Ethics Report - Clinical Summary - (PICoC Trial – Perioperative Iron in Colorectal Cancer) - Feasibility Trial

An Open Label Randomised Trial to Assess the Efficacy of Post-Operative Ferric Maltol Vs Standard Care for Anaemia Following Colorectal Cancer

Report V3 – 4/7/25

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Trial Summary

Trial Title	An Open Label Randomised Trial to Assess the Efficacy of Post-Operative Ferric Maltol Vs Standard Care for Anaemia Following Colorectal Cancer Surgery	
Short title	PICoC Trial – Perioperative Iron in Colorectal Cancer	
Clinical Phase	Feasibility	
Trial Design	Open label randomised controlled trial	
Trial Participants	Anaemic patients with colorectal adenocarcinoma undergoing surgery	
Planned Sample Size	40 participants	
Treatment duration	12 weeks from completion of surgery	
Follow up duration	12 weeks	
Planned Trial Period	24 months	
Study initiation Date	24/04/22	
Study completion date	26/01/24	
	Objectives	**Outcome Measures**
Primary	Feasibility measures	• Eligible patients from screening • Study exclusion • Acceptability of recruitment • Study retention
Secondary	1. To compare change in blood indices between intervention and control groups. 2. To compare quality of life between groups. 3. To compare post-operative complications, survival and length of stay between intervention and control groups. 4. To compare allogenic red blood cell transfusion use between groups. 5. Tolerability of ferric maltol.	1. Change in haemoglobin and haematinic markers 2. Quality of life as determined by the SF36, EQ-5D and FACT-An questionnaires 3. Post-operative morbidity and mortality and length of stay 4. Post-operative allogenic blood transfusion. 5. Side-effects and reactions to ferric maltol
IMP	Ferric Maltol (Feraccru)	
Dose, Route of Administration	Oral tablets, 30mg dose twice daily.	

Background

Colorectal cancer is associated with iron deficiency anaemia in 40-60% of cases (Leichtle, Mouawad et al. 2011). This anaemia can lead to poorer post-operative outcomes such as higher complication rates, increased length of stay and reduced survival (Muñoz, Acheson et al. 2018).

There has been a recent shift towards the correction of preoperative anaemia in order to optimize perioperative outcomes. However, despite improvements in preoperative haemoglobin there exists a group of patients who develop worsening or recurrent anaemia in the post-operative period. Without intervention up to 90% of patients in the immediate postoperative period may develop anaemia (Shander, Knight et al. 2004). This is not unexpected given the peri-operative blood loss; poor nutritional intake in the postoperative period; and the frequent blood sampling for laboratory tests. Our data from previous trials has demonstrated that despite preoperative intravenous iron therapy 75% of patients remain anaemic at the time of their colorectal cancer operation (Keeler, Simpson et al. 2017). In addition, our unpublished data has found that around 1/3 of patients treated with preoperative iron therapy develop a recurrence of their anaemia in the first year postoperatively.

Studies have identified that traditional oral ferrous iron supplementation is largely ineffective (Bisbe et al. 2014) for the treatment of postoperative anaemia. However, a newer oral iron preparation - ferric maltol (Ferracru) has been found to be better tolerated and more efficacious than ferrous iron (Schmidt, Ahmad et al. 2016, Oppong, Lovato et al. 2018). This study aimed to evaluate whether the use of iron supplementation in the form of Feraccru could lead to a more sustained or improved a response in haemoglobin if given after a colorectal cancer operation. Improving this postoperative anaemia may have important implications for clinician and patient reported outcomes.

Regulatory Approval

The study design was approved by the Wales Research Ethics Committee 2 Cardiff (reference 22/WA/0035) and the Health Research Authority and Health and Care Research Wales (HCRW) on the 18th February 2022. According to regulatory guidelines as a randomised trial the study was also registered on the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT; reference 2021-006004-32) and was allocated an International Standard Randomised Controlled Trial Number (ISRCTN; reference 12290106).

Study oversight was provided by The Royal Wolverhampton NHS Trust as Sponsor. IRAS ID: 1003910. We did not make any amendments to the trial protocol. This clinical trial

was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki (as revised in 2013), which outlines the ethical guidelines for medical research. All participants (or their legally authorized representatives) provided written informed consent prior to enrolment, in accordance with applicable local regulations and ethical standards. The study was designed to minimize risks and maximize potential benefits, and participants were given the right to withdraw from the study at any time without prejudice.

