FOxTROT Protocol

Fluoropyrimidine, **Ox**aliplatin & **T**argeted **R**eceptor pre-**O**perative **T**herapy for colon cancer

A randomised trial assessing whether preoperative chemotherapy and/or an anti-EGFR monoclonal antibody improve outcome in high-risk operable colon cancer

Postoperative chemotherapy improves survival for patients with stage III (node-positive) colorectal cancer. There is now also good evidence – from the QUASAR1 study and meta-analysis - that survival is improved in stage II (node-negative) disease. However, for many patients the current treatment strategy of surgical excision followed by adjuvant chemotherapy still fails either to clear locoregional spread or to eradicate distant micrometastases, leading to disease recurrence.

Preoperative chemotherapy has been shown to be more effective than postoperative chemotherapy in many other cancers and it has the potential to also improve outcome in colon cancer. Optimal systemic therapy at the earliest possible opportunity may be more effective at eradicating distant metastases than the same treatment given after the delay and immunological stress of surgery. Added to this, shrinking the primary tumour before surgery may reduce the risk of incomplete surgical excision, and the risk of tumour cell shedding during surgery.

FOxTROT is a randomised trial aiming to establish whether giving the first 6 weeks of combination chemotherapy prior to surgery improves the probability of cure for patients with high-risk operable colon cancer, and whether results can be further improved, in patients with *KRAS*-wildtype tumours, by adding the anti-EGFR monoclonal antibody panitumumab. As well as evaluating these two novel approaches, FOxTROT also provides a unique opportunity for translational research to identify tumour markers predictive of response to chemotherapy and to anti-EGFR therapy.

Any patient whose standard treatment is likely to comprise surgery followed by adjuvant oxaliplatin/FU combination chemotherapy should be considered for inclusion in **FOxTROT**. Entry is based on a CT scan staging algorithm, which identifies patients whose disease is locoregionally advanced, and therefore at significant risk of relapse following standard treatment. If allocated pre-operative chemotherapy, the first 6 weeks are given preoperatively and the rest of the course is given postoperatively. If allocated standard chemotherapy, the whole course is given postoperatively. The recommended chemotherapy regimen is 24 weeks of oxaliplatin plus modified de Gramont infusional fluorouracil (OxMdG). Clinicians can, however, opt to use a shorter 12-week course of chemotherapy ('FOxTROT lite') for patients for whom 24 weeks is considered excessive (eg because of age/frailty or moderate recurrence risk). Patients with *KRAS*-wildtype tumours are randomised to receive panitumumab with the first 6 weeks of chemotherapy or to control. For patients with *KRAS*-mutant tumours, who are not eligible for the panitumumab randomisation, clinicians can opt to use oxaliplatin plus capecitabine (OxCap) chemotherapy instead of OxMdG.

The **FOxTROT** pilot stage has demonstrated the feasibility, safety and tolerance of pre-operative therapy in over 100 patients, all treated with OxMdG chemotherapy. A parallel audit comparing radiological and pathological staging has also indicated that the **FOxTROT** entry criteria can be widened to include all radiological T3 tumours. The full study aims to randomise 1050 T3 and T4 patients, in a 2:1 ratio, between pre- plus post-operative and post-operative chemotherapy alone, which will provide over 80% power to detect a 25% proportional reduction in the primary outcome of recurrence at 2 years (eg 32% reduced to 24%). The primary outcome measure for the panitumumab comparison will be pathological down-staging following preoperative chemotherapy. The success of **FOxTROT** depends on the wholehearted support of the surgical, radiological, pathological and oncological communities and, to recognise this, publication of the main results will be in the names of all collaborators and not those of the central organisers.

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1. BACKGROUND

Rationale for neoadjuvant chemotherapy in colon cancer

After lung cancer, colorectal cancer (CRC) is the most common malignant disease in developed countries, with about a million new cases and 500,000 deaths worldwide each year.[1] The primary treatment is resectional surgery, which is possible in 80% of patients. Despite apparently curative surgery, about half of resected patients subsequently develop incurable recurrent disease. It is now established that adjuvant combination chemotherapy produces a moderate but persistent improvement in survival for patients with stage III (node-positive) CRC. There is now also good evidence – from the QUASAR1 study[2] and meta-analysis – that chemotherapy in stage II (node-negative) disease reduces the risk of recurrence and death from CRC. Nevertheless, for many patients the current treatment strategy of surgical excision followed by adjuvant chemotherapy fails either to clear locoregional spread or to eradicate distant micrometastases.

Preoperative ('neoadjuvant') chemo- and radiotherapy have been shown to be more effective than postoperative therapy in a number of GI and other cancers. Preoperative chemotherapy is an attractive concept for colon cancer as it has the potential to impact upon both local and distant failure. Postoperative adjuvant therapy is not usually started until 2-4 months after the initial diagnosis of cancer. The doubling time of CRC metastases is such that this delay may well reduce the likelihood of chemotherapy eradicating micrometastatic disease.[3,4] In addition, treating micrometastatic disease prior to surgery may be a better strategy because surgery stimulates enhanced growth factor activity in the early post operative period, with the capacity to promote rapid tumour progression.[5-7] Pre-operative therapy, which can be started within days of the diagnostic and staging investigations, may potentially eradicate micrometastases which would otherwise become irreversibly established during this period.

Preoperative therapy may also have beneficial effects on the primary tumour and regional spread. Only 10% of colon cancer recurrence is primarily confined to the resection site, but the proportion of metastases that subsequently develop because of incomplete local clearance is far higher, and locoregional recurrences may subsequently have a more aggressive phenotype.[8] Preoperative therapy could potentially reduce tumour cell shedding at the time of surgery, a process thought to contribute to dissemination of tumour cells at the time of operation.[9] Peritoneal metastases are a feature in around 50% of patients with recurrent disease and, once established, have a poor response to systemic therapy.[10] Other potential practical benefits exist: by giving drug therapy at a time when its effects are observable, an assessment of response may be made, which could potentially guide decisions about postoperative therapy. It is also possible that, as in oesophageal cancer, the preoperative setting may allow drug benefits to be achieved with relatively brief exposures, which would have both quality of life and cost benefits.

Although preoperative anticancer therapy has been studied in many solid tumour types, and has been shown to be of benefit in several in the GI tract (for example oesophageal, gastric and rectal cancers), it has not, until now, been studied in colon cancer. There are several reasons for this: drug therapy until recently gave low response rates, leaving a significant risk of tumour growth during the neoadjuvant treatment phase; radiological staging was inaccurate, and the value of chemotherapy in node-negative disease was unproven, which together made it difficult to exclude from treatment patients who would be better managed with surgery alone. But, recent advances in radiology and in chemotherapy mean it is now possible and timely to investigate neoadjuvant therapy for patients with colon cancer.

Advances in radiology

In the non-emergency situation, with appropriate imaging, it is possible to identify a subset of locally advanced, poor prognosis colonic cancer patients who might well benefit from neoadjuvant strategies. High-quality CT scanning is now routinely available in UK hospitals, making a national multi-centre trial of neoadjuvant therapy in poor prognosis disease feasible. In a pilot study for this proposal, 102 CT scans of the abdomen and pelvis from patients scheduled for resection of a primary colonic tumour at a single DGH over a 5-year period were reviewed by two independent consultant radiologists 'blinded' to both final histological

stage and clinical outcome.[11] CT scan evaluation criteria were developed for scoring "good" or "poor" (T4 or advanced T3) prognosis, defining groups with 87% vs 53% 3-year cancer-specific survival, with high inter-observer concordance and excellent exclusion value for early stage cancers. These imaging criteria are readily taught and their ability to identify high risk colon cancer patients suitable for neoadjuvant treatment in a multicentre trial setting has been demonstrated in the **FOxTROT** pilot study.

To assess the accuracy of radiological staging in identifying patients with tumours that would require adjuvant chemotherapy, we compared radiological and histological staging in the **FOxTROT** pilot and in a parallel audit. The CT classification criteria for poor prognosis (T4 or T3 and ≥5mm extramural extension) were shown to select a very high-risk population (93% T3 and above), and successfully exclude patients with low-risk cancers unsuitable for chemotherapy. Only 6 patients with pT2 tumours were entered into **FOxTROT**, all of whom received pre-operative chemotherapy - so histology findings may reflect downstaging of the tumours. Comparisons of radiological and pathological staging also found that 93% of patients with T3 tumours and a radiologically estimated depth of invasion less than 5mm ('intermediate risk' patients) were suitable for chemotherapy. It has, therefore, been agreed that the entry criteria for the **FOxTROT** main study can be widened to include all radiological T3 tumours.

Advances in Chemotherapy

Trials of chemotherapy in metastatic CRC have now established that it is a relatively chemo-sensitive disease. In two large UK phase III trials, FOCUS[12] (n= 2135 patients) and COIN[13] (n= 2445 patients), the "OxMdG" regimen of fluorouracil (FU) oxaliplatin gave objective major responses (PR or CR) in 56% and 53% of patients respectively. Of particular importance to **FOxTROT** is that only 14% and 9% of patients, respectively, experienced disease progression in the first 12 weeks of chemotherapy.[12-13] Even higher response rates can be achieved by adding EGFR-targeted monoclonal antibody (mAb) therapies to combination chemotherapy (see below).[14-20]

Another relevant factor is that lymph node status (Dukes' C vs B) is no longer the unique determinant of adjuvant drug therapy. Data from QUASAR1,[2] supported by meta-analyses of other trials, indicates that the proportional reduction in risk of recurrence with adjuvant chemotherapy is similar in node-positive and negative disease. QUASAR found a 22% (p=0.004) reduction in recurrence in Dukes' B patients. This is important information for a neo-adjuvant trial, where preoperative therapy will downstage a proportion of node-positive patients, so operative stage is less reliable as a determinant of postoperative treatment.

The oral fluoropyrimidine capecitabine has been shown to have equivalent efficacy to FU in advanced CRC and is well established in the adjuvant setting, both as a single agent[21] and in combination with oxaliplatin ("OxCap"),[22] offering a welcome option for some patients. The toxicity of capecitabine-based regimens differs somewhat from the FU-based equivalents, with generally more GI and skin toxicity but less myelotoxicity. The increase in GI toxicity is accentuated when EGFR-targeted therapy is also added.[13]

New epidermal growth factor targeted therapies

Novel targeted therapies, especially those directed at VEGF and EGF receptors, are now of established efficacy in colon and other cancers. EGFR is a transmembrane glycoprotein that, in response to binding of ligand, generates intracellular tyrosine kinase activity, stimulating an intra-cellular cascade leading to cell cycle progression. EGFR expression is seen in over 70% of colorectal cancer cells. Therapeutic inhibition of EGFR can be achieved with monoclonal antibodies (e.g. cetuximab, panitumumab), or small molecule inhibitors (e.g. gefitinib, erlotinib). In CRC, the more successful of these to date has been the mAb approach and around 10% of unselected patients with chemoresistant disease will have a major response to single-agent cetuximab[14] or panitumumab.[15,16] Benefits are confined to patients with normal (wildtype) *KRAS* tumours (*KRAS*-wt) with no benefit for *KRAS*-mutant tumours but, unexpectedly, are not much different in the presence or absence of EGFR expression.

Cetuximab and panitumumab are both licensed for use in patients with advanced, *KRAS*-wt colorectal cancer after failure of chemotherapy. Panitumumab is a high affinity (K_d= 5 x10^{-11}M) IgG_2 mAb against EGFR which has a similar mechanism of action to cetuximab but differs in

being fully human. It blocks the binding of ligands to EGFR and inhibits EGFR-mediated tyrosine phosphorylation, *in vitro* cell proliferation and xenograft tumour growth.[23] It does not cause the immuno-allergic side effects that are possible with murine or chimeric antibodies. Panitumumab has a clearance rate of <5 mL/day/kg, similar to that of endogenous IgG_2, with low interpatient variability. This allows infrequent administration. Several thousand patients with cancer have now been enrolled in Phase I, II and III trials of panitumumab, receiving doses ranging from 0.01 mg/kg to 5 mg/kg once weekly, 6 mg/kg fortnightly, and 9 mg/kg three weekly.[16] Panitumumab has been studied as monotherapy in metastatic colorectal cancer (mCRC) and other solid tumours (renal, prostate, pancreatic, non small-cell lung, oesophageal and head and neck). It has also been studied in mCRC in combination with chemotherapy and with chemotherapy plus bevacizumab.

Clinical trials of anti-EGFR mAbs

For patients with *KRAS*-wt mCRC, anti-EGFR mAbs used as single agents halve the rate of progression. In a multi-national, randomised trial, 463 patients with EGFR expressing mCRC who had failed standard chemotherapy were then randomised to receive panitumumab plus best supportive care (BSC) or BSC alone.[15] Patients on panitumumab had a 40% improvement in progression-free survival (PFS): Hazard Ratio = 0.60; 95% CI 0.49 to 0.74, p<0.0001. There was no relationship between EGFR staining intensity and response: however, a later retrospective analysis showed that the benefits of panitumumab were confined to patients with *KRAS*-wt tumours among whom the PFS HR was 0.49 (95%CI 0.37-0.65; p<0.0001).[16] Conversely, patients with mutant *KRAS* tumours saw no benefit: HR 1.07 (0.77-1.48); NS. These positive results and the interaction with *KRAS* status were mirrored in a similar trial of cetuximab monotherapy.[14]

Most trials assessing EGFR-targeted mAbs in addition to cytotoxic chemotherapy for mCRC have also found improved PFS and increased response rates in the *KRAS*-wt population. In the "CRYSTAL" trial of FOLFIRI ± cetuximab as first-line treatment, a significant improvement in response (59% v 43%: p=0.003) and PFS (HR=0.68; CI 0.05 to 0.93, p=0.02) was seen in 348 patients with *KRAS*-wt tumours with no effect in *KRAS*-mut patients (HR = 1.07; 0.71-1.61; NS).[17] Significantly improved response (61% v 37%; p=0.007) and PFS (HR 0.57; 0.36 to 0.91, p=0.02) was also seen in 134 patients with *KRAS-wt* tumours in the "OPUS" trial of FOLFIRI ± cetuximab but patients with *KRAS*-mut tumours did significantly worse with cetuximab (HR 1.83, p=0.02).[18] Similarly, the "PRIME" trial, testing first-line FOLFOX ± panitumumab, found significantly improved PFS (HR=0.80, p=0.02) in the 656 patients with *KRAS*-wt tumours, with a non-significant improvement in objective response rate (55% vs 48%, p=0.07).[19] As in OPUS, patients with *KRAS*-mut tumours did significantly worse if they received panitumumab raising concerns about a negative interaction between cetuximab and chemotherapy. The 181 study of FOLFIRI ± panitumumab as second line treatment of mCRC also found improved PFS (HR=0.73; 0.59 to 0.90, p=0.004) and a higher response rate (35% vs 10%, p<0.0001) in 597 patients with *KRAS*-wt tumours with similar PFS and response rates in *KRAS*-mut tumours.[20] A higher response rate (64% vs 57%, p=0.049) was also seen with cetuximab in 729 *KRAS*-wt patients in the UK COIN trial who were randomised to "± cetuximab" on a background chemotherapy of either OxMdG or OxCap, with the highest response rate, 68%, being seen in *KRAS*-wt patients treated with OxMdG+cetuximab. Disappointingly, no improvements were seen in PFS (HR=0.96; 0.84 to 1.09, p=0.6) or in the primary endpoint, survival, in the *KRAS*-wt subpopulation.[13] Neither benefit nor harm was seen in patients with *KRAS*-mut tumours.

Finally, two phase III studies assessing "triple combinations" of chemotherapy, anti-VEGF and anti-EGFR therapies have both found significantly worse outcomes. In "PACCE", chemotherapy (FU plus oxaliplatin or irinotecan) and bevacizumab were given with and without panitumumab.[24] PFS was worse in patients receiving panitumumab (HR=1.44; 95% CI: 1.13, 1.85), regardless of *KRAS* status, and there was also an increase in mortality: HR=1.56 (95% CI: 1.11, 2.17). In the Dutch trial, CAIRO2, a higher response rate (61% v 50%; p=0.06) was seen in 314 *KRAS*-wt patients with untreated mCRC received OxCap/bevacizumab ± cetuximab with no improvement in PFS.[25] *KRAS*-mut patients receiving cetuximab had significantly worse outcomes (PFS 8.1 v 12.5 mo; p=0.003).

Thus, as of spring 2010, we have learnt much but also have some remaining questions about anti-EGFR targeted therapies in CRC:

- No trial has shown benefit (and several have shown harm) in patients with *KRAS*-mut tumours. It is possible that this finding will extend to patients with other, less common sources of *RAS-RAF-AKT* pathway activation (e.g. *BRAF* V600E mutation) and this will be investigated in the FOxTROT biomarker study (see below).
- For patients with *KRAS*-wt mCRC, anti-EGFR mAbs used as single agents halve the rate of progression. When added to chemotherapy alone, they have consistently increased the response rate, with most trials also showing improved PFS.
- In contrast, when added to chemotherapy plus bevacizumab, their impact has generally been adverse.
- In COIN, adding cetuximab to OxCap (but not OxMdG) produced unacceptable toxicity and led to reduction in the chemotherapy doses. Adding cetuximab to OxMdG was also preferable to adding it to OxCap in terms of efficacy, a borderline significant difference (p=0.06), which adds to concerns about the use of EGFR-mAb with OxCap.

Panitumumab Clinical Safety Experience (please refer to the current panitumumab Investigator's Brochure and Summary of Product Characteristics[16] for up-to-date details.)

Panitumumab has generally been well tolerated with most treatment-related toxicities mild to moderate in severity. The most common side effect of panitumumab, and other EGFR inhibitors, is a dose-related, reversible, acneiform, or maculopapular skin rash, which occurs in over 90% of patients, but reaches NCTC Grade 3 in under 15%.[16] Reported less frequently (~20%) are fingertip or nail bed infection and inflammation. Beyond these skin effects, the side effects, of any grade, that were significantly increased in the randomised comparison of panitumumab with supportive care were diarrhoea (21% vs 11%), constipation (19% vs 9%), nausea (22% vs 15%), and vomiting (18% vs 12%).[16] Other AEs that have been reported as related to panitumumab are asthenia, pain, fever, back pain, abdominal pain, anorexia, arthralgia, dizziness, increased cough, dyspnoea, upper respiratory infection, throat irritation alopecia and myalgia. Grade 3 events were reported for fatigue (3%), diarrhoea, nausea and vomiting (reported at 1% each). No evidence of cardiotoxicity has been observed despite intensive monitoring.[16] Allergy is uncommon with any infusion-related reaction (anaphylactoid reaction, chills, fever, dyspnoea, or urticaria) reported in 3% and severe (grade 3 and 4) reactions in <1% of panitumumab-treated patients.[16] Although most infusion reactions are mild to moderate in intensity they can, rarely, be fatal. As of May 2010, three fatal infusion-related reactions have been reported in over 40,000 patients with mCRC treated with panitumumab. These three patients had previously experienced angioedema, and hypersensitivity reactions to cetuximab and oxaliplatin, respectively and panitumumab is now contraindicated in patients with a history of severe or life-threatening hypersensitivity reactions. Pulmonary toxicity also occurs rarely but because of a known association between EGF-directed therapy and interstitial lung disease, evidence of interstitial pneumonitis or pulmonary fibrosis is another contraindication to panitumumab.

In trials of panitumumab in combination with IFL, diarrhoea was more frequently reported than in monotherapy trials. In the COIN trial, Grade 3 diarrhoea was especially noted when the patients received OxCap with an EGFR mAb.[13] This combination also appeared less effective than panitumumab with OxMdG and hence OxCap is only allowable in the FOxTROT trial for patients excluded from the panitumumab randomisation (e.g. patients with *KRAS-mut* tumours). Other more frequent AEs were skin toxicities, asthenia and nausea. When the trial was amended with the bolus-based IFL regimen switched to the infusional FOLFIRI regimen, diarrhoea, asthenia and nausea rates were approximately halved.

Similar to findings with cetuximab, hypomagnesaemia AEs and SAEs (with or without concomitant hypocalcaemia) have been reported in clinical studies of panitumumab given as a single agent or in combination with various chemotherapy regimens with 41% of patients experiencing Grade 1 or 2 severity and 7% Grade 3 or 4.[16] Therefore, routine magnesium monitoring is mandated for patients receiving panitumumab.

To date, using a very sensitive methodology for antibody detection, the immunogenicity of panitumumab has been low. Pre-existing anti-panitumumab antibodies have been detected in <5% of patients and <5% have showed increased anti-panitumumab antibody titres after receiving panitumumab, of which ~1% were able to neutralise the biological activity.

The panitumumab SPC[16] describes 44 cases (5%) of treatment-related serious adverse events among patients receiving panitumumab monotherapy. The most frequently-reported serious, treatment-related adverse event was hypomagnesaemia, reported in seven patients (1%). All other treatment-related serious adverse events were reported in <1% of patients.

Patients receiving panitumumab in combination with bevacizumab and either oxaliplatin or irinotecan-based chemotherapy in the PACCE study,[24] experienced more severe adverse effects than those who did not get panitumumab. These effects included diarrhoea (leading to severe dehydration), severe infections and pulmonary embolism that in some cases were fatal. The safety profile of receiving panitumumab together with bevacizumab and oxaliplatin or irinotecan-based chemotherapy is not completely known - but combined EGF/VEGF therapy should not be used as it appears to increase the rate of progression.[24,25]

The need for FOxTROT: a large, multi-centre, randomised trial

Neo-adjuvant chemotherapy is a promising and practical treatment for locally advanced colon cancer but the benefits and risks of this new approach have not been evaluated. What is needed is a large randomised trial to assess the true value of neo-adjuvant chemotherapy among different types of patient. The **FOxTROT** ("**F**luoropyrimidine **Ox**aliplatin and **T**argeted **R**eceptor Pre-**O**perative **T**herapy") trial is designed to evaluate whether giving some part of an effective chemotherapy regimen pre-operatively improves disease-free survival and/or whether the addition of an EGFR targeted monoclonal antibody (panitumumab) increases tumour shrinkage for patients with normal (wildtype) *KRAS* tumours. For reliable results, **FOxTROT** will need to randomise more than one thousand patients and to encourage widespread participation trial procedures and documentation are kept to a minimum. One thousand patients is a small number compared to the many tens of thousands of future patients whose treatment will be guided by the results of **FOxTROT**.

Biomarker studies

The delivery of pre-operative therapy also provides a unique opportunity for translational research to identify tumour markers that are predictive of response to chemotherapy and to anti-EGFR therapy. Cancer Research UK is providing funding to support collection of tissue and blood samples stored at the time of biopsy and surgery, which will be analysed for biomarkers that might provide indicators of response to therapy. It is now firmly established that *KRAS* status predicts response to EGF receptor targeted therapy with an enhanced response for wildtype but no benefit for *KRAS*-mutant tumours. The correlations between other potential biomarkers and efficacy and safety endpoints will be investigated in **FOxTROT** by collecting blood and tumour tissue for biomarker analyses. See Section 4 “TREATMENT” for further information on the blood and tumour sample collection.

Such analyses may include molecular profiling methods to gain an overall picture of the mRNA, protein patterns and DNA alterations. Techniques that will be considered, include:

- Detection of *KRAS* mutations
- Detection of EGFR expression and/or functional genetic polymorphisms of the EGFR gene (by PCR)
- Detection of copy number EGFR gene amplification (by FISH)
- Detection of EGFR activation (by IHC)
- Detection of EGFR via downstream parameters (by Western blotting and/or gene expression microarray techniques)
- Proteomics and Epigenetics

The decision on which techniques will be selected will be dependent on sample specimen type, laboratory logistics, analysis timelines and emerging evidence.

