CANCER RESEARCH UK

MRC Clinical Trials Unit

FOCUS 2

Drug treatment for bowel cancer: making the best choices when a milder treatment is needed

Developed on behalf of the NCRI Colorectal Clinical Studies Group

CR09

CLINICAL PROTOCOL
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Signature:  Date: 01/11/05

MRC COLORECTAL CANCER GROUP

This document describes a clinical trial, and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care was taken in its drafting, however corrections or amendments may be necessary. These will be circulated to investigators in the trial, but centres entering patients for the first time are advised to contact the MRC Clinical Trials Unit, Cancer Division, London to confirm that they have the most up to date version of the protocol in their possession.

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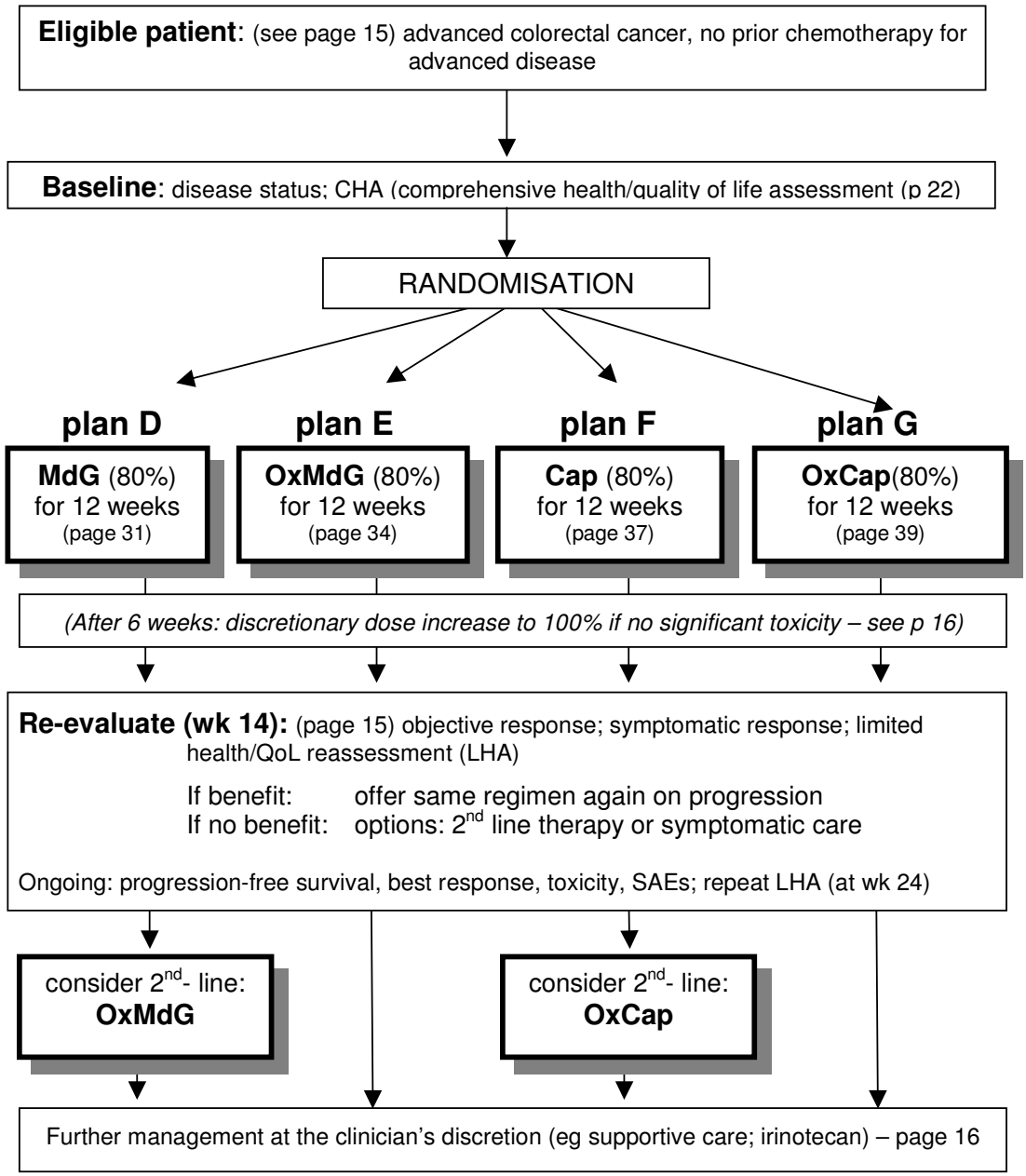
Glossary and Abbreviations

