators
4	4.0	22 September 2015	ON	Clarification on when ideal body weight should be used to calculate Monofer® dose. Clarification that patients will only receive a single dosing of Monofer if their CID requires a larger dose than the max 20mg/kg per week. (Page 7)

5	4.0	22 September 2015	ON	Modified the inclusion criteria to conform to WHO guidelines for Haemoglobin value considered to constitute anaemia.
6	4.0	22 September 2015	ON	Clarified that erythropoietin should only be recorded at baseline.
7	4.0	22 September 2015	ON	Specified that haemoglobin values within 1 month prior to the recruitment visit may be used for inclusion in the study.
8	4.0	22 September 2015	ON	Other administrative changes, and changes to wording to accommodate for RWH as a site.
9	4.1	9 May 2017	ON	Planned sample size amended to 30

Amendments were reviewed and approved, where necessary by the relevant regulatory authorities and REC and R&I.

9. Protocol Deviations

In total 18 protocol deviations were reported during this study. The most common deviations reported were use of an incorrect version of PCF/PIS (n=4) due to version control, delays in chemotherapy (n=3), IV iron not being administered (n=3) and quality of life questionnaires not being completed (n=3). No deviations affected data integrity and missing data were considered and described in the analysis. No serious breach occurred requiring reporting to the MHRA. Deviations 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. PI and CI concluded no deviation affected patient safety or data integrity.

Site	No of deviations	Details
Nottingham	18	Chemotherapy visit delayed (3) Packaging not returned to pharmacy (1) History of asthma (1) IV iron administration (3) Bloods not taken (1) Incorrect version PCF/PIS (4) QoL not performed (3) SAE not submitted <24h (1) Annual progress report (1)
Wolverhampton	0	

10. Patient Information & Consent

A named member of the research team took consent from the participant once they have ascertained that the patient fits the eligibility and inclusion criteria. Consent and eligibility was recorded in the medical notes and confirmation of eligibility was signed and dated by the PI.

The participant personally signed and dated the latest approved version of the informed consent form before any study specific procedures are performed. Written versions of the participant information and Informed consent were presented to the participants detailing no less than: 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 will be 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 be 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

Patients were randomised to each group with the use of random allocations concealed in opaque envelopes. Patients in the control arm (n=13) had their anaemia managed by traditional regimes as decided by the clinical team. The patients in the Intravenous Iron group (n=14) had the initial anaemia managed with Intravenous IIM as a first-line treatment.

Allocated study treatment was received by 25 of the 27 patients (92.5%). Two patients in the intravenous iron group did not receive their intervention. One patient died before administration of iron. The second patient developed a massive upper gastrointestinal haemorrhage, received multiple blood transfusions prior to the administration of iron and was therefore not treated because of concerns regarding iron overload. One patient in the intravenous iron group died before being administered any chemotherapy and was withdrawn from the trial.

12. Safety Reporting

14 patients were randomised to receive the drug. 11 patients have received the IMP (doses in mg: 1350, 1500, 985, 1100, 1200, 1500, 1200, 880, 1200, 1400, 1500). 2 patients died before being administered drug and one patient developed acute bleeding and was transfused prior to iron administration and therefore did not receive IMP. The remaining 13 patients have been within the (observational) control arm.

The following table summarises Serious Adverse Events by System Organ Class (SOC) for the duration of the trial to date:

System organ class (SOC) - **- Lower level term (LLT)**	**Number of SAEs**	**Study Drug (control/Monofer)**
Infections and Infestations - Septicaemia - Neutropenic Sepsis - Pneumonia	3	**2 participants: control**

System organ class (SOC) - **- Lower level term (LLT)**	**Number of SAEs**	**Study Drug (control/Monofer)**
Neoplasms benign, malignant and unspecified - Metastatic Gastric cancer - Gastrointestinal tract cancer NOS	4	**4 participants:** **3 received Monofer** **1 control**
Blood And Lymphatic System Disorders - Neutropenia	1	**1 participant: Monofer**
Gastrointestinal Disorders - Ascites - Upper Gastrointestinal haemorrhage	4	**2 participants: Monofer**
General disorders and administration site conditions - Pyrexia - Febrile neutropenia	2	**1 participant: Monofer** **1 participant: control**
Metabolism and nutrition disorders - Gout	1	**1 participant: control**
Surgical and medical procedures - Insertion of oesophageal stent	1	**1 participant: control**
Respiratory, thoracic and mediastinal disorders - Shortness of breath	1	**1 participant: control**
Skin and subcutaneous tissue disorders - Cellulitis	1	**1 participant: Monofer**
Vascular disorders - Upper gastrointestinal haemorrhage	1	**1 participant: Monofer**

Iron (III) isomlatoside is identified as having side effects, the most important of which include hypersensitivity and anaphylactoid reactions (Rare). These are the most significant of the side effects outlined, were not experienced in this study. Despite this, the drug is given in a hospital environment with full access to resuscitation equipment in the presence of appropriately trained staff.

The risks remained consistent with expectation, and we justified continuation of the trial, without the need for modification.

13. Laboratory Evaluations

Not applicable.

14. Statistical Analysis

Given the pilot nature of the study, statistical analysis was primarily aimed towards determination of an adequate sample size for a larger study, and also prediction of a likely duration that recruitment will be needed for this to take place.