Evaluating the influence of resectional quality on outcome

FOxTROT will build on the impressive advances in colorectal cancer radiology, surgery and pathology throughout the UK that have accrued from quality assured trials such as CR07, CLASICC and MERCURY, and from the PELICAN multidisciplinary advanced training programme. The **FOxTROT** study provides an excellent opportunity to prospectively evaluate resectional quality and its influence on outcome for colon cancer. Data from Yorkshire and Swedish cancer registries indicate that overall survival of colonic cancer is now inferior to that of rectal cancer.[26] It is apparent that this is partly due to the marked variation in the quality of colon cancer surgery. Data from MRC CLASICC[27] show that, as in rectal cancer, there is marked and measurable variation in the quality of surgery of colon cancers, e.g. in the degree of removal of the mesocolon and its lymphatic supply, length of resection to the high tie lymph node, and clearance of the surgically created mesocolic resection, especially in the caecum and descending colon.[27-29] **FOxTROT** will include standardised, proforma-based pathology reporting (see appendix N), and external evaluation using duplicate sections and specimen photographs, to assess the quality of surgery. Advances have been realised in rectal cancer management through such methods and require application to colon cancer.

2. TRIAL DESIGN

Objectives

FOxTROT is a multi-centre randomised controlled trial (RCT) with the following objectives:

Primary objectives:

- To determine if neoadjuvant chemotherapy ± panitumumab followed by deferred surgery and completion of chemotherapy post-operatively can reduce 2-year recurrence as compared to surgery and postoperative chemotherapy±panitumumab
- To determine if adding panitumumab in the neoadjuvant treatment of patients with *KRAS* wildtype tumours produces a measurable increase in anti-tumour efficacy as measured by tumour shrinkage.

Secondary objectives:

- To assess the accuracy of pre-treatment CT scan staging
- To assess the tolerability of the neoadjuvant therapies
- To assess the nature and frequency of surgical complications
- To measure the impact of the treatments on patient's quality of life and resource usage
- To assess the prognostic and predictive value of tumour biomarkers
- To assess the influence of resectional quality on outcome

Randomised comparison

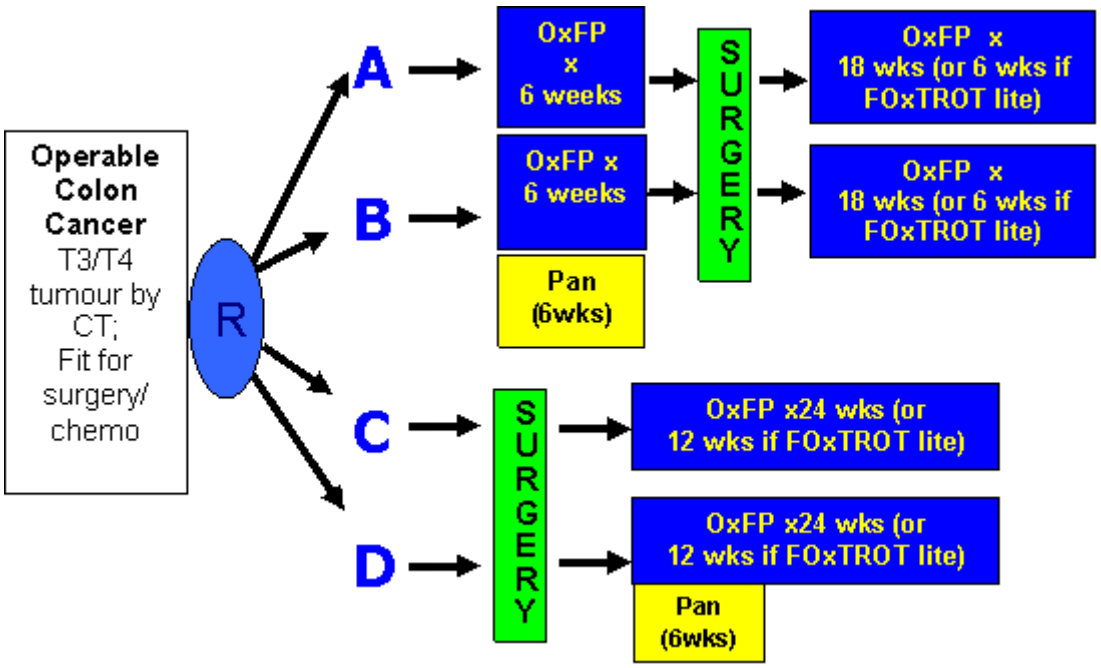
Patients with a radiological, pre-operative staging of T4 or T3 (extramural depth ≥ 1mm) cancer for whom a course (either 24 or 12 weeks, see below) of oxaliplatin/ fluoropyrimidine-based combination therapy is considered appropriate are randomised, in a 2:1 ratio, between pre- plus post-operative and post-operative chemotherapy. In addition, *KRAS* testing of the primary tumour is initiated and patients established to have *KRAS* wildtype tumours are randomised, in a 1:1 ratio, to receive panitumumab with the first 6 weeks of chemotherapy or to control (see section 3). Thus, the four treatment arms are:

A) Six weeks of pre-operative oxaliplatin/fluoropyrimidine (OxFP) chemotherapy followed by surgery then 18 (or 6) weeks of post-operative OxFP chemotherapy

B) The same chemotherapy regimen with concomitant panitumumab for the first 6 weeks

C) Surgery then 24 (or 12) weeks of post-operative OxFP chemotherapy

D) The same chemotherapy regimen with concomitant panitumumab for the first 6 weeks



Chemotherapy – 24 (or 12) weeks of OxMdG or OxCap

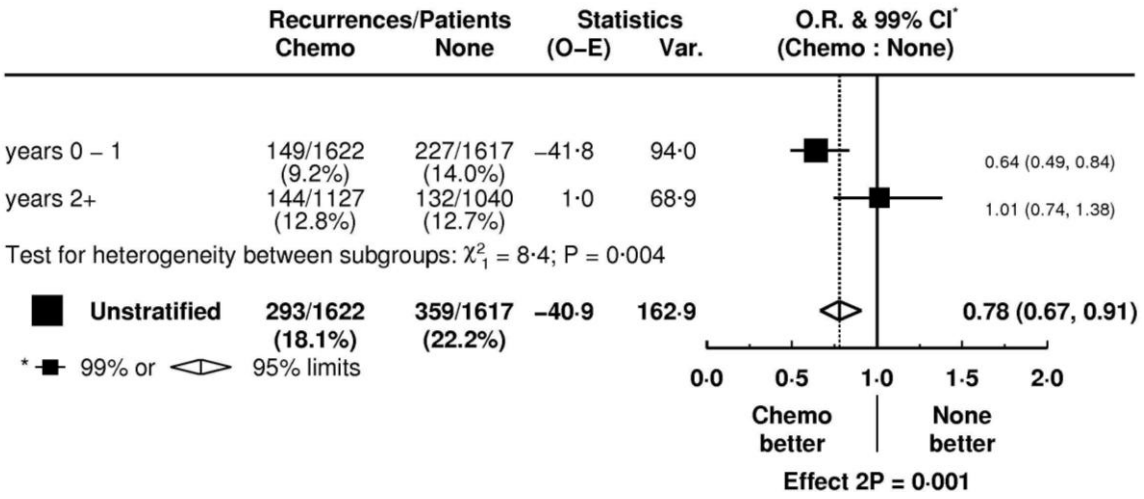
The recommended chemotherapy regimen is 24 weeks of oxaliplatin plus modified de Gramont infusional fluorouracil (OxMdG).[30] If allocated pre-operative chemotherapy, the first 6 weeks are given pre-operatively and the remaining 18 weeks post-operatively. Clinicians can, however, opt to use a shorter 12-week course of chemotherapy ('**FOxTROT lite**') for patients for whom 24 weeks is considered excessive, eg elderly patients, or intermediate risk patients (T3 and less than 5mm invasion). If 12-week treatment is considered appropriate, then chemotherapy will consist of either 6 weeks pre-operatively followed by surgery and the remaining 6 weeks of chemotherapy post-operatively or, if allocated standard treatment, 12 weeks of post-operative chemotherapy. Patients with *KRAS*-wildtype tumours who are allocated to receive panitumumab receive this with the first 6 weeks of chemotherapy.

The **FOxTROT** pilot stage has demonstrated the feasibility, safety and tolerance of pre-operative therapy in over 100 patients, all treated with OxMdG chemotherapy ± panitumumab. Oxaliplatin plus capecitabine (OxCap) has similar efficacy to OxMdG but was not allowed in the pilot phase because GI toxicity is somewhat greater with OxCap than OxMdG. Concerns about unacceptable toxicity of EGFR directed mAbs with OxCap have been reinforced by more recent data from COIN,[13] which also found that PFS was not improved in patients who received cetuximab in combination with capecitabine (in contrast to OxMdG). For these reasons, OxCap should not be used in patients randomised for panitumumab. Clinicians are, however, free to choose between OxMdG and OxCap chemotherapy for patients who are not entered in the panitumumab randomisation (i.e. patients with *KRAS* mutant tumours, or those for whom *KRAS* status is not established).

Outcome measures

The primary outcome measure for the comparison of pre- plus post-operative versus post-operative chemotherapy alone is freedom from recurrent or persistent disease two years after randomisation. This includes failure of macroscopic disease clearance at primary surgery as well as colon cancer recurrence. The rationale for choosing this primary endpoint is to maximise statistical power as most of the effect of chemotherapy on recurrence is concentrated in this period. For example, in the QUASAR study adjuvant fluorouracil/ folinic acid chemotherapy reduced the risk of recurrence by 36% (99% CI 16%-51%) in the first two years after surgery with no further benefit or loss of benefit subsequently (see below).

QUASAR1 study: effect of chemotherapy on recurrence by year of follow-up



The primary outcome measure for the comparison of preoperative chemotherapy ±panitumumab is pathological down-staging, measured by depth of extramural spread. This outcome measure is statistically efficient and will also allow early reporting, which will facilitate the design of the next generation of trials.

Secondary outcome measures are:

- Death from colon cancer
- Overall survival
- Pathological assessment of downstaging (involvement of lymph nodes; serosa; resection margin), quality of resection specimen and distance to high-tie
- Radiological assessment of response to neoadjuvant treatment
- Quality of life (EORTC QLQ C-30, EuroQol EQ-5D)
- Health Service costs
- Surgical morbidity/mortality
- Chemotherapy toxicity
- Adverse events

3. PATIENT ENTRY

Recruitment through Multi-disciplinary Teams

Recruitment to the trial will be co-ordinated through the Multi-Disciplinary Team. Patients will be diagnosed in surgical clinics, biopsy, radiological and clinical investigations undertaken and the case discussed at the MDT. If the patient meets all of the eligibility criteria (see below) and is considered suitable for **FOxTROT**, they will be referred to the oncology clinic for discussions of the timing of chemotherapy. The Nurse Specialist will coordinate the process of providing the patient with information about **FOxTROT**, obtaining consent for *KRAS* testing, arranging for a block of biopsy material to be sent for *KRAS* analysis, obtaining consent for the main **FOxTROT** study, randomisation and administration of chemotherapy. Much of this process is already in place for the management of rectal cancer and will be used for colon cancer for the purposes of the trial.

The majority of patients will be recruited from the elective setting. However, patients who present with obstruction (80% of emergency colon cancer surgery) are eligible for **FOxTROT** if obstruction is first relieved by a primary defunctioning stoma. The opportunity for neoadjuvant therapy to be used to down stage the tumour would make this treatment pathway attractive and could have the additional benefit of improving emergency surgical management of obstructed colonic cancer by allowing definitive elective treatment by specialist colorectal surgeons. Patients with signs of peritonitis or evidence of distant metastases are, however, excluded.

Eligibility Criteria

Inclusion Criteria

- Histologically proven adenocarcinoma of the colon
- Likely to benefit from adjuvant fluoropyrimidine chemotherapy, i.e. either:
  - Radiological high risk (T4 or T3 tumour with extramural invasion ≥ 5mm)
  - Or radiological intermediate risk (T3 tumour less than 5mm invasion) and younger age/good general health
- Patients presenting with acute colonic obstruction may enter the trial only after obstruction is relieved by a successful defunctioning stoma, and when recovered to a fitness level consistent with the other eligibility criteria
- Adequate full blood count (Hb >10.0 g/dl after transfusion and prior to surgery and chemotherapy; WBC >3.0 $x10^9$/l; Plts >100 $x10^9$/l)
- Adequate renal biochemistry: GFR >50 ml/min calculated by the Wright or Cockroft formula or EDTA clearance >70 ml/min.
- Adequate hepatobiliary function: bilirubin < 25 µmol/l
- Serum magnesium levels within the normal range at trial entry (which can include intravenous correction)
- Aged 18 or over
- WHO performance status of 0, 1 or 2
- If female and of childbearing potential, must:
  - have a negative pregnancy test ≤72hours prior to initiating study treatment
  - agree to avoid pregnancy during and for 6 months after study treatment
- If male with a partner of childbearing potential, must:
  - Agree to use adequate, medically approved, contraceptive precautions during and for 90 days after the last dose of study treatment
- Patient able and willing to provide written informed consent for the study

Exclusion criteria

- Tumour within 15cm of the anal verge, as judged by sigmoidoscopy, or any patient for whom radiotherapy is advised by the MDT
- Evidence of distant metastases or peritoneal nodules (M_1)
- Peritonitis (secondary to perforated tumour)
- Colonic obstruction, that has not been defunctioned
- Serious medical comorbidity, eg uncontrolled inflammatory bowel disease, uncontrolled angina or recent (<6 months) MI
- Another serious medical condition judged to compromise ability to tolerate neoadjuvant therapy and/or surgery
- Any other malignant disease within the preceding 5 years with the exception of non-melanomatous skin cancer, carcinoma in situ and early stage disease with a recurrence risk <5%.
- History of interstitial pneumonitis or pulmonary fibrosis

NB Only patients with *KRAS*-wildtype tumours are eligible for the panitumumab randomisation (see below)

Radiological staging/eligibility

Spiral/multidetector CT scanning of the abdomen and pelvis with i.v. and oral contrast (no oral if obstructed) is required prior to entry into the trial, for all patients. The scan is used to select patients of "poor prognosis" based on depth of tumour invasion on preoperative CT scan. Examples are given in appendix L.

To ensure accurate and consistent radiological staging, central radiological training for the site GI radiologist is a requirement.

Eligibility criteria by CT scanning are all of the following findings:

- Radiological high risk (T4 or T3 tumour with extramural invasion ≥ 5mm)

  OR radiological intermediate risk (T3 tumour 1-4 mm invasion) and suitable for chemotherapy because of younger age (eg<70) /good general health
- Absence of distance metastases and peritoneal nodules
- Resectable disease

Secondary benefits from **FOxTROT** will include development and validation of preoperative radiological staging criteria. An optional CT scan will be performed prior to surgery for patients in the neo-adjuvant treatment arms (if consent is available) to assess response to chemotherapy. Comparison of radiological vs pathological staging will allow fine-tuning of entry criteria and these data will also be used to further develop and validate the risk-scoring system taking into account CT evidence of the extent of extramural spread (including peritoneal infiltration), the degree of nodal involvement, extramural venous invasion and depth of mural invasion. Specifically, we will review whether patients who do not meet the above criteria but have one of the following findings should be eligible:

- 3 or more visible lymph nodes; or 1 >10mm diameter; or 1 irregular enhancing node
- definite extramural vascular invasion present

KRAS screening prior to panitumumab randomisation

It is now firmly established that *KRAS* status predicts response to EGF receptor targeted therapy. There is an enhanced response for patients with *KRAS*-wildtype (normal) tumours but no benefit for *KRAS*-mutant tumours. *KRAS* testing of the biopsy tissue is therefore a mandatory pre-requirement for the **FOxTROT** panitumumab randomisation. *KRAS*-wildtype tumours (~60% of patients) will be randomised to all four arms. *KRAS*-mutant tumours (40%) will not be eligible for panitumumab so will be randomised just between pre- plus post-operative and post-operative chemotherapy (i.e. arms A and C). A pre-randomisation *KRAS* screening information and consent form is provided (Appendices A & B) so that *KRAS* testing can be initiated while the patient is being informed about **FOxTROT** and so that treatment would not be delayed if the patient agrees to take part in **FOxTROT** and is allocated pre-operative panitumumab. Tumour analysis for *KRAS* status will be provided free-of-charge (see blood and tumour collection, pages 13-14) with the results available within 1 week.

Informed consent

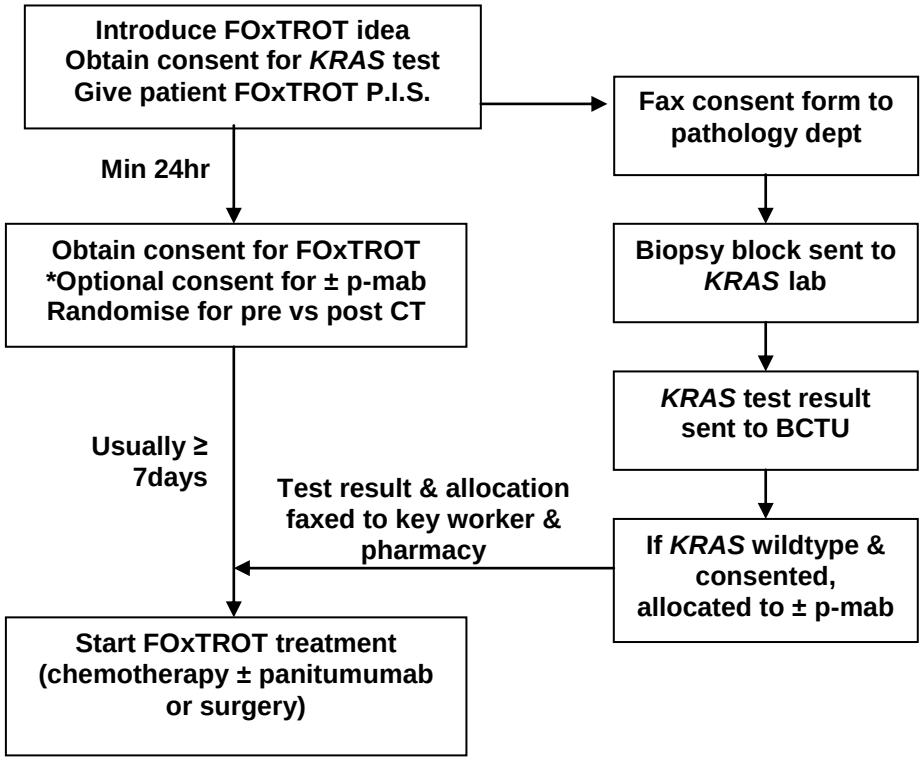
The conduct of the study will be in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004. The patient's written consent to participate in the trial must be obtained before randomisation and after a full explanation has been given of the treatment options, and the manner of treatment allocation. Patient information sheets (Appendix A and C) are provided in the **FOxTROT** trial pack so that patients can find out more about **FOxTROT** before discussing whether or not to participate. Patients can consent immediately to *KRAS* testing of their biopsy sample but should have at least 24 hours to consider whether to take part in the **FOxTROT** randomisation. The original signed Consent forms (Appendix B and D) should be kept in the **FOxTROT** study file, one copy for the patient, one kept on the patient's notes and one sent to the **FOxTROT** Study Office.

Randomisation by telephone or internet

Patients are entered in the trial by telephone call to the randomisation service (telephone number **0800 953 0274**, toll-free in the UK, or **+44 (0) 121 415 9137** from elsewhere) or by internet on the website https://www.trials.bham.ac.uk/FOxTROT. Telephone randomisation is available Monday-Friday 0900 – 1700 UK time. Randomisation out of hours is available at any time by logging on to the website. Each centre and each randomiser will be provided with a unique log-in and password to do this. Patients can be randomised between pre- plus post-operative and post-operative chemotherapy as soon as radiological staging is available and the patient has consented to participate in **FOxTROT**. The person randomising will need to answer **all** of the telephone questions, and completing the randomisation notepad (Appendix E) before calling may help in preparing for them. According to local preference, patients may be randomised either by the surgeon or by the oncologist.

Two-stage treatment allocation

To facilitate treatment planning, the **chemotherapy** treatment allocation (pre- plus post-operative or post-operative chemotherapy) will be specified at the end of the telephone call. The allocated initial treatment should be undertaken as soon as possible, ideally within two weeks of randomisation. For patients who consent to the panitumumab randomisation, and are found to have *KRAS*-wildtype tumours, the study Office will inform the oncology team and hospital pharmacy of the chemotherapy ± panitumumab allocation as soon as the *KRAS* test result has been received (see randomisation flow chart below). At time of trial entry, all patients should be given a laminated **FOxTROT** patient card. This card should be kept with them at all times. The patient's GP should be notified that they are in **FOxTROT** and a specimen "Letter to GP" is provided for this purpose (Appendix G).



*Two decisions need to be made prior to randomisation:

1. Will chemotherapy duration be standard (24 weeks) or '**FOxTROT** lite' (12 weeks) ?

This would usually be decided at the time of patient review at the MDT, with 12-week treatment for patients considered more frail (eg over 70 years of age) or with intermediate risk tumours

2. If patient is not eligible for panitumumab would OxMdG or OxCap be used ?

A centre may elect to treat all patients who are ineligible for the panitumumab randomisation with the same regimen; alternatively, the choice of OxMdG or OxCap may be made on an individual patient basis.

4. TREATMENT

The chemotherapy regimens: "dealer's choice"

(Please see appendices P and Q for details of the drug regimens and management of toxicity)

Patients in **FOxTROT** receive oxaliplatin/fluoropyrimidine chemotherapy with a **choice** (not randomisation) between two alternative regimens, and between 24 and 12 weeks of treatment (see page 7). These are:

- 'OxMdG' (2-weekly oxaliplatin with folinic acid, bolus and infusional fluorouracil)[30]
- 'OxCap' (3-weekly oxaliplatin with capecitabine). **N.B. Only for patients not eligible for panitumumab randomisation**

MRC COIN trial centres are familiar with these regimens, and with the concept of "dealer's choice". OxMdG is given on a day-case basis using a PICC or Hickman line but, if insertion of a line will incur a delay, it is better to administer the first cycle as an in-patient. OxCap is given on a day-case basis and does not require indwelling venous access. The side-effect profiles of OxMdG and OxCap, as well as their practicalities, differ somewhat; clinicians may find it helpful to refer to the interim toxicity report of COIN.[13]

For patients allocated pre- plus post-operative chemotherapy (Arms A and B), the same chemotherapy regimen is used in the neoadjuvant and postoperative phases. It is not recommended to cross over regimens unless there is a compelling clinical reason (eg failure of venous access); in that case, be aware that if crossing from OxMdG to OxCap, capecitabine may cause increased toxicity when given after recent folinic acid (in OxMdG) and a dose-reduction is required. Please refer to notes in Appendix P.

The neoadjuvant therapy phase (Arms A and B)

Patients in **Arms A and B** receive neoadjuvant treatment for six weeks starting as soon as possible after randomisation. This comprises three 2-week cycles of OxMdG or, optionally for patients not randomised for panitumumab, two 3-week cycles of OxCap.

Patients in **Arm B** (who will have been established to have *KRAS*-wildtype tumours) also receive panitumumab, by IV infusion over 60 minutes on day 1 of each cycle of neoadjuvant OxMdG chemotherapy: i.e. panitumumab (2-weekly*)* for 3 cycles at 6 mg/kg

Every effort should be made to complete neoadjuvant treatment on time and as planned unless a clear contraindication develops, in which case the **FOxTROT** office should be notified. Examples would be:

- evidence of cancer progression (eg the development of complete bowel obstruction)
- persistent severe toxicity which, in the opinion of the treating oncologist, would require more than a 20% reduction in chemotherapy doses or delays of more than 2 weeks
- withdrawal of patient consent.

The final day of chemotherapy is 31 days after the start of treatment for OxMdG and 37 days for OxCap. At the time of starting treatment, the patient should be booked for a repeat CT approximately 42-48 days after the start of treatment, and for the resection surgery to take place 52 days after the start of treatment, or as soon as possible thereafter (and certainly before 70 days). If a delay occurs during chemotherapy, the timing of the CT scan and surgery should be put back by the appropriate number of days to preserve the chemotherapy-to-surgery interval.

