Bevacizumab And Combination CHemotherapy in rectal cancer Until Surgery

A Phase II, Multicentre, Open-label, Randomised Study of Neoadjuvant Chemotherapy and Bevacizumab in Patients with MRI defined High-Risk Cancer of the Rectum

Trial Sponsor: University College London
Trial Sponsor reference: UCL/09/0176
Trial funder: Cancer Research UK & Roche Products Ltd.
Funder reference: CR UK/C10568/A11558 & ML22748
Clinicaltrials.gov no: NCT01650428
EUDRACT no: 2010-022754-17
CTA no: 20363/0308/001-0001

Protocol version: V5.0
Protocol version date: 02/03/2015
Please note: This trial protocol must not be applied to patients treated outside the BACCHUS trial. UCL CTC can only ensure that approved trial investigators are provided with amendments to the protocol.

Cancer Research UK is supporting central coordination through the Cancer Research UK & UCL Cancer Trials Centre (UCL CTC) — the coordinating centre for the trial. Problems relating to this trial should be referred, in the first instance, to the UCL CTC.
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**Appendix 11 – Quick Reference Guide to Patient Visits**

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**Appendix 14 – Protocol Version History**

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## 1 PROTOCOL SUMMARY

### 1.1 Summary of Trial Design

<table>
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<tr>
<th>Title:</th>
<th><strong>BACCHUS</strong>: Bevacizumab and Combination Chemotherapy in Rectal Cancer until Surgery. A phase II, multicentre, open-label, randomised study of neoadjuvant chemotherapy and bevacizumab in patients with MRI defined high-risk but resectable cancer of the rectum</th>
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<td>Short Title/acronym:</td>
<td>BACCHUS</td>
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<tr>
<td>EUDRACT no:</td>
<td>2010-022754-17</td>
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<tr>
<td>Sponsor name &amp; reference:</td>
<td>University College London - UCL/09/0176</td>
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<tr>
<td>Funder name &amp; reference:</td>
<td>Cancer Research UK: CR UK/C10568/A11558 and Roche Products Ltd: ML22748</td>
</tr>
<tr>
<td>Clinicaltrials.gov no:</td>
<td>NCT01650428</td>
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<tr>
<td>Design:</td>
<td>A phase II, multicentre, open-label, randomised study</td>
</tr>
<tr>
<td>Overall aim:</td>
<td>To evaluate the efficacy, toxicity and feasibility of FOLFOX/ bevacizumab and FOLFOXIRI/ bevacizumab neoadjuvant therapy in poor prognosis rectal cancer as defined by MRI</td>
</tr>
<tr>
<td>Primary endpoint:</td>
<td>• Pathological complete response (pCR)</td>
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</table>
| Secondary endpoints: | • RECIST response rate  
• CRM negative resection rate  
• T and N stage downstaging  
• Progression Free Survival (PFS)  
• Disease Free Survival (DFS)  
• Overall Survival (OS)  
• Local control (for those patients achieving a curative resection)  
• 1 year colostomy rate  
• Adverse events  
• Compliance to chemotherapy  
• Tumour Regression Grade (TRG)  
• Tumour Cell Density (TCD) |
| Target accrual: | 60 patients with histologically confirmed primary rectal adenocarcinoma |
| Planned number of Sites: | Approximately 10 – 20 sites in the United Kingdom |
| Anticipated duration of recruitment: | 18 months |
| Duration of patient follow up: | Up to 42 months after randomisation |
| Definition of end of trial: | End of trial occurs 42 months after last patient randomised, or once all patients have progressed or died, whichever happens sooner |
| Main inclusion criteria: | See detailed description of inclusion criteria in the protocol  
• Histologically confirmed diagnosis of adenocarcinoma of the rectum  
• MRI-evaluated locally advanced tumour with the following:  
  o T3 tumours extending ≥4mm beyong the muscularis propria N0–N2 |
- Or tumours involving or threatening the peritoneal surface
- OR presence of macroscopic extramural venous invasion (V2 disease)
- AND for tumours below the peritoneal reflection, the primary tumour or involved lymph node (on MRI) must be >1 mm from the mesorectal fascia
- Distal part of the tumour within 4-12 cm of the anal verge
- No evidence of established distant metastases
- WHO Performance Status: 0-1 only
- Adequate bone marrow, hepatic and renal function (see detailed description in the protocol)
- Urinalysis – protein ≤1+. For proteinuria ≥2+ or urine protein/creatinine ratio ≥1.0, 24-h urine protein excretion must be ≤2 g
- No evidence of established or acute ischaemic heart disease on ECG, and normal clinical cardiovascular assessment
- At least 18 years of age, but not more than 75 years
- Willing and able to give informed consent and comply with treatment and follow up schedule

### Main exclusion criteria:

- See detailed description of exclusion criteria in the protocol
- Disease outside of the mesorectal envelope (internal iliac/lateral pelvic lymph node)
- Clinically significant cardiovascular or coronary disease ≤2 years before randomisation
- History of interstitial lung disease or evidence of interstitial lung disease on baseline chest CT scan.
- History of an arterial thromboembolic event during the previous 2 years.
- Evidence of bleeding problems or coagulopathy
- Patients receiving warfarin/coumarin derived anticoagulants at full therapeutic doses that cannot be discontinued at least 3 days prior to treatment are excluded, but prophylactic doses of 1 mg to prevent Hickman line clotting are eligible
- Chronic use of aspirin (>325 mg/day) or clopidogrel (>75 mg/day) within 10 days of first planned study treatment
- Require regular use of anti-diarrhoeal
- Serious uncontrolled intercurrent illness including poorly controlled diabetes mellitus
- Metallic colonic or rectal stent in situ
- Previous pelvic radiotherapy
- Previous treatment with another investigational agent within 30 days prior to randomisation
- Patients with a history of previous malignancy in the past 5 years, excepting basocellular or squamous cell skin cancer, or properly treated cervicouterine cancer in situ
- Known HIV, HBV or HCV infection
- Current smoker, or clinically relevant history of drug or alcohol abuse
- Pregnant or lactating women or pre menopausal women not using adequate contraception.
- Patients with any other condition or concurrent medical or psychiatric disease who, in the opinion of the investigator, is not eligible to enter the study
- Inability or unwillingness to comply with the protocol.

| Treatment Summary: | Patients will be randomised to one of two neoadjuvant chemotherapy regimens:

  a) Arm A – FOLFOX + bevacizumab:
  - Bevacizumab 5 mg/kg IV over 30 – 90 minutes (*cycles 1 – 5*)
  - Oxaliplatin 85 mg/m² IV over 2 hours
  - Folinic acid 350 mg IV over 2 hours
  - 5FU 3200 mg/m² IV continuous infusion over 48 hours
  Given every 2 weeks for 12 weeks (6 cycles)

  b) Arm B – FOLFOXIRI + bevacizumab:
  - Bevacizumab 5 mg/kg IV over 30 – 90 minutes (*cycles 1 – 5*)
  - Irinotecan 165 mg/m² IV over 1 hour
  - Oxaliplatin 85 mg/m² IV over 2 hours
  - Folinic acid 350 mg IV over 2 hours
  - 5FU 3200 mg/m² IV continuous infusion over 48 hours
  Given every 2 weeks for 12 weeks (6 cycles) |

| Statistical Summary: | • Assuming a 5% pCR rate with radiotherapy alone and 20% in the FOLFOX + bevacizumab arm, with 5% statistical significance and 80% power, 27 patients are required to detect this difference.
  • Assuming 10% dropout, 30 patients will be recruited to the FOLFOX arm. 30 patients will also be recruited to the FOLFOXIRI arm.
  • 4/27 pCRs in either arm are required for that arm to be considered for further study. The study is not powered to directly compare the two arms. |

| Exploratory Biological studies: | • Archived Tumour Samples: potentially for cellular protein expression, immunohistochemical, morphological DNA and RNA research.

| Additional Imaging studies: | FDG PET/CT (mandatory)
  - FDG PET/CT imaging will be carried out at baseline and to assess tumour response after 3 cycles of treatment
  Additional MRI Sequences (recommended, not mandated)
  The following MRI sequences will be performed at baseline, and repeated after three cycles of treatment and after 6 cycles of treatment to assess tumour response:
  - Diffusion weighted MRI (DW-MRI) (strongly recommended)
  - Intrinsic Susceptibility MRI (ISW-MRI) (recommended)
  - Dynamic Contrast Enhanced MRI (DCE-MRI) (recommended) |
1.2 Trial Schema

ELIGIBLE PATIENT

Staging PET scan with assessment of SUV

Staging MRI scan

RANDOMISE 1:1

Group A (30 pts)
FOLFOX/Bevacizumab
Oxaliplatin
5FU/Folinic acid
Bevacizumab

Group B (30 pts)
FOLFOXIRI/Bevacizumab
Oxaliplatin
Irinotecan
5FU/Folinic Acid
Bevacizumab

3 Cycles (6 weeks)

NO RESPONSE

OFF TRIAL TREATMENT

Staging PET scan with assessment of SUV

Repeat MRI scan

RESPONSE

Group A
FOLFOX/Bevacizumab
Oxaliplatin
5FU/Folinic acid
Bevacizumab

Group B
FOLFOXIRI/Bevacizumab
Oxaliplatin
Irinotecan
5FU/Folinic Acid
Bevacizumab

3 Cycles (6 weeks)

FOLLOW UP

Staging MRI scan

SURGERY

Primary Endpoint (pCR rate) assessed

FOLLOW UP

1 SUV = Standardised Uptake Value
2 Bevacizumab is omitted from the final cycle of treatment
2  INTRODUCTION

2.1  Background

Current management of rectal cancer in the United Kingdom incorporates Magnetic Resonance Imaging (MRI)-based pre-operative staging to direct neo-adjuvant treatment strategies, which are aimed primarily at the reduction of local recurrence. Short Course Preoperative Radiotherapy (SCPRT) in Northern Europe or chemoradiotherapy (CRT) in the USA and Southern Europe, are used extensively for the majority of patients with T3 rectal cancer staged by transrectal ultrasound and MRI.

A meta-analysis of preoperative radiotherapy (RT) [1], individual recent trials of SCPRT [2, 3], and CRT [4-6] have all demonstrated improved local control, but have shown no effect on overall survival [2, 3, 7]. Low rates of local recurrence can now also be achieved from surgery alone without radiotherapy in unselected patients, especially if good quality surgery [8] is performed.

Yet, the risk of metastases in studies of clinically staged T3 cancer remains consistently at 35 - 50% [4-6]. Thus, the risk of loco-regional failure is now exceeded by the rate of distant metastases. The short-term use of chemotherapy such as 5-fluorouracil (5FU)-based preoperative CRT has not proved effective in preventing these distant metastases [5, 6, 9]. This finding contrasts with stage III colon cancer, where 5FU alone [10] or the addition of oxaliplatin to 5FU-based chemotherapy [11-13] has shown a consistent and significant improvement in 3 year disease-free survival (DFS).

Radiotherapy is associated with an increased risk of surgical morbidity – particularly in terms of anastomotic leakage and perineal wound complications [14, 15] which can compromise the delivery of postoperative adjuvant chemotherapy. There are also significant permanent radiation late side-effects [16, 17], worsening of quality of life [18], as well as a higher risk of second malignancies [19]. Hence SCPRT and CRT prior to resection may represent an over-emphasis on the risks of local recurrence and ignoring the risks of metastatic disease.

Several different drugs, including capecitabine, oxaliplatin, irinotecan, bevacizumab and cetuximab, and their combinations, are now being explored in combination with pre-operative radiotherapy to improve tumour shrinkage before surgery. However, these drugs have not been integrated at full systemic doses into chemoradiation schedules because of overlapping toxicities. This dose reduction has been most notable with the use of irinotecan and to a lesser extent capecitabine.

Oxaliplatin has often been administered in weekly schedules as a radiosensitizer [2, 20, 21]. There are two other ongoing phase III trials incorporating oxaliplatin into preoperative chemoradiation registered in the www.clinicaltrials.gov website (the NSABP-R04 trial and PETACC-6). As an alternative to concurrent chemoradiation (which only delivers 5-6 weeks of chemotherapy) either an induction component of systemically active chemotherapy prior to radiotherapy or chemoradiation [22-24], adding additional chemotherapy after SCPRT or chemoradiotherapy [25] or delivering chemotherapy alone without any radiotherapy are suitable options [26].

The Cancer Research UK supported ARISTOTLE trial also uses MRI findings as eligibility criteria, and consequently avoids any overlap in recruitment between BACCHUS and ARISTOTLE. MRI allows an accurate prediction of T and N stage and the potential risk of surgical margin involvement by tumour [27]. MRI can therefore identify patients in whom circumferential resection margin involvement is not a concern but who exhibit poor prognostic radiological features indicative of a low risk of local failure, and a high risk of metastatic disease.

T3 disease can be sub-divided into T3a, T3b, T3c and T3d disease according to the radial outgrowth of tumour distance from the breached muscularis propria [28]. This is not a TNM staging but uses pragmatic MRI based categories i.e. T3a = <1mm, T3b = 1.01-5.00mm, T3c = 5.01-15.00mm and T3d = >15.01mm. Hermanek showed that tumour penetration of >4mm was an important risk factor for the subsequent development of metastases. For T3 tumours penetration into the muscularis propria >5mm is associated
with poorer survival [29-32]. In the latter study, patients with >5mm penetration had only a 54% 5 year survival [32].

Extramural vascular invasion (EMVI) occurs in about 40% of patients [33]. This feature is also readily identified on preoperative MRI, and predicts for systemic failure with good concordance between MRI EMVI and eventual pathology EMVI prognostic outcome, suggesting that patients with macroscopic EMVI have a 30% 3 year survival.

2.1.1 Population being studied in BACCHUS

The patient population to be studied represents approximately 40-50% of patients with localised but advanced rectal cancer (i.e. approx 5000 - 6000 patients per year in the UK), and has a relatively poor prognosis. Even with low rates of local recurrence, the risk of metastases in T3 cancer remains consistently in the region of 35%-50%.

Hence if we confine eligibility for this study to patients with MRI estimated penetration of > 4mm and/or patients with N0 or N2 predicted by MRI and EMVI, we estimate a group of patients making up about 40% of rectal cancers overall who have a 50% 5 year survival - as in the CLASSIC Study [34], and a local recurrence rate of 8-12% without preoperative radiotherapy. Neoadjuvant chemotherapy therefore offers an alternative to SCPRT.

2.1.2 Why neoadjuvant chemotherapy?

Recent consensus recommendations suggest that decisions regarding the appropriateness of adjuvant chemotherapy in rectal cancer should be dictated according to initial preoperative clinical stage [35]. They recommended the evaluation of neoadjuvant treatment strategies as a priority of future research, to decrease the high metastases rate in patients with rectal cancer [35].

2.1.3 Compliance to neoadjuvant chemotherapy

Compliance to chemotherapy in the preoperative setting should be high [22, 23, 26, 36], and the neurotoxicity of oxaliplatin (which is often dose-limiting) is less than 60% with only 3 months duration of therapy [36]. Recent evidence from a Spanish trial reported that compliance with the capecitabine and oxaliplatin chemotherapy improved from 51% to 90% when chemotherapy was moved to the neoadjuvant setting [24].

2.1.4 Compliance to postoperative chemotherapy

There is a problem with delivery of, and compliance with chemotherapy following preoperative SCPRT or CRT and surgery. The EORTC 22921 trial showed compliance to postoperative adjuvant chemotherapy was very poor at 42.9%. At least 25% of patients in whom chemotherapy might be considered may not be sufficiently fit for treatment or decline [5, 6]. The Chronicle trial, in particular, highlighted this problem (R. Glynne-Jones, personal communication)

2.1.5 Rationale for neoadjuvant chemotherapy

Intuitively it would be best therefore to deliver systemic doses of the most active chemotherapy within a week or two of diagnosis, rather than delaying the 3-6 months required for SCPRT and surgery, or CRT and surgery, and recovery post surgery.

Finally, both in animal models and in clinical studies of patients with colorectal cancer, resection of the primary tumour results in an increase in vascular density, metabolism and secondary tumour growth of the distant metastases [37]. This suggests a possible inhibitory effect of the primary tumour on the growth of metastases. Both open and laparoscopic resections are associated with significantly elevated plasma VEGF levels early after surgery [37] leading to a possible positive effect on tumour growth.
Rectal tumours, which are not eradicated and re-grow within an irradiated field, show a higher frequency of metastases [38]. The hypothesis to explain this is that the hypoxic microenvironment as a result of radiotherapy stimulates angiogenic factors. The tumour bed effect has been well described [39] to upregulate metastasis-promoting gene products.

2.1.6 Neoadjuvant chemotherapy for liver metastases

The EORTC study in patients with resectable liver metastases showed that 12 patients (6.9%) progressed on 5FU, leucovorin and oxaliplatin (FOLFOX) chemotherapy, but 8/12 remained resectable, and only 4 developed new lesions [36]. In a neoadjuvant study in liver metastases, capecitabine, oxaliplatin (XELOX) and bevacizumab achieved a 70% response rate (RR), and an astonishingly high pathological complete response (pCR) rate of 9% [40, 41]. This figure is equivalent to results of studies of 5FU-based chemoradiation in locally advanced rectal cancer.

2.1.7 Neoadjuvant chemotherapy for locally advanced rectal cancer

In locally advanced rectal cancer, the NSABP-R03 study employed a weekly schedule of 5FU and folinic acid for six weeks prior to definitive preoperative chemoradiation. A response rate of 44% was achieved in the 39 patients who completed all 6 cycles [42, 43]. Only 2 patients (5%) progressed on this regimen. In a phase II study using neoadjuvant capecitabine and oxaliplatin, the clinical response rate was 88% and no patient progressed radiologically [22]. Hence, anxieties that patients will progress on neoadjuvant chemotherapy appear unfounded.

Two papers from the Sloan-Kettering Cancer Centre presented at the GI ASCO symposium meeting in Orlando 2010 appear to support the feasibility and efficacy of the neoadjuvant chemotherapy approach without radiation in rectal cancer [26, 44]. The first tested the neoadjuvant approach in primary cancers of the midrectum. These studies showed a pCR in 7/27 patients (27%) and 7/20 patients (35%) after neoadjuvant FOLFOX or FOLFOX plus bevacizumab without radiation. We might therefore expect a pCR rate of between 20 and 40% in the BACCHUS study.

2.2 Rationale for BACCHUS

Thus the above data, concerns regarding late morbidity from radiotherapy, and anxieties regarding the risks of metastases have all raised an interest in an innovative neoadjuvant approach using a highly active chemotherapy regimen which might reduce the distant failure rate with an acceptable local control. For cancers in the mid rectum with a moderate risk of local recurrence, (MRI defined non-threatened surgical CRM i.e. T3b, T3c and T3d with clinically involved nodes, and /or extramural vascular invasion), SCPRT or CRT could be replaced by neoadjuvant chemotherapy alone [22, 45].

2.3 Rationale for the chemotherapy regimens used

The underlying rationale for the treatment selection is based on the question of whether an increase of chemotherapy intensity through the addition of irinotecan to the well-established FOLFOX regimen in combination with bevacizumab would lead to a higher clinical and pathological response.

The chemotherapy regimens used in this study (FOLFOX or FOLFOXIRI) have been chosen on the basis of the higher response rates and survival durations as compared with other fluoropyrimidine-based regimens [46-48]. Bevacizumab has demonstrated its significant progression free or overall survival benefit in combination with chemotherapy in three phase III trials in metastatic colorectal cancer [49-51]. BACCHUS will therefore allow evaluation of the potential benefit of bevacizumab in combination with the two most active current chemotherapy regimens in the 1st line and postoperative treatment setting.
2.3.1 5-Fluorouracil

For 50 years the cornerstone of treatment has been the fluoropyrimidine 5-fluorouracil (5FU), which has offered modest activity with clinical response rates in the range of 10-20%, and median survival reported in the range of 6-8 months in patients with metastatic colorectal cancer.

2.3.2 Irinotecan and oxaliplatin

More recently in the 1990s combinations of cytotoxic chemotherapy using oxaliplatin [52, 53] or irinotecan [54-57], have represented the mainstay of treatment for patients with advanced and metastatic colorectal cancer (MCRC). Recently, three-drug combinations [46] have been employed. In addition, a number of molecularly targeted agents have been integrated into chemotherapy regimens to further improve response rates or extend progression free (PFS) and overall survival (OS), albeit with varying success [35, 58, 59].

2.3.3 Bevacizumab

The growth of primary tumours, as well as metastatic disease, requires an intact and expanding vasculature. Therefore vascular endothelial growth factor (VEGF) represents an attractive target for new treatments. Bevacizumab is a recombinant humanized monoclonal antibody, targeted against VEGF-A. It binds to and prevents VEGF-A from interacting with its target receptor.

In addition, solid tumours commonly manifest an elevated interstitial fluid pressure (IFP) and regions of hypoxia as compared to normal tissues, which contribute to a decreased transcapillary transport, and lead to the poor delivery of cytotoxic drugs. A clinical study in locally advanced rectal cancer, demonstrated that tumour IFP was lowered by the use of the anti-VEGF monoclonal antibody bevacizumab [60]. Two pivotal studies have shown the potential utility of these two approaches in colorectal cancer [60, 61].

Bevacizumab does not increase the classical chemotherapy induced side effects over chemotherapy alone [62], but can induce typical adverse events, including hypertension, proteinuria, mucosal bleeding, arterial thrombosis, gastrointestinal perforation and wound healing problems [58, 61]. Occasional deaths have been reported secondary to an arterial thrombosis or a gastrointestinal perforation.

In the Hurwitz trial [58], the incidence of arterial thromboembolic events (including cerebrovascular accident (CVA), myocardial infarction (MI), transient ischaemic attack (TIA), and other arterial thromboembolic events) was higher in patients receiving irinotecan, fluorouracil and leucovorin (IFL) plus bevacizumab (3.3%) compared to patients receiving IFL plus placebo (1.3%).

A history of arterial thromboembolic events or age greater than 65 years has been associated with an increased risk of arterial thromboembolic events during bevacizumab therapy. Patients receiving bevacizumab plus chemotherapy with a history of arterial thromboembolism and age greater than 65 years have a higher risk.

Bevacizumab has also been associated with gastrointestinal perforation in patients with metastatic carcinoma of the colon or rectum. The presentation of these events varied in type and severity, ranging from free air seen only on the plain abdominal X-ray, which resolved without treatment, to a colonic perforation with abdominal abscess and fatal outcome. The common feature among these cases was intra-abdominal inflammation, either from gastric ulcer disease, tumour necrosis, diverticulitis or chemotherapy-associated colitis. There are also case reports of perforation through a colonic stent. Caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab.

In the Hurwitz study, 40 patients in the IFL plus bevacizumab arm underwent major surgery while receiving bevacizumab, of which 4 patients experienced an adverse event consistent with post-operative bleeding or wound healing complications [58]. In contrast, there were no similar complications observed in the 25 patients from the IFL plus placebo arm who also underwent major surgery during the study.
There were 5 haemorrhagic events in the IFL + bevacizumab arm (three rectal haemorrhages, one gastrointestinal haemorrhage and one melaena) assessed as tumour-associated haemorrhages. However, the addition of bevacizumab did not appear to result in a significant increase in the incidence or severity of grade 3 or 4 haemorrhagic events.

Evidence from the BEAT study in metastatic colorectal cancer [63] where patients were treated with first line chemotherapy in combination with bevacizumab is helpful in examining the effect of bevacizumab on surgery and post operative healing. In the group of patients with metastatic disease confined to the liver (n=704), 102 of these patients (14.5%) underwent resection of their hepatic metastases, there was no increase in either wound healing complications or bleeding events compared with data from other large prospective studies when bevacizumab was stopped 6-8 weeks prior to major surgery. Wound healing complications were 1.3%, bleeding 3.4% and GI perforation 1.8% respectively. The BRITE study [64] and the ARIES study [65] showed similar results.

Thomas Gruenberger has already completed a phase II trial with XELOX with or without bevacizumab [40]. Patients were treated with 6 cycles of XELOX and 5 cycles bevacizumab. Surgery was performed 2 weeks after the last capcitabine administration, allowing a time window of 5 weeks between the last bevacizumab administration and surgery. There was no excess surgical morbidity.

Nevertheless, caution should be exercised with these patients. For this reason we have decided that in the BACCHUS study the interval between bevacizumab and surgery will be a minimum of 8 weeks (> 2 half lives of bevacizumab). Also in the present study an age limit of 7 years and eligibility requirements of no significant cardiac history and being a non-smoker should limit serious side effects and patients will be carefully monitored.

2.4 Summary of studies using neoadjuvant chemotherapy with bevacizumab

Two current trials with a similar design to BACCHUS are employing FOLFOXIRI prior to resection of liver metastases in colorectal cancer. The first in Italy – the (GONO-TRIBE study (Falcone PI) examines FOLFOXIRI chemotherapy with bevacizumab versus FOLFIRI with bevacizumab up to a total of 12 cycles in the neoadjuvant setting for liver metastases. There are no reports of toxicity or efficacy yet.

The second neoadjuvant trial with a similar design to BACCHUS is MO 18725, is a randomised international phase II study of bevacizumab in combination with FOLFOXIRI versus FOLFOX in patients with initially unresectable liver metastases. Patients are randomised to receive either FOLFOXIRI chemotherapy with bevacizumab every two weeks or FOLFOX and bevacizumab. The aim is to evaluate the safety and potential for resectability of liver metastases following treatment. The patients will then be assessed for resectability every 3 cycles (6 weeks) and if considered resectable will have a further cycle of chemotherapy with planned surgery after an interval of 3-5 weeks. The primary objective is the rate of surgical complications at 3 months.

