1.1 Study Recruitment

A total of 35 patients were recruited over 16 months (November 2018-February 2020) across 2 centres. The median number of patients enrolled per month up until the lockdown was 2 (range 0-4). The study was initially opened at Nottingham University Hospitals with the Royal Wolverhampton Hospital joining in April 2019.

Recruitment was disrupted due to the national lockdown imposed in response to the COVID-19 pandemic (Figure 1). As a consequence recruitment was extended until April 2021, but further accrual was not possible during this time due to the ongoing restrictions of the pandemic. As the trial had achieved its primary aimed of assessing the feasibility of the study design a decision was made not to extend recruitment past April 2021.

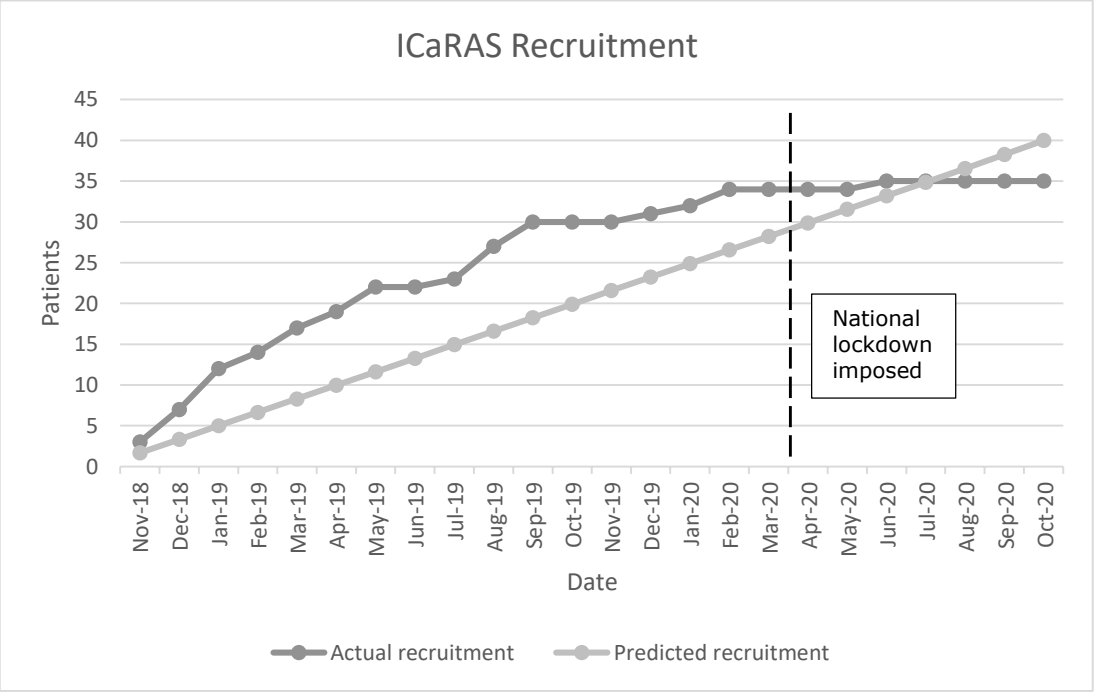

Figure 1 – ICaRAS predicted and actual accrual per month.