Post-operative chemotherapy (all Arms)

Following surgery, patients should be scheduled to start postoperative chemotherapy no earlier than 4 weeks after surgery, and preferably in the interval 4-8 weeks as per normal practice. Patients with ongoing surgical complications requiring a longer recovery period may, however, start later at the discretion of the treating oncologist.

Postoperative treatment is given according to the trial allocation as shown in Section 2 of this protocol:

- Standard treatment for patients in **Arms A and B** is 18 weeks of postoperative treatment, i.e. nine 2-week cycles of OxMdG or, optionally in Arm A only, six 3-week cycles of OxCap if not randomised for panitumumab
- FOxTROT lite treatment for patients in **Arms A and B** is 6 weeks of postoperative treatment, i.e. three 2-week cycles of OxMdG or two 3-week cycles of OxCap (arm A only).
- Standard treatment for patients in **Arms C and D** is 24 weeks of postoperative treatment, i.e. twelve 2-week cycles of OxMdG or, optionally in Arm C only, eight 3-week cycles of OxCap if not randomised for panitumumab.
- FOxTROT lite treatment for patients in **Arms C and D** is 12 weeks of postoperative treatment, i.e. six 2-week cycles of OxMdG or four 3-week cycles of OxCap (arm C only).
- Patients in **Arm D** (who will have been established to have *KRAS*-wildtype tumours) also receive panitumumab, by IV infusion over 60 minutes on day 1 of each cycle of their postoperative OxMdG treatment, i.e. panitumumab (2-weekly*)* for 3 cycles at 6 mg/kg.

On the basis of previous trials, it is anticipated that a proportion of patients in **FOxTROT** will develop cumulative toxicity, such as peripheral sensory neuropathy, that will prevent completion of the full planned postoperative treatment course. Please refer to Appendices P and Q for guidance in adjusting or stopping treatment.

Panitumumab supply

At the time of site approval, an initial supply of panitumumab, and the FOxTROT Pharmacy Manual, will be shipped to the pharmacist at the Investigator's institution, who will check the amount and condition of the drug, enter these data into the Proof of Receipt form and fax this to Amgen (+00 44 1223 228 100). The **FOxTROT** study office will notify Amgen when a patient has been allocated panitumumab to allow tracking of available supplies on site. Amgen will verify with the site that panitumumab levels are sufficient for treatment. If re-supply quantities are not adequate, the site should contact Amgen to initiate additional supply. All details of panitumumab labelling, storage and preparation are as per the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004 and detailed in the FOxTROT Pharmacy Manual.

Surgical resection

There are no proscriptive criteria for surgical resection of the primary tumour in this trial. It is however expected that resection of the tumour will be undertaken in the elective setting and by a colorectal specialist. The surgical team will be required to fill out an operative and a hospital discharge proforma (Appendix F1 and F2) to record whether there was macroscopic clearance of the tumour, surgical and/or post-operative complications and length of hospital stay.

Blood and tumour sample collection.

- **Blood samples** - A 20 ml EDTA blood sample, to be used in translational research, will be collected prior to treatment if the patient has consented for this at trial entry. The blood sample should be labelled with the **patient's initials, FOxTROT trial number and date of birth but not with their name**. The tube(s) should be sealed and sent in the prepaid safe box provided by the **FOxTROT** study office and posted to:

  Dr Susan Richman, **FOxTROT** Trial Laboratory, Leeds Institute of Molecular Medicine, Section of Pathology and Tumour Biology. Wellcome Trust Brenner Building, St James's University Hospital, Leeds, LS9 7TF.

- **FFPE tumour blocks** - Provided the patient has not withheld consent for tissue removed at surgery to be used for research, a block of tumour tissue or 20 unstained sections - 10 of 5 micron (5µm) thickness on charged slides and 10 of 10 micron (10µm) thickness on uncharged slides - will be obtained for the **FOxTROT** biomarker analyses. FFPE blocks plus the associated pathology report should be labelled with the **patient's initials, FOxTROT trial number and date of birth but not with their name** and sent to the **FOxTROT** study office. Place the sample in a sealed envelope and place in a Jiffy bag along with the pathology report and send to:

  FOxTROT Study Office, Birmingham Clinical Trials Unit, Robert Aitken Institute, School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT.

  The tissue blocks and pathology reports will be logged, anonymised and forwarded to the FOxTROT lab at St. James's University Hospital.
- **Fresh-frozen tissue** - In institutions participating in the fresh frozen tissue collection, inform the **FOxTROT** Trial Office at BCTU that the patient has banked frozen tissue using the tickbox on the randomisation form. The **FOxTROT** Trial Office will circulate details of sample preparation, freezing and transport guidelines to institutions participating in this part of the trial.

Histological evaluation of resection specimen

A primary outcome of the **FOxTROT** study is the effect of neo-adjuvant chemotherapy upon the tumour as assessed by histology and an important objective of the **FOxTROT** trial is to develop rigorous criteria for the preparation and evaluation of the resected specimen (Appendix N). Standardised specimen handling and evaluation criteria have not been established for colon cancer, whereas many of the advances seen in rectal cancer have been enabled by this approach. Adapted versions of the MRC CLASICC and CR07 pathology forms will be used to assess the quality of surgery, including measurements of the greatest length of mesentery removed. Mesocolon resection quality will be assessed using a good/ intermediate/ poor classification similar to that used in the CLASICC and CR07 trials (Appendix O). To ensure consistency, the nominated study GI histopathologist will be asked to attend CME-accredited trial-specific training days. Photographs of the specimens will be collected for central review of the quality of surgery and sections of the histology. We will collect standard data on pathology, completeness of resection and, importantly, the response to neoadjuvant chemotherapy. The histology will be centrally reviewed and digitised to create a unique archive to quality control the study and to allow further research.

Compatibility with other adjuvant studies

FOxTROT overlaps with the ongoing QUASAR2 (comparing postoperative capecitabine with and without bevacizumab) and the SCOT study (comparing 24 and 12 weeks of post-operative oxaliplatin and fluoropyrimidine chemotherapy). Because the three study designs are not compatible, patients entered into **FOxTROT** cannot subsequently be randomised in either QUASAR2 or SCOT. The **FOxTROT** trial will, however, complement these two studies. QUASAR2 is likely to recruit lower risk patients than **FOxTROT** as the chemotherapy regimen (capecitabine alone) is not much used for higher-risk patients. **FOxTROT**, which specifically targets higher-risk patients, allows a choice between either the NICE-recommended OxMdG regimen or (for patients not randomised for panitumumab) oxaliplatin plus capecitabine. Moreover, **FOxTROT** is, like QUASAR2, evaluating a targeted antibody and thus the results will be complementary and will eventually be combined in a meta-analysis of such therapies. SCOT aims to determine whether 24 weeks of oxaliplatin plus fluoropyrimidine, standard chemotherapy as used in **FOxTROT**, can be reduced to 12 weeks (i.e. FOxTROT lite) with the same efficacy. This study's results will therefore also complement those from **FOxTROT**.

Assessment schedule

Trial data will be recorded by hospital research staff on the Case Report Forms (CRFs) and submitted to the **FOxTROT** Study office at BCTU.

Radiological assessment will be performed as per Appendix L. Surgical morbidity will be recorded intra-operatively (Appendix F1). Post-operative complications should be recorded on the hospital discharge form (Appendix F2). Toxicity of chemotherapy will be recorded following completion of the 6th and 12th week of chemotherapy and then, if on standard chemotherapy, after the 18th and 24th week of chemotherapy (Appendix H). Quality of life forms (Appendix S and T) will be completed prior to surgery, prior to the first course of post-operative chemotherapy and at 1 year following randomisation. Annual follow-up forms should be completed at 12 months and annually thereafter (Appendix K). This information will be supplemented, where possible, by the use of national mortality records and hospitals episodes statistics to ensure long-term follow-up.

	Prior to patient entry	**After each 6-week treatment cycle (pre- or post)**	**Before surgery**	**After surgery**	**Before 1st post-op chemo-therapy**	**1 year post rand**	**2+ years post rand**
Informed Consent	**X**						
Radiological staging [a]	**X**		**(X)**				
Surgical morbidity				**X** [b]			
Quality of Life			**X**		**X**	**X**	
Histopathology [c]				**X**			
Chemotherapy toxicity		**X**					
Annual follow-up						**X**	**X**
Adverse Events [d]	**Monitor throughout the course of the study**						

a. After the neo-adjuvant treatment period for patients in Arms A and B, an optional CT scan will be performed prior to surgery (if consent is available)

b. Intra-operatively (Appendix F1) and at hospital discharge (Appendix F2).

c. Blood samples taken as routine haematology and tumour tissue from the resection specimen will be analysed for biomarkers. Resected specimen will be evaluated in line with standardised method (Appendix N and O)

d. See section 5, Safety Monitoring Procedures.

Clinical follow-up

Follow-up after surgery will include regular clinical follow-up as per usual practice. It is recommended that CEA should be assessed every 6 months and abdominal CT scans annually for the first 3 years, or as clinically indicated. The primary outcome of **FOxTROT** is the proportion disease-free at 2 years following randomisation and thus a full investigation for recurrent disease (including CEA and a pelvis/thorax/abdomen CT scan, colonoscopy for metachronous disease is optional as long as full bowel examination was performed prior to surgery) should be undertaken at this time point. The use of investigations after 3 years is left to clinical discretion. The information routinely recorded in normal clinical notes should be sufficient for completion of the annual follow-up forms (Appendix K).

	Prior to patient entry	Prior to 1st treatment cycle (pre- or post)	Prior to subsequent treatment cycles	Before surgery	After surgery	Clinical follow-up [a]	1 year post rand	2 yrs post rand
Medical history	X							
Clinical evaluations including physical examination [b]	X	X			X	X		X
Vital signs	X	X			X			
ECG [c]	X							
Concomitant medication		X	X		X	X		X
Pregnancy Test [d]	X							
Blood Test [e]	X	X	X			X		
Colonoscopy	X							X [f]
CT scan [g]	X			(X[g])		X		X [h]
CEA						X	X	X

a. Safety follow-up visits will be conducted regularly (6 month time-points).
b. Performance status (WHO criteria) will be assessed
c. ECG should be completed within one month prior to trial entry
d. In women of childbearing potential, urine or serum pregnancy within 72 hrs before initiating study treatment.
e. Routine blood test to include FBC, LFTs, U&Es, Mg and Ca.
f. 2 year colonoscopy is not mandatory if full bowel examination has been performed prior to surgery.
g. CT scans will be performed as per standard clinical practice annually for the first 3 years, or as clinically indicated. The pre-randomisation CT scan should be completed within a maximum of one month prior to trial entry. The post neoadjuvant chemotherapy scan is optional.
h. At 2 years a pelvis/thorax/abdomen CT scan should be performed.

5. SAFETY MONITORING PROCEDURES

General definitions

Investigational Medicinal Product (IMP)

Within the trial, only one drug is defined as an IMP: panitumumab.

Adverse event (AE)

An AE is:

- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing disease or illness
- any clinically relevant deterioration in any laboratory assessments or clinical tests

The following are not AEs:

- A pre-existing condition (unless it worsens significantly during treatment).
- Diagnostic and therapeutic procedures, such as surgery (although the medical condition for which the procedure was performed must be reported if new)

Serious adverse event (SAE)

An SAE is an untoward event which:

- is fatal or immediately life threatening
- requires or prolongs hospitalisation
- is significantly or permanently disabling or incapacitating
- constitutes a congenital anomaly or a birth defect or
- may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

Events NOT considered to be SAEs are hospitalisations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study, and did not worsen
- admission to a hospital or other institution for general care, not associated with any deterioration in condition
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

Although death as a result of disease progression is also not an SAE, an SAE form (Appendix I) should be completed and returned to BCTU to inform the Study Office of the event.

Expected SAEs for specific drugs/treatments

Expected SAEs are those listed in the current Investigator's Brochure (IB) and Summary of Product Characteristics (SPC) for the drugs used in the study. These events do not meet the criteria of SUSAR unless for reason of their unexpected severity. For convenience, the current expected events for panitumumab are listed in Appendix J but please always use the most recently updated IB or SPC. The BCTU will ensure that any IB updates are circulated to all investigators; in addition, up-to-date SPCs of the drugs used in **FOxTROT** are all available at http://emc.medicines.org.uk/.

Serious adverse reaction (SAR)

All adverse events judged as having a possible causal relationship to a product qualify as serious adverse reactions.

Suspected unexpected serious adverse reaction (SUSAR)

A SUSAR is an SAE suspected to be related to a product, which is of a **type or severity** which is NOT consistent with the up-to-date product information (i.e. IB for panitumumab).

Reporting AEs

From the first administration of trial treatment until 3 weeks after the last trial drug administration, all toxicities related to the underlying colorectal cancer or its treatment, whether observed directly or reported by the patient, will be collected and recorded on the Chemotherapy Form (Appendix H).

Reporting SAEs

SAEs will be collected for all patients in the study from the first trial treatment to 60 days after the last trial treatment. All SAEs must be recorded on the SAE Form and faxed to the BCTU on +44 (0) 121 415 9135 within 24 hours of the research staff becoming aware of the event. Please ensure that the local Principal Investigator has assigned causality and expectedness to the SAE before reporting.

For each SAE, the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates; times, if applicable)
- action taken
- outcome
- causality, in the opinion of the investigator*
- whether the event would be considered expected or unexpected* (refer to the most recent IB or Summary of Product Characteristics see http://emc.medicines.org.uk/.)

*Assessment of causality and expectedness must be made by a doctor. If a doctor is unavailable, initial reports without causality and expectedness assessment should be submitted to the BCTU by a healthcare professional within 24 hours, but must be followed up by medical assessment as soon as possible thereafter. An SAE which is assessed as possibly, probably or definitely related to study treatment is classified as a Serious Adverse Reaction (SAR)

The local investigator and others responsible for patient care should institute any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors and provide further follow-up information as soon as available. If a patient dies, any

post-mortem findings including histopathology must be provided to the BCTU. The BCTU will report all fatal SAEs to the DMEC for continuous safety review.

SAEs still present at the end of the study must be followed up at least until the final outcome is determined, even if it implies that the follow-up continues after the patient finishes the study treatment and, when appropriate, until the end of the planned period of follow-up.

The BCTU will inform the owner of panitumumab (Amgen Inc.) of all SAEs in patients receiving panitumumab, regardless of whether the event is suspected to be related to panitumumab. BCTU will inform Amgen of SAEs at 3-monthly intervals.

The BCTU will report all SAEs to the DMEC approximately 3-monthly, to the main REC annually, and to the Trial Steering Committee 6-monthly. Local Investigators are responsible for reporting SAEs to their host institution, according to local regulations, but they do not need to inform MHRA or main REC as this will be done by the BCTU as detailed above. All adverse drug reactions suspected to be related to other licensed drugs used in standard care should be reported by the local investigator using the yellow card system.

Reporting SUSARs

SAEs categorised by the local investigator as **both** suspected to be related to the trial drugs **and** unexpected are SUSARs, and are subject to expedited reporting. The Chief Investigator (CI) or nominated individual will undertake urgent review of SUSARs within 24 hours of reporting and may request further information immediately from the patient's clinical team. The CI will not overrule the causality, expectedness or seriousness assessment given by the local investigator but may comment on these.

The BCTU will report all SUSARs to the MHRA, DMEC and the main REC. If the SUSAR resulted in death or was life-threatening this will be done within 7 days of the initial report being received, or within 15 days for any other SUSAR. BCTU will also notify all SUSARs related to panitumumab to the marketing authorisation holders.

If information is incomplete at the time of initial reporting, or the event is ongoing, the BCTU will request follow-up information, including information for categorisation of causality, from the local investigator and will send the follow-up information to the MHRA and main REC within an additional 8 days for fatal or life-threatening SUSARs and as soon as possible for any other events.

Pharmacovigilance responsibilities

Local Principal Investigator (or nominated individual in PI's absence):

- Medical judgement in assigning seriousness, expectedness and causality to AEs.
- To fax SAE forms to BCTU within 24 hours of becoming aware, and to provide further follow-up information as soon as available.
- To report SAEs to local committees if required, in line with local arrangements.
- To sign an Investigator's Agreement accepting these responsibilities.

Chief Investigator (or nominated individual in CI's absence):

- To assign causality and expected nature of SAEs where it has not been possible to obtain local assessment.
- To review all events assessed as SAEs in the opinion of the local investigator.
- To review all events assessed as SUSARs in the opinion of the local investigator. In the event of disagreement between local assessment and Chief Investigator with regards to SUSAR status, local assessment will not be over-ruled, but the Chief Investigator may add comments prior to reporting to MHRA.

Birmingham Clinical Trials Unit:

- To report SUSARs to MHRA and main REC within required timelines as detailed above
- To prepare annual safety reports to MHRA, main REC and TSC.
- To prepare SAE safety reports for the DMEC at 3-monthly intervals.
- To notify Investigators of SUSARs which compromise patient safety.
- To notify Amgen of cases of abuse, misuse or overdose of panitumumab within 15 days of idebtification.

Trial Steering Committee:

- To provide independent supervision of the scientific and ethical conduct of the trial on behalf of the Trial Sponsor and funding bodies.
- To review blinded data, including accuracy of radiological staging, patient compliance, completion rates, adverse events (during chemotherapy and post surgery) and overall response data.
- To receive and consider any recommendations from the DMEC on protocol modifications.

Data Monitoring & Ethics Committee:

- To review (initially at approx 3-monthly intervals) unblinded overall safety data to identify safety issues which may not be apparent on an individual case basis.
- To review interim analyses of unblinded safety and efficacy data at least annually.
- To advise the TSC whether the DMEC's review of unblinded interim safety and response data provides any good reason why the TSC's review should also be of unblinded data.
- To recommend to the TSC whether the trial should continue unchanged, continue with protocol modifications, or be halted following the pilot phase.

AMGEN INC:

- To report all SUSARs related to panitumumab to the Global Regulatory Authorities (except MHRA), within the required timelines.
- To provide the BCTU with quarterly safety update reports.
- To report to BCTU any new data that might impinge on safety monitoring.

End of Trial

The end of the trial for regulatory purposes is defined as the date of the last visit of the last patient undergoing the protocol based drug therapy. Long-term follow-up, to at least 5 years after randomisation of the last patient, constitutes the non-interventional phase of the trial.

6. SIZE, STATISTICS & DATA MONITORING

Projected accrual

FOxTROT aims to randomise at least 1050 patients over three to four years (less than 2% of the 80,000 colon cancers that will be diagnosed in the UK alone in this time). An average Trust treating about 140 new cases of colorectal cancer per year should see 40-50 potentially eligible **elective** patients for this trial per year.

FOxTROT is the first trial to examine whether giving chemotherapy for colon cancer preoperatively reduces the risk of recurrence and, therefore, incorporated a pilot phase, which has demonstrated the feasibility and practicability of this novel approach and established the new clinical pathways necessary for recruitment. Recruitment to the pilot phase (~10 per month) was, however, slower than anticipated mainly because the deliberately conservative entry criteria considerably reduced the numbers deemed eligible. The reassuring data from the pilot phase on the safety of preoperative therapy, and the confirmation of the accuracy of preoperative radiological staging in identifying high-risk patients for the trial, now indicate that the entry criteria can be safely widened to include ‘intermediate risk’ T3 tumours with less than 5mm extramural extension on the CT scan. This should substantially increase the eligible patient number while still selecting locally advanced tumours with an event rate

sufficient to enable a robust result from the trial. A further measure to boost recruitment is the introduction of an option for shorter, 12-week chemotherapy for patients for whom there are concerns that 6 months of oxaliplatin and fluoropyrimidine chemotherapy might be excessive. OxCap, which was not used in the pilot phase because GI toxicity is more frequent with OxCap than OxMdG,[13] will now be allowed but only for patients who are not randomised for panitumumab. Recruitment should be substantially increased with these protocol amendments allowing the target recruitment for the **FOxTROT** full study of at least 10 patients per centre per annum, making 1050 in total within 3 years, to be achieved.

Statistical considerations

The primary endpoint for the main comparison of "pre-plus-postoperative" and "postoperative alone" chemotherapy will be recurrence in the first two years following randomisation. 1050 randomised will provide over 80% power, at $p<0.05$, to detect a 25% proportional reduction (~8% absolute difference) in recurrence at 2 years (eg 32% reduced to 24%). The randomisation between "pre-plus-postoperative" and "postoperative alone" chemotherapy is in a 2:1 ratio (i.e. 700 vs 350 patients). This increases the numbers of patients randomised for the important questions of whether the addition of the monoclonal antibody alters tumour response prior to surgery and whether tumour markers predict response to chemotherapy or anti-EGFR therapy. The 2:1 allocation ratio does not materially affect statistical power nor will any quantitative treatment interactions (e.g. greater treatment effect in the presence than absence of panitumumab).

The primary outcome measure for assessment of the effect of adding panitumumab to preoperative chemotherapy will be pathological down-staging as measured by depth of extramural spread among patients allocated pre-operative chemotherapy ± panitumumab. As tumour shrinkage is a continuous outcome measure, there will be higher statistical power to detect differences between treatments than for the dichotomous (recurrence yes/no) outcome variables. It is anticipated that about 60% (n=420) of the 700 patients randomised to pre-operative chemotherapy will have *KRAS*-wildtype tumours and hence be eligible for the 1:1 panitumumab randomisation. Despite the reduced sample size for the panitumumab comparison - because entry is restricted to *KRAS*-wildtype tumours - no adjustment to the overall sample size is considered necessary. With 420 patients with *KRAS*-wildtype tumours randomised to pre-operative chemotherapy±panitumumab, **FOxTROT** would have 90% statistical power to detect a small to moderate (0.38sd) difference in tumour shrinkage at $p<0.01$. A 0.38sd difference for 60% with *KRAS*-wildtype (responsive) tumours would translate into a small (0.23sd) overall treatment effect for a *KRAS*-untested population, 40% of whom would have *KRAS*-mutant (resistant) tumours. The original pre-*KRAS* testing **FOxTROT** protocol was powered (90% at $p<0.01$) to detect a 0.3sd benefit applied to the whole population, equivalent to a 0.5sd effect in *KRAS*-wildtype (panitumumab-sensitive) tumours. Should panitumumab produce the originally projected 0.3sd overall benefit, **FOxTROT** would have ample (>99%) power to detect a 0.5sd effect at $p<0.01$ between panitumumab and control and good statistical power to detect any clinically useful predictive variables. The power to detect a 0.3 sd effect just in *KRAS*-wildtype tumours (equivalent to a 0.18sd effect in a *KRAS*-untested population) would still be adequate: 86% at $p<0.05$.

Randomisation will be obtained by telephone or internet from the **FOxTROT** Study office. A minimised randomisation procedure will be used to ensure balance of treatment allocation overall and by the following variables to be used in the pre-specified sub-group analyses:

- **a)** Age (<50, 50-59, 60-69, 70+ years)
- **b)** Radiological T-stage (T3 <5mm invasion, T3 ≥5mm, T4)
- **c)** Radiological nodal status (Nx, N0, N1, N2)
- **d)** Site of primary tumour
- **e)** Defunctioning colostomy (Yes, No)
- **f)** Proposed chemotherapy (OxMdG, OxCap)
- **g)** Planned chemotherapy duration (24 weeks, 12 weeks)

The main analysis will be undertaken once all patients have reached 2 years from randomisation. The statistical analyses will use standard methods (e.g. t-tests for continuous variables and log-rank for time to event analyses). Subgroup analyses will be undertaken,

appropriately cautiously, for variables for which the randomisation is stratified using standard tests for interactions. Additional exploratory analyses will be undertaken of the potential impact of *KRAS*, EGFr, MMR status and other potential biomarkers on prognosis and treatment efficacy.

