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

Perioperative Iron for Colorectal Cancer (PICoC Study)

This protocol has regard for the HRA guidance and order of content

PROTOCOL VERSION NUMBER AND DATE: **0.6 27th October 2023**

SPONSOR: **The Royal Wolverhampton NHS Trust**

FULL/LONG TITLE OF THE TRIAL
An Open Label Randomised Trial to Assess the Efficacy of Post-Operative Ferric Maltol Vs Standard Care for Anaemia Following Colorectal Cancer Surgery

SHORT TRIAL TITLE / ACRONYM

Perioperative Iron for Colorectal Cancer (PICoC Study)

PROTOCOL VERSION NUMBER AND DATE – V0.6 27th October 2023

RESEARCH REFERENCE NUMBERS

IRAS Number:	1003910
EudraCT Number:	2021-006004-32
ISRCTN Number / Clinical trials.gov Number:	Clinical Trials- NCT05177484 ISRCTN submission number 40928
SPONSORS Number:	2021GAS120
FUNDERS Number:	IIS-2020-UK-131

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

.....

(Optional)

Statistician:

Signature:

.....

Name: (please print):

.....

KEY TRIAL CONTACTS

Chief Investigator - 1	Professor. Matthew James Brookes Consultant Gastroenterologist and Honorary Senior Lecturer, Gastroenterology Department, Royal Wolverhampton Hospital NHS Trust
Chief Investigator - 2	Miss Nuha Yassin Consultant Colorectal Surgeon University Hospitals Birmingham NHS Foundation Trust Headquarters Queen Elizabeth Hospital Birmingham Mindelsohn Way, Edgbaston Birmingham West Midlands B15 2GW
Trial Co-ordinator/ Clinical Research Fellow	Dr Alexandra Marley
Sponsor	The Royal Wolverhampton NHS Trust, New Cross Hospital, Wolverhampton Rd, Heath Town, Wolverhampton WV10 0QP
Funder(s)	Norgine Pharmaceuticals Ltd.
Key Protocol Contributors	Mr. Edward Alexander Dickson Clinical Research Fellow, Academic Department of Surgery and Biomedical Research Unit, University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH Mr. Austin George Acheson Associate Professor in Academic Colorectal Surgery Department of Surgery, Queen's Medical Centre, Nottingham NG7 2UH
Additional Trial Steering Committee Members	Statistical support: Dr Niall Galbraith Patient Representative: Miss Sue Blackwell

	Lead Scientist: Dr Hafid Omar

i. LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AR	Adverse Reaction
ARBT	Allogenic Red Blood Cell Transfusion
CA	Competent Authority
CI	Chief Investigator
CPA	Clinical Pathology Accreditation
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice

GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MDT	Multidisciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
NICE	National Institute for Clinical Excellence
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

ii. 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	
	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.	

iii. FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Norgine Ltd	An unrestricted open commercial grant to fully support trial delivery and consumables

iv. ROLE OF TRIAL SPONSOR AND FUNDER

The Royal Wolverhampton NHS Trust is the sponsor of this study and assumes overall responsibility for the initiation, and management of the study.

Funding and drug supply for the study (Ferric iron) has been provided by Norgine Pharmaceuticals Ltd.