ADL	Activities of Daily Living	MI	Myocardial Infarction
ALT	Alanine Aminotransferase	MMSE	Mini-Mental State Examination
AST	Aspartate Aminotransferase	MNA	Mini-Nutritional Assessment
bd	Twice daily	MRC	Medical Research Council
Cap	Capecitabine	MREC	Multi-centre Research Ethics Committee
CEA	Carcino-embryonic Antigen	NCRI	National Cancer Research Institute
CHA	Comprehensive Health Assessment	NCI	National Cancer Institute
CRF	Case Report Form	NICE	National Institute of Clinical Excellence
CR-UK	Cancer Research UK	od	Once daily
CTU	Clinical Trials Unit	Ox	Oxaliplatin
DPA	Data Protection Act	ONS	Office of National Statistics
DPD	Dihydropyrimidine dehydrogenase	OS	Overall Survival
DMEC	Data Monitoring & Ethics Committee	PI	Principal Investigator
DNA	Deoxyribonucleic acid	PFS	Progression Free Survival
dG	de Gramont	prn	pro re nata; when necessary
ECG	Electrocardiograph	PS	Performance Status
EDTA	Ethylene diamine tetraacetic acid	QALY	Quality Adjusted Life-Years
FA	Folinic acid (a.k.a. leucovorin)	qds	quarter In die; 4 times daily
FBC	Full Blood Count	QL	Quality of Life
FFS	Failure-free Survival	RECIST	Response Evaluation Criteria in Solid Tumours
5FU	5-Fluorouracil	SAE	Serious Adverse Event
GFR	Glomerular Filtration Rate	SPC	Summary of Product Characteristics
HADS	Hospital Anxiety and Depression Scale	tds	ter die sumeudum,Three times daily
HRQL	Health-Related Quality of Life	TMA	Tissue Microarray
IADL	International Activities of Daily Living	TMG	Trial Management Group
ITT	Intention-to-treat	TSC	Trial Steering Committee
IV	Intravenous	U&Es	Urea and Electrolytes
LFTs	Liver Function Tests	ULN	Upper Limit of Normal
LHA	Limited Health Assessment	WBC	White Blood Cells
LREC	Local Research Ethics Committee	WHO	World Health Organisation
m^2	Metre Squared		
mg	Milligram		
Ml	Millilitre		
MdG	Modified de Gramont		
MHRA	Medicines and Healthcare Products Regulatory Agency (formally Medicines Control Agency – MCA)		

1 Trial Design



Trial plans are named for consistency with FOCUS, which is why there is no plan A, B or C in this trial

Abbreviations: MdG – modified de Gramont (2-weekly 5FU/FA schedule) OxMdG – MdG + oxaliplatin
Cap – capecitabine (3-weekly schedule) OxCap – Cap + oxaliplatin

Recruitment is in two phases, with a total target accrual period of 2 years:

- Pilot phase: 120 patients (30 in each treatment arm) will be recruited. Data from these patients will be reviewed by the Trial Management Group (TMG) and Data Monitoring and Ethics Committee (IDMC) before continuing to the next phase:
- Continuation Phase: a further 340 patients (85 in each treatment arm) will be recruited.

2 Trial Summary

FOCUS2 assesses lower-dose treatment for patients with advanced colorectal cancer who are ineligible or unsuitable for trials of full-dose combination chemotherapy because of borderline performance status, advanced age or both.

After baseline assessments including disease measurement and a comprehensive assessment of general health and quality of life (CHA), patients are randomised in a 2x2 factorial fashion to receive one of the following treatment plans:

1st-line: 5FU/FA (MdG) 2nd-line option: OxMdG	1st -line: capecitabine (Cap) 2nd-line option: OxCap
1st-line: OxMdG	1st-line: OxCap

Chemotherapy is started at 80% of standard doses, but may be increased to 100% after 6 weeks if well tolerated. Treatment is given for 12 weeks then stopped; further treatment with the same regimen is then given, on progression, to patients who benefited from their initial treatment; 2nd-line therapy is considered after failure of 1st-line. Disease status and limited general health/QoL reassessment (LHA) are measured after completing the initial 12 weeks' treatment, and again at 24 weeks.

Initially, 120 patients (30 in each arm) will be randomised in a pilot phase assessing toxicity, safety and the need for dose adjustment. Then (and after any schedule adjustments mandated by the pilot phase) a further 340 patients will be randomised to give a total of 460 for the main trial comparisons.

The principal outcome measures are progression free survival (for the oxaliplatin comparison) and QoL (for the FU/capecitabine comparison). Secondary outcome measures (both randomisations) also include Limited Health Assessments (LHA), chemotherapy toxicity/adverse events, overall failure-free survival, and overall survival. Baseline CHA will be correlated with outcome in each treatment arm to identify thresholds for treatment benefit. Cross-trial comparisons will be made with *FOCUS*, which shares two treatment arms.

