

# Protecting Vital Organs in High Risk Patients - The Present & Future Role of Noninvasive Smart Technology in Advancing Patient Safety



**Location:** Strauss 1 Room, Messe Wien Congress Center  
Vienna, Austria

**Date and Time:** Sunday June 2<sup>nd</sup> • 12:15 - 13:45  
*Lunch will be provided*

**Chairperson:** Basil Matta, MD, BA, BAO, BCh, MB, FRCA, FFICM

[Please click here to register.](#)



## Presenters



### *Caring for High Risk Patients - New Insights, New Challenges in Optimizing Vital Organ Monitoring*

**Basil Matta, MD, BA, BAO, BCh, MB, FRCA, FFICM**

Divisional Director, MSK. Digestive Diseases, Major Trauma and Perioperative Care Medicine  
Clinical Lead - Cambridge University Hospitals Trust  
Consultant, Anaesthesia and Critical Care  
Associate Lecturer, University of Cambridge  
Cambridge, United Kingdom



### *Hypoxaemia or Hyperoxia - Which Is Worse? - New Horizons*

**Sigismund Lasocki, MD, PhD**

Professor of Anesthesiology and Intensive Care  
Chief Department of Anesthesiology and Intensive Care  
Chairman - Pôle ASUR (Anesthésie SAMU Urgences Réanimation), CHU Angers  
Angers, France



### *Optimizing Oxygen Delivery: Do We Need to Redefine Our Haemodynamic Goals?*

**Azriel Perel, MD**

Professor of Anesthesiology and Intensive Care  
Department of Anesthesiology and Intensive Care  
Sheba Medical Center, Tel Aviv University  
Tel Aviv, Israel



### *Cerebral Oxygenation: New Insights into the Mechanism of Delirium in Cardiac Surgery - Reasons for a Change!*

**André Denault, MD, PhD, ABIM-CCM, FRCPC, FASE, FCCS**

Professor of Anesthesiology and Intensive Care  
Department of Anesthesiology, Critical Care Program  
Montreal Heart Institute, and Centre Hospitalier de l'Université de Montréal  
Université de Montréal  
Montreal, Quebec, Canada



### *Post-operative Cognitive Dysfunction (POCD) & Delirium: Preventing Damage and Improving Outcome - The Role of Bilateral EEG*

**Massimo Lamperti, MD, MBA**

Clinical Professor of Anesthesiology  
Acting Institute Chair  
Anesthesiology Institute-Cleveland Clinic Abu Dhabi  
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University  
Abu Dhabi, United Arab Emirates



Interactive Session, please ask any questions to our Faculty now! For more information, please stop by Masimo,  
Stand #B0401. [Please click here to register and ask your questions.](#)

## Original Article

# The impact of pre-operative intravenous iron on quality of life after colorectal cancer surgery: outcomes from the intravenous iron in colorectal cancer-associated anaemia (IVICA) trial

**B. D. Keeler,<sup>1</sup> E. A. Dickson,<sup>2</sup> J. A. Simpson,<sup>3</sup> O. Ng,<sup>4</sup> H. Padmanabhan,<sup>5</sup> M. J. Brookes,<sup>5,6</sup> A. G. Acheson,<sup>3,7</sup> and the IVICA Trial Group<sup>a</sup>**

1 Consultant Colorectal Surgeon, Milton Keynes University Hospital NHS Foundation Trust, Eaglestone, UK

2, 4 Clinical Research Fellow, NIHR Biomedical Research Unit in Gastrointestinal and Liver Diseases at Nottingham, University Hospitals NHS Trust and the University of Nottingham, UK

3 Consultant Colorectal Surgeon, Department of Colorectal Surgery, Nottingham University Hospitals NHS Trust, Nottingham, UK

5 Consultant Gastroenterologist, New Cross Hospital, Royal Wolverhampton NHS Trust, Wolverhampton, UK

6 Associate Professor of Gastroenterology, University of Wolverhampton, UK

7 Associate Professor of Surgery, University of Nottingham, UK

## Summary

Anaemia is associated with a reduction in quality of life, and is common in patients with colorectal cancer. We recently reported the findings of the intravenous iron in colorectal cancer-associated anaemia (IVICA) trial comparing haemoglobin levels and transfusion requirements following intravenous or oral iron replacement in anaemic colorectal cancer patients undergoing elective surgery. In this follow-up study, we compared the efficacy of intravenous and oral iron at improving quality of life in this patient group. We conducted a multicentre, open-label randomised controlled trial. Anaemic colorectal cancer patients were randomly allocated at least two weeks pre-operatively, to receive either oral (ferrous sulphate) or intravenous (ferric carboxymaltose) iron. We assessed haemoglobin and quality of life scores at recruitment, immediately before surgery and at outpatient review approximately three months postoperatively, using the Short Form 36, EuroQoL 5-dimension 5-level and Functional Assessment of Cancer Therapy – Anaemia questionnaires. We recruited 116 anaemic patients across seven UK centres (oral iron  $n = 61$  (53%), and intravenous iron  $n = 55$  (47%)). Eleven quality of life components increased by a clinically significant margin in the intravenous iron group between recruitment and surgery compared with one component for oral iron. Median (IQR [range]) visual analogue scores were significantly higher with intravenous iron at a three month outpatient review (oral iron 70, (60–85 [20–95]); intravenous iron 90 (80–90 [50–100]),  $p = 0.001$ ). The Functional Assessment of Cancer Therapy – Anaemia score comprises of subscales related to cancer, fatigue and non-fatigue items relevant to anaemia. Median outpatient scores were higher, and hence favourable, for intravenous iron on the Functional Assessment of Cancer Therapy – Anaemia subscale (oral iron 66 (55–72 [23–80]); intravenous iron 71 (66–77 [46–80]);  $p = 0.002$ ), Functional Assessment of Cancer Therapy – Anaemia trial outcome index (oral iron 108 (90–123 [35–135]); intravenous iron 121 (113–124 [81–135]);  $p = 0.003$ ) and Functional Assessment of Cancer Therapy – Anaemia total score (oral iron 151 (132–170 [69–183]); intravenous iron 168 (160–174 [125–186]);  $p = 0.005$ ). These findings indicate that intravenous iron is more efficacious at improving quality of life scores than oral iron in anaemic colorectal cancer patients.

Correspondence to: E. A. Dickson

Email: edward.dickson@nhs.net

Accepted: 12 March 2019

Keywords: anaemia; colorectal cancer; intravenous iron; peri-operative care; quality of life

aMembers are listed in Appendix A.

This article is accompanied by an editorial by Shah and Bailey, *Anaesthesia* 2019; **74**: 696-9.