Secondary aims include evaluation of transfusion rates and haemoglobin changes. A descriptive analysis was performed on the data. Numbers and percentages are presented for categorical data, mean and standard deviations for normally distributed continuous data, and median and inter-quartile ranges for non-normally distributed data. The study outcome measures were compared between groups using an independent samples T-test. Changes within groups over time points were compared using a pair samples T-test. All tests were 2-sided, with type I error rates of .05. Minimal clinically important difference (MCID) for quality of life was determined using a distribution method and defined as one standard deviation difference from baseline.

15. Main Findings of the Study

Feasibility

From the 23rd September 2013 to 24th July 2017, 901 patients were screened for the IRON trial (see Figure 1). Of these 400 (44%) had histologically confirmed adenocarcinoma. 206 patients were anaemic at diagnosis in this group (51.5%). 62 patients were recommended for palliative chemotherapy and therefore eligible for the IRON trial (30%). Pre-screening eligibility was therefore 6.9% and screen failure rate 93.1%. 23 patients (37%) subsequently declined palliative chemotherapy. In comparison, in those offered neoadjuvant chemotherapy only 2 patients of 59 patients declined (3.3%). 41 patients were approached for the trial and acceptability was 66%, with 27 patients willing to participate. Allocated study treatment was received by 25 of the 27 patients (92.5%). Two patients in the intravenous iron group did not receive their intervention. One patient died before administration of iron. The second patient developed a massive upper gastrointestinal haemorrhage, received multiple blood transfusions prior to the administration of iron and was therefore not treated because of concerns regarding iron overload. One patient in the intravenous iron group died before being administered any chemotherapy and was withdrawn from the trial. Study retention was 88.9% and data were available to analyse 24 patients.

General

There were no statistically significant differences in age, sex, body mass index, Charlson score or staging between standard care and intravenous iron groups at recruitment (see Table 1). Four patients in the intravenous iron group had received oral iron at some time point in the previous six weeks prior to recruitment to the trial. One of these patients was still taking oral iron at recruitment. This was discontinued prior to administration of intravenous iron. No patients in either group received any oral iron therapy during the trial.

The majority of patients were treated with epirubicin, oxaliplatin and capecitabine (EOX) chemotherapy (standard care group n=11, 84.6% versus intravenous iron group n=10, 90.9%, see Table 2). The remainder of patients received cisplatin, capecitabine and Herceptin. 17 patients completed the full three cycles of chemotherapy (62.9%), two patients had chemotherapy stopped after two cycles (7.4%) and five patients received only one cycle of chemotherapy (18.5%). No statistically significant differences were seen between groups and number of chemotherapy cycles completed.

Clinical

Haemoglobin

Haemoglobin was significantly higher in the standard care group at recruitment (mean haemoglobin 11.5 g/dL standard care group versus 10.0 g/dL intravenous iron group p=0.044) (see Table 3). Mean haemoglobin decreased by 0.6 g/dL over three cycles of chemotherapy in the standard care group to 10.8 g/dL (see Figure 2A). In comparison the haemoglobin in the intravenous iron group increased by 0.5 g/dL during the three cycles of chemotherapy to 10.5 g/dL, resulting in a difference between groups in mean haemoglobin change of 1.1 g/dL (see Figure 2B). No statistical difference between haemoglobins was seen after recruitment.

Haematinics

Ferritin levels were similar at recruitment between groups (p=0.282) (see Table 3). Ferritin showed a significant increase after chemotherapy cycle one in the group treated with intravenous iron 105 ng/mL to 1015 ng/mL ($p<0.05$) and then began to decline with the mean ferritin 558 ng/mL after cycle three (see Figure 3A). Ferritin also increased in the standard care group despite no oral or intravenous iron administration from 161 ng/mL at recruitment to 340 ng/mL after cycle three. No statistical differences between groups were seen beyond cycle one of chemotherapy.

Transferrin saturations increased above 20% in the intravenous iron group rising from 11.1% to 26.1% (see Figure 3B). Transferrin saturations never exceeded 20% in the standard care group but did rise from 11.9% to 19% after cycle three of chemotherapy. No statistical differences between groups were seen.

Transfusions

After cycle one of chemotherapy, three patients in the intravenous iron group had received blood transfusions with a mean 5.3 units of blood transfused for this group (see Table 3). In comparison only one patient received 3 units of blood in the standard care group at the same time point. No further patients received transfusions in the intravenous iron group while three further patients and one previous patient received an average of 1 unit of blood in the standard care group. No patients required a transfusion after cycle three of chemotherapy. The indication for transfusions were severe anaemia (haemoglobin < 8 g/dL) in six patients (one patient from

intravenous iron group) and acute upper gastrointestinal haemorrhage in two patients (both in the intravenous iron group).

Subgroup analysis non-transfused

Haemoglobin in subgroup analysis of patients not transfused during the trial again showed a significant difference at recruitment (mean haemoglobin 12.1 g/dL standard care group versus 10.4 g/dL intravenous iron group p=0.021, see Table 4). No difference was seen after cycle two (mean haemoglobin 10.9 g/dL standard care group versus 10.8 g/dL intravenous iron group p=0.737). Haemoglobin dropped with each cycle of chemotherapy in the standard care group from 12.1 g/dL at recruitment to 10.9 g/dL after cycle three, mean difference -1.2g/dL. No drop in haemoglobin was seen in the intravenous iron group from a recruitment haemoglobin of 10.4 g/dL to a haemoglobin after cycle three of 10.6 g/dL, mean difference 0.2 g/dL.

Ferritin again showed a significant increase in the intravenous iron group after cycle one (mean ferritin 62 ng/mL standard care group versus 770 ng/mL intravenous iron group p=0.027). Ferritin then dropped with each cycle of chemotherapy in the intravenous iron group but remains higher than the standard care group throughout. Transferrin saturations also increased in both groups with no significant difference between groups at any time point.