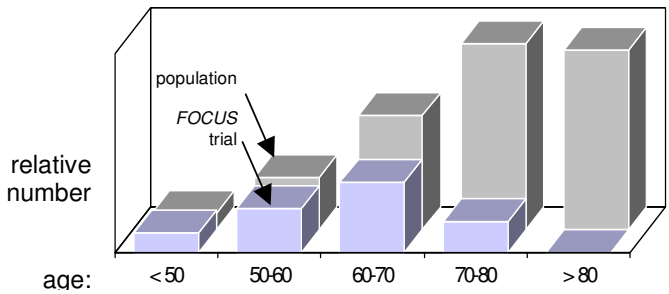
Patients are asked for separate consent for retrieval of surplus stored pathological material (eg the primary colon tumour resection) for research to identify molecular factors predicting for benefit from, or toxicity with, each of the drugs under test.

3 Introduction

Background

Chemotherapy for colorectal cancer has advanced in recent years, and although debate continues as to the optimum sequencing of new drugs, there is no doubt that combination chemotherapy is now a treatment option.[1,2,3] The current MRC/NCRI trial, *FOCUS,*[4] is assessing different sequences of irinotecan or oxaliplatin in combination with an intensive ("MdG") schedule of fluorouracil and folinic acid (FU/FA)[5,67] in fit patients with metastatic disease. Meanwhile, combination chemotherapy is also being evaluated in the adjuvant setting.

Colorectal cancer is predominantly a disease of older people. Of the 16,250 deaths/year it causes in the UK, 67% are in the over-70's, and 50% in the over-75's.[8] But these elderly patients are under-represented in research: most trials of palliative chemotherapy include fewer than 20% of patients over the age of 70, and many industry-led trials of combination chemotherapy have excluded patients over 75 altogether.[1,2,9] Even when there is no upper age limit in the trial protocol, oncologists are highly selective with elderly patients: for example, *FOCUS* has no upper age limit, but of the 1200 patients recruited up to Sept 2002, only 6% were over 75 (figure).



However, many patients who are not included in trials are still treated with chemotherapy. In March 2002, fifty-nine *FOCUS* oncologists (representing 80% of the trial's accrual at that time) responded to a questionnaire about patients with advanced colorectal cancer whom they were treating **outside** the trial. These clinicians, who randomised 422 patients in *FOCUS* during 2001, meanwhile treated a further 715 patients off trial. Many factors will have influenced these oncologists' and their patients' decisions:

- Poor WHO performance status (PS ≥3, see p 58) predicts for poor outcomes: these patients are excluded from *FOCUS,* and are usually best managed without chemotherapy. On the other hand, borderline (PS2) patients are usually offered treatment, but only 8% of *FOCUS* patients are PS2, compared with 22% in our previous trial, CR06.[10] This suggests that most PS2 patients are now being treated out-with the trial, reflecting oncologists' concerns that the adverse effect of intensive treatment are more marked in PS2 patients.[11]

- The age bias in *FOCUS* entry (see figure) – despite the lack of a fixed age limit – suggests oncologists are extremely cautious with elderly patients. It is well-established that age does not of itself mitigate against response to chemotherapy: data from patients aged 70-75 who have entered trials shows no evidence of reduced benefit, hence the lack of an age-limit in *FOCUS* eligibility.[12,13,14] However, the toxicity of chemotherapy may be affected by age-

dependent pharmacokinetics and pharmacodynamics, so dosing schedules determined from trials in younger patients will produce higher rates of toxicity in the elderly. [11,13,14,15,16,17]

- Elderly patients may sometimes be less inclined to give consent for trials including intensive treatments, opting instead for treatment with a lower chance of side-effects.

In our march 2002 questionnaire, 80% of *FOCUS* clinicians said they were offering some or all of their non-trial patients infusional 5FU, most commonly MdG, often at reduced dose. 37% were offering capecitabine to some or all patients, again often at less than the full licensed dose.

The need for a trial

Multidisciplinary team care for colorectal cancer[18] has led to a welcome increase in referral of elderly and less fit patients for an oncology opinion, but our survey underlines the fact that for many of these patients oncologists do not offer full-dose chemotherapy, particularly full-dose combination chemotherapy. Reduced-dose schedules are often used, but we lack an evidence-base on which to base these decisions.

The MdG schedule, although less expensive and less inconvenient than the original dG regimen, still requires indwelling venous access. There is only limited published data for MdG,[5] although it is being used in the *FOCUS* trial, and data from the first 450 patients treated confirm it has a high response rate and good toxicity profile (data on file, MRC CTU).