Twitter: @Ed\_Dickson; @GastroMJB; @austin\_acheson

---

## Introduction

Colorectal malignancy is often associated with anaemia, with a reported incidence of up to 40% in newly diagnosed cases [1]. The aetiology of this anaemia is frequently due to iron deficiency secondary to chronic blood loss (absolute iron deficiency) or impaired utilisation of iron stores (iron sequestration, and functional iron deficiency) [2, 3]. In addition, treatment of the underlying colorectal cancer using surgery or chemotherapy can lead to a worsening of anaemia in these patients.

It is recognised that anaemia causes a variety of symptoms including fatigue, lethargy and dyspnoea [4]. It has been shown that reducing haemoglobin (Hb) levels are associated with decreasing quality of life (QoL) scores in the context of malignancy, and hence it has been proposed that reversal of this anaemia will improve cancer-related QoL [4]. Furthermore, in relation to operative cases, there has been a recent focus on standardising end points in peri-operative medicine, with cancer-related QoL emerging as a key patient-centric end point [5].

Iron replacement therapies such as oral iron are associated with deleterious side-effects including abdominal pain, constipation and diarrhoea. Treatment non-adherence rates attributed to such side-effects have been reported to be in the region of 40% [6]. In addition, absorption pathways and access to oral iron supplementation may be impaired in patients with malignancy [4]. Newer intravenous iron preparations have been developed which are proposed to offer safer, better tolerated and more efficacious treatment of iron deficiency anaemia [7].

We aimed to compare the QoL scores of colorectal cancer patients who were randomly allocated to receive either oral or intravenous iron as pre-operative treatment for their anaemia, in order to review if either treatment conferred an advantage in terms of improving QoL scores.

## Methods

We conducted this multicentre study in accordance with the Declaration of Helsinki, with full ethical approval from the National Research and Ethics Service, East Midlands,

Nottingham. We registered the study with both the MHRA and Clinical Trials.Gov. We obtained written informed consent from all study participants.

We have previously reported the methods as part of a trial comparing blood transfusion rates of anaemic colorectal cancer treated with pre-operative oral and intravenous iron [8]. Anaemic colorectal cancer patients with non-metastatic disease were randomly allocated pre-operatively in a 1:1 fashion using variable block allocation, stratified by sex and age, to receive either oral iron (ferrous sulphate 200 mg twice daily until surgery) or intravenous iron (ferric carboxymaltose – Ferinject™; Vifor Pharma, Glattbrugg, Switzerland) dosed by weight and haemoglobin in accordance with the summary of product characteristics. Treatment allocation was un-blinded owing to the change in stool colour associated with oral iron supplementation. To minimise the risks of including patients with non-iron deficiency anaemia, those with the following conditions were not included: metastatic disease; pre-existing haematological disease; renal failure; and those currently undergoing chemotherapy. All patients were included at recruitment and surgery. Only those who underwent resectional surgery and attended the outpatient follow-up were included at outpatient review.

Quality of life assessments and haemoglobin measurements were performed at the following time-points: recruitment before iron administration; on the day of surgery before intervention; and at their outpatient follow-up visit between two and three months following discharge. If an outpatient appointment was expedited due to a complication, this appointment was not used for trial purposes, and review was delayed until the subsequent appointment falling within the correct 2–3-month postoperative period. This was to ensure that all reviews occurred at a comparable postoperative time-point.

The QoL measures we used included the EuroQoL 5-dimension 5-level (EQ5D5L) [9] questionnaire and the modified Short Form 36 v1 (SF36) [10] as overviews of general well-being. These were augmented with the Functional Assessment of Cancer Therapy – Anaemia

(FACT-An) questionnaire [11]. This validated questionnaire assesses specific quality of life concerns related to anaemia and fatigue in cancer patients.

The EQ5D5L questionnaire has been widely used in cancer and cancer-related anaemia studies [12]. Scoring involved two components; health state description and evaluation. For the first component, we recorded patient-reported scores by level of severity: a score of 1 indicates no problems; 2, slight problems; 3, moderate problems; 4, severe problems; and 5, extreme problems. The five dimensions included: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. For the second component, we asked patients to rate their health status on the day of the questionnaire using a 20-cm vertical scale with end-points of 0 and 100; the point 0 corresponded to the 'worst health you can imagine', and 100 corresponded to 'the best health you can imagine'. Missing data were not imputed for the EQ5D5L as values obtained were not utilised for generation of further scores.

Scoring for the SF36 form has been previously described and validated in this patient group [13]. In total, eight sections derive a scaled score based on the weighted sums of the questions in that section. We then transformed scores into a 0–100 scale, based on the assumption that each question carried equal weight. Lower scores indicated a higher level of disability. The eight sections included: physical functioning; bodily pain; role limitations due to physical health problems; role limitations due to personal or emotional problems; emotional well-being; social functioning; energy/fatigue; and general health perceptions. We assessed SF36 data using the validated software as recommended and provided by the questionnaire developers (QualityMetric Health Outcomes™, SF36 Scoring Software version 4.0).

