EXCITE

EXCITE: Erbitux, Xeloda, Campto, Irradiation Then Excision for locally advanced rectal cancer (North West/North Wales Clinical Oncology Group-04 on behalf of the NCRI rectal cancer subgroup)

A phase II trial from the North West/North Wales Clinical Oncology Group on behalf of the NCRI rectal cancer subgroup examining the toxicity and efficacy of Cetuximab, Capecitabine and Irinotecan in combination with radiotherapy as preoperative downstaging treatment for MRI-defined locally advanced rectal cancer

Final protocol
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Protocol Version 4.3 authorised by:	**Signature**	**Date**
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For the Sponsor: Prof Jonathan Ledermann, Director, CR UK & UCL CTC	.....	.....
Sandy Beare, Tumour Group Lead	.....	.....

GENERAL INFORMATION

This document describes the EXCITE trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the GI Trials Coordinator at the CR UK & UCL Cancer Trials Centre (CTC) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the CTC in the first instance.

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1.1 Summary of trial design

Aims: To assess the downstaging effectiveness and tolerability of preoperative chemoradiotherapy (CRT) using capecitabine/irinotecan/cetuximab plus radiotherapy.

Subjects: Patients will have been diagnosed with biopsy-confirmed adenocarcinoma of the rectum with MRI staging indicating that a primary surgical resection would be unlikely to achieve clear margins.

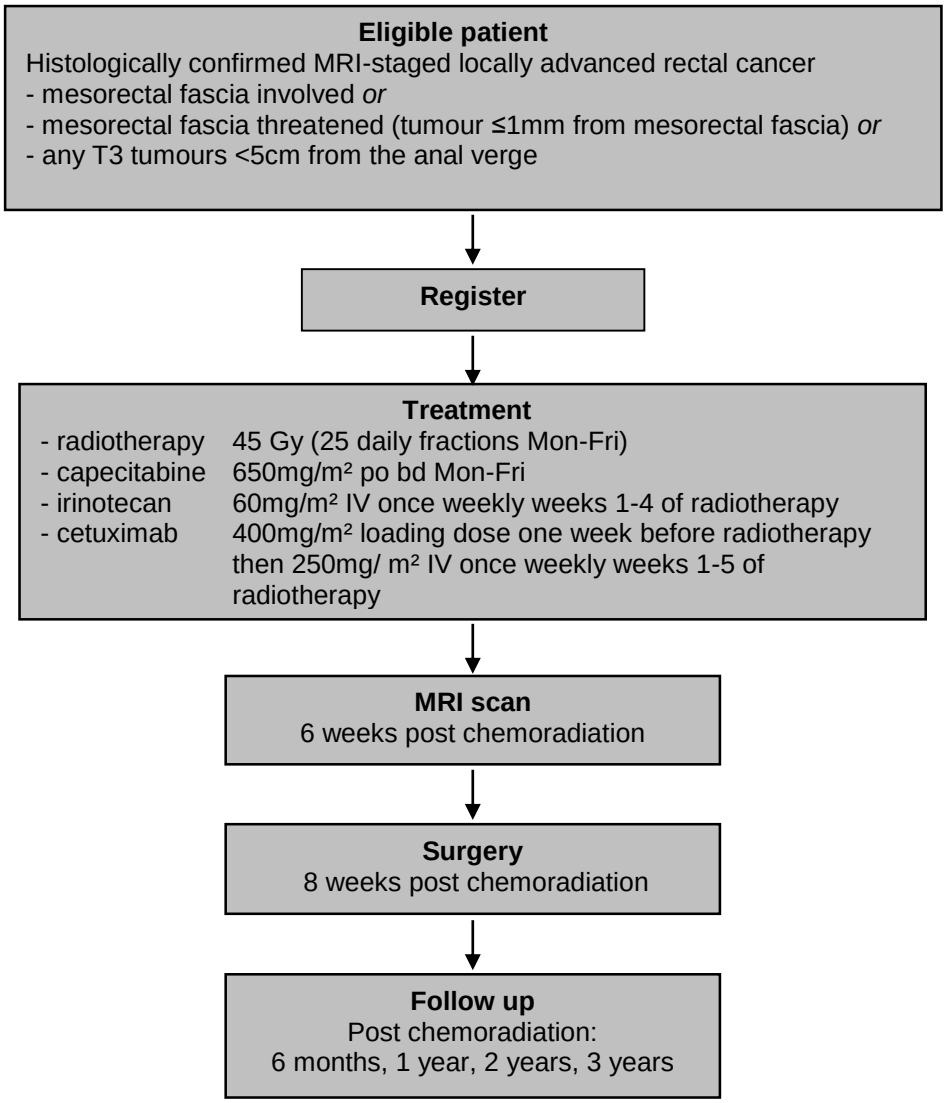
Primary endpoint:	histologically confirmed R0 resection rate
Secondary endpoints:	radiotherapy compliance
	grade 3 or 4 toxicity
	pathological complete response
	morbidity – post operative and long term
	disease-free survival and local failure-free survival

Treatment summary: Patients will be treated with pelvic radiotherapy to a planned volume at a dose of 45 Gy in 25 daily fractions of 1.8 Gy treating 5 days per week from Monday-Friday for five weeks in total.

Concurrently they will receive oral capecitabine at 650 mg/m^2 bd for 5 days per week on the days of radiotherapy only. In addition they will receive IV irinotecan at 60 mg/m^2 once per week during the 1st, 2nd, 3rd and 4th weeks of radiotherapy. In addition, they will receive a loading dose of IV cetuximab at 400 mg/m^2 one week before the commencement of radiotherapy then at 250 mg/m^2 once per week during the 1st, 2nd, 3rd, 4th and 5th weeks of radiotherapy.

Six weeks post completion of chemoradiation (CRT) patients will receive an MRI scan to judge response. At eight weeks post CRT patients will undergo surgery.

1.2 Trial schema



1.3 Treatment schedule

Week	1	2	3	4	5	6
	Day 1 (7 days before RT)	Days 8*-12	Days 15-19	Days 22-26	Days 29-33	Days 36-40
Radiotherapy: 45Gy/25#		• • • • •	• • • • •	• • • • •	• • • • •	• • • • •
Cetuximab 400mg/m^2 iv	•					
Cetuximab 250mg/m^2 iv		•	•	•	•	•
Irinotecan 60mg/m^2 iv		•	•	•	•	
Capecitabine 650mg/m^2 bd		• • • • •	• • • • •	• • • • •	• • • • •	• • • • •

**Day 8 is first day of radiotherapy*

2 Introduction

2.1 Background

Rectal cancer affects 10,000 new patients and causes 4,700 deaths each year in England and Wales. Historically a high risk of local recurrence has been recorded for patients treated with surgery alone. In particular, approximately 20% of patients present with disease with T3/T4 tumour which is partially or totally fixed and which has a high risk of involved resection margins and recurrence if surgery is attempted.

Local recurrence can be reduced with improvement in surgical technique through the adoption of the procedure of total mesorectal excision (TME) [Heald ’92, Kapiteijn ‘01].

Local recurrence can also be reduced with the use of pelvic radiotherapy. There is a clear established role for the use of adjuvant radiotherapy in resectable rectal cancer. Two meta-analyses [Camma 2000, Colorectal Cancer Collaborative Group ‘01] have demonstrated a significant reduction in local recurrence and improvement in cancer specific survival. This evidence base consists of 8500 patients in 28 randomised trials [Colorectal Cancer Collaborative Group ‘01].

A short-course (typically a one week course) of preoperative pelvic radiotherapy reduces the rate of local recurrence of operable rectal cancer [Kapiteijn ‘01, Sebag-Montefiore ‘06]. However, this has no benefit if the circumferential resection margin (CRM) is contaminated with tumour (within a millimetre of the CRM) [Nagtegaal ’02, Kapiteijn ‘01].

Long-course preoperative radiotherapy (typically a five week course) used concurrently with chemotherapy can also reduce local recurrence. Recent trials have established that pre-operative fluoropyrimidine concurrent chemoradiotherapy (CRT) is superior to long course RT alone [Bosset ‘06, Gerard, 05] and that pre-operative CRT is superior to post-operative CRT [Sauer ‘04].

2.2 Magnetic Resonance Imaging staging of rectal cancer

In the UK, pelvic MRI has become the standard method of staging rectal cancer pre-operatively and is routinely used to select patients for pre-operative CRT. The accuracy of pelvic MRI has been demonstrated in a large multi-centre UK led international prospective study (MERCURY) [MERCURY Study Group ‘06]. The impact of this and preceding smaller studies [Beets-Tan ’01, Bissett ’01, Botterill ’01, Brown ‘03] has changed UK practice with MRI being used in many centres to define potentially involved surgical CRM.

High quality histopathological examination of resected rectal cancer specimens has become standard in the UK on the back of the CR07 trial [Sebag-Montefiore ‘06] with the CRM status being used to predict the risk of both local recurrence and survival. Research by Quirke and colleagues [Quirke ‘86] in Leeds demonstrated that the CRM is the most important histopatholgical factor that predicts outcome. A clear CRM (>1mm microscopic clearance from tumour to the CRM) is associated with a lower risk of local recurrence and improved survival. These findings have been confirmed in a large national population based audit [Wibe ‘02], and in three phase III trials (CLASSIC [Guillou ‘05], MRC CR07 [Sebag-Montefiore ‘06] and the Dutch rectal cancer trial [Kapiteijn ‘01]). Recent data confirms that CRM status is also reliable in predicting outcome when assessed after pre-operative CRT [Sebag-Montefiore ‘05]. In addition the prospective grading of the surgical resection specimen is shown to significantly influence the risk of local recurrence in the MRC CR07 trial [Quirke ‘06].

2.3 Single agent 5-Fluorouracil as a radiation sensitiser

Until recently, a single agent fluoropyrimidine was used as the radiation sensitiser in preoperative long-course downstaging radiation regimens (Sauer ’04, Bosset ’06).

Retrospective data on 677 patients treated in 6 UK centres with pre-op 5FU CRT is available [Sebag-Montefiore, 05] to calculate the expected outcome measures for the standard arm. This data demonstrates that 13% of patients have complete sterilisation of the resected specimen (pCR) and 55-60% of patients obtain an uninvolved (CRM negative) resection margin (using the number of patients who commenced CRT as the denominator). The important causes of failure include:- the primary tumour is unresectable, a palliative resection is performed and the development of distant metastases (all these events are captured within a disease free survival end point). This data clearly demonstrates the need to improve outcome in this patient group,

2.4 Capecitabine as a radiation sensitiser

Capecitabine (Xeloda^{TM}) is an oral tumour-activated fluoropyrimidine. The preferential conversion to 5-FU at the tumour site exploits the higher levels of thymidine phosphorylase found in tumour cells compared to normal cells.

Two large randomised phase III trials have compared capecitabine against low dose leucovorin and 5FU in patients with advanced or metastatic colorectal cancer. Patients

treated with capecitabine achieved a superior response rate. There was no evidence of a difference in time to progression and overall survival in the two groups.

Capecitabine potentially offers a therapeutic advantage over 5FU in a chemoradiation schedule. The activating enzyme thymidine phosphorylase is found at a level four times higher in tumours than in normal tissues. In a small study where patients were given capecitabine for seven days prior to surgery, the levels of 5FU in the tumour were 3.4 times higher than in normal colonic mucosa [Sculler, 00]. In addition in cell lines thymidine phosphorylase is itself upregulated both by radiation [Sawada, 99] and other cytotoxic drugs such as mitomycin and paclitaxel. In clinical studies TP has been shown to be over-expressed in 100% of regional lymph nodes and 82% of primary rectal cancers. At 7 days TP is further over-expressed in 76% of rectal cancer patients with over-expression 4.3 times compared to pre-irradiation values [Yoon, 01].

Phase I dose finding studies have been performed using capecitabine combined with radiation by [Dunst '02] and [Ngan '02] with recommended doses of 825mg/m^2 bd continuously and 900mg/m^2 bd five days per week respectively. Further phase II studies have used the continuous regimen [Glynne-Jones et al '06] and demonstrate similar efficacy, toxicity and compliance to intravenous 5FU CRT regimens.

2.5 Chemoradiation with capecitabine and irinotecan

A number of groups have evaluated this combination (reviewed in Glynne-Jones et al ,06). Klautke updated experience with irinotecan (Campto™) and capecitabine at ASCO 2006 [Klautke, 06]. Acceptable toxicity was reported for a capecitabine regimen of 750mg/m^2 bd for weeks 1-3 and 4-5 combined with irinotecan 50mg/m^2 weekly (n=20) and 60mg/m^2 (n=11) weekly x6 combined with 50.4Gy +/- boost of 5.4Gy. Mitchell et al (2006) have also reported early results using a regimen of capecitabine 625mg/m^2 bd continuous with irinotecan 50mg/m^2 weekly x 4 and 50.4Gy with 3(27%) patients achieving pCR.

Kennedy et al (2002) delivered radiotherapy using 54 Gy as preoperative downstaging treatment in rectal cancers. Patients received weekly infusions of irinotecan at 50 mg/m^2/week. In addition, they received capecitabine at 500 mg bd, 650 mg bd or 1,000 mg bd on radiotherapy days. The Maximum Tolerated Dose (MTD) had not been reached at a dose of 1,000 mg bd of capecitabine. All patients were staged uT3 or uT4 prior to chemoradiation. All were downstaged by at least one T-stage and there was one pCR.

In the UK, the NWCOG completed recruitment to a larger phase I/II study in December 2006. There were 100 patients in the phase II element of the study. Initial phase II data were presented at ASCO 2006 [Gollins et al,'06]. 56 patients were treated at the recommended dose level (Irinotecan 60 mg/m^2 weekly weeks 1,2,3,4 plus capecitabine 650 mg/m^2 bd po 7 days per week during the 5 weeks of radiotherapy). Fourteen (25%) of these developed a grade 3 or 4 toxicity. Most were grade 3. Nine (20%) of these were diarrhoea (8 grade 3, one grade 4); two were lethargy (both grade 3); one was febrile neutropenia (grade 3). At the recommended dose the mean amount of the intended dose received of radiotherapy, irinotecan and capecitabine are 97%, 92% and 86% respectively. An analysis of efficacy is based on the 81 patients in both the phase I and phase II components. Seven (9%) did not undergo resection, two developed liver metastases, four deteriorated in terms of general condition and one died of pneumonia. Seventy four (91%) underwent resection, of which 65 were CRM negative [80% intention to treat], 19 (29%) had a complete pathological response (pCR) and11 (17%) had microfoci of disease only (scattered individual cells).