Oral fluoropyrimidines offer an attractive alternative to 5FU infusion-based regimens: they are more convenient for patients,[19] and less demanding of Health Service resources.[20,21] But to date, phase III trials[22,23,24,25] have compared them only with the Mayo Clinic bolus 5FU/FA schedule, which is relatively toxic and ineffective,[26,27] in a typical trial population of good performance status and median age 63. It is not known whether the benefits seen over bolus FU/FA in that setting will hold up against infusional 5FU, or in a more elderly and less fit population. For this reason, the National Institute for Clinical Excellence (NICE), whilst approving oral drugs as a treatment option for advanced colorectal cancer, also drew attention to the need for further research to address these questions.[28]

Currently, in line with NICE guidance,[29] most non-trial patients in the UK receive a fluoropyrimidine (+/- FA) alone first-line. However, combination therapy offers an increased therapeutic index over 5FU,[3] so there is an argument that we should not deny our older and less fit patients the potential benefits of combination chemotherapy, but instead we should be developing our evidence base for this population. In particular, we need a rational basis for adjusting drug doses, based on objective measures of general fitness, to bring toxicity within acceptable levels.[13]

How this trial will fit in with other evidence

Recent NICE-commissioned systematic reviews have looked at issues of combination therapy[30] and oral fluoropyrimidines.[21] The use of chemotherapy in elderly patients with colorectal cancer has also been reviewed recently.[9] All these reviews highlight the under-representation of elderly and less fit patients in clinical trials. *FOCUS2* is the first large trial in the UK to look specifically at this patient group. The design particularly takes into account the following ongoing and planned trials:

- ***FOCUS:***[4] two of the treatment arms of the main *FOCUS* trial are [D] MdG initially, followed by OxMdG on progression; and [E] OxMdG from the start of treatment. *FOCUS2* uses reduced-dose versions of the same treatment arm, which will allow us to detect any heterogeneity of the treatment effect and tolerability in the two populations.
- ***EORTC***, the ***US Intergroup*** and ***Roche*** are all currently performing trials of "Infusional FU/FA + new drug" *vs* "capecitabine + new drug". They are powered to assess equivalence of response rate and progression-free survival (PFS). We wish to make the same comparison in the elderly population, but the existence of these trials allows us to focus instead on quality of life as the principle outcome measure for this comparison in our study.

Treatment schedules in older and less fit patients

The *FOCUS2* schedules are reduced-dose versions of regimens used in recent randomised clinical trials[22,23] and pilot studies[5,13,31] in predominantly young, fit patients, but data for the selected minority of elderly patients taking part in these trials is encouraging. For example, a recent report from Sanofi combined evidence from 3 trials including 1408 patients receiving FOLFOX4 (dG + oxaliplatin), 213 of whom were aged 70-75.[13] Response rates were maintained and treatment was felt to be tolerable, although higher rates of grade 3-4 toxicities were seen in patients over 70, supporting the concept of dose modification for pharmacokinetic/dynamic reasons in older patients. This is also supported by meta-analysis data showing age to be a strong independent predictor of grade 3-4 toxicity with 5FU/FA treatment.[11]

In the MRC trial CR06, 10% of patients were over the age of 75, and 22% were of borderline performance status (WHO PS2). Good safety and QoL data for the two infusional 5FU arms in that trial confirm that it can be safely applied across a wide range of patients.[10] The ongoing *FOCUS* trial includes a lower proportion of elderly and PS2 patients, but interim analysis has shown no evidence of safety problems with the MdG or OxMdG schedules (data on file, MRC CTU).

Phase III studies have included 603 patients treated with capecitabine, with median age 64, and median Karnofsky PS 90% (=PS1). Some elderly (age up to 86) and low PS (Karnofsky 70%) patients were included, but the numbers treated, and toxicity in these patients, is not reported.[22,23] Since its licensing, many oncologists have used a reduced starting dose of capecitabine when treating elderly or frail patients, although this practice is currently not evidence-based.

4 Aims

4.a Principal study questions

- Do patients in this population benefit from chemotherapy – including modern combination chemotherapy – at modestly reduced starting doses?
- Can infusional 5FU/FA (MdG) be replaced with an oral drug (capecitabine) without compromising its low toxicity rates?
- Does the use of first-line combination chemotherapy (at doses suited to this trial population) improve outcomes?

4.b Secondary trial questions

- Can an objective baseline Comprehensive Health Assessment (CHA) be used to predict which patients will benefit from chemotherapy?
- Does chemotherapy result in measurable changes in the health assessment scores?
- Is Quality of life (QoL) improved by the trial treatments (capecitabine in place of MdG, and the addition of oxaliplatin)?
- What is the most cost-effective therapy in this population?

4.c FOCUS2 – vs – *FOCUS* planned cross-trial comparisons

- Are any incremental benefit of combination chemotherapy in *FOCUS2* patients different from those found in the clinical trial population taking part in *FOCUS*?
- Does the impact of combination therapy upon QoL differ between *FOCUS2* patients and the typical clinical trial population taking part in *FOCUS*?

4.d Molecular Study aims

- Do molecular variables in surplus stored tumour, normal tissue material or blood DNA predict for benefit from the trial drugs?
- Do molecular variables in normal tissue or blood DNA predict for abnormal toxicity with the trial drugs?