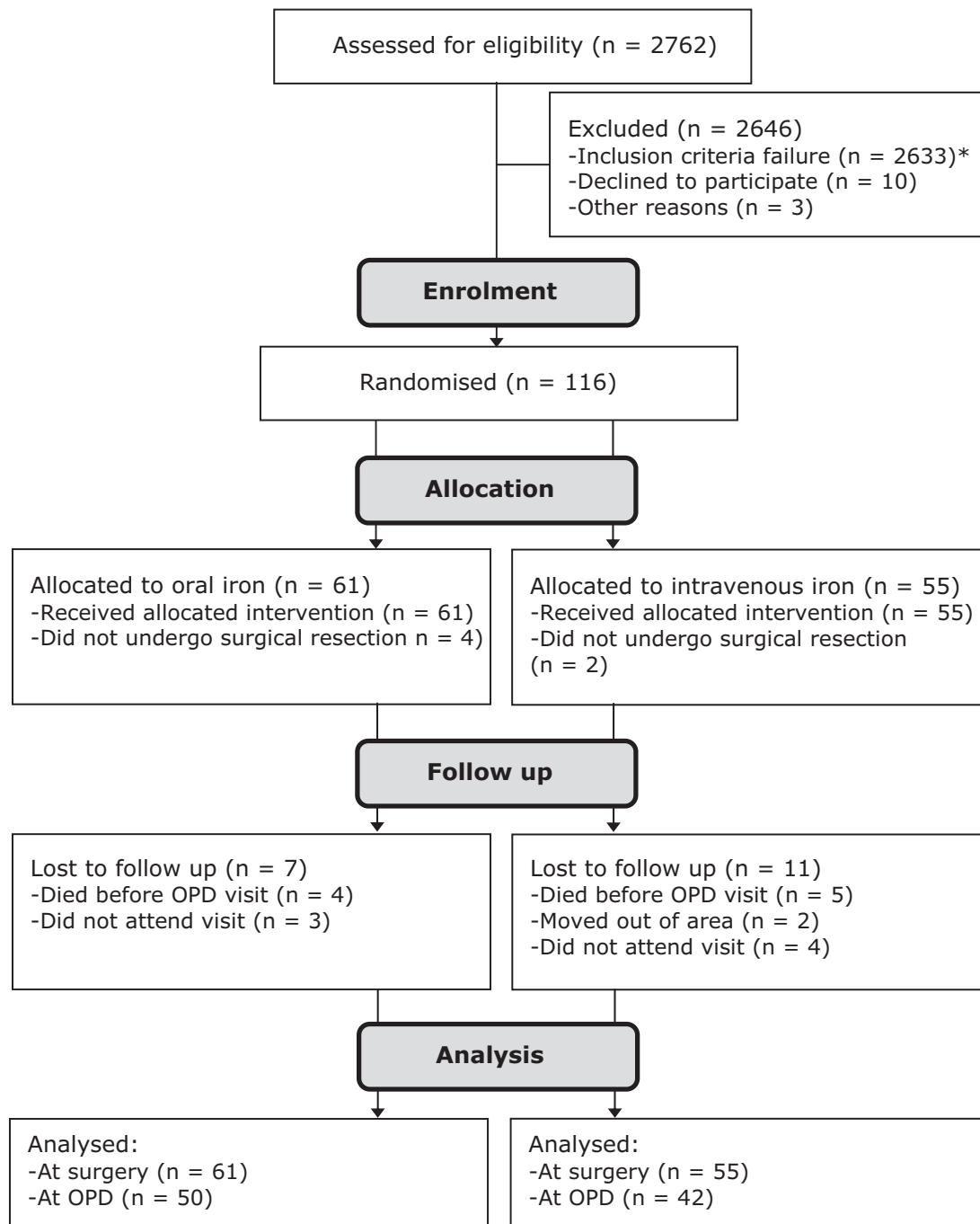
The components of the Functional Assessment of Cancer Therapy – Anaemia (FACT-An) tool included measures comprising 48 questions (each scored 1–4) on Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, Functional Well-Being, and an Anaemia-Specific Subscale. These component values were then combined to calculate three further composite total scores: The FACT-An Trial Outcome Index; the FACT-G (General) and FACT-AN (Anaemia Specific). In accordance with FACT-AN administration guidelines, subscale scores were prorated if more than 50% of the data was available (i.e. greater than four of the relevant seven questions answered), but responses were excluded if they failed to meet this level. Derived values were only calculated if all the component subscale values were available [14]. Additional missing data were therefore not imputed.

The statistical level of significance for all tests was defined as  $p < 0.05$ . We compared paired continuous data with Student's paired t-tests, and unpaired with Student's t-tests. The relationship between Hb levels and selected components of each QoL tool was investigated to ensure Hb change was a key causal factor underlying changes in QoL. This has been described in previous studies for components including SF36 Vitality [1], SF36 Physical Component Summary [15], FACT-Trial Outcome Index [16], FACT-Anaemia Subscale scores, FACT-G scores [1] and also visual analogue scale equivalents [17]. These components were used as markers of validity, and were tested using pooled paired Hb and QoL scores at recruitment and surgery. We excluded outpatient review values from this process due to the potential confounding effects of adjuvant chemotherapy. Validity was indicated by significant positive correlations between Hb and QoL scores (Pearson's two-tailed test). We compared qualitative data with the two-tailed Chi-squared test. We performed statistical analyses using SPSS® version 21 (SPSS, Chicago, IL, USA).

The magnitude of clinical effects for changes in QoL scores within each group between recruitment and the day of surgery was calculated using effect size [18]. This standardised measure of change was obtained by dividing the difference between baseline and post-treatment scores by the standard deviation of baseline scores. We considered effect sizes of 0.2 to be small, 0.5 moderate and 0.8 large. This effect size was then used to calculate if a minimal clinical difference (MCD) had been exceeded, using the recognised definition of an effect size of greater than 0.2 [18]. We then used this same definition to calculate the Hb change that would be required to have a clinically apparent change in QoL score. For this, all patients were pooled to determine paired Hb and QoL scores at recruitment and at outpatient visits, irrespective of treatment administered, for the key variables previously tested to assess the validity of Hb and QoL association. A clinically-relevant response in QoL change was defined as an effect size either small ( $\text{score} \geq 0.2$ ) or moderate ( $\text{score} \geq 0.5$ ) in magnitude [18]. Responders were defined as those who reached the threshold of the corresponding effect size, whereas non-responders were those who failed to reach this threshold. The mean Hb changes in those who responded and did not respond were then calculated and compared with the two-tailed Student's t-test.

## Results

We randomly allocated 61 patients to receive oral iron and 55 to intravenous iron (Fig. 1). As previously reported [8], all



**\*Exclusion details:**

- |                                      |   |
|--------------------------------------|---|
| Haemoglobin level normal (n = 1807)  | Metastatic disease (n = 240)                    |
| Not for surgery/palliative (n = 192) | No Hb available at diagnosis (n = 124)          |
| Not adenocarcinoma (n=108)           | Chemo/radiotherapy as primary therapy (n = 73)  |
| Operation date too soon (n = 38)     | Medical comorbidity exclusion criteria (n = 35) |
| Endoscopic resection/observe (n = 8) | Clinical team deemed unsuitable (n = 3)         |
| Prisoner (n = 3)                     | Unable to consent (n = 2)                       |

**Figure 1** CONSORT diagram for the trial. \*Patients who did not have surgical resection were not included in the final outpatient appointment. OPD, outpatients department.

of the intravenous iron group patients received the drug and did not receive oral iron. This study's oral iron treatment protocol was adhered to by 50 out of 55 (91%) patients who did not have the date of surgery moved; no patients randomly allocated to oral iron received intravenous iron.

Patients were well-matched across groups (Table 1). There were no differences in any of the following measures: baseline characteristics; initial QoL scores; baseline Hb; haematinic levels; operative access; operation performed; tumour stage/location; iron therapy duration; and median time from recruitment to outpatient review (oral iron 101 (IQR 62–193[range 62–335]) days; intravenous iron 91 (48–321 [61–135]) days,  $p = 0.980$ ) [8]. One hundred and ten patients underwent resectional surgery (oral iron  $n = 57$  (52%), intravenous iron  $n = 53$  (48%)) and 92 patients attended their outpatient review (oral iron  $n = 50$  (54%), intravenous iron  $n = 42$  (46%)). Hb levels were higher at surgery, and in outpatients with intravenous iron; however, there were no differences in blood transfusion use [8]. There was no difference in adjuvant chemotherapy use in those reviewed as outpatients (oral iron  $n = 23$  (25%); intravenous iron  $n = 12$  (7.6%),  $p = 0.134$ ).