2.5 Rationale for FOLFOXIRI

A phase II study (Masi 2004) used FOLFOXIRI at a dose of irinotecan of 165 mg/m² and oxaliplatin of 85 mg/m², whilst 5FU was administered at 3200 mg/m² as a 48 hour continuous infusion. This was a highly efficacious regimen with a response rate of 72%, median progression free survival 10.8 months and overall survival 28.4 months [66]. Grade 3/4 toxicities included diarrhoea (16%), neutropenia (34%), stomatitis (6%) and peripheral neuropathy (37%). For the GONO study [46] the measure of the efficacy of this regimen was that the use of FOLFOXIRI in a randomised phase II trial was associated with a response rate of 66%, and improved the resection rate in liver only patients from 12% to 36% - although the median duration of chemotherapy (5 months) is longer than intended in the present study. Overall survival also improved in the novel arm. Toxicity was acceptable with G3/4 diarrhoea 20% and febrile neutropenia 23%. However, in a small study of 18 patients [67] the clinical RR with FOLFOXIRI and bevacizumab was even higher at 87% with 13% achieving stable disease, and no patients progressed. Toxicity was acceptable with grade 3/4 neutropenia 23% and diarrhoea 12%. Neutropenia is a relatively frequent
toxicity, but is usually short lasting and rarely complicated. Therefore, prophylactic G-CSF is not routinely indicated.

A randomised comparison of FOLFOXIRI with FOLFIRI included 244 subjects with measurable metastatic colorectal cancer that was previously untreated for advanced disease [46]. Toxicity demonstrated grade 3/4 diarrhoea (12% v 20%, p=NS), vomiting (2% v 7%, p=NS), stomatitis (3% v 5%, p=NS), grade 2-3 peripheral neuropathy (0% v 18%, p<0.05), grade 3/4 neutropenia (28% v 49%, p=0.0002) and febrile neutropenia (3% v 5%, p=NS). The response rate was significantly higher in the triplet arm (66% v 41%, p=0.0002) with longer progression free survival (9.9 months v 6.9 months, p=0.0009). In addition, overall survival was improved (23.6 months v 16.7 months, p=0.04).

In the present trial we are intensifying both chemotherapy and adding a biological agent in the form of bevacizumab to either FOLFOX or FOLFOXIRI.

2.6 PET Scanning

The evaluation of clinical response is recognised to be inaccurate. Standard response criteria in terms of size according to WHO or RECIST do not take into account minor responses. There is poor differentiation on imaging of residual areas within the radiation field to distinguish viable tumour from replacement with fibrosis, and clinical response has not been shown to act as a robust surrogate endpoint to predict outcome in this setting. CT is often limited by not reliably distinguishing necrotic tumours, fibrosis, inactive scar tissue and residual active tumour.

Positron emission tomography (PET) is a functional imaging technique, which uses the radioactive tracer 18F-fluorodeoxyglucose (FDG) as a marker of glucose metabolism to image tumour cells. It is well recognised that neoplastic cells have increased glycolytic activity, and that imaging based on metabolic characteristics can be quantified using standard techniques. The main technique in current use is the standardised uptake value (SUV).

\[
SUV = \frac{\text{decay corrected dose (kBq)/tumour (mL)}}{\text{Injected dose (kBq)/body weight (g)}}
\]

This metabolic activity is occasionally over-estimated because of uptake from inflammatory changes in macrophages and because granulation tissue can also uptake FDG. But in the main, FDG uptake is related to the number of viable cells within a tumour, and the proliferative activity of that tumour. FDG may also relate to other biological parameters such as tumour cell density, hypoxia and angiogenesis within a tumour. All these factors are related to aggressiveness, so some authors believe that the initial uptake of the baseline tumour, the initial SUV max has a prognostic value because it can determine the aggressiveness of a tumour [68, 69].

Current hybrid scanners combine PET and CT technology to enable optimal co-registration of anatomical and functional images. In general, treatment induced modifications of this glucose metabolism can be captured at an earlier time than can be found on conventional morphological (CT based) imaging. PET imaging therefore has the potential to predict response to chemotherapy and radiotherapy much earlier than techniques such as MRI and CT alone, which only show structural changes [70, 71]. Accurate quantification of the SUV can also be measured sequentially during treatment to give a more sensitive assessment of response, since quantification of SUV can distinguish highly active from less active tumours. Also the degree of PET SUV changes, induced by chemotherapy, appears highly predictive of outcome for the patient [71].

Primary rectal cancer is recognised to have a higher avidity for FDG but this avidity is less so with mucinous tumours, which could present as false negatives. Sensitivity has been documented in the region of 90-95% with a specificity of 85-90%. Confusion may occur with variable physiological uptake in the large bowel and uptake because of colitis, diverticulitis or adenomas. Response rates are usually higher in primary tumours than metastases.
Preliminary promising results have also been reported with colorectal cancer. There is now evidence that shows that FDG PET and more recently PET CT after CRT is an accurate method for predicting pathological response. In 20 patients with T3/T4 adenocarcinoma, a fall in SUV of 36% separated responders from non-responders. Surgery confirmed that FDG PET defined metabolic changes defined as a decrease in SUV max greater than 36% were a more accurate predictor of response than EUS, and correlated well with histopathological response [72]. In patients with locally advanced (PT3-4) primary rectal cancer semi-quantitative measurements of FDG uptake including SUV(max) between pre- and post-CRT PET correlate with pathological response, assessed both by histopathological staging of the surgical specimens (pTNM) and by the tumour regression grade (TRG) according to Mandard’s criteria (patients with TRG1-2 being defined as responders and patients with TRG3-5 as non-responders [68, 73-75]. In a further study, a complete pathological response was found in 6 patients and FDG PET predicted this in 5 of the six patients. The authors also found that response on FDG PET was associated with a significantly longer time to disease progression and a significantly higher life expectancy compared to those patients who did not show an FDG PET response [69].

The above studies scanned during RT, which may be a confounding factor because of inflammatory changes within the radiation field resulting from ionising radiation. In addition, tumour cell loss is associated with an increase in potential doubling time – although proliferation of the viable cell fraction is maintained [76]. Further studies are required to determine the optimal timing for the second PET/CT, since some argue that results are confounded at this time by inflammatory changes. Hence, the majority of studies have focussed on FDG PET after completion of neoadjuvant treatment and before surgery.

We will use a predefined prospective definition of metabolic response for the calculated fractional change between the first and second PET scans, to avoid the bias of data driven cut offs. Primary tumours are expected to have a higher response rate than metastases. The European Organisation for Research and Treatment of Cancer has produced guidelines for categorising cut off values for PET SUV according to RECIST criteria where a decrease of > 30% represents a complete or partial response, we have therefore predefined and selected 30% as a cut off. An initial pilot of 24 patients will validate the 30% cut off as relevant in rectal cancer patients treated with chemotherapy. With the use of two sequential PET scans the patient will serve as their own control (the body weight is unlikely to change in a matter of weeks).

The SUV changes with the patient as their own control will be robust, even if the absolute SUV is not robust. However, it is important that measurements are undertaken on the same machine. We will need to control for the time of injection to time of imaging for reproducibility, as well as single plane/ multiple planes for SUV calculation.

See Appendix 2 for details of FDG PET/CT protocol.
3 TRIAL DESIGN

BACCHUS is a multicentre, randomised phase II trial which aims to recruit 60 patients with poor prognosis but resectable rectal cancer. Patients will be randomised to receive one of two treatment regimens:

![Diagram showing trial design]

Patients failing to respond at 6 weeks (i.e. after 3 cycles) should come off trial treatment. Subsequent treatment will be at the discretion of the treating investigator.

3.1 Objectives

The main objective for the feasibility study is to assess the efficacy and safety of these two highly active cytotoxic chemotherapy regimens combined with bevacizumab, prior to surgery in rectal cancer.

An effective chemotherapy regimen with acceptable toxicity would be suitable for testing as the novel arm against both/either of the current standards of SCPRT and/or 5FU based chemoradiotherapy in a future randomised phase III trial.

3.2 Primary Endpoint

- Pathological complete response (pCR) in the histological specimen (see Appendix 9)

3.3 Secondary Endpoints

- RECIST response rate (see Appendix 10)
- CRM negative (>1mm) resection rate (see Appendix 9)
- T and N stage downstaging
- Progression Free Survival (PFS)
- Disease Free Survival (DFS)
- Overall Survival (OS)
- Local control (for those patients achieving a CRM negative resection)
- 1 year colostomy rate
- Frequency and severity of adverse events

¹ SUV=standardised uptake value; ² Bevacizumab is omitted from the final cycle of treatment
• Compliance of chemotherapy treatment
• Tumour Regression Grade (TRG)
• Tumour Cell Density (TCD)

3.4 Exploratory Biological Analyses

Tissue and blood samples will be collected and stored for future research (see section 21, Ancillary studies). In addition all of the H&E stained slides from the diagnostic biopsy and resection samples will be collected to undertake Tumour Regression Grading and Tumour Cell Density.

3.5 Trial Activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to opening the trial:

• Research Ethics Committee approval
• Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA)
• NHS permission
• Adequate funding for central coordination
• Confirmation of sponsorship
• Adequate insurance provision
• ‘Adoption’ into NIHR portfolio
4 SELECTION OF SITES AND INVESTIGATORS

4.1 Site selection

In this protocol trial “Site” refers to the hospital where trial-related activities are conducted.

Sites should be able to comply with:

- Trial treatments, imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Research Governance Framework and the Medicines for Human Use (clinical trials) Act (SI 2004/1031 and all amendments)
- Data collection requirements
- Collection, storage and shipment of biological samples
- Monitoring requirements, as outlined in the protocol (section 14) and trial monitoring plan
- ARSAC license

Sites must inform UCL CTC of any additional sites involved in the patient pathway. Recruiting sites which will be referring patients to a different site, for all or some of the trial activities, will not be activated until the relevant site involved is ready to be activated.

4.2 Selection of Principal Investigator and other investigators at sites

Sites must have an appropriate Principal Investigator (PI) i.e. a health care professional authorised by the site and ethics committee to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI. All investigators must be medical doctors and have experience of treating rectal cancer.

4.3 Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). An up-to-date, signed copy of the CV for the PI must be forwarded to UCL CTC prior to site activation and upon request.

Appropriate and proportionate GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

4.4 Site Initiation and activation

4.4.1 Site initiation

Before a Site is activated, the UCL CTC trial team will arrange a Site initiation, with the Site which the PI, the pharmacy lead, the pathology lead and Site research team must attend. The Site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed by either teleconference or on-site visit with each Site.

4.4.2 Required documentation

The following documentation must be submitted to UCL CTC prior to a Site being activated by the UCL CTC trial team:
• Trial specific Site Registration Form (identifying relevant local staff)
• All relevant institutional approvals (e.g. local NHS permission)
• A completed Site delegation log with all staff entries signed and dated by the PI
• A copy of the PI’s current CV that is signed and dated with evidence of up-to-date GCP training (or copy of GCP certificate)
• A copy of the ARSAC certificate (depending on individual local practise, e.g. for Site/centre providing PET scans)
• The Site performing PET scans must have also attained approval from the NCRI PET core lab prior to entering patients into the trial
• Trial specific prescriptions
• Drug accountability logs/records – for sites that will be using their own logs In addition a signed Clinical Trial Site Agreement (CTSA) between the Sponsor and the relevant institution (usually a NHS Trust) must be in place.

4.4.3 Site activation

Once the UCL CTC trial team has received all required documentation and the Site has been initiated, a Site activation letter will be issued to the PI. **Site must not approach any patients until they have received an activation letter from UCL CTC.**

Once the Site has been activated by UCL CTC, the PI is responsible for ensuring:

• Adherence to the most recent version of the protocol
• All relevant Site staff are trained in the protocol requirements
• Appropriate recruitment and medical care of patients in the trial
• Timely completion and return of CRFs (including assessment of all adverse events)
• Prompt notification and assessment of all serious adverse events and adverse events of special interest (see section 12.2.7)
• That the Site has facilities to provide **24 hour medical advice** for trial patients

The PI, other investigators and all staff involved in the conduct of the trial at the Site must be identified on the Site delegation log, held at Site and copied to UCL CTC on request.
5 INFORMED CONSENT

Sites are responsible for assessing a patient’s capacity to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheet, are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent form.

The PI or where delegated by the PI, other appropriately trained Site staff, are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions the current approved patient information sheet for the trial should be discussed with the patient. A minimum of twenty four hours must be allowed for the patient to consider and discuss participation in the trial. Written informed consent on the current approved version of the consent form must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient’s notes.

Sites must assess a patient’s ability to understand verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent throughout their participation in the trial. If a patient requires an interpreter and none is available, the patient should not be considered for the trial.

Site staff are responsible for:

- Checking that the correct (current approved) versions of the patient information sheet and consent form are used
- Checking that information on the consent forms is complete and legible
- Checking that the patient has completed/initialled all relevant sections and signed and dated the form
- Checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient
- Checking that an appropriate member of staff has made dated entries in the patient’s medical notes relating to the informed consent process (i.e. information given, consent signed, etc.)
- Ensuring that all consent information has been completed on the randomisation form, prior to randomising the patient
- Following randomisation:
  - Adding the patient trial number to all copies of the consent form which should be filed in the patient’s medical notes and Investigator Site File (ISF)
  - Giving the patient a copy of their signed consent form, patient information sheet, patient diary and patient contact card

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time (see section 15 – Withdrawal of patients).
6 SELECTION OF PATIENTS

6.1 Pre-randomisation evaluation

All patients must provide written informed consent before any trial-specific assessments or procedures are performed.

The following assessments or procedures are required to evaluate the suitability of patients of the trial prior to patient entry:

- Histological confirmation of rectal cancer
- Within 35 days prior to randomisation:
  - Demographics and medical history (including age, gender, ethnicity, and previous and current diseases, cancer and treatment history)
  - Chest/abdominal/pelvis CT scan to exclude liver or pulmonary metastases
  - MRI scan of the pelvis for locoregional staging
    Tumour measurement/assessment will be performed based on RECIST v1.1 criteria using MRI scan (see appendix 10).
  - Diffusion weighted MRI is strongly recommended but not mandatory. Additional intrinsic susceptibility MRI and dynamic contrast enhanced MRI sequences are also recommended but not mandated (see appendix 8). This will be reviewed centrally.
    - Note: may be carried out after randomisation as scan is not required to assess eligibility, but must be performed before start of treatment.
  - FDG-PET CT scan
    - Note: may be carried out after randomisation as scan is not required to assess eligibility, but must be performed before start of treatment. PET scan must be performed in accordance to the guidelines set out in Appendix 2.
- Within 7 days prior to randomisation:
  - Clinical examination and vital signs, including height, weight, neurological examination, temperature, pulse and blood pressure
  - Documentation of concomitant medications
  - Assessment of adverse events (AEs)
  - New York Heart Association functional classification assessment (see appendix 5)
  - WHO performance status
  - Haematology:
    - Full blood count plus white blood cell differential including absolute neutrophil (ANC) and lymphocyte counts
  - Biochemistry:
    - Sodium, potassium, urea, creatinine, albumin, total bilirubin, alkaline phosphatase (ALP), AST and/or ALT, γGGT, CRP
  - CEA
    - Note: may be carried out after randomisation as CEA result is not required to assess eligibility, but must be measured before start of treatment.
  - Estimated GFR (calculated creatinine clearance (CrCl) using Cockcroft and Gault formula – see Appendix 4). If the calculated CrCl is <50 mL/min, a $^{51}$Cr-EDTA or $^{99m}$Tc-DTPA clearance test must be carried out demonstrating GFR ≥ 50mL/min.
  - Coagulation:
    - INR, aPTT
  - Urinalysis (if urine dipstick is ≥2+, 24-hour urine is required)
  - ECG (cardiac assessment)
6.2 Screening log

A screening log must be maintained by the Site and kept in the Investigator Site File. This must record each patient identified at Site with locally advanced rectal cancer and screened for the trial and the reasons why they were not randomised in the trial if this is the case. The log must be sent to UCL CTC when requested with patient identifiers removed prior to sending.

6.3 Patient eligibility

There will be no exception to the eligibility requirements at the time of randomisation. Queries in relation to the eligibility criteria must be addressed prior to faxing for randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

6.3.1 Patient inclusion criteria

- Histologically confirmed diagnosis of adenocarcinoma of the rectum
- Distal part of the tumour within 4-12 cm of the anal verge
- No unequivocal evidence of established metastatic disease (on chest/abdominal/pelvis CT). Patients with equivocal lesions (as determined at MDT) are eligible
- MRI-evaluated locally advanced tumour with the following:
  - T3 tumours extending (≥ 4 mm), beyond the muscularis propria N0–N2
  - Or tumours (involving or threatening the peritoneal surface)
  - OR presence of macroscopic extramural venous invasion (V2 disease)
  - OR presence of macroscopic extramural venous invasion (V2 disease)
  - OR presence of macroscopic extramural venous invasion (V2 disease)
  - AND for tumours below the peritoneal reflection, the primary tumour or involved lymph node (on MRI) must be >1 mm from the mesorectal fascia
- Measurable disease (according to RECIST criteria v1.1)
- WHO performance status 0 – 1
- In the opinion of the investigator:
  - General condition considered suitable for radical pelvic surgery
  - Candidate for systemic therapy with FOLFOX/FOLFOXIRI plus bevacizumab
- Adequate bone marrow, hepatic and renal function:
  - Haemoglobin ≥80 g/L
  - ANC ≥2 x 10^9/L
  - Platelet count ≥100 x 10^9/L
  - ALT or AST ≤1.5 x ULN (upper limit of normal)
  - ALP ≤1.5 x ULN
  - Total bilirubin ≤1.5 x ULN
  - Serum creatinine ≤1.5 x ULN
  - Creatinine clearance ≥50 mL/min using the Cockcroft–Gault formula (see Appendix 4). If the calculated GFR is below <50 mL/min, a 51Cr-EDTA or 99mTc-DTPA clearance test must be carried out demonstrating GFR is ≥50 mL/min
- INR ≤ 1.1
- Urine protein ≤1+ with dipstick or urine analysis.
  - For proteinuria ≥2+ or urine protein/creatinine ratio ≥ 1.0, 24-h urine protein should be obtained and the level must be ≤2 g for eligibility
- No evidence of established or acute ischaemic heart disease on ECG and normal clinical cardiovascular assessment
- No known significant impairment of intestinal absorption
At least 18 years of age, but not more than 75 years
Willing and able to give informed consent, comply with treatment and follow up schedule

6.3.2 Exclusion criteria

Patients with any of the following exclusion criteria will not be eligible for the study:

- Disease outside of the mesorectal envelope (internal iliac/lateral pelvic lymph node)
- Clinically significant cardiovascular or coronary disease (including myocardial infarction (MI), angina (stable or unstable), symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤2 years before randomisation, New York Heart Association Classification ≥III (see appendix 5)
- History of interstitial lung disease e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan
- History of an arterial thromboembolic event during the previous 2 years
  - This includes MI, transient ischaemic attack (TIA), cerebrovascular accident (CVA), symptomatic peripheral vascular disease or other relevant history in the opinion of the investigator.
- Evidence of bleeding problems or coagulopathy
- Significant and continuing rectal bleeding leading to a haemoglobin <80 g/L
- Patients receiving warfarin/coumarin derived anticoagulants at full therapeutic doses that cannot be discontinued at least three days prior to treatment are excluded, but patients receiving prophylactic doses of up to 1 mg to prevent Hickman line clotting are eligible.
  - **Note:** patients being anticoagulated for atrial fibrillation or other conditions can participate if they are receiving a low stable dosage of anticoagulant therapy as above. Clinicians must consider the higher risk of therapy with bevacizumab among patients with a history of thromboembolic disorders so the decision to allow the patients to participate remains at the discretion of the physician.
- Chronic use of aspirin (>325 mg/day) or clopidogrel (>75 mg/day) within 10 days of first planned study treatment
- Taking phenytoin or sorivudine or its chemically related analogues, such as brivudine
- Require regular use of anti-diarrhoeal (e.g. daily use of loperimide)
- Serious uncontrolled intercurrent illness including poorly controlled diabetes mellitus
- Known hypersensitivity to any of the study drugs
- Serious wound, ulcer or bone fracture
- Current or impending rectal obstruction
- Metallic colonic or rectal stent *in situ*
  - **Note:** patients with ileostomy are eligible, however should be treated with caution. Patients with ileostomy will not be able to participate if they require regular use of anti-diarrhoeal
- Previous pelvic radiotherapy
- Previous intolerance to fluoropyrimidine chemotherapy
- Concurrent use of bisphosphonates
- Infectious illness requiring antibiotics within 1 week of randomisation
- Previous treatment with another investigational agent within 30 days prior to randomisation
- Patients with a history of previous malignancy in the past 5 years, excepting basocellular or squamous cell skin cancer, or properly treated cervicouterine cancer *in situ*
- Known HIV, HBV or HCV infection
- Current smoker, or clinically relevant history of drug or alcohol abuse
- Pregnant or lactating women or pre menopausal women not using adequate contraception. Men and women of child-bearing potential must use adequate contraception (see section 6.3.3)
Patients with any other condition or concurrent medical or psychiatric disease who, in the opinion of the investigator, is not eligible to enter the study

Inability or unwillingness to comply with the protocol

6.3.3 Pregnancy and birth control

The risks to the human embryo or foetus from exposure to bevacizumab, irinotecan, oxaliplatin and 5-fluorouracil are currently unknown. However serious birth defects have been observed in animal studies. It is therefore essential that female patients and partners of male patients do not become pregnant during treatment and for at least 6 months after end of chemotherapy treatment.

Women must discontinue breast-feeding during therapy and not breast-feed for at least 6 months following the last dose of chemotherapy.

Bevacizumab may impair female fertility. Fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with bevacizumab.

Oxaliplatin may irreversibly impair male fertility. Fertility preservation strategies should be discussed with male patients prior to starting treatment with oxaliplatin.

6.3.4 Pregnancy testing

All women of childbearing potential who are at risk of becoming pregnant must undergo a pregnancy test prior to trial entry.

A woman of childbearing potential is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who has not:

• undergone a hysterectomy or bilateral oophorectomy/salpingectomy
• been postmenopausal for 24 consecutive months (i.e. who has had menses at any time in the preceding 24 consecutive months without an alternative medical cause)

If a patient or the partner of a male trial patient becomes pregnant at any point during the trial UCL CTC must be informed immediately (See section 12 Pharmacovigilance for details on the reporting procedure). If the subject is on study drug the study drug is to be discontinued. The Investigator will follow the subject until completion of the pregnancy, and must notify the UCL CTC of the outcome. The Investigator will provide this information as a follow-up to the initial pregnancy information

Contraceptive advice

Due to the effects of trial treatment during pregnancy and lactation, patients must consent to use two acceptable methods of contraception until 6 months post last treatment administration. Two forms of contraception should be used, however, in case of true abstinence, a second method of contraception is not required, and in case of male sterilisation, an additional contraceptive method may be advisable upon discussion with the treating physician.

Acceptable methods of effective contraception for this trial are:

• Established use of oral, injected or implanted hormonal methods of contraception.
• Placement of an intrauterine device (IUD) or intrauterine system (IUS).
• Barrier methods of contraception: condom or occlusive cap ( diaphragm or cervical/vault caps with spermicidal foam/gel/film/cream/suppository). The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:
  o Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection.
However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and must not be used alone.

- Male sterilisation (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomised male partners must be the sole partner for that patient. Please note that sterilisation is not usually regarded as completely reliable enough on its own to ensure that pregnancy can never occur. This should be discussed with treating physician.

- Absolute and continuous abstinence: When this is in line with the preferred and usual lifestyle of the patient. Please note that periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

The method(s) of contraception used must be stated in the patient medical notes and CRFs.
7 RANDOMISATION PROCEDURES

7.1 Randomisation

Patient randomisation will be performed centrally at the UCL CTC and this must be performed prior to commencement of any trial treatment. Eligible patients will be assigned to one of the two treatment arms using a minimisation algorithm in a 1:1 ratio with the following stratification factors:

- Treating Centre
- Gender
- Extramural Vascular Invasion (EMVI) or none

Following pre-randomisation evaluations (as detailed in section 6.1) confirmation of eligibility and consent of a patient at a Site, the randomisation form, baseline form, disease assessment (baseline) form and pre-treatment adverse events form must be fully completed and then faxed to UCL CTC. The faxed case report forms will be used to confirm patient eligibility at UCL CTC.

It is important that the randomising site is aware of all sites where trial activities are due to take place and that all such sites are open within the BACCHUS trial. This information will be required during the randomisation process.

Once the patient has been randomised a trial number and treatment allocation will be assigned for the patient and should be added to the form.

UCL CTC will email confirmation of the patient’s inclusion in the trial, their trial number and treatment allocation to the PI, main Site contact, pharmacy and the NCRI PET Core Lab.

Please contact UCL CTC if the randomisation confirmation or request for more information has not been received within 2 hours after faxing the forms. If forms are received at UCL CTC after 3pm, the randomisation may not be processed until the next working day.