Adverse events and complications

There were no serious adverse events related to intravenous iron administration. One patient reported some diarrhoea following intravenous iron administration that settled within 24 hours. There were no significant differences in unplanned hospital admissions between the two groups (p=0.675, see Table 3). Seven patient deaths occurred during the study; 2 patients in standard care, 5 patients in the intravenous iron group (p=0.182, see Table 3). All deaths related to progression or complications from their oesophagogastric malignancy. No statistical difference was seen between groups.

Quality of life

FACT-An quality of life scores were higher in the standard care group compared to the intravenous iron group at recruitment (see Table 5). Quality of life scores increased for all dimensions of the FACT-An in the intravenous iron group (see Figure 4). In particular physical well-being, emotional well-being, anaemia-specific outcomes, trial outcome index and total scores all exceeded the minimum clinically important difference (see Table 5). No similar increase was

seen in the standard care group and no changes reached the minimum clinically important difference.

EQ-5D quality of life scores were again higher in the standard care group compared to the intravenous iron group at baseline in all dimensions except pain and discomfort. Change in EQ-5D scores showed no trend in either group (see Figure 5). Two scores in the intravenous iron group exceeded the minimum clinically important difference (see Table 6), usual activity and visual analogue score both after cycle two of chemotherapy.

Table 1 Demographic and clinical data

	Standard care (n=13)	**Intravenous iron (n=11)**	**P value**
Age median range (years)	68 (38-79)	69 (48-85)	ns
Sex ratio (M:F)	11:2	7:4	ns
BMI (m/kg^2)	27.4 (17.4-41.9)	25.7 (19.9-37.9)	ns
Received oral iron previous 6 weeks	0 (0%)	4 (36%)	
Charlson score	6 (2-8)	6 (6-8)	ns
TNM			
T1-2 **T3-4**	0 (0%) 13 (100%)	1 (9%) 10 (91%)	ns
N0 **N1** **N2** **N3**	0 (0%) 2 (15%) 8 (61.5%) 3 (23%)	1 (9%) 4 (36.3%) 5 (45.4%) 1 (9%)	ns
M0 **M1**	1 (8%) 12 (92%)	0 (0%) 11 (100%)	ns

Table 2 Treatment data

	Standard care (n=13)	**Intravenous iron (n=11)**
Chemotherapy regime		
Epirubicin, oxaliplatin and capecitabine (EOX) (n)	11 (84.6%)	10 (90.9%)
Cisplatin, Capecitabine and Herceptin (n)	2 (15.4%)	1 (9.1%)
Dose reductions (n) **20%** **25%** **50%**	 1 (7.7%) 2 (15.4%) 1 (7.7%)	 0 1 (9.1%) 1 (9.1%)
Cycle delays (n)	5 (38%)	2 (18%)
Cycles of chemotherapy completed (n)		
0 **1** **2** **3**	0 2 1 10	3** 3 1 7
Iron therapy		
Oral iron (n) **Intravenous iron (n)**	0 0	0 11
Dose (mg)	-	1200 (880-1500)

Table 3 Clinical outcome data

	Standard care (n=13)	**Intravenous iron (n=11)**	**P value**
Haemoglobin (g/dL) mean (SD)			
Recruitment	11.45 (1.79) (n=13)	9.96 (1.60) (n=11)	0.044 *
After cycle 1	11.08 (1.10) (n=12)	10.15 (1.49) (n=11)	0.101
P value	0.403	0.628	
After cycle 2	10.83 (1.15) (n=10)	10.79 (0.99) (n=8)	0.935
P value	0.318	0.680	
After cycle 3	10.70 (1.49) (n=10)	10.60 (1.19) (n=7)	0.885
P value	0.336	0.903	
MCV	84 (5)	85 (6)	0.789
Platelets	326 (144)	356 (138)	0.616
CRP	56 (87)	40 (30)	0.547
Ferritin mean (SD)			
Recruitment	161 (123)	105 (120)	0.282
After cycle 1	200 (170)	1015 (880)	0.021*
After cycle 2	264 (213)	581 (489)	0.102
After cycle 3	340 (325)	558 (637)	0.366
Transferrin saturations mean (SD)			
Recruitment	11.9 (4.8)	11.1 (8.7)	0.811
After cycle 1	12.1 (4.2)	26.3 (29)	0.196
After cycle 2	18.3 (8.1)	20.7 (8.6)	0.580
After cycle 3	19 (9)	14 (7)	0.260
Blood transfusions (mean number of units transfused)			
After cycle 1	3 (n=1)	5.3 (3.2) (n=3)	0.594
After cycle 2	4 (n=4)	0	
After cycle 3	0	0	
Blood transfusion received (n)	4 (31%)	3 (27%)	0.851 (chi squared)
No blood	9 (69%)	8 (73%)	

transfusion (n)			
Unplanned hospital admissions (n)	4 (31%)	5 (45%)	0.675 (fishers)
Death (n)	2 (15%)	5 (45%)	0.182 (fishers)