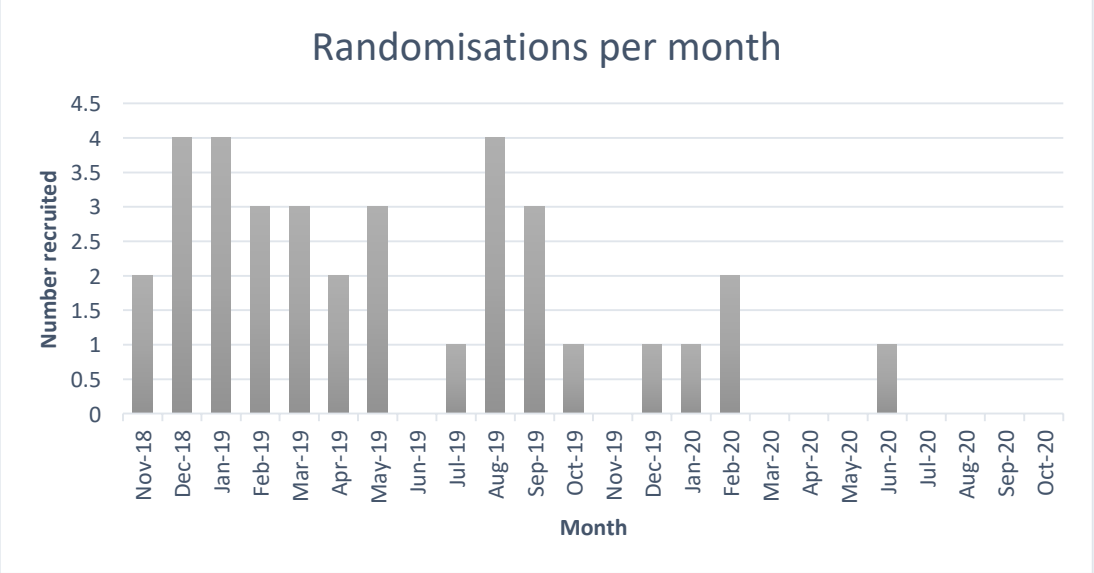

Figure 2 – ICaRAS monthly patient recruitment

1.2 Feasibility

709 patients assessed for eligibility (596 from palliative care clinics or day-therapy, 113 from cancer MDT cancer). From these 628 of 709 were ineligible giving a screen failure rate of 88.5%. From those ineligible 144 did not have a solid epithelial tumour or had a non-malignant diagnosis, 133 were not anaemic, 196 were undergoing active anti-cancer therapy, 89 had a performance status >2 and 66 were ineligible according to other trial exclusion criteria (see CONSORT diagram

Figure 3)

A total of 81 patient screened were eligible with 72 approached to participate. Among these acceptability was 47.2% with 34 recruited to the study. A further 9 patients had been eligible but had a deterioration in their physical condition before the study team had an opportunity to approach them.

Those declining to participate in the study were not required to share their reasoning. However, many patients volunteered their thoughts. In the majority of cases this was due to the extra burden of visits required to participate in the study or the fact that the patient did not feel well enough in themselves to participate. There were two instances of patients declining on the grounds of randomisation – with both stating they would not want to risk being in the placebo arm. One patient stated that his

health insurance would not permit participation in a clinical trial None of the patients declined due to the chosen outcome measures..

After enrolment one patient was withdrawn prior to randomisation due to acute physical deterioration and a move to end of life care. 34 patients were randomised to the placebo or intravenous iron arm of the study. There were no significant differences in baseline characteristics between groups (