Confidentiality of subject data was maintained throughout the study, and all procedures were conducted in accordance with Good Clinical Practice (GCP) guidelines and relevant regulatory requirements.

Methodology

Patients were recruited to the PICoC Trial from June 2022 – Nov 2023. Recruitment was completed in 19 months with the trial closing in Jan 2024 when the final patient completed their follow up. Identification of suitable patients was done via the colorectal cancer multidisciplinary team (MDT) meetings. The list of patients was reviewed weekly and those patients presenting with new diagnoses were screened for eligibility according to the inclusion and exclusion criteria. Patients then attended a colorectal clinic appointment with their surgical consultant. It was at the clinic that the diagnosis was explained in detail. At this appointment we introduced the research team and the study and gave the patients the patient information leaflet to review in their own time. Occasionally, if the research team were unable to attend clinic or the patient had been seen quickly by the surgeon prior to screening the patients were contacted by phone and if the patients were happy to take the call the trial was explained over the telephone and trial information posted out to them.

The next pre-operative appointment for the patients was often the appointment for their IV iron infusion and / or their anaesthetic review prior to surgery. It was at this point that patients were recruited to the trial. Consent was taken by the research team.

Following screening 91.5% of patients were ineligible, however, we were able to recruit our cohort of patients because recruitment to the study was acceptable to patients and uptake amongst eligible patients was 85.7%. Below are the trial inclusion and exclusion criteria. Most patients were ineligible due to not being anaemic, having metastatic disease or not having colorectal cancer.

PiCoC Trial Inclusion Criteria
Participant is willing and able to give informed consent for participation in the study.
Male or Female, aged 18+ years.
Diagnosed with histologically or radiologically diagnosed colorectal adenocarcinoma.

Anaemic at point of diagnosis of colorectal adenocarcinoma (Defined as haemoglobin 10g/L below WHO criteria: 120g/L for males and 110g/L for females, to account for a 10% fluctuation in Hb)
Undergoing surgery for colorectal cancer with curative intent.
Date of planned surgery is ≥ 14 days from date of planned initiation of recruitment.
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.

PiCoC Trial Exclusion Criteria
Patients with mental health issues or learning disabilities resulting in their inability to consent to the study
Patients who do not have a histological diagnosis of colorectal adenocarcinoma
Female participants who are pregnant, lactating or planning a pregnancy during the study.
Patients with evidence of iron overload or disturbances in utilisation of iron as stated in the product SPC.
Previous gastric, small bowel or colorectal surgery (where ≥50% of stomach or terminal ileum has been resected)
Chemotherapeutic treatment within the last 4 weeks.
Known previous anaemia not attributable to colorectal carcinoma (i.e. anaemia in patients with well established, inflammatory disorders)
Known haematological disease.
Features necessitating urgent surgery (e.g. obstructive symptoms).
Previous allergy to intravenous or oral 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.
Participants who have participated in another research study involving an investigational product in the past 12 weeks
Confirmed liver or lung metastases

We aimed to recruit 40 colorectal cancer patients who were anaemic at diagnosis of their cancer. We ultimately recruited 42 patients as 2 patients were withdrawn prior to randomisation. One patient was withdrawn as they were admitted for emergency and the second withdrew consent because they changed their mind about being involved in the study. Concomitant medications were reviewed by the trial team and following discussion with the trial steering committee a patient was withdrawn due to having been given intravenous iron post-operatively by their clinical team. This patient was withdrawn as this concomitant medication was neither trial intervention nor standard care.

Following recruitment to the study patient were then seen on the day of surgery and throughout their inpatient admission and at follow up following 12 weeks of treatment. Trial samples including serum, stool and tumour specimens were obtained throughout the study as outlined in the protocol. All blood samples were taken and delivered immediately for process in an NHS laboratory at the Royal Wolverhampton NHS Trust. Processing of blood samples followed the NHS laboratory protocols in keeping with Good Laboratory Practice. Other trial samples were transferred to the University of Wolverhampton in accordance with the material transfer agreement (MTA).