* $p < 0.05$

Table 4 Subgroup analysis non-transfused

	Standard care (n=9)	**Intravenous iron (n=8)**	**P value**
Haemoglobin (g/dL) mean (SD)			
Recruitment	12.06 (0.957) (n=9)	10.44 (1.58) (n=8)	0.021*
After cycle 1	11.58 (0.821) (n=8)	10.31 (1.29) (n=8)	0.035*
After cycle 2	10.96 (1.05) (n=8)	10.79 (0.99) (n=8)	0.737
After cycle 3	10.90 (1.54) (n=8)	10.60 (1.19) (n=7)	0.683
Ferritin mean (SD)			
Recruitment	127 (94)	62 (58)	0.119
After cycle 1	116 (61)	770 (563)	0.027*
After cycle 2	176 (104)	581 (489)	0.054
After cycle 3	296 (331)	558 (637)	0.326
Transferrin saturations mean (SD)			
Recruitment	12.1 (5.3)	11.0 (9.3)	0.934
After cycle 1	14.2 (4.0)	18.3 (10.6)	0.138
After cycle 2	19.0 (9.1)	20.7 (8.6)	0.975
After cycle 3	20.4 (9)	14 (7.6)	0.246

* $p < 0.05$

Table 5 FACT-An quality of life scores

FACT-An Dimension	Time point	Standard care Mean Score (SD)	Intravenous iron Mean Score (SD)
PWB	REC	20 (5.4)	16.8 (6.9)
	C1	19.6 (5.4)	16.6 (6.7)
	C2	20.8 (3.3)	21.3 (4.2)*
	C3	20.7 (4.4)	18.7 (5.7)
SWB	REC	25 (3.7)	21 (7.4)
	C1	25.2 (3.3)	22.7 (4.7)
	C2	24.3 (2.9)	21.6 (3.9)
	C3	25.1 (3.1)	22.6 (4.9)
EWB	REC	16.1 (5.6)	13 (6.1)
	C1	15.1 (5.8)	14 (3.9)
	C2	18.9 (3.6)	12.7 (7.4)
	C3	19 (3)	16.5 (3.3)*
FWB	REC	16.8 (5.5)	14.2 (7.4)
	C1	15.8 (6.3)	12.2 (5.3)
	C2	15.3 (6.3)	16.7 (7.6)
	C3	14.5 (5.1)	18.3 (4.3)
AnS	REC	50.5 (16.3)	43.6 (21.5)
	C1	48.9 (16)	42.5 (18.1)
	C2	49.1 (14.5)	59.1 (9.8)*
	C3	46.1 (11.2)	55.5 (9)*
TOI	REC	87.3 (24.3)	71 (36.5)
	C1	84.3 (26.6)	71.4 (27.4)
	C2	85.2 (21.4)	94.3 (19.7)*
	C3	81.3 (17.7)	92.5 (17.7)*
FACT-G	REC	77.9 (12.9)	65 (17.1)
	C1	75.6 (15.5)	65.6 (17)
	C2	79.3 (10.6)	69.4 (20.6)
	C3	79.3 (10.5)	76.1 (14.8)
Total	REC	128.4 (27.5)	105 (38.9)

Score	C1	124.6 (30.6)	108.1 (31.5)
	C2	128.4 (22)	128.5 (27.8)
	C3	125.3 (17.9)	131.6 (22.7)*

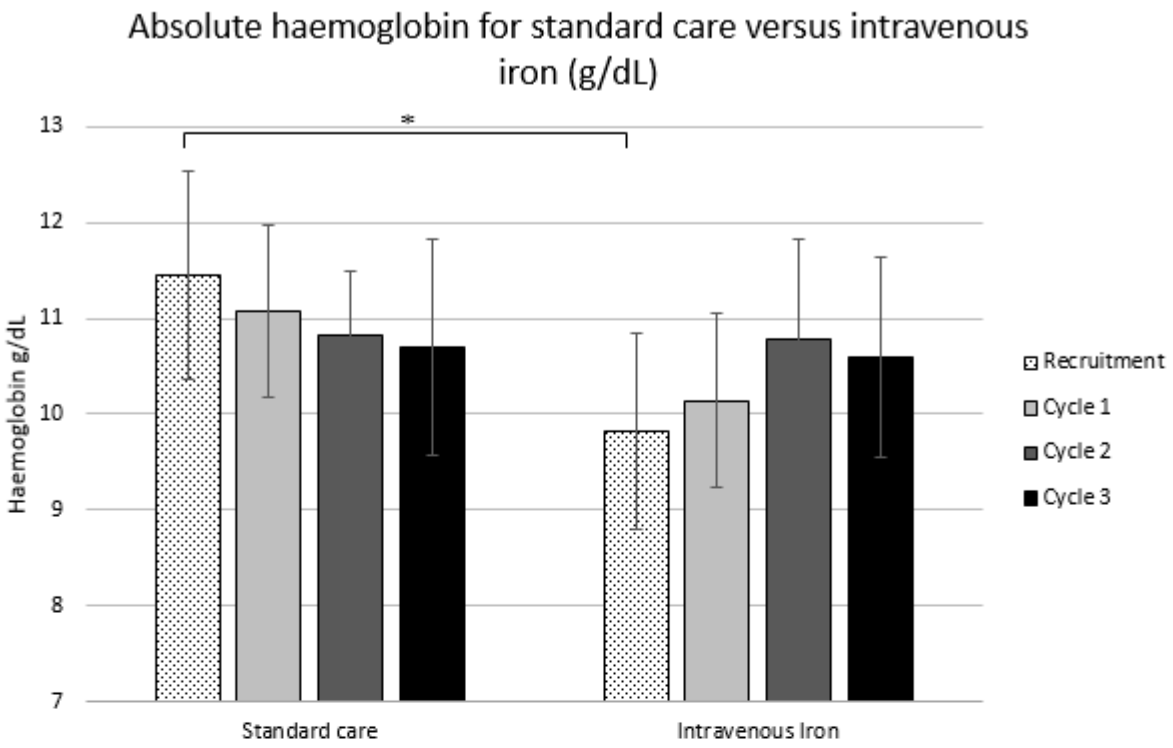
* Minimum clinically important difference exceeded