Data monitoring and ethics committee

During the period of intake of the study, interim analyses of safety, response, recurrence and mortality data (and of any other information on major endpoints that is available) will be supplied, in strict confidence, to an independent data monitoring and ethics committee (DMEC) along with any other analyses that the committee may request. The DMEC will advise the chair of the trial steering committee (TSC) if, in their view, the randomised comparison in **FOxTROT** has provided both (a) "proof beyond reasonable doubt"[a] that for all, or for some, types of patient one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in the main outcome measures, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC can then decide whether to modify intake to the study. Unless this happens, however, the steering committee, the collaborators, funding bodies, study sponsor and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain ignorant of the interim results.

If the clinical coordinators are unable to resolve any concern satisfactorily, collaborators, and all others associated with the study, may write through the **FOxTROT** trial office to the chairman of the DMEC, drawing attention to any worries they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

During the pilot phase of the study, the **FOxTROT** TSC will also review data, including accuracy of radiological staging, patient compliance, completion rates, adverse events (during chemotherapy and post surgery) and overall response data and will recommend whether the **FOxTROT** treatment arms should continue unchanged (with regular DMEC scrutiny), continue with protocol modifications, or be halted. The TSC's evaluation of the safety of preoperative treatment will be blinded with respect to panitumumab allocation unless the DMEC advise the TSC that their review of unblinded interim safety and response data provides any good reason why the TSC's review should also be of unblinded data.

7. ORGANISATION

To ensure the smooth running of **FOxTROT** and to minimise the overall procedural workload, it is proposed that each oncology centre should designate individuals who would be chiefly responsible for local coordination of clinical, radiological, pathological and administrative aspects of **FOxTROT**. The **FOxTROT** Trial Office, working together with NCRN networks, will provide as much assistance as they can to local co-ordinators and investigators in obtaining Trust approval in each centre, and by providing lists of local surgeons and oncologists who have expressed interest, and helping resolve any local problems that may be encountered.

[a] Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

Principal Investigator at each centre

Each Centre should nominate one person to act as the Local Principal Investigator. Their responsibilities will include:

1. **Liaising with local surgeons, radiologists, oncologists, nurses and pathologists** The Principal Investigator will need to liaise with all surgeons who refer patients to the oncology centre to encourage them to consider suitable patients for **FOxTROT**. Local Operating Procedures will need to be developed to ensure prompt radiological staging, discussion of individual patient's suitability for **FOxTROT** at Multi-Disciplinary Team meetings, providing eligible patients with **FOxTROT** information sheets, arranging *KRAS* testing and an appointment to discuss taking part in the study. Any member of the clinical team can obtain consent and randomise patients into **FOxTROT** although it is obviously essential that surgical and oncological teams liaise closely to agree who randomises, which patients are suitable for **FOxTROT**, and to ensure that surgical and chemotherapy slots are available if allocated.
2. **To ensure that all medical and nursing staff involved in the care of colon cancer are reasonably well informed about the study** This involves distributing the **FOxTROT** materials to all relevant staff, displaying the wall-chart where it is likely to be read, and distributing the **FOxTROT** newsletters. A regularly updated PowerPoint presentation will be provided for each hospital so that they can be shown from time to time, especially to new staff.
3. **To ensure compliance with research governance requirements** This involves obtaining management approval for **FOxTROT**, ensuring that all members of the clinical team are familiar with the protocol and trial procedures, in particular serious adverse event reporting, maintaining the Local Study Site File with copies of trial materials, approval documents, consent forms and any other required documents as advised by the **FOxTROT** Study office.

Chief Radiological Coordinator at each centre

High quality radiological staging is an essential component in **FOxTROT**. It is suggested that each Centre should designate one person as Local Radiological Coordinator. This person will be required to attend a CME-credited trial training day, and will provide scans for centralised study evaluation. This person will be responsible for ensuring that potentially eligible patients are carefully staged prior to randomisation and that all suitable patients are considered for entry to **FOxTROT**. This person will be sent updates and newsletters, and will be invited to **FOxTROT** progress and training meetings.

Chief Pathological Coordinator at each centre

High quality pathology is another essential component in **FOxTROT**. It is suggested that each Centre should also designate one person as Local Pathological Coordinator. This person will be required to attend a CME-credited trial training day, and will provide tissue and pathological reports for centralised study evaluation. This person will be sent updates and newsletters, and will be invited to **FOxTROT** progress and training meetings.

Chief Nursing Coordinator at each centre

It is suggested that each Oncology Centre should designate one nurse as Local Nursing Coordinator. This person would be responsible for ensuring that all eligible patients are considered for **FOxTROT**, that patients are provided with **FOxTROT** information sheets, and have an opportunity to discuss the study as required, consent is obtained, a biopsy sample is sent for *KRAS* testing, randomisation, and referral to oncological and surgical units as appropriate. The Nursing Coordinator will also ensure that **FOxTROT** trial forms, questionnaires and treatments are administered as scheduled (unless some contraindication develops). Again, this person would be sent updates and newsletters, and would be invited to **FOxTROT** progress meetings.

Central coordination, randomisation data collection and analysis

The **FOxTROT** Study Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing collaborating centres with the **FOxTROT** folders containing trial materials. The **FOxTROT** Study Office will assist the local Principal Investigators in obtaining Trust approval. Patient entry in a centre can start as soon as Trust approval is given. Additional supplies of any printed material can be obtained on request. The **FOxTROT** Study Office also provides the 24-hour randomisation service and is responsible for collection of data (including reports of serious adverse events thought to be due to trial treatment) and for data analyses.

Clinical Queries

During office hours, the clinical coordinators (see inside front cover for contact details) provide an on-call service for any **clinical** queries about the trial.

Finance

FOxTROT is funded by Cancer Research UK. Panitumumab is being provided free-of-charge by Amgen who also fund *KRAS* testing, the additional CT scan and provide support for meetings. The general structure of the study was, however, designed by the UK National Cancer Research Institute's colorectal cancer Clinical Studies Group, independently of any pharmaceutical companies, who will, like the Trial Steering Committee (which has no Amgen representation), remain blind to the results as they accumulate. This arrangement is intended to ensure that no suggestions of lack of objectivity of the findings can be justified.

Cost implications

The **FOxTROT** trial can offer no financial support to the collaborating hospitals for treatments, other than provision of *KRAS* testing and free supplies of panitumumab. However, **FOxTROT** should not involve any extra research costs for participating hospitals. The OxMdG chemotherapy used in **FOxTROT** is that recommended in the recent NICE guidance for Dukes' C patients, and so does not represent any increase in costs. The alternative option, OxCap, is of similar duration and cost. The panitumumab is supplied free-of-charge and **FOxTROT** requires just one optional extra investigation for two thirds of patients (a CT scan following neoadjuvant chemotherapy) that would not be undertaken in routine practice. Funding for this additional CT has been acquired and will be provided to participating centres. No additional follow-up visits or investigations are needed other than those that would normally be required for standard patient care.

Indemnity

FOxTROT was developed by the NCRI colorectal cancer Clinical Studies Group independently of any pharmaceutical companies. It is funded by Cancer Research UK and the University of Birmingham is the trial 'Sponsor'. As it is not an industry-sponsored trial, ABPI guidelines on indemnity do not apply and there are no special arrangements for compensation for any non-negligent harm suffered by patients as a result of participating in the study. The normal NHS indemnity liability arrangements for clinician initiated research will, therefore, operate – see NHS Executive Health Service Guidelines HSG (96) 48, 8th November 1996. It should be noted, however, that negligent liability remains the responsibility of the hospital, whether or not a patient is part of a clinical trial, because of the duty of care that the hospital has for their patients.

Publication and ancillary studies

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators **prior** to publication. The success of **FOxTROT** depends entirely on the wholehearted collaboration of a large number of surgeons, oncologists, radiologists, pathologists and nurses. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study. It is requested that any proposals for formal additional studies of the effects of the trial treatments on some **FOxTROT** patients (e.g. special investigations in selected hospitals) be referred to the steering committee for consideration. In general, it would be preferable for the trial to be kept as simple as possible, with very few add-on studies.

Appendix A: Patient Information Sheet for KRAS screening

To be printed on local Trust headed paper

FOxTROT: Fluoropyrimidine, Oxaliplatin and Targeted Receptor pre-Operative Therapy

Screening for possible inclusion in the FOxTROT study

Patient Information Sheet v1.0, 01/08/2008

Request for permission to do an additional test

As you will have been told, you have been diagnosed as having a cancer of the colon (bowel). Once all the usual tests and investigations have been completed, your team of cancer specialists will meet to discuss what the best form of treatment would be for you. In the meantime, we would like to ask your permission to do one additional test, which is needed to screen patients for possible participation in a research study called **FOxTROT**. This test, called 'K-RAS', is done on the sample that was taken from your bowel cancer when you had an examination with a flexible telescope (a 'colonoscopy' or 'sigmoidoscopy') and does not require any extra investigations or clinic visits.

The K-RAS test

The sample is tested for alterations in a gene called "K-RAS", which can influence the choice of treatments. In particular, one part of the **FOxTROT** study is to test a new drug (called panitumumab) that blocks the cell mechanisms that make cancer cells grow. Unfortunately, though, panitumumab only works if the cancer cells have normal K-RAS and not with altered K-RAS cancers.

Do I have to have the K-RAS test?

No. You can choose not to have the K-RAS test. This would not affect the quality of your care. All that it would mean is that you would not be eligible for the panitumumab part of the **FOxTROT** research study.

What will happen if I do agree to the K-RAS test?

If you agree to this additional test, then we will ask you to sign a consent form to confirm your agreement. We will then arrange for the sample of your cancer to be taken out of storage and sent for laboratory tests. It can take up to a week to get the test result, which is why we would like to get the test done as soon as possible so that there would be no delay in treatment if you were to take part in **FOxTROT**.

Do I have to decide now?

No. If you need more time to think about it, you can take this information sheet with you and let us know whether you agree to the K-RAS test at your next clinic appointment.

Does agreeing to the test mean that I have to take part in the FOxTROT study?

No. You may decide that you do not wish to take part in the **FOxTROT** study, in which case the doctors will discuss with you the best possible alternative treatment. It is also possible that the usual tests and investigations will show that entering **FOxTROT** is not the best way forward for you - again, the doctors will discuss the best possible alternative options.

How do I find out more about FOxTROT?

You will be given an information leaflet with full details of what the study involves, and what the alternative options are. We will discuss possible participation at your next clinic visit. You will have plenty of time to ask any questions that you may have, to consider whether or not you would like to take part in **FOxTROT**, and to discuss your decision with your friends, family or your GP.

Appendix B: Consent form for K-RAS screening

To be printed on local Trust headed paper

Consent for screening for possible inclusion in the FOxTROT study

1. I confirm that I have read and understood the information sheet "Screening for possible inclusion in the **FOxTROT** study" (version 1.0 dated 01/08/2008) and have had the opportunity to ask questions. ☐
2. I give my consent for samples of my cancer tissue, previously obtained for diagnostic purposes, to be retrieved and sent to a research laboratory to test for abnormalities of the K-RAS gene. ☐
3. I understand that agreeing to undergo screening for possible inclusion in the **FOxTROT** study does not commit me to take part in this study. ☐
4. I understand that the **FOxTROT** Study Office at the University of Birmingham Clinical Trials Unit will be sent a copy of this consent form to inform them that I am being screened for possible participation in the **FOxTROT** study. ☐
5. I understand that all information and samples will be used for medical research only. ☐
6. I understand that all information about me and the test result will be held in strict confidence and that I will not be identified in any way in the reporting of the results. ☐
7. In signing this form, I agree to be screened for the **FOxTROT** study: ☐

Name of Patient:……..……..…….....……Signature: ……Date:…..…….

Person taking Consent: ……..……..…....Signature:……...……Date:……..……

To the Research Nurse:
After obtaining signed consent, **complete the details in the box below clearly, in black ink,** and fax this complete form (**do not cut**) to the histopathology department where samples are currently held. Also **fax the form to BCTU on 0121 415 9135**.

To the Histopathologist: Urgent request for Biopsy Sample material.

Name of Pathologist ……Hospital……..……

Patient ID: Initials…….. DoB…… Hospital Number……....

Biopsy type: ☐ colonoscopy/sigmoidoscopy ☐ other…….... Date:.....

Pathology Lab Number……..... Sample identifier if different…….

The above-named patient is currently undergoing screening for inclusion in the National Cancer Research Institute's **FOxTROT** Study, which requires prospective determination of *K-RAS* oncogene mutational status. This information is required before the patient can be randomised and start treatment with panitumumab.

The patient has given consent for release of tumour material as shown above (item 2). Please arrange immediate transfer of a tumour sample (FFPE block preferred) to:

Dr Susan Richman, FOxTROT Trial Laboratory, Leeds Institute of Molecular Medicine, Section of Pathology and Tumour Biology, Wellcome Trust Brenner Building, St James University Hospital, Leeds LS9 7TF, UK. (Cardiff or Birmingham for selected sites)

Cut off the bottom half of this form as indicated, and enclose it with the sample to identify it.

Please note that receipt of this sample is a rate-limiting step in starting the patient's treatment, and your urgent attention is very much appreciated. If any delay (>24 hours) or other problem is anticipated, please telephone the BCTU on 0800 953 0274 (UK) or +44 (0)121 415 9137 (from outside the UK). Sample retrieval expenses of £20 per patient will be payable on receipt. Please send an invoice to the **FOxTROT** Study Office

v2.0 21/04/2010

Appendix C: PATIENT INFORMATION SHEET

To be printed on local Trust headed paper

FOxTROT: Fluoropyrimidine, Oxaliplatin and Targeted Receptor pre-Operative Therapy:

Patient Information Sheet

Version 3.0, 21/04/2010

Invitation to join FOxTROT, an international research study of drug treatment for bowel cancer

- You have cancer of the bowel (colon) that your surgeon thinks can be removed by an operation
- But, there is still a risk that bits of the cancer might have spread to other parts of the body and so your oncologist has recommended treatment with cancer killing drugs (chemotherapy) to reduce the risk of the disease coming back.
- Chemotherapy for bowel cancer is usually given after surgery but studies in other types of cancer have found that giving chemotherapy before surgery is better than after surgery.
- The aim of the **FOxTROT** study is to find out whether giving some of the chemotherapy before surgery reduces the risk of bowel cancer coming back.
- One group of people who take part in the study will have the first 6 weeks of their chemotherapy before surgery and the rest after surgery. The other group will receive the standard treatment with all of the chemotherapy given after surgery.
- Some of those who take part will also receive a new drug called panitumumab during the first 6 weeks of chemotherapy.
- If you do decide to take part in this research study, then neither you nor your doctors will know beforehand which group you would be in: that will be determined at random, after you've made a firm decision to join the study
- Although taking part in the study may not help you directly, it will help others because, through the **FOxTROT** study, we will find out how best to treat people in the future who develop bowel cancer.

A large-print version of this sheet is available on request.

*Your doctors have told you that you have cancer of the bowel (colon) and have invited you to take part in a research study called "**FOxTROT**". Before you decide whether or not to take part in the **FOxTROT** study, we would like to explain why the research is being done and what it would involve. Please read this information carefully, and discuss it with others if you wish. Ask us if anything is unclear, or if you would like more information. Take your time to decide whether or not you wish to take part.*

What are the treatments for bowel cancer?

The most important treatment for cancer of the bowel ("colon cancer") is an operation to remove it, along with part of the bowel. In fact, for many patients this operation completely cures the cancer. However unfortunately, in some patients, tiny cancer deposits, too small to see or detect, can spread before or during the operation; these then develop into a recurrence of the cancer months or years later. Research over the past decades has shown that a course of drug treatment given after the operation helps to reduce the risk of cancer recurrence. This treatment is called **adjuvant chemotherapy**, and it is recommended for most patients if they are at risk of a recurrence after bowel cancer surgery.

What is the FOxTROT study?

Although adjuvant chemotherapy certainly helps, it does not eliminate the risk of cancer recurrence. **FOxTROT** is a research study testing two new types of treatment to see if these are improvements over standard treatment:

The first is to give some of the chemotherapy **before** the operation (**"preoperative chemotherapy"**) with the aim of killing off any cancer deposits as soon as possible before they grow any bigger. Drug treatment before the operation may also shrink the tumour, making it easier for the surgeon to completely remove it and also make it less likely to spread during the operation. Previous research has found that giving chemotherapy before surgery in other types of intestinal cancer is better than after surgery. **FOxTROT** aims to find out whether it is also better to give some of the chemotherapy for bowel cancer before surgery.

The second treatment being tested is a new drug called **"panitumumab"**. This is an "antibody" treatment designed to bind directly to cancer cells and stop their growth. Panitumumab used on its own, or with chemotherapy, has been shown to be relatively safe and is effective in helping control bowel cancer that has spread to other parts of the body. We are trying to find out in **FOxTROT** whether giving panitumumab along with chemotherapy also helps people with less advanced disease whose cancer can be treated by surgery.

Another part of the research is to try to find out why some people benefit from drug treatment and some don't. We know that patients vary widely in the way that they react to anti-cancer drugs, with different amounts of side-effects and benefits. We suspect that this is partly due to differences in the genes inside cancer cells. For example, people whose cancer has alterations in a gene called '*KRAS*' do not benefit from panitumumab (and so would not receive this drug). The **FOxTROT** study is collecting blood samples and tissue removed at the time of surgery from people taking part in **FOxTROT** to find out what other genetic factors might influence response to treatment. This knowledge could potentially allow doctors to choose the best treatment for each individual patient that gives them the most benefit with the least side-effects.

Why am I being invited to take part in FOxTROT?

Your specialist will have invited you to consider taking part in **FOxTROT** because you have a form of bowel cancer that requires an operation, and for which adjuvant chemotherapy is likely to be helpful. All patients like you are being invited to take part to see when the best time is to give chemotherapy and whether the new drug panitumumab helps with chemotherapy. The **FOxTROT** study aims to include over 1000 people with colon cancer from dozens of hospitals throughout the UK and elsewhere.

Do I have to take part?

No. Taking part in research is always voluntary. If you decide not to take part, then you don't have to give a reason why and no-one will think badly of you for not wishing to take part. Similarly, if you do decide to take part, you would be free to withdraw at any time and without giving a reason. Your surgeon and your oncologist (cancer specialist) will be happy to talk through alternative options, for example the standard treatment of surgery followed by adjuvant chemotherapy.

What does the standard treatment involve?

The standard treatment starts with an operation to remove the part of the bowel containing the cancer. There are several different types of bowel operation, depending on the exact position of the cancer and various other factors, and your surgeon will discuss with you in detail which is best in your case. After surgery, patients spend about a week in hospital and then need a period at home to fully recover from the effects of surgery. This varies from patient to patient, but usually takes between 4 and 8 weeks. Following this, it is recommended that patients at risk of recurrence receive a course of adjuvant chemotherapy. There are several different types of adjuvant chemotherapy available, usually involving about 6 months of treatment with a combination of two or three drugs. Standard chemotherapy does not include panitumumab as this new drug is only available in clinical trials.

What exactly does the FOxTROT chemotherapy involve?

All patients who take part in **FOxTROT** will receive chemotherapy with two types of drug called oxaliplatin and fluoropyrimidine (OxFP). This usually involves a total of 24 weeks of treatment although, for some patients, a shorter option of 12 weeks of treatment may be recommended.

Most patients in **FOxTROT** will receive a form of OxFP called "**OxMdG**" This is a standard chemotherapy that has been tried and tested in many thousands of patients. We know that it is one of the most effective treatments for colon cancer and it is one of the types of chemotherapy recommended by the National Institute for Clinical Excellence (NICE). The OxMdG treatment starts with two chemotherapy drugs, called oxaliplatin and folinic acid, given as a "drip" into a vein over two hours. After that, another drug called fluorouracil is given very slowly into the vein, over the next 46 hours. This 48-hour treatment is given at 2-week intervals usually twelve times amounting to 24 weeks of treatment in all – but for some patients a shorter (12-week) treatment may be recommended. There are several different methods of giving OxMdG and your doctor or nurse will discuss with you the way that suits you best. Most commonly it is given at home, using a small portable pump. To receive OxMdG chemotherapy, you will need to have a thin flexible tube fitted in either your arm or your chest. This leads into one of your veins, and chemotherapy is given through it. Once fitted, it avoids many needles, and can stay in for the duration of your treatment.

Some patients will receive another form of the OxFP combination called "**OxCap**". Again, this is a standard chemotherapy known to be one of the most effective treatments for colon cancer that has been tried and tested in many previous patients. The two drugs used are oxaliplatin and a drug that works in a similar way to fluorouracil and folinic acid called capecitabine. Oxaliplatin is given as a "drip" into a vein over two hours and capecitabine is a pill taken twice daily for two weeks afterwards. Courses of OxCap are given at 3-week intervals, usually for 8 courses amounting to 24 weeks of treatment in total. Again, for some patients a shorter (12-week) treatment may be recommended.

Your medical team will discuss with you, before starting any treatment, which type of chemotherapy they recommend in your case, and what it involves.

What are the FOxTROT study treatments?

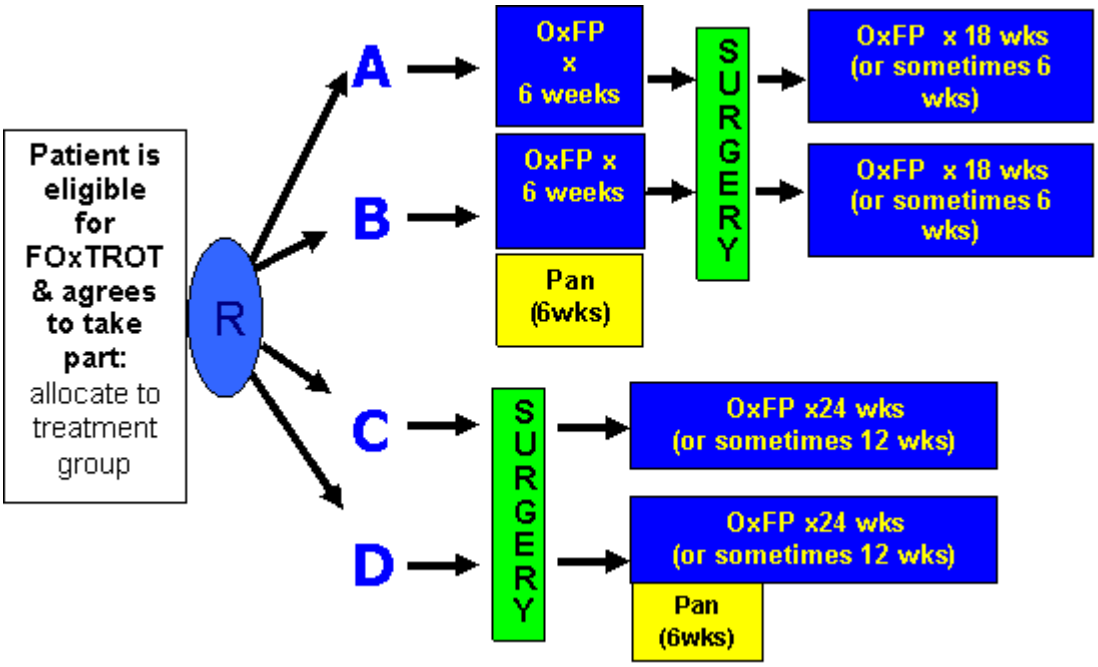
If you decide to take part in **FOxTROT**, you would receive one of four treatments:

A) Oxaliplatin and fluoropyrimidine (OxFP) chemotherapy for 6 weeks before surgery (pre-operative chemotherapy) and then the rest of the chemotherapy after surgery

B) The same 6-week course of pre-operative OxFP chemotherapy but with panitumumab added followed by surgery and then the rest of the chemotherapy after surgery

C) Standard treatment (i.e. surgery followed by OxFP chemotherapy)

D) Standard treatment (surgery followed by OxFP chemotherapy) but with panitumumab added for the first 6 weeks



When the study is complete, we will compare the four groups of patients who received each of these treatments to see which gives the best results. This will include looking at the results of surgery, whether cancer recurrence occurred, and assessing any unwanted side-effects of each treatment. We will also see whether different types of cancer or patients with different genetic or other characteristics have a different reaction to the treatments.

Which of these treatments would I receive?