Randomisation Fax Number: 020 7679 9871

Office hours: 9am to 5pm, Monday to Friday

Once a patient has been randomised onto the trial they must be provided with the following:

- A copy of their signed consent form and patient information sheet
- A patient diary booklet. Patients should be asked to record any adverse events or symptoms they experience. They must be reminded to bring this with them every time they visit the hospital
- A patient contact card. Site on-call contact details for 24 hour medical care must be added to this card and patients advised to carry this with them at all times while participating in the trial

7.2 Initial trial drug supply

Bevacizumab will be supplied to all treating sites. UCL CTC will inform Roche Products Ltd (drug supplier) when all necessary approvals for the trial are in place and the treating Site has been activated. On confirmation of Site activation, Roche will provide the Site with initial supplies. Bevacizumab is supplied in concentrations of 100 mg/4ml or 400 mg/16ml vials. Sites are responsible for monitoring level of stock and re-ordering drug when required. Please refer to the Summary of Drug Arrangements document in the Pharmacy File for details of the initial supply of bevacizumab for the trial and drug re-ordering.

Fluorouracil, irinotecan and oxaliplatin are to be supplied from hospital commercial stock as detailed in the Summary of Drug Arrangements.
8 TRIAL TREATMENTS

8.1 IMPs and NIMPs

Investigational Medicinal Products
For the purpose of this protocol the Investigational Medicinal Products (IMPs) are:

- bevacizumab
- oxaliplatin
- irinotecan
- 5-fluorouracil (5FU)

All IMPs are licensed products in the UK.

Non-Investigational Medicinal Products
The following products have been indicated in this protocol and are Non-Investigational Medicinal Products (NIMPs):

- **Background treatment**: d/l-folinic acid (FA)
- **Medicine used for imaging in the clinical trial**: $^{18}$F-fluorodeoxyglucose (FDG)
- **Treatment for adverse events**:
  - atropine
  - calcium gluconate
  - chlorphenamine
  - ciprofloxacin
  - codeine phosphate
  - hydrocortisone
  - loperamide
  - magnesium sulphate
  - ranitidine

8.2 Treatment summary

**Arm A – FOLFOX + bevacizumab:**
Given every 2 weeks for 12 weeks (6 cycles), chemotherapy to be given in the following order:

- Bevacizumab 5 mg/kg IV over 30 – 90* minutes (cycles 1 – 5 only)
- Oxaliplatin 85 mg/m$^2$ IV over 2 hours
- Folinic acid 350 mg IV over 2 hours
- 5FU 3200 mg/m$^2$ IV continuous infusion over 48 hours

**Arm B – FOLFOXIRI + bevacizumab:**
Given every 2 weeks for 12 weeks (6 cycles), chemotherapy to be given in the following order:

- Bevacizumab 5 mg/kg IV over 30 – 90* minutes (cycles 1 – 5 only)
- Irinotecan 165 mg/m$^2$ IV over 1 hour
- Oxaliplatin 85 mg/m$^2$ IV over 2 hours
- Folinic acid 350 mg IV over 2 hours
- 5FU 3200 mg/m$^2$ IV continuous infusion over 48 hours

*The first dose of bevacizumab should be administered over 90 min. If the first infusion is well tolerated, the second infusion may be administered over 60 min. If the 60 min infusion is well tolerated, subsequent infusions may be administered over 30 min (see also section 8.3.1 - Bevacizumab). d/l-folinic acid should be used and should be administered as a flat dose of 350 mg.
The doses of oxaliplatin, irinotecan and 5FU will be capped in obese patients. See Appendix 6 for more information on dose capping.

**Dose banding is not permitted for any of the IMPs.**

FOLFOX or FOLFOXIRI will be given for a maximum of 6 cycles.

The last cycle of BACCHUS study treatment should end a minimum of 6 weeks prior to surgery (the last dose of bevacizumab should be at least 8 weeks prior to surgery). Trial treatment should be stopped in the event of progressive disease, unacceptable toxicity or at the request of the patient.

In case it is necessary to discontinue oxaliplatin and/or irinotecan for relevant and specific toxicities, 5FU, FA and bevacizumab can be continued (see section 8.5 Management of adverse events, for more information).

**8.3 Trial Treatment Details**

**8.3.1 Bevacizumab**

Bevacizumab (Avastin) is licensed in the UK for the treatment of cancer. Bevacizumab will be supplied for the BACCHUS trial by Roche.

Bevacizumab 5 mg/Kg will be administered initially over a 90 (±15) minute period on day 1 of cycle 1. If the first infusion is well tolerated, especially without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over a 60 (±10) minute period. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over a 30 (±10) minute period.

The dose for bevacizumab will be calculated as milligrams per kilogram body weight (mg/Kg). If a patient’s weight changes by ≥ 10% from baseline during the course of the study, the dose of bevacizumab should be recalculated. If a patient’s weight changes by <10% the dose may be adjusted if desired, according to the local investigator’s discretion. Bevacizumab should be made up according to local practice and/or the Summary of Product Characteristics (SPC). Any planned deviation from the SPC must be approved by UCL CTC first.

**Bevacizumab should be given for cycles 1 – 5 only (i.e. it should be omitted during cycle 6).**

**NB Bevacizumab infusions should not be administered or mixed with dextrose or glucose solutions.**

**8.3.2 Irinotecan**

Irinotecan is currently licensed for use in cancer treatment in the UK. Irinotecan will be sourced from hospital stock and its handling and management will be subject to standard procedures of the hospital pharmacy. No specific brand of irinotecan is specified for use on this trial; however, Sites must ensure the active substance used is irinotecan.

**Irinotecan is administered in Arm B only**

Irinotecan should be made up according to local practice and/or the SPC. Any planned deviation from the SPC must be approved by UCL CTC first.

A dose of 165 mg/m² Irinotecan should be given as an IV infusion over 1 hour after bevacizumab at cycles 1-5, and as the first IMP infusion at cycle 6.

Irinotecan diluted from plastic vials should be protected from light.

**Patients should not take St. Johns Wort whilst receiving irinotecan therapy.**
8.3.3 Oxaliplatin

Oxaliplatin is currently licensed for use in cancer treatment in the UK. Oxaliplatin will be sourced from hospital stock and its handling and management will be subject to standard procedures of the hospital pharmacy. No specific brand of oxaliplatin is specified for use on this trial; however, Sites must ensure the active substance used is oxaliplatin.

Oxaliplatin should be made up according to local guidelines and/or the SPC. Any planned deviations from the SPC must be approved by UCL CTC first.

A dose of 85 mg/m² oxaliplatin should be administered by IV infusion over 2 hours either after bevacizumab (for Arm A) or after irinotecan (for Arm B).

Please refer to the current SPC for instructions regarding the preparation, stability and final concentration of the oxaliplatin infusion.

The administration of 5-HT3 antagonists with corticosteroids is recommended for prevention and treatment of oxaliplatin-induced emesis as per local guidelines.

8.3.4 d/l-folinic acid

d/l-folinic acid (FA) is a racemic mixture of the d and l forms of folinic acid. The active form of folinic acid is the l enantiomer. d/l-folinic acid is currently licensed for use in conjunction with 5FU in the UK. d/l-folinic will be sourced from hospital stock and its handling and management will be subject to standard procedures of the hospital pharmacy. No specific brand of d/l-folinic acid is specified for use on this trial; however, Sites must ensure the product contains the racemic mixture of d/l-folinic acid.

FA should be prepared for administration as per local practice. A flat dose of 350 mg FA should be administered over 2 hours after oxaliplatin.

8.3.5 5-Fluorouracil

5-fluorouracil (5FU) is currently licensed for use in cancer treatment in the UK. 5FU will be sourced from hospital stock and its handling and management will be subject to standard procedures of the hospital pharmacy. No specific brand of 5FU is specified for use on this trial; however, Sites must ensure the active substance used is 5FU.

5FU should be prepared for administration according to local practice and/or the SPC. A dose of 3200 mg/m² 5FU should be administered by IV continuous infusion over 48 hours, after FA.

8.4 Pharmacy Responsibilities

All pharmacy aspects of the trial at participating sites are the responsibility of the PI, who may delegate this responsibility to the local pharmacist, or other appropriately qualified personnel, who will be the Pharmacy Lead. The delegation of duties must be recorded on the Site staff delegation log.

Bevacizumab is supplied for BACCHUS patients only and must not be used outside the context of this protocol.

8.4.1 Temperature Excursions

For supplied bevacizumab - all temperature excursions outside the storage conditions specified in the SPC must be reported to UCL CTC as per the ‘Pharmacy Procedure for Reporting Temperature Excursions’ (see Pharmacy Site File for more information).

Upon identifying an excursion:

- All affected trial stock must be quarantined IMMEDIATELY
The ‘Notification of Temperature Excursion’ form and Roche ‘IMP Deviation’ form must be completed and e-mailed to ctc.excursions@ucl.ac.uk or faxed to 020 7679 9871

Please note that UCL CTC must be informed immediately if a patient has been administered drug affected by a temperature excursion.

8.4.2 Drug accountability for IMP

The Pharmacy Lead must ensure that appropriate records are maintained.

For bevacizumab these records must include receipt, dispensing, storage conditions and destruction of expired/unused medication. Template accountability forms (stock and per patient) will be supplied.

A template patient log for oxaliplatin, fluorouracil and irinotecan will also be supplied; however, sites may be permitted to use their own drug accountability records, providing the same information is captured, as a minimum. Such in-house records must be submitted to UCL CTC for review and authorisation for use prior to Site activation.

Copies of completed drug accountability logs must be submitted to UCL CTC for all trial patients upon request. Also refer to section 14.1 (Central monitoring).

Refer to the Summary of Drug Arrangements in the Pharmacy Site File for further details.

8.4.3 Drug accountability for NIMP

The Pharmacy Lead must ensure that appropriate records are maintained to ensure traceability of the movements and administrations of NIMPs to trial patients.

8.5 Management of adverse events

8.5.1 Principles of adverse event management

The following general guidance should be followed for management of adverse events (AEs) and dose reductions.

1. AEs should be graded according to the NCI Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03).

2. Treat each AE with maximum supportive care (including withholding administration of the agent suspected of causing the adverse event where required). If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of trial medications along with appropriate continuing supportive care, except where this conflicts with guidance in section 8.6 (Management of adverse events).

3. For AEs which are considered by the Investigator unlikely to develop into serious or life-threatening events (e.g. alopecia, altered taste etc.), treatment may be continued at the same dose without reduction or interruption. Rationale for this should be clearly documented in the patient’s notes.

4. No dose reductions or interruptions are required for anaemia (non-haemolytic) if it can be satisfactorily managed by transfusions or erythropoietin.

5. Where several AEs with different grades or severity occur at the same time, the dose modifications applied should be the greatest reduction applicable.

6. If, in the opinion of the Investigator, an AE is considered to be due solely to one drug (e.g. Palmar-Plantar Erythrodysesthesia secondary to 5FU continuous infusion, neurotoxicity due to oxaliplatin), then it is only the dose of the responsible drug that needs to be reduced or
interrupted as appropriate. The rest may continue as before UNLESS this would lead to any of the conditions listed in point 8 below.

7. There will be no dose modification of bevacizumab during this study. However, the dosing schedule of bevacizumab will be interrupted in case of certain AEs such as hypersensitivity, hypertension, proteinuria, clotting problems/reactions, as explained in the sections below.

8. Individual drugs in the regimen may be interrupted or stopped and the rest continued EXCEPT where this would leave the patient receiving one of the following:
   - oxaliplatin monotherapy
   - oxaliplatin plus bevacizumab
   - bevacizumab monotherapy
   - irinotecan monotherapy
In such cases, all drugs should be interrupted or stopped as appropriate.

9. The dose of FA should not be changed, even if the dose of 5FU is changed. If 5FU is discontinued, FA should also be discontinued.

10. All dose modifications should be documented with clear reasoning and documentation of the approach taken in the case report forms and in the medical notes.

8.5.2 Criteria for commencing the next cycle of treatment

Patients must meet the following criteria before starting each new cycle:

- Absolute neutrophil count ≥1.5 x10^9/L
- Platelet count ≥100 x10^9/L
- Haemoglobin ≥80 g/L
- Serum creatinine ≤1.5 x ULN
- Calculated CrCl ≥50 mL/min (except where dose modifications have been implemented for GFR <50mL/min. See section 8.6.10 - Management of renal impairment)
- ALT/AST ≤5 x ULN (except where dose modifications have been implemented for ALT/AST levels >5 x ULN. See section 8.6.11 - Management of hepatobiliary function)
- Bilirubin <1.5 x ULN (except where dose modifications have been implemented for bilirubin ≥1.5 x ULN. See section 8.6.11 - Management of hepatobiliary function)
- Treatment–related diarrhoea and/or abdominal cramps must have fully resolved to grade 0 AND no anti-diarrhoeals administered (e.g. loperamide) during the preceding 24 hours prior to start of cycle (see sections 8.6.2 and 8.6.8)
- Recovery from any treatment–related grade 3/4 non-haematological AE (except alopecia) to baseline, or grade 1 or better

If any of the above criteria are not met, all treatment should be deferred until all criteria are met or, if applicable, dose/treatment modifications should be applied as specified in section 8.6 (Management of adverse events) below. Treatment may be deferred for up to 3 weeks. Patients who cannot recommence treatment after 3 weeks should be discontinued from all protocol treatment. All dose reductions or treatment modifications are permanent, unless specified otherwise in the applicable sections below.

8.6 Management of adverse events

8.6.1 Dose modifications based on AEs at the beginning of each cycle

The dose modifications in Table 8-1 below should be carried out based on the AEs present at the beginning of each cycle of treatment.
### Table 8-1: Dose modifications for AEs at start of cycle

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Irinotecan</th>
<th>Oxaliplatin</th>
<th>5FU</th>
<th>BVZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmar-Plantar Erythrodysesthesia</td>
<td>≥ 3</td>
<td>Discontinue until recovery to grade 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity (see also 8.6.3)</td>
<td>≥ 3</td>
<td>100%</td>
<td>DISCONTINUE PERMANENTLY</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

### 8.6.2 Dose modifications based on AEs during the previous cycle

The dose modifications in Table 8-2 below should be carried out according to the worst grade of AE experienced during the previous cycle of treatment.

### Table 8-2: Dose modifications for worst grade of AE

<table>
<thead>
<tr>
<th>Adverse Event (if applicable)</th>
<th>Grade</th>
<th>Irinotecan</th>
<th>Oxaliplatin</th>
<th>5FU</th>
<th>BVZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia &gt; 5 days</td>
<td>4</td>
<td>75%</td>
<td>75%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4</td>
<td>75%</td>
<td>75%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 – 4</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Diarrhoea (see also 8.6.8)</td>
<td>3</td>
<td>75%</td>
<td>100%</td>
<td>75%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Mucositis oral (see also 8.6.9)</td>
<td>3</td>
<td>100%</td>
<td>100%</td>
<td>75%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>100%</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Myocardial Infarction or acute coronary syndrome</td>
<td>Any</td>
<td>DISCONTINUE PERMANENTLY</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 8.6.3 Management of neurological AEs

**Cold-related dysesthesia and paraesthesia**

Oxaliplatin is consistently associated with two types of peripheral neuropathy: paraesthesias and dysestheasias of the hands and feet and peri-oral region (early onset). Patients treated with oxaliplatin in this study should be advised to avoid cold drinks and exposure to cold water or air, especially for 3 to 5 days following oxaliplatin administration. In case of neurological toxicity dose reductions should be made to oxaliplatin only according to Table 8-3 below.
### Table 8-3: Management of oxaliplatin-induced neurological AEs (dose modifications refer to oxaliplatin only)

<table>
<thead>
<tr>
<th>Adverse Event Grade</th>
<th>Duration</th>
<th>Persisting between cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-7 days</td>
<td>&gt;7 days</td>
</tr>
<tr>
<td>Dysaesthesia (cold–related)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>DISCONTINUE OXALIPLATIN PERMANENTLY</td>
<td></td>
</tr>
</tbody>
</table>

If oxaliplatin is discontinued due to neurotoxicity, treatment should be continued with remaining drugs unless this is prohibited according to section 8.5.1 point 8.

**Management of laryngopharyngeal dysaesthesia**

An unusual laryngopharyngeal dysaesthesia has been observed which provokes a sensation of loss of breath (acute respiratory distress) without any objective evidence of respiratory distress. There is no accompanying hypoxia, laryngospasm, or bronchospasm. This neurotoxicity is usually induced or exacerbated upon exposure to cold, or moving from the warm air of the ward to the cold air outside.

If a patient develops laryngopharyngeal dysaesthesia, the patient's oxygen saturation should be evaluated via a pulse oximeter and, if normal, reassurance, a benzodiazepine or other anxiolytic agent should be considered and the patient should be observed in the clinic until the episode has resolved. The oxaliplatin infusion may then be continued at 1/3 of the previous rate.

This syndrome may be associated with the rapidity of oxaliplatin infusion, so subsequent doses of oxaliplatin should be administered over a more prolonged period as 6-hour infusions (instead of the normal 2-hour infusion).

Patients receiving oxaliplatin should not receive cold drinks or ice chips on day 1 of each cycle as this may exacerbate oral or throat dysaesthesias, as well as laryngopharyngeal dysaesthesia.

Administration of prophylactic medication such as Mg++, Ca++ infusions or others is at the discretion of the investigator. If used, a recommended schedule is calcium gluconate 1 g (4 mmol) + magnesium sulphate 1 g (4 mmol) in 100 mL 5% dextrose administered over 15 minutes immediately prior to and immediately after oxaliplatin infusion or as per local practice.
8.6.4 Management of hypersensitivity reactions

Oxaliplatin hypersensitivity reactions

In case of oxaliplatin hypersensitivity reactions, the procedures in Table 8-4 below should be followed.

| Grade 1 or 2 hypersensitivity reaction | • No dose modification of oxaliplatin is required if, in the investigator’s opinion, it is in the patient’s best interest to continue
| | • Suggested pre-medication 30 minutes prior to oxaliplatin administration with
| | o hydrocortisone 100 mg IV,
| | o chlorphenamine 10 mg IV or equivalent,
| | o ranitidine 50 mg IV
| | • If an allergic reaction persists into the next cycle, it is recommended that oxaliplatin is permanently discontinued

| Grade 3 or 4 acute hypersensitivity reactions | • Treatment with oxaliplatin should be permanently discontinued.

Table 8-4: Management of oxaliplatin hypersensitivity reactions

Bevacizumab hypersensitivity reactions

Patients may be at risk of developing infusion / hypersensitivity reactions. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanised monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving bevacizumab in combination with chemotherapy than with chemotherapy alone. The incidence of these reactions in some clinical trials of bevacizumab is common (up to 5% in bevacizumab treated patients).

In general, patients experiencing mild to moderate hypersensitivity/infusion reactions (grade 1 or 2 allergic reaction) in particular after the first exposure may tolerate readministration of the agent at reduced infusion rates and with treatment using antihistamines and corticosteroids after complete resolution of symptoms. Re-challenge is generally discouraged in patients who experienced a severe initial reaction (grade 3 or 4).

8.6.5 Management of pulmonary fibrosis

Respiratory symptoms indicative of pulmonary fibrosis include a non-productive cough, dyspnoea, crackles, rales, hypoxia, tachypnea or the new appearance of radiological pulmonary infiltrates.

If the investigator suspects pulmonary fibrosis, then oxaliplatin should be interrupted pending further investigation. If pulmonary fibrosis of any grade is confirmed, oxaliplatin must be permanently discontinued.

8.6.6 Management of nausea/vomiting

The administration of 5-HT3 antagonists with corticosteroids is recommended for prevention and treatment of oxaliplatin-induced emesis as per local guidelines.
8.6.7 Management of acute cholinergic syndrome

Irinotecan frequently provokes an acute cholinergic syndrome with early diarrhoea, abdominal cramps, sweating, salivation, lacrimation, and bradycardia. These symptoms usually start during the irinotecan infusion or shortly after, and within the first 24 hours. If these symptoms occur, administration of 0.25mg – 0.3mg atropine given subcutaneously is recommended before each further infusion, if not contraindicated.

8.6.8 Management of diarrhoea

The side effect profile of irinotecan is dominated by diarrhoea, which usually occurs at 7 – 10 days post chemotherapy. Early intervention with loperamide is important. Diarrhoea may be prolonged, if untreated, it can lead to dehydration and electrolyte imbalance and can be life threatening.

Patients should be instructed to contact their treating clinician/care team urgently if diarrhoea is not controlled after 12 hours of loperamide therapy. Hospitalisation may be indicated – see Table 8-6.

The precondition of resolution of diarrhoea back to grade 0 and no anti-diarrhoeals administered in the preceding 24 hours must be met before the start of the next cycle. Otherwise a treatment break is mandated until the above criteria are met. Dose modifications for grade 3 or above diarrhoea should be made according to Table 8-2.

Following a delay of up to 2 weeks, patients receive the starting dose; but following a delay of more than 2 weeks on account of diarrhoea, irinotecan should be reduced to 75% of the starting dose, see Table 8-5.

When diarrhoea from irinotecan occurs, it is necessary to wait for a week after symptoms have resolved prior to commencing the next cycle of treatment. If the above criteria lead to delay in treatment of more than 3 weeks, all trial treatment should be permanently discontinued.

In summary:

<table>
<thead>
<tr>
<th>Length of Delay</th>
<th>Dose Modification to Irinotecan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 2 weeks</td>
<td>Continue on starting dose</td>
</tr>
<tr>
<td>2 – 3 weeks</td>
<td>Recomence on 75% of starting dose</td>
</tr>
<tr>
<td>More than 3 weeks</td>
<td>Stop treatment</td>
</tr>
</tbody>
</table>

Table 8-5: Management of diarrhoea

For severe diarrhoea requiring drug treatment, timely use of high dose loperamide is recommended. Give loperamide 4 mg initially after the first loose stool, followed by 2 mg every 2 hours until 12 hours after last loose stool for a maximum of 48 hours.

Codeine phosphate up to 30 mg 4 times a day can be added if diarrhoea is not controlled with 16mg loperamide per day. Please note the criteria for admission stated below.

If diarrhoea persists for more than 24 hours despite loperamide, it is strongly recommended that ciprofloxacin 500 mg twice daily should be commenced.
Hospital admission is necessary:

- If severe diarrhoea (grade ≥3) lasts for longer than 48 hours
- If diarrhoea (grade 3) and vomiting (grade 3) occurs
- If diarrhoea (any grade) is accompanied by fever >38°C
- In febrile neutropenia.

Particular care should be taken to replace fluid losses.

For neutropenic diarrhoea or fever plus diarrhoea, this is a potentially life-threatening event and adequate antibiotic therapy is essential, plus broad-spectrum systemic IV antibiotics (e.g., β-lactams plus aminoglycoside) according to local policy.

Table 8-6: Hospital admissions for management of diarrhoea

8.6.9 Management of mucositis oral

Routine mouthcare is recommended. If grade 3-4 mouth ulcers persist, reduce 5FU as set out in Table 8-2.

8.6.10 Management of renal impairment

At the time of entry into the trial, renal function must satisfy the eligibility criteria (see section 6.3.1). GFR must be ≥50 mL/min as estimated either by calculated creatinine clearance (CrCl) using the Cockcroft & Gault equation (see Appendix 4), or by isotope clearance (51Cr-EDTA or 99mTc-DTPA) in cases where calculated CrCl is <50 mL/min.

Serum creatinine should be checked prior to each cycle. If calculated CrCl falls to levels from 30 to 49 mL/min, defer the next cycle until GFR recovers to ≥50 mL/min. Following a delay of up to 2 weeks, patients receive the starting dose; but following a delay of more than 2 weeks, the dose of all chemotherapy drugs (but not bevacizumab) should be reduced to 75% of the starting dose. For patients who required an isotope clearance test at trial entry to confirm adequate renal function, a repeat 51Cr-EDTA or 99mTc-DTPA test should be considered if there is >10% increase in serum creatinine and any dose modifications will be at the discretion of the Investigator. Patients who do not recover completely and still have GFR 30–49 mL/min, can continue on study but all chemotherapy drugs (but not bevacizumab) should be reduced to 75% of the starting dose.

If estimated GFR falls below 30 mL/min all chemotherapy should be permanently discontinued.

Special care is necessary for patients with a defunctioning ileostomy and those patients who have experienced irinotecan induced diarrhoea.

<table>
<thead>
<tr>
<th>GFR (mL/min)</th>
<th>5-FU</th>
<th>Oxaliplatin</th>
<th>Irinotecan</th>
<th>Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td></td>
<td></td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>≥30 – &lt;50</td>
<td></td>
<td>Delay treatment up to 2 weeks until GFR ≥50 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continue at 100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delay treatment &gt;2 weeks until GFR stable at ≥30 – &lt;50 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continue at 75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>DISCONTINUE ALL TREATMENT PERMANENTLY</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 8-7: Management of renal impairment
8.6.11 Management of hepatobiliary function

LFTs should be checked before each treatment cycle. Underlying hepatic disease can alter the metabolism and excretion of chemotherapy drugs that rely upon the liver for their clearance. This can result in higher and/or more persistent drug levels, thereby causing increased systemic toxicity (particularly myelosuppression) or worsening of chemotherapy-induced hepatotoxicity. Elevations of serum transaminases and bilirubin can occur in patients treated with irinotecan, but are rare with 5FU.

Patients with serum ALT/AST >5 x ULN or serum bilirubin >1.5 - 3 x ULN, irinotecan should be administered at 50% of starting dose. If LFTs subsequently fall below these levels, then the irinotecan can be re-escalated to 100% of the starting dose.

Patients with bilirubin >3 x ULN should not receive irinotecan. If bilirubin falls to <3 x ULN, irinotecan should be delayed until <1.5 x ULN and can then be given at 50% of starting dose. Irinotecan should be permanently discontinued if after a three week delay bilirubin has not fallen to <1.5 ULN.