5 Outcome Measures

The 2x2 factorial trial uses different primary and secondary outcome measures for the two factorial comparisons:

Comparison	Primary Outcome Measure	Secondary Outcome Measure
[D vs E] + [F vs G] 1st-line combination *vs* 1st-line single-agent	Progression-free survival (PFS)	• Health Assessment (LHA) including QoL, at 14 and 24 weeks vs baseline • toxicity/adverse events • overall failure-free survival (FFS)* • overall survival (OS) • Health economics
[D vs F] + [E vs G] MdG *vs* capecitabine	Health Assessment (LHA) at 14 weeks vs baseline	• LHA at 24 weeks, vs baseline • Toxicity/adverse events • patient acceptability • progression-free survival (PFS) • Health economics

* *overall FFS is defined as the time from start of treatment until failure of the full plan, which may include re-treatment and (in plans E and G) scheduled 2nd-line treatment*

6 Centre and Patient Selection

6.a Institution and Investigator Selection

In order to participate in the FOCUS 2 trial, investigators/institutions must fulfill a set of basic criteria and witness this by signature of the FOCUS 2 Investigator Statement. This form will be sent to institutions as soon as they express an interest in the trial. Criteria are:

- The institution regularly undertakes the treatment of advanced colorectal cancer.
- Staff are familiar with the appropriate use of the investigational products, as described in the protocol (and in the current Summary of Product Characteristics (SPC)).
- The institution has an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
- All staff assisting with the trial are adequately informed about the protocol, the investigational products and their trial related duties.

- The study will be conducted in accordance with the current protocol and changes will only be made when necessary to protect the safety, rights or welfare of patients.
- Formal protocols are in place at the institution to deal with neutropenic sepsis.
- The trial will be conducted in compliance with GCP and applicable regulatory requirements.
- The institution will permit monitoring and auditing by the MRC Clinical Trials Unit (CTU) and inspection by the appropriate regulatory authorities. Direct access will be made available to all trial related sites, data/documents and reports.
- The institution will maintain a trial master file, which will contain essential documents for the conduct of the trial.
- All trial data will be submitted in a timely manner, and as described in the protocol. Individual institutions may be suspended if data returns are poor or if trial conduct is violated in other ways.
- All Serious Adverse Events (SAEs) will be reported immediately to the MRC CTU, except for those that the protocol or SPC identifies as not requiring immediate reporting (these should be reported on the CRFs for the trial). The initial SAE report shall be promptly followed by detailed written reports.
- No trial data will be disclosed without the approval of the Trial Steering Committee.
- All trial related documents will be retained for 15 years after the completion of the trial.

The FOCUS 2 investigator statement is signed by the Chief Investigator for that institution on behalf of all staff at that site who will be working on the FOCUS 2 trial.

In addition and in compliance with ICH GCP all institutions participating in the trial will complete a delegation log and forward this to the MRC CTU. Each person working on the FOCUS 2 trial must complete a section of this log and indicate their responsibilities. The MRC CTU must be notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the trial master file at the institution and also at the MRC CTU.

Finally prior to entering patients into the trial the MRC CTU must receive full contact details for all site personnel. This must be updated whenever there are changes to trial staff or their contact details. The Clinical Trial Authorisation (CTA) for the FOCUS 2 trial requires that the Medicines and Healthcare Products Regulatory Agency (MHRA) be supplied with the names and addresses of all participating investigators/institutions. Trial staff at the MRC CTU will perform this task, hence it is vital to receive full contact details for all investigators prior to their entering patients.

6.b Patient Selection

Inclusion Criteria

- Confirmed colorectal adenocarcinoma:
  - **either** previous or current histologically confirmed primary adenocarcinoma of colon or rectum, together with clinical/radiological evidence of advanced / metastatic disease.
  - **or** histologically/cytologically confirmed metastatic adenocarcinoma, together with clinical/radiological evidence of colorectal primary tumour.

- Unidimensionally measurable disease (RECIST criteria, see appendix, page 59).

- No previous systemic palliative chemotherapy for metastatic disease
  - adjuvant chemotherapy with fluoropyrimidines alone may have been given, if completed > 4 months prior to trial entry.
  - rectal chemoradiotherapy with fluoropyrimidines alone may have been given, if completed > 1 month prior to trial entry.

- WHO performance status (PS) 0, 1 or 2 (see appendix, p 58) and considered by responsible consultant to be fit to undergo any of the possible treatment schedules.

- Baseline laboratory tests (within 1 week prior to randomisation):
  - WBC > 3 x10^9/l and platelet count >100 x10^9/l
  - serum bilirubin ≤ 3 x upper limit of normal (ULN), **and** serum transaminase (either AST or ALT) ≤ 2.5 x ULN
  - **either** estimated creatinine clearance (Cockroft; page 56) >50ml/min **or** measured GFR (EDTA clearance) >30 ml/min.
    - Patients with GFR of 30-49 ml/min may be randomised but if allocated oxaliplatin and/or capecitabine require a 25% reduced dose. (page 57)
- For women of childbearing potential, negative pregnancy test and adequate contraceptive precautions.