Postoperative recovery was similar across both groups. There were no significant differences in complication rates (oral iron  $n = 40$  (70.2%), and intravenous iron  $n = 33$  (62.3%),  $p = 0.381$ ) or Clavien–Dindo grade ( $p = 0.995$ ) between recruitment and outpatient follow-up. Infective complications were more frequent in the intravenous iron group, with 15 patients (28%) experiencing complications by postoperative day seven, and 21 patients (39.6%) by day 28. This compared with nine patients (15.8%) by day seven and 14 patients (24.6%) by day 28 for oral iron. These differences, however, were not statistically significant ( $p = 0.112$  and  $p = 0.091$ , respectively), and neither was the grade of these complications (up to day seven,  $p = 0.106$ , and up to day 28,  $p = 0.083$ ). Types of infection included: wound (oral iron  $n = 11$  (19%), and intravenous iron  $n = 15$  (28%)); lower respiratory tract (oral iron  $n = 7$  (12%), and intravenous iron  $n = 11$  (21%)); urinary tract (oral iron  $n = 9$  (16), intravenous iron  $n = 6$ , 11%) and sepsis of unknown source (oral iron  $n = 4$  (7%), and intravenous iron  $n = 4$  (7%)).

Mean Hb changes from recruitment to outpatient review in relation to clinical improvements in QoL scores

**Table 1** Patient baseline characteristics and operative information. Values are number, mean (SD) or median (IQR [range]).

	<b>Oral iron n = 61</b>	<b>Intravenous iron n = 55</b>
Men	37	35
Age; years	76.5(10.9)	73.8(8.9)
Height; m	1.67(9.2)	1.69(10.3)
Weight; kg	72.7(17.2)	79.1(15.3)
Inclusion Hb g.l <sup>-1</sup>	99(11)	96(13)
Patients receiving oral iron at recruitment	30	25
Days of iron pre-treatment, if applicable	20(6–34 [9–151])	27(13–37 [6–223])
Days of study treatment	21(15–33 [14–49])	21(15–34 [14–52])
ASA physical status 1–2	43	30
Physical status ASA 3–4	18	25
Cr-POSSUM mortality score at recruitment %	3.6(2.6–9.3 [1.0–33.0])	3.5(2.6–6.6 [0.7–33.0])
Adjusted Charlson Score at recruitment	2.5(1.5)	2.8(0.9)
No operation performed	4	2
Laparoscopic	30	26
Converted laparoscopic	4	5
Open	23	22
Right colonic tumour	41	35
Left colonic tumour	12	11
Rectal tumour	4	7
Tumour T stage: T ≤ 2	5	8
Tumour T stage: T3 and T4	52	45
Tumour size; mm	45.5(35–60 [15–120])	40(34–55 [0–90])
Blood loss; ml	100(58–200 [20–1400])	100(55–390 [15–2000])
Intra-operative fluid; l	1.3(1.3)	1.1(1.2)

**Table 2** Comparison of mean haemoglobin changes between those who did and did not have a clinical quality of life improvement from recruitment to outpatient review. Values are mean (SD). Effect size [18] was calculated by dividing the difference between baseline and post-treatment scores by the standard deviation of baseline scores, where effect sizes of > 0.2 were regarded to be small, > 0.5 moderate and > 0.8 large. Responders are those who reached the threshold of the specified effect size. Non-responders failed to reach the specified effect size.

Component	Grade of effect size	Group	Hb change g.l <sup>-1</sup>	p value
EQ5D5L visual analogue scale	Mild	Responders	30.6(17.9)	0.016
	Mild	Non-responders	20.9(16.8)	
	Moderate	Responders	33.4(17.0)	0.002
	Moderate	Non-responders	20.8(17.0)=112)	
SF36 vitality	Mild	Responders	28.8(18.3)	0.126=112)
	Mild	Non-responders	22.6(17.0)=112)	
	Moderate	Responders	31.3(17.1)	0.026=112)
	Moderate	Non-responders	22.2(17.6)	
SF36 mental component summary	Mild	Responders	29.7(19.4)	0.017
	Mild	Non-responders	19.4(10.7)	
	Moderate	Responders	30.5(19.7)	0.020
	Moderate	Non-responders	20.9(12.8)	
SF36 physical component summary	Mild	Responders	29.7(17.2)	0.108
	Mild	Non-responders	23.1(17.9)	
	Moderate	Responders	30.9(18.0)	0.078
	Moderate	Non-responders	23.4(17.2)	
FACT-An anaemia subscale	Mild	Responders	26.0(17.5)	0.311
	Mild	Non-responders	21.3(17.1)	
	Moderate	Responders	26.8(19.2)	0.246
	Moderate	Non-responders	21.8(14.9)	
FACT-An trial outcome index	Mild	Responders	23.8(17.4)	0.968
	Mild	Non-responders	23.6(17.55)	
	Moderate	Responders	24.6(18.1)	0.648
	Moderate	Non-responders	22.3(16.3)	
FACT-G	Mild	Responders	26.0(17.4)	0.252
	Mild	Non-responders	20.3(16.7)	
	Moderate	Responders	25.7(17.1)	0.445
	Moderate	Non-responders	22.1(17.6)	

EQ5D5L, EuroQoL 5-dimension 5-level questionnaire; SF36, modified Short Form 36 v1 questionnaire; FACT-AN, Functional Assessment of Cancer Therapy – Anaemia questionnaire.

and effect size are illustrated in Table 2. When we compared scores for all components which showed a significant intragroup change from recruitment to surgery, only one component in the oral iron group was of a magnitude to meet a minimal clinically important difference (i.e. effect size > 0.2). This compared with 11 patients in the intravenous iron group (see Table 3). On review of the entire cohort at recruitment and on the day of surgery, the Hb level at each time-point was positively correlated with the following QoL scores: FACT-Trial Outcome Index (R = 0.416, p = 0.002); FACT-G (R = 0.234, p = 0.013); FACT-An Anaemia Subscale (R = 0.279, p = 0.011); EQ5D5L visual analogue scale (R = 0.251, p = 0.001); SF36

Physical Component Summary (R = 0.227, p = 0.003); and SF36 Vitality (R = 0.252, p = 0.001). The results of some of these scores are reported below.

In the intravenous iron group, all components of the FACT-An score increased significantly during at least one inter-visit period, with the exception of social well-being, and six of the eight components increased from both recruitment to surgery and from surgery to outpatient review. Despite the general trend for increases in each component score noted in both groups throughout the study period, these increases were only significant for one component at one time period for oral iron (Fig. 2). Median (IQR [range]) intravenous iron scores were significantly

**Table 3** Evaluation of magnitude of clinical effect for component scores which increased significantly between recruitment and day of surgery. Effect size [18] was calculated by dividing the difference between baseline and post-treatment scores by the standard deviation of baseline scores where grading of effect sizes of > 0.2 were regarded to be small, > 0.5 moderate and > 0.8 large.