2.6 Rationale for the Use of Epidermal Growth Factor Receptor (EGFR) Inhibitors

The EGFR is a commonly expressed transmembrane glycoprotein of the tyrosine kinase growth factor receptor family. EGFR is expressed in many normal human tissues, and activation of this proto-oncogene results in over expression in many types of human tumours. As a transmembrane glycoprotein, the extracellular domain of the EGFR is a ligand-binding site for transforming growth factor alpha (TGFα) and epidermal growth factor (EGF). Upon ligand binding, the intracellular domain of EGFR is activated, thereby triggering cellular mechanisms that regulate cell growth. EGFR is overexpressed in approximately four fifths of colorectal cancers [Cunningham, '04].

Monoclonal antibodies to EGFR block the ligand-binding site, and have been shown to inhibit proliferation of cells that produce both TGFα and EGF [Baselga et al '93]. The effects of EGFR blockade on cell cycle progression have been investigated in several human cell types, including DiFi colon adenocarcinoma cells, non-transformed breast epithelial MCF10A cells, A431 squamous epithelial carcinoma cells, and DU145 prostatic cancer cells. These studies suggest that blocking EGFR with monoclonal antibodies such as cetuximab leads to cell cycle arrest in G1 which is accompanied by a decrease in cyclin dependent kinase (CDK) 2 activity, and an increase in the expression of CDK inhibitor p27^{KIP1} [Fan '97]. In addition to inducing G1-phase arrest, EGFR blockade was also shown to lead to cell death via apoptosis in DiFi colon adenocarcinoma cells [Wu '95].

2.7 Cetuximab

Cetuximab (Erbitux™) is an antibody of the IgG1 subclass, created by chimerisation of the murine monoclonal antibody M225. The chimerisation process resulted in an antibody with binding affinity to EGFR greater than the natural ligand EGF [Kawamoto '83]. Cetuximab blocks binding of EGF and TGFα to EGFR and inhibits ligand-induced activation of this tyrosine kinase receptor. Cetuximab also stimulates EGFR internalization, effectively removing the receptor from the cell surface for interaction with ligand [Baselga '93].

Phase II studies have evaluated the combination of cetuximab and irinotecan in patients with metastatic colorectal cancer. Patients with colorectal cancer were treated with an initial dose of cetuximab of 400 mg/m^2, followed by weekly doses of 250 mg/m^2, and irinotecan at the same dose and schedule on which the patient had previously been treated [Saltz '02]. The second trial used irinotecan, 125 mg/m^2, 5-FU, 500 mg/m^2, and LV, 20 mg/m^2, administered weekly for 4 weeks, followed by a 2-week rest period [Rosenberg '02]. Both studies show the combination of cetuximab and irinotecan has antitumour activity in this population.

The BOND study randomized 329 patients with CRC, who had progressed on irinotecan based chemotherapy and were EGFR positive. Patients received either cetuximab alone or in combination with the same irinotecan-containing regimen that the patients had progressed on. Despite the fact that the majority had been heavily pre-treated, this study confirmed an impressive response rate for the combination of 22.9% versus 10% for the cetuximab alone. The time to progression was also significantly increased on the combination arm (4.1 versus 1.5 months) [Cunningham '04]. As a single agent, cetuximab has a 10% response rate in heavily pre-treated patients [Cunningham '04].

KRAS is a molecule involved in the intracellular signaling pathway of the EGFR and it has been demonstrated that in the context of metastatic colorectal cancer, patients whose tumour is KRAS wild type demonstrate an increased response rate and progression free survival when cetuximab is added to conventional chemotherapy, compared with chemotherapy alone. The minority of patients whose cancers are KRAS mutant and thus constitutively activated (35-40% of cancers) do not (Van Cutsem,'08). Subsequent retrospective analysis showed that cetuximab combined with 5FU and irinotecan demonstrated a significant overall survival advantage in KRAS wild-type cancers compared to 5FU/irinotecan alone within the phase III CRYSTAL trial [Van Cutsem 2009] and an

advantage in disease-free survival (DFS) when added to 5FU/oxaliplatin within the phase II OPUS trial [Bokemeyer 2009]. Both trials demonstrated significantly increased tumour response rates. Likewise the recently-reported phase III PRIME trial showed an improvement in progression-free survival when the fully human anti-EGFR monoclonal antibody panitumumab was added to 5FU/oxaliplatin [Douillard 2009]. No advantage is seen in these trials of adding an anti-EGFR antibody in KRAS mutant cancers.

The molecule BRAF is intimately involved in the KRAS signalling pathway and there are similar indications (though at an earlier stage in terms of clinical trial investigation) that the benefit of adding anti-EGFR therapy is confined to patients with BRAF wild type cancers [Di Nicolantonio 2008].

Recent NICE guidance has approved the use of cetuximab in combination with FOLFOX or FOLFIRI in unresectable KRAS wild-type cancer confined to the liver [NICE Technology Appraisal Guidance176, August 2009].

In contrast to all hitherto reported studies, recently-presented data from the COIN trial (Maughan 2009) failed to demonstrate any advantage in adding the anti-EGFR monoclonal antibody cetuximab to fluoropyrimidine/oxaliplatin in the first line treatment of patients with KRAS wild type metastatic colorectal cancer. One possible reason might be reduced dose intensity in the majority of patients who received capecitabine because of enhanced toxicity with cetuximab (Adams 2009) but further analysis is being carried out.

2.8 Current evidence of efficacy of cetuximab in combination with radiotherapy.

Preclinical data suggests that EGFR inhibition influences radio-responsiveness [Saleh ‘99, Bianco ‘00, Bonner ‘00] and that there may be a synergistic reaction between radiotherapy and cetuximab in squamous cell carcinomas of the head and neck [Huang ‘00]. Phase I studies have shown cetuximab can be administered safely in combination with radiotherapy in head and neck cancer [Robert ‘01]. In addition, in head and neck cancer the combination of cetuximab and radiation does not impair surgical wound healing as compared with patients who received radiation alone [Harari, 03]. A large multicentre randomised phase III study (CP02-9815) in locally advanced head and neck cancer comparing radiation alone versus radiation therapy plus treatment concurrently with the monoclonal anti-EGFR antibody cetuximab was carried out by Bonner et al [Bonner ‘06].

Four hundred and twenty four patients with locoregionally advanced squamous cell carcinoma of the head and neck were randomly assigned to receive radical radiotherapy

with or without the addition of cetuximab [Bonner ‘06]. The cetuximab was given as an initial loading dose of 400 mg/m^2 one week prior to commencing radiotherapy and then weekly at 250 mg/m^2 once a week during the six or seven-week course of radiotherapy. There was a marked increase in locoregional control for patients treated with cetuximab versus those who did not (24.4 m versus 14.9 m). There was also an increase in median overall survival from 29 to 49 months in favour of those receiving cetuximab. The incidence of toxicity did not differ between the two groups with the exception of acneform rash more commonly in the cetuximab-treated patients [Bonner ‘06].

It is possible that concurrent cetuximab may act as a radiation sensitizer in the down staging chemoradiation of locally advanced rectal. A phase I/II trial in 40 patients using a loading dose of cetuximab at 400 mg/m2 followed by cetuximab 250 mg/m2 weeklyplus capecitabine at 825 mg/m2 Mon-Fri through RT showed a 5% pCR rate [Machiels,’07].

A study of 40 rectal cancer patients receiving an initial loading dose of three, weekly cycles of cetuximab followed by weekly cetuximab/5FU concurrent with RT, demonstrated an 8% pCR rate in resected specimens [Bertolini ’09].

A phase I trial delivering 50.4 Gy of RT with concurrent cetuximab/irinotecan/capecitabine demonstrated a 25% pCR rate [Hofheinz ‘06]. The subsequent phase II trial in 50 patients using cetuximab (400 mg/m2 Day 1, 250 mg/m2 Days 8, 15, 22, 29), weekly irinotecan 40 mg/m2 x 6 and capecitabine 500 mg/m2 twice daily (Days 1–38) concurrently with RT to a dose of 50.4 Gy and demonstrated an 8% pCR rate [Horisberger ‘09].

One study suggested that greater tumour regression occurred in KRAS wild type than mutant tumours and in tumours with higher EGFR nuclear gene copy number [Bengala ‘09]. In contrast, a recent study in 38 patients did not detect a relationship between histological response and KRAS status [Debucquoy ‘09]. In the latter study it was proposed that an anti-proliferative effect of cetuximab was responsible for a reduced capecitabine uptake and consequent low rate of pCR [Debucquoy ‘09]. Further work on molecular profiling and biomarkers is required in this area in larger numbers of patients and including longer-term survival outcomes.

2.9 Proposed trial

The regimen of irinotecan and capecitabine used in addition to radiotherapy in a CRT regimen for downstaging locally advanced rectal cancer has been studied within the UK NWCOG-2 (RICE) trial. Within this trial the recommended phase II dose of radiotherapy at 45 Gy in 25 daily fractions, oral capecitabine at 650 mg/m^2 bd taken 7 days per week and

irinotecan at 60 mg/m^2 iv weeks 1,2,3 and 4 [Gollins '09], has now been used in 96 patients in the phase II element of the trial.

It is clearly of interest to study the effects of a biological agent on top of conventional chemotherapy as a radiation sensitiser. Cetuximab is the only agent of proven worth as a radiation sensitiser in a randomised trial, in the context of head and neck cancer [Bonner '06]. It may be the case that in the context of rectal cancer the triplet sensitising regime of capecitabine, irinotecan and cetuximab confers an additional advantage compared to capecitabine and irinotecan alone and could be included in a future phase III trial. It is also of interest to analyse the molecular markers KRAS and BRAF to determine their influence with regard to response in this context.

Data from 250 rectal cancer biopsies within the FOCUS trial (Prof P Quirke, personal communication) indicates that approximately 52% will be KRAS/BRAF wild type 45% KRAS mutant and 3% BRAF mutant (one patient was KRAS/BRAF mutant).

The current protocol EXCITE (NWCOG-4) examines this triplet combination. In view of the recognised acceptable but nevertheless significant grade 3 and 4 toxicity encountered in NWCOG-2 [Gollins '09], the current protocol keeps the doses of radiotherapy, capecitabine and irinotecan identical to NWCOG-2 but introduces a weekend break in the capecitabine schedule so that this is delivered five days per week from Monday to Friday only.

3 Selection of Clinicians

3.1 Centre/Clinician inclusion criteria

This study will be conducted within the four centres which make up the NWCOG (North Wales, Christie, Clatterbridge, Preston) plus two to four other centres as long as they can fulfil the trial requirements.

Participating centres will be required to complete a feasibility questionnaire to confirm that they have adequate resources and experience to conduct the trial.

The following documentation must be received by the CR UK & UCL Cancer Trials Centre (CTC) prior to the site being initiated:

- Confirmation of Local Ethics approval (site specific assessment).
- Confirmation of Trust R&D approval.
- Signed agreement between the participating site and the sponsor.
- Confirmation from the MHRA that sites/investigators have been added to the CTA.
- Completed site responsibility and contact log.

Once all this documentation has been received the CTC will send confirmation of site approval to the PI and funders who are supplying drugs.

All this documentation will be stored in the Trial Master File (TMF) at the CTC. The CTC must be notified of any changes to the trial personnel and their responsibilities during the running of the trial.

4 Informed Consent

Sites are responsible for assessing a patient's capability to give informed consent.
Sites are responsible for ensuring all patients have been given the current 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 a consent form. The PI or other delegated site investigators 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 detailed patient information sheet for the trial will be given to 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 version of the consent form for the trial must be obtained before any trial-specific procedures are conducted.

Site staff are responsible for:

- checking that information on the consent form is complete and legible
- checking that the patient has 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. info given, consent signed etc.)
- Adding the patient trial number to all copies of the consent form to be filed in the medical notes and investigator site file following registration

The original signed consent form and a copy must be stored at site (in the Investigator Site File and the patient's medical notes). A further copy must be given to the patient.

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 10).

5 Selection of Patients

5.1 Patient inclusion criteria

- Histologically confirmed rectal adenocarcinoma with lower (distal) limit ≤12 cm from the anal verge using rigid sigmoidoscopy
- Rectal Cancer staged with MRI as locally advanced:
  - Mesorectal fascia threatened (tumour ≤1mm from mesorectal fascia)
  - Mesorectal fascia involved or breached
  - Low tumours arising <5cm from the anal verge
- No evidence of metastatic disease
- No pre-existing condition which would deter radiotherapy, e.g. fistulas, severe ulcerative colitis (particularly patients currently taking sulphasalazine), Crohn's disease, prior adhesions
- Estimated GFR (using Cockroft-Gault formula) >50 ml/min. If this is less than 50ml/min a 24-hour urine collection for estimation of GFR is required or a serum EDTA clearance
- Absolute neutrophil count ≥ 1.5 x 10^9/l. Platelets ≥ 100 x 10^9/l, serum bilirubin <1.25 x upper limit of normal (ULN); serum transaminase(s) < 3 x ULN; serum ALP < 5 x ULN
- Fit to receive all study treatments
- Able to comply with oral medication
- WHO performance status 0 or 1
- Written informed consent

5.2 Patient exclusion criteria

- Previous chemotherapy
- Previous radiotherapy to the pelvis
- Patients who have very significant small bowel delineated within the radiation fields
- Current or impending rectal obstruction (unless de-functioning stoma present), metallic colonic rectal stent in situ
- Pelvic sepsis
- Uncontrolled cardiac, respiratory or other disease, or any serious medical or psychiatric disorder that would preclude trial therapy or informed consent
- Known dihydropyrimidine dehydrogenase deficiency
- Pregnant, lactating women or potentially childbearing patients not using adequate contraception
- WHO performance status of 2 or more
- Gastrointestinal disorder which would interfere with oral therapy or oral bioavailability.
- Patients who are deemed unsuitable for surgery because of co-morbidity or coagulation problems.
- Participation in other studies except genetic studies such as NSCCG (National Study of Colorectal Cancer Genetics)
- Patients taking St. John's Wort

6 Investigations Before Registration

To confirm eligibility, the patients must have had the following investigations and assessments prior to registration (data from routine investigations can be used):

- Diagnostic histology
- MRI to stage the disease (within 35 days **of registration**)
- Liver imaging and chest x-ray to exclude metastatic disease
- FBC, U&Es, LFTs
- Estimated GFR using Cockcroft-Gault Formula (See Appendix 4)
- Pregnancy test if applicable
- Clinical examination including height, weight, vital signs and WHO performance score (see Appendix 2)

7 Registration Procedure

Following a verbal and written explanation of the study, consenting patients will be registered as follows:

- Contact Cancer Research UK & UCL Cancer Trials Centre to check eligibility.
- Allocation of trial number.