Exclusion Criteria

- Patients who are fit and suitable for full-dose combination chemotherapy, e.g.:
  - Eligible and suitable for 1st-line combination as per NICE guidance.[29]

- Patients who are unfit for the reduced-dose treatments in this protocol, eg:

- severe uncontrolled concurrent medical illness (including poorly-controlled angina or very recent MI) likely to interfere with protocol treatments.
- Any psychiatric or neurological condition which is felt likely to compromise the patient's ability to give informed consent or to comply with oral medication.
- Partial or complete bowel obstruction.
- Pre-existing neuropathy (> grade 1).

- Patients requiring ongoing treatment with a contraindicated concomitant medication (see section 8.d)

- Patients with another previous or current malignant disease which, in the judgement of the treating consultant, is likely to interfere with FOCUS2 treatment or assessment of response.

7 Treatment of Patients

7.a Starting Chemotherapy

- Following randomisation, patients should start chemotherapy as soon as possible (see section 0 page 22 for details of acceptable time windows).
- The initial treatment plan is for 12 weeks of chemotherapy (see section 7.c below).
- Appendix I (pages 40 – 51) contains protocols for the four trial regimens. It is the responsibility of the treating consultant to ensure that these protocols are followed. In particular:
  - Renal, hepatic and bone marrow function must be monitored carefully, and dose-adjustments made as indicated (see appendix page 57).
  - Dose modifications should only be made after consulting the written protocols (if in doubt, please discuss with MRC CTU).
  - Note that significantly obese patients are dosed using 1.15 x ideal body weight (see appendix page 52).
- Ambulatory techniques for MdG and OxMdG are described in the appendix (page 54); these regimens may also be given on an inpatient basis, but clinicians are urged to use outpatient ambulatory treatment whenever possible.

7.b Discretionary dose increase at 6 weeks

- For each of the four regimens, the starting doses given in this protocol are 20% lower than the typical doses used in other recent or ongoing phase III trials. Patients should

be reviewed by the responsible clinician at 6 weeks, when a dose increase from the initial *FOCUS2* doses up to full standard doses may be considered.

- Only patients who tolerate the first 6 weeks of treatment with no or minimal toxicity should be considered for dose increase:
  - do not dose-increase any patients who has experienced grade 3 haematological or grade 2 non-haematological toxicity at the starting dose level, or has required dose delay whether for toxicity or inter-current illness.
  - patients considered unfit for dose increase at the 6-week review should not subsequently be dose-increased.
- Even in the absence of toxicity, dose increase is at the discretion of the treating consultant, not mandatory. It requires clinical review and discussion with the patient.
- Where pre-prescribing systems operate, it is acceptable for the dose increase to be started at the next-but-one cycle.

7.c Chemotherapy duration and breaks

- The initial treatment period is 12 weeks (6x MdG/OxMdG or 4x Cap/OxCap)
- The patient should be scheduled for repeat CT scan during week 13, then a clinic visit (approx 14 weeks after initiating treatment) for review by the treating clinician. The LHA is also due at this time point.
- On the basis of the radiological and clinical review, the clinician should decide whether the outcome of treatment has been:
  - **"Treatment benefit":** (= No radiological progression, **and** no clinical deterioration). or
  - **"No treatment benefit":** (= Radiological disease progression, **or** clinical deterioration).
- Patients with **treatment benefit** should remain off treatment for a treatment break, but with the intention of resuming the same chemotherapy regimen at the first indication of disease progression (see section 7.d below). Monitoring during this period should include clinical assessment at least 6-weekly and radiological assessment 12-weekly.
- Patients with **no treatment benefit** may be considered for second-line therapy. If the patient is on plan D or F, consider the planned second-line treatment (see section 0 below).
- Treatment may be stopped before the 12 week course is complete, at the discretion of the responsible consultant, if clear early evidence of "no treatment benefit" emerges.

7.d Re-treating after a treatment break

- Patients being observed off treatment should be monitored at least 6-weekly (scans 12-weekly) and **treatment restarted when any evidence of progression occurs** (this may be clinical, tumour marker or radiological evidence).
- When treatment is restarted this is, as with initial treatment, for a planned 12 weeks, followed by reassessment. Patients with chemo-sensitive disease may have an unlimited number of 12-week treatments alternating with breaks before moving on to second-line therapy or supportive care.
- If a patient progresses very early during a break (eg within 8 weeks), consideration should be given to second-line treatment or supportive care, rather than resuming the same treatment.

7.e Planned second-line treatment (plans D and F)

- In Plans D and F, the planned second-line treatment should be considered if disease progression occurs during or soon after MdG (D) or Cap (F). Evidence for disease progression may be radiological or clinical.
- The patient should be evaluated for fitness before starting second-line treatment.
- If the 5FU or capecitabine dose has been modified during first-line therapy, a proportional change is made to that drug in the second-line schedule.
- The disease must have been measured (eg CT scan) within the 5 weeks prior to starting second-line therapy so that response assessment will be possible.