Protocol contributors

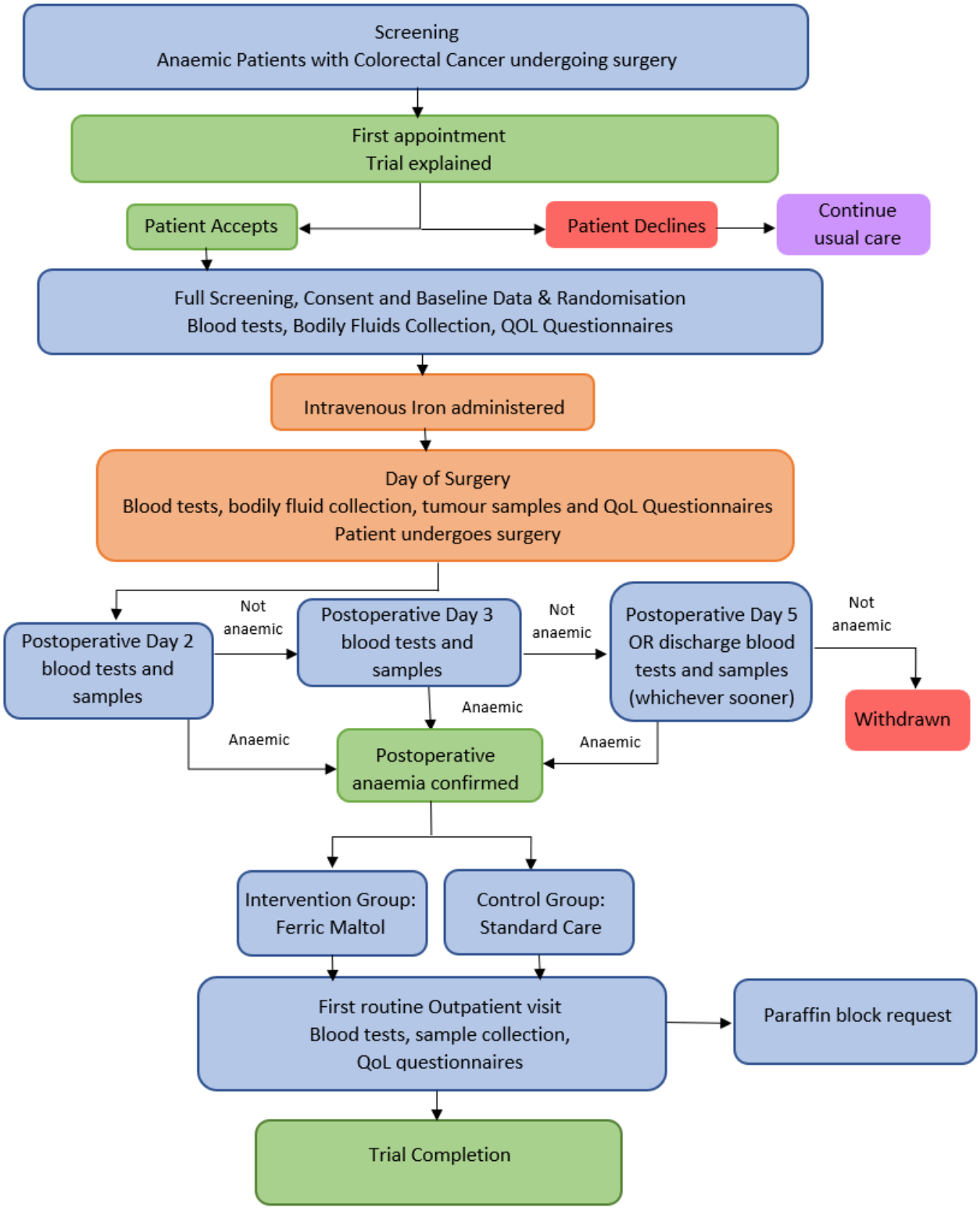
The study design, conduct, data analysis and interpretation, manuscript writing, and result dissemination will be the responsibility of the research team, overseen by the sponsor.

The protocol will be reviewed by Norgine Ltd. prior to ethics submission but they will not be involved in the study conduct, data analysis or interpretation

v. KEY WORDS:

Anaemia, Colorectal Cancer, Ferric maltol, Iron, Peri-operative

vi. TRIAL FLOW CHART



1 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 aims 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. The Perioperative Iron in Colorectal Cancer (PICoC) trial will run as a feasibility study to assess the proposed design, recruitability and outcome measures. Anaemic colorectal cancer patients treated with

preoperative intravenous iron will be randomised in an open label design to receive a course of Ferric maltol (intervention group) or standard care (control group) postoperatively. Secondary outcome measures will focus on a comparison of change in blood indices, quality of life, allogenic red blood transfusion rates and postoperative complications between groups. Follow up will continue until the first postoperative outpatient visit at approximately 12 weeks following discharge.

2 RATIONALE

The PICoC study aims to investigate whether oral ferric maltol given postoperatively offers an improvement in patient and clinician reported outcomes compared to standard care. If postoperative anaemia can be improved this could lead to fewer complication rates, better quality of life and a shorter length of stay in colorectal cancer patients after operation. Traditionally oral ferrous (Fe^{2+}) iron preparations, such as ferrous fumarate or ferrous sulphate have been used to treat iron deficiency anaemia. However, these forms of iron supplementation can damage the gut mucosa by the process of oxidative stress leading to symptoms of abdominal pain, nausea, constipation or diarrhoea.

Ferric maltol is a novel oral iron therapy which has shown promise as an effective treatment for iron deficiency anaemia in conditions such as inflammatory bowel disease (Gasche, Ahmad et al. 2014). After oral ingestion of ferric maltol, ferric iron reaches the intestinal mucosa as a complex, allowing more efficient absorption of ferric iron by the gut compared to ferrous iron (Levey, Barrand et al. 1988), even at a low dose. This is also thought to lead to a more favourable side effect profile with patients (Schmidt, Ahmad et al. 2016, Oppong, Lovato et al. 2018)

Current standard care involves monitoring for signs of worsening anaemia in the postoperative period with the option of transfusing allogenic blood (ARBT) if the clinical need

arises. Existing NICE guidance advises a haemoglobin threshold of 70g/L to trigger ARBT. This leaves a large number of postoperative anaemic patients without an effective treatment leading to higher complication rates, increased length of stay. In addition, where transfusions are used they carry a small but significant risk of infection, immune reaction as well as a high cost. Studies have also drawn links between ARBT and cancer recurrence (Amato and Pescatori 2006, Acheson, Brookes et al. 2012).