Neither you nor your doctor can choose which treatment you receive. The decision as to which treatment group people are allocated to is made by the **FOxTROT** study office randomly (like a lottery draw). This is essential so that a fair comparison can be made between the different treatment groups. Dividing people into treatment groups in this way is what is called a **'randomised clinical trial'** and it is the standard and most reliable way of comparing different treatments. However, **FOxTROT** is not a 'placebo' trial; there are no "dummy treatments", all patients will be treated with the most effective available chemotherapy, which we know will help reduce the chance of the cancer coming back, and both you and your doctors will know which treatment you are receiving.

How long does treatment go on?

A third of the patients (1 in 3) who take part in **FOxTROT** receive standard **Post-operative Chemotherapy.** That is to say an operation first, then a period of recuperation, then a 24-week (or sometimes 12-week) course of adjuvant chemotherapy, as described above. The operation will usually take place 1-3 weeks after entry into the study, followed by a 4-8 week recuperation period after surgery, and then 24 (or 12) weeks of adjuvant chemotherapy. So, the full course of treatment is normally completed in 29 – 35 weeks (or 17 – 23 weeks with the 12-week chemotherapy option).

The remaining two thirds of patients in **FOxTROT** receive **Pre-operative Chemotherapy**. This treatment starts before the operation, and involves giving the first 6 weeks of chemotherapy before surgery with the remaining 18 (or 6) weeks of chemotherapy given after surgery. The 6-week course of pre-operative chemotherapy would normally start about a week after entry into **FOxTROT**, and would be followed by a rest period of 3-4 weeks, to allow the treatment to have its full effect and for any side effects to settle, then the operation, a 4-8 week recuperation period after surgery, and then the remaining 18 (or 6) weeks of adjuvant chemotherapy. So, the full course of treatment is normally completed in 32 – 37 weeks (7 to 8 months) or 20 – 25 weeks with the 12-week chemotherapy option).

Some patients in the pre-operative and post-operative chemotherapy groups will receive, in addition, **panitumumab** treatment for the first six weeks of chemotherapy. This will entail an additional drip of about 1 hour, given through a vein, before the start of each course of chemotherapy (i.e. three injections at 2-weekly intervals). Taking panitumumab should not make any difference to the total length of treatment.

What risks are there from these treatments?

Whether or not you take part in the **FOxTROT** study, the recommended treatment for your condition would involve surgery and a course of adjuvant chemotherapy. There are small risks from any form of major surgery and chemotherapy can also produce unwanted effects. Your doctor will explain in detail what these treatments involve. Some patients get no side-effects, but it is helpful to be forewarned of some of the things that could possibly happen with OxMdG or OxCap chemotherapy:

- For a few hours or days after starting treatment, you may feel tingling ('pins and needles') in the hands and feet if you touch cold things or go out in the cold. You may also feel tingling in the throat. This is harmless and will settle without treatment.
- Just occasionally, people can become allergic to one of the drugs, though this is rare. If, while the drip is running, you develop a racing heart beat, an itchy rash, wheezing or a swollen tongue, please tell the nurses immediately.
- Chemotherapy can cause diarrhoea. You will be given anti-diarrhoea tablets to use if this is mild, but if you have severe diarrhoea (more than 4 watery stools in a day) please telephone the hospital for advice.
- Some patients find they feel a little sick for a few days after starting treatment, but vomiting is unusual. You will be provided with some anti-sickness tablets to take if you start feeling sick. If you vomit more than once in a 24-hour period, please telephone the hospital for advice.
- Some people notice soreness in the mouth or a change in taste for some foods. You will be provided with a mouthwash which may help. If you develop ulcers or pain in the mouth, please telephone the hospital for advice.
- Some people feel more tired than usual during chemotherapy treatment. There is no easy answer to this, but if you are affected you may find it helps to set aside a rest period in the middle of each day.
- Any chemotherapy treatment may temporarily reduce your resistance to infections, so if you develop a high temperature or other symptoms of infection between treatments, you may need to come to the hospital for an urgent check-up.
- Occasionally, we meet someone who is particularly sensitive to the effects of chemotherapy and has more severe side-effects than expected. If that happens, treatment is stopped until the problems have settled; it is usually then possible to continue treatment at a lower dose.
- Women of childbearing potential must: have a negative pregnancy test prior to trial entry and avoid pregnancy during and for 6 months after study treatment. Men with a partner of childbearing potential must use adequate, medically approved, contraceptive precautions during and for 90 days after the last dose of study treatment.

In **FOxTROT**, some patients will receive the antibody treatment, **panitumumab**, in addition to chemotherapy, which can cause additional side-effects. Nearly all patients receiving antibody will develop a **rash**, which is usually mild. It can take the form of red blotches or spots, or may resemble acne. Occasionally it can become more severe with itching, blisters or flaking. Other skin side-effects from panitumumab may include swelling and soreness around your nails and at the tips of your fingers and toes. Some patients receiving antibody have reported loss of appetite, or feeling tired, dizzy, anxious or short of breath. It may cause your muscles and joints to ache or cause slight swelling in your hands and feet. Having antibody alongside chemotherapy also increases the risk that you will experience diarrhoea after the chemotherapy. About 3% of people who have been treated with panitumumab have had allergic reactions, most of which are mild or moderate in intensity. More severe reactions occur in less than 1 in 100 patients treated and can, very rarely (less than 1 in 10,000 patients treated), be fatal. The three fatal infusion-related reactions that have been reported with panitumumab (as of May 2010) were all in patients who had advanced (incurable) cancer, though, and all had previously experienced hypersensitivity reactions. Panitumumab is no longer used in patients who have had any previous severe hypersensitivity reactions. We believe, therefore, that the chance of such severe reactions in FOxTROT is extremely low and all patients will be carefully monitored during treatment to minimise the risk. There is also a very small chance that antibody treatment might cause a heart attack: this does not seem to be a problem with panitumumab, the antibody used in **FOxTROT**, but some patients treated with a similar drug have experienced heart damage. If you experience a racing heart beat, chest pain or any other symptom that you believe may be related to your heart, please contact the hospital immediately. Panitumumab has been tried and tested in several thousands of patients but, as with any new drug, there is a potential that you may experience other side-effects not previously observed.

How will my condition be monitored?

Your progress will be monitored carefully. Before starting **FOxTROT** you will have had investigations to assess your cancer, including a CT scan, a colonoscopy, a biopsy and blood tests. Before starting the study, your medical team will check your records and the results of your examinations and blood tests to make sure you are suitable for the study.

During chemotherapy, you will be asked about any side-effects you have experienced and will have a blood test at each treatment visit. If you are one of the two-thirds of patients receiving preoperative chemotherapy, you will be asked to have another CT scan after the treatment and before surgery, to assess your response to chemotherapy and how this might impact on the type of surgery you receive. A second scan is currently not standard practice for colon cancer patients although in other cancer types where preoperative chemotherapy is the standard of care - for example stomach, lung and oesophageal cancer - a post-chemotherapy pre-surgery CT scan is the routine clinical practice. This second scan is, however, optional and so if you do not wish to have this scan, you can still take part in **FOxTROT**.

When you have your operation, you will of course be carefully monitored throughout the operative period. Your surgeon will send the removed cancer tissue for examination in the hospital's pathology laboratory, and will discuss the result of the operation with you. After you have recovered from the operation, you will be assessed by the oncologist and, when sufficiently fit, you will start your post-operative chemotherapy. You will be monitored throughout this time for any side-effects or other problems. After completing your treatment, there will be a period of follow up, during which you will be asked to attend the clinic regularly for check ups, with occasional blood tests and scans to assess your progress.

What are the possible benefits from taking part in FOxTROT?

We are taking part in the **FOxTROT** study because we hope that **pre-operative chemotherapy** and/or **panitumumab** treatment may give better results than standard treatment. However we cannot be sure in advance whether this is the case – that is the reason for doing this study. The main benefit from **FOxTROT** will be that the information gained from the study will help improve the treatment of future patients with bowel cancer.

What are the possible disadvantages of taking part?

The majority of patients' cancers are controlled (i.e. shrink or stop growing) during chemotherapy treatment. However, occasionally, cancers grow despite treatment. We cannot rule out the possibility that your cancer could grow during pre-operative treatment, in which case surgery could be less, rather than more, effective. This is why we are collecting blood samples to try and find out why some cancers are sensitive to chemotherapy and some are not. Also, while the chemotherapy and antibody treatment have been tried and tested in many patients, the majority did not go on to have surgery. It is possible that the complication rates of surgery could be increased by giving these treatments before surgery. It is standard practice to assess and monitor your cancer using CT scans (these take images of your body using x-rays). By taking part in the trial you may receive one CT scan more than for standard care and so will receive extra radiation. Any radiation is associated with an increased risk of developing cancer. However the risk associated with a single CT scan is very small (less than 1 in 1300) and negligible when compared with the 1 in 4 lifetime risk of cancer.

To protect patients' safety, an independent committee of cancer experts will regularly review the results of the **FOxTROT** trial, as well as information from other relevant trials around the world. This is so that if the new treatments unexpectedly turn out to be worse than the standard, that would be detected as soon as possible and the trial stopped.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. But, whether or not you take part, you would retain the same legal rights as any other patient treated in the National Health Service. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part be kept confidential?

If you decide to take part in **FOxTROT**, the information collected about you during the course of the trial will be kept strictly confidential in the same way as all of your other medical records. Information about your disease and progress will be sent by your doctors to the **FOxTROT** Study Office at the University of Birmingham Clinical Trials Unit (BCTU), on paper and electronically, where it will be securely stored under the provisions of the 1998 Data Protection Act and/or applicable laws and regulations. Your details will also be sent to the NHS Information Centre so that NHS and government records can be used to follow your progress. Your GP, and the other doctors involved in your clinical care, will be kept informed, but otherwise all information about you and your treatment will remain confidential.

If you take part in the study, your relevant medical records may be inspected by authorised individuals from the BCTU and by Cancer Research UK (who are funding the study). They may also be looked at by the regulatory authorities. The purpose of this is to check that the study is being carried out correctly. A pharmaceutical company, Amgen, is providing antibody (panitumumab). At the end of the study, a copy of the trial data will be sent to Amgen or its subsidiary companies. It will not be possible to identify you from these data and it will be kept strictly confidential. When the trial is complete, the results will be published in a medical journal but no individual patients will be identified. If you would like to obtain a copy of the published results, please ask your doctor.

You can decide not to continue with study treatment at any time but, if you do, we would still like to follow up your progress. An important aim of the study is to find out how many patients complete their treatment and how people get on if they withdraw from treatment. For this reason, your data and samples would remain on file and be included in the final study analysis. In line with Good Clinical Practice guidelines, at the end of the study, the data will be securely archived for a minimum of 15 years. Arrangements for confidential destruction will then be made. If you withdraw consent for your data to be used, it will be confidentially destroyed.

Additional research

If you take part in **FOxTROT**, we would like to request your permission to take an extra blood sample and to send this along with some of the surplus material from your biopsy and from the specimen removed at surgery to a laboratory where some genetic tests will be done, for bowel cancer research. The research involves extracting DNA or other chemicals from the tumour to see whether it is possible to predict which patients will benefit most from each treatment. All such work is anonymous: your specimens will be identified by a code number, not your name, and neither you nor your relatives will be identified or contacted and the results will not be added to your medical records.

We need to test the biopsy sample for any abnormalities of the *KRAS* gene for patients to be eligible for panitumumab. Otherwise, these studies will not affect your treatment in any way, and you are free to withhold this permission without affecting your participation in **FOxTROT** or your relationship with your doctor.

In some hospitals, patients taking part in **FOxTROT** may be invited to participate in an extra piece of research to obtain an additional biopsy sample of the tumour. Your doctor or nurse will talk to you about this if your hospital is participating.

Who has organised, reviewed and funded the research?

The **FOxTROT** study was developed by the National Cancer Research Institute's Colorectal Cancer Clinical Studies Group, and is funded by the medical charity, Cancer Research UK. The study also has the full support of the Bobby Moore Fund. The study is coordinated by the Clinical Trials Unit at the University of Birmingham. Amgen Inc is providing the panitumumab free-of-charge and support for scans and meetings but is not involved in the design, running or analysis of the study. The research has been reviewed and approved by all of these organisations, and also by the West Glasgow Multi-centre Research Ethics Committee.

What do I need to do if I decide to take part?

If you do decide to take part, you will be asked to sign a consent form. If you want to think about it for longer, or discuss it with friends or relatives, then you can take this information sheet and the consent form away with you and then sign the form at your next visit to hospital. You may not need to make an extra visit to the hospital. Whether you agree to take part now or later, you would be free to withdraw at any time after and without giving a reason. All you would need to do is to contact your surgeon or oncologist either in writing or by telephone and you will be withdrawn from the study. This will not adversely affect the care that you receive.

Further information

If you have any further questions about your disease or clinical trials, please discuss them with your doctor. You may also find it helpful to contact an independent patient advisory group such as CancerBACUP, (freephone: 0800 800 1234; address: 3 Bath Place, Rivington Street, London, EC2A 3DR; web site www.cancerbacup.org) or the CancerHelp website http://www.cancerhelp.org.uk/index.htm.

For any queries about the study or for further information please contact:

Name: .....

Tel No: .....

Position: .....

The FOxTROT Study Office is located at the University of Birmingham Clinical Trials Unit, Robert Aitken Institute, College of Medical Sciences, Birmingham B15 2TT.

e-mail: FOxTROT-trial@contacts.bham.ac.uk; Web address: www.bctu.bham.ac.uk

Appendix D: Consent Form

To be printed on local Trust headed paper

FOxTROT: Fluoropyrimidine, Oxaliplatin and Targeted Receptor pre-Operative Therapy for colon cancer

FOxTROT trial number ☐☐☐☐

	Initial box to confirm consent	
1.	I have read and understood the information sheet for the **FOxTROT** study (version 3, dated 21st April 2010) and have had the opportunity to ask questions.	☐
2.	I understand that my participation in this study is voluntary and that, if I take part, I may withdraw at any time, without giving reasons, and without the standard of my medical care or legal rights being affected.	☐
3.	I understand that a copy of this consent form and information about my progress will be sent in confidence to the study coordinators at the University of Birmingham, by my doctors and by NHS registries for use in the **FOxTROT** study.	☐
4.	I agree that my hospital and other health records may be looked at in confidence by authorised individuals from the **FOxTROT** study and by regulatory authorities to check the study is being carried out correctly.	☐
5.	I understand that the study researchers may contact me by letter, telephone or email to remind me to complete the Quality of Life questionnaires or to ask me the questions over the telephone.	☐
6.	I understand that my GP will be informed of my participation in the study and may be contacted to provide information about my progress, in confidence, to the central organisers.	☐
7.	If allocated to pre- plus post-operative chemotherapy, I give consent for one additional CT scan to be performed: this scan may be in addition to what is required for my treatment.	**Yes** ☐ **No** ☐
8.	I agree to parts of the tissue removed at surgery being stored and used for research, both within this study and in future related studies. Any such study on this material would require Research Ethics Committee approval.	**Yes** ☐ **No** ☐
9.	I agree to a blood sample being taken to be used for additional research.	**Yes** ☐ **No** ☐
10.	I understand that all information and samples collected will be used for medical research only and that I will not be identified in any way in the analysis and reporting of the results and that any results from the additional research will not be recorded on my medical records. Any such study on information and samples collected would require Research Ethics Committee approval.	☐
11.	If *KRAS* screening shows that I am eligible, I agree to receive panitumumab if allocated	**Yes** ☐ **No** ☐
12.	I agree to take part in the **FOxTROT** study.	☐

Name of Participant _____

Signature _____ Date _____

Name of Clinician _____

Signature _____ Date _____

Original to be kept in the **FOxTROT** study file, one copy for patient, one kept with patient's notes and one sent to the **FOxTROT** Study Office:

FOxTROT Study Office, The University of Birmingham Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham, B15 2TT **V3.0 21/04/10**

Appendix E: Randomisation notepad

Complete this form then contact randomisation service: **+44 (0) 800 953 0274** or **https://www.trials.bham.ac.uk/FOxTROT**

Part A – Identifying Details

Date of Randomisation dd____/mm____/yyyy____

Randomising centre: _____ Randomising clinician: _____

Patient's full name: _____ Date of Birth: dd____/mm____/yyyy____

NHS No: : _____ Hospital number: _____

Part B – Radiological assessment

1. Primary tumour site? ☐ Caecum ☐ Ascending colon ☐ Hepatic flexure ☐ Transverse colon ☐ Splenic flexure ☐ Descending colon ☐ Sigmoid ☐ Rectosigmoid

2. TNM staging
   - T-stage: TX ☐ T1/T2 ☐ T3 ☐ T4 ☐
   - N-stage: NX ☐ N0 ☐ N1 ☐ N2 ☐
   - M-stage: M0 ☐ M1 ☐

3. Max distance of tumour spread beyond muscularis propria: _____ mm

Part C – Eligibility checklist

4. T4 or definite tumour ≥ 1mm beyond muscularis propria?	Yes ☐	No ☐	
5. Free of metastases or omental nodules?	Yes ☐	No ☐	
6. Resectable disease?	Yes ☐	No ☐	
7. Has the patient had any other malignant disease within the past 5 years?	Yes ☐	No ☐	
8. Is the tumour within 15cm of the anal verge or is radiotherapy advised by the MDT?	Yes ☐	No ☐	
9. Is there evidence of peritonitis?	Yes ☐	No ☐	
10. Does patient have a serious medical comorbidity? (such as uncontrolled IBD, uncontrolled angina or recent MI)	Yes ☐	No ☐	
11. If the patient has presented with acute colonic obstruction, has the obstruction been relieved by a defunctioning stoma?	Yes ☐	No ☐	N/A ☐
12. If the patient is female – Is the patient pregnant or lactating?	Yes ☐	No ☐	
Does the patient have an adequate:			
13. Hepatobiliary function?	Yes ☐	No ☐	(must be <25 μmol/l)
14. Serum magnesium level?	Yes ☐	No ☐	
15. Renal function?	Yes ☐	No ☐	(GFR >50 or EDTA clearance>70 ml/min)
16. Full blood count?	Yes ☐	No ☐	
(Hb must be >10.0g/dl or confirm patient will be transfused before chemotherapy or surgery)			
17. What is the patient's WHO performance status?	0 ☐	1 ☐	2 ☐ ≥3 ☐
18. Has the patient given written informed consent?	Yes ☐	No ☐	
19. Which version of the consent form was used?	v 1.2 ☐	v 2.0 ☐	v3.0 ☐

*If shaded boxes are ticked, patient **not eligible** for **FOxTROT***

Part D – Randomisation – Treatment allocation

20. Has biopsy sample been sent for *KRAS* testing?	Yes ☐	No ☐	
21. If patient is *KRAS* mt or *KRAS* is not determined, which chemotherapy regimen will be prescribed?	OxMdG ☐	OxCap ☐	(OxCap not allowed with panitumumab)
22. Will chemotherapy duration be 24 wks or 12 wks ('Foxtrot lite')?	24wks ☐	12wks ☐	
23. If allocated, when would pre-operative chemotherapy begin?	dd____/mm____/yyyy____		
24. Has patient consented to panitumumab treatment?	Yes ☐	No ☐	

Chemotherapy allocation:
- Pre- plus post-operative chemotherapy ☐
- Post-operative chemotherapy ☐

Panitumumab allocation
- OxMdG plus panitumumab ☐
- OxMdG alone ☐

FOxTROT trial number ☐☐☐☐

Please return this form within 1 week of entry into the trial to: **FOxTROT** Study Office, The University of Birmingham Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham, B15 2TT or fax to +44 (0) 121 415 8871 v3.0 21/04/10

Appendix F1: Surgical Details: Intraoperative Form

Patient's name: _____ Date of Birth: ___/___/_____

NHS No: _____ Hospital No: _____ **FOxTROT** No: ☐☐☐☐

Surgeon: _____ Hospital: _____

Please answer ALL questions

PART A

Has there been any clinical evidence of ongoing toxicity since completion of neoadjuvant chemotherapy? Yes ☐ No ☐ N/A ☐

If 'Yes' : i) What was the toxicity? _____

ii) Was the patient admitted to hospital? Yes ☐ No ☐
If 'Yes', please complete SAE form

iii) Was surgery delayed? Yes ☐ No ☐

PART B - Surgery:

Date of surgery: ___/___/_____ No surgery ☐

Was surgery laparoscopic? Yes ☐ No ☐

If surgery performed, type of resection:
Right hemicolectomy ☐
Left hemicolectomy ☐
High anterior resection ☐
Other (please specify) _____

If no surgery, why not? _____

PART C

Has the procedure resulted in a stoma?			Y ☐	N ☐
	If 'Yes' was it:		End ☐	Loop ☐
Liver:	Irregularities on surface?		Y ☐	N ☐
	Appearances of metastatic carcinoma?		Y ☐	N ☐
	Biopsy?		Y ☐	N ☐
Omentum:	Abnormalities in omentum?		Y ☐	N ☐
	Suspicious of tumour?		Y ☐	N ☐
	Biopsy?		Y ☐	N ☐
Peritoneum:	Evidence of peritoneal seedlings?		Y ☐	N ☐
	Free fluid evident at start of operation?		Y ☐	N ☐
	Biopsy?		Y ☐	N ☐
Serosal surface:	Tumour evident on serosa?		Y ☐	N ☐
Lymph nodes:	Lymph nodes palpable in mesentry?		Y ☐	N ☐
	Fluid stent for cytology?		Y ☐	N ☐
Macroscopic evidence of residual tumour following resection:				
	Primary tumour?	Uncertain ☐	Y ☐	N ☐
	Mesentry?	Uncertain ☐	Y ☐	N ☐
	Retroperitoneal?	Uncertain ☐	Y ☐	N ☐
	Other?	Uncertain ☐	Y ☐	N ☐

Form completed by: _____ Date completed: ___/___/_____

Sign name: _____ Telephone no: _____

Appendix F2: Surgical Details: Hospital Discharge Form

Patient's name: _____ Date of Birth: ____/____/____

NHS No: _____ Hospital No: _____ **FOxTROT** No: ☐☐☐☐

Surgeon: _____ Hospital: _____

Date of surgery: ____/____/____ Date of hospital discharge* ____/____/____ N/A ☐

*date fit for discharge, exclude time hospitalised for social reasons

Complications – Please complete for all patients

PART A

Did the patient experience any complications that required or prolonged hospitalisation, were fatal or life-threatening? Yes ☐ No ☐

If 'Yes' please complete SAE form.

PART B

Please ✓ one box for each question

Did the patient experience:		
Haemorrhage:		
Primary	Yes ☐	No ☐
Secondary	Yes ☐	No ☐
Anastomotic leak	Yes ☐	No ☐
Wound Infection	Yes ☐	No ☐
Intra-abdominal abscess	Yes ☐	No ☐
Pulmonary complications:		
Bronchopneumonia	Yes ☐	No ☐
Pulmonary embolus	Yes ☐	No ☐
Deep vein thrombosis	Yes ☐	No ☐
Urinary tract infection	Yes ☐	No ☐
Drug reaction:		
Rash	Yes ☐	No ☐
Neutropenia	Yes ☐	No ☐
Death – ***complete SAE form***	Yes ☐	No ☐
Other complications If 'Yes' please specify _____	Yes ☐	No ☐

PART C

Was further abdominal surgery required? Yes ☐ No ☐

If 'Yes', please specify _____

Form completed by: _____ Date completed: ____/____/____

Sign name: _____ Telephone number: _____

Please return this form to: **FOxTROT** Study Office, The University of Birmingham Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham B15 2TT or fax to +44 (0) 121 415 8871 **v1.1 21/04/10**

Appendix G: Sample Letter to GP

To be printed on local Trust headed paper

GP name
Surgery
Street name
City
Postcode

Date

Dear Dr

Name _____ D.o.B _____ NHS No _____

Your patient, named above, has been diagnosed with colon cancer which is locally advanced but does appear to be operable. Chemotherapy is likely to be of benefit and we usually recommend a 24 week course of treatment with a combination of oxaliplatin and a fluoropyrimidine - either fluorouracil and folinic acid by infusion ('OxMdG') or oral capecitabine ('OxCap') - although for some patients a shorter 12-week course is considered appropriate.