7.f Further chemotherapy after the *FOCUS2* plan

- When there is disease progression after first and second-line (plans D, F) or first-line combination (plans E, G) treatment within *FOCUS2*, options of further chemotherapy or purely symptomatic treatment may be considered.
- Please note that patients may be considered for irinotecan therapy after *FOCUS2,* according to NICE guidance.[29]

7.g Other anticancer treatment modalities

- If, in the opinion of the treating consultant, an alternative treatment modality becomes indicated at any stage, it may be offered (eg hepatic resection, palliative radiotherapy, bypass surgery).
- If appropriate, *FOCUS2* trial treatment may be continued after the other treatment.

7.h Follow-up

- Once randomised, patients remain evaluable for the intent-to-treat analysis regardless of their subsequent course and treatment. Follow-up data on all patients, including details of other treatments given, is therefore important.
- Patients enrolled from the UK will be registered with the Office of National Statistics (ONS) in order to obtain long term follow-up information on survival, in the event that patients are lost to follow-up in the clinical centres.

8 Trial drugs

8.a Drug supplies

- All drugs and other products used in this trial are commercially available. No special trial stock is available. No special accountability arrangements are required.
- The guidelines in this protocol are in line with manufacturers' recommendations at the time of writing, but Summaries of Product Characteristics (SPCs) are updated from time to time. Up-to-date SPCs are posted on the Electronic Medicines Compendium website (www.emc.vhn.net)

8.b Prescribing and compliance

- Chemotherapy prescriptions should conform to local best practice including computerised prescribing systems where available.
- Capecitabine prescriptions to take home should include exactly the correct number of tablets for the current cycle.
  - All capecitabine prescriptions must be accompanied by the diary sheet, completed by the pharmacist or research nurse, with instructions of how many tablets of each strength to take at each dose.
  - Ask the patient to return any unused tablets with the completed diary sheet, at the next visit.
  - Non-compliance is reported on the CRF at 6 and 12 weeks.

8.c Crossover from 5FU to capecitabine or *vice versa*

- Crossover from 5FU to capecitabine or *vice versa* should be avoided, especially during the first 12 weeks of therapy. Patients on plan D or E who are unable to tolerate permanent venous access (eg because of a Hickman line complication), may

receive MdG or OxMdG on an inpatient basis via a peripheral vein for a few cycles during this period (see page 55)

- Thereafter, if crossover is deemed to be essential and in the patient's best interests, this may occur. Please notify the MRC CTU at the time, stating the reason for cross-over; follow-up data will still be required.

8.d Concomitant Medications

- **brivudine** or **sorivudine** may produce a dangerous interaction with capecitabine. These medications are not licensed in the UK but may be prescribed for viral infections in other countries.
- The following medications may interact with *FOCUS2* medications. These medications are not contraindicated but should be avoided unless there no reasonable alternative:
  - **warfarin**: no interaction with 5FU or oxaliplatin, but INR control may be affected by capecitabine. If a patient requiring warfarin is randomised to Cap or OxCap, more frequent INR monitoring is required.
  - **phenytoin:** blood phenytoin levels may increase with capecitabine.
  - **folic acid**: for patients randomised to Cap or OxCap, multivitamin supplements containing folic acid should be avoided as it could potentially increase capecitabine toxicity
  - **allopurinol**: may potentially reduce the effectiveness of 5FU or capecitabine.

9 Trial procedures

	Baseline	Each cycle whenever on chemo	If any SAE occurs	6 weeks (from start of chemo)	12-14 weeks	24 weeks	36, 48, 60, 72 weeks etc
Clinical evaluation	X*	X			X	X	X
FBC, U&Es, LFTs	X*	X					
Blood for DNA	X‡						
ECG, GFR†	X*						
NCI CTC scores		X					
WHO PS	X*				X	X	X
CT Scan (or equivalent)	X¶				X	as clinically indicated	as clinically indicated
tumour marker (CEA or alternative)	X¶			X (if raised at baseline)	X (if raised at baseline)	as clinically indicated	as clinically indicated
RECIST response + clinical benefit status					X	X	X
Questionnaires:	CHA				LHA	LHA	EQ-5D
Data to be returned to MRC CTU	CHA; Randomisation & Pretreatment form	Enter data on Treatment Form (return to CTU 6-weekly)	SAE Report Form	6-Week Early Assessment Form	LHA; 3-Month Progress Report Form	LHA; 6-Month Progress Report Form	EQ-5D; Follow-up Progress Report Form

** within 1 week prior to starting chemotherapy*

¶ within 5 weeks prior to starting chemotherapy

† not required if Cockcroft estimate Creatinine Clearance >50 ml/min

‡ not required if patient has withheld consent for molecular research

9.a Within the week prior to randomisation

- **Confirm the patient's eligibility with:**
  - history and examination
  - assessment of performance status
  - full blood count and biochemistry. Calculate GFR using Cockroft formula (see page 56). If the Cockroft estimate is < 50 ml/min, a measured GFR is required (eg by EDTA clearance)
  - other baseline tests required: ECG.
  - ensure patient has measurable disease (RECIST criteria, page 59) and that a baseline CT scan has been (or will be) performed **within 5 weeks prior to the planned start date for chemotherapy**
  - check all other inclusion and exclusion criteria in protocol section 6.b page 15.