Patients also undertook health related quality of life questionnaires, grip strength assessment at pre-determined timepoints. At follow up patients were asked about any side effects, complications, readmissions to hospital that have occurred since discharge.

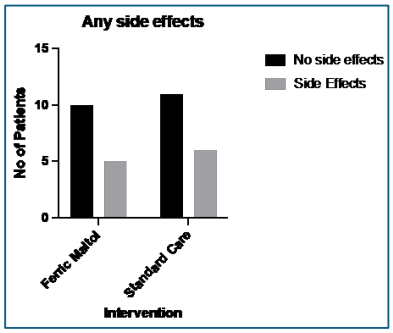
The Trial Steering Committee (TSC) provided oversight and strategic guidance for the PiCOC trial, ensuring that the study was scientifically sound, ethically conducted, and aligned with regulatory and protocol requirements. The committee was responsible for monitoring trial progress, data quality, and protocol compliance, and for reviewing any protocol deviations as well as safety and efficacy data in the context of overall trial conduct. The TSC were supported by clinical trial monitors who ensured that the study was conducted in compliance with the protocol, Good Clinical Practice (GCP) guidelines, and regulatory requirements. The monitors performed regular site visits to oversee the quality and integrity of the trial. Monitors ensured that informed consent was properly obtained and documented and that data was recorded accurately in the case report forms (CRFs), they also reviewed the site files to confirm that regulatory and study records were complete and up to date. They ensured adherence to the study protocol and addressed any protocol deviations, and confirmed that the investigational product was managed appropriately, including its storage, dispensing, and accountability. In addition, the trial monitors ensured that adverse events and serious adverse events were reported in a timely and accurate manner. Finally, the monitors ensured that the trial sample log was accurate and up to date.

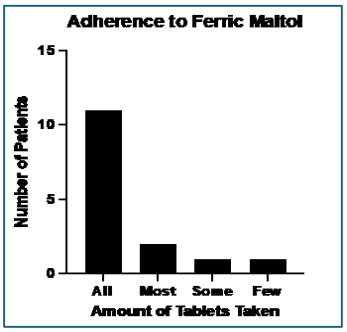
Results

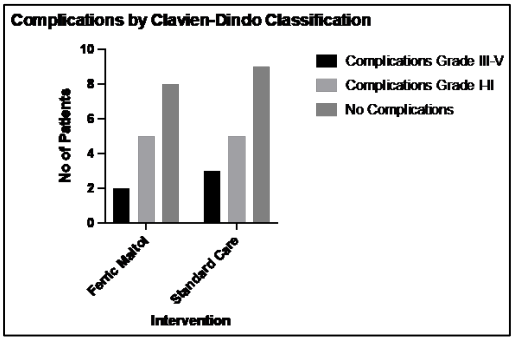
Adherence to the trial protocol was good but we did report some protocol deviations due to timing of recruitment and follow-up. This was due to challenging logistics meaning that some surgery dates were given at short notice (within 2 weeks of recruitment) and follow up clinics being challenging to organise. There were also inadvertent withdrawals in patients who were slightly anaemic post-operatively due to protocol deviations. This has highlighted where the trial protocol and flow chart could be made clearer in the definitive study. In relation to study retention of those 40 patients randomised 32 patients remained in the study to analysis, this was 80%.

In this study we demonstrated that Ferric Maltol is safe and well tolerated in post-operative colorectal cancer patients. There was no difference in side effects reported in those patients taking Ferric Maltol and those randomised to standard care. Patient

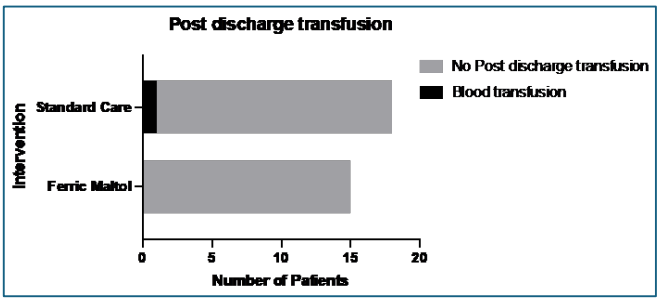
adherence to treatment was good with only one patient stopping the treatment due to intolerance. The majority, 86.67% of patients reported taking most or all their tablets. Only 13.33% patient took some or few of the tablets. We analysed complications and there was no difference between rates or severity of complications between the two groups. In the ferric maltol group 53.33% of patients had a complication, whereas this was 52.94% in the standard care group (p>0.9999).