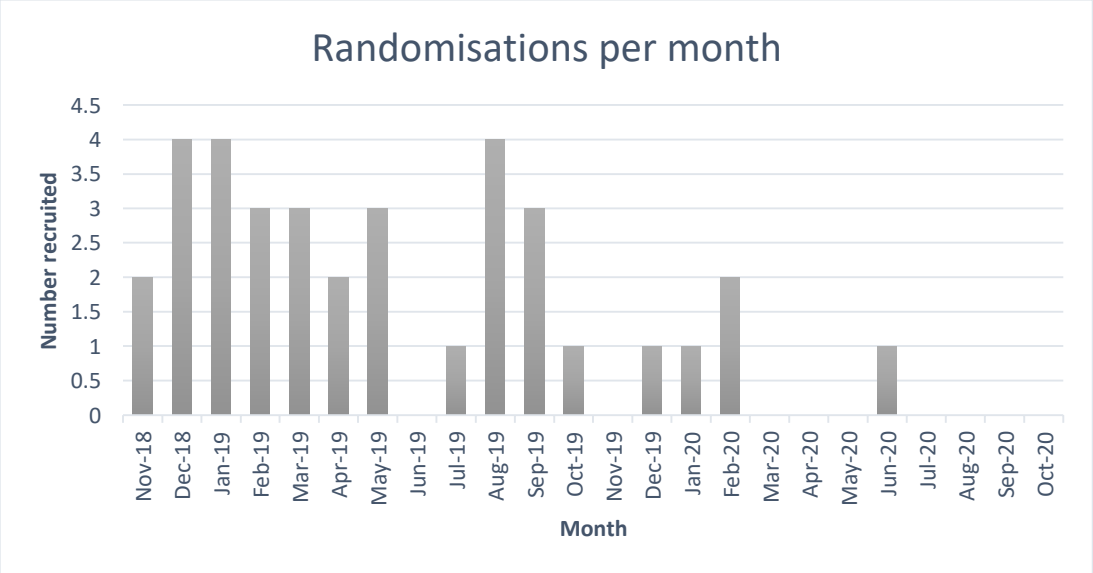

Figure 2 – ICaRAS monthly patient recruitment

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1.2.1 Study Attrition

Dropout from enrolment to infusion 8 days later was 5.7% (n=2) At 4 weeks after infusion a further 5 patients had dropped out (3 deaths, 1 withdrawn consent and 1 clinical deterioration) giving a combined attrition rate of 20% at this timepoint. By 8 weeks a further 2 patients were withdrawn, both due to cancer progression and worsening health giving a total attrition rate of 25.7% for the duration of the study. There were also 2 patients (1 in each study arm) who did not attend their 4 week follow up appointment due to ill health. However, both of these patients were willing to continue in the study and attended their 8 week follow up visit.

1.3 Safety

There were no serious adverse reactions reported during the study. One patient who received intravenous iron reported nausea and mild abdominal pain which was self-limiting within 24 hours of their infusion and did not require medical attention. One patient also reported a headache after their infusion which was mild and self limiting.

During the trial a total of 10 serious adverse events were reported to the independent medical monitor all of which were deemed unrelated to the

study intervention (Table 1). 6 patients died during the study (3 in each study arm). Reasons for death had been progression of their existing cancer (n=4), pneumonia (n=1) and complications following a myocardial infarction (n=1). One patient underwent unplanned radiotherapy during the study and required admission due to diarrhoea and vomiting.

Table 1 - Serious adverse events reported during the ICaRAS trial.

System organ class (SOC) **- Lower level term (LLT)**	**Number of SAEs**
Infections and Infestations - Pneumonia	1 (IV iron)
Cardiac disorders - Myocardial Infarction	1 (IV iron)
Neoplasms benign, malignant and unspecified - Brain metastasis secondary to ovarian cancer	1 (IV iron)
Blood and Lymphatic System Disorders - Anaemia requiring blood transfusion	1 (placebo)
Gastrointestinal Disorders - Diarrhoea and vomiting	1 (placebo)
Skin and subcutaneous tissue disorders - Leg oedema and cellulitis - Pressure sore	2 (placebo)
Musculoskeletal and connective tissue disorders - Exacerbation of chronic back pain - Exacerbation of chronic leg pain	2 (placebo)
Surgical and medical procedures - Insertion of oesophageal stent	1 (IV iron)

1.3.1 Iron dosing

Blinding was maintained during the administration of infusions in all cases. 7 participants required a split dose infusion due to their allocated or 'dummy' dose exceeding the 20mg/kg/week limit for Monofer. All patients were infused over at least 30 minutes with physical observations including heart rate, blood pressure and pulse oximetry being recorded prior to, during and after infusion. All participants were observed for 15 minutes after infusion for signs of early adverse reaction. Among those receiving intravenous iron 41% (n=7) patients received 1000mg and 59% (n=10) received 1500mg. Median number of days from enrolment to infusion was 8 (range 7-15) and in those requiring a second infusion median duration was 7 days (range 7-14).