Table 6 E5QD quality of life scores

E5QD Dimension	**Time point**	**Standard care Mean score (SD)**	**Intravenous iron Mean score (SD)**
Mobility	REC	4.45 (0.66)	4 (1.15)
	C1	4.22 (1.03)	3.78 (1.55)
	C2	4.44 (0.68)	4.5 (0.5)
	C3	4.22 (0.42)	4.33 (0.47)
Self-care	REC	4.82 (0.39)	4.67 (0.62)
	C1	4.56 (0.68)	4.22 (1.31)
	C2	4.78 (0.63)	4.83 (0.37)
	C3	4.67 (0.47)	4.83 (0.37)
Usual activities	REC	3.91 (1.24)	3.25 (1.59)
	C1	4 (1.05)	3.22 (1.23)
	C2	4 (1.33)	4.33 (0.75)*
	C3	3.67 (1.05)	3.67 (0.75)
Pain and discomfort	REC	3.64 (0.98)	4.08 (0.95)
	C1	3.78 (1.03)	3.89 (0.99)
	C2	4.11 (0.87)	4.5 (0.5)
	C3	4 (0.94)	4.5 (0.76)
Anxiety and depression	REC	4.36 (0.64)	4.25 (0.83)
	C1	4.33 (0.94)	3.89 (0.87)
	C2	4.56 (0.68)	4.17 (0.69)
	C3	4.33 (0.82)	4.33 (0.47)
Visual analogue score	REC	66.7 (16.32)	62.27 (17.1)
	C1	71.67 (17.07)	61.88 (26.8)
	C2	68.13 (26.42)	76.5 (11.31)*
	C3	72.44 (15.02)	71.67 (15.46)

* Minimum clinically important difference exceeded

A



B

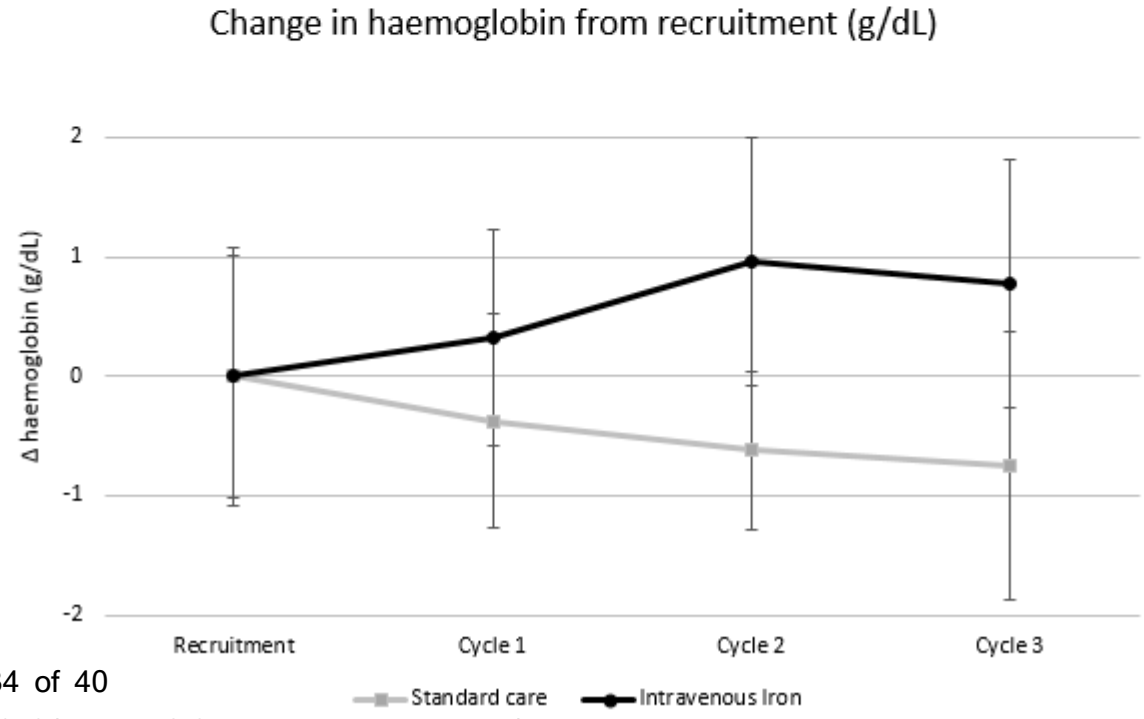


Figure 2 Haemoglobin A. Absolute haemoglobin B. Change in haemoglobin from recruitment