QoL	Component	Group	Recruitment to day of surgery change (score)	SD	Effect size	Effect grade
FACT-AN	Physical well-being	iv iron	2.5	5.47	0.46	Small
	Functional well-being	iv iron	3.87	6.52	0.59	Moderate
	Anaemia subscale	iv iron	9	16.14	0.56	Moderate
	Trial outcome index	iv iron	15.3	24.96	0.61	Moderate
	FACT-G	iv iron	7.1	13.01	0.55	Moderate
	FACT-total	iv iron	7.1	27.24	0.26	Small
EQ5D5L	Mobility	Oral iron	0.31	1.08	0.29	Small
	Self-care	iv iron	0.08	0.51	0.16	NCD
	Pain and disability	iv iron	0.47	1.01	0.47	Small
	Visual analogue score	iv iron	8.4	19.93	0.42	Small
SF36	General health	iv iron	3.25	20.26	0.16	NCD
	Vitality	iv iron	13.22	23.79	0.56	Moderate
	Social functioning	iv iron	7.09	29.49	0.24	Small
	Mental component summary	iv iron	2.85	9.34	0.31	Small

EQ5D5L, EuroQoL 5-dimension 5-level questionnaire; SF36, modified Short Form 36 v1 questionnaire; FACT-AN, Functional Assessment of Cancer Therapy - Anaemia questionnaire; iv, intravenous iron; NCD, no clinical difference.

higher than oral iron responses at outpatient follow-up for emotional well-being (oral iron 21 (20–22 [7–24]); intravenous iron 22 (21–24 [10–28]),  $p = 0.033$ ); functional well-being (oral iron 22 (15–25 [9–28]); intravenous iron 26 (23–28 [12–28]),  $p = 0.001$ ); FACT-An subscale (oral iron 66 (55–72 [23–80]); intravenous iron 71 (66–77 [46–80]),  $p = 0.002$ ), FACT-An trial outcome index (oral iron 108 (90–123 [35–135]); intravenous iron 121 (113–124 [81–135]),  $p = 0.003$ ) and FACT-An total score (oral iron 151 (132–170 [69–183]); intravenous iron 168 (160–174 [125–186]),  $p = 0.005$ ).

Intra-group changes in each component of EQ5D5L are illustrated in Fig. 3. Median visual analogue scores were significantly higher with intravenous iron than with oral iron at outpatient review (oral iron 70, (60–85 [20–95]); intravenous iron 90 (80–90 [50–100]),  $p = 0.001$ ).

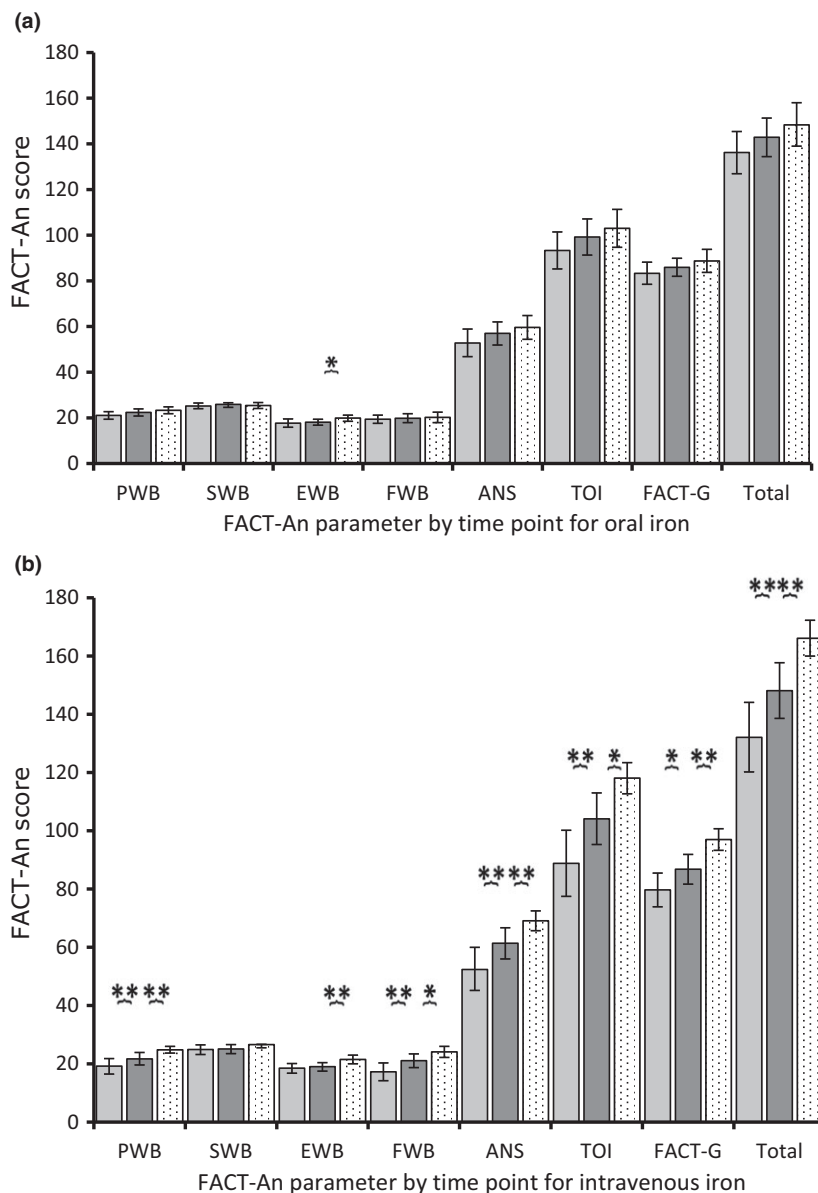
Within the oral iron group, only the mental component summary score of the SF36 between surgery and outpatient review showed a significant increase ( $p = 0.041$ ). In contrast, within the intravenous iron group, all factors significantly increased between surgery and outpatients: Physical Functioning mean difference (MD) 10.52, ( $p = 0.04$ ); Role Limitation due to emotion MD 23.89, ( $p = 0.020$ ); Role Limitation due to pain MD 33.33, ( $p = 0.004$ ); General Health MD 8.68, ( $p = 0.005$ ); Vitality MD 18, ( $p = 0.001$ ); Social Functioning MD 17.08,

( $p = 0.008$ ); Mental Health MD 10.8, ( $p = 0.001$ ); Physical Component Summary MD 5.7, ( $p = 0.003$ ); Mental Component Summary MD 7.36, ( $p = 0.001$ ) and Bodily Pain MD 15.56, ( $p = 0.002$ ). Furthermore, General Health MD 3.25, ( $p = 0.049$ ), Mental Component Score MD 2.85, ( $p = 0.018$ ); Vitality MD 13.22, ( $p = 0.001$ ) and Social Functioning MD 7.09, ( $p = 0.005$ ) also increased significantly from recruitment to surgery. Significant differences were evident between groups at outpatient review in all but two of the SF36 components, as illustrated in Table 4.