A confirmation fax will then be sent to the recruiting site and pharmacy.

REGISTRATIONS

Mon to Fri 9am to 5pm

Tel: 0207 679 9880

8 Study Design/Treatment Protocol

8.1 Overall study structure

This is a multi-site phase II enrolment study. Centres participating in the study will include the four North West centres in the NWCOG, plus up to four others.

THE PRIMARY ENDPOINT is the histologically confirmed R0 resection rate.

THE SECONDARY ENDPOINTS are as follows:

- Radiotherapy compliance.
- Grade 3 or 4 toxicity.
- Pathological complete response
- Morbidity – post operative and long term.
- Disease-free survival and local failure-free survival.

Patients will be assessed for eligibility prior to recruitment (see inclusion/exclusion criteria).

Treatment should be started as soon as possible after registration. The MRI scan that has been used for eligibility and disease evaluation needs to be within 35 days of registration. Patients should have an acceptable haematological and biochemical profile within 7 days of the first day of chemotherapy administration.

If blood tests and calculated GFR used to confirm eligibility are not within 7 days of treatment start, further testing will be required (see Section 9 for details). If the following were not included in routine investigations prior to registration, they too need to be obtained prior to the start of study treatment as part of the required baseline investigations: CEA, serum magnesium, clotting (see Section 9)

A calculated glomerular filtration rate (GFR) using the Cockroft Formula is acceptable but if this is less than 50 ml/min then a formal 24-hour urine collection or serum EDTA clearance should be carried out to determine GFR (see Appendix 4).

Before CRT begins, 2 x 10 ml blood samples will be collected from consenting patients. One sample will be used for testing for UGT1A1 polymorphisms and the other will be stored for future research studies (see Section 19). Patients will receive a six week (in total) course of treatment: week 1, cetuximab only; weeks 2 – 6 radiotherapy combined with cetuximab, irinotecan and capecitabine.

A defunctioning stoma will be fashioned for severe symptoms due to the primary tumour at the discretion of the treating team.

A clinical evaluation will be carried out (doctor/nurse) at the commencement of cetuximab, every week during radiotherapy and for four weeks following completion of treatment to record blood count, biochemical profile, estimated GFR, and toxicity scores (using NCI CTC V.3.0). Serum magnesium is to be monitored weekly for 8 weeks post completion of cetuximab treatment. In patients on anticoagulants or those with an abnormal initial clotting profile, clotting profile is measured weekly during chemotherapy then weekly for four weeks post-termination (and longer if deemed clinically appropriate) if this is abnormal.

An MRI scan will be carried out at six weeks following radiotherapy completion then an attempt at surgery will take place eight weeks post radiotherapy completion.

Following surgery, adjuvant chemotherapy is given according to the discretion of the treating physician but recorded on the relevant CRF.

A sample of formalin-fixed paraffin-embedded tumour tissue removed during surgery will be sent to a central lab for analysis of KRAS mutation status. The tumour tissue will be stored and used in future research studies if the patient has consented to this. Otherwise, it will be returned to the site.

From the point of view of late toxicity, patients will be assessed at 6, 12, 24 and 36 months post completion of radiotherapy.

On confirmed tumour progression further formal follow-up within the trial ceases apart from ultimately recording date and cause of death. Further clinical management, including second-line chemotherapy is at the discretion of the treating physician. On study withdrawal for any reason then the CRF Off Study Form is completed, providing reason for treatment withdrawl and/or complete withdrawl. On patient death, CRF Death Form is (also) completed.

No other concomitant cytotoxic treatment or radiotherapy is permitted during the trial*.*

Specified dose limiting toxicities:

All toxicities below must adhere <u>strictly</u> to definitions specified in the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0:

- Grade 3 diarrhoea that does not improve to grade 2 or less, within 24 hours on intensive anti-diarrhoeal therapy

- Grade 4 diarrhoea
- Grade 3 or 4 fatigue
- Grade 3 or 4 neutropenia accompanied by fever (>38°C) or ≥grade 3 infection
- Grade 4 thrombocytopenia (platelet count < 25 x 10^9/L)
- Grade 4 nausea/vomiting despite full antiemetic treatment
- Grade 3 or 4 palmar-plantar erythrodysesthesia (Hand Foot Syndrome).
- Dose delay of > 2 weeks because of drug-related toxicity.

8.2 Treatment details

8.2.1 Treatment summary

Patients will be treated with pelvic radiotherapy to a planned volume at a dose of 45 Gy in 25 daily fractions of 1.8 Gy treating 5 days per week from Monday-Friday.

Concurrently they will receive oral capecitabine at 650 mg/m^2 bd 5 days per week from Monday-Friday on the days of radiotherapy only.

In addition, they will receive a loading dose of iv cetuximab at 400 mg/m^2 one week before the commencement of radiotherapy then at 250 mg/m^2 once per week during weeks 1, 2, 3, 4 and 5 radiotherapy i.e. six doses of cetuximab in total.

In addition they will receive iv irinotecan at 60 mg/m^2 once per week for four doses in total during weeks 1, 2, 3 and 4 of radiotherapy. Administration of irinotecan follows the administration of cetuximab.

Antiemesis: Prior to weekly treatments including iv irinotecan and cetuximab it is recommended that patients will receive premedication using a 5HT3 antagonist such as 8 mg iv ondansetron plus a steroid such as 8 mg iv dexamethasone (in addition they will receive an antihistamine such as 10 mg iv chlorpheniramine to reduce the likelihood of a cetuximab-related infusion reaction). Prior to treatment with iv cetuximab alone, it is recommended that patients receive an antihistamine plus steroid. Oral antiemetics following iv infusions including irinotecan might include dexamethasone for one or two days but otherwise antiemetics such as metaclopramide or domperidone are to be used as required according to standard local practice.

Patients may have a Hickman line or peripherally inserted central catheter (PICC) inserted at the physician's discretion if required to give adequate venous access for the administration of cetuximab and irinotecan. In these patients prophylactic warfarin should not be given because of the interaction between warfarin and capecitabine.

Body surface area (BSA) will be calculated using actual body weight and no dose capping is carried out. No change in the dose calculation is carried out for obese patients.

No dose banding is carried out for irinotecan or cetuximab although it is for capecitabine (detailed in Section 8.2.2).

Instructions for storage use and handling of each drug should be according to each SmPC and hospital policies.

8.2.2 Capecitabine

Administration: Capecitabine is taken orally twice a day in equal doses for five days per week (Monday to Friday) throughout the 5 week course of radiotherapy. **There is no capecitabine treatment on Saturday or Sunday**. Patients will be asked to take the capecitabine approximately 12 hours apart as close to 8am-9am and 8pm-9pm each day within 30 minutes of the ingestion of food (ideally after breakfast and evening meal) with approximately 200 ml of water, with the first dose prior to radiotherapy on day 1. For patients who find swallowing capecitabine difficult it is possible to dissolve the tablets in lukewarm water. The capecitabine tablets should be placed in approximately 200 ml of lukewarm water. By stirring for about 15 minutes the tablets should dissolve. There is no stability data for any form of capecitabine suspension, so this should be done immediately prior to use and the solution swallowed immediately, rinsing to ensure that all the contents are ingested. As the solution will have a bitter taste it could be flavoured with a fruit juice or squash, but grapefruit juice should not be used. The solution may also be administered through a naso-gastric tube or other enteral feeding tube.

Capecitabine dose calculation according to body surface area

Capecitabine dose = 650 mg/m^2 bd		**Number of tablets to be taken at each dose (morning and evening) Mon-Fri**	
Surface area (m^2)	**Twice daily dose (mg)**	**150 mg**	**500 mg**
< 1.46	900	6	-
1.47-1.66	1000	-	2
1.67-1.89	1150	1	2
1.90-2.12	1300	2	2
>2.13	1450	3	2

Figure12: Capecitabine dose banding at 650 mg/m²

Drug supply: Capecitabine will be available through routine medical supplies. Chemotherapy prescriptions should conform to local best practice including electronic prescribing systems where available. Capecitabine prescriptions to take home should include the exact number of tablets for that current cycle.

Capecitabine will require 'clinical trial' labelling by the site pharmacy in compliance with regulatory requirements, but no additional accountability records other than the pharmacy's standard tracking/dispensing log are required. Unused capecitabine should be disposed of as per hospital policy.

Capecitabine side effects: The side effect profile of capecitabine is similar to 5FU. The main toxicities are hand-foot syndrome, diarrhoea, nausea and stomatitis. Vomiting, fatigue, abdominal pain, dermatitis, fever, parasthesia, headache, dizziness, insomnia, anorexia and a drop in white blood cells are also experienced.

Occasionally, the following problems have been reported: taste disturbance, chest pain, angina pectoris, abnormal drowsiness or lethargy, weakness, dehydration and alopecia.

Capecitabine is contraindicated in patients with moderate or severe renal impairment. Antacids containing aluminium hydroxide may interfere with the absorption of capecitabine and so an alternative should be prescribed if possible.

Capecitabine precautions: Altered coagulation and/or bleeding have been reported in patients taking coumarin-derivative anticoagulants concomitantly with capecitabine. These events occurred within several days and up to several months after initiating capecitabine and also within one month of stopping capecitabine. Patients should be monitored regularly (twice weekly during CRT) for alterations in their coagulation parameters.

Phenytoin plasma concentrations have been shown to increase when used concomitantly with capecitabine. Again, patients should be regularly monitored for increase in phenytoin plasma concentrations and associated clinical symptoms.

Capecitabine should not be administered together with sorivudine [an antiviral] or its chemically related analogues such as brivudine. A chemically significant drug-drug interaction between sorivudine and 5FU, resulting from the inhibition of dihydropyrimidine dehydrogenase [DPD] by sorivudine has been described in literature. This interaction is potentially fatal as it leads to increased fluoropyrimidine toxicity.

It has been the experience of the Trial Management Group (TMG) in the NWCOG-2 trial that despite warnings of potential side effects, there sometimes remains in the patient's mind, the perception that because capecitabine is a tablet, it does not have the same potential to cause side effects as intravenous chemotherapy. It has to be emphasised to patients that oral chemotherapy has the same potential to cause side effects as intravenous chemotherapy and if rapidly worsening side effects are occurring, that they must stop the capecitabine tablets immediately and ring in to contact numbers for medical advice.

8.2.3 Cetuximab

Administration: Cetuximab is given intravenously as a 2 hour infusion at 400 mg/m^2 one week prior to the commencement of radiotherapy. It is then given and as a 1 hour infusion at 250 mg/m^2 once per week during weeks 1, 2, 3, 4 and 5 of radiotherapy. There is to be equal spacing between infusions.

Cetuximab must be administered under the supervision of a physician experienced in the use of antineoplastic medical products. Close monitoring is required during the infusion and for at least one hour after the end of the infusion. Availability of resuscitation equipment must be ensured.

Prior to cetuximab infusion, patients must receive premedication with an antihistamine (e.g. chlorpheniramine). Recently the MABEL study has demonstrated that the rate of severe (grade 3 and 4) infusion-related reactions in patients receiving cetuximab was 7.1% for 422 patients receiving premedication with an antihistamine alone versus 1.1% for 700 patients receiving any antihistamine plus a corticosteroid (Siena et al,'07). In the light of these data it is recommended that patients within the EXCITE trial should receive premedication using a corticosteroid, for example 8 mg of intravenous dexamethasone, in addition to an antihistamine.

Drug supply: Drug supply of cetuximab will be from special trial stock. The trial centre will inform Merck when all necessary approvals for a centre have been received. Centres should arrange initial supplies once their first patient is screened. Further supplies will be coordinated by hospital pharmacies directly with Merck using a drug request form. The monoclonal antibody is supplied at a concentration of 5mg/ml. The starting dose is 400mg/m^2 (=80ml/m^2). 'Clinical trial' labelling will be provided by Merck in compliance with

regulatory requirements and additional accountability records need to be maintained by the pharmacy.

At the end of the trial the CTC will inform participating sites of the procedure for unused drug return/destruction.

Cetuximab side effects: In approximately 5% of patients hypersensitivity reactions may occur during treatment with cetuximab, approximately half of these reactions being severe.

Mild or moderate reactions (grade 1 or 2) include symptoms such as fever, chills, nausea, rash or dyspnoea. Severe hypersensitivity reactions (grade 3 or 4) usually occur during or within 1 hour of the initial cetuximab infusion, but may occur after several hours or with subsequent infusions, therefore it is recommended to warn patients of the possibility of late onset infusion-related reactions and instruct them to contact their physician. Symptoms include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness, difficulty in speaking), urticaria, and/or hypotension.

Recently the MABEL study has demonstrated that premedication with corticosteroids can reduce the rate of infusion related reactions for patients receiving cetuximab (see Section 8.2.3 above).

Conjunctivitis may be expected in approximately 5% of patients. Dyspnoea has been reported in 25% of patients with end stage colorectal cancer.

Skin reactions will develop in more than 80% of patients: approximately 15% of these are severe (≥ grade 3). They mainly present as acne-like rash affecting face, upper chest and back. On longer term therapy paronychia can develop in approximately 10% of patients and can be painful. The majority of skin reactions develop within the first 1-3 weeks of therapy. They generally resolve, without sequelae, following the cessation of treatment if the recommended adjustments in dose regimen are followed (see dose modifications Section 8.4.4-8.4.6).

Cetuximab precautions: Cetuximab is contraindicated in patients with known severe (grade 3 or 4) hypersensitivity reactions to cetuximab. There are no specific drug interactions documented with cetuximab. However, any agent that may interfere with the immune system of the patient should preferably be avoided except the indicated study regimen and necessary supportive treatment (including corticosteroids, antiemetics etc).

8.2.4 Irinotecan

Administration: Irinotecan is given as a 60 minute intravenous infusion in 250 mls of normal saline during weeks 1, 2, 3 and 4 of radiotherapy (with equal, weekly spacing between infusions).