Such patients are suitable for entry to **FOxTROT**, an international multi-centre randomised clinical trial assessing whether giving the first 6 weeks of chemotherapy pre-operatively improves outcome compared with the standard treatment of post-operative chemotherapy according to NICE guidelines. **FOxTROT** is also assessing whether panitumumab, a monoclonal antibody targeted at EGF receptors, improves outcome for patients with tumours that are sensitive to EGF-directed therapy (i.e. *K-RAS* wildtype). **FOxTROT** was developed by the National Cancer Research Institute's colorectal cancer Clinical Studies Group. The University of Birmingham Clinical Trials Unit (address below) are acting as coordinating centre. The study is funded by Cancer Research UK and receives no commercial support other than free supplies of panitumumab and help for CT scans and meetings. The trial has been approved by West Glasgow Research Ethics Committee and the Local Research Ethics Committee at each participating centre.

Your patient has consented to take part in the **FOxTROT** trial and has been allocated to:

- ☐ Six weeks of pre-operative oxaliplatin/fluoropyrimidine chemotherapy followed by surgery then the rest of the chemotherapy post-operatively
- ☐ The same chemotherapy regimen with concomitant panitumumab for the first 6 weeks
- ☐ Surgery then post-operative oxaliplatin/fluoropyrimidine chemotherapy
- ☐ The same chemotherapy regimen with concomitant panitumumab for the first 6 weeks

The chosen chemotherapy regimen will be: OxMdG ☐ OxCap ☐

The chosen chemotherapy duration will be: 24 weeks ☐ 12 weeks ☐

I, or another member of the multi-disciplinary team responsible for your patient, will be updating you regularly on progress. If you have any queries about the patient's management, please feel free to contact me. If you require any further information about the **FOxTROT** trial, it can be obtained from the **FOxTROT** study office (see address below). Please file this letter in the patient's notes. I would appreciate being notified if they are no longer one of your patients.

Yours sincerely

……

FOxTROT Study Office, The University of Birmingham Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham, B15 2TT
Tel: 0121 415 9105 Fax: 0121 415 8871 Email: foxtrot-trial@bham.ac.uk www.foxtrot.bham.ac.uk

v2.0 21/04/10

Appendix H: Chemotherapy Form

Patient name: _____ FOxTROT Trial No: _____

Hospital: _____ Oncologist: _____

Patient Hospital No: _____ NHS No: _____

Height (m) : _____ Date of Birth: ____/____/____

PART A

Which chemotherapy regimen did the patient receive? OxMdG ☐ OxCap ☐

Post-operative chemotherapy alone ☐ Pre-plus post operative chemotherapy alone ☐

Post-operative chemo plus Panitumumab ☐ Pre-plus post operative chemo plus Panitumumab ☐

PART B

Did patient complete current 6 week cycle of chemotherapy? Yes ☐ No ☐

Date of cycle start:	☐☐ ☐☐ ☐☐ (dd mm yy)	☐☐ ☐☐ ☐☐ (dd mm yy)	☐☐ ☐☐ ☐☐ (dd mm yy)
Cycle No (for this regimen):	☐☐	☐☐	☐☐
Weight	☐☐☐ Kg	☐☐☐ Kg	☐☐☐ Kg
WBC	☐☐.☐ 10^9/l	☐☐.☐ 10^9/l	☐☐.☐ 10^9/l
Neutrophils	☐☐.☐ 10^9/l	☐☐.☐ 10^9/l	☐☐.☐ 10^9/l
Platelets	☐☐☐ 10^9/l	☐☐☐ 10^9/l	☐☐☐ 10^9/l
Serum bilirubin	☐☐☐ µmol/l	☐☐☐ µmol/l	☐☐☐ µmol/l
Estimated Creatinine	☐☐☐ ml/min	☐☐☐ ml/min	☐☐☐ ml/min
or Measured GFR	☐☐☐ ml/min	☐☐☐ ml/min	☐☐☐ ml/min
Chemo given as:	☐ I/P ☐ O/P	☐ I/P ☐ O/P	☐ I/P ☐ O/P

Actual dose given (In mg, not mg/m^2): (If a protocol drug is omitted for any reason enter '0')

5FU - bolus	☐☐☐ mg	☐☐☐ mg	☐☐☐ mg
5FU - infusion	☐☐☐☐ mg	☐☐☐☐ mg	☐☐☐☐ mg
Daily capecitabine	☐☐☐☐ mg/day	☐☐☐☐ mg/day	
Oxaliplatin	☐☐☐☐ mg	☐☐☐☐ mg	☐☐☐☐ mg
Panitumumab	☐☐☐☐ mg	☐☐☐☐ mg	☐☐☐☐ mg
Cycle Delayed*	☐ ☐	☐ ☐	☐ ☐
Dose(s) modified*	☐ ☐ 5FU	☐ ☐ 5FU	☐ ☐ 5FU
	☐ ☐ Capecitabine	☐ ☐ Capecitabine	☐ ☐ Capecitabine
	☐ ☐ Oxaliplatin	☐ ☐ Oxaliplatin	☐ ☐ Oxaliplatin
	☐ ☐ Panitumumab	☐ ☐ Panitumumab	☐ ☐ Panitumumab

*specify major reason(s) for dose delay/modification(s)using codes below.

Codes

0 = No dose/delay modification
1 = Allergic reaction
2 = Neutropenia
3 = Thrombocytopenia
4 = Diarrhoea
5 = Hand foot syndrome
6 = Cardiac dysfunction
7 = Neurotoxicity
8 = Hepatobiliary dysfunction
9 = Renal dysfunction
A = Skin toxicity
B = Stomatitis
C = Venous access problems
D = Capecitabine non-compliance
E = Hospital administrative
F = Patient choice
G = other, specify (including combination of reasons): _____

PART C

TOXICITY ASSESSMENT

Please complete after every 6 weeks (i.e. 3 cycles if patient receiving the OxMdG regimen or after 2 cycles if patient is receiving OxCap).

☐☐ ☐☐ ☐☐ **Date of assessment**

dd mm yy

Please record worst CTC grade (CTC version 3.0) experienced during the past six weeks of chemotherapy. Please record 9 if not known.

☐ Nausea	☐ Vomiting	☐ Anorexia	☐ Alopecia
☐ Pain	☐ Stomatitis	☐ Nail Changes	☐ Diarrhoea
☐ Lethargy	☐ Platelets	☐ Haemoglobin	☐ WBC
☐ Neutrophils	☐ Skin rash	☐ Vein pain	☐ Hand-foot
☐ Peripheral neuropathy	☐ Other, specify _____		

Current WHO Performance Status

☐

0 = Able to carry out normal activity without restriction
1 = Restricted in physical strenuous activity but ambulatory and able to carry out light work
2 = Ambulatory and capable of self-care but unable to carry out any work; up and about more than 50% of working hours
3 = Capable only of limited self-care; confined to bed or chair ore than 50% of waking hours
4 = Completely disabled; cannot carry out any self-care; totally confined to bed or chair

Has the patient experienced any SAEs in the past 6 weeks?

Yes ☐ **No** ☐

If Yes, has an SAE form been completed? If not, please complete and fax it immediately to the Birmingham Clinical Trials Unit (Fax no. 0121 415 8871)

In the past 6 weeks how many nights has the patient spent in hospital?
(Please complete each field even if the entry is 0)

ICU _____ HDU _____ General/acute _____ In-patient chemotherapy _____

In the past 6 weeks how many days has the patient attended hospital as an:
(Please complete each field even if the entry is 0)

Outpatient _____ Day Case _____

Has the patient completed their QoL forms?

Prior to surgery ☐ Yes ☐ No If No, give reasons _____

Prior to first cycle of post-op chemotherapy ☐ Yes ☐ No If No, give reasons _____

Form completed by: _____ Date completed: _____/_____/_____

Sign name: _____ Telephone number: _____

Please return this form, along with the completed entry form, to: **FOxTROT** Study Office, The University of Birmingham Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham, B15 2TT or fax to +44 121 415 8871. **v2.0 21/04/10**

Appendix I: Serious Adverse Event Form

Please report immediately any SERIOUS ADVERSE EVENTS (see protocol page 15 for definition) by completing all of the details below and faxing this form to the FOxTROT Trial Office on +44 121 415 8871. Please also complete the SAE form if the patient dies of any cause other than colorectal cancer.

Patient's name: _____ Date of Birth: ____/____/____

NHS No: _____ Hospital No: _____ **FOxTROT** No: |__|__|__|

Responsible Oncologist: _____ Hospital: _____

SAE description

Is this an initial or follow up report? Initial ☐ Follow up ☐

Is this the final report? Y ☐ N ☐

Reason for reporting

Death? Y ☐ N ☐ Date of death ___/___/____

Life threatening event? Y ☐ N ☐

In-patient hospitalisation or prolongation of existing hospitalisation? Y ☐ N ☐ If yes, no of days? _____

Persistent or significant disability/incapacity? Y ☐ N ☐

Other pertinent reason for reporting, e.g. new primary cancer? Y ☐ N ☐

If other, please specify: _____

Date even started: ____/____/____ Date event ceased: ____/____/____

Details of adverse event (please attach copies of relevant reports): _____

_____

_____

Trial treatment

Is SAE related to chemotherapy or surgery? Chemotherapy ☐ Surgery ☐

What was the date of surgery? ____/____/____

If SAE considered to be related to surgery, please assess causality (use codes given below): _____

This section must be completed by a clinician

Drug	Date last dose administered	Dose last given	No. of whole cycles given	Causality assessment (use codes given below)
5FU	____/____/____	_____ mg		
Oxaliplatin	____/____/____	_____ mg		
Capecitabine	____/____/____	_____ mg		
Panitumumab	____/____/____	_____ mg		

Causality assessment codes:

1 Probably unrelated to treatment
2 Possibly related to treatment
3 Probably related to treatment
4 Definitely related to treatment

Please give reasons if you consider the event to be treatment related: _____

_____

_____

Was the SAE **unexpected**, i.e. of a **type** or **severity** which is NOT consistent with the up-to-date SPC (available at http://emc.medicines.org.uk/)? **This section must be completed by a clinician**

Unexpected ☐ Expected ☐

Please give reasons if you consider the event to be unexpected: _____

_____

_____

Was the patient disease-free at the time of the event?

Yes ☐ No (residual disease) ☐ No (pre surgery) ☐ No (recurrent disease) ☐ Date of recurrence: ___/____/___

What was the outcome of the SAE? Fatal ☐ Recovered ☐ Continuing ☐

Signature of Person Reporting: _____ Date: _____/_____/_____

You must have signed the site Delegation log

Name: _____ Position: _____

Telephone number: _____

Signature of Investigator: _____ Date: _____/_____/_____

If not completed by Investigator

SUSAR Reporting – BCTU USE ONLY

SAE reference number: _____

Date reported to BCTU: _____/_____/_____

Date reported to CI: _____/_____/_____ Date reply received from CI: _____/_____/_____

Is this event a SUSAR? Yes ☐ If Yes: 7 day report ☐ OR 15 day report ☐

No ☐ If No, is this an SAE? Yes ☐ No ☐

CI comments: _____

_____

_____

_____

Date due to be reported to MHRA and MREC: _____/_____/_____

When you have faxed the form, please then send (with copies of any relevant reports) to the FOxTROT Study Office, The University of Birmingham Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, Robert Aitken Institute, School of Cancer Sciences, Birmingham B15 2TT

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Appendix J: Panitumumab – Expected toxicities

Toxicities/side-effects that have previously occurred and are listed in the current panitumumab Investigator's Brochure (IB) and Summary of Product Characteristics (SPC) do not have to be reported to the MHRA. If the outcome of the side-effect is serious, the SAE form should be completed. Any SAE not described below (or in the most recent IB or SPC), i.e. a serious toxicity that is unexpected, and believed to be related to study treatment, will be reported as a SUSAR (see pages 14-15).

Based on an analysis of all patients receiving panitumumab monotherapy (N = 920), the most commonly reported adverse reactions are skin reactions occurring in approximately 90% of patients. These reactions are related to the pharmacologic effects of panitumumab, and the majority are mild to moderate in nature with approximately 10% severe (grade 3 or higher, NCI-CTC).

Except where indicated, the data describe adverse reactions reported from clinical studies in patients with metastatic colorectal carcinoma who received panitumumab as a single agent:

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA Organ System	Frequency	Undesirable Effect
Skin and subcutaneous tissue disorders	Very common (≥ 1/10)	Rash Erythema Skin exfoliation Pruritus Dry skin Skin fissures Paronychia
Gastrointestinal disorders		Diarrhoea
General disorders and administrative site conditions		Fatigue
General disorders and administrative site conditions	Common (≥ 1/100 to < 1/10)	Infusion reactions (pyrexia, chills)
Metabolism and nutrition disorders		Hypomagnesaemia Hypocalcaemia Hypokalaemia Dehydration
Gastrointestinal disorders		Nausea Vomiting
Respiratory, thoracic and mediastinal disorders		Dyspnoea Cough
Nervous system disorders		Headache
Eye disorders		Conjunctivitis Growth of eyelashes Increased lacrimation Ocular hyperaemia Dry eye Eye pruritus
Skin and subcutaneous tissue disorders		Stomatitis Mucosal inflammation Onycholysis Hypertrichosis Alopecia Nasal dryness Dry mouth

Appendix K: Annual Follow-up Form

FOxTROT TRIAL: ANNUAL FOLLOW-UP

PLEASE COMPLETE AND RETURN THIS FORM PROMPTLY

N.B. Please give details of any important protocol deviations, serious toxicity (requiring hospitalisation), cause of death, change of follow-up doctor, etc. in the COMMENTS field.

Patient name Date of Birth Hospital No. Date Randomised **FOxTROT** trial No.	Date of surgery	Has patient had a recurrence of disease?	If yes, how detected:	Has patient **died**?	If patient is **alive**, approx date last seen:	COMMENTS: (See above)
		Yes ☐ No ☐ approx date: ____/____/____ Site:_____	CT CEA Other	Yes ☐ No ☐ Date of death: ____/____/____		
		Yes ☐ No ☐ approx date: ____/____/____ Site:_____	CT CEA Other	Yes ☐ No ☐ Date of death: ____/____/____		
		Yes ☐ No ☐ approx date: ____/____/____ Site:_____	CT CEA Other	Yes ☐ No ☐ Date of death: ____/____/____		

Thank you for your help.

Name of person completing form……..…… **Date form completed**: ……../……../……...
dd mm yy

Signature…… ……..……e-mail:…….....……**Tel no**……..……

Please send this form to the **FOxTROT** Study Office, The University of Birmingham Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, BCTU, Robert Aitken Institute, School of Cancer Sciences, Birmingham, B15 2TT

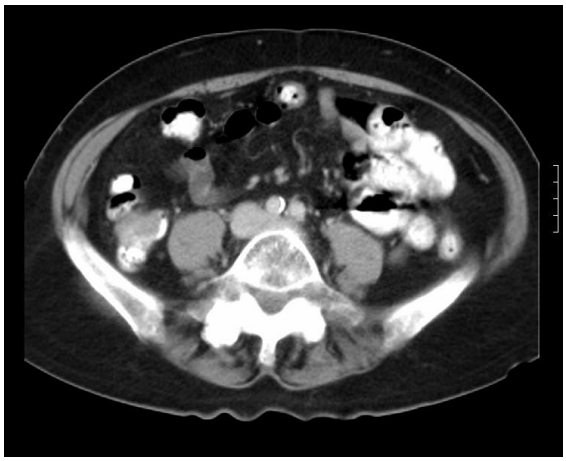
v1.2 01/08/08

Appendix L: Pre operative radiological staging for colon cancer

In colon cancer, T4 stage, N2 stage and extramural vascular invasion, along with emergency presentation, are independent predictors of disease recurrence. These risk factors should be identifiable through radiological evaluation, enabling tumours with a poor prognosis to be identified prior to resection and targeted for neoadjuvant chemotherapy. All patients will require a spiral CT of abdomen and pelvis with IV contrast and ideally oral contrast (oral contrast not required in obstructed patients). All participating centres must agree to undertake central specific radiological training for the site GI radiologist.

Patients with T4 or 'T3 bad' (extramural depth of ≥5mm) were eligible for the **FOxTROT** pilot study, in which we assessed the accuracy of radiological staging in identifying patients with high risk tumours that would require adjuvant chemotherapy. This audit indicates that these CT eligibility criteria (T4 or T3 and ≥5mm extramural extension) are selecting a very high-risk population (93% T3 and above), and successfully excluding patients with low-risk cancers unsuitable for chemotherapy. Comparisons of radiological and pathological staging also found that 93% of patients with T3 tumours and a radiologically estimated depth of invasion of less than 5mm ('intermediate risk' patients) were suitable for chemotherapy. The entry criteria for the **FOxTROT** main study will accordingly be widened to include all radiological T3 tumours not just those with ≥5mm extramural invasion.

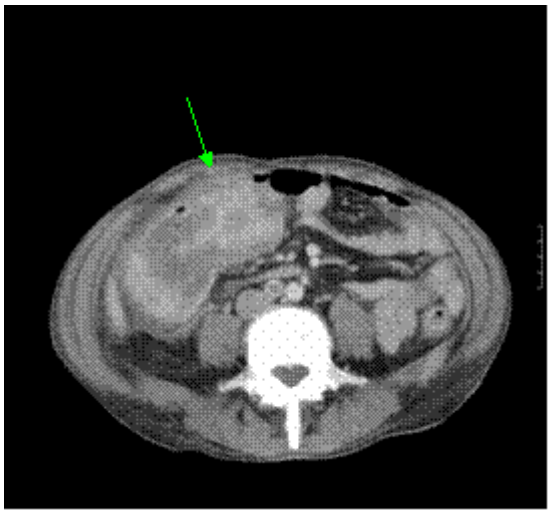
CT demonstration of an early stage good prognosis tumour

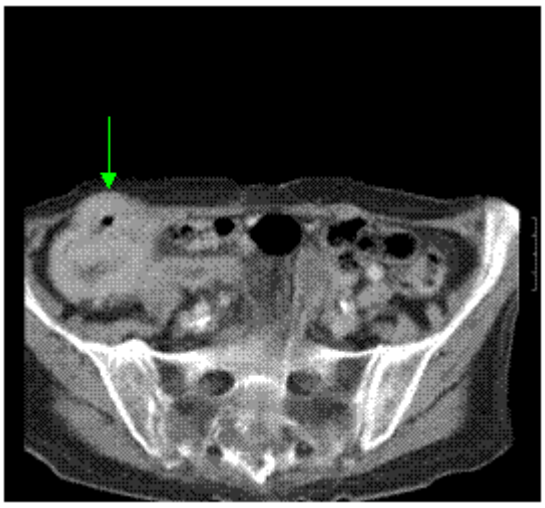


There is a polypoidal tumour with no evidence of bowel wall disturbance and no evidence of spread beyond the contour of the bowel wall. This corresponded to a pT2 tumour on histology and would not have been selected as a high risk patient for preoperative neoadjuvant therapy.

CT identified poor prognosis tumours.

Loss of plane anteriorly suggesting T4 peritoneal involvement in two different caecal tumours. This was confirmed on histology.





Appendix M: Pre-randomisation radiological assessment

PART A: Identification details (please print in capitals)

Hospital: _____ Radiologist: _____

Patient's name: _____

Date of birth: ____/____/____ Sex: Male ☐ Female ☐ Hospital number _____

Radiology Ref. No. _____ Radiological Report Date ____/____/_____

PART B: Tumour location

Primary tumour site? ☐ Caecum ☐ Ascending colon ☐ Hepatic flexure
☐ Transverse colon ☐ Splenic flexure ☐ Descending colon
☐ Sigmoid ☐ Rectosigmoid ☐ Other

Is tumour: ☐ Peritonealised ☐ Non-peritonealised

PART C: Radiological staging

Maximum tumour thickness : ____mm Tumour to nearest retroperitoneal fascial margin ____mm ☐ N/A

Local invasion: ☐ Submucosa (T1) ☐ Muscularis propria (T2)
☐ Beyond muscularis propria (T3) ☐ Adjacent organs (T4) ☐ Peritoneal (T4)

Max distance of tumour spread beyond muscularis propria: _____ mm

Is definite extramural vascular invasion present? ☐ No ☐ Minimal stranding
☐ Nodular spread into small vessel ☐ Spread along large vein

No. lymph nodes visualised: n= _____ Node >10mm diameter present? No ☐ Yes ☐

No. of enhancing irregular positive lymph nodes: n= _____

N-stage ☐ N0 ☐ N1 (1-3 nodes) ☐ N2 (4+ nodes)

M-stage ☐ M0 ☐ M1 site(s): _____

PART D: Eligibility for FOxTROT

Free of metastases and peritoneal nodules? Yes ☐ Probably Yes ☐ Probably No ■ No ■

Resectable disease? Yes ☐ Probably Yes ☐ Probably No ■ No ■

T4 or definite T3 tumour ≥1mm beyond muscularis propria? Yes ☐ Probably Yes ☐ Probably No ■ No ■

If shaded boxes are ticked, patient is ineligible for FOxTROT

If T3 tumour with less than 5mm spread, patient may be suitable for 'FOxTROT lite' chemotherapy

Will the patient be entered into ***FOxTROT***? Yes ☐ No ☐

If patient is eligible but will not be entered, why is this?

☐ Surgeon/oncologist preference ☐ Patient preference

☐ Other reason: _____

Form completed by: _____ Date completed: ____/____/____

Sign name: _____ Telephone number: _____

Please return this form to: **FOxTROT** Trial Office, The University of Birmingham Clinical Trials Unit, FREEPOST RRKR-JUZR-HZHG, School of Cancer Science, Robert Aitken Institute, Edgbaston, Birmingham, B15 2TT or Fax +44 (0)121 415 8871 v2.0 21/04/10

Appendix N: Histological Assessment

THE PATHOLOGICAL REPORTING AND AUDIT OF SURGERY – COLONIC CANCER

Bryan Warren and Phil Quirke, Oxford and Leeds

The overall survival of colonic cancer is now lower than that of rectal cancer both in the Yorkshire cancer registry data and in Swedish data. Following observations in the MRC CLASICC study and courses on colonic surgery that PQ has taught on at the Karolinska Hospital, Sweden it is apparent that, as is the case in rectal cancer, there is marked variation in the quality of surgery of colorectal cancers. This variation takes the form of incomplete removal of the mesocolon and its lymphatic supply, different lengths of resection to the high tie lymph node and different clearances of the surgically created mesocolic resection margin, e.g. caecum and ascending colon (Bateman et al). A primary outcome of the **FOxTROT** study is the effect of neo-adjuvant chemotherapy upon the tumour as assessed by histology. It also provides a unique opportunity to prospectively evaluate resectional quality and its influence on outcome for colon cancer. The trial management committee contains the necessary surgical, histological and radiological expertise to complete this important aspect of the study. Future trials of adjuvant and neoadjuvant chemotherapy will gain considerable benefit, if this study can establish criteria for grading resectional quality.

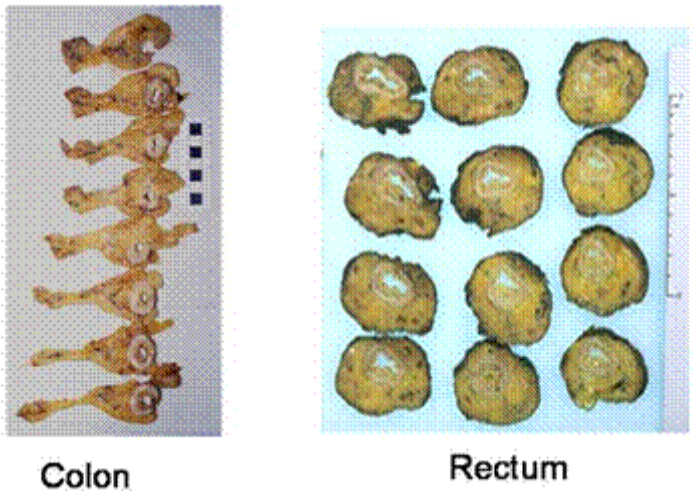


Figure 1 Mesocolon vs mesorectum showing good resections of both structures

Preparation of specimen

Dissection should be by protocol using the method described here which is consistent with the MRC CLASICC trial, the Royal College guidelines and the UKCCCR booklet (1997).