33 of 34 patients randomised received their allocated infusion. One patient in the placebo arm was withdrawn after randomisation due to acute deterioration and did not proceed to receive their infusion. One patient in the intravenous iron arm only received one dose (1000mg) of their split dose infusion due to a fall requiring admission to hospital. They later died due to the development of community acquired pneumonia and subsequent clinical deterioration.

After infusion one patient from the intravenous iron arm withdrew consent and did not proceed to any follow up visits. One patient from the placebo

arm crossed over to the treatment arm after their usual medical team administered a dose of intravenous iron due to worsening anaemia. There was no other cross-over among patients.

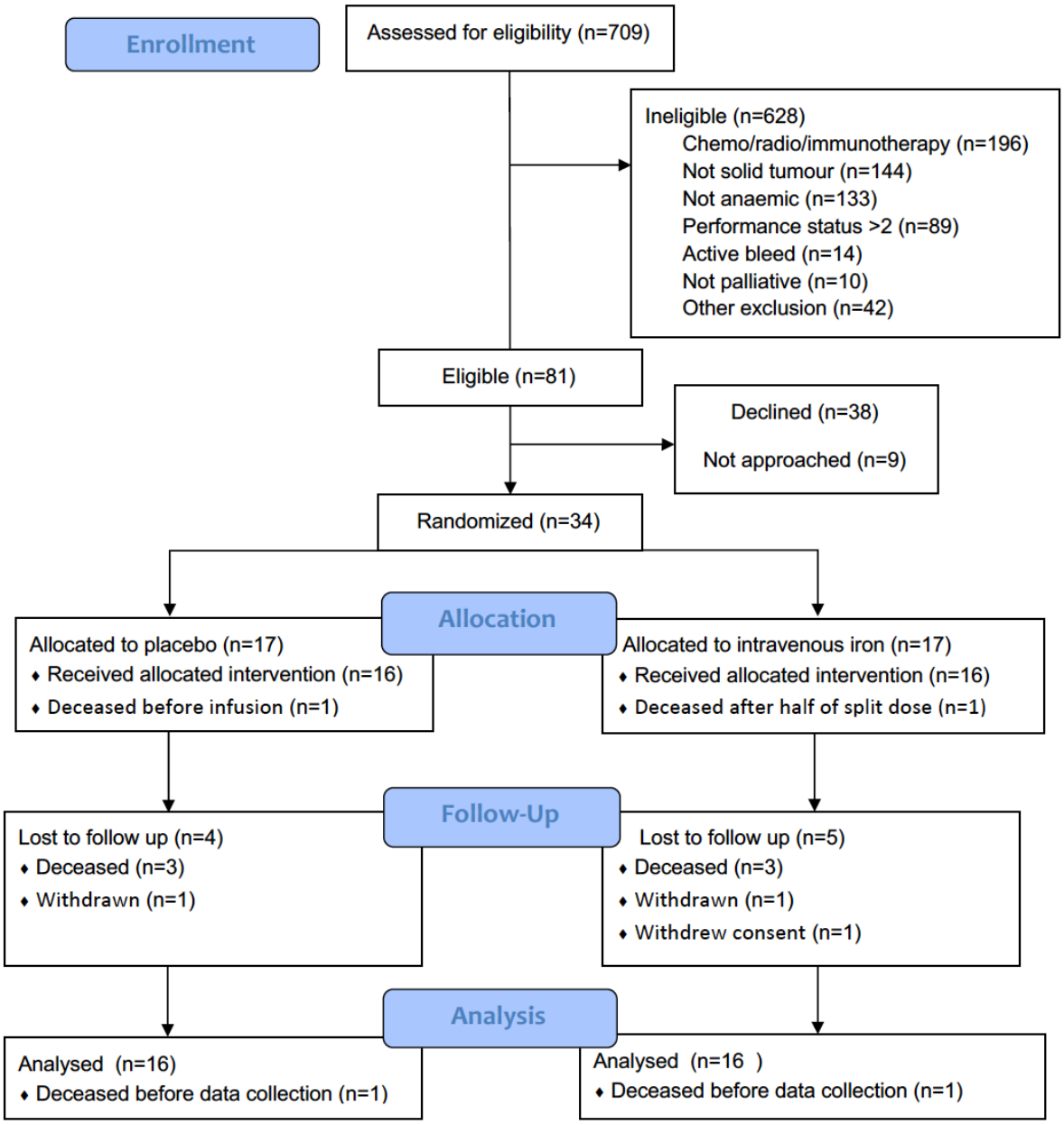

Figure 3 - ICaRAS Trial CONSORT diagram

Table 2 - ICaRAS baseline demographics. Continuous variables are presented as mean (SD) or median (IQR [range]). Categorical variables are presented as % (total). No significant baseline differences existed between groups.

	Placebo (n=17)	Intravenous iron (n=17)
Sex	9F/8M	13M/4F
Age	77 (69.2-79 [58-84])	74 (64-82 [61-93])
Height	165 (9.1)	169 (10.1)
Weight	75.5 (16.9)	73 (17.9)
BMI	26.4 (5.9)	25.2 (5.3)
Ethnicity		
White British	88.2 (n=15)	88.2 (n=15)
Asian Pakistani	5.9 (n=1)	5.9 (n=1)
Black Carribean	5.9 (n=1)	5.9 (n=1)
Fatigue score (range 0-10)	5.6 (1.4)	7 (1.7)
Performance status		
0	5.9 % (n=1)	5.9% (n=1)
1	41.2 % (n=7)	47.1% (n=8)
2	52.9% (n=9)	47.1% (n=8)
Existing oral iron	11.8% (n=2)	5.9%
Yes	88.2% (n=15)	94.1%
No		
Smoker		
Current	11.8% (n=2)	11.8% (n=2)
Ex	58.8 (n=10)	64.7% (n=11)
Never	29.4% (n=5)	23.5% (n=4)

1.4 Haemoglobin and Iron Studies

1.4.1 Haemoglobin