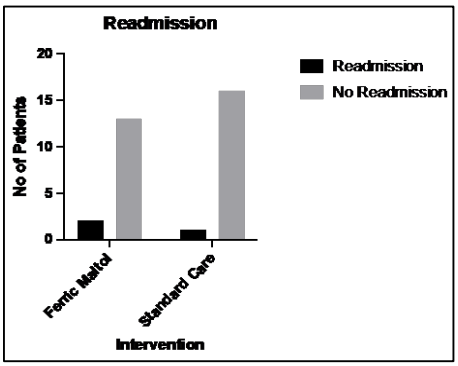






In addition, there was no significant difference in the between length of stay in hospital, patients in the ferric maltol group had a mean hospital stay of 7.133 days (4.809), with a range of (3-18 days). The standard care group had a mean hospital stay of 7.333 (6.202) with a range of (3-29 days) (p=0.9195). There was no significant difference in hospital readmission, there were two patients (13.33%) readmitted in the ferric maltol group, and 1 patient (5.88%) readmitted in the standard care group (p = 0.5887). There was one death, this patient was in the Ferric Maltol cohort, death was a result of a known surgical complication, there was not a significant difference between the groups, p=0.4687. Looking at post-discharge transfusion. There was one patent who required a blood transfusion follow discharge and this patient was in the standard care cohort.

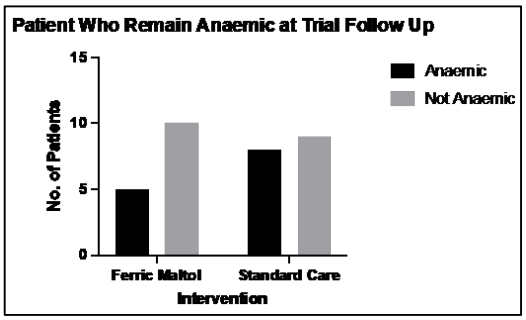




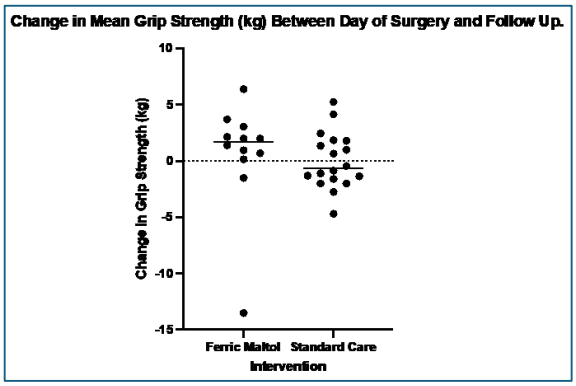
There were 11 serious adverse events (SAEs), six in the Ferric Maltol cohort, four in the standard care cohort and one prior to randomisation. None of these were due to the trial intervention, all were surgical complications, apart from the one prior randomisation which was due to an emergency admission for surgery. There were seven AEs – with one related to intolerance to ferric maltol resulting in headache and gastrointestinal side effects which settled on stopping the medication, the other AEs were related to patient' surgery.

Further secondary outcomes were looking at blood indices, including haemoglobin and iron studies, in addition to patient grip strength and patient reported outcomes (quality of life results). Being a feasibility trial the study was not powered to detect significant differences, but we were looking of signals of efficacy and potentially a change in the minimally clinically important difference (MCID), demonstrating improvement which noticeable to patients.

We demonstrated that haemoglobin was higher at follow up amongst those patients who has been randomised to receive Ferric Maltol, mean Hb was 129.7g/l (19.8) compared to 128.1g/l (12.8) in the standard care cohort. Whilst this was not significant, p=0.7812 we also looked at the change in haemoglobin which showed a greater improvement in Hb in the Ferric Maltol group, again whilst this difference was not significant it gave a signal of efficacy and suggests that in a larger study this may reach significance. We also demonstrated that at follow up 66.67% of the ferric maltol cohort were not anaemic, whilst only 52.92% of patients had a normal haemoglobin in the standard care group.