The specimen should have the front and back surfaces digitally photographed (preferably prior to inking of any non-peritonealised surfaces) to allow audit of the quality of surgery. The specimen should then be opened down to just above the tumour but not through the tumour. The anterior surface in the area of the tumour should be preserved to allow assessment of this surface for direct and peritoneal spread. Anterior and posterior non-peritonealised surfaces are painted with ink. It should be remembered that the circumferential margin only applies to the surgically incised mesocolic planes and not to the peritonealised surfaces. After the resection surfaces have been inked, and the specimen fixed in formalin for a minimum of 2 days, it should then be described and the tumour thinly (3-5mm) sliced transversely from 2 cm below to 2 cm above. **The slices should also be photographed as a valuable demonstration of the quality of the surgery and copies of the slides forwarded to the trials office. Three views are required: front, back and cross sectional slices with a metric scale e.g. ruler (figure 2). An assessment of the quality of surgery should be made by the reporting pathologist.** A second assessment will be made centrally to identify

inter-observer agreement. This will be done on the digital photographs, which will be uploaded to a central data base.

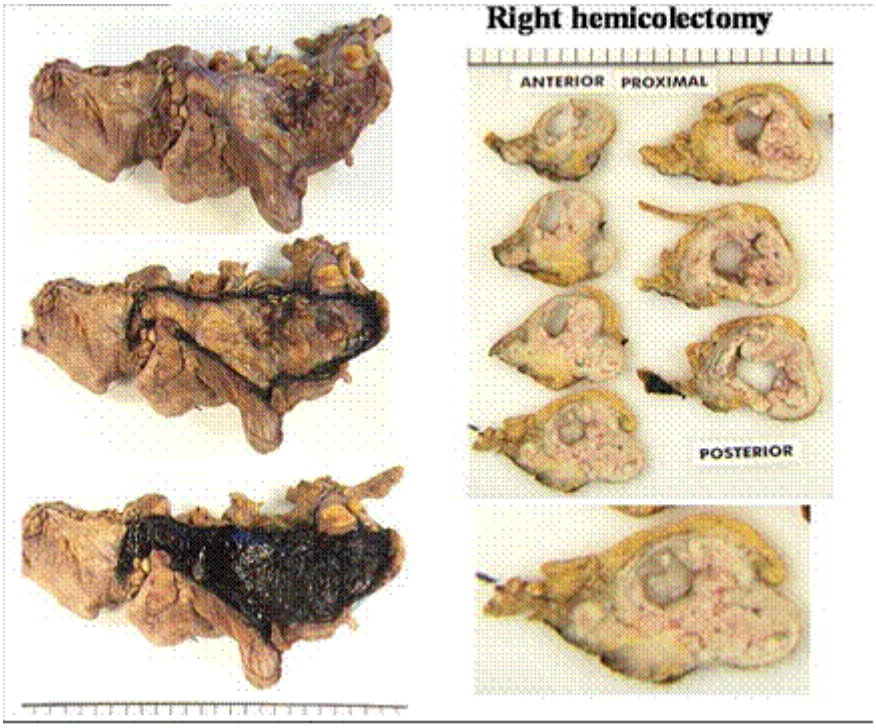


Figure 2 Dissection method showing inking of the retroperitoneal margin and cross sectioning to assess tumour spread.

Not opening the specimen facilitates comparison with MRI/CR imaging.

The distance of direct spread outside the muscularis propria and the distance of spread to local lymph nodes should be recorded. The area in which the tumour spreads closest to the mesocolic surgical margin should be identified. Large blocks should be taken from the area closest to the circumferential margin and any area where the tumour extends to within less than 3 mm from the margin. Any area identified as interesting by the radiologist should also be large blocked. Other blocks should be taken to allow at least 5 blocks of tumour to confirm presence or absence of extramural venous invasion. The number of any large blocks containing tumour can be subtracted from these 5. Likewise the peritoneal surface should be sampled by a minimum of 2 blocks if the tumour impinges on it.

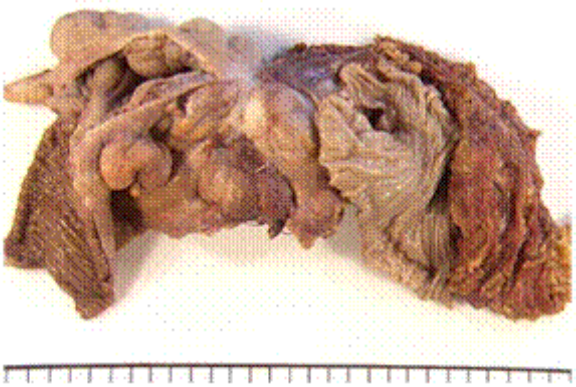


Figure 3 Peritoneal/serosal involvement by tumour

The local lymph nodes should be identified and embedded as should all the lymph nodes above and below the tumour. The tumour should be staged by both Dukes' and TNM 5 methods. **FOxTROT** will use the UICC TNM 5 not TNM 6 criteria as the latter are not recommended by the Royal College of Pathologists. An added advantage is that MRC CLASICC and MRC CR07 used TNM5 criteria and inter-trial analysis will therefore be possible. Dukes' allows easy communication between surgeons and the clinical team whereas TNM 5 gives more prognostic information, especially with respect to early tumours and local spread,

e.g. peritoneal and direct spread (figure 3). It is mandatory to fill out the trial proforma and return it to the trial office.

Between 10 and 20 plus blocks will need to be taken. **The original sections must be cut and forwarded to the trials office. Alternatively, a duplicate set of sections can be cut**.

The circumferential margin is considered involved (i.e. an an incomplete excision) if the tumour extends to within 1 mm of the circumferential excision margin. Measurement is best made by using a sheet of graph paper that is photocopied onto a sheet of acetate and cut to size. This will be provided. This is more easily used than the Vernier scale. This is shown in Figure 4 and can also be used for measuring the EMVI to see if it is greater than 3mm. No distinction is currently made between the various modes of involvement, e.g. direct spread, lymph node spread, vascular, etc. Although all are associated with an increased local recurrence rate, this is lower in the case of involvement by tumour within a lymph node. A measurement of tumour at 1mm or less from a resection margin is considered involved.

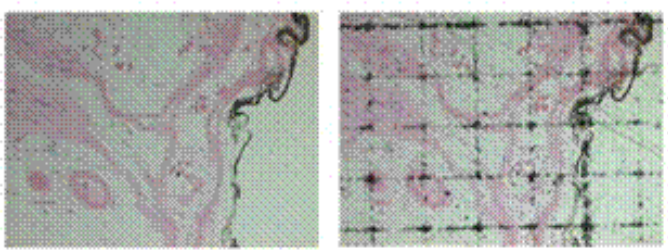
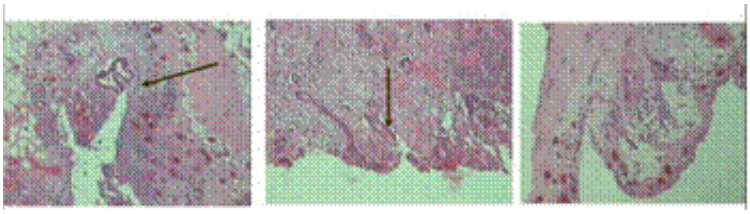


Figure 4 Easy measurement of distance of tumour to circumferential resection margin by overlaying a simple grid

Tumour must penetrate the peritoneal surface



Yes **Yes** **No**

Figure 5 Peritoneal involvement Peritoneal involvement should be assessed by the method of Shepherd et al 1995

Regression grading and complete response

Regression grading should be by the Dworak modification of Mandard grading thus 5 grades could be assigned. Subsequently these will be collapsed into the Wheeler method (Wheeler et al 2002) as well as the Rodel modification of Mandard grading. These methods will be compared. Assessment of complete response will be by the CORE method (CORE protocol) where 5 blocks of tumours are taken initially. If no tumour is found, the entire area is blocked and if tumour is still absent these blocks are levelled. If no tumour is seen at this point then the tumour has undergone a complete response.

Grading the quality of mesocolic resection

The quality of a mesocolic resection can be easily assessed. We recommend a 4 grade classification, first used in the MRC CLASICC trial but modified to include an extra grade. This system has been demonstrated to be usable in the context of phase III clinical trials and was shown to predict a higher risk of local recurrence in the Dutch rectal cancer trial (Nagetaal et al, JCO 2002). The frequency of mesocolic CRM involvement can also be determined and it is likely that this is a good early determinant of the quality of surgery and subsequent risk of local recurrence, as has been shown in rectum (Birbeck et al, Ann Surg 2005). The 4 grades are:

1. Mesocolic plane – Mesocolic tissue removed intact with no lacerations of the mesocolic surface.

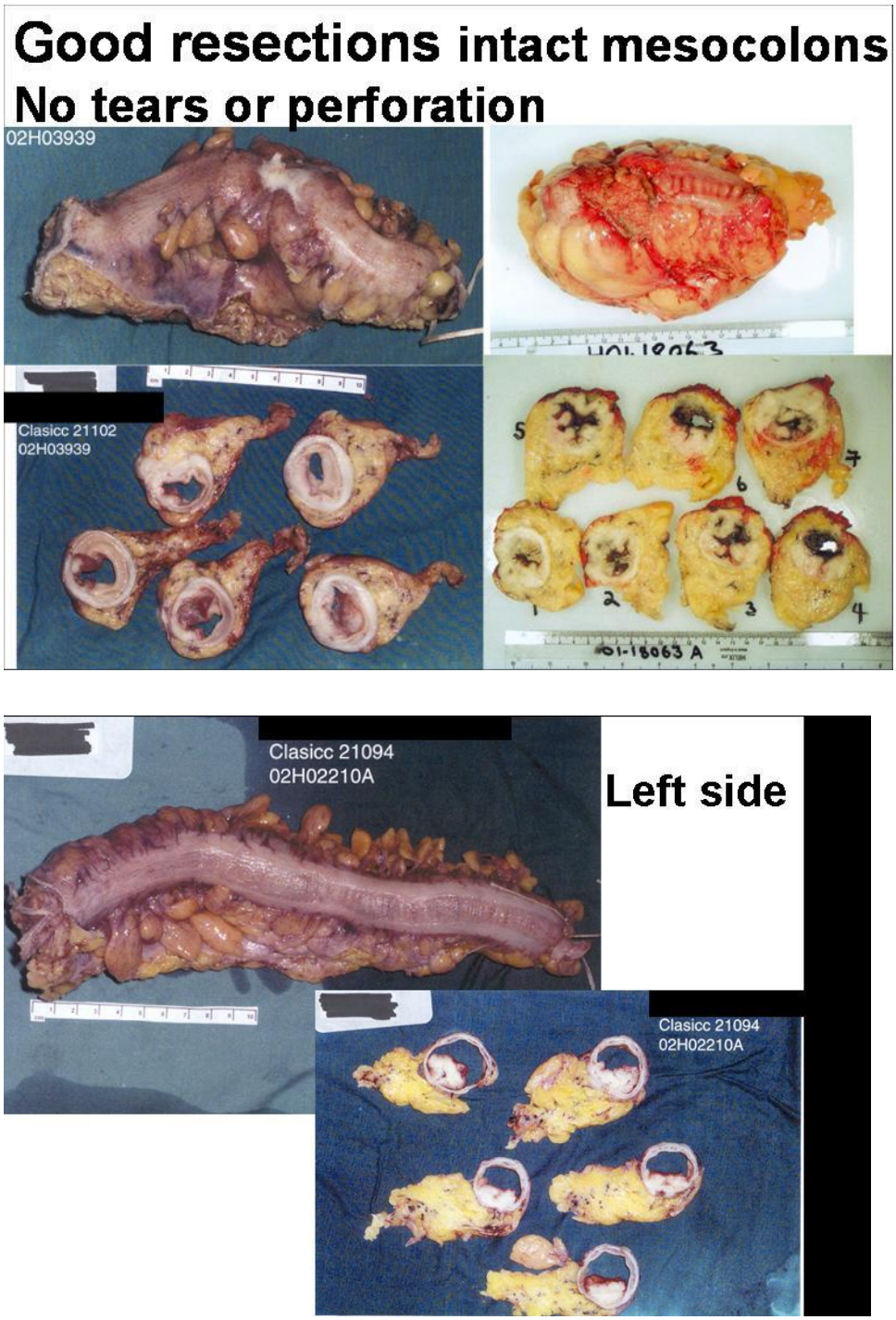


Figure 6 showing good surgery in different areas of the colon

2. Intramesocolic plane – Mesocolic tissue largely intact but the mesocolon shows irregularity/laceration/defects that do not reach down to the muscularis propria.

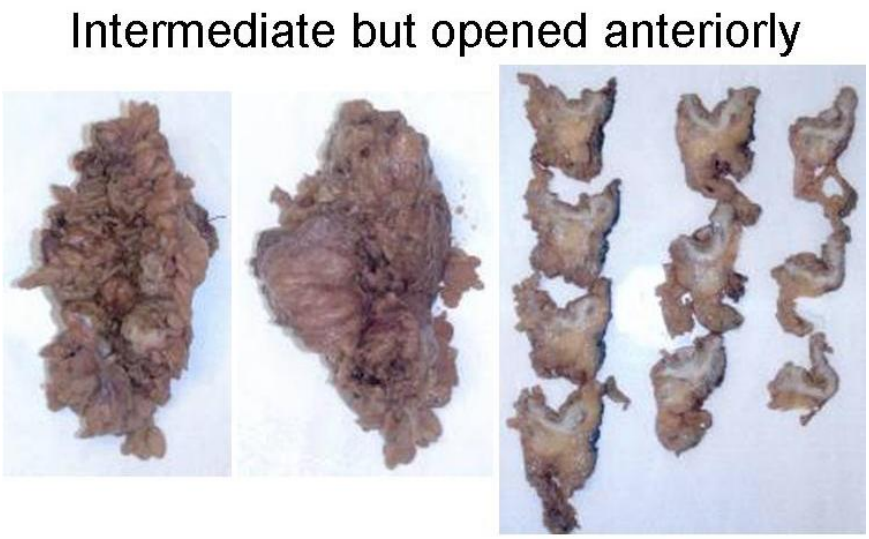


Figure 7 Showing intermediate surgery where there are superficial incursions, areas of mesocolon missing and, most importantly, in no area is the muscularis propria exposed in an area covered by mesocolon.

3. Muscularis propria plane – Mesocolic tissue extensively disrupted with marked irregularity of the mesocolon. The surgical margin may extend down onto the muscularis propria in mesocolic areas. Please note that this feature should only be assessed on the areas covered in mesocolon and not in the areas where peritoneum is closely adherent to the muscularis propria.

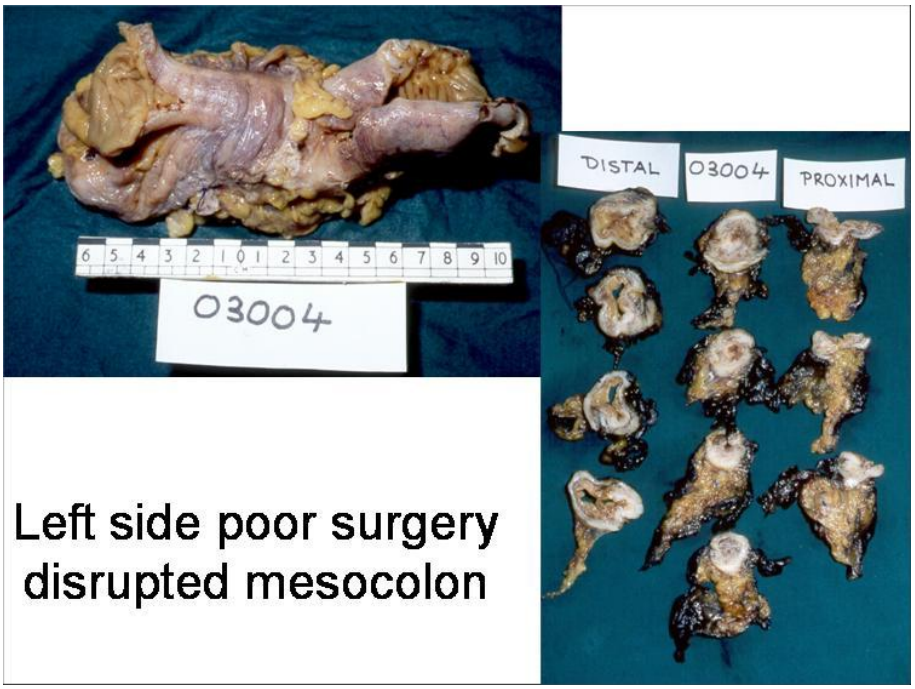


Figure 8 A poor/incomplete resection specimen shows many areas of substantial loss of mesorectal tissue, area(s) of the muscularis propria are seen, and deep cuts and tears down onto the muscularis propria may also be present.

4. Mesocolic plane plus high ties – Mesocolic tissue removed intact with no lacerations of the mesocolic surface AND a central vascular ligation i.e. at the origin of the supplying vessels.

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Appendix O: Pathologic Evaluation Form

Patient's name _____ FOxTROT Trial No |_|_|_|

Hospital _____ Pathologist _____

Hospital No _____ NHS number _____ Histology Ref No _____

PART A - Gross description

Photographs needed of front/back and cross sections and extra block of tumour/normal please

Site of tumour _____

Maximum tumour diameter _____ mm

Distance of tumour to nearer margin (cut end) _____ mm

Grade of colonic resection: Muscularis propria ☐

Intramesocolic ☐ Mesocolic ☐ Mesocolic plus high ties ☐

Measurement of distance between closest tied mesocolic vessel and primary cancer _____ mm

Tumour involves:

Anterior ☐ Posterior ☐

Left ☐ Right ☐

Perforation through tumour Yes ☐ No ☐

Perforation through bowel wall Yes ☐ No ☐

PART B – Histology

Type

Adenocarcinoma Yes ☐ No ☐

(Also tick box below if mucinous and signet ring adenocarcinomas)

Mucinous >50% mucin ☐

Signet ring ☐

If No, other _____

Differentiation by predominant area Poor ☐ Other ☐

Local invasion

Submucosa (pT1) ☐

Muscularis propria (pT2) ☐

Beyond muscularis propria (pT3) ☐

Tumour cells have breached the peritoneal surface (pT4) ☐

Invaded adjacent organs (pT4) ☐

Perforated tumour (pT4) ☐

Margins

Tumour involvement	**N/A**	**Yes**	**No**
Donut	☐	☐	☐
Margin (cut end)	☐	☐	☐
Retroperitoneal margin	☐	☐	☐

Histological measurement

From tumour to retroperitoneal margin (CRM) _____ mm

Maximum distance of spread of primary tumour from muscularis propria _____ mm

Maximum tumour thickness _____ mm

PART C

Metastatic spread

No. of lymph nodes examined _____

No. of positive lymph nodes (N1 1-3, N2 4+) _____

	Yes	**No**
Apical node positive (Dukes' C2)	☐	☐
Extramural vascular invasion	☐	☐
Intramural vascular invasion	☐	☐

Background abnormalities

	Yes	**No**
Adenoma(s)	☐	☐
Synchronous carcinoma(s)	☐	☐
Complete a separate form for each cancer		
Ulcerative colitis	☐	☐
Crohn's disease	☐	☐
Familial adenomatous polyposis	☐	☐

Other comments

_____

_____

PART D

Regression grading

No regression ☐

Mild regression ☐

Moderate regression ☐

Marked regression ☐

Complete response ☐

Pathological staging

Complete resection at all margins (>1mm) Yes ☐ No ☐

TNM (version 5)

T ☐ N ☐ M ☐ R (R0 complete resection R1 0mm involved margin) ☐

Dukes' stage

No tumour ☐

Dukes' A ☐ (Growth limited to wall, nodes negative)

Dukes' B ☐ (Growth beyond muscularis propria, nodes negative)

Dukes' C1 ☐ (Nodes positive and apical node negative)

Dukes' C2 ☐ (Apical node positive)

	Yes	**No**	
Histologically confirmed liver metastases	☐	☐	
Histologically confirmed peritoneal metastases	☐	☐	Mx
Other metastases _____	☐	☐	☐

Snomed Code _____

Form completed by: _____ Date completed: ___/___/___

Sign name: _____ Telephone number: _____

Thank you for the time you have taken to help the trial. Please return completed form to: **FOxTROT** Study Office, FREEPOST RRKR-JUZR-HZHG, The University of Birmingham Clinical Trials Unit, Robert Aitken Institute, The Medical School, Birmingham B15 2TT or fax to +44 (0) 121 415 8871

V2.0 21/04/10

Appendix P: The OxMdG regimen

Treatment is given in two-weekly schedules as follows:

Day 1 of treatment schedule (14 day cycle):

0:00	IV bolus granisetron 3 mg (or equivalent) IV bolus dexamethasone 8 mg flush line with 5% dextrose
0:00 – 2:00	l-folinic acid 175mg (or d,l-folinic acid 350 mg) not adjusted for surface area. IV infusion over 2 hrs in 250 ml 5% dextrose concurrently with:
0.00 – 2:00	oxaliplatin 85 mg/m^2 IV infusion, 2 hrs, 250 ml 5% dextrose
2:00	flush line with 5% dextrose
2:00 - 2:05	5-fluorouracil 400 mg/m^2 IV bolus injection over 5 minutes
2:05 - 48:00	5-fluorouracil 2400 mg/m^2 IV infusion over 46 hours
48:00	Disconnect pump and flush line (5 ml heparinised saline).

Days 3-14: No treatment

Notes:

- For patients who are obese (BMI >30 approx), the surface area used to calculate doses of oxaliplatin and fluorouracil should be capped using the following scheme:

Patient's height (cm):	<150	150-159	160-169	170-179	180+
Cap surface area (m^2) at:	1.5	1.7	1.9	2.1	2.3

- Bolus 5FU must be given as a 5 minute injection and not as a short 15 or 30 minute infusion
- Because of a potential *in vitro* chemical reaction between oxaliplatin and chloride ions, care is taken to avoid contact with normal saline in the drip-tubing etc.
- The OxMdG regimen is designed to be given via an indwelling central venous catheter. If given through a peripheral vein, appropriate dilutions of drugs are essential. Peripherally-administered oxaliplatin may cause vein pain, which is helped by applying an electric heat pad over the vein throughout the 2-hour infusion. Suitable therapeutic heat pads are available from Winterwarm® (38x30cm, model HP5/LT) or Dimplex® (38x28cm) each costing under £20. If this fails extending the infusion time to 4-6 hours may be helpful.
- It is not recommended to cross over from the OxMdG to OxCap regimens unless there is a compelling clinical reason (eg failure of venous access); in that case, be aware that capecitabine may cause increased toxicity when given after recent folinic acid (in OxMdG) and a capecitabine dose-reduction is required (50% in first, 75% in 2nd and 3rd OxCap cycles).
- Do not use injection equipment containing aluminium
- Local dose-banding may be applied by pharmacies, as long as the delivered dose falls within ± 5% of the calculated dose as per protocol. If wider dose bands are local practice, please contact the **FOxTROT** study office.

Oral antiemetics (starting day 2):

- Dexamethasone 4 mg tds x 1 day; 4 mg bd x 1 day; 4 mg od x 1 day
- Domperidone or metoclopramide prn

Note on the use of dexamethasone: For patients at high risk of steroid side effects (e.g. diabetics) or for those who develop toxicity attributable to steroids (e.g. dyspepsia; dysphoria; etc), the oral steroid should be omitted and "p.r.n." oral 5HT3 inhibitor given.