Patients are recommended to receive premedication of atropine sulphate subcutaneously prior to irinotecan infusion to help prevent cholinergic syndrome.

Irinotecan must not be administered earlier than one hour after the end of the cetuximab infusion.

Patients should not receive St. Johns Wort whilst receiving irinotecan therapy.

Drug supply:

Patients 1-40:

Irinotecan for the first 40 patients will be from special trial stock, supplied by Pfizer and distributed by Aptuit. Supplies will be coordinated by CTC who will liaise with the hospital pharmacies directly.

'Clinical trial' labelling will be provided by Pfizer in compliance with regulatory requirements and additional accountability records will need to be maintained by the pharmacy.

At the end of the trial the CTC will inform participating sites of the procedure for unused drug return/destruction.

Patients 41-80:

Irinotecan for the remaining 40 patients will be from routine hospital supply and **will require 'clinical trial' labelling by the site pharmacy in compliance with regulatory requirements. No additional accountability records other than the pharmacy's standard tracking/dispensing log are required. Unused irinotecan should be disposed of as per hospital policy.**

Irinotecan side effects: When used as a single agent the major dose-limiting side effects of irinotecan are neutropenia and delayed diarrhoea.

Other toxic effects include a cholinergic-like syndrome (with 'early' diarrhoea, abdominal cramps, profuse perspiration, salivation and lacrimation), nausea, vomiting, constipation, mucositis, asthenia and alopecia.

Irinotecan precautions: Irinotecan and its metabolites are cleared by biliary excretion and patients with cholestasis have delayed clearance. If hepatobiliary function deteriorates below eligibility criteria limits during treatment, irinotecan should not be given.

8.2.5 Radiotherapy

TARGET VOLUME DEFINITION

All patients will undergo contouring of their treatment volume using CT planning scans. Conventional fluoroscopy simulation is not permitted.

The radiotherapy treatment planning process will require: -

- A CT planning scan using CT slices of not more than 5mm thickness.
- All available diagnostic imaging (including pelvic MRI), together with clinical information such as that obtained from examination under anaesthetic.
- A digital rectal examination for the distal tumour extent by the planning clinical oncologist.

Patients should be preferably scanned (and treated) prone although supine is allowed in elderly patients or those with a defunctioning stoma in whom the prone position is not feasible. A radio-opaque anal marker should be used during planning CT to identify the anal margin. Patients should have a comfortably full bladder prior to the CT scan and during radiotherapy. Patients are scanned to include the superior aspect of L5, to 2cm inferior to the anal marker in order to ensure coverage of the whole of the pelvis, recto sigmoid and rectum. Small bowel contrast with Gastrografin (20mls in 1 litre of water approximately 1 hour prior to scan) is recommended to delineate small bowel in the pelvis and to determine if this can be safely excluded from the planning target volume.

The following target volumes will be defined. Some institutions will be able to co-register diagnostic MRI and CT planning scans although this is not mandatory.

Gross tumour volume (GTV): As much of the tumour is identified using diagnostic MRI scans to assist. On each slice all macroscopic visible tumour is outlined. Tumour involving large intramural veins or extra nodal deposits, imaged on MRI should also be included. The discontinuous nature of many rectal cancers with extra-nodal deposits may require the demarcation of more than one GTV area.

Clinical target volume (CTV): the volume of tissue that includes the GTV but also takes account of potential microscopic spread of the primary tumour including the mesorectal

subsite, the posterior pelvic subsite, regions at risk of lymph node spread and, for lower third rectal cancers, the inferior pelvic subsite (Roels et al,'06).

CTV for LOWER THIRD rectal tumours (0-5 cm from anal verge on rigid sigmoidoscopy)

Posterior: Along the inner bony edge of the sacrum.

Anterior: GTV + 1cm, or mesorectal fascia + 1cm, whichever is most anterior.

Lateral: Contoured around the bony lateral pelvic side wall.

Superior: GTV + 2cm or 1cm inferior to the S2/3 junction, whichever is the most superior. (The PTV would not normally extend superiorly to the sacral promontory).

Inferior: GTV+2cm but the inferior pelvic subsite should also be included (Roels et al,'06). (The inferior pelvic subsite includes the ischiorectal fossa and the internal and external anal sphincter, with the penile bulb as the anterior border. Laterally the ischiorectal fossa is bounded by the fascia of internal obturator muscle and the ischial tuberosity. Posteriorly the border of the ischiorectal fossa is coccyx and the surface of gluteal muscle).

CTV for MIDDLE THIRD rectal tumours (5-10 cm from anal verge on rigid sigmoidoscopy)

Posterior: Along the inner bony edge of the sacrum.

Anterior: GTV + 1cm, or mesorectal fascia + 1cm, whichever is most anterior.

Lateral: Contoured around the bony lateral pelvic side wall.

Superior: GTV + 2cm. (The PTV would not normally extend superiorly to the sacral promontory).

Inferior: GTV + 2 cm or 1 cm superior to the anorectal junction, whichever is the more inferior. (If the anorectal junction is used then a Foley catheter with the balloon inflated can be used to determine the level of the anorectal junction if necessary, in order to avoid including the anal sphincters in the CTV).

CTV for UPPER THIRD rectal tumours (10-12 cm from anal verge on rigid sigmoidoscopy)

Posterior: Along the inner bony edge of the sacrum.

Anterior: GTV + 1cm, or mesorectal fascia + 1cm, whichever is most anterior.

Lateral: Contoured around the bony lateral pelvic side wall.

Superior: GTV + 2cm or 1 cm below the sacral promontory, whichever is the most superior.

Inferior: GTV + 2 cm.

Planning target volume (PTV): This adds a safety margin around the CTV to account for variation in patient and tumour position. A 1cm margin is applied in all directions to the CTV to derive the PTV.

Treatment delivery

The PTV is treated with any combination of at least 3 coplanar or non-coplanar 3D conformal fields, at the clinician's discretion. These are shaped to deliver the specified dose to the target while restricting the dose to the normal surrounding tissues using either MLC or custom-made blocks.

Radiation therapy should be delivered with effective photon energies of more than 6 MV generated by a linear accelerator. 3-D conformal radiotherapy is permitted. Mixed beams are allowed with higher photon energy for the lateral beams compared to the posterior beam.

A total dose of 45Gy in 25 daily fractions over a total time of 5 weeks should be delivered treating 5 days per week, 1 fraction per day, 1.8Gy per fraction. All fields must be treated during one treatment session. It is conventional to report the dose to the ICRU reference point, the maximum dose to the PTV and the minimum dose to the PTV. The isocentric treatment plan is usually specified to receive 100% with the 95% isodose line encompassing the PTV and no more than +5% and -5% in homogeneity within the target volume.

Normal critical tissues such as small bowel, femoral heads, ureter and bladder can be contoured and doses to these organs kept to a minimum. It appears that the small bowel is often close to the target volume, and the dose should be specified such that not more than 250 ml of small bowel receives in excess of 45Gy.

Verification and correction procedures

The rectum does move during a course of radiotherapy (Roeske et al 1995, Lebesque et al 1995). However, there is little data to quantify rectal motion and set up variation. Anatomical considerations suggest the rectum is more fixed at the distal end than proximally.

Verification of CT-contoured plans can be carried out prior to treatment commencing using either conventional simulator images or using DRRs as the reference images.

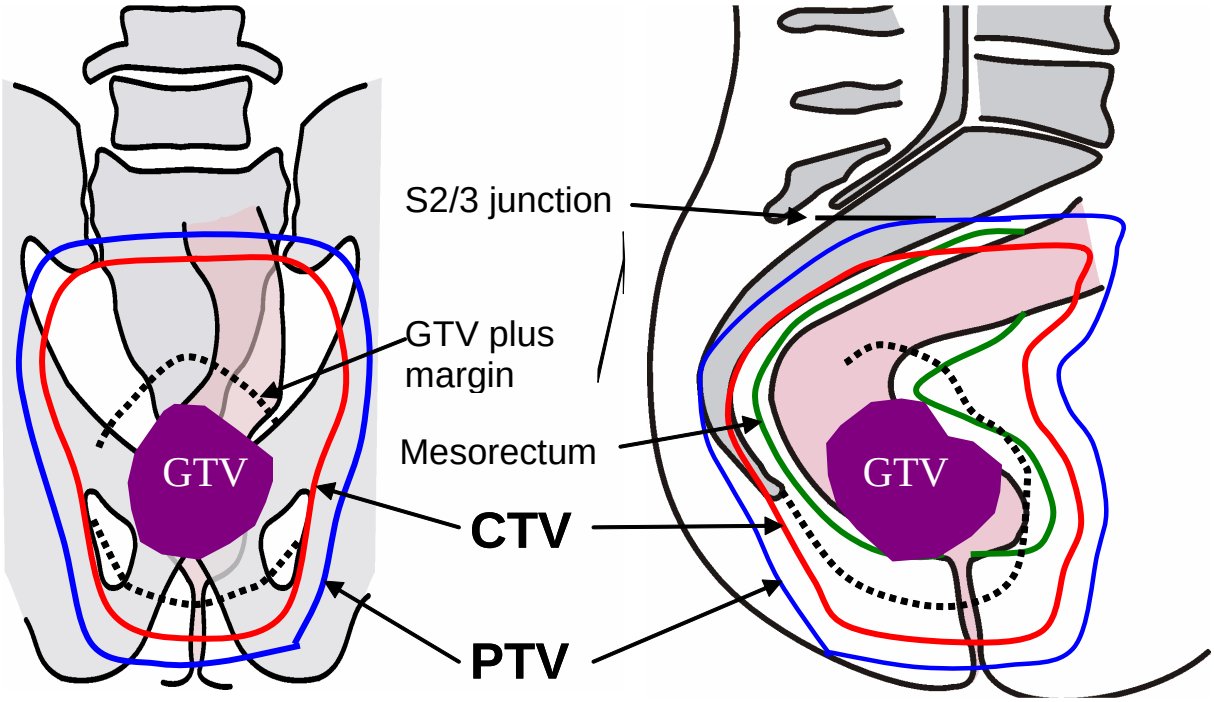


Figure 2: Radiotherapy planning diagram for lower rectal cancers

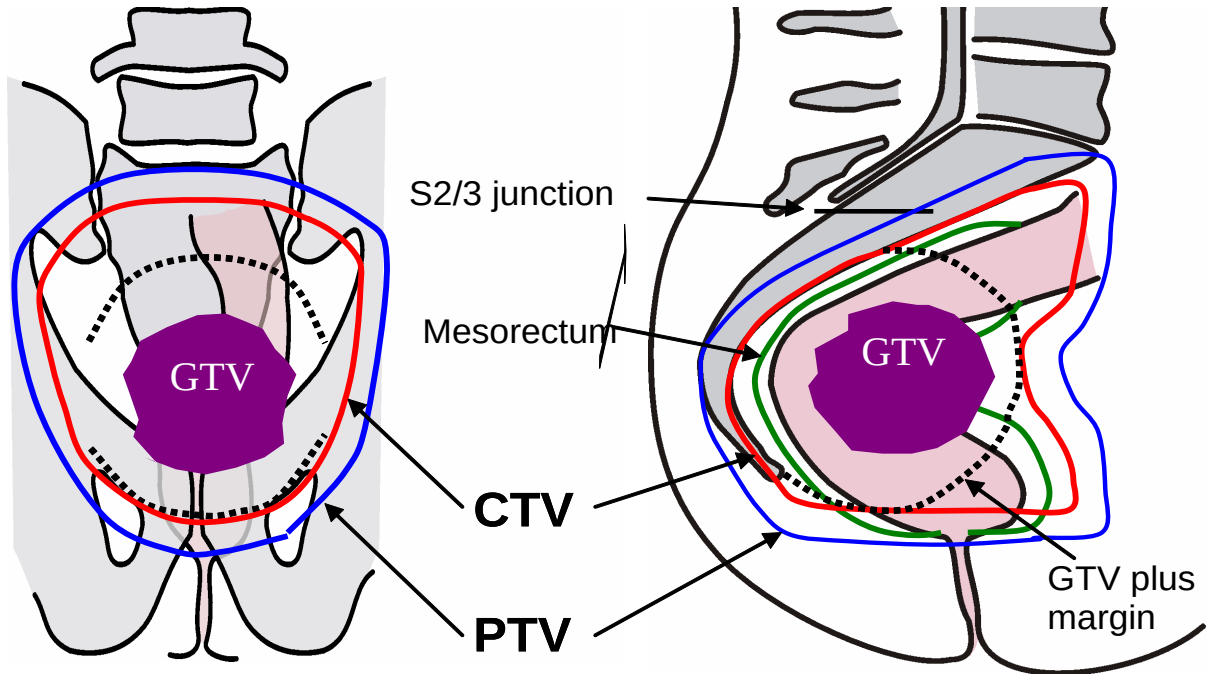


Figure 3: Radiotherapy planning diagram for upper third rectal cancers

Portal imaging

Portal imaging for verification of isocentre position and treatment fields should be acquired on the first treatment session both for AP and lateral images and compared to the reference images. Electronic portal imaging (EPI) can monitor set-up displacement on a daily basis in the initial phase of treatment (Tinger 1996). Simulator or DRR reference images can be compared with portal images manually or via automatic co-registration.

Fields should be moved if they fall outside an agreed tolerance level – usually 5 mm for patients who are treated prone. This process also allows clinicians and radiographers to evaluate the treatment field set-up with respect to bony landmarks and to assess and correct any systematic errors. The MLC configuration can also be verified for consistency and reproducibility. It is recommended to measure set up accuracy on a weekly basis.

8.2.6 Quality Assurance for radiotherapy

For quality assurance purposes in the EXCITE trial, a Radiotherapy Plan Assessment form will be collected for each patient on the trial. The form will collect data on the dose given (planned and actual), the different volumes (GTV, CTV & PTV), treatment fields, target coverage, dose volume constraints and other treatment details and interruptions. Each form will be sent directly to the Research Superintendent Radiographer at Glan Clwyd Hospital, using the following email address cathryn.wood@wales.nhs.uk.

8.3 Ionising Radiation (Medical Exposure) Regulations (IRMER)

Taking account of potential variations in practice at other sites, there are no additional radiation exposures within this trial (radiotherapy and CT scanning during the planning of radiotherapy) when compared to standard practice, and to comply with the above regulations, the radiation exposures will be approved by the Main REC.