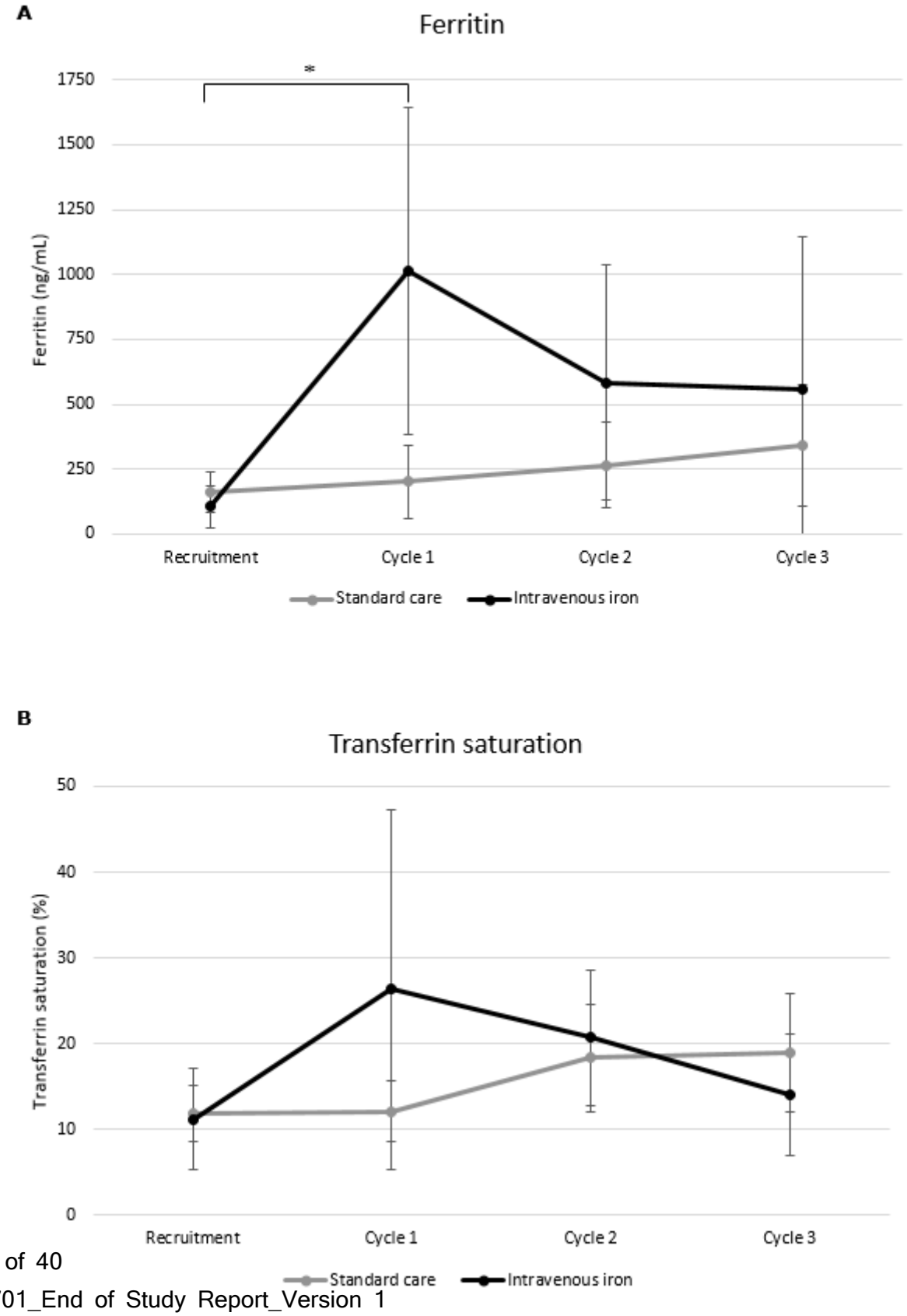


Figure 3 Ferritin (A) and Transferrin saturation (B) changes by group

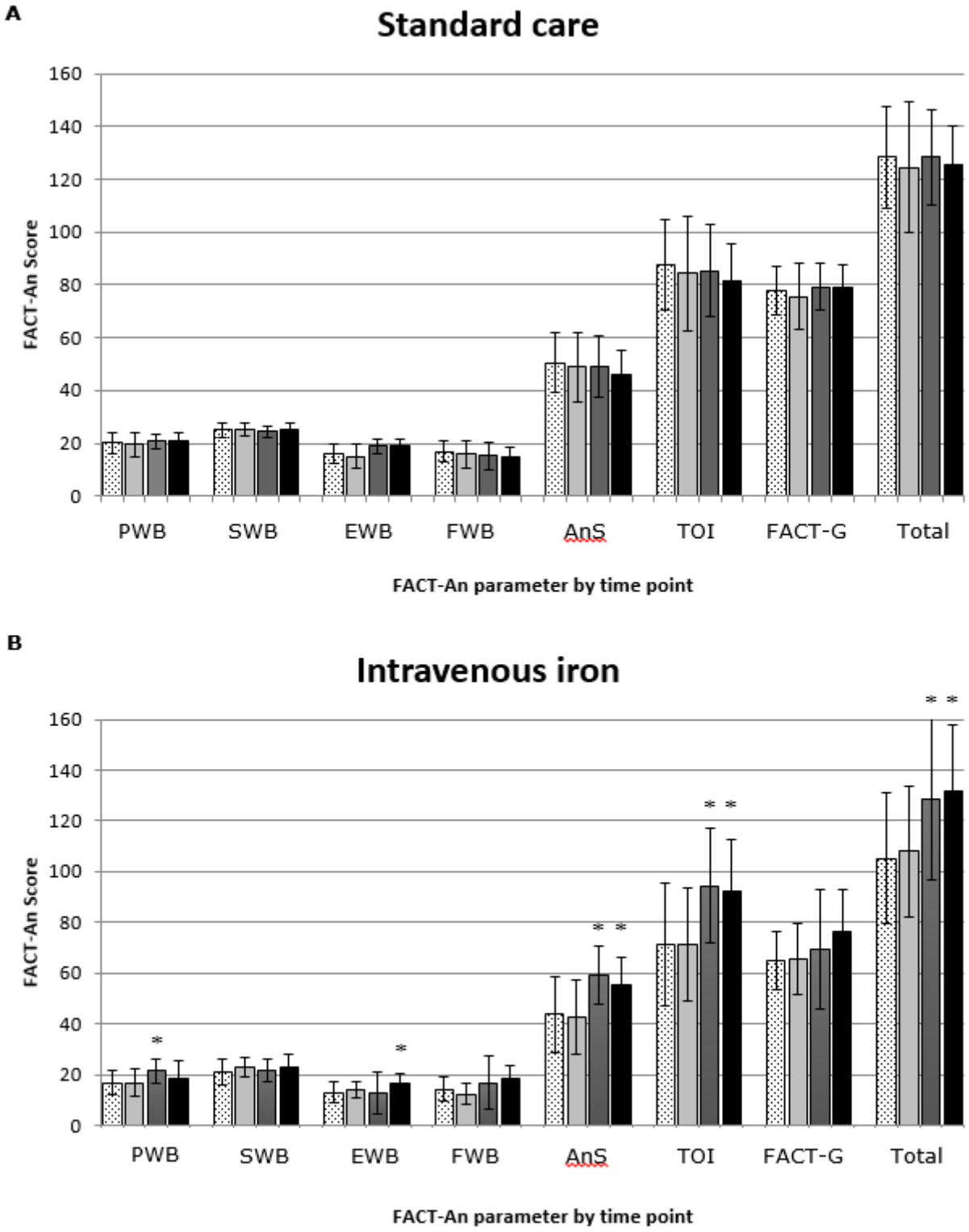


Figure 4 FACT-An Quality of Life A. Standard care B. Intravenous iron