No dose modifications are required for 5FU or oxaliplatin unless bilirubin level is >5 x ULN, in which case the dose of 5FU and oxaliplatin should be at 50% of starting dose and irinotecan permanently discontinued (refer to Table 8-8).

<table>
<thead>
<tr>
<th></th>
<th>Irinotecan</th>
<th>5FU &amp; Oxaliplatin</th>
<th>Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT/AST ≤5 x ULN</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>ALT/AST &gt;5 x ULN</td>
<td>50%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Re-escalate to 100% if ALT/AST fall below 5 x ULN prior to start of next cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin &lt;1.5 x ULN</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Bilirubin 1.5 – 3 x ULN</td>
<td>50%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Re-escalate to 100% if bilirubin falls below 1.5 x ULN prior to start of next cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin &gt;3 x ULN</td>
<td>Delay treatment until bilirubin falls to &lt; 1.5 x ULN (max. 3 weeks delay)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Resume treatment at 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin &gt;5 x ULN</td>
<td>DISCONTINUE PERMANENTLY</td>
<td>50% dose reduction</td>
<td>Full dose*</td>
</tr>
</tbody>
</table>

*Table 8-8: Management of hepatobiliary function.
Dose modifications are based on the LFT values at the START of each cycle.
*Full dose unless otherwise contraindicated

8.6.12 Management of hypertension

An increased incidence of hypertension has been observed in patients treated with bevacizumab. Hypertension has then generally been treated with simple oral anti-hypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. The appearance of hypertension rarely resulted in discontinuation of therapy (only 0.7% of all patients treated with bevacizumab) or required hospitalisation – although a hypertensive encephalopathy was reported in one case (0.1%) only.

The risk of bevacizumab-associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Blood pressure must be monitored during bevacizumab therapy prior to each cycle of treatment. In case of grade 3/4 hypertension, blood pressure measurements should be performed on a weekly basis until resolution of the event.

Recommendations for antihypertensive therapy are listed in Table 8-9. All doses of antihypertensive medicines should be recorded at all visits.
Grade of hypertension | Description | Anti-hypertensive treatment | Dose modification for bevacizumab
--- | --- | --- | ---
Grade 1 | Prehypertension (systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg) | Intervention not indicated | Intervention not indicated – continue bevacizumab

Grade 2 | Stage 1 hypertension (systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg); recurrent of persistent (≥24 hrs); symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg if previously within normal limits; monotherapy indicated | Monotherapy with ACE inhibitor may be indicated. | Discontinue bevacizumab until BP controlled to < 150/100 mmHg,

Grade 3 | Stage 2 hypertension (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg); more than one anti-hypertensive or more intensive therapy than previously used indicated | Addition of diuretic to ACE-inhibitor may be indicated; if hypertension is not controlled a third anti-hypertensive drug (calcium channel blocker) should be added. | Bevacizumab should be withheld for persistent or symptomatic hypertension and should be permanently discontinued if hypertension is not controlled with triple-drug medication.

Grade 4 | Life threatening consequence (e.g. malignant hypertension. Transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated | As clinically indicated. | Permanent discontinuation of bevacizumab.

Table 8-9: Management of bevacizumab-induced hypertension

8.6.13 Management of proteinuria

Proteinuria has been observed in 23.3% of all patients treated with bevacizumab - ranging in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome, although the great majority only experienced grade 1 proteinuria. Proteinuria has rarely required permanent discontinuation of bevacizumab therapy.

Patients with a history of hypertension and diabetes appear to be at increased risk for the development of proteinuria when treated with bevacizumab. There is some evidence suggesting that grade 1 proteinuria may be related to bevacizumab dose. Therefore monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and each subsequent administration of bevacizumab therapy. A urinalysis will be performed within 3 days prior to each bevacizumab dose. Refer to Table 8-10 for guidance on the management of proteinuria. Bevacizumab should be immediately discontinued in patients who develop grade 4 proteinuria (nephrotic syndrome).

| Grade 1: | Continue bevacizumab. No additional investigation; continue to monitor |
| Grade 2: | Continue bevacizumab and collect 24-hour urine within 3 days prior to next cycle |
| Grade 3: | Hold bevacizumab and check 24-hour urinary protein. Recommence bevacizumab if 24-hour urinary protein decreases to <2 g. If not <2g after 3 weeks, permanently discontinue bevacizumab. |

Table 8-10: Management of proteinuria
8.6.14 Management of arterial thrombosis

Arterial thromboembolic events including CVAs, MIs, TIAs, and other thromboembolic events occur more frequently in patients treated with bevacizumab. Patients with a medical history of diabetes or a previous history of arterial thromboembolism are at an increased risk of developing arterial thromboembolism. Bevacizumab should be permanently discontinued in patients who develop arterial thromboembolic events during treatment.

8.6.15 Management of venous thrombosis

Patients who developed venous thrombosis (of any grade) while receiving bevacizumab should be withdrawn from further treatment with bevacizumab.

8.6.16 Management of haemorrhagic events

In the case of a CNS haemorrhage of grade 2 or higher, patients should permanently discontinue bevacizumab.

If a grade 3 or 4 haemorrhagic event of any sort occurs, then bevacizumab should be permanently discontinued.

8.6.17 Management of reversible posterior leukoencephalopathy syndrome (RPLS)

Rare reports suggest bevacizumab-treated patients may develop signs and symptoms consistent with RPLS, a rare neurological disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. MRI brain imaging needs to be performed to confirm the diagnosis of RPLS. In patients developing RPLS, treatment of specific symptoms including control of hypertension are required.

If RPLS is suspected on MRI, bevacizumab should be discontinued.

8.6.18 Surgical procedures/wound healing complications

Bevacizumab can cause wound healing complications. In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed.

8.6.19 Necrotising fasciitis

Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

8.7 Support medication

The administration of 5-HT3 antagonists with corticosteroids is recommended for prevention and treatment of oxaliplatin-induced emesis as per local guidelines.

Atropine 0.25–0.3 mg SC (subcutaneous) infusion can be given either as a result of a cholinergic reaction to irinotecan, or as a preventative measure according to local practice.

It is recommended that ciprofloxacin at a dose of 500 mg bd is administered for 7 days in case of irinotecan toxicity (diarrhoea and/or neutropenia).

Haematopoietic growth factors: G-CSF is not recommended as primary prophylaxis, but it can be used as secondary prophylaxis following appropriate dose reductions due to:
• preceding febrile neutropenia;
• preceding grade 4 diarrhoea lasting 5 days or more;
• more than 2 delays of the planned therapy due to neutropenia.

8.8 Concomitant medication

Patients are not permitted to receive other investigational drugs or anticancer treatment (including radiotherapy) whilst on trial treatment.

Dipyridamole (Curantyl®, Persantin®, Asasantin®), a nucleoside transport inhibitor, is not permitted during treatment. Patients should not take St. Johns Wort for 14 days prior to starting trial treatment and whilst receiving irinotecan therapy. Bisphosphonates, Phenytoin, Sorivudine and cimetidine are not permitted during treatment. In addition, the most severe toxicities seen with bevacizumab to date have been haemorrhage, thrombosis and gastro-intestinal perforation. For this reason, the guidance in the following paragraphs must be followed.

Full-dose oral coumarin-derived anticoagulants (INR>1.5) or heparin, thrombolytic agents, or chronic, daily treatment with aspirin (>325 mg/day) or non-steroidal anti-inflammatory medications (those known to inhibit platelet function at doses used to treat chronic inflammatory diseases) are excluded at entry into the study.

N.B. Low-dose warfarin (≤1 mg) or heparin (i.e. anything that is not full dose, for example heparin given for prophylactic means whilst a patient is in hospital) are permitted, as is low-dose aspirin (<325 mg/day), or regular use of non-steroidal anti-inflammatory medication of the kind known not to inhibit platelet function.

If the patient requires warfarin or full-dose heparin to be started once they are on treatment, then this can be instituted. However, this should be done with careful monitoring because of the risk of bleeding with bevacizumab, and clexane is recommended over warfarin.

8.9 Other Precautions

8.9.1 DPD Deficiency

Dihydropyrimidine dehydrogenase (DPD) plays an important role in the metabolism of fluorouracil. Patients with DPD deficiency may experience increased toxicity when administered 5-FU, and in some cases these events can be fatal. There is no routine screening test for DPD deficiency, therefore severe adverse events considered related to 5-FU should be treated promptly and with maximum supportive care.

8.10 24 hour/Out-of-office hours emergency drug-specific advice

For 24 hour/Out-of-office emergency drug-specific advice please see below:

<table>
<thead>
<tr>
<th>Bevacizumab</th>
<th>Office hours:</th>
<th>All other times:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>09:00 to 17:00 Monday to Friday, (excluding Bank Holidays)</td>
<td>Out of Office hours</td>
</tr>
<tr>
<td>Contact:</td>
<td>UCL CTC</td>
<td>Contact:</td>
</tr>
<tr>
<td></td>
<td>0207 679 9287</td>
<td>Roche Products Limited*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0800 328 1629</td>
</tr>
</tbody>
</table>

*When calling Roche ask for emergency advice for Bevacizumab for the BACCHUS trial (Roche reference ML22748). Sites should only follow this route once all other options have been explored (i.e. clinical management of emergency, following safety management guidance in protocol, SPC, consulting with Chief Investigator etc).
8.11 Surgery

Patients deemed suitable will undergo surgical resection a minimum of 8 weeks after last administration of bevacizumab and 6 weeks after last administration of cytotoxic chemotherapy, to a maximum of 10 weeks after last administration of trial treatment.

NB It is recommended that a provisional date of surgery 8 – 12 weeks after planned end of bevacizumab treatment is booked soon after randomisation of the patient.

Patients should have recovered from chemotherapy side effects and be considered fit enough to undergo surgery.

8.11.1 Surgical procedure

Surgery after neoadjuvant chemotherapy should be performed according to local practice. However, the following information is provided as a recommendation.

Total Mesorectal Excision

The concept of the ‘holy plane’ has led to a technique of total mesorectal excision (TME) for rectal cancer (Heald 1988). The mesorectum is the embryological hindgut mesentery, consisting of fat, rectal venous and lymphatic drainage and the descending branches of the superior rectal artery. This structure should be removed along with the rectum, by dissecting in the areolar tissue that lies between the mesorectal fascia and the parietal pelvic fascia (holy plane).

TME may be less appropriate for some upper rectal cancers, as this may add morbidity to the procedure, introducing consequences of increased anastomotic leak rate and poorer function, without improving oncological outcome. Tumours of the upper third are treated with anterior resection, which involves high ligation of the inferior mesenteric vessels and adequate mobilisation of the proximal colon to allow a tension-free anastomosis with a good blood supply. The rectum and its mesorectum are divided 5 cm below the lower end of the tumour and a primary anastomosis is constructed.

Anteriorly, the mesorectal fascia fuses with the remnant of the urogenital septum, creating a fascial band – the fascia of Denovillier in the male, and the rectovaginal septum in the female. When performing a TME, the surgeon dissects in front of this fascial layer. At this level, sphincter-preserving surgery will usually be covered with a defunctioning loop colostomy or ileostomy, to allow healing of a coloanal anastomosis.

TME can be performed by either open or laparoscopic surgery, according to the experience of the surgeon. Traditionally, an abdominoperineal excision (APE) of the rectum and anus is performed for most lower third rectal tumours.

A full exploration of the abdominal cavity should be undertaken, and any suspicious areas (except liver metastases) should be subjected to biopsy.

Stomas

A covering stoma is recommended. A covering ileostomy or colostomy in these patients leads to less morbidity from anastomotic leaks [77]. However, closure of a stoma requires a second operation and also has associated morbidity.

8.11.2 Surgical Assessments

Surgery data, including type of surgery and hospitalisation length, will be recorded in the CRF.

Surgical complications will be assessed at 48 hours and at 1 and 3 months post-surgery (see Appendix 7 Classification of Surgical Complications and Section 9.4 - Assessments after surgery).
8.12 Postoperative adjuvant chemotherapy

Postoperative adjuvant chemotherapy is at the discretion of the investigator for patients who responded to the neoadjuvant chemotherapy, but is not recommended for patients who failed to have a clinical response.

8.13 Management after discontinuation of trial treatment

Subsequent treatment will be at the discretion of the treating clinician.

Also refer to section 15 (Withdrawal of patients) for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.
9 ASSESSMENTS

For pre-randomisation assessments, please see section 6.1. Also refer to Appendix 11 for a table summarising the schedule of events and assessments for BACCHUS.

9.1 Assessments prior to starting protocol treatment

The following assessments must be carried out prior to the patient starting protocol treatment. Those assessments that have been carried out as part of the pre-randomisation assessment and are within the time frames stipulated below do not need to be repeated.

- **Prior to start of treatment cycle 1:**
  - FDG-PET CT scan (baseline SUV will be calculated. See section 9.2.1 for method of calculating SUV) (see appendix 2) *(not to be repeated if carried out prior to randomisation)*
  - Blood sample for ancillary studies (see section 21.3 - Blood Samples)
  - Diffusion weighted MRI is strongly recommended but not mandated; Additional intrinsic susceptibility MRI and dynamic contrast enhanced MRI sequences are also recommended but not mandated, *(not to be repeated if carried out prior to randomisation)* (see appendix 8)

- The below assessments do not need to be repeated if carried out as part of the pre-randomisation assessment and are **within 7 days prior to cycle 1 day 1 (with the exception of Assessment of AEs):**
  - Clinical examination including weight and blood pressure
  - Documentation of concomitant medications
  - Assessment of AEs *(within 3 days of start of cycle 1 day 1)*
  - WHO performance status
  - Haematology:
    - Full blood count plus white blood cell differential including absolute neutrophil (ANC) and lymphocyte counts
  - Biochemistry:
    - Sodium, potassium, urea, creatinine, albumin, total bilirubin, alkaline phosphatase (ALP), AST and/or ALT, yGGT, CRP
    - CEA
  - Estimated GFR (calculated CrCl using Cockcroft and Gault formula, see Appendix 4)
  - Clotting profile:
    - INR, aPTT
  - Urinalysis (if urine dipstick is ≥2+, 24-hour urine is required)
  - ECG (only if clinically indicated)
  - Pregnancy test (only if clinically indicated)

9.2 Assessments during treatment

The following assessments should be carried out during treatment according to the timeframes stipulated. More frequent monitoring may be required in case of adverse events. Please refer to sections 8.5 and 8.6 for guidance on managing AEs.

- **Within 3 days prior to day 1 of each cycle:**
  - Clinical examination including weight and blood pressure. In case of hypertension the guidelines specified in section 8.6.12 (Management of hypertension) should be followed.
  - Documentation of concomitant medications
  - Assessment of AEs
  - WHO performance status
  - Haematology:
- Full blood count plus white blood cell differential including absolute neutrophil (ANC) and lymphocyte counts
  - Biochemistry:
    - Sodium, potassium, urea, creatinine, albumin, total bilirubin, alkaline phosphatase (ALP), AST and/or ALT, γ-GT, CRP
  - CEA (prior to cycle 4 only)
  - Estimated GFR (calculated CrCl using Cockcroft and Gault formula, see Appendix 4)
  - Urinalysis (if urine dipstick is >2+, 24-hour urine is required). Urinalysis is required prior to bevacizumab administration only, therefore required prior to cycles 1-5 only. See section 8.6.13 for management of proteinuria.
  - ECG (only if clinically indicated)
  - Blood sample for ancillary studies (see section 21.3 - Blood Samples) (cycles 2, 3 and 4 only, and upon progression, if applicable)

- Within one week prior to cycle 4 day 1:
  - FDG-PET CT (to assess response to treatment by SUV. See section 9.2.1)
    - (PET must be performed on the same accredited PET scanner, using the same parameters as the baseline scan, see appendix 2)
  - MRI pelvis (to assess response to treatment by RECIST).
    - Diffusion weighted MRI is strongly recommended; additional intrinsic susceptibility MRI and dynamic contrast enhanced MRI sequences are also recommended (see appendix 8).

- The following should be carried out if there is concern that the patient is progressing on treatment:
  - Chest/abdominal/pelvis CT scan
  - MRI scan of the pelvis
    - Diffusion weighted MRI is strongly recommended; additional intrinsic susceptibility MRI and dynamic contrast enhanced MRI sequences are also recommended (see appendix 8).

- Patients should be reminded to bring their patient diary with them to every hospital visit. Any adverse events recorded should be reviewed with the patient and documented in the Adverse Events CRFs and medical notes as appropriate.

Placement of a central venous access device (CVAD) and complications will be monitored as an assessment of treatment-related complications. Episodes of CVAD-related thrombosis, infection, or dysfunction will also be recorded in the medical record and recorded in the Adverse Events CRF.

9.2.1 Assessment of Tumour Response

**PET/CT Scan:**

All patients should have a second PET/CT scan prior to cycle 4 treatment to assess tumour response. Patients who do not respond will come off trial treatment and should proceed to follow up.

Tumour response will be assessed using measurement of SUV.

\[
SUV = \frac{\text{decay corrected dose (kBq)}/\text{tumour (mL)}}{\text{Injected dose (kBq)}/\text{body weight (g)}}
\]

Response is defined as follows:

<table>
<thead>
<tr>
<th>Response</th>
<th>≥30% decrease in SUV compared to baseline PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Response</td>
<td>&lt;30% decrease in SUV compared to baseline PET/CT</td>
</tr>
</tbody>
</table>
Adverse Events during PET/CT:

All AEs and SAEs occurring during this procedure will be recorded and documented by the local investigational team in patients’ notes and on trial CRFs.

MRI Scan:

Tumour measurement will also be made using MRI scan prior to cycle 4 and post end of all chemotherapy treatment. Response assessment should be made according to RECIST v1.1 and to assess neoadjuvant chemotherapy downstaging efficacy in terms of MRI defined T and N stage and tumour regression grade (MRI TRG) (and documented on the case report forms).

9.3 Assessments on completion of treatment

The following assessments should be carried out after the patient has received their final treatment with FOLFOX + bevacizumab or FOLFOXIRI + bevacizumab.

- The following assessments should be carried out two weeks (+/- 3 days) after day 1 of the final cycle of treatment, 4 weeks (+/- 3 days) after day 1 of final cycle of treatment, and prior to surgery, but not if tumour progression occurs:
  - Clinical examination including weight and blood pressure
  - Documentation of concomitant medications
  - Assessment of AEs
  - WHO performance status
  - Haematology:
    - Full blood count plus white blood cell differential including absolute neutrophil (ANC) and lymphocyte counts
  - Biochemistry:
    - Sodium, potassium, urea, creatinine, albumin, total bilirubin, alkaline phosphatase (ALP), AST and/or ALT, γGGT, CRP
    - CEA (2 weeks after final treatment administration only)
  - Estimated GFR (calculated CrCl using Cockcroft and Gault formula, see Appendix 4)
  - ECG (only if clinically indicated)
- The following should be carried out within 4 weeks prior to surgery:
  - Chest/abdominal/pelvis CT scan
  - Tumour measurements:
    - MRI scan of the pelvis (mandatory)
    - It is also recommended but not mandated that diffusion weighted MRI, intrinsic susceptibility MRI and dynamic contrast enhanced MRI be performed on the same occasion to enable assessment of changes in ADC, R2* and DCE-MRI parameters (IAUGC, Ktrans, ve, vp) following completion of chemotherapy. This will be reviewed centrally.

9.4 Assessments after surgery

An additional CT scan (chest/abdominal/pelvis) must be performed between 3 – 6 months after surgery.

Patients that do not undergo surgery do not need to have an additional CT at the equivalent timepoint after completing chemotherapy. The post treatment CT scan (as specified in section 9.3) can be used as the baseline CT scan for follow up.

9.4.1 Surgical Complications

Surgical complications should be assessed at 48 hours, and at 1 and 3 months post-surgery.
Parameters will include peri-operative mortality (within 60 days from surgery), intra-operative bleeding/transfusion, post-operative transfusions, general complications and local pelvic complications.

General complications include:
- pulmonary complications
- cardiovascular complications
- urinary tract infections
- impaired wound healing
- iatrogenic complications

Local pelvic complications include:
- anastomotic leakage
- haemorrhage
- pelvic sepsis
- breakdown of perineal wound

The degree of each complication as well as the need for surgical reintervention will be noted using classification grading in Appendix 7.

9.4.2 Resection Sample

Appendix 9 describes the method of examination of the resected specimen. The pathology CRF must be completed to capture data necessary for assessment of the pathological secondary endpoint: Tumour Regression Grade (TRG). Ancillary studies and measurement of secondary endpoints using histopathological material are described in Section 21.

9.5 Assessments during follow-up

Patients will be followed up every 6 months after surgery (or after completing chemotherapy if they do not have surgery) for up to 42 months after randomisation, to document progression, recurrence and survival.

A blood sample for ancillary studies (see section 21.3 - Blood Samples) should be taken at the time of relapse.

Postoperative investigations/surveillance will be according to local practice. All efforts should be made to contact the patient’s GP to assess their condition, if a patient fails to attend a clinic or cannot be followed up at Site.
10 QUALITY ASSURANCE AND QUALITY CONTROL

Quality assurance and/or quality control will be carried out for MRI, PET, and histopathology.

10.1 MRI QA

Standard MRI QA will be performed. For sites intending to perform the recommended DW-MRI and DCE-MRI sequences, phantom calibration (T1 phantom and diffusion phantom) should be undertaken as per protocol (see appendix 8) prior to trial commencement.

10.1.1 Reporting MRI

Standardised criteria will be used for reporting the staging MRI as per Royal College of Radiologist guidelines. The staging MRI will be reviewed centrally, independent of the local report. Differences in reporting between the local hospital and the central laboratory will be resolved by consensus.

The additional DW-MRI, ISW-MRI and DCE-MRI sequences will be analysed centrally.

10.2 PET QA

The full PET QA procedures and forms will be provided by the NCRI PET Core Lab on application (see appendix 2 for contact details). Sites accredited by the NCRI PET Core Lab for other clinical trials may already fulfil all or some of the site accreditation requirements for BACCHUS. Therefore sites are advised to get in touch with the NCRI PET Core Lab as soon as possible to determine the specific aspects of the QA procedures necessary for accreditation of the PET Centre.

We have taken the advice from the NCRI PET Core Lab which has recommended the package of QA and QC checks below.

10.2.1 Pre-Trial QA and QC

- The PET/CT Scan Quality Control document must be completed and forwarded to the core lab.
- Initial ‘start-up’ scanner quality control procedures must be performed.
- Two anonymised patient studies (attenuation corrected PET, CT and non-attenuation corrected PET) acquired using the proposed study protocol should be transferred to the Core Lab for quality assessment together with the TEST PATIENT DATA FORM.
- The data transfer and anonymisation procedure must be set up and validated.

10.2.2 Ongoing QA Requirements

- Retrospective review of each scan for each patient
- Plan and PAF export for all trial patients

10.3 Surgery and Histopathology QA

Sites are asked to provide the following material for central review:

- Copies of H&E stained glass slides (or originals which will be returned to site after scanning) of:
  - Pre-treatment diagnostic biopsy tissue (all slides)
  - Post-treatment resection tissue (all slides including whole mounts)
- Anonymised histopathology report identifiable by trial number
- Digital photographs of the resection specimens (front, back and slices)

Please also refer to Appendix 9 – Histopathology Guidance.
10.3.1 Pathology Endpoint Analysis

The resection specimen H&E-stained glass slides will be used to determine two secondary endpoints: Tumour Regression Grade (TRG) and Tumour Cell Density (TCD). The H&E-stained slides from the resection specimen for all patients must be sent to the central laboratory for review as requested by the UCL CTC. Once these have been scanned, the slides will be returned to the sites – approximately 4-6 weeks after receipt.

**Tumour Regression Grade** will be performed using the established five point Dworak method that is based upon a subjective assessment of the degree of damage to the tumour [78]– refer to Appendix 9 for Dworak grading technique. This should be performed by the local pathologists on the resection specimen which should be available after surgery, and will also be independently scored during central review of the scanned H&E slides once all material has been collected centrally from the biopsy and resection specimens.

**Tumour Cell Density** is an objective morphometrical assessment of the number of residual tumour cells within the tumour area given as a percentage [79]. This will be done in both the whole tumour area and also the area of greatest residual tumour cell density to look at both the overall response and the area of least response. This will be undertaken centrally using a point counting technique on virtual tissue sections (scanned H&E slides). This technique is more sensitive than TRG and more likely to detect smaller differences between groups. The technique is currently being used in a number of UK rectal cancer trials including MRC CR07, EXCITE, RICE, ARISTOTLE, SONATINA and TREC. This will be performed during central review of the scanned H&E slides once all material has been collected centrally from the biopsy and resection specimens.

10.3.2 Shipping

Glass slides should be carefully packaged to avoid breakage and sent to the address below. Slides should be packed in dedicated slide boxes surrounded by bubblewrap which should be securely sealed. Any queries should be sent to either Dr Nick West (n.p.west@leeds.ac.uk) or Professor Phil Quirke (p.quirke@leeds.ac.uk). If any of the held material is required for clinical purposes prior to its standard return then it will be returned temporarily as soon as possible.

The above material for central review may be shipped together with the tissue blocks requested for future research (see section 21 Ancillary studies).