Trials to be undertaken on multiple sites have to meet all the applicable requirements of IRMER at each site, therefore each PI needs to comply with their employer's policies and procedures for the use of ionising radiation in research prior to recruitment.

8.4 Modification of trial treatment

Dose modifications should be made according to the worst grade of adverse event (NCI CTC v3.0).

8.4.1 Capecitabine: General principles of dose modification

Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction). Once the dose has been reduced, it should not be increased at a later time. Patients should be informed of the need to interrupt treatment immediately if moderate (grade 2) or severe (grade 3 or 4) toxicity occurs.

In the case of capecitabine doses being omitted because of toxicity or other reasons (such as patient forgetfulness) or if a dose of capecitabine is compromised because a patient vomits following an oral dose, then no attempt should be made to add extra doses of capecitabine to account for this and instead treatment should simply resume at the next due dose.

8.4.2 Capecitabine: Dose modification and treatment for skin toxicity

Emollients such as Diprobase are helpful for hand-foot syndrome (HFS) (also known as hand-foot skin reaction or palmar–plantar erythrodysaesthesia).

Dose modifications should be made as indicated in the chart below.

HFS dose modifications:	**Appearance of toxicity**			
Toxicity (CTCAE v3) Grade	**1st**	**2nd**	**3rd**	**4th**
	Interrupt until ≤ grade 1 and restart at			
2	100%	75%	50%	Stop
3	75%	50%	Stop	

Figure 4: Capecitabine dose modifications for hand foot syndrome

8.4.3 Cetuximab: General principles of dose modification

Cetuximab dose reductions are permanent. Patients must discontinue cetuximab if more than 2 consecutive infusions are withheld.

8.4.4 Cetuximab: Dose modification for infusion related toxicity

If the patient experiences a mild or moderate infusion-related reaction, the infusion rate may be decreased. It is recommended to maintain this lower infusion rate in all subsequent infusions.

Severe infusion-related reactions have been reported in patients treated with cetuximab (see side effects Section 8.2.3). Symptoms usually occur during the first infusion and up to 1 hour after the end of the infusion.

Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of cetuximab therapy.

In each case of allergic/hypersensitivity reaction, the investigator should implement treatment measures according to the best available medical practice. Based on previous experience with cetuximab allergic/hypersensitivity reactions, the treatment guidelines as described in Figure 7 may be applicable (below).

CTCAEv3.0 Grade Allergic/ Hypersensitivity Reaction	**Treatment**
Grade 1	Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening. The total infusion time for cetuximab should not exceed 4 hours.
Grade 2	Stop cetuximab infusion. Administer bronchodilators, oxygen, etc. as medically indicated. Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening
Grade 3 or Grade 4	Stop the cetuximab infusion immediately and disconnect infusion tubing from the subject. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. **Subjects must be withdrawn immediately from the treatment and must not receive any further cetuximab treatment**.

Figure 5: Treatment adjustment in the event of cetuximab caused allergic/hypersensitivity reaction.

Re-treatment following allergic/hypersensitivity reactions:

Once a cetuximab infusion rate has been decreased due to an allergic/hypersensitivity reaction, it will remain decreased for all subsequent infusions. If the subject has a second allergic/hypersensitivity reaction with the slower infusion rate, the infusion should be stopped and cetuximab should be discontinued. If a subject experiences a Grade 3 or 4-allergic/hypersensitivity reactions at any time, cetuximab should be discontinued.

8.4.5 Cetuximab: Dose modification and treatment for skin toxicity

If pruritus occurs an oral antihistamine is advised. Dry skin often occurs (and may contribute to pruritus) general advice on replacing soap with oil for washing, avoidance of hot water for baths or showers and use of emollient creams are beneficial. Fissures may occur in dry skin and topical dressings (e.g. hydrocolloid dressings and as advised by your dermatologist) are helpful.

Discussion with a local dermatologist prior to study initiation would be helpful to agree local plans of management and mechanisms for rapid referral in case of severe skin toxicity.

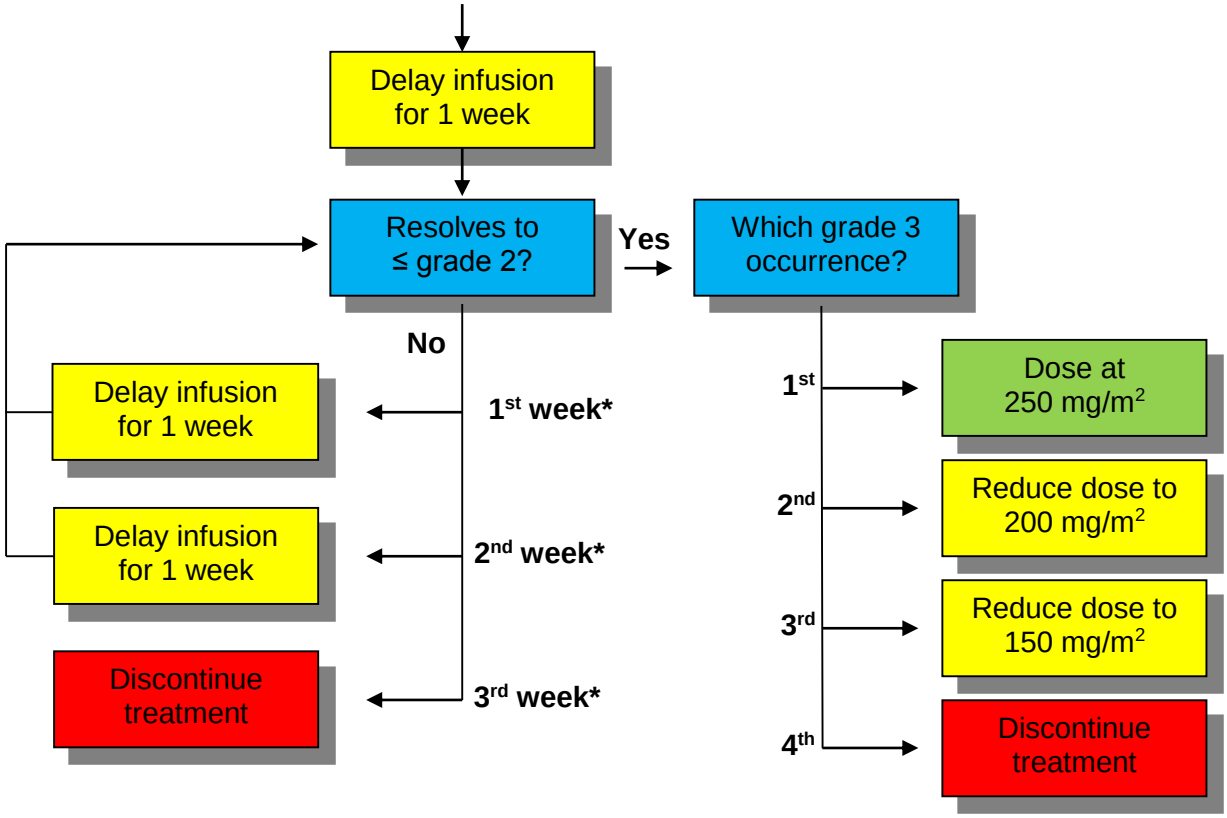
Dose modifications are summarised on the algorithm below. For CTC grade 1 or 2: continue treatment with cetuximab.

It is most important that oral and topical therapy is commenced as soon as the patient experiences signs of cetuximab skin related toxicity. Systemic antibiotics (e.g. a second generation tetracycline such as doxycycline 100mg po daily) should be used and addition of a topical steroid or combination steroid and antibiotic cream should be considered (as duration of therapy is short). Colloidal oatmeal cream or lotion can also be effective.

If grade 3 skin toxicity occurs for a second and third time, cetuximab therapy may again be delayed for up to 14 days with concomitant dose reductions to 200mg/m^2 and then 150mg/m^2. Cetuximab dose reductions are permanent. Patients must discontinue cetuximab if more than 2 consecutive infusions are withheld. If the toxicity resolves to grade 2 or less by the following treatment period, treatment may be resumed.

Nail toxicities occur in 8% of patients with cetuximab, characterised by a paronychial inflammation with associated swelling of the lateral skin folds of toes and fingers, especially great toes and thumbs, which may be painful. It may persist for up to three months after cessation of cetuximab therapy. Dermatological advice should be sought. Use of daily salt baths and local antiseptic / astringent ointments have been found to be helpful. Anti-inflammatory drugs may help to ease the pain.

Cetuximab modification flowchart



* These refer to the second and third consecutive week of non-resolving grade 3 skin toxicity

Figure 6: Flowchart for cetuximab modification due to skin toxicity

8.4.6 Cetuximab: Dose modification and treatment for hypomagnesemia

Hypomagnesemia has been reported in up to 65% of patients following cetuximab therapy. Fatigue, malaise, tremor, ataxia, carpopedal spasm, hyperreflexia, confusion, hallucinations, convulsions and arrhythmias may occur.

Patients should have magnesium concentration monitored at baseline, prior to each cycle of chemotherapy and for up to 8 weeks after the last dose of chemotherapy, or until magnesium has normalised, whichever is the longer. Hypomagnesemia should be corrected by intravenous supplementation if grade 3 (<0.4 mmol/l) or symptomatic. If lesser degrees of hypomagnesemia are detected, oral supplementation may be considered

8.4.7 Irinotecan: General principles of dose modification

Irinotecan dose reductions are permanent

8.4.8 Dose modification and treatment for acute gastrointestinal toxicity

Toxicity grade	Diarrhoea	Radiotherapy	Cetuximab	Capecitabine	Irinotecan
1	increase of <4 stools per day over pretreatment level	Continue	100%	100%	Continue
2	increase of 4-6 stools per day over pretreatment levels or moderate cramping	Continue	100%	100%*	Interrupt until grade 0-1; then 100%
3**	increase of 7-9 stools/day or incontinence (if patient continent prior to treatment), severe cramping	Interrupt until grade 0-1	100%	Interrupt until grade 0-1; then 75%	Interrupt until grade 0-1; then 75%
4	increase of => 10 stools per day, grossly bloody diarrhoea, need for parenteral support haemorrhagic dehydration	Interrupt until grade 0-1	Discontinue	Discontinue	Discontinue

*If no response to loperamide, reduce capecitabine dose to 75%
****** if grade 3, lasts more than 24 hours and delays radiotherapy, stop chemotherapy until recovery

Figure 7: Dose modification for acute GI toxicity.

For grade 1 and 2 diarrhoea, loperamide (2 mg as required up to 8 times per day) can give symptomatic relief.

Radiation treatment will be interrupted when grade 3 or 4 toxicity occurs. Treatment can then be re-commenced after recovery from toxicity. However it is important that recovery to either grade 0 or 1 occurs prior to restarting therapy.

In the event of severe toxicity (grade 3 or 4 diarrhoea), the patient should receive full supportive care. It is recommended that such patients should be admitted to hospital and treated with intravenous fluids, loperamide and antibiotics, especially when there is concomitant grade 3 or 4 neutropenia. In the presence of rapidly falling serum albumin, total parenteral nutrition should be added. If ≥ grade 3 gastrointestinal toxicity occurs in the presence of ≥ grade 3 neutropenia then GCSF at 30 MU subcutaneously (or equivalent according to local practice) should be added for five days or until recovery to ≤ grade 2 neutropenia.

Some patients receiving CRT will experience diarrhoea which may initially present as grade 3 but become controlled by loperamide within a few hours and can then be managed in routine clinical practice as the recommendations above for grade 2 diarrhoea.

8.4.9. Dose modification in the event of renal toxicity

Although neither cetuximab nor capecitabine is nephrotoxic, serum creatinine and calculated GFR should be monitored weekly during radiotherapy. If the calculated GFR deteriorates to 50 ml/min or below a formal measurement (24 hour urine or EDTA) is required. Dose reduce capecitabine as shown below. If GFR falls below 30 ml/min the patient should stop capecitabine.

Formal GFR	Radiotherapy	Capecitabine	Cetuximab	Irinotecan
> 50 ml	Continue	100%	100%	100%
30-50 ml	Continue	75%	100%	100%
< 30 ml	Continue	Do not give	100%	100%

Figure 8: Dose modification for renal toxicity

8.4.10 Dose modifications in the event of other non-haematological toxicities

The following table represents a general guideline for dose reduction recommendations for relevant side effects that are associated with radiotherapy or particular chemotherapy agents and which are not described in the previous sections.

Toxicity grade CTC criteria	Radiotherapy	Capecitabine	Cetuximab	Irinotecan
1	Continue	100%	100%	100%
2	Daily review	Interrupt until grade 0 or 1; then 100%	Interrupt until grade 0 or 1; then 100%	Interrupt until grade 0 or 1; then 100%
3	Daily review	Interrupt until grade 0 or 1; then 75%	Interrupt until grade 0 or 1; then 75%	Interrupt until grade 0 or 1; then 75%
4	Discontinue treatment unless symptoms settle to grade 0-1 within two weeks	Discontinue treatment	Discontinue treatment	Discontinue treatment

Figure 9: Dose modifications for other non-haematological toxicities

8.4.11 Modifications of drug therapy for haematological toxicity

WBC (10^9/l)	Neutrophils (10^9/l)	Platelets (10^9/l)	Radiotherapy	Capecitabine	Cetuximab	Irinotecan
≥ 3 *(grade 1)*	≥ 1.5 *(grade 1)*	≥ 75 *(grade 1)*	Continue	100%	100%	100%
≥2 - <3 *(grade 2)*	≥ 1.0 <1.5 *(grade 2)*	≥ 75 *(grade 1)*	Continue	100%	100%	100%
≥1 - <2 *(grade 3)*	≥ 0.5 - <1.0 *(grade 3)*	≥ 50 - <75 *(grade 2)*	Interrupt until grade 0-1	Interrupt until Grade 0-1; then 75%	100%	Interrupt until Grade 0-1; then75%
<1 *(grade 4)*	<0.5 *(grade 4)*	<50 *(grade 3 or 4)*	Interrupt until grade 0-1	Interrupt; if recovers to Grade 0-1 discuss with TMG prior to 50%	100%	Interrupt; if recovers to Grade 0-1 discuss with TMG prior to 50%

Figure 10: Dose modifications for haematological toxicities

8.4.12 Unplanned breaks in radiotherapy

During unplanned breaks in radiotherapy not due to treatment-related toxicity (for example machine breakdown or bank holidays) chemotherapy will be interrupted and then resume to run concurrently with radiotherapy once radiotherapy resumes.