* Minimum Clinically Important Difference exceeded

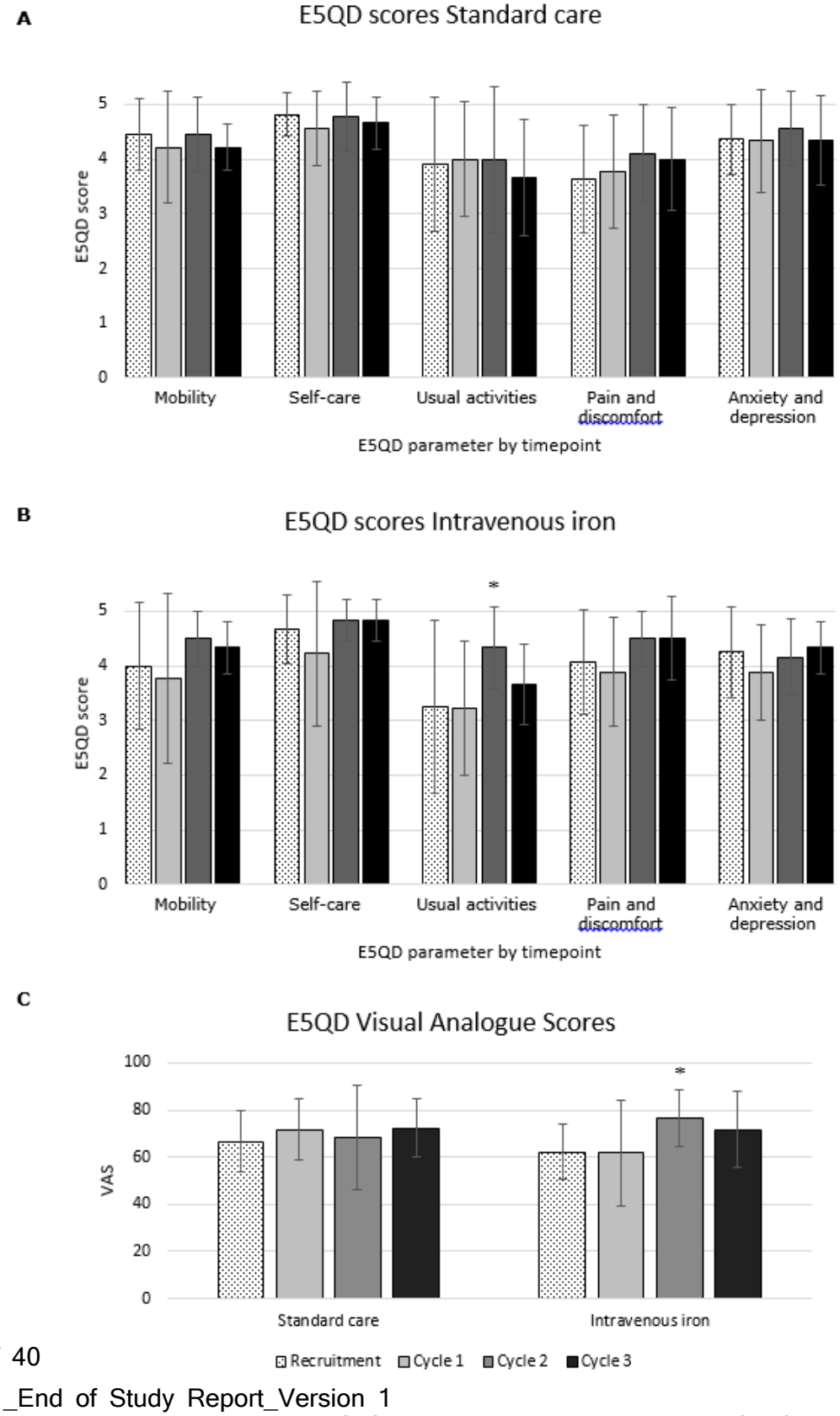


Figure 5 E5QD scores A. Standard care B. Intravenous iron C. E5QD Visual analogue scores standard care and intravenous iron