Ship slides, tissue blocks for future research (if applicable), histopathology report and photographs (see section 21 Ancillary studies) to:

- **Dr Nick West**
- **Pathology and Tumour Biology**
- **Level 4**
- **Wellcome Trust Brenner Building**
- **St. James’s University Hospital**
- **Beckett Street**
- **Leeds**
- **LS9 7TF**
11 DATA MANAGEMENT GUIDELINES

Data will be collected from sites on version controlled case report forms (CRFs) designed for the trial and supplied by UCL CTC.

Where supporting documentation (e.g. autopsy reports, pathology reports, CT scan images etc) is being submitted to UCL CTC, the patient’s trial number must be clearly indicated on all material and any patient identifiers removed/blacked out prior to sending to maintain confidentiality.

Data must be accurately transcribed onto CRFs and must reflect source documents at site. Examples of source documents include patient notes, laboratory and other clinical reports etc.

Some data may be recorded directly onto the CRFs (i.e. no prior written or electronic record of the data) and it will be considered to be the source document. Such CRFs will include the disease assessment forms and the pathology form.

11.1 Completing Case Report Forms

All CRFs must be completed and signed by staff who are listed on the Site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported in the CRF.

Once completed the original CRFs must be sent to UCL CTC and a copy kept at Site. All entries must be clear, legible and written in ball point pen. The use of abbreviations and acronyms must be avoided.

Any corrections made to a CRF at Site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialled. Correction fluid must not be used. The amended CRF must be sent to the UCL CTC and a copy retained at Site.

11.2 Missing data

To avoid the need for unnecessary data queries, CRFs should be checked at Site to ensure there are no blank fields before sending to the UCL CTC. When data are unavailable because a measure has not been taken or test not performed, enter “ND” for not done. If an item was not required at the particular time the form relates to, enter “NA” for not applicable. When data are unknown enter the value “NK” (only use if every effort has been made to obtain the data).

11.3 Timelines for data return

CRFs must be completed at Site and returned to the UCL CTC as soon as possible after patient visit but must be within one month of the patient being seen.

Sites who persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and subjected to a ‘for cause’ monitoring visit. See section 14.2 (‘For Cause’ On-Site Monitoring) for details.

11.4 Data queries

Data arriving at the UCL CTC will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values. Query reports will be sent to the data contact at Site. Further guidance on how data contacts should respond to Data Queries can be found on the Query Reports.
12 PHARMACOVIGILANCE

12.1 Definitions of Adverse Events

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting” and ICH GCP E6:

**Adverse Event (AE)**

Any untoward medical occurrence or effect in a patient treated on a trial protocol, which does not necessarily have a causal relationship with a trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a trial treatment, whether or not related to that trial treatment.

**Adverse Reaction (AR)**

All untoward and unintended responses to a trial treatment related to any dose administered. A causal relationship between the trial treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

**Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)**

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (the term “life-threatening” refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above)

**Suspected Unexpected Serious Adverse Reaction (SUSAR)**

A serious adverse reaction, the nature or severity of which is not consistent with the applicable trial treatment information.

12.2 Reporting procedures

12.2.1 All adverse events (AEs)

All adverse events that occur between informed consent and 3 months after surgery to remove the rectal tumour must be recorded in the patient notes and the trial CRFs. Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to UCL CTC using the trial specific SAE Report. Also refer to section 12.2.6 (Serious Adverse Events (SAEs)). Pre-existing conditions do not qualify as adverse events unless they worsen.

12.2.2 Overdoses

All accidental or intentional overdoses, whether or not resulting in an adverse event, must be recorded in the patient notes and CRFs. Overdoses resulting in an adverse event are classified as SAES and must be reported to UCL CTC according to SAE reporting procedures. The fact that an overdose has occurred must be clearly stated on the SAE Report. Also refer to section 12.2.6 (Serious Adverse Events (SAEs)).
Sites must inform UCL CTC immediately when an overdose has been identified. Also refer to section 13 (Incident reporting and serious breaches).

12.2.3 Adverse Event Term

An adverse event term must be provided for each adverse event, preferably using the term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v4.03, available online at:


12.2.4 Severity

Severity for each adverse event must be determined by using CTCAE v4.03 as a guideline, wherever possible. The criteria are available online at:


In those cases where the CTCAE criteria do not apply, severity should be coded according to the following criteria:

1 = Mild (awareness of sign or symptom, but easily tolerated)
2 = Moderate (discomfort enough to cause interference with normal daily activities)
3 = Severe (inability to perform normal daily activities)
4 = Life threatening (immediate risk of death from the reaction as it occurred)
5 = Fatal (the event resulted in death)

12.2.5 Causality

The PI, or other delegated Site investigator, must perform an evaluation of causality for each adverse event. Causal relationship to the trial treatment must be determined as follows:

- **None**
  There is no evidence of any causal relationship.

- **Unlikely**
  There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of a trial treatment). There is another reasonable explanation of the event (e.g. the patient’s clinical condition, other concomitant treatments).

- **Possibly**
  There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of a trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient’s clinical condition, other concomitant treatments).

- **Probably**
  There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- **Definitely**
  There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
12.2.6 Serious Adverse Events (SAEs)

All SAEs that occur between the signing of informed consent and 30 days after last drug administration (or after this date if the Site investigator feels the event is related to a trial treatment) must be submitted to UCL CTC by fax within 24 hours of observing or learning of the event, using the trial-specific SAE Report. All sections on the SAE Report must be completed. If the event is not being reported within 24 hours to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

12.2.7 Adverse Events of Special Interest

The following adverse events of special interest for Bevacizumab (Avastin) that occur between start of treatment and 3 months after surgery to remove the rectal tumour, must be reported using the trial specific SAE report within 24 hours of becoming aware of the event:

- Bleeding/Haemorrhage
- Fistula
- Gastrointestinal perforation
- Heart Failure
- Hypertension (grades 3 – 5 only)
- Proteinuria
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
- Thromboembolic events (Arterial and Venous)
- Wound Complication

12.2.8 Exemptions from SAE Report Submission

For this trial, the following events are exempt from requiring submission on an SAE Report, but must be recorded in the relevant section(s) of the trial CRFs:

- any event that occurs after 30 days post last trial drug administration that is not an AE of special interest listed in section 12.2.7 or considered to be causally related to trial treatment
- disease progression (including disease related deaths)
- Please note that hospitalisation for elective treatment or palliative care does not qualify as an SAE

Completed SAE Reports must be faxed within 24 hours of becoming aware of the event to UCL CTC
Fax: 020 7679 9871
12.2.9 Adverse Event reporting flowchart

Adverse event

Assign severity grade

Investigator to assess causality
Is the event causally related to the trial treatment?

Was the event serious?

Criteria:
- Results in death
- Is life threatening
- Results in persistent or significant disability/incapacity
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in a congenital anomaly or birth defect
- Is otherwise medically significant

Event exempt from requiring submission on an SAE Report?
(as stated in protocol)

Complete SAE Report

Fax Report to UCL CTC within 24 hours of becoming aware of the event

Complete CRF (to be submitted at time point stated in protocol)
12.2.10 SAE follow-up reports

All SAEs must be followed-up until resolution and until there are no further queries. The PI, or other delegated Site investigator, must provide follow-up SAE Reports if the SAE had not resolved at the time the initial report was submitted.

12.2.11 SAE processing at the UCL CTC

On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the list of expected adverse events in appendix 13 for the FOLFOX and FOLFOXIRI regimens, and the current SPCs for bevacizumab, oxaliplatin, 5-fluorouracil and irinotecan.

The CI, or their delegate (e.g. a clinical member of the TMG), will be contacted to review the SAE and to perform an evaluation of causality on behalf of UCL CTC. If UCL CTC has considered expectedness difficult to determine, the CI, or their delegate, will be consulted for their opinion at this time.

UCL CTC will submit SAE Reports that indicate a causal relationship to bevacizumab and AEs of special interest to Roche within 15 calendar days. SAE Reports, for patients administered bevacizumab, which indicate no causal relationship to bevacizumab will be submitted to Roche within 30 calendar days.

UCL CTC will also provide Roche with quarterly line listings of all SAEs concerning patients who have received bevacizumab for reconciliation purposes.

12.3 SUSARs

If the event is evaluated as a Suspected Unexpected Serious Adverse Reaction (SUSAR), UCL CTC will submit a report to the MHRA and the REC within 7 calendar days for fatal/life threatening events, with a follow-up report within a further 8 calendar days, and 15 calendar days for all other events. In the case of conflicting evaluations of causal relationship by the Site and UCL CTC/CI, both opinions will be reported.

UCL CTC will submit copies of all SUSAR reports concerning bevacizumab to Roche within 15 calendar days.

Informing sites of SUSARs

UCL CTC will inform all PIs of any SUSARs which occur on the trial. PIs will receive a quarterly line listing which must be processed according to local requirements.

12.4 Safety monitoring

UCL CTC will provide safety information to the TMG on a periodic basis for review.

Trial safety data will be monitored to identify:

- new adverse reactions to the trial treatment regimen or any trial treatment;
- a higher incidence in rare adverse events than is stated in the SPC for a trial treatment;
- trial related events that are not considered related to the trial treatment regimen.

Should UCL CTC identify or suspect any issues concerning patient safety at any point throughout the trial, the CI or TMG will be consulted for their opinion.

12.5 Pregnancy

If a patient or the partner of a male patient becomes pregnant at any point during the trial, a completed trial specific Pregnancy Report must be submitted to UCL CTC by fax within 24 hours of learning of its occurrence. Consent to report information regarding the pregnancy must be obtained from the mother.
The trial-specific pregnancy monitoring information sheets and informed consent forms for trial patients and the partners of trial patients must be used for this purpose.

All pregnancies must be reported by faxing a completed Pregnancy Report within 24 hours day of becoming aware of the pregnancy to UCL CTC
Fax: 020 7679 9871

12.5.1 Pregnancy follow-up reports

All pregnancies must be followed-up until an outcome is determined. Follow-up Pregnancy Reports must be submitted to the UCL CTC by fax within **24 hours** of learning of the outcome. Reports must include an evaluation of the possible relationship of the trial treatment to the pregnancy outcome.

12.5.2 SAEs during pregnancy

Any SAE occurring in a pregnant patient must be reported using the trial specific SAE Report, according to SAE reporting procedures. Refer to section 12.2.6 (Serious Adverse Events (SAEs)) for details.

12.5.3 Pregnancy report processing at UCL CTC

UCL CTC will submit all Pregnancy Reports concerning patients who have received bevacizumab to Roche within 30 calendar days.

UCL CTC will submit a report to the MHRA and the REC should the pregnancy outcome meet the definition of a SUSAR. Refer to section 12.3 (SUSARs) for details.

12.6 Development Safety Update Reports (DSURs)

Safety data obtained from the trial will be included in DSURs that UCL CTC will submit to the MHRA and the REC.

UCL CTC will provide Roche with DSURs that include information regarding bevacizumab.
13 INCIDENT REPORTING AND SERIOUS BREACHES

13.1 Incident reporting
Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. UCL CTC may require a report on the incident(s) and a form will be provided if the organisation does not have an appropriate document (e.g. Trust Incident Form for UK sites).

If Site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach.

13.2 Serious breaches of safety
Systematic or persistent non-compliance by a Site with GCP and/or the protocol, including failure to report SAEs occurring on trial within the specified timeframe, may be deemed a serious breach.

In cases where a potential or actual serious breach has been identified, UCL CTC will inform the MHRA within 7 calendar days of becoming aware of the breach.

Sites must have written procedures for notifying the sponsor of serious breaches (MHRA Guidance on the Notification of Serious Breaches).

UCL CTC will use an organisation’s history of non-compliance to make decisions on future collaborations.
14 TRIAL MONITORING AND OVERSIGHT

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form.

UCL CTC will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

14.1 Central monitoring

Sites will be requested to submit logs (e.g. screening logs, delegation logs) and documents detailed in the BACCHUS monitoring plan to UCL CTC at the frequency detailed in the trial monitoring plan or on request and these will be checked for consistency and completeness. Also refer to sections 4.4.2 (Required Documentations) and 6.2 (Screening Logs).

Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). Checks of the criteria listed on the randomisation form will be undertaken by an appropriately trained UCL CTC staff member prior to randomisation. Also refer to section 7.1 (Randomisation).

Details relating to the informed consent process will be collected on the randomisation form and are subject to review by CTC as part of patient eligibility. Copies of completed drug accountability logs must be returned to UCL CTC for all trial patients. Sites will be required to submit logs following the patient’s completion of trial treatment or on request. A proportion of these will be monitored centrally to ensure completeness and correlation with data captured in the CRF. Also refer to section 8.4.2 (Drug accountability for IMP).

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File and Pharmacy Site File at the frequency detailed in the trial monitoring plan. Checklists detailing the current version/date of version controlled documents will be provided for this purpose.

Data received at UCL CTC will be subject to review in accordance with section 11.4 (Data queries).

Where central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk (for example evidence of an overdose having been administered, indication that dose modification for an IMP not observed following an adverse reaction, etc.), the matter will be raised urgently with Site staff and escalated as appropriate (refer to section 13 (Incident reporting and serious breaches) and 14.2 (‘For Cause’ On-Site Monitoring) for further details.

14.2 ‘For Cause’ On-Site Monitoring

On-site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance at a Site with important aspect(s) of the trial protocol/GCP requirements. Sites will be sent a letter in advance outlining the reason(s) for the visit. The letter will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities, who will be performing the visit and when the visit is likely to occur.

Following a monitoring visit, the Trial Monitor/Trial Coordinator will provide a report to the Site, which will summarise the documents reviewed and a statement of findings, deviations, deficiencies, conclusions, actions taken and actions required. The PI at each Site will be responsible for ensuring that monitoring findings are addressed in a timely manner, and by the deadline specified.

UCL CTC will assess whether it is appropriate for the Site to continue participation in the trial and whether the incident(s) constitute a serious breach. See section 13 (Incident reporting and serious breaches) for details.
14.3 Oversight committees

14.3.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator, a Deputy Chief Investigator, selected Principal Investigators, experts from relevant specialities and BACCHUS trial staff from UCL CTC (see page 3). The TMG will be responsible for overseeing the trial. The group will meet regularly (approximately twice a year) and will send updates to PIs (via newsletters or at Investigator meetings) and to the NCRI Colorectal Clinical Studies Group.

The TMG will review substantial amendments to the protocol prior to submission to the REC and MHRA. All PIs will be kept informed of substantial amendments through their nominated responsible individuals. Members of the TMG will be asked to sign the TMG charter.

14.3.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder and Sponsor.

Members of the TSC will be asked to sign the TSC charter.

14.3.3 Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held periodically to review interim analyses, or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

14.3.4 Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL). UCL CTC is responsible for all duties relating to pharmacovigilance which are conducted in accordance with section 12 (Pharmacovigilance).
15 WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, assessments, follow-up, data collection, (optional) additional MRI scans (DW/DCE/ISW-MRI) and the (optional) collection of biological samples for future research and (mandatory) central review of archived tissue samples.

15.1 Discontinuation of trial treatment

A patient may discontinue trial treatment whenever continued treatment is no longer in the patient’s best interests, but the reasons for doing so must be recorded. Reasons for discontinuing treatment may include:

- No response following 3 cycles of treatment (measurement of SUV on PET scan)
- Disease progression whilst on therapy
- Unacceptable toxicity
- Delay of more than 3 weeks of trial treatment due to toxicity
- Intercurrent illness which prevents further treatment
- Patient withdrawing consent to further trial treatment
- Any alterations in the patient’s condition which justifies the discontinuation of treatment in the Site investigator’s opinion
- If a female patient becomes pregnant or fails to use adequate birth control (for patients of childbearing potential)

In these cases patients remain within the trial for the purposes of follow-up and data analysis according to the treatment option to which they have been allocated.

15.2 Patient decision to discontinue treatment

If a patient expresses their wishes to discontinue trial treatment, sites should explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes and for allowing existing collected data to be used. If the patient gives a reason for their decision, this should be recorded.

15.3 Withdrawal of consent to data collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected, the exception of safety data, and recorded on the relevant CRF. In this event details should be recorded in the patient’s hospital records, no further CRFs must be completed and no further data sent to UCL CTC, except for SAEs.

15.4 Losses to follow-up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating trial Site and for this new centre to take over the responsibility for the patient, or for follow-up via GP. Details of participating trial sites can be obtained from the UCL CTC trial team who must be informed of the transfer of care and follow up arrangements.

If a patient is lost to follow-up at a Site every effort should be made to contact the patient’s GP (if consented) to obtain information on the patient’s status.
16 TRIAL CLOSURE

16.1 End of trial

End of trial occurs 42 months after the last patient is randomised, or once all patients have progressed or died, whichever happens sooner.

Following this, UCL CTC will advise sites on the procedure for closing the trial at the Site.

16.2 Archiving of trial documentation

At the end of the trial, the UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial held at Site are retained for a minimum of 5 years after the end of the trial, in accordance with national legislation and for the maximum period of time permitted by the Site.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the Site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

16.3 Early discontinuation of trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see sections 14.3.2 TSC and 14.3.3 IDMC). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards to the treatment and follow up of patients.

16.4 Withdrawal from trial participation by a Site

Should a Site choose to close to recruitment, the PI must inform UCL CTC in writing. Follow up as per protocol must continue for all patients recruited into the trial at that Site and other responsibilities continue as per CTSA.
17  STATISTICS

17.1  Population for analysis

The population for analysis in this trial will be the intention to treat population (ITT).

17.2  Analysis of the primary objective

The primary endpoint for this trial is the pathological complete response rate (pCR). The proportion of patients in each arm who achieve a pCR will be presented, along with a 95% confidence interval (CI). pCR will be assessed after surgery. Within each group the achieved pCR rate will be compared to the rate achieved by radiotherapy alone (5%).

The study is powered on the assumption that a substantial proportion of patients will have a pCR. It is well recognised that patients who have a complete clinical response both on imaging and clinical examination will from time to time refuse surgery. For the purpose of this study, patients who have a sustained clinical complete response at 12 months will be considered the same as a patient with a complete pathological response. In contrast, patients with a transient clinical response where local endoluminal or pelvic relapse is observed within this 12 month timeframe will not.

The trial is not powered to perform any comparisons between the groups with regard to any outcome.

17.3  Analysis of secondary objectives

The following secondary outcomes will be assessed

- RECIST response rate
- CRM negative resection rate
- T and N stage downstaging
- Progression free survival (PFS)
- Disease free survival (DFS)
- Overall Survival (OS)
- Local control
- 1 year colostomy rate
- Adverse events
- Compliance of chemotherapy treatment
- Tumour Regression Grade (TRG)
- Tumour Cell Density (TCD)

RECIST response rate, CRM negative resection rate, downstaging, colostomy rate, adverse events, compliance and tumour cell density (TCD) will be presented as percentages with corresponding 95% CIs. Time to event outcomes will be estimated using the Kaplan-Meier method. If sufficient number of events occur, then the median event-free times will be presented; if data is mature then 1-year, 2-year and 3-year event rates will be provided. Tumour regression grade (TRG) will be presented as data categorised into five groups – TRG 0, TRG 1, TRG 2, TRG 3 and TRG 4.

**RECIST response rate:** this will be assessed after chemotherapy has ended. Complete response and Partial response will be considered as responses. The best response during chemotherapy will be given for each patient.

**CRM negative resection rate:** those with a resection distance >1mm amongst those having surgery.
T and N stage downstaging: this will examine T and N stage to assess whether stage has worsened from baseline to post-treatment. A patient will be considered to have downstaged if i) both T and N stage decrease; or ii) either T or N stage decreases and the other remains stable.

Progression-free survival (PFS): defined as time from randomisation to disease progression or death, whichever occurs first. Disease progression will be assessed by the RECIST criteria at pre-cycle 4 and post-treatment.

Disease-free survival (DFS): defined as the time from surgery with complete resections (R0) to the occurrence of relapse, second colorectal primary or death from any cause, whichever occurs first. Only subjects who have a complete resection (R0) will be included in this analysis. Patients who are alive, without recurrence and with no secondary colorectal cancer at the time of cut-off will be right-censored at the most recent date of assessment.

Overall survival (OS): defined as the time from study entry until death. The OS of all subjects and of the subgroup who had complete resection (R0) will be calculated.

Local control: will be assessed just for those patients who attain a CRM negative resection. This will be measured from date of surgery until local failure.

1-year colostomy rate: will be assessed post-surgery. The proportion of patients with an unreversed stoma one-year after surgery will be considered to have a colostomy at 1-year.

Adverse events: will be tabulated for both treatment arms, including all grade 1–5 toxicities.

Chemotherapy compliance: dose reductions and dose delays to all chemotherapy agents will be recorded.

Tumour Regression Grade: results from the post-resection tumour sample will be used to categorise TRG into five groups using the Dworak method.

Tumour Cell Density: results from the post-resection tumour sample will be used to provide an estimate of the average TCD and its 95% CI. This may be expressed as a mean, or if the data is skewed, the median.

17.4 Sample size calculation

Based on pCR with similar regimens prior to liver resection, and the fact that primary tumours respond better than metastases, we anticipate a pathological complete response rate of 20%. Compared to 5% pCR rate for radiotherapy alone, a type I error $\alpha=0.05$ and a type II error $\beta=0.8$, 27 patients for the FOLFOX arm are required (exact sample size using A’Hern [80]). The same number of patients are required for the FOLFOXIRI arm. Assuming that 10% of patients will be non-evaluable, 30 patients will be recruited to each arm (i.e. a total of 60 patients). A regimen will be considered successful if at least 4/27 pCRs are observed. In the instance of more than 27 patients being assessed for pCR, the first 27 randomised patients per arm will be assessed. The study is not powered for a direct comparison between the two arms.

We have estimated conservatively that (mainly because of set-up time) the study will take 18 months to recruit, and these numbers will confirm feasibility of recruiting patients into a phase III study.
18 ETHICAL AND REGULATORY COMPLIANCE

In conducting the Trial the Sponsor, UCL CTC and sites shall also comply with all laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

- the Human Rights Act 1998
- the Data Protection Act 1998
- the Freedom of Information Act 2000
- the Human Tissue Act 2004
- the Medicines Act 1968
- the Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments
- Good Manufacturing Practice
- the Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

18.1 Ethical approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled ‘Ethical Principles for Medical Research Involving Human Subjects’ (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from the London Riverside Research Ethics Committee.

UCL CTC will submit Annual Progress Reports to the REC, which will commence one year from the date of ethical approval for the trial.

18.2 Regulatory approval

A Clinical Trial Authorisation (CTA) has been granted for the trial.

The trial will be conducted at approved sites in accordance with the trial protocol and the terms of the CTA granted by the MHRA

18.3 Site approvals

The Lead Comprehensive Local Research Network (CLRN) Central & East London has given NHS permission following global governance checks. Local governance checks will be undertaken by local CLRNs associated with individual trial sites.

Evidence of approval from the Trust R&D for a trial Site must be provided to UCL CTC. Sites will only be activated when all necessary local approvals for the trial have been obtained.

18.4 Protocol amendments

UCL CTC will be responsible for gaining ethical and regulatory approvals for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites and CLRNs as appropriate.
Site staff will be responsible for acknowledging receipt of documents and for gaining local Trust R&D acknowledgement and implementing all amendments.

**18.5 Patient confidentiality & data protection**

Patients’ identifiable data, including date of birth and NHS number will be required for the randomisation process and will be provided to UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 1998 with the Data Protection Officer at UCL.
19 SPONSORSHIP AND INDEMNITY

19.1 Sponsor details

University College London will act as the sponsor for this trial. Delegated responsibilities will be assigned to the local principal investigators and pharmacies taking part in this trial.

Sponsor Name: University College London
Address: Joint Research Office
          Gower Street
          London
          WC1E 6BT
Sponsor Contact: Director of Research Support
Telephone: 020 3447 9995/2178 (unit admin)
Fax: 020 3447 9937

19.2 Indemnity

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital’s duty of care, or any negligence on the part of the hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor’s Insurers, via the Sponsor’s office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.
20 PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal’s policy. The TMG will form the basis of the writing committee and advise on the nature of publications. If there are named authors, these should include the Chief Investigator(s), Trial Coordinator(s), Statistician(s), members of the TMG and key contributors involved in the trial. Contributing Site investigators in this trial will also be acknowledged. Data from all sites will be analysed together and published as soon as possible. Participating sites may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. The trial data is owned by the TMG. However, drug companies who have provided grants towards the trial will be permitted to see the draft manuscripts and make comments at least 30 days prior to submission for publication. The ClinicalTrials.gov number (NCT01650428) allocated to this trial will be quoted in any publications resulting from this trial.
21 ANCILLARY STUDIES

21.1 Collection of Tissue and Blood Samples

At the time of trial entry, patients will be asked to provide informed consent to donate blood samples for future research. Consent will also be requested to allow collection and testing to be performed on existing and future routine tissue samples from their rectal cancer specimen (tumour and normal tissue).

Consent for future research on blood and tissue samples is optional for patients and refusal will not preclude trial entry.

Refer to the BACCHUS lab manual in the Investigator site file for more details on sample collection, processing, storage and shipping.

Refer to section 10 (Quality Assurance) for details of the collection and shipping of histopathology slides for quality assurance and to determine two secondary endpoints.

21.2 Tissue Blocks

21.2.1 Samples to Collect

Sites are asked to provide the following for patients who have consented to collection of tissue:

- Formalin-fixed paraffin-embedded Tissue Blocks from:
  - Pre-treatment diagnostic biopsy (tumour and normal mucosa if present)
  - Post-treatment resection (one or more blocks from tumour and one block from normal mucosa)

The tissue blocks from the resection will be used in further molecular studies of the response to radiotherapy/chemotherapy. This should preferably be material that is not required for diagnosis locally i.e. additional blocks should be taken at the time of specimen dissection if there is sufficient material. In cases with no residual tumour, a block of normal mucosa only is required. Tissue will be kept in wax blocks and stored separately for future studies.