9 Assessments

9.1 Assessment investigations

9.1.1 Baseline: Prior to registration

- MRI scan (within 35 days of registration)
- FBC, U&Es, LFTs, serum magnesium (within 7 days)
- Calculated GFR (within 7 days) using Cockcroft formula (Appendix 4)
  (if ≤ 50ml/min, formal measurement using 24 hour urine/EDTA)
- CEA (within 4 weeks)
- Clotting profile (within 4 weeks)
- Vital signs: blood pressure, pulse rate, temperature (within 7 days)
- Height & weight (within 7 days)
- WHO performance status (within 7 days)
- Baseline toxicity assessment (using NCI CTCAE V.3.0)

9.1.2 During treatment phase: within 48 hours prior to cetuximab/irinotecan infusions

Weekly

- FBC, U&Es, LFTs
- Calculated GFR using Cockcroft formula (Appendix 4)
  (if ≤ 50ml/min, formal measurement using 24 hour urine/EDTA)
- Clotting profile if abnormal at baseline
- Serum Magnesium
- Toxicity assessment (using NCI CTCAE v3.0)
- Capecitabine compliance
- Blood samples for ancillary studies (at start of CRT only) if patient has consented to these (see Section 19)

During each cetuximab infusion

- Vital signs (blood pressure, temperature, pulse, respirations) to be monitored before during and immediately on completion of infusion, and 1 hour post-infusion.

9.1.3 Post chemoradiation

Weekly for 4 weeks

- FBC, U&Es, LFTs
- Serum Magnesium (continue for 8 weeks in total or until magnesium has normalised; whichever is the longer)
- Toxicity assessment (using NCI CTCAE v3.0)

6 weeks post chemoradiation

- CEA
- Pelvic MRI scan

8.1.4 Post-surgery

- Send tumour tissue blocks for KRAS testing (see Section 19)

9.1.5 Follow-up phase (all assessments are from the end of chemoradiotherapy)

- 6 months: Physical exam & late toxicity assessment
- 12 months: Physical exam & late toxicity assessment
- 24 months: Physical exam & late toxicity assessment
- 36 months: Physical exam & late toxicity assessment

All other investigations if clinically indicated at the discretion of the clinician.

9.2 Efficacy endpoints

Resectability will be defined in terms of:

- R0 resection rate i.e. the carcinoma is resected with margins clear by >1mm.
- R1 resection rate i.e. the carcinoma has microscopically-involved margins
- R2 resection rate i.e. the carcinoma is resected but has macroscopically-involved margins at the time of surgery.

Response rate will be defined in terms of:

- Pathological complete response (pCR) i.e. no residual viable carcinoma on extensive examination of the resected specimen.

The following will also be recorded:

- 'Near' pCR i.e. microscopic foci of occasional single carcinoma cells remaining on extensive examination of the specimen.
- Decrease in size of the carcinoma in superior-inferior and transaxial dimensions on comparing pre- and post- CRT MRI scans.
- Change in MRI-defined TNM stage of tumour on pre- and post-CRT MRI scans.
- TNM stage of resected specimen compared to predicted on pre-CRT MRI scan.

The denominator will be total numbers of subjects recruited for the trial and commencing CRT treatment.

The following categories of patient will be distinguished:

- Patients undergoing CRT and an attempt at laparotomy but tumour not resected because found to be too locally advanced at surgery.
- Patients undergoing CRT and an attempt at laparotomy but tumour not resected because found to have developed metastatic disease.
- Patients undergoing CRT and an attempt at laparotomy but tumour not resected because of other reasons.
- Patients undergoing CRT but not undergoing surgery because tumour remains too locally-advanced on restaging MRI.

Disease free survival - the 'event' will be time from randomisation to confirmation of local failure or recurrence, distant metastases, or death from any cause, whichever occurs first, disease-free patients being censored at the date last seen.

Local failure – A local failure is defined as:

- pelvic disease extent is considered unresectable (after pre-op CRT has been given and reassessment has taken place).
- when at laparotomy there is residual macroscopic pelvic malignancy.
- when during the follow up period (after macroscopic clearance of tumour was achieved) there is evidence of confirmed local recurrence. Confirmed local recurrence includes biopsy confirmation of local recurrence, unequivocal local recurrence on imaging (MRI scanning and /or PET) or equivocal local recurrence on imaging in the definite absence of metastatic disease and in the presence of a rising CEA.

Therefore local failure will be the time from randomisation to the first confirmation of local failure as defined above.

Local failure-free survival will be the time from randomisation to local failure or death whichever occurs first, survivors with no local recurrence being censored at the date last seen.

9.3 End of trial

The end of the trial will be 31st December 2016, or earlier if the biological studies are completed before then. At this point the 'declaration of end of trial' form will be submitted to the MHRA and REC.

9.4 Assessment flowchart

		Pre Reg	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	post op	Months after end CRT			
																		6	12	24	36
Treatment	Radiotherapy			→	→	→	→	→													
	Cetuximab		→	→	→	→	→	→													
	Capecitabine			→	→	→	→	→													
	Irinotecan			→	→	→	→	→													
	Surgery															X					
Assessments and other trial activities	Physical exam	X																X	X	X	X
	Vital signs	X	X	X	X	X	X	X													
	Height & weight	X																			
	WHO	X																			
	Capecitabine compliance			X	X	X	X	X													
	FBC	X	X	X	X	X	X	X	X	X	X	X									
	Clotting profile	X																			
	U+E+creat	X	X	X	X	X	X	X	X	X	X	X									
	Magnesium	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
	Calc GFR	X	X	X	X	X	X	X													
	LFT	X	X	X	X	X	X	X	X	X	X	X									
	Histological confirmation	X																			
	CEA	X												X							
	Liver (US or CT)	X																			
	MRI pelvis	X												X							
	CXR	X																			
	Toxicity	X	X	X	X	X	X	X	X	X	X	X						X	X	X	X
	Consent form	X																			
	Collection of diagnostic tissue block for KRAS testing																				
	Ancillary study blood samples x 2 (optional)	X																			
Data management	Registration/baseline CRF	X																			
	Copy of baseline MRI	X																			
	Treatment CRF		X	X	X	X	X	X	X	X	X	X									
	Post treatment summary CRF													X							
	Copy of post CRT MRI report													X							
	Surgery CRF																X				
	Copy of histology report																X				
	Follow-up CRF																	X	X	X	X

In this chart Week 1 is the week in which cetuximab alone is given and Week 2 is the week in which radiotherapy is started.

Serious Adverse Event Forms, Patient Withdrawal Form and Death Form to be completed as needed.

Figure 11: Flowchart for assessments and CRF completion

10 Withdrawal of Patients

In consenting to the trial, patients are consenting to trial treatment, trial follow-up and data collection. If a patient wishes to withdraw from trial treatment, institutions should nevertheless explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes.

10.1 Withdrawal from Trial Treatment

A patient may stop trial treatment for the following reasons:

- Progression whilst on therapy
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- Withdrawal of consent for treatment by patient
- Any alterations in the patient's condition which justifies the discontinuation of treatment in the investigator's opinion.

The reason should be recorded on the Treatment CRF and Withdrawal form.

The patient should however remain in the trial for the purposes of follow-up and data analysis, therefore, patients who withdraw from trial treatment for any reason other than disease progression and withdrawal of consent from trial including data collection, will continue to be followed-up for disease progression and late toxicity.

On confirmed tumour progression, further formal follow-up within the trial ceases apart from ultimately recording date and cause of death of death.

10.2 Withdrawal of Consent

If a patient explicitly states their wish not to contribute further data to the study their decision must be respected and recorded on the Withdrawal form. Details should be recorded in the patient's hospital records and no further CRFs should be completed.

10.3 Moving

For patients moving from the area, every effort should be made for the patient to be followed up at another participating trial centre and for this new centre to take over the responsibility for the patient, or for follow-up via GP.

10.4 Lost to follow-up

If a patient is lost to follow-up every effort should be made to contact the patient's GP (if consented) to obtain information on the patient's status.

11 Data Handling

Please photocopy all completed CRFs, and retain the photocopy in the patient file at site. The original copy should be sent to the CTC.

Incoming forms will be checked for completeness, timeliness and compliance with the protocol prior to entry on database.

Any omissions in data should be noted on the CRFs. Regular data query requests and requests for any missing or outstanding will be made at intervals by the Data Manager. Any amendments to the CRFs must be initialled and dated by authorised personnel.

12 Confidentiality and Archiving

All information collected during the course of the trial will be kept strictly confidential. Information will be held on paper and electronically at the CTC. Both will comply with all aspects of the 1998 Data Protection Act.

All data collection forms will be coded with a trial number and will include two patient identifiers, usually the patient's initials and date of birth.

Any hospital reports received from the local sites must have personal details removed and identified using patient initials and trial number.

Consent from patients for access to their medical records by responsible individuals from the research staff or from regulatory authorities will be confirmed at site monitoring visits.

If a patient withdraws consent from further trial treatment but not from data collection, their data will remain on file and will be included in the final study analysis.

At the end of the trial, the CTC will archive securely all trial related documentation for 5 years. Arrangements for confidential destruction will then be made. Each local site must also retain trial documentation for 5 years.

If a patient withdraws consent for their data to be used, it will be confidentially destroyed immediately.

13 Statistical Considerations

If the results indicate that the R0 resection rate is consistent with a true rate of at least 75% then the proposed regimen is deemed worthy of further investigation in a future phase III trial. The R0 resection rate is about 50-60% in the intention-to-treat population using single agent fluoropyrimidine (5FU or capecitabine) as a radiation sensitiser - we use the midpoint of 55% in the sample size calculation. With the addition of irinotecan and cetuximab we expect this to increase to at least 75%. Using a Fleming's design with 80% power (and one-sided test of statistical significance at the 5% level), 35 patients would be required. Initially the recruitment target was 40 patients, which would allow for some drop-outs, this has been updated to 80 patients.

In the NWCOG-2 (RICE) trial and other studies of irinotecan-containing CRT regimes, diarrhoea is the most common serious toxicity. Within RICE 20% of 91 patients suffered grade 3 or 4 diarrhoea (all grade 3 apart from one grade 4). In the proposed study a true grade 3 or 4 diarrhoea rate of more than 30% would be unacceptable (as is standard for chemoradiation studies in pelvic cancers). We will monitor the number of grade 3 or 4 toxicities during the course of the trial. Given the original sample size of 40 patients, we would consider stopping the study early if 17 patients with a grade 3 or 4 diarrhoea were observed, since the probability of this occurring by chance if the true toxicity rate were 30% is 0.03.

Data on toxicity from the first 20 patients followed for at least one month following completion of CRT will be reviewed by an Independent Data Monitoring Committee (IDMC). This analysis, will be performed by the trial statistician and remain confidential to the IDMC. The IDMC will be asked to give advice on whether the trial should stop early because of unacceptable toxicities.

An analysis of the main outcomes will also be carried out, comparing the results of patients based on whether they are found to be KRAS wildtype or KRAS mutant.

The original proposal for EXCITE was based on seeing an increase in the R0 resection rate from 55% when using single agent fluoropyrimidine to 75% with the addition of irinotecan and cetuximab. This would have required 35 patients to achieve 80% power, using a Fleming's design, and the aim was to recruit 40 patients.

Since the planning of EXCITE, evidence has emerged that cetuximab is not effective in patients who have a KRAS mutant tumour (Lievre A , Bachet JB , Le Corre D , et al, Cancer

Res. 2006 ; and reviewed in Siena S, Sartore-Bianchi A, Di Nicolantonio F, et al, JNCI 2009). However as yet it is not known whether this would also be true when cetuximab is used in combination with radiotherapy as a radiation sensitiser, as is happening in EXCITE.

We are therefore proposing to increase the sample size of EXCITE from 40 to 80 patients. KRAS has been found to be mutated in 35-40% of colorectal adenocarcinomas (Barault L , Veyrie N , Jooste V , et al . Int J Cancer . 2008). Increasing the sample size to 80 patients would ensure that there are at least 40 K-RAS wild type tumours that can be analysed with respect to the R0 resection rate, as per the original design of the trial. Based on a 60% prevalence of wild type tumours, the chances of getting at least 40 such tumours from 80 patients are 97%. The increase in sample size is entirely due to having sufficient evidence to evaluate the effect of the planned treatment regimen on the R0 resection rate in K-RAS wild type tumours. This trial has not been powered to test for any significant differences between the patients with KRAS wild type and mutant tumours.

14 Trial Monitoring and Oversight

Participating sites and Principal Investigators 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 On-site monitoring

The degree of on-site monitoring will be proportionate to the objective, purpose, phase, design, size, complexity, blinding, endpoints and risks associated with the clinical trial.

Sites will be sent a letter in advance confirming when a routine monitoring visit is due. 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.

The Trial Coordinator will visit high recruiting sites at least once over the duration of the trial, as documented in the trial monitoring plan.
The purpose of these visits is to:

- Verify that the rights and well-being of patients/participants are protected
- Verify accuracy, completion and validity of reported trial data from the source documents.
- Evaluate the conduct of the trial within the institution with regard to compliance with the currently approved protocol, GCP and with the applicable regulatory requirements.

As detailed in the trial Monitoring Plan, the following checks will be undertaken for a proportion of patients:

- Source Data Verification of patient informed consent, eligibility, safety reporting and capturing of trial endpoints.

- Review of the Investigator Site File for filing of essential documents
- Visit pharmacy to perform checks on drug accountability, drug storage, temperature recording and filing of essential documentation.

Monitoring report

Following a monitoring visit, the 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 Principal Investigator at each site will be responsible for ensuring that monitoring findings are addressed (this may be delegated to an appropriate member of staff).

14.2 Central monitoring

Data stored at UCL CTC will be checked for missing or unusual values (range checks) and checked for consistency over time. If any problems are identified data queries will be issued to the site. Sites are required to resolve any queries and update the relevant CRF as required. All changes must be initialled and dated. The amended version must be sent to UCL CTC and a copy retained at site.

Sites will also be requested to submit screening logs and staff delegation logs to UCL CTC on request and these will be checked for consistency and completeness.