Mean baseline haemoglobin was 102 g/L (SD 18.1 [range 75-129]) for the placebo group and 108 g/L (SD 12.5 [81-125]) for the IV iron group P=0.393. At week 4 mean haemoglobin for the placebo group was 106g/L (17.9 [76-137]) with a mean difference from baseline of 4g/L (SD 11.2) and 117 g/L (17.5 [86-139]) for the IVI group with a mean difference of 9g/L (8.5). At 8 weeks mean haemoglobin was 107g/L (15.8 [80-133]) for the placebo group with a mean difference from baseline of 5g/L (7.3) and 118.1g/L (13.9 [87-138]) for the IV iron group with a mean difference of 10.1g/L (10.1). Among the placebo group 92% (n=12) remained anaemic at week 4 and week 8 compared to 61% (n= 8) of participants in the IVI group.

Median baseline erythropoietin levels were 15.3 ([IQR 11.5-36] range 7.8-227) for the placebo group and 12.1([IQR 9.3-34.2] range 2.9-47) for the IV iron group (P=0.165). Across the entire cohort only one individual in the IV iron group was identified as having a low baseline EPO level. Their haemoglobin response was in keeping with the rest of the group (Baseline – week 4 Hb + 8 g/L, baseline - week 8 +13 g/L). In addition, one way ANOVA found no significant variation in anaemia severity according to EPO level (F=0.803, P=0.504)

Measurements of zinc were undertaken at all 3 study visits. Baseline values were comparable between groups (placebo 11.5 umol/L, IV iron 11.0 umol/L , P=0.520). In addition, no significant intergroup differences were found in mean serum zinc concentration any timepoint and baseline values. However, severity of anaemia did vary significantly according to serum zinc concentration (F=8.216, P=<0.001) with significant differences between non-anaemia and moderate anaemia (MD 3.81, SE 0.79, P=<0.001) and mild and moderate anaemia (MD 1.8, SE 0.59, P=0,.018). Baseline zinc was low in 3 participants in the IV iron group. All 3 individuals saw a rise in week 4 haemoglobin compared to baseline (MD 8g/L [SD 2], P=0.02) but by week 8 mean haemoglobin had fallen below baseline levels (MD -10 [SD 9.1], P=0.199).