21.2.2 Shipping

All blocks should be carefully packaged to avoid breakage and sent to the address below when requested by the UCL CTC. Blocks should be wrapped in a protective layer e.g. bubble wrap. Any queries should be sent to either Dr Nick West (n.p.west@leeds.ac.uk) or Professor Phil Quirke (p quirke@leeds.ac.uk). If any of the held material is required for clinical purposes prior to its standard return then it will be returned temporarily as soon as possible.

Tissue blocks may be shipped together with material requested for Quality Assurance (see section 10).

Ship blocks (and material for QA if applicable) to:

Dr Nick West
Pathology and Tumour Biology
Level 4
Wellcome Trust Brenner Building
St. James’s University Hospital
Beckett Street
Leeds
LS9 7TF
21.3 Blood Samples

21.3.1 Timing of Collection

Blood samples will be collected from patients at up to 5 timepoints during the trial for plasma and buffy coat samples:

- Baseline (pre-treatment)
- Prior to Cycle 2
- Prior to Cycle 3
- Prior to Cycle 4 (preferably at 1st radiological response assessment)
- A sample should also be taken if a patient relapses

21.3.2 Preparation of samples

Blood samples should be collected in 3 x 8ml Cell Preparation (CPT) Sodium Heparin tubes (which will be provided by UCL CTC). The blood samples should be centrifuged at room temperature and plasma and white cells (buffy coat) aliquoted into cryovials. Refer to the BACCHUS lab manual in the Investigator site file for full details on sample processing.

21.3.3 Storage and Shipping

Store plasma and buffy coat samples at -80°C until the end of the trial or until requested. UCL CTC will arrange for a courier to collect the frozen samples in batches. The courier will arrive with dry ice and packaging material to ensure samples remain frozen during transport. Upon request, samples will be shipped to:

BACCHUS Study Blood Collection  
c/o Tissue Collector  
GI Unit Trial Office  
Royal Marsden Hospital  
Downs Road  
Sutton  
Surrey  
SM2 5PT
REFERENCES


## APPENDIX 1 – ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>5FU</td>
<td>5-fluorouracil</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>ALP</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine transaminase</td>
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<tr>
<td>ANC</td>
<td>Absolute Neutrophil Count</td>
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<tr>
<td>APE</td>
<td>Abdomino-Perineal Excision</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
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<tr>
<td>CEA</td>
<td>Carcinoembryonic Antigen</td>
</tr>
<tr>
<td>CI</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous Systems</td>
</tr>
<tr>
<td>CPT</td>
<td>Cell Preparation Tube</td>
</tr>
<tr>
<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<tr>
<td>CRM</td>
<td>Circumferential resection margin</td>
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<tr>
<td>CRT</td>
<td>Chemoradiotherapy</td>
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<tr>
<td>CT</td>
<td>Computerised Tomography</td>
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<tr>
<td>CTA</td>
<td>Clinical Trial Authorisation</td>
</tr>
<tr>
<td>CTAAC</td>
<td>Clinical Trials Advisory &amp; Awards Committee</td>
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<tr>
<td>CTCAE</td>
<td>see NCI CTCAE</td>
</tr>
<tr>
<td>CTSA</td>
<td>Clinical Trial Site Agreement</td>
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<tr>
<td>CVAD</td>
<td>Central Venous Access Device</td>
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<tr>
<td>DCE MRI</td>
<td>Dynamic Contrast–Enhanced MRI</td>
</tr>
<tr>
<td>DFS</td>
<td>Disease Free Survival</td>
</tr>
<tr>
<td>DPA</td>
<td>Data Protection Act</td>
</tr>
<tr>
<td>DPD</td>
<td>Dihydropyrimidine dehydrogenase</td>
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<tr>
<td>DSUR</td>
<td>Development Safety Update Report</td>
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<tr>
<td>DTPA</td>
<td>Diethylene Tetramine Penta Acetate</td>
</tr>
<tr>
<td>DW MRI</td>
<td>Diffusion Weighted MRI</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>EDTA</td>
<td>Ethylene Diamine Tetra Acetate</td>
</tr>
<tr>
<td>EudraCT</td>
<td>European Clinical Trials Database</td>
</tr>
<tr>
<td>EMVI</td>
<td>Extramural Vascular Invasion</td>
</tr>
<tr>
<td>FA</td>
<td>Folinic Acid</td>
</tr>
<tr>
<td>FBC</td>
<td>Full Blood Count</td>
</tr>
<tr>
<td>FDG</td>
<td>Fluorodeoxyglucose</td>
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<tr>
<td>FOLFOX</td>
<td>5FU, Folinic acid and Oxaliplatin</td>
</tr>
<tr>
<td>FOLFOXIRI</td>
<td>5FU, Folinic acid, Oxaliplatin and Irinotecan</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>G-CSF</td>
<td>Granulocyte Colony Stimulating Factor</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>Hb</td>
<td>Haemoglobin</td>
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<tr>
<td>H&amp;E</td>
<td>Haematoxylin &amp; Eosin (Staining)</td>
</tr>
<tr>
<td>ICH GCP</td>
<td>International Conference of Harmonisation-Good Clinical Practice</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<tr>
<td>INR</td>
<td>International Normalised Ratio</td>
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<tr>
<td>IPEM</td>
<td>Institute of Physics and Engineering in Medicine</td>
</tr>
<tr>
<td>ISRCTN</td>
<td>International Standard Randomised Controlled Trial Number</td>
</tr>
<tr>
<td>ISW MRI</td>
<td>Intrinsic Susceptibility MRI</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention To Treat</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LD</td>
<td>Longest Diameter</td>
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<tr>
<td>LFT</td>
<td>Liver Function Tests</td>
</tr>
<tr>
<td>LLN</td>
<td>Lower Limit of Normal</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Image</td>
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<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
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<tr>
<td>NCI CTCAE</td>
<td>National Cancer Institute Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>NCRI</td>
<td>National Cancer Research Institute</td>
</tr>
<tr>
<td>NCRN</td>
<td>National Cancer Research Network</td>
</tr>
<tr>
<td>NOS</td>
<td>Not Otherwise Specified</td>
</tr>
<tr>
<td>NRES</td>
<td>National Research Ethics Service</td>
</tr>
<tr>
<td>OS</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>PBL</td>
<td>Peripheral Blood Leucocytes</td>
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<tr>
<td>pCR</td>
<td>Pathological Complete Response</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive Disease</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
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<tr>
<td>PFS</td>
<td>Progression Free Survival</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PR</td>
<td>Partial Response</td>
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<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
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<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumours</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>RPLS</td>
<td>Reversible Posterior Leukoencephalopathy Syndrome</td>
</tr>
<tr>
<td>SA</td>
<td>Surface Area</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SC</td>
<td>Subcutaneous</td>
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<tr>
<td>SCPRT</td>
<td>Short Course Preoperative Radiotherapy</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>SD</td>
<td>Stable Disease</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>SSA</td>
<td>Site Specific Assessment</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>SUV</td>
<td>Standardised Uptake Value</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient Ischemic Attack</td>
</tr>
<tr>
<td>TME</td>
<td>Total Mesorectal Excision</td>
</tr>
<tr>
<td>TMF</td>
<td>Trial Master File</td>
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<tr>
<td>TMG</td>
<td>Trial Management Group</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
</tr>
<tr>
<td>UCL CTC</td>
<td>Cancer Research UK and UCL Cancer Trials Centre</td>
</tr>
<tr>
<td>U&amp;E</td>
<td>Urea and Electrolyte</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
<tr>
<td>WBC</td>
<td>White Blood Cells</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
APPENDIX 2 – PET/CT PROTOCOL & SCANNING PROCEDURES

1. PET/CT PROTOCOL

1.1. Patient Scheduling:
- Sequential PET exams for a patient must be performed in the same centre using the same accredited PET/CT system as the baseline scan. The patient preparation, FDG administration, image acquisition and reconstruction for these scans must be matched for each subsequent patient scan acquired for the study. Please make it clear on referral forms that a patient is either on the BACCHUS trial or being considered for the trial to ensure PET protocol is followed and data is transferred to the applicable centres (see 1.8 and 2 below).
- If a diagnostic contrast-enhanced CT with intravenous or bowel contrast (other than water) is indicated this should ideally be performed after the PET/CT scan. If a contrast-enhanced CT has already been performed, the PET/CT scan should be performed a minimum of 3 days after the CT scan.

1.2. Patient Preparation:
- Non-diabetic patients should fast for at least 6 hours prior to the start of the PET study.
- Plain (non sugary/unflavoured) water should be taken during the period of fasting and the uptake period to ensure good hydration.
- Diabetics on oral medication should ideally be given a morning appointment, asked to fast for 6 hours and should omit their hypoglycaemic medication that morning.
- Diabetics on insulin should eat and administer their insulin as normal before fasting for 6 hours prior to the PET scan. If blood glucose level is > 11mmol/l (> 200mg/dl) then consideration should be given to rescheduling the scan. Insulin should not be administered to lower blood glucose prior to subsequent appointment.
- The blood glucose level of all patients should be measured on arrival at the imaging centre. This should be performed using a calibrated glucometer or similar bedside device, and recorded on trial CRFs.
- Patients should avoid strenuous exercise for 6 hours prior to the scan.
- Patients should be weighed without shoes and coats using a calibrated device.
- Intravenous CT contrast media should not be administered prior to the PET study.
  - If local protocols include a diagnostic CT scan using contrast as part of the PET/CT examination this should be performed after the PET scan. In this case a separate low dose CT without contrast should also be acquired before the PET acquisition and this scan should be used for attenuation correction of the PET images.
1.3. Radiopharmaceutical Administration:

Radiopharmaceutical: $^{18}$F-fluorodeoxyglucose (FDG)

Route of Administration: Intravenous administration under quiet conditions.

Dosage: The injected dose is dependent on the PET system that is utilised and the patient weight. The injected activity should meet the following recommendations based on a 70kg patient:

a) for 2D acquisitions using a minimum of 5 minutes per bed position:
- The target activity is 385 MBq (+/-10%). The injected activity must not exceed 400 MBq.

b) for 3D acquisitions:
- With an overlap of < 25% the minimum activity is 322 MBq using 3 minutes per bed position
- With an overlap of 50% the minimum activity is 240 MBq using 2 minutes per bed position

For all patients the injected activity must not exceed 400 MBq. For patients >90 kg, increase of scanning time (time per bed position) rather than an increase in FDG activity is recommended to improve image quality.

The actual injected activity must be recorded on the PET acquisition form.

1.4. Uptake Period:

- During the $^{18}$F-FDG administration, uptake phase and the PET/CT exam, the patient should remain seated and be kept warm to avoid uptake in the muscles or brown fat.
- Patients should be asked to void (empty bladder) immediately prior to the PET/CT scan to reduce bladder activity.
- The PET emission acquisition should be started 90 minutes after the dose administration.
- The response scans must be performed at the same time after injection as the baseline scan + 10 minutes.

1.5. Image Acquisition:

- The PET and CT scan region should include the base of the brain to the upper thigh.
- Patients should be scanned with arms above the head if tolerated. Patient positioning should be matched on the response scans.
- Separate body and head and neck scans can be performed if locally accepted practice. If a separate head and neck scan is acquired the arms should be down by the sides.
- All other imaging parameters, i.e. with regard to time per bed position, 2D or 3D, CTAC parameters must be agreed with the NCRI PET Core Lab prior to the start of the study (see Section 4 of appendix 2). These should then be used throughout the study. Any changes to these parameters must be agreed with the Core Lab before scanning any more patients.

1.6. Image Reconstruction:

- Attenuation correction should be performed using the low dose CT.
- Iterative reconstruction should be used e.g. OSEM or similar
- Both attenuation-corrected and non attenuation-corrected PET images should be reconstructed.
- All other reconstruction parameters, i.e. with regard to number of iterations or filtering parameters, must be agreed with the Core Lab prior to the start of the study (see Section 4 of appendix 2). These
should then be used throughout the study. Any changes to these parameters must be agreed with the Core Lab before scanning any more patients.

1.7. Information to be recorded for each patient:

For each study patient, the PET/CT acquisition information and patient information must be recorded on the PET/CT ACQUISITION FORM and sent to the Core Lab with the PET/CT images. In addition, the PET/CT Assessment Worksheet must also be completed for each patient and sent to the Paul Strickland Scanner Centre.

1.8. Data Transfer & Archive:

PET/CT data must be transferred to the NCRI PET Core Lab at the same time as the completed PET/CT acquisition form.

The baseline and pre-cycle 4 PET/CT data should be saved locally on an approved data storage device. The following DICOM files are required:

- CT attenuation corrected half body images (skull base to mid thigh)
- Non-attenuation corrected half body images
- Half body CT scan
- PET/CT report from local imaging team

All image files must be compliant with DICOM PART 10 format. It is highly recommended that CD’s or images be created and sent directly from the acquisition PET/CT workstation rather than from a secondary PACS system or file library. Specifically, image files that have been converted to screen saves and then reconverted back to DICOM format are NOT acceptable. Projection images (MIPs) and fused images are not required.

1.9. All PET-CT studies must be clearly named using the following filename convention:

BACCHUS_<patient trial ID>_<patients initials>_baseline
BACCHUS_<patient trial ID>_<patients initials>_PreCycle4

1.10. Images and acquisition forms should be sent on CD by post to:

NCRI PET Core Lab
PET Imaging Centre
First Floor, Lambeth Wing
St Thomas’ Hospital
London SE1 7EH

It is strongly recommended that scans be sent by registered post (recorded or special delivery) or courier. These can be tracked on the Royal Mail/courier website.

Alternatively scans can be sent electronically using secure file transfer. This will be established and validated for each scanning Site by the NCRI PET Core Lab. In this case PET acquisition forms can be emailed (pet-trials@kcl.ac.uk) or faxed (0207 620 0790) to the Core Lab

Following review, all scan data will be archived at the central review lab at the Paul Strickland Scanner Centre at Mount Vernon Hospital by Dr Bal Sanghera.

2. PET/CT REPORTING AND REASSESSMENT

A PET/CT Assessment Worksheet must be transferred by the local centre to the Paul Strickland Scanner Centre at Mount Vernon Hospital for central review after each scan. Discordance between local report and central review will be resolved by a discussion between local reporter and central review reporter.
3. **RADIATION DOSIMETRY**

The effective dose associated with an administration of 400 MBq $^{18}$FDG is 8.0 mSv [81]. The target organ is the bladder wall, which will receive 68.0 mGy [82]. The CT attenuation correction using 80 mA and 140 kV will be approximately 8 mSv for the half body with an upper bound of approximately 12mSv. (This will be Site specific).

National regulations must be complied with regard to the administration of radioactive substances and the CT exposure for the purpose of this study.

3.1. **ARSAC approval:**

Depending on individual local practice and should an ARSAC research certificate need to be obtained at the local centre, this must be obtained individually for each participating PET centre prior to starting the study, and a copy of the certificate sent to the UCL CTC.

4. **PET/CT QC PROCEDURES**

Common standards and careful quality control is essential for the success of multi-centre trials such as this one. The procedures below fulfil the requirements of the NCRI PET Core Lab and are based on the EANM procedure guidelines for tumour PET Imaging [83].

4.1. **Imaging Facilities:**

- Scanning facilities must undergo the site accreditation process as detailed below and have received written confirmation that they fulfil the requirements of the study before scanning any patients as part of the trial.
- A documented quality assurance program must be in place and records kept covering daily, weekly, monthly, quarterly and annual QC testing.
- Anonymised scan data will be transferred between scanning facilities and the Core Lab using established secure electronic transfer or via CD.
- All files must be clearly named using the pre-arranged file naming convention.
- Named persons (and their deputies) should be identified with responsibility for scanning, QC and data transfer at participating PET/CT centres.
- It must be demonstrated that image quality is comparable between centres and standard uptake values can be reliably determined from the PET/CT images.
- The proposed data acquisition/reconstruction protocol (including details of the time per bed position, 2D or 3D, CTAC parameters, reconstruction parameters etc) must be agreed with the Core Lab before scanning can start. Generally a time per bed of less than 2 minutes for 3D and less than 3 for 2D are not acceptable.
- All image files must be compliant with DICOM PART 10 format.

4.2. **Site Accreditation Process:**

Before a PET centre can participate in the trial it must undergo the formal site accreditation process.

**Scanning as part of the clinical trial must not start until written confirmation of compliance with the technical requirements of the trial is received from the Core Lab.**

The site accreditation must also be repeated by a PET Centre in the following situations:

- After any software or hardware changes which may affect the scanner image quality.
- If there are any significant changes to the acquisition or reconstruction parameters originally specified in the **PET/CT SCAN QUALITY CONTROL DOCUMENT**.
Any other circumstances which arise that the Core Lab deems may alter the image quality, such as QC failures, apparent scanner degradation or poor image quality.

It is the responsibility of the PET centre to inform the Core Lab of any upgrades to the scanner hardware or software prior to the upgrade. If the upgrade is likely to affect the image quality the Site will be required to repeat the phantom scans before continuing to scan patients as part of the trial.

**No patients are to be scanned until all of the following steps have been completed:**

1. The **PET/CT Scan Quality Control document** must be completed and forwarded to the core lab.
2. Initial ‘start-up’ scanner quality control procedures must be performed.
3. Two anonymised representative patient studies must be transferred to the Core Lab.
4. The data transfer and anonymisation procedure must be set up and validated.
5. Written confirmation from the core lab that scanning can now start at your centre must be received.
6. A copy of the ARSAC certificate must be sent to UCL Cancer Trial Centre (UCL CTC).

**4.3. Initial start-up QC procedures:**

All PET/CT scanners to be used for the trial should be calibrated against the institution’s own radionuclide calibrator.

In order to ensure that the images acquired at all centres are of a comparable quality and check the SUV accuracy of each scanner, a standard phantom should be scanned at each of the participating centres using the local study protocol. This could be done by a representative from the NCRI Core Lab who visits the scanning facility or an agreed local representative.

The phantom will consist of the NEMA IEC PET body phantom or EU chest phantom, filled with water throughout, containing 6 small spheres. The spheres will be filled with 25 kBq/ml of $^{18}$F- solution and the rest of the phantom with 5 kBq/ml of $^{18}$F- to simulate small regions of tracer uptake in the abdomen.

Data will be acquired using the same acquisition and processing parameters that will be used for the patient studies. These parameters may vary between sites. Data will be evaluated in terms of absolute activity measurements for the background and the spheres. Two nuclear medicine physicians or radiologists trained in PET/CT will also assess the visual quality of the scans. If significant disparities are observed, for example, from the use of widely differing reconstruction parameters, these will be resolved prior to the start of the study.

The phantom images will be assessed at the NCRI PET Core Lab based at St Thomas’ Hospital.

**4.4. Ancillary Equipment:**

- As this study uses SUVs defined in terms of patient weight, the scales used to weigh the patients must be calibrated. As a minimum the scales must be checked using a standard weight at least annually and should be accurate to within ± 1kg of a standard weight of 70 kg and records kept.
- The BM glucometer QC should be performed according to the manufacturer’s or institution’s procedure to ensure proper functioning.
- Quality assurance procedures for the radionuclide calibrator must be in place and activity measurements for $^{18}$F should be traceable to a primary standard. QC tests should include daily constancy checks and annual accuracy and linearity.
- Clocks used to record the assay time and injection time should be synchronized to the scanner time.
4.5. Representative Patient Studies:

Two anonymised patient studies (attenuation corrected PET, CT and non-attenuation corrected PET) acquired using the proposed study protocol should be transferred to the Core Lab for quality assessment together with the TEST PATIENT DATA FORM.

4.6. Data Format and Archiving:

All studies to be transferred to the Core Lab (attenuation corrected PET, non-attenuation corrected PET, and CT) must be in DICOM format. BMP files, jpeg files, screen saves and hard copies are not acceptable. In general, image data transferred through a PACS system will not be accepted, as many PACS systems convert DICOM images to another format and then reconvert them back to DICOM when exporting to a CD or FTP (file transfer protocol). Data should ideally be recorded directly onto CD using the PET scanner’s workstation or other multimodality image viewing software. The data transfer procedure will be tested and validated by the Core Lab. The reconstructed CT, PET AC (CT-attenuated PET) and NAC (non-attenuated PET) data are to be archived locally. Raw PET data must be archived according to local protocol, and at least until the images have been accepted by the Core Lab in case additional reconstructions are required.

4.7. Data transfer and anonymisation procedure:

All patient identifying information must be removed from the images prior to transfer. A procedure for naming, anonymising and transferring studies from the scanning Site must be established. This will vary between sites. This can be validated when transferring the test phantom and patient data as above.

4.8. Routine scanner QC procedures:

A documented PET/CT scanner quality assurance program must be in place and records kept, covering daily, monthly, quarterly and annual QC testing. A copy of the QC schedule must be sent to the Core Lab along with example results. Records should be made available for inspection by the Core Lab if requested.

The PET scanner should have up-to-date calibration and normalisation. On the day of scanning a trial patient the manufacturer’s recommended daily QC should be performed and if any failures or abnormalities are identified that could affect the quality of the PET scan; consideration should be given to rescheduling the scan.

The routine CT QC should be performed according to the manufacturer’s recommendations, but must include a water filled phantom scanned on a weekly basis, to measure image noise and CT number as described in IPEM (Institute of Physics and Engineering in Medicine) report 91 [84].

4.9. Additional scanner QC required during the trial:

Standardised Uptake Value (SUV) is used as a primary tumour response endpoint, therefore accurate and consistent estimation of SUV for all patient scans and between all participating centres is required. This will be achieved via a rigorous and regular testing of SUV accuracy and consistency of all participating scanners.

A uniform phantom must be scanned prior to the start of each scanning session in which a patient is to be scanned as part of the trial. This can either be a resin $^{68}$Ge phantom (where available) or an $^{18}$F water filled phantom. The activity concentration in the $^{18}$F phantom should be approximately 5kBq/ml. The average SUV for a large ROI (region of interest) placed at the centre of the phantom must be 1.00 ± 10% and on visual inspection the image should show no artefacts. The relevant sections of the patient data sheet must be completed to confirm the results of this test. The $^{18}$F or $^{68}$Ge phantom images must be sent, with the patient images to the core lab. If the test fails, the named physicist at the Core Lab should be contacted. The scan must not take place until the reason for this failure has been resolved.
4.10. Confirmation that study can start at your Site:

When all the above has been completed, an email/letter will be forwarded to both the PET centre and the UCL CTC to confirm that the centre can now participate in the trial. No subjects should be scanned before this confirmation has been received.

Scanning sites must inform the Core Lab of any upgrades to the scanner hardware or software prior to the upgrade. If the upgrade is likely to affect the image quality the Site will be required to repeat the phantom scans before continuing to scan patients as part of the trial. Sites must also notify the Core Lab immediately of any deviations in QC and scan acquisition or reconstruction parameters from those agreed.

4.11. Contact:

For enquiries relating to the scanning protocol, please contact the following at the core lab:

<table>
<thead>
<tr>
<th>Name:</th>
<th>Wai Lup Wong or Wendy Sookram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Review Centre:</td>
<td>Paul Strickland Scanner Centre</td>
</tr>
<tr>
<td></td>
<td>Mount Vernon Hospital</td>
</tr>
<tr>
<td></td>
<td>Northwood</td>
</tr>
<tr>
<td></td>
<td>HA6 2RN</td>
</tr>
<tr>
<td>Email Address:</td>
<td><a href="mailto:wailup.wong@nhs.net">wailup.wong@nhs.net</a>, <a href="mailto:wendy.sookram@stricklandscanner.org.uk">wendy.sookram@stricklandscanner.org.uk</a></td>
</tr>
</tbody>
</table>

For enquiries relating to the quality control and data transfer only, please contact the following at the Core Lab:

<table>
<thead>
<tr>
<th>Name:</th>
<th>Lucy Pike or Donald Sinclair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core Lab Centre:</td>
<td>NCRI PET Core Lab</td>
</tr>
<tr>
<td></td>
<td>PET Imaging Centre</td>
</tr>
<tr>
<td></td>
<td>First Floor, Lambeth Wing</td>
</tr>
<tr>
<td></td>
<td>St Thomas’ Hospital</td>
</tr>
<tr>
<td></td>
<td>London SE1 7EH</td>
</tr>
<tr>
<td>Phone No:</td>
<td>0207 188 7445</td>
</tr>
<tr>
<td>Fax No:</td>
<td>0207 620 0790</td>
</tr>
<tr>
<td>Email Address:</td>
<td><a href="mailto:pet-trials@kcl.ac.uk">pet-trials@kcl.ac.uk</a></td>
</tr>
</tbody>
</table>

For all other enquiries please contact the BACCHUS trial team at the UCL CTC.
### APPENDIX 3 – WHO PERFORMANCE STATUS

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>
APPENDIX 4 – COCKCROFT AND GAULT EQUATION

Male = \[
\frac{1.23 \times (140 - \text{Age in years}) \times \text{weight in Kg}}{\text{Serum creatinine (\(\mu\text{mol/l}\))}}
\]

Female = \[
\frac{1.05 \times (140 - \text{Age in years}) \times \text{weight in Kg}}{\text{Serum creatinine (\(\mu\text{mol/l}\))}}
\]
The New York Heart Association (NYHA) functional classification system [85] relates symptoms to everyday activities and the patient's quality of life:

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (Mild)</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea (shortness of breath).</td>
</tr>
<tr>
<td>Class II (Mild)</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.</td>
</tr>
<tr>
<td>Class III (Moderate)</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnoea.</td>
</tr>
<tr>
<td>Class IV (Severe)</td>
<td>Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>
APPENDIX 6 – DOSE CAPPING IN OBESE PATIENTS

For patients who are obese, doses of drugs based on surface area (SA) (5FU, irinotecan, oxaliplatin) will be capped using the following scheme:

<table>
<thead>
<tr>
<th>Patient’s height in cm:</th>
<th>Cap surface area at:</th>
</tr>
</thead>
<tbody>
<tr>
<td>under 150 cm</td>
<td>1.5 m²</td>
</tr>
<tr>
<td>150-159 cm</td>
<td>1.7 m²</td>
</tr>
<tr>
<td>160-169 cm</td>
<td>1.9 m²</td>
</tr>
<tr>
<td>170-179 cm</td>
<td>2.1 m²</td>
</tr>
<tr>
<td>180 cm or taller</td>
<td>2.3 m²</td>
</tr>
</tbody>
</table>

To use this system, calculate the patient’s SA in the normal way, then check against the patient’s height on this table. If the calculated SA is higher than the cap value indicated for that patient’s height, use the cap value instead [86].