## Discussion

We found that intravenous iron resulted in a faster clinically evident increase in QoL scores than oral iron, and may be more efficacious at improving QoL scores in anaemic colorectal cancer surgical patients. The differences seen were most profound over a longer duration from initiation of treatment, which is expected given the lag between intravenous iron administration and response, as noted in previous trials [19]. Despite this, the significant clinical effect of intravenous iron was also evident after short periods of pre-operative optimisation. This benefit of intravenous iron was not solely limited to the specific symptomatology of anaemia but was also evident across generic measures of well-being. We believe that it is most likely that the



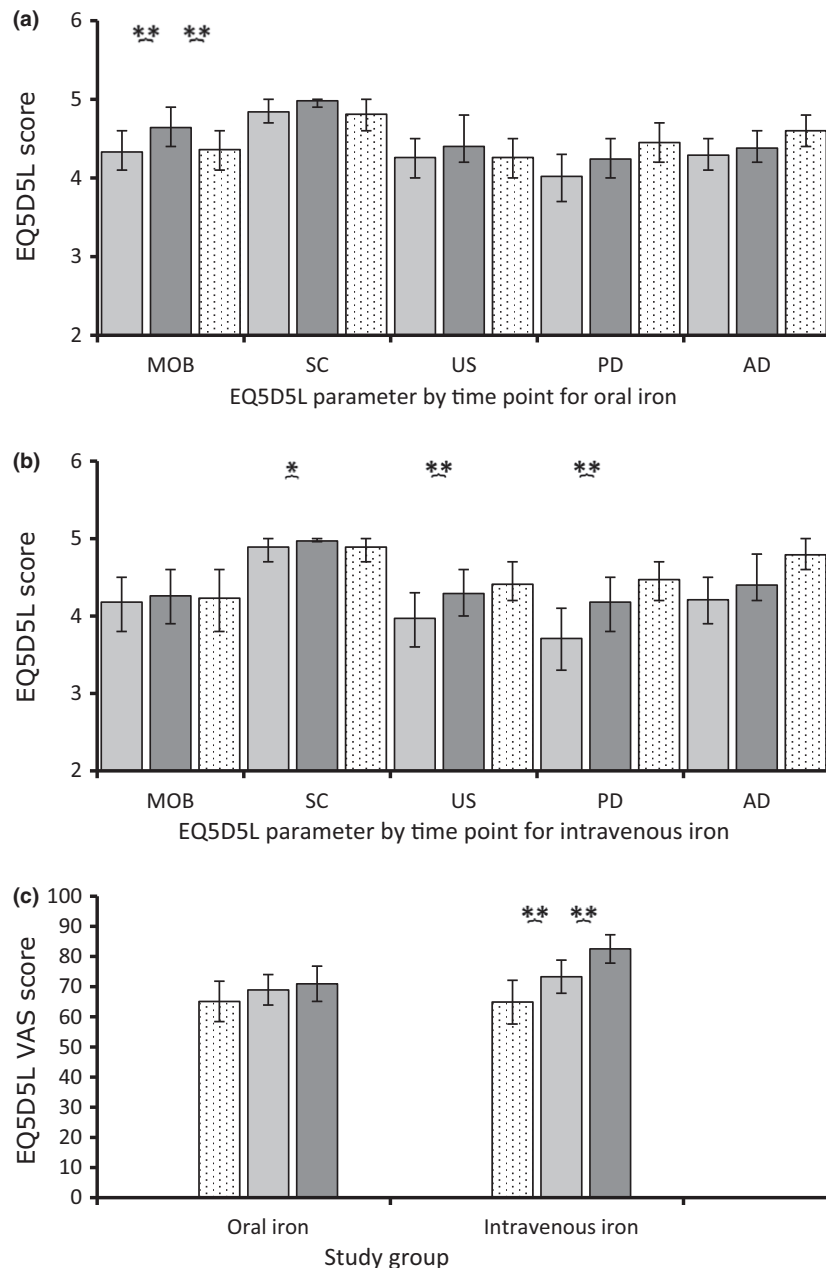


**Figure 2** FACT-An mean scores at each time-point for (a) oral iron and (b) intravenous iron. Recruitment□; Day of surgery■; Outpatient Department appointment▣; PWB, Physical Well-being; SWB, Social/Family Well-being; EWB, Emotional Well-being; FWB, Functional Well-being; ANS, Anaemia Subscale; TOI, FACT-An Trial Outcome Index; Fact-G, Fact G total score; FACT Total, FACT-An Total Score. \*Significance to  $p < 0.05$ , and \*\*to  $p < 0.01$ . Error bars display 95%CI.

improvements in QoL were secondary to more efficacious treatment of anaemia. Intravenous iron is thought to produce more rapid and greater rises in Hb levels than oral iron [8, 20–22], and as demonstrated in the present study, QoL scores were closely correlated with absolute Hb values. This is further supported by a lack of other key confounders which may influence QoL including operative access and adjuvant therapy.

Our results show that only the intravenous iron group showed significant changes in QoL scores between

recruitment and day of surgery, which met a minimal clinical difference. Based on the definition of effect size, ‘small’ improvements were seen in seven components across broad aspects of QoL, with anaemia-specific components showing ‘moderate’ improvements. The literature argues that a moderate effect size ( $> 0.5$ ) is required to demonstrate a significant clinical change in QoL [18, 23]. This threshold of discrimination for changes in health-related quality of life has been validated clinically [23], and is based on the psychological assessment of the limits of



**Figure 3** Changes in EQ5D5L component scores at each time-point for (a) oral iron and (b) intravenous Iron and (c) visual analogue scale scores. □ Recruitment ■ day of surgery ▨ Outpatient Department appointment; MOB, Mobility; SC, Self-care; US, Usual Activity; PD, Pain and Disability; AD, Anxiety and Depression; VAS, visual analogue scale. \*Significant change in  $p < 0.05$  and \*\*of  $p < 0.01$ . Error bars display 95%CI.

human discrimination [24]. Measures of Vitality (SF36), Functional Well-Being and specific scores of anaemia symptomatology (FACT-AN) still met this higher threshold of MCD, and hence changed significantly even over the short period from recruitment to day of surgery. These components would appear to be closely linked to anaemia and thus also Hb levels (Table 2).