Scheduled tests

- FBC and clinical assessment (NCI toxicity scores) should be performed on the day of starting each drug therapy cycle (or within 3 working days before) and the results available before starting.
- Biochemistry (including creatinine, bilirubin, and either AST or ALT) is done at the same time as FBC.

- If patient is clinically jaundiced bilirubin level must be reviewed prior to administration of oxaliplatin.
- On day 1 of each cycle or within 3 days prior, LFTs, U&Es, magnesium and calcium should be tested. Only patients allocated to panitumumab need to be tested for magnesium.

Toxicity and dose adjustments for OxMdG

Haematological

- Check FBC on (or up to 3 working days before) day 1 of each cycle. Delay 1 week if neutrophils < 1.5 x 10^9/l or platelets < 75 x 10^9/l. Only treat when neutrophils and platelets are above these limits.
- If >1 delay, or 1 delay of ≥ 2 weeks occurs, reduce doses of oxaliplatin and both bolus and infusional 5FU by 20% for subsequent doses.
- If a further delay(s) for myelotoxicity occurs despite dose reduction, further dose adjustments may be made at the treating consultant's discretion (eg a further 20% reduction).

Neurotoxicity

- Oxaliplatin commonly causes transient paraesthesia of hands, feet and sometimes throat, precipitated by cold and lasting up to a few days after each dose. This does not require treatment or dose reduction.
- With cumulative dosing, some patients develop more severe neurotoxicity, requiring omission of oxaliplatin. For example:
  - persistent paraesthesia occurring in warm as well as cold conditions with significant discomfort
  - Numbness with loss of function (eg dropping objects) or pain

If one or more of these occur and persist through the cycle until the next dose is due, omit oxaliplatin from the regimen for the remainder of the **FOxTROT** therapy course.

If OxMdG has been well tolerated apart from neurosensory toxicity, the 5-FU dose should be increased from 2400 to 2800 mg/m^2 over 46 hours. Bolus 5-FU and folinate remain the same. This should occur from the start of the oxaliplatin-free cycles. If there is significant non-neurological toxicity in addition to neurosensory toxicity, 5-FU should remain at 2400 mg/m^2. It can be escalated to 2800 mg/m^2 if the first two oxaliplatin-free cycles are well tolerated.

Renal function

In **FOxTROT**, renal function needs to be above a threshold for safe administration of the chemotherapy schedules. Centres can use either the Wright or the Cockroft formula to estimate GFR (eGFR). The most commonly used is the Cockroft but is has low precision and low accuracy as it systematically underestimates clearance. This can result in systematic under-dosing when GFR is used as part of the dose calculation (eg. For carboplatin in the Calvert AUC formula). However, the purpose of the eGFR calculation in **FOxTROT** is simply to identify patients in whom EDTA clearance needs to be measured and Cockroft eGFR is a safe way of screening patients for renal function measurements, since very few patients have a Cockroft eGFR which is higher than the actual GFR.

The Wright formula is not more precise than Cockroft, but it is more accurate, therefore Wright is better for calculating carboplatin dose but possibly not as good as a screen for poor renal function; in approximately 50% of patients Wright eGFR will be higher then the actual GFR.

Clinicians should arrange EDTA clearance measurement for patients with a low eGFR (<50 ml/min), or in any patient in whom renal impairment is suspected.

- Before starting, ensure patient fulfils eligibility for renal function, i.e. GFR >50ml/min.
- Thereafter, if serum creatinine rises above normal limit, and >25% from baseline, check EDTA clearance. A significant deterioration in renal function should be investigated to exclude a postoperative complication or disease progression/relapse.
- If, after investigation, treatment is to continue despite the reduced renal function, the following adjustments should be made:
  - GFR 30-50 ml/min: full dose FU; reduce oxaliplatin by 25%
  - GFR <30 ml/min: reduce FU by 25%; omit oxaliplatin

Hepatobiliary function

- Bilirubin ≤ 1.25 x ULN and transaminase (either AST or ALT) ≤ 3 x ULN is required for study entry.
- Thereafter, any significant deterioration in hepatic function should be investigated to exclude a postoperative complication or disease progression/relapse.
- If, after investigation, treatment is to continue despite the altered hepatic function, the dose of both FU and oxaliplatin should be reduced by 50% if bilirubin is over 3x ULN.

Stomatitis

- Routine mouthcare (e.g. Corsadyl, nystatin) is recommended.
- If mouth ulcers occur despite this, reduce the 5FU doses (bolus and infusion) by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.
- If further toxicity occurs, reduce 5FU (bolus and infusion) and oxaliplatin doses by a further 20%.

Diarrhoea

- For diarrhoea occurring between cycles, treat symptomatically initially: loperamide 2-4 mg qds. and/or codeine phosphate 30-60 mg qds. as required.
- If diarrhoea has not resolved by the time the next cycle is due, delay 1 week.
- If diarrhoea is a problem despite symptomatic treatment, or if more than one delay is required, reduce the oxaliplatin and 5FU (bolus and infusion) doses by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.

Hand-foot syndrome (HFS)

- Treat symptomatically. Pyridoxine 50 mg tds by mouth or topical corticosteroid may help.
- If HFS is still a problem, reduce the 5FU doses (bolus and infusion) by 20% for subsequent cycles.

DPD deficiency; cardiotoxicity

- With any 5FU regimen, the occasional patient is encountered (approx. 1-3%) who has markedly exaggerated toxicity due to reduced catabolism. If this occurs, await full recovery. Further treatment at much reduced 5FU dose (e.g. 50%) or with single agent oxaliplatin may be considered. Please discuss with one of the clinical coordinators.
- Rarely, 5FU may provoke angina attacks or even MI in patients with ischaemic heart disease. In this event, the risk of continuing adjuvant therapy is likely to outweigh its benefits, and discontinuation is recommended.

Hypomagnesaemia management

- Patients should be evaluated and, if hypomagnesaemia is present, replacement should be managed as per local medical practice. A patient's serum magnesium level should be at or above 0.41 mmol/L throughout the study. It is important to assess and manage serum potassium and ionized calcium (corrected for albumin) in patients who have hypocalcaemia.

Allergic reactions to oxaliplatin

- Approx. 0.5% patients develop acute hypersensitivity to oxaliplatin, usually after more than 6 cycles. During drug administration, the patient may develop rash, fever, swollen mouth or tongue, hypo- or hypertension and other signs/symptoms of hypersensitivity. This rarely develops to full-blown anaphylaxis, even with repeated treatment.
- If acute hypersensitivity occurs, discontinue the infusion and treat with IV corticosteroid and antihistamine.
- After full recovery, the patient may continue with the MdG for that cycle.
- At the investigator's discretion, the patient may be rechallenged with oxaliplatin at the next cycle. In this case, premedication is recommended as follows:
  - Dexamethasone 4mg p.o. 6 hourly starting 24 hours pre-treatment, + 8mg IV 30 minutes pre-dose.
  - Chlorphenamine 10mg (or equivalent) + ranitidine 50mg (or equivalent) IV 30 minutes pre-dose.
  - Continue dexamethasone, chlorphenamine and ranitidine for 24-48 hours after treatment with oxaliplatin.

Appendix Q: The 3-weekly OxCap (XelOx) regimen

Treatment is given in three-weekly schedules as follows:

Treatment schedule (21 day cycle)

Day 1, 0:00	IV bolus granisetron 3 mg (or equivalent) IV bolus dexamethasone 8 mg flush line with 5% dextrose
0.00 – 2:00	oxaliplatin 130 mg/m^2 IV infusion, 2 hrs, 250 ml 5% dextrose
2:00	flush line with 5% dextrose
Day 1, evening	capecitabine 1000 mg/m^2 p.o.
Day 2-14	capecitabine 1000 mg/m^2 p.o. twice daily
Day 15, morning	capecitabine 1000 mg/m^2 p.o.
Day 16-21	no treatment

Notes:

- For patients who are obese (BMI >30 approx), the surface area used to calculate doses of oxaliplatin and capecitabine should be capped using the following scheme:

Patient's height (cm):	<150	150-159	160-169	170-179	180+
Cap surface area (m^2) at:	1.5	1.7	1.9	2.1	2.3

- The treatment cycle includes 28 capecitabine doses taken 12-hourly. This starts with the evening dose on day 1 and ends with the morning dose on day 15.
- The capecitabine dose is rounded to the nearest achievable dose.
- Patients are instructed to take capecitabine within 30 minutes after food, approximately 12 hourly (e.g. 8 am and 8pm).
- Because of a potential *in vitro* chemical reaction between oxaliplatin and chloride ions, care is taken to avoid contact with normal saline in the drip tubing etc.
- Peripherally-administered oxaliplatin may cause vein pain, which is helped by applying an electric heat pad over the vein throughout the 2-hour infusion. Suitable therapeutic heat pads are available from Winterwarm® (38x30cm, model HP5/LT) or Dimplex® (38x28cm) each costing under £20. If this fails extending the infusion time to 4-6 hours may be helpful, or consider fitting an indwelling central venous catheter.
- It is not recommended to cross over from the OxMdG to OxCap regimens unless there is a compelling clinical reason (eg failure of venous access); in that case, be aware that capecitabine may cause increased toxicity when given after recent folinic acid (in OxMdG) and a capecitabine dose-reduction is required (50% in first, 75% in 2nd and 3rd OxCap cycles).
- Do not use injection equipment containing aluminium
- Local dose-banding may be applied by pharmacies, as long as the delivered dose falls within ± 5% of the calculated dose as per protocol. If wider dose bands are local practice, please contact the **FOxTROT** study office.

Oral antiemetics (starting day 2):

- Dexamethasone 4 mg tds x1 day; 4 mg bd x1 day; 4 mg od x1 day.
- Domperidone or metoclopramide prn

Note on the use of dexamethasone: For patients at high risk of steroid side effects (e.g. diabetics) or for those who develop toxicity attributable to steroids (e.g. dyspepsia; dysphoria; etc), the oral steroid should be omitted and "p.r.n." oral 5HT3 inhibitor given.

Scheduled tests

- FBC and clinical assessment (NCI toxicity scores) should be performed on the day of starting each cycle, (or within 3 working days before) and the results available before starting.
- Biochemistry (including creatinine, bilirubin, and either AST or ALT) is done at the same time as FBC; these results should either be available before starting the cycle or, if not,

should be reviewed within 24 hours after starting the cycle (so that capecitabine can be interrupted if dictated by an elevated bilirubin level).
- If patient is clinically jaundiced, bilirubin level must be reviewed prior to administration of oxaliplatin.
- On day 1 of each drug therapy cycle, or within 3 days prior, patients should be tested for LFTs, U&Es, magnesium and calcium.

Toxicity and dose adjustments for OxCap

Haematological

- Check FBC on (or up to 3 working days before) day 1 of each cycle. Delay 1 week if neutrophils < 1.5 x 10^9/l or platelets < 75 x 10^9/l. Only treat when neutrophils and platelets are above these limits.
- If >1 delay, or 1 delay of ≥ 2 weeks occurs, reduce the capecitabine and oxaliplatin doses by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.
- If a further delay(s) for myelotoxicity occurs despite a 20% reduction, a further dose reduction may be made, at the discretion of the treating investigator.

Neurotoxicity

- Oxaliplatin commonly causes transient paraesthesia of hands, feet and sometimes throat, precipitated by cold and lasting up to a few days after each dose. This does not require treatment or dose reduction.
- With cumulative dosing, some patients develop more severe neurotoxicity, requiring omission of oxaliplatin. For example:
    - persistent paraesthesia occurring in warm as well as cold conditions with significant discomfort
    - Numbness with loss of function (eg dropping objects) or pain

  If one or more of these occur and persist through the cycle until the next dose is due, omit oxaliplatin from the regimen for the remainder of the **FOxTROT** therapy course.

Renal function

- Before starting, ensure patient fulfils eligibility for renal function, i.e. GFR >50ml/min.
- Thereafter, if serum creatinine rises above normal limit, and >25% from baseline, check EDTA clearance. A significant deterioration in renal function should be investigated to exclude a postoperative complication or disease progression/relapse.
- If, after investigation, treatment is to continue despite the reduced renal function, the following adjustments should be made:
    - GFR 30-50 ml/min: reduce both drugs by 25%
    - GFR <30 ml/min: discontinue OxCap. Any further alternative treatment is at investigator's discretion.

Hepatobiliary function

- Bilirubin ≤ 1.25 x ULN and transaminase (either AST or ALT) ≤ 3 x ULN is required for study entry.
- Patients on capecitabine may have temporary treatment-related elevation of transaminases, which require interruption of treatment. Other alterations in hepatic function should be investigated to exclude a postoperative complication or disease progression/relapse.
- If, after investigation, treatment is to continue, the following adjustments should be made:
    - AST/ALT >5x ULN: withhold chemotherapy until recovered below this limit
    - Bilirubin >3x ULN: reduce both capecitabine and oxaliplatin by 50%

Stomatitis and Diarrhoea

- Patients should be provided with routine mouthcare. Loperamide should be provided for symptomatic treatment of diarrhoea.

- Grade 1 toxicity is managed symptomatically and does not usually require dose reduction or interruption
- For any toxicity of grade 2 or higher, **stop capecitabine** and treat symptomatically until the toxicity has resolved to grade 0 or 1.
  - NB: when capecitabine is stopped for toxicity the **doses are omitted, not delayed**. If resolution to grade 0–1 occurs before day 14, capecitabine is resumed for the remainder of the planned cycle; otherwise wait until the next cycle.
- When resuming after a pause for toxicity, use the following dose reduction scheme:
  - Grade 2 toxicity: resume at the same dose after first pause, but reduce both capecitabine and oxaliplatin to 80% of the previous doses if a second pause is required.
  - Grade 3 toxicity: resume at 80% of original doses (both capecitabine and oxaliplatin)
  - Grade 4 toxicity: discontinue permanently.
- If further toxicity of grade ≥2 occurs after a dose-reduction, the doses should be reduced by a further 20%.

Hand-foot syndrome (HFS)

- Treat symptomatically. Pyridoxine 50 mg tds by mouth or topical corticosteroid may help.
- If HFS is still a problem, interrupt capecitabine and treat symptomatically until the toxicity has resolved to grade 0 or 1, then resume with a 20% dose reduction.

DPD deficiency; cardiotoxicity

- With any fluoropyrimidine regimen, the occasional patient is encountered (approx 1-3%) who has markedly exaggerated toxicity due to reduced catabolism. If this occurs, await full recovery. Further treatment at much reduced capecitabine dose (e.g. 50%) or with single agent oxaliplatin may be considered. Please discuss with the CI or one of the clinical co-investigators.
- Capecitabine may provoke angina attacks or even MI in patients with ischaemic heart disease. In this event the risks of continuing adjuvant treatment are likely to out-weigh the benefits, and discontinuation is recommended.

Hypomagnesaemia Management

- Patients should be evaluated and managed as per local medical practice. If hypomagnesaemia is present, replacement should be managed as per local medical practice. A patient's serum magnesium level should be at or above 0.41 mmol/L throughout the study. It is important to assess and manage serum potassium and ionized calcium (corrected for albumin) in patients who have hypocalcaemia.

Allergic reactions to oxaliplatin

- Approx. 0.5% patients develop acute hypersensitivity to oxaliplatin, usually after more than 6 cycles. During drug administration, the patient may develop rash, fever, swollen mouth or tongue, hypo- or hypertension and other signs/symptoms of hypersensitivity. This rarely develops to full-blown anaphylaxis, even with repeated treatment
- If acute hypersensitivity occurs, discontinue the infusion and treat with IV corticosteroid and antihistamine
- After full recovery, the patient may continue with that cycle's capecitabine.
- At the investigator's discretion, the patient may be rechallenged with oxaliplatin at the next cycle. In this case, premedication is recommended as follows:
  - Dexamethasone 4mg p.o. 6 hourly starting 24 hours pre-treatment, + 8mg IV 30 minutes pre-dose
  - Chlorphenamine 10mg (or equivalent) + ranitidine 50mg (or equivalent) IV 30 minutes pre-dose.
  - Continue dexamethasone, chlorphenamine and ranitidine for 24-48 hours after treatment with oxaliplatin.

Appendix R: Administration of Panitumumab

Patients who have been established to have *KRAS* wild-type tumours, and are randomised to the panitumumab (Vectibix) arm, should receive panitumumab at 6 mg/kg by IV infusion over 60 minutes, immediately prior to the start of each 2-week cycle of OxMdG chemotherapy for the first 6 weeks of the regimen, i.e. the full duration of neoadjuvant therapy in Arm B, the first 6 weeks of postoperative therapy in Arm D. **Panitumumab should not be given with OxCap.**

The dose in mg/kg is calculated using body weight at baseline and is diluted in a minimum of 100 mL of pyrogen-free 0.9% sodium chloride solution. For patients who are obese (BMI >30 approx), doses of panitumumab should be capped using the following scheme:

Patient's height (cm):	<150	150-159	160-169	170-179	180+
Cap weight (kg) at:	65	75	85	100	110

Panitumumab will be packaged by Amgen and delivered to the hospital pharmacy. Each vial of panitumumab contains a nominal 10ml of a sterile solution containing 20 mg/ml of panitumumab.

Panitumumab is administered IV by an infusion pump through a peripheral line or indwelling catheter **using a 0.22-micron in-line filter infusion set-up** (If these are not routinely available in your institution, please contact the **FOxTROT** Study Office) over approximately 60 minutes. Strict adherence to aseptic technique is used during preparation and administration. The bag should be labelled per site pharmacy Standard Operating Procedures (SOPs) and promptly forwarded to the chemotherapy unit for infusion.

Panitumumab hypersensitivity reactions

About 3% of patients treated with panitumumab have experienced infusion-related reactions, including chills, dyspnoea, flushing, hypertension, hypotension, pyrexia, tachycardia and vomiting, with most infusion reactions being mild to moderate (NCI-CTC grade ≤2) in severity. Severe infusion reactions (anaphylaxis, angioedema, bronchospasm, cardiorespiratory arrest and hypotension), occur in less than 1% of patients treated and, very rarely (<1 in 10,000), can be fatal. As of May 2010, three of over 40,000 patients with mCRC treated with panitumumab have died following hypersensitivity reactions. A fatal case of angioedema occurred 2 days after exposure, following a prior episode of angioedema that occurred 6 days after exposure. There have been two further post-marketing reports of hypersensitivity reactions with fatal outcomes during and immediately following an infusion of panitumumab. Both patients had previously experienced hypersensitivity reactions to cetuximab and oxaliplatin, respectively.

- **Panitumumab is, therefore, contraindicated in patients with a history of severe or life threatening hypersensitivity reactions**.
- Serious infusion-related reactions are unpredictable and can occur suddenly. Panitumumab should be permanently discontinued if a severe or life threatening reaction occurs.
- In patients experiencing a mild or moderate infusion-related reaction, the infusion rate should be reduced for the duration of that infusion. It is recommended to maintain this lower infusion rate in all subsequent infusions.
- Hypersensitivity reactions occurring more than 24 hours after infusion have also been reported. Patients should be warned of the possibility of a late onset reaction, made aware of possible symptoms and instructed to contact their physician if symptoms of a hypersensitivity reaction occur.
- An SAE form should be completed and sent to the **FOxTROT** Study office for any serious adverse events suspected to be associated with the use of panitumumab

Panitumumab dermatological toxicity

- Over 90% of patients treated with panitumumab in previous trials developed skin or nail side-effects, usually a mild-to-moderate acneiform rash, similar to that seen during cetuximab therapy. This reached NCI CTC Grade 3 in 4% and resulted in discontinuation of the drug in 1% of patients.
- All patients allocated to receive panitumumab should be forewarned that they are very likely to develop a rash. At the first development of a rash we recommend:
  - start an oral tetracyline, e.g lymecycline 408 mg b.d.
  - start topical emollients (e.g. E45®) and bath additives (e.g. Hydromol®)
- Skin toxicities will be recorded as adverse events on the Treatment Case Report Form (Appendix H) and will be graded using the modified NCI CTC version 3.0.

Panitumumab non-dermatological toxicity

- In single-agent panitumumab studies, grade 1-2 diarrhoea, nausea, vomiting, abdominal pain and fatigue have been reported.
- In ongoing trials of combination chemotherapy + anti-EGFR therapy, including COIN, the addition of antibody increases the incidence of nausea, vomiting and diarrhoea. In the PACCE trial of combination chemotherapy + bevacizumab +/- panitumumab, patients on the 4-drug combination arm had increased rates of severe diarrhoea and infections.
- It is therefore possible that panitumumab may contribute to a range of toxicities when given in combination with OxMdG or OxCap
- Toxicities will be recorded as adverse events on the AE Case Report Form

Panitumumab dose omissions and reductions

Toxicity should be assessed before giving the second and third dose of panitumumab. The brief treatment duration with panitumumab in **FOxTROT** - just 3 doses at 2-weekly intervals - means that few dose adjustments are anticipated. The following guidelines should be used for adjusting panitumumab in the event of toxicity.

- All patients should receive their first panitumumab treatment at the full protocol dose of 6 mg/kg. If this is tolerated with mild or moderate toxicity, the subsequent treatment(s) should be administered at the same dose.
- If the first panitumumab treatment produces severe skin or nail toxicity, which remains severe at the time the second or third chemotherapy dose is due, panitumumab should be withheld from that cycle. Examples of reasons for withholding panitumumab are:
  - Symptomatic skin- or nail-related toxicity of a severity requiring strong analgesia, systemic steroids, intravenous antimicrobial therapy or surgical debridement
  - Symptoms felt to be intolerable by the patient
  - If the second dose of panitumumab has been withheld for toxicity, panitumumab may be reintroduced at the third cycle at 50% dose (3mg/kg), provided the adverse event has improved to ≤ Grade 2, and systemic steroids, IV antibiotic or IV antifungal treatment are no longer required.
- Non-dermatological symptoms should be managed as advised in the chemotherapy regimen sections above, including dose reduction of OxMdG as appropriate. If the patient has severe non-dermatological toxicity to which, in the opinion of the investigator, panitumumab has contributed significantly, panitumumab should be withheld for the next cycle.
  - In this event, panitumumab may be re-introduced in the third cycle at 50% dose (3mg/kg), by IV infusion over 60 minutes prior to OxMdG, provided that the adverse event has improved to ≤ Grade 2

Panitumumab delays

- Panitumumab may only be added to the first 3 cycles of OxMdG. Where a panitumumab dose is omitted for toxicity, it should **NOT** be added on to later chemotherapy cycles.
- If a chemotherapy cycle is delayed for chemotherapy-related reasons (e.g. neutropenia), panitumumab is also delayed, and given alongside the chemotherapy when next administered.

Appendix S : EUROQOL QUESTIONNAIRE (EQ-5D)

Health Questionnaire

(English version for the UK)
(Validated for use in Eire)

EuroQol Questionnaire (EQ-5D)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

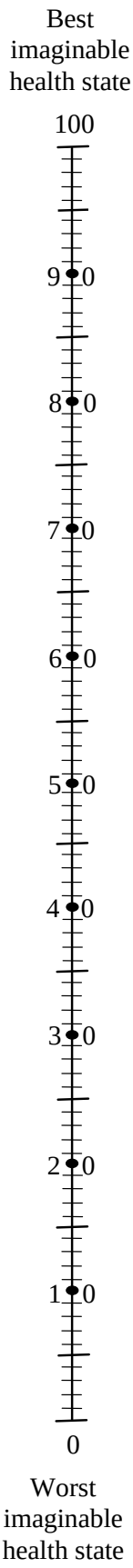
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix T: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |__|__|__|__|

Your birthdate (Day, Month, Year): |__|__||__|__||__|__|__|__|

Today's date (Day, month, Year): |__|__||__|__||__|__|__|__|

		Not at All	A Little	Quite a Bit	Very Much
1	Do you have any trouble doing strenuous activities like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2	Do you have any trouble taking a long walk?	1	2	3	4
3	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4	Do you need to stay in bed or a chair during the day?	1	2	3	4
5	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17.	Have you had diarrhoea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix U: REFERENCES

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