Owing to the change in stool colour with oral iron supplementation it is not possible to blind patients to the study group allocation and therefore the intervention will be compared to standard care rather than placebo.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

To determine the feasibility of a phase IV open label, controlled multi-centre randomised trial of oral ferric maltol versus standard care postoperatively for colorectal cancer patients who have been treated with preoperative intravenous iron for anaemia. Feasibility measures will include:

- Eligible patients from screening
- Study exclusion
- Acceptability of recruitment
- Study retention

3.2 Secondary objectives

- To investigate whether the use of ferric maltol could improve the postoperative quality of life of patients after colorectal cancer surgery compared to standard care.

- To calculate the change in postoperative haemoglobin and haematinics in response to ferric maltol compared to standard care.
- To compare postoperative allogenic red blood cell transfusion rates in patients receiving ferric maltol or standard care
- To review the tolerability of ferric maltol for the treatment of postoperative colorectal cancer patients
- To compare length of stay and complication rates in patients receiving ferric maltol or standard care postoperatively.
- To assess for immunological and metabolomic peri-operative differences between patients receiving ferric maltol preparations and standard care.

3.3 Outcome measures/endpoints

3.3.1 Primary endpoint/outcome

Study feasibility will be the primary endpoint. No a priori criteria will be used to determine study feasibility. We will use the data generated by PICoC to determine the sample size and outcome measures of a definitive trial

3.3.2 Secondary endpoints/outcomes

1. Levels of haemoglobin and haematinic markers (full blood count, ferritin, iron, transferrin, and transferrin saturation). Immunological and metabolomic markers will also be assessed. These will be measured at a point preoperatively before intravenous iron treatment, on the day of surgery and at defined time points postoperatively during the administration of oral ferric maltol or during standard care
2. Side-effects and reactions to ferric maltol administration
3. Peri- and post-operative morbidity and mortality
4. Post-operative complications

5. Post-operative length of stay
6. Post-operative allogenic blood transfusion.
7. Quality of life as determined by the SF36, EQ-5D and FACT-An questionnaires.

4 TRIAL DESIGN

This study will be a single centre, open labelled, randomised controlled trial comparing the effect of postoperative oral ferric maltol (intervention group) to standard care (control group), in patients with colorectal adenocarcinoma who have received pre-operative intravenous iron for anaemia. Each patient will be expected to participate for a period of 10 to 20 weeks, depending on the time between their diagnosis and the planned operation date. The participant will be recruited after the cancer MDT meeting confirming the diagnosis of colorectal adenocarcinoma and the ensuring that the patient is suitable for operative management. All study procedures will be undertaken at the time of existing hospital appointments where possible.

Recruitment will take place following the explanation of the cancer diagnosis by the clinical team. The patients will be asked by a member of the clinical or research team to state whether they consent to being approached by the research team for further information regarding the study. If they agree, a face-to-face conversation or a phone call to the patient will be arranged to discuss the research. A letter of invitation to participate in the trial (accompanied by a patient information leaflet) will then be given or posted to the patients. The patient will be given adequate time to consider participation in the study and they will be given the opportunity to ask any questions they may have. Patients who are eligible will then be invited to consent to the study.

After consenting to participate baseline data including demographics, past medical history and existing medications will be noted. Patients will be asked to complete the 3 quality of life questionnaires and they will have their blood taken including a full blood count, haematinics

(including iron, ferritin, transferrin and transferrin saturation) urea and electrolytes, liver function tests and erythropoietin. If the patients have consented to the optional sample sub-study, the patients may be asked to give other samples of faeces, urine, saliva or sweat. Following this visit the patient will receive their preoperative intravenous iron infusion as is standard care. If they are taking any existing oral iron supplementation they will be asked to stop this treatment prior to receiving their preoperative intravenous iron. Once the surgical procedure has been performed, tissue samples from the resected bowel may be obtained for analysis.

The participant is next reviewed when they are admitted on the morning of the operation. Blood tests and the quality of life questionnaires will be repeated.

Preoperatively patients will undergo randomisation to one of the two study arms. After operation the participants haemoglobin will be checked on day 2 of their recovery. If, at this point, postoperative anaemia is confirmed they will enter into their study arm. The intervention group will commence a course of oral ferric maltol provided oral intake has recommenced and the control group will receive standard care. All patients will have blood tests checked again at day 3 and day 5 postoperatively if they remain as an inpatient. If they are found to be anaemic on either of these two blood tests they will, at this stage, enter their allocated treatment pathway. If a patient shows no evidence of anaemia on either day 2, 3 or 5 blood tests they will be withdrawn from the study. If the patients have consented to the optional sample sub-study, the patients may be asked to give other samples of faeces, urine, saliva or sweat at days 2, 3 or 5 along with the blood tests. Patients will continue treatment according to their randomisation allocation until 12 weeks after the operation, at which point the patient attends a routine surgical outpatient follow-up clinic. During the outpatient visit the participants will undergo their final blood and optional sample sub-study testing (if consented) as well as questionnaire completion.