The QoL tools employed requested patients to report their QoL over periods ranging from 1–4 weeks. Considering that the initial time period of iron treatment from recruitment to surgery was in the order of 3 weeks, there would have been a degree of overlap of the pre-treatment period when QoL was reported on the day of surgery, leading to perhaps an underestimation of the

**Table 4** SF36 component scores at review in each group. Values are mean (SD) or median (IQR [range]). p values below scores denote intra-group differences from the previous time-point, and p values in the right column denote inter-group differences between oral and intravenous iron at each time-point.

Field	Time	Oral iron	Intravenous iron	Oral vs. intravenous p value
Physical functioning	Recruitment	65 (31–85 [0–100])	60 (20–84 [0–100])	0.589
	Day of surgery	65 (40–85 [10–100]) p = 0.735	65 (30–90 [10–100]) p = 0.154	0.887
	Outpatient	70 (32–87 [0–96]) p = 0.237	74 (45–95 [0–100]) p = 0.041	0.377=112)
Role limitation due to pain	Recruitment	25 (0–100 [0–100])	12.5 (0–100 [0–100])	0.713
	Day of surgery	25 (0–100 [0–100]) p = 0.924	50 (0–100 [0–100]) p = 0.297	0.34
	Outpatient**	25 (0–100 [0–100]) p = 0.502	100 (50–100 [0–100]) p = 0.004	0.01
Bodily pain	Recruitment	72 (51–100 [0–100])	68 (41–100 [12–100])	0.981
	Day of surgery	72 (46–92 [0–100]) p = 0.641	80 (51–100 [22–100]) p = 0.056	0.3
	Outpatient	74 (52–100 [31–100]) p = 0.053	84 (74–100 [2–100]) p = 0.001	0.229
General health	Recruitment	57 (46–72 [15–92])	55 (45–77 [20–95])	0.776
	Day of surgery	62 (50–77 [27–92]) p = 0.112	63 (52–77 [25–90]) p = 0.049	0.758
	Outpatient**	62 (50–77 [10–92]) p = 0.652	77 (65–86 [45–100]) p = 0.005	0.002
Vitality	Recruitment	47 (24)	44 (24)	0.625
	Day of surgery*	52 (21) p = 0.177	59 (22) p = 0.001	0.048
	Outpatient**	59 (19) p = 0.065	72 (16) p = 0.001	0.00
Social functioning	Recruitment	75 (50–86 [25–100])	63 (34–88 [0–100])	0.159
	Day of surgery	62.5 (50–100 [0–100]) p = 0.716	75 (50–100 [0–100]) p = 0.005	0.349
	Outpatient*	75 (50–100 [0–100]) p = 0.391	100 (88–100 [25–100]) p = 0.008	0.03
Role limitation due to emotion	Recruitment	57 (44)	61 (47)	0.849
	Day of surgery	68 (44) p = 0.631	60 (46) p = 0.202	0.261
	Outpatient*	74 (43) p = 0.230	80 (37) P = 0.020	0.03
Mental health	Recruitment	76 (65–87 [44–100])	76 (64–88 [12–100])	0.947
	Day of surgery	78 (64–89 [40–100]) p = 0.539	80 (72–92 [24–100]) p = 0.080	0.178
	Outpatient**	84 (72–92 [20–100]) p = 0.093	92 (88–92 [56–100]) p = 0.001	0.00
Physical component summary	Recruitment	42 (11)	41 (11)	0.71
	Day of surgery	43 (10) p = 0.915	43 (11) p = 0.060	0.678
	Outpatient	43 (9) p = 0.889	47 (9) p = 0.003	0.119

(continued)

**Table 4** (continued)

Field	Time	Oral iron	Intravenous iron	Oral vs. intravenous p value
Mental component summary	Recruitment	47 (9)	46 (10)	0.773
	Day of surgery	48 (10) p = 0.352	51 (10) p = 0.018	0.1
	Outpatient**	51 (10) p = 0.041	57 (6) p = 0.001	0.001

\*Statistical significance to  $p < 0.05$ .

\*\*Statistical significance to  $p < 0.01$ .

treatment effect for both treatments. If indeed Hb levels were closely linked to QoL scores as suggested by the present study, then such an underestimate of clinical effects would be further evident in the more efficacious treatment of anaemia which recent data indicate is attributed to intravenous iron. This may account for why, although clinically-relevant increases in scores were seen with intravenous iron at the point of surgery, few scores were significantly higher than those within the oral iron group. We also acknowledge that current recommendations suggest at least a three-week timeframe for haemoglobin incrementation with intravenous iron administration [25]. Likewise, oral iron was given over a similar timescale, and in both cases the treatment effect may have been underestimated. However, our trial was designed to be pragmatic and applicable to current cancer treatment timelines. It must be acknowledged that in some European countries the timing of surgery for malignancy is subject to legal regulations [26]. Consequently, a balance between timely cancer treatment, haemoglobin improvement and quality of life is needed. Therefore, the constraints of the clinical timeline were factored into the trial design.

It must be re-emphasised that in the current randomised controlled trial, the study was powered to detect a difference in transfusion rates, and not for QoL as the primary outcome measure. QoL outcomes were specified as secondary outcomes in the original trial design, and we, therefore, acknowledge that further studies powered to analyse QoL outcomes are required to validate these findings. Furthermore, due to difficulties in concealing oral iron administration from patients due to stool discoloration [27], the study was not blinded by design. This does leave our study vulnerable to the placebo effect, and the influence of patient beliefs on QoL perception. In addition, questionnaires were distributed at follow-up between two and three months following surgery. Quality of life can change over time, and this may have, therefore, influenced patient-reported

scores. There were, however, no significant differences in mean time to postoperative follow-up between the two groups.

Haemoglobin was positively correlated with six subscales across all three QoL questionnaires. Although we found that the correlation was modest, it is important to acknowledge that there are a multitude of factors influencing QoL. Therefore, it could be argued that over this timescale, the improvements in QoL scores seen with Hb changes as a discrete factor emphasise the clinical importance of treating anaemia in this patient group. On review of the entire cohort, it appeared that as Hb increases approached the  $30 \text{ g.l}^{-1}$  increment, small improvements in QoL scores were evident, which rose to a moderate clinical effect when changes exceeded this mark. This could be used as a target for both future research and in clinical practice to guide therapy in this patient population.

## Acknowledgements

The authors wish it to be known that, in their opinion, the last two authors should be regarded as joint senior authors. This article presents independent research funded by the National Institute for Health Research (NIHR), UK. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The Ferinject used within the trial was donated to all study centres except Nottingham University Hospitals NHS Trust by Vifor Pharma, Glattbrugg, Switzerland.