**Example 1:** an obese patient 153 cm tall has a calculated SA of 1.95 m². This is more than the SA cap of 1.7 m², therefore prescribe using 1.7 m².

**Example 2:** a large patient 185 cm tall has a calculated SA of 2.25 m². This is lower than the SA cap of 2.3 m², therefore prescribe using 2.25 m².

Please note that this system results in “capped” doses being used for patients of BMI >30 on average, although within each height band shorter patients (e.g. 170-173 cm) are capped at BMI 32-34, and taller patients (e.g. 177-179) are capped at BMI 27-28. Overall, the cap will apply to around 5% of patients in an average oncology practice.
# APPENDIX 7 – CLASSIFICATION OF SURGICAL COMPlications

## Table 1: Classification of Surgical Complications [87]

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.</td>
</tr>
<tr>
<td>Grade II</td>
<td>Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.</td>
</tr>
<tr>
<td>Grade III</td>
<td>Requiring surgical, endoscopic or radiological intervention.</td>
</tr>
<tr>
<td>Grade IIIa</td>
<td>Intervention not under general anaesthesia required.</td>
</tr>
<tr>
<td>Grade IIIb</td>
<td>Intervention under general anaesthesia required.</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Life-threatening complications (including CNS complications) requiring IC/ICU management.</td>
</tr>
<tr>
<td>Grade IVa</td>
<td>Single organ dysfunction (including dialysis).</td>
</tr>
<tr>
<td>Grade IVb</td>
<td>Multi-organ dysfunction.</td>
</tr>
<tr>
<td>Grade V</td>
<td>Death of a patient.</td>
</tr>
<tr>
<td>Suffix “d”</td>
<td>If patient suffers from a complication at the time of discharge (see examples in Table 2). The suffix “d” (for “disability”) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.</td>
</tr>
</tbody>
</table>

1. Brain haemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks
2. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

## Table 2: Clinical Examples of Complication Grades [87]

<table>
<thead>
<tr>
<th>Grade</th>
<th>Organ System</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Cardiac</td>
<td>Atrial fibrillation converting after correction of K⁺-levels</td>
</tr>
<tr>
<td></td>
<td>Respiratory</td>
<td>Atelectasis requiring physiotherapy</td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
<td>Transient confusion not requiring therapy</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Non-infectious diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>Transient elevation of serum creatinine</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Wound infection treated by opening of the wound at the bedside</td>
</tr>
<tr>
<td>Grade II</td>
<td>Cardiac</td>
<td>Tachyarythmia requiring β-receptor antagonists for heart rate control</td>
</tr>
<tr>
<td></td>
<td>Respiratory</td>
<td>Pneumonia treated with antibiotics on the ward</td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
<td>TIA³ requiring treatment with anticoagulants</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Infectious diarrhoea requiring antibiotics</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>Urinary tract infection requiring antibiotics</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Same as for Grade I but followed by treatment with antibiotics because of additional phlegmonous infection</td>
</tr>
<tr>
<td>Grade III</td>
<td>Cardiac</td>
<td>Bradyarythmia requiring pacemaker implantation in local anaesthesia</td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
<td>See Grade IV</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Biloma after liver resection requiring percutaneous drainage</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>Stenosis of the ureter after kidney transplantation treated by stenting</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Closure of dehiscent non-infected wound in the OR³ under local anaesthesia</td>
</tr>
<tr>
<td>Grade</td>
<td>Organ System</td>
<td>Examples</td>
</tr>
<tr>
<td>---------</td>
<td>--------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Grade IIIb</td>
<td>Cardiac</td>
<td>Cardiac temponeade after thoracic surgery requiring fenestration</td>
</tr>
<tr>
<td></td>
<td>Respiratory</td>
<td>Bronchopleural fistulas after thoracic surgery requiring surgical closure</td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
<td>See Grade IV</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Anatomotic leakage after descendorectostomy requiring relaparotomy</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>Stenosis of the ureter after kidney transplantation treated by surgery</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Wound infection leading to eventration of small bowel</td>
</tr>
<tr>
<td>Grade IVa</td>
<td>Cardiac</td>
<td>Heart failure leading to low-output syndrome</td>
</tr>
<tr>
<td></td>
<td>Respiratory</td>
<td>Lung failure requiring intubation</td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
<td>Ischemic stroke/brain hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Necrotizing pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>Renal insufficiency requiring dialysis</td>
</tr>
<tr>
<td>Grade IVb</td>
<td>Cardiac</td>
<td>Same as for IVa but in combination with renal failure</td>
</tr>
<tr>
<td></td>
<td>Respiratory</td>
<td>Same as for IVa but in combination with renal failure</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Same as for IVa but in combination with hemodynamic instability</td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
<td>Ischemic stroke/brain hemorrhage with respiratory failure</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>Same as for IVa but in combination with hemodynamic instability</td>
</tr>
<tr>
<td>Suffix “d”</td>
<td>Cardiac</td>
<td>Cardiac insufficiency after myocardial infarction (IVa–d)</td>
</tr>
<tr>
<td></td>
<td>Respiratory</td>
<td>Dyspnea after pneumonectomy for severe bleeding after chest tube placement (IIIb–d)</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Residual faecal incontinence after abscess following descendorectostomy with surgical evacuation (IIIb–d)</td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
<td>Stroke with sensorimotor hemisyndrome (IVa–d)</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>Residual renal insufficiency after sepsis with multiorgan dysfunction (IVb–d)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Hoarseness after thyroid surgery (I–d)</td>
</tr>
</tbody>
</table>

3 TIA, transient ischemic attached; OR, operating room
APPENDIX 8 – MRI PROTOCOL

Scheduling:

MRI will be performed pre-study, after 3 cycles of neoadjuvant treatment, and then after completion of neoadjuvant treatment, within 4 weeks prior to surgery.

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Neoadjuvant Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Study</td>
</tr>
<tr>
<td>CT chest/abdomen/pelvis</td>
<td>✔</td>
</tr>
<tr>
<td>MRI pelvis</td>
<td>✔</td>
</tr>
</tbody>
</table>

*aAll imaging performed to assess resectability must be reviewed by MDT*

Mandatory MRI sequences:

MRI for locoregional staging and response assessment is mandatory. This should include a T1 axial sequence of the whole pelvis to assess nodes from the aortic bifurcation to the inguinal regions, T2 sagittal, and high resolution T2 axial and coronal sequences centred on the rectal tumour [88]. This will enable anatomical staging of the rectal tumour pre-study and response assessment by RECIST.

<table>
<thead>
<tr>
<th>MRI sequencing</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphological MRI (T1 &amp; T2 sequences)</td>
<td>Mandatory</td>
</tr>
<tr>
<td>Diffusion weighted MRI (DW-MRI)</td>
<td>Strongly Recommended</td>
</tr>
<tr>
<td>Intrinsic susceptibility MRI (ISW or BOLD-MRI)</td>
<td>Recommended</td>
</tr>
<tr>
<td>Dynamic contrast enhanced MRI (DCE-MRI)</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

Additional recommended MRI sequences:

It is widely acknowledged that better imaging tools are required to assess the response of targeted therapy. Options that have been developed for contrast enhanced CT include the addition of enhancement criteria to conventional imaging, e.g. Choi criteria [89]. Potential MRI tools include diffusion weighted (DW) MRI, intrinsic susceptibility weighted (ISW) MRI, and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), which this multicentre study has the expertise to perform.

<table>
<thead>
<tr>
<th>MRI sequence</th>
<th>Biologic property on which this is based</th>
<th>Parameter derived</th>
<th>Pathophysiological correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>DW-MRI</td>
<td>Diffusivity of water</td>
<td>Apparent diffusion coefficient (ADC)</td>
<td>Cell density, tissue architecture, extracellular space tortuosity, cell membrane integrity</td>
</tr>
<tr>
<td>ISW-MRI</td>
<td>Relaxivity of deoxyhaemoglobin versus oxyhaemoglobin: measurement also reflects blood volume, perfusion and intrinsic tissue composition</td>
<td>IAUGC, $K^{trans}$, $K_{ep}$, $V_o$, $V_p$</td>
<td>Vessel density, vascular permeability, perfusion, tissue cell fraction, plasma volume</td>
</tr>
</tbody>
</table>

DW MRI, ISW- MRI and DCE-MRI should be performed during the same MRI examination, where possible, in order to provide comprehensive assessment of the changes in the primary tumour apparent diffusion.
coefficient ADC, R2* and vascular parameters (IAUGC$_{60}$, Kt$^{trans}$, νs, νp) following completion of chemotherapy. These will be correlated with pathological response.

With the use of three sequential MRI scans the patient will serve as their own control. However, it is important that measurements are undertaken on the same MRI scanner, where possible.

**Patient preparation:**

No additional preparation from standard MRI. Nil by mouth for 4 hours prior to a contrast enhanced study.

**Contrast dose for the DCE-MRI sequence:**

0.1 mmol/kg IV for the DCE-MRI

**Archive:**

All MRI data should be archived locally.

**Quality Assurance and Control:**

See section 10 (Quality Assurance and Quality Control)

**Reporting MRI:**

Standardised criteria will be used for reporting the staging MRI as per Royal College of Radiologist guidelines. The staging MRI will be reviewed centrally, independent of the local report. Differences in reporting between the local hospital and the central laboratory will be resolved by consensus.

The additional DW-MRI, ISW-MRI and DCE-MRI sequences will be analysed centrally.

**MRI data transfer for central review:**

Transfer of the anonymised data will be sent to the central laboratory at the Paul Strickland Scanner Centre and King’s College London once all MRI scans have been performed as per agreed protocol.

Sites should send all anonymised data to UCL CTC once all MRI scans have been performed (data will be transferred to King’s College London by UCL Cancer Trials Centre):

BACCHUS Trial Coordinator  
Cancer Research UK & UCL Cancer Trials  
90 Tottenham Court Road  
London W1T 4TJ

**Adverse and Serious Adverse Effects during MRI:**

AEs and SAEs will be recorded and documented by the local investigational team according to the protocol (see section 12, Pharmacovigilance).
APPENDIX 9 – HISTOPATHOLOGY GUIDANCE

1. INTRODUCTION

The guidance below is provided to assist the key role of the histopathologist in the assessment of the excised rectal cancer specimen. This section should be used in conjunction with the BACCHUS Pathology CRF. Refer to section 21 (Ancillary studies) and section 10 (Quality Assurance and Quality Control) of the BACCHUS protocol for details of histopathology samples that will be collected for the trial for future research (optional) and central review (mandatory). Consent will be sought from all patients for the collection and use of their histopathology samples.

Histopathologists at participating sites will be requested to collaborate in the BACCHUS study in the following ways:

- By following the guidance in this appendix
- By submitting and/or facilitating submission of information and specimens for central review (see section 10 Quality Assurance and Quality Control for details)
- By submitting and/or facilitating submission of archival tissue blocks for future tissue-based cancer research (see section 21 Ancillary studies for details)

2. PATHOLOGY DISSECTION

High quality histopathology is a key component of this trial. The pathologist has a key role to play in assessing the circumferential resection margin (CRM), identifying and describing perforations and evaluating the planes of surgery of the mesorectum and the levator/anal sphincter. It is important that the pathologist determines the degree of response to pre-operative therapy, (tumour regression grade), retrieves substantial numbers of lymph nodes (in cases with strong chemotherapy), and confidently identifies extramural venous invasion (EMVI) and peritoneal involvement to the highest standards.

For the TNM staging in this trial, we are using TNM5, not TNM6 or TNM7. This is in line with current RCPath reporting recommendations. This is because of the poor reproducibility associated with the TNM6 definitions of EMVI and lymph nodes, and the introduction of tumour deposits (pN1c) in TNM7, which was based on little evidence with no assessment of interobserver variability. Thus, in this trial, any tumour deposits that are 3mm or larger in size are classed as fully replaced lymph nodes (the so called ‘3mm rule’). Any deposit less than 3mm in size is counted as discontinuous tumour spread. This allows this trial to be consistent with other trials such as the Dutch TME trial and MRC CR07 trial. In order to collect further prospective data on the importance of tumour satellite nodules, we will ask you to separately list within the pathology CRF the number of true lymph nodes identified, the number of true lymph nodes involved by tumour, the number of tumour deposits that are 3mm or greater in size (and therefore would be counted in the final lymph node count in TNM5) and whether or not additional tumour deposits less than 3mm in size are present.

Thank you for your efforts and for participating. The key issues are specimen photography, consistent high quality specimen dissection and providing the slides for scanning to create a permanent record of the pathology.

3. PREPARATION OF THE SPECIMEN AND PHOTOGRAPHY PRIOR TO DISSECTION

The surgeon will be asked to provide information regarding the height of the tumour and its location within the bowel wall on the histopathology request form. This will help the pathologist to identify the tumour and is particularly important in cases showing an excellent response to pre-operative therapy.
The intact resection specimen should be photographed whole prior to opening the bowel and further dissection. It is preferable for the specimen to be submitted fresh from the operating room to the pathology department as soon as possible after resection.

Upon receipt in the pathology department, digital colour photographs should be taken of the anterior and posterior surface of the intact fresh specimen (see example below). It may be advisable, where possible, to ask the surgeon to take photographs of the fresh specimen following resection if this opportunity is likely to be missed in the pathology laboratory.

All photographs must include a metric ruler (for calibration) and the site of the tumour and the high vascular ties should be marked (e.g. with forceps or pre-printed labels). If the tumour location cannot be ascertained by palpation, this should be indicated on the photograph with an additional label.

Additional images of the lateral views (left and right side), close ups of the anterior and posterior surfaces of the levator/sphincters (in abdominoperineal excision specimens), close ups of any perforation site or other defects, and any other unusual findings should also be taken if possible.

The plane of surgery should then be assessed by the local pathologist on the fresh intact specimen (prior to opening) for both the mesorectum and the levator/sphincters (as appropriate). If the specimen is received already fixed in formalin, grading and photography can be done at this stage prior to opening the specimen (although it is preferable to undertake this on the fresh specimen wherever possible). Surgeons should be asked not to open specimens prior to receipt in the pathology department as this can affect the assessment of the surgical planes and the status of the CRM. The grading systems for the planes of surgery are given below (section 4).

After photography and grading of the planes, the specimen can then be opened along the anterior peritonealised surface from the proximal resection margin down to a point approximately 20 to 50 mm above the level of the tumour or down to the level of the anterior peritoneal reflection if the tumour is lower down in the rectum. The mesorectum and bowel wall distal to the tumour should ideally be kept intact, although the distal resection margin can be opened if desired to aid fixation or obtain fresh tissue for local tissue banking. **THE AREA OF THE TUMOUR MUST NEVER BE OPENED AS THIS DESTROYS THE ANTERIOR CRM AND/OR PERITONEUM.** A piece of foam/paper soaked in formalin can be inserted through the tumour if felt appropriate to aid fixation. The specimen should then be pinned out onto a cork board and placed in formalin fixative for approximately 48 hours prior to further dissection. It is acceptable to inflate the specimen with formalin after receipt, leave it to fix and then take the
photographs, but this should always be done before opening the specimen and undertaking any further dissection.

4. **ASSESSMENT OF THE PLANE OF SURGERY**

The planes of surgery in the area of the mesorectum and the levator/sphincters should both be graded separately (where present). Thus for anterior resection specimens there will only be one grade (the grade for the mesorectum). For abdominoperineal excision specimens there will be a grade for the mesorectum and a separate grade for the levator/sphincters. The final specimen grade should always be based on the area of the 'worst' plane of excision.

4.1. **Quality of resection of the mesorectum (all specimens)**

The quality of the mesorectal surface can be determined from the intact specimen and confirmed from the cross-sectional slices. The three-point grading system described below has been used in the MRC CR07 trial [8], MRC CLASICC trial [9] and the Dutch TME/RT [91] study, where poor planes have been shown to predict a higher risk of local recurrence and poorer survival.

<table>
<thead>
<tr>
<th>Plane</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mesorectal (good plane of surgery)</strong></td>
<td>The mesorectum should be smooth with no violation of the fascial covering. There should be a good bulk to the mesorectum both anteriorly and posteriorly, and the distal margin should appear adequate with no coning near the tumour. Any defect should not be more than 5 mm deep.</td>
</tr>
<tr>
<td><img src="image" alt="Mesorectal plane showing shiny fascial covering over the CRM and no defects" /></td>
<td></td>
</tr>
<tr>
<td><strong>Intramesorectal (moderate plane of surgery):</strong></td>
<td>There should be a moderate bulk to the mesorectum with irregularity of the mesorectal surface. Moderate coning of the specimen may be seen towards the distal margin. Importantly, the muscularis propria should not be visible, except at the area of insertion of the levator muscles. Moderate irregularity may be seen at the CRM.</td>
</tr>
<tr>
<td><img src="image" alt="Intramesorectal plane with significant defects into the mesorectum without the muscularis propria being visible (yellow arrow)" /></td>
<td></td>
</tr>
</tbody>
</table>
4.2. Quality of resection of the levator/sphincters (APE specimens only)

The quality of the levator/sphincter area around the anal canal and below the mesorectum needs to be assessed separately in APE specimens.

<table>
<thead>
<tr>
<th>Plane</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Levator</strong></td>
<td>The surgical plane lies external to the levator ani muscles which are removed en bloc with the mesorectum and anal canal. This creates a more cylindrical-shaped specimen with the levators forming an extra protective layer above the sphincters. There should be no significant defects into the sphincter muscles or levators.</td>
</tr>
<tr>
<td><strong>Sphincteric</strong></td>
<td>Either there are no levator muscles attached to the specimen or only a very small cuff, and the CRM is formed by the surface of the sphincter muscles. There should be no deviations into the sphincter muscles themselves. The specimen shows coning at the level of the puborectalis muscle resulting in the classic surgical waist.</td>
</tr>
</tbody>
</table>
5. MACROSCOPIC SPECIMEN DISSECTION

Once photographs of the whole specimen have been taken and the planes of surgery graded (preferably on the fresh specimen but if not on the unopened formalin-fixed specimen), the specimen is then ready to be dissected.

5.1. Assessing for the presence of intra-operative perforations

The specimen should firstly be described in detail, in particular, the pathologist should search for the presence of intra-operative perforations, irrespective of whether these are located at the tumour site (tumour perforation) or in the rest of the bowel away from the tumour (bowel perforation). For perforations that involve the tumour site, it should be specifically stated whether the perforation is in an area covered by peritoneum (TNM stage pT4) or in an area of a surgically created margin e.g. below the peritoneal reflection (RCPath guidelines also recommend staging these cases as pT4 and you should look very carefully for the presence of CRM involvement in the area of perforation). Additionally it is useful to document whether the perforation is above or at the height of the sphincters in APE specimens.

5.2. Relationship of the tumour to the anterior peritoneal reflection

The crucial landmark for recording the height of rectal cancers is the anterior peritoneal reflection. This is identified from the exterior surface of the anterior aspect of the specimen. Rectal cancers are classified according to whether they are (see diagram below):

1. Entirely ABOVE the level of the anterior peritoneal reflection
2. Astride (or AT) the level of the anterior peritoneal reflection
3. Entirely BELOW the level of the anterior peritoneal reflection
5.3. Distance from the tumour to the distal and proximal resection margins

This is measured from the longitudinal cut-ends of the specimen (distal and proximal). It is only necessary to examine the longitudinal margins histologically if tumour extends macroscopically to within 30 mm of one of these. For tumours located further away, it can be assumed that the cut ends are not involved. Exceptions to this recommendation are adenocarcinomas that are found on subsequent histology to have an exceptionally infiltrative growth pattern, show extensive vascular or lymphatic permeation or are undifferentiated carcinomas.

5.4. Inking the specimen

It is recommended that the whole of the CRM (i.e. the non-peritonealised mesorectum and levator/sphincters) is painted with ink (e.g. India ink or silver nitrate) before dissecting the specimen to facilitate the assessment of the CRM. Inking can be done before or after fixation according to local practice. It should be remembered that the CRM only applies to the surgically incised tissue planes and not the peritonealised surfaces. Anteriorly, the upper rectum is covered by peritoneum. Only the area below the peritoneal reflection is at risk of CRM involvement. The mesorectal surface of the CRM is larger posteriorly and extends up to a higher level than it does anteriorly (see diagram below).
5.5. Cross-sectional slicing and photography

The specimen should then be cross-sectioned into slices as thinly as possible (3 to 4 mm thickness is recommended) starting from the distal resection margin to at least the anterior peritoneal reflection or 20 to 50 mm above the tumour if this is higher. These slices should be laid out in order on a board and the cut surface presented to the camera should be consistent in all of the slices (preferably the distal aspect to correlate with MRI scans).

The slices should then be photographed, either as a whole (with additional close ups of individual slices containing the tumour), or alternatively individual photographs of each slice can be taken. It is important that it is made clear on the photographs which slice is the most distal and the most proximal one by using appropriate labels. The photographs must always include a metric ruler scale for calibration.

An example of cross-sectional slicing and photography is given below:

5.6. Assessment of the CRM and maximal extent of spread

The cross-sectional slices should be carefully assessed after photography and the minimum distance of the macroscopic tumour to the inked CRM as well as the maximum depth of tumour invasion beyond the outer muscle coat of the muscularis propria should be recorded. In APE specimens, both the maximal extent of tumour spread beyond the muscularis propria at the level of the mesorectum and additionally the maximal extent of tumour spread beyond the internal sphincters at the level of the levator/sphincters should be recorded.

These macroscopic measurements should be confirmed histologically, preferably on whole mount sections e.g. using the Vernier scale. The minimum distance from the tumour to the CRM should be reported to the nearest millimetre, apart from CRM positive tumours (1 mm or less from the inked CRM), which should be reported to the nearest 0.1 mm. If the position of the muscularis propria and/or internal sphincter is obscured by tumour or fibrosis, the position of these structures should be estimated by comparison to subsequent slices.
5.7. Position of the tumour

The position of the tumour should be accurately noted on the BACCHUS Pathology CRF. This involves documentation of the quadrant of involvement from the cross-sectional slices – i.e. anterior quadrant, posterior quadrant, lateral quadrant or combinations of these. Also it would be helpful to trace the position of the tumour at the point of maximum extension above and below the sphincters in the region of the mesorectum and below the levator/sphincters on the diagrams provided in the CRF (see below for a copy of the CRF diagram).

![Diagram of quadrant involvement](image)

To correlate the position of the tumour with the MRI report, the tumour should be described using a clock-face with the anterior peritoneal reflection being 12 o’clock and looking at the specimen slice from the distal aspect. All positions should be reported from the patients’ perspective to correlate with the MRI.

5.8. Sampling the specimen

If possible, each tumour bearing slice should be processed into a ‘large’ (mega)block to produce whole mount sections. However, it is recognised that this is not possible in all laboratories, and therefore a minimum of five tumour blocks should be taken (either in standard or large cassettes or a combination of both). If using large blocks then sampling different areas of the tumour should still be undertaken with a total of at least 5 blocks if the tumour is big enough. Tumour blocks should be taken to demonstrate the point of deepest tumour invasion, areas suspicious for CRM and/or peritoneal involvement, and areas with possible EMVI. Please see below for the sampling protocol in cases where tumour cells are difficult to find after pre-operative therapy.

All of the lymph nodes within the specimen should be identified, retrieved and assessed, regardless of their site and size. A running mean of at least fifteen is to be expected. The number of positive lymph nodes must be equal to or less than the number of lymph nodes sampled. The apical node (the lymph node closest to the high vascular tie) should be identified and embedded separately to allow staging according to Dukes’ classification. If lymph nodes lie close to or against the CRM then these should be included in the block in such a way that the minimum distance from any tumour to the inked CRM can be assessed.

6. MICROSCOPIC REPORTING

6.1. Peritoneal involvement and venous invasion

Involvement of the peritoneum by tumour should be carefully looked for and is defined as per the definition of Shepherd et al [92] (see figure below). Tumour cells must actually perforate through the serosa and lie on the surface of the specimen. It is expected that on average peritoneal involvement will be present in 10% of rectal cancer specimens.
Venous invasion is defined as involvement of a vascular structure which has smooth muscle in the wall. EMVI can frequently be seen macroscopically as finger like protrusions extending beyond the muscularis propria. If tumour is present close to an artery and the accompanying vein is not visible, then there should be a high level of suspicion for venous invasion. This should be looked for closely as it is often missed. New RCPPath reporting guidelines mandate that pathologists should report the deepest level of venous invasion (extramural, intramuscular or submucosal). On average, it is expected to see venous invasion in greater than 30% of rectal cancer specimens.