The participants may only be required to attend the hospital for one extra visit to consent and where possible this will be arranged to coincide with existing appointments. The study is designed such that all other procedures are carried out when the participant attends for their routine visits as per the normal clinical pathway.

5 TRIAL SETTING

The trial will initially run as a single center study in order to assess reproducibility and feasibility across different sites. The main host center will be The Royal Wolverhampton NHS Trust.

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 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.

6.2 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 course of the study.
- Patients with evidence of iron overload or disturbances in utilisation of iron as stated in the product SPC.
- Previous gastric, small bowel or colorectal surgery (where ≥50% of stomach or terminal ileum has been resected)
- 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

7 TRIAL PROCEDURES

7.1 Recruitment

Identification of suitable subjects will occur via the surgical outpatient clinics and the colorectal cancer MDT meetings. This will be conducted by the clinical team, nurse specialists, research nurses and the clinical research fellow. Recruitment will take place following explanation of the cancer diagnosis and treatment plan by the clinical team. The patient will be aware of the diagnosis and the plan for surgery at the point of attendance. The patient will also be aware that they are anaemic.

Initially the patient will be approached by a member of the clinical team. Following this the research team will explain the trial to the patient and provide them with a patient information

sheet. Alternatively, the patient may be sent the information sheet in the post by any of the relevant clinical or research teams. Following explanation of the trial the patient will be given adequate time to deliberate the information and ask questions. If the patient wishes to join the trial at that point, they will be invited to sign the informed consent form. Patients will be offered participation in the optional sample sub-study. After valid informed consent is given, the study procedures will commence at this visit and baseline assessments will be undertaken. The additional visits for intervention and follow up will then be planned.

7.1.1 Participant identification

All patients who attend the surgical outpatient clinic for a two-week wait appointment or who are found to have an abnormal lesion on lower gastrointestinal endoscopy or who are discussed at the colorectal cancer MDT will be screened for eligibility. As part of standard clinical practice all patients will have their haemoglobin level checked to determine if they are anaemic. Patients who are found to have an abnormal lesion will be discussed at the weekly colorectal cancer MDT meeting. Patients who are anaemic and who are diagnosed to have adenocarcinoma within the lower gastrointestinal tract will be identified at the MDT meeting. The research team will liaise with the colorectal nurse specialists who attend the MDT meetings. After the MDT meeting a patient will be called to clinic to inform them of the diagnosis, outcome and any plan for surgical management. In certain cases this clinic visit may be replaced by a phone call from a colorectal nurse specialists.

Once the patients have been informed of their diagnosis and the management plan, a member of the clinical or research team will introduce the trial to the patient and subsequently the first discussion with the research team will take place. Eligibility will be confirmed by a medical practitioner.

7.1.2 Screening

Screening will be undertaken using the results of existing investigations carried out as part of the normal colorectal cancer pathway as stated above. If a potentially eligible patient is identified by the screening process but is found to not have had a recent haemoglobin level checked within one month, then the research team will identify and refer this patient to the clinical team. The patient can then be advised to have their blood retested at their GP practice, or be provided with a blood form to undergo the testing in the hospital setting. This blood testing is part of standard pre-treatment clinical practice.

7.1.3 Payment

No payments or incentives will be given to study participants

7.2 Consent

A named member of the clinical or research team, who are on the study's delegation log, will take consent from the participant once they have ascertained that the patient fits the eligibility and inclusion criteria.

It will be clearly stated that the participant is free to withdraw from the study or the optional sample sub-study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. The participant will be 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 will participate in the study. Written informed consent will 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 will have been authorised to do so by the Chief/Principal Investigator. A copy of the signed informed consent will be given to the participants. The original signed form will be retained at the study site. A copy of the signed informed consent will be placed in the participant's medical notes.

7.3 The Randomisation scheme

Randomisation will be undertaken via an online platform in a 1:1 fashion to either the control group (standard care) or the intervention group (postoperative ferric maltol). The study will be an open label design and participants will be informed of their group allocation after their operation. Randomisation alerts with allocation details will be emailed to the CI, research fellow, research nurses and the pharmacy team.

7.4 Blinding

Patient and investigator will not be blinded to the study treatment allocation due to the change in stool colour with oral iron intake. It is not possible to simulate this change with a placebo “dummy” drug for the control group.