16. Conclusions

Clinical endpoints have shown higher than reported rates of anaemia in this group of patients with over half of patients anaemic at presentation. Haemoglobin dropped over three cycles of chemotherapy in the standard care group and either increased or remained stable in the intravenous iron group. This appeared to translate into no transfusions beyond cycle one of chemotherapy in the intravenous iron group. This is in keeping with findings from the two gynaecological studies where iron was effective as a preventative strategy to avoid anaemia and hence blood transfusions at their transfusion threshold of haemoglobin less than 10 g/dL (Dangsuwan and Manchana 2010, Athibovonsuk, Manchana et al. 2013). However, our small numbers and no power calculation prevent us from concluding this definitively.

Intravenous iron compared to standard care was effective at replenishing iron stores and restoring transferrin saturations to greater than 20%. After increasing initially, ferritin then declined over the three cycles of chemotherapy and transferrin saturations again fell below 20% by cycle three suggesting that these patients would have become iron deficient again beyond cycle three. A repeat dosing regimen used in other trials (Kim, Kim et al. 2007, Athibovonsuk, Manchana et al. 2013) might therefore be advantageous. We have used a high single dose preparation of iron isomaltoside compared to low dose repeat dosing regimens of iron sucrose in other trials. The merits of both strategies could be further researched but in inflammatory bowel disease, these high dose regimens appear more effective (Evstatiev, Marteau et al. 2011).

Quality of life scores were higher at baseline in the standard care group. The higher haemoglobin at baseline might explain this and reports from other studies suggest that higher haemoglobin is associated with better quality of life. Despite this, intravenous iron improved quality of life while standard care did not. This supports studies that have demonstrated correcting anaemia improves quality of life (Crawford, Cella et al. 2002, Cella, Kallich et al. 2004, Yakymenko, Frandsen et al. 2017).

No new safety concerns were raised during this trial including no differences in infection or venous thromboembolism. Current intravenous iron preparations already have a well-regarded safety profile (Auerbach and Macdougall 2014).

17. Future Research

In the UK 21,133 oesophagogastric cancers were diagnosed in 2013-2015. Of these patients 6,226 received palliative oncology. This study examined intravenous iron for anaemia in 27 patients from this group while undergoing palliative chemotherapy. The feasibility outcomes have highlighted factors that may prevent a definitive study of this design being deliverable on a wider scale. These include the high decline rate of palliative chemotherapy, high transfusion rates, poor prognosis and poor acceptability within this palliative care group. Applying our feasibility outcomes to the national figures, 402 patients per year could potentially be recruited. Based upon our data however, the sample size to detect an expected difference in Hb of 1.5 g/dL by cycle three of chemotherapy (standard deviation 1.48 g/dL; effect size 30%) at a 1-sided alpha of 0.05 and a power of 80 % is 774 patients. A study designed to examine the broader subject of chemotherapy-induced anaemia in oesophagogastric cancer (including those receiving neoadjuvant in whom chemotherapy is very infrequently declined) or the broader palliative cancer population in whom anaemia and fatigue are common may be more pragmatic and generalisable study than the small subset of patients presented here.

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

Not applicable.

20. References

Athibovonsuk, P., T. Manchana and N. Sirisabya (2013). "Prevention of blood transfusion with intravenous iron in gynecologic cancer patients receiving platinum-based chemotherapy." Gynecol Oncol **131**(3): 679-682.

Auerbach, M. and I. C. Macdougall (2014). "Safety of intravenous iron formulations: facts and folklore." Blood Transfus **12**(3): 296-300.

Cella, D., J. Kallich, A. McDermott and X. Xu (2004). "The longitudinal relationship of hemoglobin, fatigue and quality of life in anemic cancer patients: results from five randomized clinical trials." Ann Oncol **15**(6): 979-986.

Crawford, J., D. Cella, C. S. Cleeland, P. Y. Cremieux, G. D. Demetri, B. J. Sarokhan, M. B. Slavin and J. A. Glaspy (2002). "Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy." Cancer **95**(4): 888-895.

Dangsuwan, P. and T. Manchana (2010). "Blood transfusion reduction with intravenous iron in gynecologic cancer patients receiving chemotherapy." Gynecologic Oncology **116**(3): 522-525.

Evstatiev, R., P. Marteau, T. Iqbal, I. L. Khalif, J. Stein, B. Bokemeyer, I. V. Chopey, F. S. Gutzwiller, L. Riopel, C. Gasche and F. S. Group (2011). "FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease." Gastroenterology **141**(3): 846-853 e841-842.

Kim, Y. T., S. W. Kim, B. S. Yoon, H. J. Cho, E. J. Nahm, S. H. Kim, J. H. Kim and J. W. Kim (2007). "Effect of intravenously administered iron sucrose on the prevention of anemia in the cervical cancer patients treated with concurrent chemoradiotherapy." Gynecologic Oncology **105**(1): 199-204.

Yakymenko, D., K. B. Frandsen, I. J. Christensen, A. Norgaard, P. I. Johansson, G. Daugaard and M. Mau-Sorensen (2017). "Randomised feasibility study of a more liberal haemoglobin trigger for red blood cell transfusion compared to standard practice in anaemic cancer patients treated with chemotherapy." Transfus Med.