Table 3 Change in haemoglobin and iron studies across follow up. P values relate to intragroup change from baseline.

		Baseline	**Week 4**	**Week 8**
Placebo	**Haemoglobin** g/L	102 (18.1)	106 (17.9) P=0.418	107 (15.8) P=0.848
	Iron mmol/L	8.57 (4.7)	6.7 (2.8) P=0.153	8.1 (3.8) P=0.715
	Ferritin ng/ml	201 (220)	243 (294) P=0.636	209 (197) P=0.947
	TSAT %	16.5 (8.6)	14.8 (6) P=0.602	18.4 (10.3) P=0.310
IV iron	**Haemoglobin** g/L	108 (12.5)	117 (17.5) P=0.035	118.1 (13.9) P=0.034
	Iron mmol/L	10.2 (3.2)	14.1 (6.2) P=0.015	11 (6.1) P=0.560
	Ferritin ng/ml	211 (283)	908 (737) P=<0.001	996 (907) P=0.001
	TSAT %	16.8 (4.5)	31.2 (12.2) P=0.003	22.6 (8.2) P=0.010

Both groups had an even distribution of functional iron deficiency (FID; placebo 46% n= 7, IV iron 50%, n=8) and absolute iron deficiency (AID; placebo 53% n=8, IV iron 50% n=8). A comparison of those participants with FID (ferritin >100ng/ml) and AID found that baseline Hb was lower in FID patients in both groups (placebo FID 105g/L [SD 19.9], AID 109g/L [20.1], P=0.741; IV iron FID 100g/L [14.7], AID 121 [8.4] P=0.015). Haemoglobin change among AID and FID participants at each study point is shown in Figure 4. Haemoglobin response in the IV iron group was more immediate in the AID group with peak haemoglobin being reached at week 4 whereas the FID group only saw a significant increase after 8 weeks.