7.5 Baseline data

Following the consent process the following baseline data will be recorded

- *Demographics*

  Date of birth, gender, race, smoking status, alcohol intake, height and weight

- *Medical History*

  History of any disease or surgical interventions including the relevant dates

- *Concomitant medication & drug allergies*

  Dose, route, start date (and end date of medication if medication was stopped within the six weeks prior to recruitment)

  Start and end date of any iron supplements

  Compliance to medication

- *Laboratory tests*

  Haematologic markers: Full blood count, iron, ferritin, transferrin, transferrin saturation, erythropoietin

  Inflammatory markers: C-reactive protein levels

Female participants of child-bearing age will undergo a urine pregnancy test, as is routine with patients undergoing surgery

- *Optional samples for sub-study*

Urine, stool, saliva and sweat samples may be taken for analyses

- *Questionnaires*

Quality of life score (using SF36, EQ-5D and FACT-An questionnaires)

- Grip strength may be recorded

7.7 Trial assessments

Following the consent process and baseline data collection the patient will attend for their preoperative iron infusion, as is routine care. They will then undergo the following trial assessments:

Day of Surgery (on the morning of their operation.):

- A brief interview will take place at the surgical pre-operative assessment ward to ascertain if the patient had any questions or if they experienced any side-effects in the intervening time. Any pre-operative blood transfusion will be noted. Information will be documented in the CRF.
- Blood will be drawn for the following tests: Full blood count, C reactive protein, iron, ferritin, transferrin, transferrin saturation, and erythropoietin.
- Optional sub-study urine, stool, saliva and sweat samples may be taken for analyses
- Grip strength may be recorded

- The participant will be requested to complete Quality of Life (QoL) questionnaires SF36, EQ-5D and FACT- An questionnaires.

Postoperatively they will be randomised to either the intervention group or the control group and the following assessments will be undertaken

Day 2 postoperatively.

- Information regarding the peri-operative period, intraoperative blood loss and any transfusion requirements will be documented in the CRF.
- Blood will be drawn for the following tests: Full blood count, erythropoietin, C-reactive protein, iron, ferritin, transferrin, transferrin saturation.
- Optional sub-study urine, stool, saliva and sweat samples may be taken for analyses
- Grip strength may be recorded
- At this point the Haemoglobin will be used to confirm postoperative anaemia (Hb <130g/L men, <120g/L women) allowing patients to commence their allocated treatment pathway according to randomisation.

Day 3 postoperatively.

- Blood will be drawn for the following tests: Full blood count, erythropoietin, C reactive protein, iron, ferritin, transferrin, transferrin saturation.
- Optional sub-study urine, stool, saliva and sweat samples may be taken for analyses
- Grip strength may be recorded

Day 5 postoperatively (if remains an inpatient).

- Blood will be drawn for the following tests: Full blood count.
- Optional sub-study urine, stool, saliva and sweat samples may be taken for analyses
- Grip strength may be recorded

Entry into postoperative treatment pathway

If a patient is found to be not anaemic on day 2 postoperatively (Hb ≥130g/L men, ≥120g/L women) they will complete screening and remain in the study but will not enter their allocated treatment pathway (i.e ferric maltol or standard care). If they remain anaemic on day 3 or day 5 blood tests they will, at this stage, enter their allocated treatment pathway. If patients have a normal haemoglobin on days 2, 3 or 5 they will be withdrawn from the study.

Outpatient Follow Up

Finally, after discharge the patient will be seen in their first outpatient clinic at 8-12 weeks postoperatively. Where follow up occurs earlier, for example, due to the clinician's normal practice or due to a complication, then the usual 8-12 week outpatient visit will still be used. At this visit the following assessments will be undertaken

- Information regarding postoperative complications, the length of hospital stay and readmissions to hospital will be documented in the CRF
- Any postoperative transfusion requirements will be documented in the CRF.
- Blood will be drawn for the following tests: Full blood count, erythropoietin, C-reactive protein, iron, ferritin, transferrin, transferrin saturation
- Optional sub-study urine, stool, saliva and sweat samples may be taken for analyses
- Grip strength may be recorded
- The participant will be requested to complete Quality of Life questionnaires: SF36, EQ-5D and FACT- An questionnaires.

7.8 Withdrawal criteria

There will be intention-to-treat analyses carried out. Analysis of all participants who have been randomised will be undertaken regardless of withdrawal. The reason for withdrawal will

be recorded in the CRF. Each participant has the right to withdraw study at any time. A participant will be withdrawn from the study if any of the following occurs:

- Absence of anaemia on postoperative days 2, 3 and 5.
- Pregnancy
- Ineligibility (either arising during the study or retrospective having been inadvertently overlooked at screening)
- Significant protocol deviation as defined by the CI
- An adverse event which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Disease progression which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Patients who do not undergo an operation as a result of a change in fitness for surgery will be excluded.
- Consent withdrawn.
- Lost to follow up

7.9 Collection, storage and analysis of clinical samples

All blood samples will be taken and delivered immediately for process in a CPA NHS laboratory at the individual study site. Processing of blood samples will follow the NHS laboratory protocols in keeping with Good Laboratory Practice. If consented for the optional sample sub-study, samples will be stored within the research secure repository within the trust in keeping with standard research protocols.

Please refer to the laboratory manual for details of sample collection, storage and destruction protocols.