MB's research department has received grant support from Syner-Med (UK) and Vifor Pharma (Switzerland). He has received honoraria and travel support for consulting or lecturing from Vifor Pharma and Merck Sharp and Dohme Limited (UK). AA's research department has received grant support from Syner-Med (UK), Vifor Pharma (Switzerland) and Pharmacosmos A/S (Denmark). He has received honoraria and travel support for consulting or lecturing from Ethicon Endosurgery (UK), Johnson and Johnson Ltd (UK), Olympus (UK) and Vifor Pharma (Switzerland). ON has

received honoraria and travel support for consulting from Pharmacosmos A/S, Denmark.

## References

- Ludwig H, Van Belle S, Barrett-Lee P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. *European Journal of Cancer* 2004; **40**: 2293–306.
- Khanbhai M, Shah M, Cantanhede G, Ilyas S, Richards T. The problem of anaemia in patients with colorectal cancer. *ISRN Hematology* 2014; **2014**: 547914.
- Ludwig H, Evstatiev R, Kornek G, et al. Iron metabolism and iron supplementation in cancer patients. *Wiener Klinische Wochenschrift* 2015; **127**: 907–19.
- Lind M, Vernon C, Cruickshank D, et al. The level of haemoglobin in anaemic cancer patients correlates positively with quality of life. *British Journal of Cancer* 2002; **86**: 1243–9.
- Buggy DJ, Freeman J, Johnson MZ, et al. Systematic review and consensus definitions for standardised endpoints in perioperative medicine: postoperative cancer outcomes. *British Journal of Anaesthesia* 2018; **121**: 38–44.
- Gereklioglu C, Asma S, Korur A, Erdogan F, Kut A. Medication adherence to oral iron therapy in patients with iron deficiency anemia. *Pakistan Journal of Medical Sciences* 2016; **32**: 604–7.
- Auerbach M, Ballard H. Clinical use of intravenous iron: administration, efficacy, and safety. *American Society of Hematology Education Program* 2010; **2010**: 338–47.
- Keeler BD, Simpson JA, Ng O, Padmanabhan H, Brookes MJ, Acheson AG. Randomized clinical trial of preoperative oral versus intravenous iron in anaemic patients with colorectal cancer. *British Journal of Surgery* 2017; **104**: 214–21.
- Euroqol. EQ-5D Questionnaire 1990. 2018. [https://euroqol.org/wp-content/uploads/2016/10/Sample\\_UK\\_English\\_EQ-5D-3L\\_Paper\\_Self\\_complete\\_v1.0\\_ID\\_23963.pdf](https://euroqol.org/wp-content/uploads/2016/10/Sample_UK_English_EQ-5D-3L_Paper_Self_complete_v1.0_ID_23963.pdf). (accessed 10/10/2018).
- Health R. 36-Item Short Form Survey Instrument (SF-36) 2018. [https://www.rand.org/health/surveys\\_tools/mos/36-item-short-form/survey-instrument.html](https://www.rand.org/health/surveys_tools/mos/36-item-short-form/survey-instrument.html). (accessed 10/10/2018).
- FACIT.org. FACT-An Questionnaire 2010. 2018. <http://www.facit.org/LiteratureRetrieve.aspx?ID=42367>. (accessed 10/10/2018).
- Pickard AS, Wilke CT, Lin HW, Lloyd A. Health utilities using the EQ-5D in studies of cancer. *Pharmacoeconomics* 2007; **25**: 365–84.
- Antonescu I, Carli F, Mayo NE, Feldman LS. Validation of the SF-36 as a measure of postoperative recovery after colorectal surgery. *Surgical Endoscopy* 2014; **28**: 3168–78.
- Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. *Seminars in Hematology* 1997; **34** (3 Suppl. 2): 13–19.
- Boogaerts M, Coiffier B, Kainz C. Impact of epoetin beta on quality of life in patients with malignant disease. *British Journal of Cancer* 2003; **88**: 988–95.
- Bremberg ER, Brandberg Y, Hising C, Friesland S, Eksborg S. Anemia and quality of life including anemia-related symptoms in patients with solid tumors in clinical practice. *Medical Oncology* 2007; **24**: 95–102.
- Case DC Jr, Bukowski RM, Carey RW, et al. Recombinant human erythropoietin therapy for anemic cancer patients on combination chemotherapy. *Journal of the National Cancer Institute* 1993; **85**: 801–6.
- Copay AG, Subach BR, Glassman SD, Polly DW Jr, Schuler TC. Understanding the minimum clinically important difference: a review of concepts and methods. *The Spine Journal: Official Journal of the North American Spine Society* 2007; **7**: 541–6.
- Evstatiev R, Marteau P, Iqbal T, et al. FERGlor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. *Gastroenterology* 2011; **141**: 846.e1–53.e2.
- Jatoth P, Countdjidapadam CS. Intravenous versus oral iron therapy for postpartum anaemia. *British Journal of Obstetrics and Gynaecology* 2007; **114**: 655.
- Bhandal N, Russell R. Intravenous versus oral iron therapy for postpartum anaemia. *British Journal of Obstetrics and Gynaecology* 2006; **113**: 1248–52.
- Khalafallah A, Dennis A, Bates J, et al. A prospective randomized, controlled trial of intravenous versus oral iron for moderate iron deficiency anaemia of pregnancy. *Journal of Internal Medicine* 2010; **268**: 286–95.
- Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Medical Care* 2003; **41**: 582–92.
- Miller GA. The magical number 7, plus or minus 2 – some limits on our capacity for processing information. *Psychological Review* 1956; **63**: 81–97.
- Low MS, Grigoriadis G. Iron deficiency and new insights into therapy. *Medical Journal of Australia* 2017; **207**: 81–7.
- Munoz M, Acheson AG, Auerbach M, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. *Anaesthesia* 2017; **72**: 233–47.
- DeMarkles MP, Murphy JR. Acute lower gastrointestinal bleeding. *Medical Clinics of North America* 1993; **77**: 1085–100.

## Appendix IVICA Trial Group Collaborators

Nottingham University Hospitals NHS Trust: A. Banerjee, C. Walter, C. Maxwell-Armstrong, J. Williams, J. Scholefield, M. Robinson, P. Vitish-Sharma, N. Bhandal, C. Gornall, A. Petsas, K. Ward, S. Pyke, P. Johnson, H. Cripps.

Royal Wolverhampton NHS Trust: G. Williams, M. Green, J. Rankin.

University Hospitals Birmingham NHS Foundation Trust: T. Pinkney, T. Iqbal, D. Ward, C. Tselepis, M. Narewal, K. Futaba, M. Ghods-Ghorbani.

Royal Derby Hospital Foundation NHS Trust: J. Lund, E. Theophilidou, O. Peacock.

University Hospitals Bristol NHS Foundation Trust: R. Longman. The Surgical Trials Team, University Hospitals Bristol NHS Foundation Trust.

Yeovil District Hospital NHS Foundation Trust: N. Francis, K. Spurdle.

Leeds Teaching Hospitals NHS Trust: D. Miskovic, C. Moriarty.