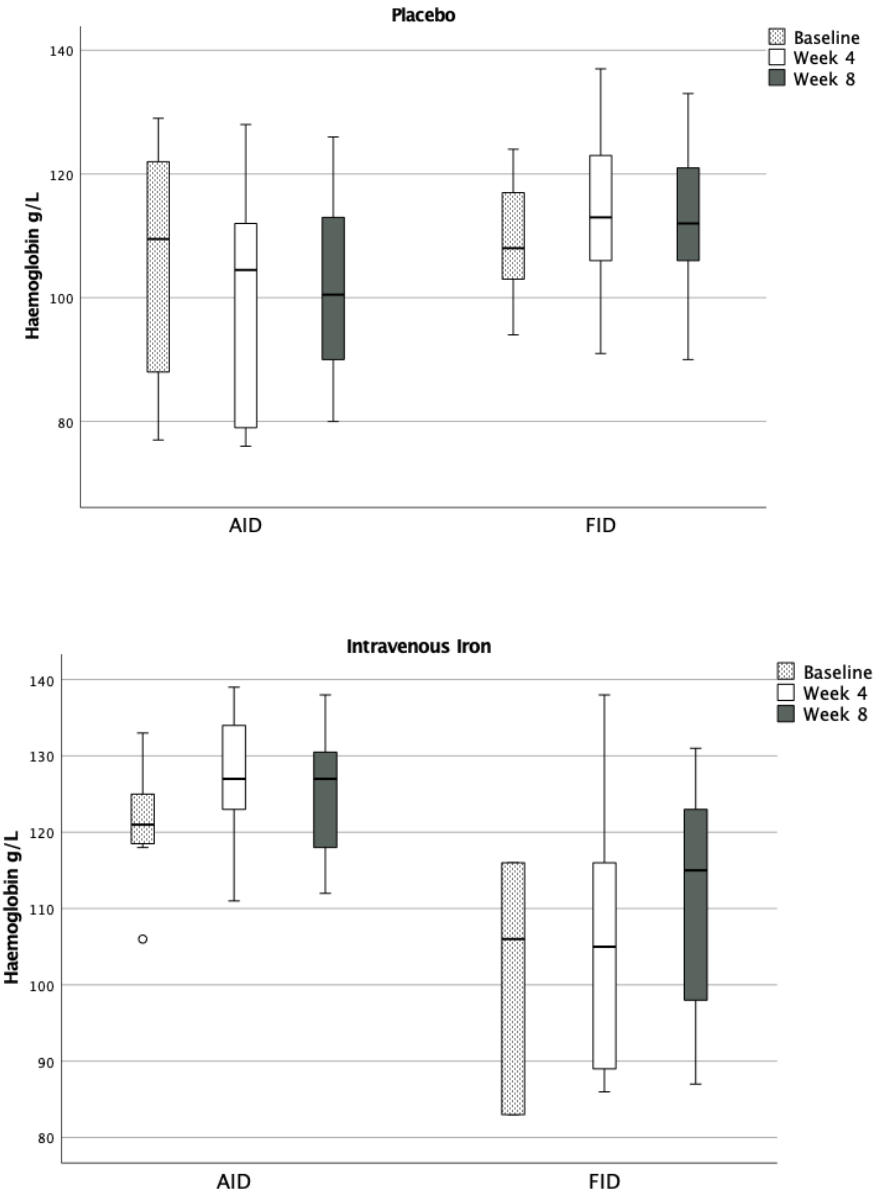

Figure 4 - Change in haemoglobin for placebo and intravenous iron groups according to baseline iron deficiency anaemia status. AID, absolute iron deficiency; FID, functional iron deficiency

1.4.2 Change in Iron Studies

Both groups were well matched for baseline ferritin (Table 3). As previously described mean baseline ferritin was high in both groups

(placebo 201 ng/ml [SD 220] range 11-756]; IV iron 211 ng/ml [SD 283] range 19-953]) due to half of cases in both arms displaying biochemical evidence of functional iron deficiency. Baseline CRP was significantly higher at baseline for pooled FID patients compared to those with AID (FID 16 [16], AID 48 [55], P=0.042). Among the placebo group ferritin remained unchanged during the 8 weeks of study follow up. In contrast, the IV iron group saw increases at both 4 weeks (mean difference 594 ng/ml [95% CI -74-1264], P=0.078) and 8 weeks (MD 770 ng/ml [28-1511], P= 0.043) compared to the placebo group (Figure 5).

Both groups had an equivalent mean transferrin saturation at baseline. By week 4 the placebo group saw a reduction in TSAT % whereas the IV iron group saw a statistically significant increase (MD 13.8% [5.1-22.6], P=0.004). By week 8 increases in TSAT had reduced for the IVI group but remained higher than the placebo group (MD 5.2 [-4.2-14.7], P=0.259). (Figure 6)