Sampling methods include:

Faecal and blood samples will be collected at base line and days 2, 3, 5 and 12 postoperatively. Surgical resections will be collected at time of surgery.

1. Faecal samples will be collected in universal tubes 2-3 tubes per patient and put on ice until transferred to -80 freezer.

2. Serum will be prepared from the blood samples as follows:

Collect blood in a sterile 15 ml test tube or a plastic vacutainer containing no anticoagulants.

Incubate tubes in an upright position at room temperature for 30-45 minutes (no longer than 60 minutes). This will allow enough time for the blood to clot.

If using vacutainers with clot activators such as the BD Vacutainer Plus Plastic Serum Tube (red top), invert carefully 5 times before incubation.

Centrifuge tubes at 1500 x g for 10 minutes with the break OFF.

Use Pasteur pipette to carefully transfer equal amount of the supernatant into two cryotubes without disturbing the cloudy cell layer below the supernatant (10 ml of whole blood produces 4-6 ml of serum).

Immediately store tubes in -80 freezer.

Serum samples will be tested for chemokines and inflammatory markers by Multiplex immune assays.

3. Surgical resections will be collected in 2ml tubes on ice (preferably liquid nitrogen or dry ice) and immediately frozen in -80 freezer.

Tissue resections will be used to determine the expression of immune cells and their activation markers as well as proliferation and apoptotic markers using immunofluorescence microscopy. Resections will also be used to study the microbiome using 16s-rRNA gene sequencing and taxonomic analysis to determine changes in probiotic and pathogenic bacterial populations.

4. Paraffin embedded sections will be collected from the pathology archives at a later date.

Paraffin embedded sections may also be used to determine the expression of inflammatory markers using immunohistochemistry.

7.10 End of trial

The end of trial will be defined as the date of the last study visit of the last patient undergoing the trial. The sponsor will notify the MHRA of the end of the trial within 90 days of its completion.

8 TRIAL TREATMENTS

8.1 Name and description of the medicinal product

The study intervention treatment is oral ferric maltol (Feraccru®). The recommended dose is one 30mg capsule twice daily, morning and evening, on an empty stomach. Feraccru is indicated in adults for the treatment of iron deficiency. No dose adjustment is needed in elderly patients or patients with renal impairment (eGFR ≥15 ml/min/1.73 m^2). The control group will receive standard care only. Any treatments will be at the discretion of the patient's usual clinical team. The study treatments will be randomly allocated in a 1:1 fashion but there will be no blinding of the treatment

8.2 Regulatory status of the drug

The marketing authorisation holder for Feraccru is Norgine B.V. Amsterdam, Netherlands (MA number EU/1/15/1075/001)

8.3 Product Characteristics

The Summary of Product Characteristics will be used to inform the clinical management of ferric maltol. Accessed via https://www.medicines.org.uk/emc/product/2083/smpc.

8.4 Drug storage and supply

The drug will be stored in Trials Pharmacies at each study site. At all sites the drug will be stored in a temperature-controlled room below 25°C. The study drug will be donated by Norgine Ltd.

8.5 Dosage schedules

Participants in the intervention arm will take one 30mg capsule twice daily, morning and evening, on an empty stomach. Treatment will commence as soon as postoperative anaemia is confirmed on day 2, 3 or 5 blood tests provided oral intake has been resumed and will continue until the first routine outpatient visit. If a dose is missed the subject will be allowed to take their missed dose within 6 hours of the correct time. If there is any interruption to treatment, for

example due to vomiting or illness, the patient will be asked to recommence treatment as soon as they are deemed safe to do so by a medical practitioner.

8.6 Known drug reactions and interaction with other therapies

Oral iron is known to reduce the absorption of penicillamine, bisphosphonates, ciprofloxacin, entacapone, levodopa, levofloxacin, levothyroxine (thyroxine) moxifloxacin, mycophenolate, norfloxacin and ofloxacin. If applicable, these medicinal products will be given at least 2 hours apart from Feraccru. Absorption of both iron and antibiotic may be reduced if oral iron is given with tetracycline. Administration of Feraccru and tetracyclines will be separated by 2 to 3 hours. Absorption of oral iron may also be reduced by calcium and magnesium salts (such as magnesium trisilicate). Administration of Feraccru with such compounds will be separated by at least 2 hours.

8.7 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 trial will be recorded in the CRF. Participants who are on existing oral iron supplementation at time of recruitment to the trial will stop taking this as prescribed for the duration of the study and after discussion with the patient.

8.8 Assessment of compliance with treatment

Participants will self-administer the oral ferric maltose tablets. Patients will be asked to declare their compliance with the study drug during the final follow up study visit. If there is a high level of non-compliance (<70%), the patient will be included in the trial under the intention-to-treat-analysis. The reasons for non-compliance will be documented in the CRF.

9 PHARMACOVIGILANCE

9.1 Definitions

9.1.1 Adverse Event (AE)

An AE or adverse experience is:

Any untoward medical occurrence in a patient or clinical investigation in participants administered a medicinal product, which does not necessarily have to have a causal relationship with this treatment (the study medication).