6.2. CRM involvement

Involvement of the CRM is defined as viable tumour cells being present at or within 1 mm of the inked CRM. The CRM is at risk not only from direct tumour spread but also metastatic deposits in lymph nodes that lie close to or against the CRM, and through extension along lymphatics, blood vessels and nerves. If the CRM is involved by tumour then the mode of involvement should be stated (e.g. primary spread, lymph node deposit (contained within a lymph node or extra nodal spread), isolated tumour deposit, vascular, lymphatic, perineural etc), as well as the minimum distance between the closest tumour and the CRM. The maximum length of CRM involvement in millimetres should also be estimated in the slice showing the greatest extent of CRM involvement.

If the CRM is free of tumour it should be noted whether there is normal tissue at the margin or whether the margin contains abnormal fibrotic tissue suggestive of tumour regression.

6.3. pT staging of low rectal cancers

The pT staging of cancers above the sphincters is straightforward; however, many low rectal cancers are partly located within the region of the sphincters. The anatomy of the levator/sphincters area is very complex and shows considerable variation between individuals. pT staging of adenocarcinoma in the area of the sphincters is currently controversial. The TNM7 supplement 4 is contradictory over this area of staging due to a misprint. Both TNM6 and TNM7 state that such tumours should be staged as anal cancers according to tumour size. However, in the absence of a robust evidence-based staging system, the only solution is to separately describe the anatomical extent of tumour spread both above the sphincters (in
the area of the mesorectum) and at the height of the levator/sphincters to allow subsequent analysis e.g. submucosal, internal sphincter, intersphincteric space, external sphincter or ischio-anal fat.

6.4. Tumour differentiation

The grade of differentiation of the tumour should be defined by the predominant area of tumour and not on the area of the worst grade. Other types of differentiation, i.e. mucinous adenocarcinomas, signet ring adenocarcinomas and undifferentiated tumours should be documented.

6.5. Lymph node assessment and tumour deposits

As stated in TNM5, extramural tumour deposits measuring ≥ 3 mm in maximum size are counted as involved lymph nodes even if no residual lymph node structure can be identified. Smaller deposits are regarded as apparent discontinuous extensions of the main tumour. The number of ≥ 3 mm tumour deposits classified as lymph nodes should be indicated in the report separately to the number of true lymph nodes. Mucin or fibrosis only within a node should be commented upon in the report as a sign of tumour regression but should not be classed as lymph node metastases.

In the TNM staging system, pN1 corresponds to involvement of 1-3 nodes and pN2 to involvement of 4 or more nodes.

6.6. Preoperative chemotherapy regression scoring – Dworak Method

The Dworak method is recommended and is summarised below [78]. However, it is preferable to use descriptive text rather than a numeric grading system to avoid confusion with other tumour regression grading systems. The final grading should be based on the overall assessment of all tumour blocks (there should be a minimum of five) but should not include the assessment of lymph nodes.

<table>
<thead>
<tr>
<th>Dworak Grading Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>No regression:</td>
</tr>
<tr>
<td>no regression detectable</td>
</tr>
<tr>
<td>Minimal regression:</td>
</tr>
<tr>
<td>dominant tumour mass with obvious fibrosis and/or vasculopathy</td>
</tr>
<tr>
<td>Moderate regression:</td>
</tr>
<tr>
<td>dominantly fibrotic changes with few tumour cells or groups (easy to find)</td>
</tr>
<tr>
<td>Good regression:</td>
</tr>
<tr>
<td>very few (difficult to find microscopically) tumour cells in fibrotic tissue with or without mucin</td>
</tr>
<tr>
<td>Total regression:</td>
</tr>
<tr>
<td>no tumour cells, only fibrotic mass or mucin</td>
</tr>
</tbody>
</table>

6.7. Assessment of specimens where tumour cells are difficult to find

Where tumour cells cannot be found on the first assessment of at least five blocks of tumour, the whole area of the tumour/fibrotic scar should be embedded and examined. If no tumour cells can be seen following assessment of these extra blocks, then three deeper levels should be taken and examined from each tumour/fibrotic scar block. If after these assessments still no tumour cells are identified then the tumour should be considered to have undergone a complete pathological response (TNM stage ypT0, ypN0). Additional levels beyond the above should not be taken as it is important to standardise the degree of effort made to find residual tumour cells.

7. COLLECTION OF PHOTOGRAPHS, TISSUE, AND CASE REPORT FORM

7.1. Photographs

- Photographs of the resection specimen should be taken with a digital colour camera and include:
- The whole intact resection specimen from both the anterior and posterior aspects. Additional lateral views and close ups of the sphincters (if present), any defects or perforations will be helpful. Photographs of the fresh unopened specimen are preferable although fixed specimens are acceptable. The site of the tumour (if palpable) and the closest high vascular tie should be marked (e.g. with pre-printed labels or forceps).

- All of the serial cross-sectional slides in order (3 to 4 mm slices from the distal margin of excision to a level above the tumour). Please mark the proximal and distal slices with labels and indicate the direction if not clear. These can be either taken as one whole image (containing all slices) or sequential images of individual slices (in which case the order should be make explicit using labels e.g. slice 1 (distal), slice 2 (...), ..., slice 12 (proximal)).

  - All photographs must include a metric scale to allow calibration.
  - The whole specimen (or slices) should be visible in the image. A white background is ideal although any plain colour is acceptable. Photographs should be taken directly above the specimen and not at an angle to reduce any distortion artefact.
  - Images should not contain any direct patient identifiers (e.g. name, NHS number) but should be identifiable by trial name (BACCHUS), laboratory number, and patient’s initials, date of birth, and trial number (BAC-###).
  - All images should be copied to CD-ROM and upon request from the UCL CTC sent to:
    
    **Dr Nick West**  
    **Pathology & Tumour Biology**  
    **4th Floor, Leeds Institute of Molecular Medicine**  
    **Wellcome Trust Brenner Building**  
    **St. James’ University Hospital**  
    **Beckett Street**  
    **Leeds LS9 7TF**

If copying the images to a CD-ROM is problematic in your NHS Trust please contact Dr Nick West (n.p.west@leeds.ac.uk) or Professor Phil Quirke (p.quirke@leeds.ac.uk) to explore other alternatives.

7.2. Tissue and histopathology reports

All of the H&E stained glass slides from both the original diagnostic biopsy and the surgical resection specimens should be sent to Leeds for scanning along with a copy of the completed but anonymised histopathology reports upon request by the UCL CTC. Copies of the slides can be cut and sent if the local Site does not want to release the originals. Alternatively high resolution digital slides can be sent if Aperio slide scanning facilities are available locally but please check with Dr Nick West (n.p.west@leeds.ac.uk) or Professor Phil Quirke (p.quirke@leeds.ac.uk) first to ensure that the systems are compatible.

The glass slides will be returned as soon as possible after scanning – this is likely to take around 4-6 weeks. Please package the slides carefully and send to:

**Dr Nick West**  
**Pathology & Tumour Biology**  
**4th Floor, Leeds Institute of Molecular Medicine**  
**Wellcome Trust Brenner Building**  
**St. James’ University Hospital**  
**Beckett Street**  
**Leeds LS9 7TF**

All material forwarded to Leeds should be identifiable by trial name (BACCHUS), laboratory number and patient’s initials, date of birth, and trial number (BAC-###). Any direct identifiers, e.g. patient name and NHS number, should be blanked out. The local laboratory number should remain visible on all slides and blocks as the main identifier if the trial number is not easily included.
7.3. Case Report Form

Please complete the BACCHUS Pathology CRFs using guidance in the protocol. Once completed, please submit the original to UCL CTC and include a copy with the shipment of slides to Pathology & Tumour Biology, University of Leeds (full address above).

8. RETENTION OF TISSUE FOR FUTURE RESEARCH

We would also like one or more block(s) of tumour and one block of normal mucosa from the resection along with the pre-treatment diagnostic biopsy block to allow further molecular study of response to chemotherapy. From the resection, this should preferably be material that is not required for diagnosis locally. In cases with no residual tumour, a block of normal mucosa only is required.

Retention of tissue for future research is optional for BACCHUS patients.

Please see section 21 (Ancillary studies) for further information.

9. CONTACTS

If you have any queries about anything in this histopathology appendix then please direct them to either:

Dr Nick West or Professor Phil Quirke

Email: n.p.west@leeds.ac.uk Email: p.quirke@leeds.ac.uk
Tel: 0113 3438509 Tel: 0113 3438408
APPENDIX 10 – RECIST V1.1

- **Response Evaluation Criteria in Solid Tumours (RECIST) Quick Reference Eligibility** [93]
  Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint.

- **Measurable disease**
  The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

- **Measurable lesions**
  **Tumour lesions** must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable)
  - 20 mm by chest X-ray

  **Malignant lymph nodes**: To be considered pathologically enlarged and measurable, a lymph node must be:
  - ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

- **Non-measurable lesions**
  All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

- **Measurement of lesion**
  All measurements should be taken and recorded in metric notation, using callipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

- **Method of assessment**
  The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluations should always be done rather than clinical examinations unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.
  - **Clinical lesions**: Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm diameter as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.
  - **Chest X-ray**: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on the chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. CT scans of the chest, abdomen and pelvis should be contiguous throughout all the anatomic region of interest (ROI). As a general rule, the minimum size of a measurable lesion at baseline should be no less than double the slice thickness and also have a minimum size of 10 mm. MRI is also acceptable in certain situations (e.g. for body scans). Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, laparoscopy: The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response.

Baseline documentation of “Target” and “Non-Target” lesions

All measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be those that lend themselves to reproducible repeated measurements. On occasion, the largest lesion may not lend itself to reproducible measurement, in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15mm by CT scan. Only the short axis of lymph nodes identified as target lesions contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterise the objective tumour.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases ‘unequivocal progression’ of each should be noted throughout follow-up. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. multiple enlarged pelvic lymph nodes or multiple liver metastases).
### Response Criteria

<table>
<thead>
<tr>
<th>Evaluation of target lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Complete Response (CR):</td>
</tr>
<tr>
<td>* Partial Response (PR):</td>
</tr>
<tr>
<td>* Progressive Disease (PD):</td>
</tr>
<tr>
<td>* Stable Disease (SD):</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evaluation of non-target lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Complete Response (CR):</td>
</tr>
<tr>
<td>* Incomplete Response / Stable Disease (SD):</td>
</tr>
<tr>
<td>* Progressive Disease (PD):</td>
</tr>
</tbody>
</table>

(1) Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

### Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

<table>
<thead>
<tr>
<th>Target lesions</th>
<th>Non-Target lesions</th>
<th>Evaluation of non-target lesions</th>
<th>Overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Incomplete response/SD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.
In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

- **Confirmation of objective response**
  There will be no formal confirmation of objective response. However, in the case of SD, measurements must meet the SD criteria at least once, not less than 6 weeks after study entry.

- **Duration of overall response**
  The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

- **Duration of stable disease**
  SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

  The clinical relevance of the duration of SD varies for different tumour types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

- **Response review**
  For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study’s completion. Simultaneous review of the patients’ files and radiological images is the best approach.

- **Reporting of results**
  All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

  All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

  All conclusions should be based on all eligible patients.
## APPENDIX 11 – QUICK REFERENCE GUIDE TO PATIENT VISITS

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Treatment</th>
<th>Post Trial Tx</th>
<th>Surgery</th>
<th>Follow up (post surgery/chemotherapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycle 1</td>
<td>Cycle 2</td>
<td>Cycle 3</td>
<td>Cycle 4</td>
</tr>
<tr>
<td>Pre Randomisation</td>
<td>Pre Tx</td>
<td>During Tx</td>
<td>Pre Tx</td>
<td>During Tx</td>
</tr>
<tr>
<td>CT Scan¹ (chest/abdo/pelvis)</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI Scan¹ (mandatory)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DW-MRI, ISW-MRI, DCE-MRI (optional)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET Scan</td>
<td>√²</td>
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<td>Medical History</td>
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<td>Con Meds</td>
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<td></td>
</tr>
<tr>
<td>Height/Weight</td>
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<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Neurological Exam</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>√</td>
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</tr>
<tr>
<td>Pulse</td>
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<td></td>
</tr>
<tr>
<td>Blood pressure</td>
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<td>ECG</td>
<td>√</td>
<td>√</td>
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<td></td>
</tr>
<tr>
<td>WHO PS</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New York Heart Assessment (Appendix 5)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
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<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
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<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil (ANC)</td>
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<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
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<td>Creatinine</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
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<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEA</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR</td>
<td>√</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>INR, aPTT</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
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<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma &amp; PBL³</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan (Arm B only)</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5FU</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folinic Acid</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAEs⁴</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE of Special Interest¹¹</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical Complications³</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical Assessment³</td>
<td>√</td>
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</tr>
<tr>
<td>pCR rate³</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Glossary

1. CT Scan: Computed Tomography Scan
2. MRI: Magnetic Resonance Imaging
3. PET Scan: Positron Emission Tomography Scan
4. WHO PS: World Health Organization Performance Status
5. ANC: Absolute Neutrophil Count
6. DCE: Dynamic Contrast Enhanced
7. BACCHUS: Baseline Assessment of Comorbidity, Health Status and Use of Services
8. SAEs: Serious Adverse Events
9. AE of Special Interest: Adverse Events of Special Interest
10. Surgical Complications: Complications Related to Surgery
11. Surgical Assessment: Assessment Related to Surgery

BACCHUS protocol version 5.0, 02/03/2015
Protocol Template FINAL version 2.0 31Jan11
1 **CT/ MRI Scan** – should be repeated at any time during treatment if there is any concern that the patient is progressing whilst on treatment.

2 **PET Scan and DWI/ISW/DCE MRI scans** – not required for eligibility. If not performed prior to randomisation, must be carried out prior to start of cycle 1 treatment. DWI-MRI, ISW-MRI and DCE-MRI scans are not mandatory, however, they are strongly recommended.

3 **Surgical Assessments** – only applicable if the patient had surgery. Surgical assessments not applicable if the patient did not undergo surgery.

4 **Pre cycle 1 assessment** – should only be repeated if pre-randomisation assessments were performed more than 7 days prior to start of cycle 1 treatment, or more than 3 days prior to start of cycle 1 day 1 for adverse events.

5 **Adverse Events** – assessment must be performed and criteria set out in the protocol met before treatment is administered.

6 **Pregnancy Test and ECG** – should be performed if clinically indicated (not mandatory at these timepoints).

7 **Post Surgery CT Scan** – should be performed at least 3 months after surgery, up to 6 months post-surgery as baseline for follow up.

8 **Height/Weight** – weight should be repeated at the timepoints specified. Height does not need to be repeated if taken pre-randomisation.

9 **Plasma & PBL** – section 21, an additional sample should also be taken if the patient relapses (at any timepoint).

10 **Serious Adverse Events** - all SAEs that occur between the date the consent form is signed and 30 days after last drug administration, or after this date if the investigator feels the event is causally related to trial treatment) should be reported within 24 hours of becoming aware of the event.

11 **Adverse Events of special interest** - Refer to Protocol section 12.2.7 for a list of Adverse Events of special interest that require urgent reporting on an SAE report within 24 hours of becoming aware of the event, even if they do not meet the definition of “serious”.
APPENDIX 12 – TREATMENT MODIFICATIONS

Refer to the relevant sections of the protocol specified below for specific treatment or dose modifications guidance according to adverse events:

<table>
<thead>
<tr>
<th>Event</th>
<th>Bevacizumab</th>
<th>Oxaliplatin</th>
<th>5FU/Folinic Acid</th>
<th>Irinotecan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute cholinergic syndrome</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>8.6.7</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>8.6.14</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Cold–related dyseaesthesia</td>
<td>none</td>
<td>8.6.3</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>none</td>
<td>100%</td>
<td>8.6.2</td>
<td>8.6.2 &amp; 8.6.8</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>none</td>
<td>8.6.2</td>
<td>100%</td>
<td>8.6.2</td>
</tr>
<tr>
<td>Haemorrhagic event</td>
<td>8.6.16</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Hepatobiliary function (ALT/AST, Bilirubin)</td>
<td>none</td>
<td>8.6.11</td>
<td>8.6.11</td>
<td>8.6.11</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td>none</td>
<td>8.6.4</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8.6.12</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Laryngopharyngeal dyseaesthesia</td>
<td>none</td>
<td>8.6.3</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Mucositis Oral</td>
<td>none</td>
<td>100%</td>
<td>8.6.2 &amp; 8.6.9</td>
<td>100%</td>
</tr>
<tr>
<td>Myocardial infarction or acute coronary syndrome</td>
<td>8.6.2</td>
<td>8.6.2</td>
<td>8.6.2</td>
<td>8.6.2</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>none</td>
<td>8.6.6</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Necrotising Faciitis</td>
<td>8.6.19</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>none</td>
<td>8.6.1</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Neutropenia (&gt; 5 days)</td>
<td>none</td>
<td>8.6.2</td>
<td>100%</td>
<td>8.6.2</td>
</tr>
<tr>
<td>Palmar-Plantar Erythrodysesthesia</td>
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<td>8.6.1</td>
<td>8.6.1</td>
<td>8.6.1</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>none</td>
<td>8.6.3</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>8.6.13</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>none</td>
<td>8.6.5</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Renal impairment (Serum Creatinine, GFR)</td>
<td>8.6.10</td>
<td>8.6.10</td>
<td>8.6.10</td>
<td>8.6.10</td>
</tr>
<tr>
<td>Event</td>
<td>Bevacizumab</td>
<td>Oxaliplatin</td>
<td>5FU/Folinic Acid</td>
<td>Irinotecan</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>------------------</td>
<td>------------</td>
</tr>
<tr>
<td>RPLS</td>
<td>8.6.17</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Surgical procedure/ wound healing</td>
<td>8.6.18</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>none</td>
<td>8.6.2</td>
<td>100%</td>
<td>8.6.2</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>8.6.15</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>

**Treatment Modifications Guidance** – where specific guidance for dose and treatment modification has been provided for any chemotherapy agent, refer to the section specified for further detail of modification.

**No Treatment Modifications Guidance** – if there is no guidance available pertaining to a chemotherapy agent this has been indicated as “none”.

**No Treatment Modifications** – where specific sections pertaining to dose/treatment modification indicate treatment should be given at full dose for the specified chemotherapy agent (i.e. no modifications) this has been indicated as “100%”.
APPENDIX 13 – EXPECTED ADVERSE EVENTS

AEs Expected for the Treatment Regimens

Certain AEs are expected for the FOLFOX and FOLFOXIRI treatment regimens (see references [11, 12, 46-48, 62, 63, 66, 94]).

FOLFOX (Fluorouracil, Folinic Acid and Oxaliplatin)

The following AEs are commonly associated with the FOLFOX regimen and will be considered expected for each of the trial drugs:

- Abdominal pain
- Allergic reaction
- Alopecia
- Anaemia
- Anorexia (Grade ≤ 3)
- Cardiac disorders (e.g. arrhythmias, heart failure, ischemia)
- Constipation (Grade ≤ 3)
- Decreased platelet count
- Dehydration
- Diarrhoea
- Dysaesthesia
- Fatigue
- Febrile neutropenia
- Fever (Grade ≤ 3)
- Mucositis oral (Grade ≤ 3)
- Nausea
- Neuropathy – peripheral and sensory
- Neutrophil count decreased
- Neutrophil count decreased with infection
- Pain
- Paresthesia
- Skin NOS (inc. Palmar-plantarerythrodysesthesia syndrome)
- Thromboembolic events (thrombosis and embolism)
- Vomiting

FOLFOXIRI (Fluorouracil, Folinic Acid, Oxaliplatin and Irinotecan)

The following AEs are commonly associated with the FOLFOXIRI regimen and will be considered expected for each of the trial drugs:

- Mucositis oral (Grade ≤ 4)

AEs Expected for Individual IMPs

Where the event does not appear in the above lists of expected AEs for the treatment regimens, the most recent SPC for 5-fluorouracil, oxaliplatin and irinotecan will be checked.
## APPENDIX 14 – PROTOCOL VERSION HISTORY

<table>
<thead>
<tr>
<th>Version no.</th>
<th>Date</th>
<th>No.</th>
<th>Section no.</th>
<th>Summary of main changes from previous version.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>25/06/12</td>
<td>-</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
| 2.0         | 06/12/2013 | 4   | Front Cover + Section 19 | Clinicaltrials.gov number inserted  
1.1 Planned number of Sites increased  
1.1 and 6.3 Clarified/emphasised in the inclusion criteria that TNM5 will be used as mentioned elsewhere in the protocol.  
3.4 Detail of translational samples removed from this section  
5 Detail added about Sites responsibility to ensure patients give fully informed consent.  
6.1 Changed from “race” to “ethnicity” in the pre-randomisation assessments.  
6.3 and 7.1 Updated the randomisation procedures as randomisations will be by fax  
6.3.1 Updated the inclusion criteria as part of the sentence had been missed off - T3 tumour must be ≥2 mm from the mesorectal fascia.  
6.3.1 Changed the inclusion criteria for proteinuria  
6.3.1 and 6.3.2 Changed the units for haemoglobin measurements from g/dL to g/L (eligibility has not changed).  
6.3.2 Added to the exclusion criteria that patients with New York Heart Association Classification ≥III are ineligible.  
8.2 Added a note that dose banding is not permitted.  
8.4.1 An additional form (IMP deviation form) was added as an additional form to complete and fax to CTC upon identification of a temperature excursion.  
8.5.1 Clarification to the principles of AE management for bevacizumab and FA.  
8.6 Additional detail added and clarifications made to the section on the Management of AEs  
8.6.19 Recommendations for the management of Necrotising fasciitis were added following updated safety information received regarding bevacizumab  
9.2 and 9.4 Moved the assessment of CVAD from the surgical assessment section (9.4) to the assessment during treatment section (9.2) and removed a few CVAD related data that will not need to be captured on the CRFs.  
9.3 Removal of a sentence regarding urinalysis prior to bevacizumab as it is not applicable in this section at the end of treatment.  
9.5 Clarified that follow-up will be for up to 42 months after randomisation.  
10 A QA Section was added to summarise all the QA involved in the trial  
11.2 and 11.5 Updates to the Data management section in line with the updated DM SOP.  
12.2.8 An additional exemption from SAE reporting was added.  
14.1 Update to the central monitoring section in line with the updated central monitoring SOP. |
<table>
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<th>Date</th>
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<tr>
<td>3.0</td>
<td>11/07/2014</td>
<td>7</td>
<td>Change to TMG membership</td>
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<td>6.1</td>
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<td>Assessment of New York Heart Association Classification added</td>
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<td>6.3.1</td>
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<td>Increased the upper age limit of patients for the inclusion criteria</td>
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<td>7.1</td>
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<td>Clarification to the CRFs required for randomisation</td>
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<td>NIMPs put in alphabetical order. No NIMPs added/removed,</td>
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<tr>
<td>8.9</td>
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<td>A new section added to the protocol for DPD deficiency</td>
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<tr>
<td>9.3</td>
<td>And Appendix 11</td>
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<td>Removed assessment of urinalysis at post treatment time-points as it is only required to assess whether patients are fit to receive bevacizumab</td>
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<td>9.5</td>
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<td>Clarification to timing of follow-up assessments</td>
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<td>10.3</td>
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<td>Pathology CRF no longer needs to be sent with tumour samples to the central laboratory in Leeds.</td>
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<tr>
<td>10.3.1</td>
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<td>Pathology samples will now be sent to the central laboratory in Leeds upon request (and not as soon as they are available as previously)</td>
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<td>12.2.7</td>
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<td>Clarification to procedure for reporting Adverse Events of Special Interest</td>
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<td>Appendix 5</td>
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<td></td>
<td>A reference was added</td>
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<td>Pre-surgery assessments added to the table</td>
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<td>Other minor formatting, clarifications and corrections</td>
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<tr>
<td>4.0</td>
<td>14/11/2014</td>
<td>10</td>
<td>Inclusion Criteria changed to include patients with T4b tumours that involve or threaten the peritoneal surface</td>
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<td>Exclusion criterion changed from “Previous treatment with bisphosphonates” to “Concurrent use of bisphosphonates”</td>
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<td>8.8</td>
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<td></td>
<td>Bisphosphonates added to list of concomitant medications</td>
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<td>Appendix 2</td>
<td></td>
<td></td>
<td>Clarification to PET reporting procedures: PET/CT worksheet to be completed for each patient</td>
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<tr>
<td>Appendix 9</td>
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<td>Information about new RCPass reporting guidelines added</td>
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<td>1.1</td>
<td><strong>Summary section update to reflect the Main inclusion criteria and Main exclusion criteria changes</strong></td>
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<td>6.3.1</td>
<td>Inclusion criteria changed to clarify</td>
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<td>T3 tumours extending (≥ 4 mm), beyond the muscularis propria N0–N2</td>
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<td>Tumours (involving or threatening the peritoneal surface)</td>
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<td>OR presence of macroscopic extramural venous invasion (V2 disease)</td>
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<td></td>
<td>AND for tumours below the peritoneal reflection, the primary tumour or involved lymph node (on MRI) must be &gt;1 mm from the mesorectal fascia</td>
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<td>6.3.2</td>
<td>Exclusion criterion regarding circumferential resection margins removed from exclusion criteria</td>
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<td>Change to Fax Number</td>
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