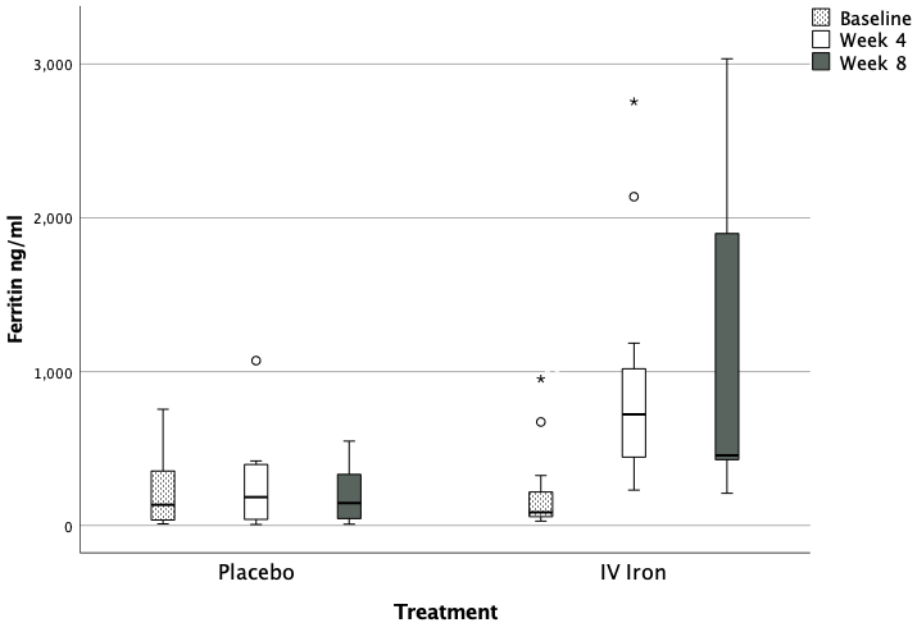

Figure 5 – Ferritin (ng/ml) at baseline, week 4 and week 8 for placebo and IV iron groups.

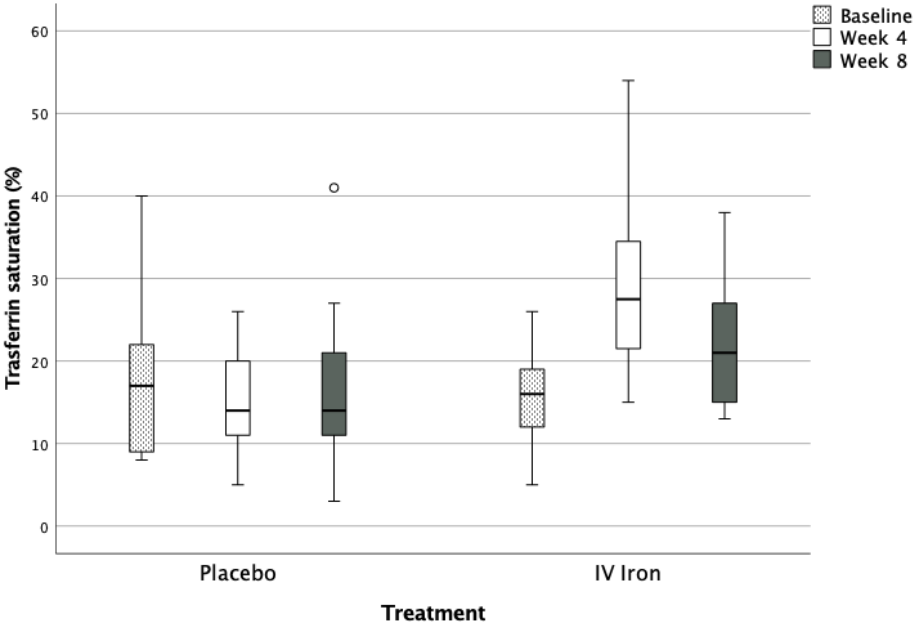

Figure 6 – Transferrin saturation (%) at baseline, week 4 and week 8 for placebo and IV iron groups.

1.5 Allogenic blood transfusion

There were only two transfusion events during the study. One patient received a 2 unit transfusion due to an acute drop in haemoglobin before randomisation and was later withdrawn due to clinical deterioration. The other event occurred in a patient in the placebo arm of the study prior to their 8 week follow up. This patient was admitted following an episode of haematemesis due to their oesophageal cancer where they received a 2 unit blood transfusion. No transfusion events occurred in the intravenous iron arm of the study.