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication.

9.1.2 Adverse Reaction (AR)

All untoward and unintended responses to a medicinal product related to any dose.
The phrase "responses to medicinal products" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

9.1.3 Severe Adverse Events

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:
The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which

is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.1.4 Serious Adverse Event or Serious Adverse Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

9.1.5 Expected Serious Adverse Events/Reactions

Serious adverse events that could be expected during the course of the study according to the SmPC include vomiting, hematemesis, gastrointestinal perforation, abdominal pain and dysphagia which could be related to the progression of the disease. Adverse events may also be anticipated in relation to any postoperative chemotherapy used. These would include anaemia, neutropenia (and consequences of sepsis), thrombocytopenia (and consequences or

coagulopathy), rashes, photosensitivity, taste/hearing disturbance, hair loss, discoloured urine, diarrhoea, oral ulceration and renal failure. These adverse events will be recorded in the CRF as significant clinical events.

Events which are not deemed secondary to the underlying cancer will be reported to the sponsor as a Serious Adverse Event within 24 hours of the Investigator becoming aware of the event.

9.1.6 Suspected Unexpected Serious Adverse Reactions

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information as stated in the reference safety information in the SmPC that follows: Common symptoms: “Abdominal pain (including upper abdomen), Flatulence, Constipation, Abdominal discomfort/ distension, Diarrhoea, Discoloured faeces, Nausea”

9.2 Recording and reporting of SAEs, SARs AND SUSARs

All AEs occurring during the study observed by the investigator or reported by the participant, whether or not attributed to study medication, will be recorded on the CRF. These adverse events will be recorded in the CRF. All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The sponsor will inform the MHRA, the REC and Marketing Authorisation Holder (if not the sponsor) of SUSARs within the required expedited reporting timescales. All related AEs that result in a participant’s withdrawal from the study or are present at the end of the study, will be followed up until a satisfactory resolution occurs.

It will be left to the investigator’s clinical judgment whether or not an AE is of sufficient severity

to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant will undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

The severity of events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCEA V 5.0) the following scale:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE

The relationship of AEs to the study medication will be assessed by a medically qualified investigator. Any pregnancy occurring during the clinical study and the outcome of the pregnancy, will be recorded and followed up for congenital abnormality or birth defect**.**

9.3 Responsibilities

Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated using the Reference Safety Information approved for the trial.
2. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information

as soon as available. Ensuring that SAEs are chased with the sponsor if a record of receipt is not received within 2 working days of initial reporting.

3. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated (in line with the Reference Safety Information) where it has not been possible to obtain local medical assessment.
3. Immediate review of all SUSARs.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
5. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
6. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor: (NB where relevant these can be delegated to CI)

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.

2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
7. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC)

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis. Mr Graham Williams, Consultant Colorectal Surgeon, will lead the DMC.

9.4 Notification of Deaths

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event. This report will be issued within 24 hours of the study team being notified of the death.

Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

9.5 Development safety update reports

The CI will provide DSURs once a year throughout the clinical trial, or as necessary, to the Competent Authority (MHRA in the UK), where relevant the Research Ethics Committee and the sponsor. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

No sample size calculation will be performed for this feasibility study. We will recruit a total of 40 patients to this trial (20 per arm), based on literature and guidance that 30 or more patients would be sufficient to estimate a parameter (Lancaster, Dodd et al. 2004)

10.2 Statistical analysis plan

As this is a feasibility study, a descriptive analysis will be performed on the data. Numbers and percentages will be presented for categorical data, mean and standard deviations for normally distributed continuous data, and median and inter-

quartile ranges for skewed data. Change in the outcome measures for the secondary objectives will also be presented between the intervention and control groups.

Further, data will also be used to help determine 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. The level of statistical significance to be used is $p<0.05$.

10.3.2 Primary outcome analysis

The primary objective will be assessed using feasibility outcomes measures. This will include the number of eligible patients (pre-screening eligibility), willingness to be recruited to study (acceptability), willingness to be randomised (acceptability/concordance), study exclusion (screen failure rates), withdrawal of patients (non-concordance), compliance with the randomised treatment, study retention (retention rates), number of patients recruited over a given time (recruitment rate), and completion of outcome measures.

10.3.3 Secondary outcome analysis

Outcomes for the secondary objectives include evaluation of transfusion rates, change in blood indices and change, quality of life. The median change in transfusion rates and haemoglobin will be reported. Quality of life will be reported as change from baseline and assessed for minimal clinically important difference.

10.4 Interim analysis and criteria for the premature termination of the trial

The trial will be terminated if there is an unacceptable number of SUSARs or SARs. Any interim data analysis will be performed at the request of the DMC.