Copies of completed drug accountability logs will be collected at UCL CTC for all trial patients. Sites will be required to submit logs following the patient's completion of trial treatment or on request. At least 10% of the logs from each site, always including the log for the first patient enrolled at site, will be monitored centrally (unless already conducted at an on-site visit) to ensure completeness and correlation with data collected in the CRF.

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.

Where central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk (e.g. evidence of an overdose having been administered, indication that dose modifications for an IMP were not observed following an

adverse reaction, etc.), the matter will be raised urgently with site staff and escalated as appropriate (refer to section 14.4 (‘For cause’ on-site monitoring) and 16 (Incident Reporting and Serious Breaches) for further details).

14.3 'For cause’ on-site monitoring

Additional 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/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.

15 Pharmacovigilance

15.1 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

All untoward and unintended responses to a trial treatment related to any dose administered. A causal relationship between a 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

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 or 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.

15.2 Reporting Procedures

15.2.1 All Adverse Events (AEs)

All adverse events that occur between the signing of informed consent and 36 months after patient completes CRT 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 The fact that an overdose has occurred must be clearly stated on the SAE Report. Also refer to section 15.2.2 (Serious Adverse Events (SAEs)).

Pre-existing conditions do not qualify as adverse events unless they worsen.

15.2.1.1 Overdoses

All accidental or intentional overdoses, whether or not they result in adverse events, must be recorded in the patient notes and CRFs. Overdoses resulting in an adverse event are classified as SAEs and must also be reported to UCL CTC according to SAE reporting procedures. Also refer to section 15.2.2 (Serious Adverse Events (SAEs)).

Sites must inform UCL CTC immediately when an overdose has been identified. Refer to section 16 (Incident Reporting and Serious Breaches).

15.2.1.2 Adverse Event Term

An adverse event term needs to be provided for each adverse event, preferably using the Short Name as listed in the Common Terminology Criteria for Adverse Events (CTCAE) v3.0, available online at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

15.2.1.3 Severity

Severity for each adverse event must be determined by using the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 as a guideline, wherever possible. The criteria are available online at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

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

1 = Mild (aware 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 results in death)

15.2.1.4 Causality

The PI, or other delegated site investigator, must perform an evaluation of causality for each adverse event. Causal relationship to each 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.

15.2.2 Serious Adverse Events (SAEs)

All SAEs that occur between the signing of informed consent and 30 days post the last trial treatment administration (or after this date if the site investigator feels the event is related to the trial treatment) must be submitted to UCL CTC by fax within **1 business day** 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 1 business day to UCL CTC, the circumstances that led to this must be detailed in the SAE report to avoid unnecessary queries.

15.2.2.1 Exemptions from SAE Report Submission

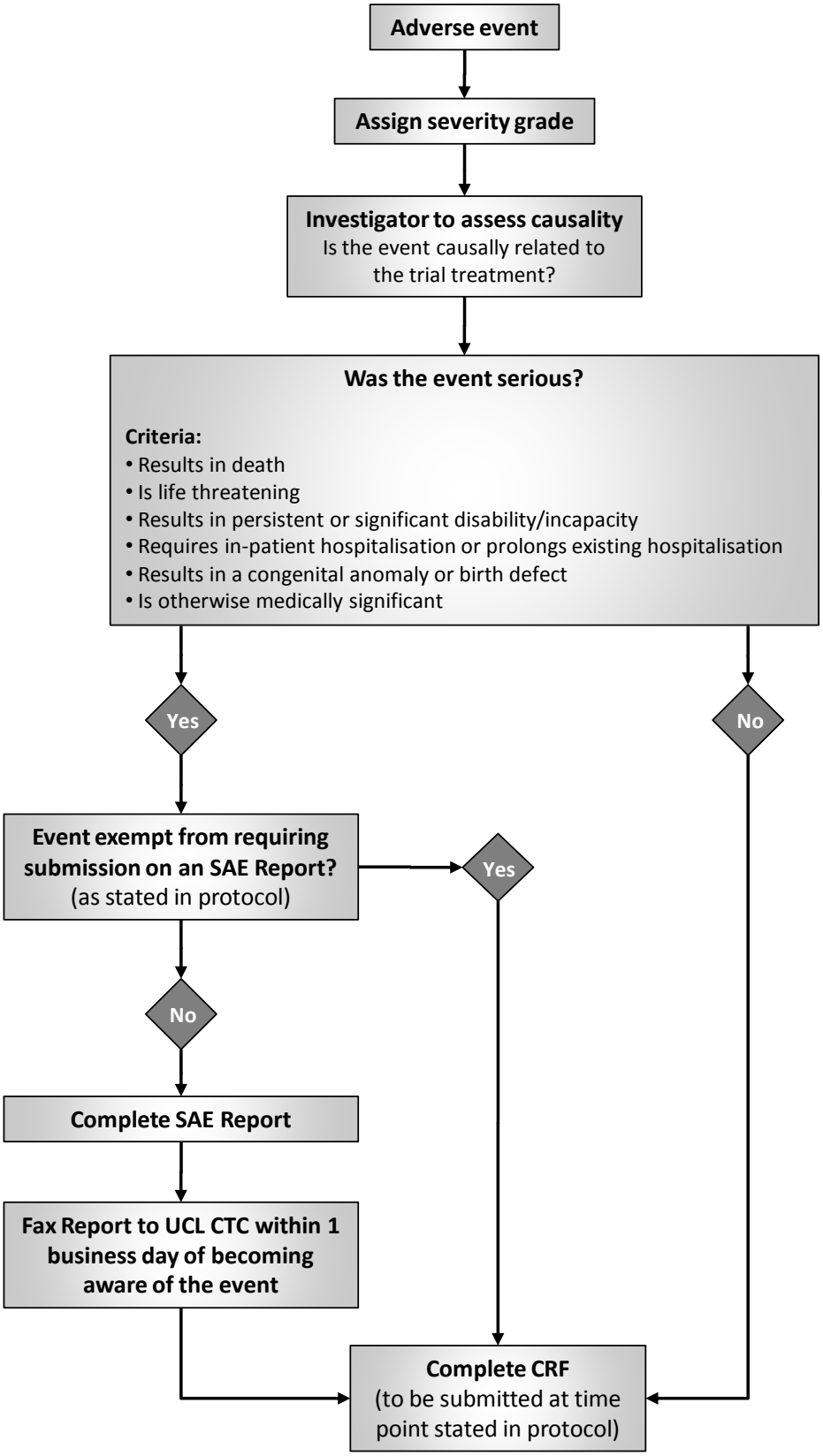
For this trial, the following events are exempt from requiring submission on an SAE Report, but must be recorded in the relevant section(s) of the trial CRF:

- 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 1 business day of becoming aware of the event to UCL CTC
Fax: 020 7679 9871

15.2.2.2 Adverse Event Reporting Flowchart



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.

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. Expectedness will be evaluated using the list of expected adverse events in the current IB for cetuximab and SPC for capecitabine and irinotecan.

The SAE Report will be submitted to the Chief Investigator, or their delegate (e.g. a clinical member of the TMG), for review and for them to perform an evaluation of causality on behalf of UCL CTC. If UCL CTC has considered expectedness difficult to determine, the Chief Investigator will be consulted for their opinion. The Chief Investigator must respond to the trial team within 1 business day.

UCL CTC will submit reports of SARs related to irinotecan to Pfizer within 1 business day if the patient received trial supplies (rather than hospital commercial supplies) of irinotecan. SAE Reports that are related to the trial drug cetuximab are not required to be reported to Merck, unless the event is a SUSAR.

15.3 SUSARs

If the event is evaluated as a Suspected Unexpected Serious Adverse Reaction (SUSAR), UCL CTC will submit a report to the MHRA and 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 the Chief Investigator, both opinions will be reported.

All SUSARs which are related to irinotecan will be reported to Pfizer and those related to cetuximab will be reported to Merck within 1 business day.

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.

UCL CTC will forward reports regarding SUSARs that have occurred on other trials using cetuximab to all PIs. These must be processed according to local requirements and filed with the applicable IB*.*

15.4 Additional Safety Monitoring at UCL CTC

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

Trial safety data will be monitored to identify:

- new adverse reactions to the trial treatment regimen or individual trial treatments;
- a higher incidence in rare adverse events than is stated in the IB/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.

15.5 Pregnancy

If a female patient or a female 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 **1 business day** of learning of its occurrence. Consent to report information regarding the pregnancy must be obtained from the pregnant patient/partner. 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 1 business day of becoming aware of the pregnancy to UCL CTC

Fax: 020 7679 9871

15.5.1 Pregnancy Follow-Up Reports

For pregnant patients or partners who consent, their pregnancies must be followed-up until an outcome is determined. Follow-up Pregnancy Reports must be submitted to UCL CTC by fax within **1 business day** of learning of the outcome. Reports must include an evaluation of the possible relationship of the trial treatment to the pregnancy outcome.

15.5.2 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 15.2.2 (Serious Adverse Events (SAEs)) for details.

15.5.3 Pregnancy Report Processing at UCL CTC

UCL CTC will fax all Pregnancy Reports to Merck where the pregnancy has occurred in patients, or their partners, who have been exposed to cetuximab, and Pfizer where the patient has been exposed to irinotecan within 1 business day of CTC becoming aware.

UCL CTC will submit Pregnancy Reports to the MHRA and REC should the pregnancy outcome meet the definition of a SUSAR. Pfizer and Merck will be notified of the submission to the MHRA and REC where the pregnancy outcome is evaluated as having a causal relationship to the drugs they provide.

15.6 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.

16 Incident Reporting and Serious Breaches

16.1 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).

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

16.2 Serious Breaches

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, 2009).

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

17 Ethical and Regulatory Approvals

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 principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) as set out in Schedule 1 (Conditions and Principles of Good Clinical Practice and for the Protection of Clinical Trial Subjects) of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the GCP Directive 2005/28/EC, as set out in SI 2006/1928
- 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)

17.1 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 National Research Ethics Service Committee: South Central – Oxford B.

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

17.2 Regulatory Approval

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

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

17.3 Local Site Approval

Any new sites joining this study must submit evidence of local Trust R&D approval to UCL CTC prior to site activation. The trial will only be conducted at sites where all necessary approvals for the trial have been obtained.

17.4 Protocol Amendments

UCL CTC will be responsible for gaining ethical and regulatory approvals, as appropriate, for all amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for gaining local Trust R&D acknowledgement for all amendments and approval for substantial amendments, and for providing UCL CTC with evidence of this.

17.5 Patient Confidentiality & Data Protection

Patient identifiable data, including initials, date of birth and hospital 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.

18 Sponsorship and Indemnity

18.1 Sponsor Details

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

18.2 Indemnity

Non-negligent harm: University College London, as Sponsor, holds insurance cover that will provide compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London. Participants who sustain injury and wishing to make a claim for compensation should do so in writing to the Chief Investigator in the first instance.

Negligent harm: Participants in this clinical trial are also able to seek compensation via a negligent harm route but this would involve proving negligence on the part of University College London. Insurance cover is held by University College London to cater for this but it is expected that any claim for compensation would be via the non-negligent harm route by virtue of compensation being paid without the need to prove negligence. 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 employees of hospitals. This applies whether the hospital is a UK NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

19 Biological Studies

19.1 Collection of tumour tissue

19.1.1 DNA analysis

For all patients entering the study, formalin-fixed paraffin-embedded (FFPE) tumour tissue samples removed during a routine diagnostic biopsy and at surgery will be collected for DNA

analysis. The tissue will be analysed in the laboratory of Dr Nick West at Leeds Institute of Molecular Medicine for the presence of mutations in the KRAS and BRAF genes. The results of these analyses will not be used to influence the clinical management of the patient but instead will be used to examine the association of KRAS and BRAF mutations with patient outcome after CRT.

Extracted DNA will be transferred to the laboratory of Dr Edgar Hartsuiker in the School of Biology, University of Bangor who will examine genetic mechanisms of resistance to irinotecan.

19.1.2 Immunohistochemical analyses

FFPE tumour tissue will also be used to investigate the levels of a variety proteins that may be of prognostic or predictive significance in rectal cancer patients receiving CRT. These investigations will include immunohistochemical (IHC) analysis of proteins including, but not necessarily limited to: Topo-1, TS, p53, Ki67, EGFR, HMLH-1, HMSH-2, HMSH-6, PMS-2, ERCC-1 and MGMT.

19.1.3 Storage for future research

Patients will be asked to consent to their FFPE tumour tissue samples (collected during routine biopsies or surgery) to be stored and used in future research studies and specifically for testing *TP53* mutations in rectal cancer as outlined in Appendix 4. These studies may include genetic analyses. All samples used for such work will be coded and kept in premises licensed for storage of such specimens for research purposes. All future research will be ethically approved. The FFPE tumour tissue samples will be returned to the site after the testing has been completed, unless the patient has consented to storage of their tumour tissue for future research.

Patients who do not wish to consent to the storage and use of their tissue samples will still be eligible to enter the trial.

19.1.4 Testing for UGT1A1 genetic polymorphisms

The regimen being tested being tested in the EXCITE trial includes irinotecan as a radiation sensitiser. The use of irinotecan and capecitabine as radiation sensitisers in the present trial directly follows their use in this context in the NWCOG-2 trial (RICE; Gollins et al,'06). The most common serious toxicity seen in the NWCOG-2 trial was diarrhoea, occurring in approximately 20% of patients (almost always grade 3 rather than grade 4). It is impossible to precisely define the relative contributions to diarrhoea of the components used in CRT

regime (RT, capecitabine, irinotecan). However, it is likely that irinotecan plays a large part in this in view of the fact that diarrhoea is one of the main toxicities associated with this drug.

It would be of major benefit if patients liable to develop grade 3 or 4 diarrhoea on the regimen being tested in the EXCITE trial, could be identified prior to treatment starting. If this was due to the irinotecan component of the regimen, for example, then these patients could be directed away from an irinotecan-containing regimen towards an alternative regimen without irinotecan.

Irinotecan metabolism

In normal and tumour tissues the hydrolysis of irinotecan leads to the formation of SN-38, a potent topoisomerase inhibitor. SN-38 formation within the tumour may be an important determinant of antitumour activity. The inactivation of SN-38 occurs by glucuronidation to SN-38 glucuronide (SN-38G) via the enzyme uridine diphosphate glucuronyltransferase (UGT). The isoform UGT1A1 is mainly responsible for this conversion and is located in the liver and also in extrahepatic tissues (Innocenti et al,'06). Canalicular transport of both SN-38 and SN-38G occurs into the biliary tree, with subsequent excretion to small bowel where it is thought that the SN-38 causes diarrhoea.