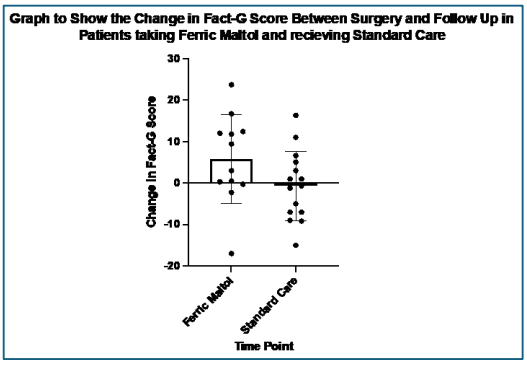
Looking at the iron studies we showed a significant improvement in iron studies, demonstrating that patients taking Ferric Maltol had improved patients' iron stores. Patients who took Ferric maltol had higher serum iron levels and transferrin saturation, although these results were not significant, p=0.333 and p=0.125 respectively, they are likely to be significant in a larger cohort. We did however show a significantly reduced transferrin and total iron binding capacity.

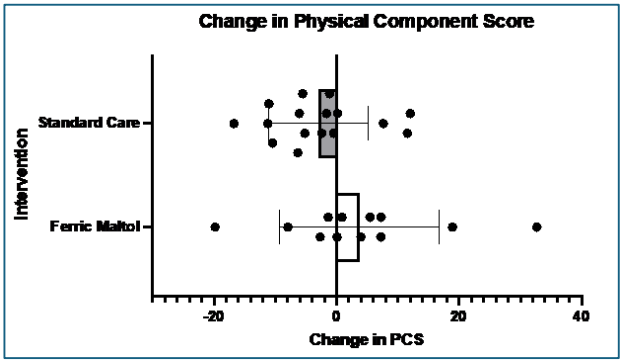


We then looked at grip strength as a measure of patients' muscle strength. Comparing the change in grip strength between day of surgery and follow up we demonstrate a trend to improved grip strength in the ferric maltol cohort when compared to the standard care cohort. However, this is not significant p=0. 0.6582.

Finally looking at the patient reported outcomes. We asked patients to undertake 3 quality of life (QoL) questionnaires at 4 specified time points. The QoL questionnaires used were the EuroQoL 5- dimension 5-level (EQ-5D-5L) questionnaire, the modified Short Form 36 v1 (SF-36) questionnaire and the Functional Assessment of Cancer Therapy – Anaemia (FACT-An) questionnaire. This questionnaire specifically assesses specific quality of life related to anaemia and fatigue in cancer patients and was therefore particularly applicable to our patient population.

Results showed that there was a significant difference in some of the QoL data at baseline, with higher mean QoL reported by the standard care group. As a result, we looked at change in QoL scores rather than the absolute scores at the different time points. In this analysis we demonstrated that QoL improved between day of surgery and follow up for those patients in the Ferric Maltol cohort. For example, in the Fact An total





Score the mean change was an increase of 8.85, compared to -2.264 in the standard care cohort. In addition, in the SF-36 questionnaire we show an increase in QoL in the Ferric Maltol cohort and a decrease in the Standard care cohort (p=0.2001). The mean change in PCS in the Ferric maltol group was 3.720 (13.06), compared with a mean change of -2.922 (8.08) in the standard care cohort p=0.1090. We found that whilst this was not statistically significant the increase in Fact-An Total score, Fact-G score and the Fact – An Trial Outcomes Index (TOI) exceeded the minimally clinically important difference (MCID) suggesting that the change in QoL is at a level which is noticeable and of benefit to patients. These changes in QoL results may well also reach statistical significance in a larger definitive study.

We also showed that there was a significant correlation between the QoL results and improved haemoglobin and transferrin saturation suggesting that these changes in QoL may be related to the treatment of their anaemia.

Conclusions

In conclusion we demonstrated that it is feasible to run a definitive study looking at the treatment of post-operative anaemia with Ferric Maltol in colorectal cancer patients. We believe that this is important as our feasibility data suggests that treatment of post-operative anaemia with oral Ferric maltol is potentially efficacious and may improve patient quality of life, blood indices and muscle strength (grip strength) in post operative colorectal cancer patients.

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