10.5 Procedure to account for missing or spurious data

All attempts will be made to avoid and to recover any missing data. In the event of missing data being unrecoverable, a repeat sample may be taken in the case of a blood test. If this is

not possible (e.g. due to interventions being commenced), the participant will be excluded from the trial. Any unused or spurious data will be recorded in the CRF in the section for additional information.

11 DATA MANAGEMENT

11.1 Data collection tools and source document identification

Source documents will include the hospital records, drug charts, fluid balance charts, blood test reports and computer record of any blood transfusion. In this study, the CRF will be used as the source document for any correspondence with the patient, height, weight and blood pressure measurements. All study documentation will have the official letterhead of the centre on correspondence. All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

11.2 Data handling and record keeping

All study data will be entered onto the CRF and subsequently entered onto a password protected database that will be saved on an NHS computer. A password protected back-up copy of the database will be saved on the Chief Investigator's computer. The participants will be identified by a study specific participants number and/or code in any database. The name and any other identifying detail will NOT be included in any study data electronic file.

11.3 Access to Data

Direct access to data will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

11.4 Archiving

As soon as practicably possible after the completion of the study the Sponsor will give permission to the Investigator site to archive their essential documentation. The site will be required to archive their documentation for at 5 years after completion of the study, and no study documentation will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location written agreement must be obtained from the sponsor. Likewise, the sponsor will archive its study documentation for 5 years. All documents will be stored in such a way that they can be accessed at a later date. Consideration will be given to security and environmental risks.

12 MONITORING, AUDIT & INSPECTION

The research sponsor will ensure that arrangements and systems are in place for the management and monitoring of research. The arrangements for monitoring and auditing the conduct of the study will reflect the allocation of responsibilities set out in the Research Governance Framework. As this is a CTIMP, sponsors and investigators will fulfil statutory obligations relating to pharmacovigilance under Part 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004. A Trial Monitoring plan will be developed and agreed by the Sponsor. This will be informed by a Trial Risk Assessment which will consider the safety or physical or mental integrity of the trial participants and the scientific value of the research (including the potential risk associated with the implementation of the intervention and

recruitment which can, if not monitored and mitigated, affect the integrity and smooth running of this trial). This monitoring plan will detail the timing and content of reports to monitor trial conduct and implementation and adherence with the Consolidated Standards of Reporting Trials (CONSORT). This monitoring plan may also include site monitoring.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review & reports

The Investigators will ensure that this study is 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 Investigator will ensure that this study is 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 any proposed advertising material will be submitted to the HRA, an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.2 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA and Favourable REC opinion. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in

place. For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

13.3 Protocol compliance

Protocol non-compliances will be defined as departures from the approved protocol.

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Accidental protocol deviations will be adequately documented on the relevant protocol deviation form and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

13.4 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

a. the safety or physical or mental integrity of the participants of the trial; or
b. the scientific value of the trial

In the event of a serious breach the sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. In addition, the sponsor will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or

(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

13.5 Data protection and patient confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act 2018 which requires data to be anonymised as soon as it is practical to do so.

13.6 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG (96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

13.7 Amendments

A request for a substantial amendment to the CTA or the documents that supported the original application for the CTA, will be submitted via a valid notice of amendment to the licencing authority (MHRA) for consideration. To request a substantial amendment to the REC application or the supporting documents, a valid notice of amendment will be submitted to the REC for consideration. The MHRA and/or the REC will provide a response regarding the

amendment within 35 days of receipt of the notice. The sponsor and study team will make the decision to amend the protocol and will decide whether an amendment is substantial or non-substantial. Any amendments will be tracked to identify the most recent protocol version.

13.8 Access to the final trial dataset

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

14 DISSEMINIATION POLICY

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.

15 REFERENCES

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16. APPENDICIES

16.1 Appendix 1 – Schedule of Procedures

Procedures	**Screening**	**Baseline**	**Treatment Phase**				**Follow Up**
	Visit 1	**Visit 2**	**Visit 3 Day of surgery**	**Visit 4 Day2**	**Visit 5 Day 3**	**Visit 6 Day 5**	**Vist 7 8-12 weeks**
Screening	X						
Informed consent		X					
Demographics		X					
Medical history		X					
Concomitant medications		X					
Eligibility assessment	X						
Randomisation			X				
Dispensing of trial drugs				(X)	(X)	(X)	
Blood Sample		X	X	X	X	X	X
Urine Sample*		X	X	X	X	X	X
Tumour Sample			X				
Paraffin embedded sections							X at a later date
Faeces/stool sample*		X	X	X	X	X	X
Saliva sample*		X	X	X	X	X	X
Sweat sample*		X	X	X	X	X	X
QoL questionnaire completion		X	X				X
Grip Strength			X	X	X	X	X
Adverse event assessments		X	X	X	X	X	X
CRF Data collection		X	X	X	X	X	X
Physician's Withdrawal Checklist		X	X	X	X	X	X

*If consented for sample sub-study.

16.2 Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
n/a				

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.

16.3 Appendix 3 - Study Questionnaires

Provided separately