UGT1A1 genotype and the relationship to irinotecan toxicity

More than 50 genetic lesions in the promoter and coding regions of the gene UGT1A1 gene have been described (Kadakol et al,'00), leading to constitutional unconjugated jaundice (Crigler-Najar or Gilbert's syndrome). One of the most common genotypes causing Gilbert's syndrome in Caucasian populations is the inheritance of a promoter region containing an extra TA dinucleotide [A(TA)7TAA], which results in a 70% reduction in transcriptional activity compared with wild-type UGT1A1 [A(TA)6TAA]. Patients who are either heterozygous or homozygous for this variant allele (designated as UGT1A1*28) exhibit an attenuated expression of UGT1A1 and are theoretically exposed to a higher exposure to SN-38 and consequent side effects including diarrhoea. The frequency of *1 / *1, *1 / *28 and *28 / *28 genotypes varies depending on different ethnicities (24% to 77%, 13% to 39% and 1% to 24% respectively) (Innocenti et al,'06).

Recent studies have identified an increased risk of irinotecan toxicity in patients with the UGT1A1*28 allele compared to homozygotes for the wild type allele (UGT1A1*1). The risk of severe toxicity of irinotecan (both haematologic and GI) is higher in *28 / *28 patients compared to *1 / *1 and *1 / *28 patients, with an odds ration ranging from 7.2 to 11 in different studies (Ando et al,'00; Innocenti et al,'04; Rouits et al,'04; Marcuello et al,'04).

For example, Marcuello et al (2004) reported on 95 patients with metastatic colorectal cancer treated with an irinotecan-containing chemotherapy. Severe diarrhoea was observed in 7/10 (70%) patients homozygous for the UGT1A1*28 allele and 15-45 (33%) heterozygous for the allele in comparison to 7/40 (17%) of homozygous wild-type patients (P=0.005). The presence of severe haematological toxicity increased from wild-type patients to UGT1A1*28 homozygotes, but without reaching statistical significance. No relationship was found between the UGT1A1*28 genotypes and infection, nausea, mucositis, response rate or overall survival. In multivariate analysis this result was confirmed.

19.2 Consent for donation of blood samples (RAPPER study)

Patients will be asked to consent to the collection (prior to chemoradiation) of two, 10 ml samples of venous blood. These will be collected simultaneously. One sample will be used for testing for UGT1A1 polymorphisms. The other will be stored for use in future research, which may include genetic analyses and specifically the translational studies to test for *FcγRIIa-H131R* and *FcγRIIIa-V158F* single nucleotide polymorphisms in rectal cancer as outlined in Appendix 4. All future research will be ethically approved. The samples will be stored at the Paterson Institute in Manchester until use (Paterson Institute for Cancer Research, Christie Hospital, Wilmslow Road, Manchester M20 9BX, Tel 0161 446 3156). The Paterson Institute is licensed (licence number 11081) for the storage of human tissue for research, by the Human Tissue Authority as stipulated in the Human Tissue Act 2004.

The full title of the RAPPER study is; Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of Radiotherapy. Consent for participation in the RAPPER study is obtained under the auspices of the EXCITE study, however, the RAPPER study is a separate, ethically approved study approved by Cambridge Research Ethics Committee (05/Q0108/365) and the responsibility for these samples rests with the sponsor, University of Manchester.

19.2.1 Proposed ancillary study

The evidence described above (section 19.1.4) points to UGT1A1 polymorphisms as being involved in irinotecan toxicity. Up until the present time, UGT polymorphism testing has only been carried out to any significant degree in patients receiving irinotecan-containing chemotherapy alone and not in the context of CRT regimens containing irinotecan.

It is of great interest to be able to identify which patients might develop serious toxicity on treatment with irinotecan-containing chemoradiation regimens before they embark on treatment. A donation of a single sample of blood in a standard 10 ml EDTA tube (to be

obtained simultaneously with 2nd sample to be used in RAPPER study) which will then be stored at the Paterson Institute for Cancer Research in Manchester until use. The blood sample will be tested for the presence of the following panel of UGT1A1 polymorphisms:

Allele Name	**Nucleotide Change**
UGT1A1 Promoter TA repeat (*28, *36, *37)	5-8 TA repeats
UGT1A1 *60	3279 T to G
UGT1A1–3156	3156 G to A
UGT1A1 *6	211 G to A
UGT1A1 *27	686 C to A

All blood samples will be stored and tested anonymously and no results will be fed back to patients.

The UGT1A1 analysis will be conducted by Dr William Newman at the University of Manchester (Genetic Medicine, MAHSC, University of Manchester, St Mary's Hospital, Manchester, M13 9WL).

20 Trial Management & Trial Committees

20.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities and EXCITE trial staff from UCL CTC (see page 2). The TMG will be responsible for overseeing the trial. The group will meet regularly twice a year and will send updates to Principal Investigators (via newsletters or at Investigator meetings) and to the NCRI Rectal Cancer 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.

20.2 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 of behalf of the funder and Sponsor.

20.3 Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. The data will be reviewed at significant points during the trial by an IDMC, consisting of at least two clinicians not entering patients into the trial and a statistician. The IDMC will be asked to recommend whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

20.4 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 15 (Pharmacovigilance).

21 Publication

The results from all centres will be analysed together and published as soon as possible. Individual participants may not publish data concerning their patients that are directly relevant to questions posed by the study until the Trial Management Group has published its report. The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications.

All publications shall include a list of participants, and if there are named authors, at a minimum these should include the Chief Investigator(s), Clinical Trial Manager(s), and Statistician(s) involved in the trial.

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.

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Appendix 1 - Abbreviations and Glossary

ALT	Alanine Aminotransferase
AE	Adverse Event
AR	Adverse Reaction
ASCO	American Society for Clinical Oncology
AST	Aspartate Aminotransferase
bd	Twice daily
C225	Cetuximab
Cap	Capecitabine
CDK	Cyclin Dependent Kinase
CEA	Carcino-Embryonic Antigen
CI	Chief Investigator
CRC	Colorectal cancer
pCR	pathological Complete Response
CRF	Case Report Form
CR-UK	Cancer Research UK
CRM	Circumferential Resection Margin
CRT	Chemoradiotherapy
CT	Computed Tomography
CTA	Clinical Trials Authorisation
CTAAC	Clinical Trials Advisory and Awards Committee
CTC	Cancer Trials Centre
DPA	Data Protection Act
DPD	Dihydropyrimidine dehydrogenase
DNA	Deoxyribonucleic acid
DRR	Digitally reconstructed radiograph
DSUR	Development Safety Update Report
EDTA	Ethylene diamine tetraacetic acid
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
EPI	Electronic portal imaging
FA	Folinic acid (a.k.a. leucovorin)
FBC	Full Blood Count
FDA	Food and Drug Administration
FFS	Failure-free Survival
5FU	5-Fluorouracil
GCSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GP	General Practitioner
HCG	Human Chorionic Gonadotrophin
HR	Hazard Ratio
IB	Investigator's Brochure
IBW	Ideal Body Weight
ICH	International Congress on Harmonisation
IDMC	Independent Data Monitoring Committee
IFL	Irinotecan, 5FU and leucovorin
IgG	Immunoglobulin gamma
IHC	Immunohistochemistry
INR	International Normalised Ratio
ITT	Intention-to-treat

IV	Intravenous
LFTs	Liver Function Tests
m^2	Metre Squared
mg	Milligram
ml	Millilitre
MdG	Modified de Gramont
MHRA	Medicines and Healthcare Products Regulatory Agency
MLC	Multileaf collimator
MRC	Medical Research Council
MRI	Magnetic Resonance Image
MREC	Multi-centre Research Ethics Committee
MTD	Maximum Tolerated Dose
M225	Murine anti-EGFR antibody
NCRI	National Cancer Research Institute
NCI	National Cancer Institute (USA)
NICE	National Institute for Clinical Excellence
NWCOG	North West/North Wales Clinical Oncology Group
od	Once daily
Ox	Oxaliplatin
ONS	Office of National Statistics
OS	Overall Survival
PI	Principal Investigator
PFS	Progression-Free Survival
po	By mouth
prn	When necessary
PS	Performance Status
PVI	Protracted venous infusion
QALY	Quality Adjusted Life-Years
qds	Four times daily
QL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
tds	ter die sumeudum. Three times daily
TGF-α	Transforming Growth Factor alpha
TMA	Tissue Microarray
TMG	Trial Management Group
TP	Thymidine Phosphorylase
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
U&Es	Urea & Electrolytes
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organisation

Appendix 2 - WHO Performance Status

Score	Description
0	Able to carry out all normal activity without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to do light work.
2	Ambulatory and capable of all self-care but unable to carry out any work. Up and about more than 50 % of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Appendix 3 - Cockroft-Gault Formula

The estimated GFR is given by:

Males: $\frac{\textbf{1.25} \times (140-\text{age}) \times \text{weight (kg)}}{\text{Serum creatinine } (\mu\text{mol/l})}$

Females: $\frac{\textbf{1.05} \times (140-\text{age}) \times \text{weight (kg)}}{\text{Serum creatinine } (\mu\text{mol/l})}$

Appendix 4 - Translational Study and Methodology

Since the conception of the EXCITE trial, interesting data have emerged on potential biomarkers which can predict clinical benefit of a cetuximab-based chemoradiotherapy in locally advanced rectal cancer. Therefore, we plan to investigate the predictive role of these biomarkers in this study population.

The sections below outline the planned research to be performed on the collected tissue samples, clarify the methodology and provide the rationale for testing additional biomarkers.

Any patient material will be used with the only purpose to correlate patient characteristics with treatment outcome. All specimens will be anonymised and patient identification by a third party will not be allowed. Results on specific analyses will not be corresponded with patients or third parties, since results will be of no diagnostic or therapeutic value.

All patient data will be held in accordance with the Data Protection Act 1998 and the Freedom of Information Act 2000.

There is currently no evidence that any of the below mentioned germ-line sequence variations and gene mutations have genetic implications and therefore the outcome of these analyses will not produce findings of clinical significance to the patients or their relatives.

1. Rational for testing *TP53* mutations in rectal cancer

TP53 is a tumour suppressor gene located in chromosome 17p and encodes a nuclear phosphoprotein involved in the regulatory control of cell proliferation and response to DNA damage. In the presence of a variety of damage signals, p53 acts as a transcription factor mediating changes in gene expression that ultimately promote cell cycle arrest, senescence or apoptosis. In colorectal cancer, *TP53* mutations have been reported in approximately 50% of cases and are associated with the late stage of the classical adenoma-carcinoma pathway of carcinogenesis. Most *TP53* mutations involve the DNA-binding domain and result in the inactivation of p53 function and an increased risk of cellular transformation and tumour progression.

Several studies showed that *TP53* mutations predicted resistance to radiotherapy in rectal cancer. Recently, in a retrospective analysis of the EXPERT-C trial, *TP53* status was found

to predict clinical benefit from cetuximab in locally advanced rectal cancer patients treated with neoadjuvant systemic chemotherapy followed by pre-operative chemoradiotherapy [1]. In particular, patient with *TP53* wild-type tumours had a significant survival benefit (in terms of both progression-free survival and overall survival) when cetuximab was added to standard therapy. Of note, this effect was independent of other variables including the tumour *RAS* status.

2. TP53 analysis

DNA will be extracted from sections which are representative of the tumour (i.e. contain more than 30-50% tumour cells if possible) according to standard laboratory procedures. The extracted DNA will be sent for mutational analysis to the Department of Molecular Diagnostics, Centre for Molecular Pathology, The Royal Marsden NHS Foundation Trust, Sutton, SM2 5NG.

The mutational status of *TP53* will be assessed by using a highly sensitive next generation sequencing (NGS) technique. This allows the simultaneous mutational analysis of four additional genes (including *KRAS*, *NRAS*, *BRAF* and *PI3KCA*) which are downstream of EGFR and could be potentially associated with the activity of cetuximab in this setting.

The mutational status of *TP53* and the above mentioned genes will be correlated with short-term (tumour response to treatment and pathologic complete response rate) and long-term outcomes (local relapse-free survival, distant metastases-free survival, progression-free survival, overall survival) of the study population.

3. Rational for testing *FcγRIIa-H131R* and *FcγRIIIa-V158F* single nucleotide polymorphisms in rectal cancer

Cetuximab may exert its antitumour activity by enhancing the mechanism of antibody-dependent cellular cytotoxicity (ADCC). When the antigen-binding fragment (Fab) and the crystalline fragment (FC) of cetuximab engage the tumour cell antigen and a FC gamma receptor (FcγR) on an effector cell, respectively, immune cells (including monocytes, macrophages and activated natural killer (NK) cells) recognise and attack antibody-coated tumour cells.

Single nucleotide polymorphisms in the coding regions of *FcγRIIA* (C>T substitution at position 131 which changes the amino acid from histidine to arginine) and *FcγRIIIA* (T>G substitution at position 158 which changes the amino acid from valine to phenylalanine) have been reported to modulate the anti-tumour activity of monoclonal antibodies.

In a recent retrospective analysis of the EXPERT-C trial, these polymorphisms have been found to correlate with clinical benefit from cetuximab in locally advanced rectal cancer patients treated with neoadjuvant systemic chemotherapy followed by pre-operative chemoradiotherapy [2]. In particular, patients carrying 131R and 158F alleles had better survival compared to patients homozygous for the 131H and/or 158V allele when cetuximab was administered in association with standard treatment.

4. *FcγRIIa-H131R* and *FcγRIIIa-V158F* single nucleotide polymorphism analysis

DNA will be extracted from peripheral blood mononuclear cells (PBMC) according to standard laboratory procedures and sent to the Department of Molecular Diagnostics, Centre for Molecular Pathology, The Royal Marsden NHS Foundation Trust, Sutton, SM2 5NG.

Polymorphism analyses of *FcγRIIa* and *FcγRIIIa* will be done as previously described by Sclafani et al [2].

The single nucleotide polymorphisms of *FcγRIIa* and *FcγRIIIa* will be correlated with short-term (tumour response to treatment and pathologic complete response rate) and long-term outcomes (local relapse-free survival, distant metastases-free survival, progression-free survival, overall survival) of the study population.

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