- **Then obtain the patient's written consent:**
  - The patient should have a minimum of 24 hours after the initial invitation to participate before being asked to sign the consent form.

- Ensure that the patient understands that they are free to give or withhold permission for the molecular study (single blood sample + access to stored pathology samples) without affecting their participation in the clinical study.
- The patients written consent may be witnessed by either the research nurse or investigator, if indicated in the centre's delegation of responsibilities

- **After obtaining written consent:**
  - Perform **Comprehensive Health Assessment (CHA)** – see section 11 page 29, and appendix, page 86. NB this will take 30-60 mins so may require a separate visit.

9.b Randomisation

- **Enrolment will only be accepted if eligibility criteria have been checked, written consent obtained and the baseline CHA has been completed.**
- Complete the first page of the Randomisation Form and telephone the MRC CTU on **020 7670 4777** (9am – 5pm, Mon-Fri)
- Details will be taken and the patient will be allocated a treatment and trial number. At that point, complete the remainder of the Randomisation Form and fax it to the MRC CTU on **020-7670-4818**, together with the baseline CHA reports and a copy of the signed Consent Form.
- Also at this point, provided the patient has not withheld consent for the molecular study:
  1. ensure that the patient's pathology details are recorded on the **Randomisation and Pretreatment Form**.
  2. take 8-10 ml blood in an EDTA tube (2 tubes required if 4 ml size), label with the **date and patient's trial ID number but not name**. Seal the tube(s) in a plastic bag with padding to prevent breakage (Jiffy bag or padded plastic/cardboard box), mark the envelope "Diagnostic Specimens" and post first-class to:

     FOCUS2 Trial Sample Laboratory
     The IMMECR Building
     St. James's University Hospital
     Beckett St
     Leeds, LS9 7TF

9.c Start of chemotherapy

- Treatment should start as soon as possible after randomisation.
- However, a delay of up to 3 weeks from randomisation to start of treatment (e.g. for venous line insertion) may elapse if clinically acceptable.

- If patient has been allocated to infusional 5FU but the line cannot be fitted sufficiently quickly, give first cycle of treatment as an inpatient.

9.d Every chemotherapy cycle

(Day 1, or up to 3 days before):

- Clinical evaluation (doctor/nurse), to include toxicity scores from previous cycle (see appendix page 61) and current WHO PS (see appendix, page 58)
- Check FBC, U&Es, and LFTs (see regimens, pages 40 – 51 for critical values)
- (Cap and OxCap only): record capecitabine compliance from previous cycle using tablet returns and patient diary
- These data should be collated on the **Treatment Form** which is returned to the MRC CTU every 6 weeks (ie after every 3 cycles of MdG/OxMdG, or every 2 cycles of Cap/OxCap)

9.e Six weeks after starting chemotherapy

(before cycle #4 MdG/OxMdG; before cycle #3 Cap/OxCap):

- Schedule clinic appointment with consultant/Specialist Registrar to assess progress
- Recheck tumour marker (CEA and/or alternative) if raised at baseline
- Consideration of dose increase is made at this appointment (see section 7.b page 16)
- This decision is recorded and returned to MRC CTU using the **6-Week Early Assessment Form**

9.f Three months after starting chemotherapy

(wk 12-14)

- Schedule reassessment imaging (usually CT scan)
- Perform the Limited Health assessment (**LHA**):
  - This is a shortened version of the collection of QoL and general health assessment tools used in the CHA. It is administered by the research nurse or data manager (see section 11 page 29, and appendix page 94)
- Complete the **3-Month Progress Report Form**. This includes:
  - treatment response (RECIST criteria, see appendix page 59)
  - “treatment benefit” assessment

9.g Six months after starting chemotherapy

- Schedule a follow-up visit with any further assessments (eg repeat CT scan) as clinically indicated
- Repeat the **LHA** at this visit
- Complete the **6-Month Progress Report Form**. This includes details of current response status and treatment

9.h Three-monthly thereafter

- Follow-up data are reported every 3 months until death, using the **Follow-up Progress Report Form**
- No further detailed LHA data are required, but a short questionnaire (**EQ-5D**) is required, to give limited QoL data for health economic evaluation (page 99).
- When death occurs, this should be reported to the MRC CTU using the **Follow-up Progress Report Form**.

10 Safety Reporting

ICH GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol. Section 10.a lists definitions, section 10.b gives details of the institution/investigator responsibilities and section 10.c provides information on MRC CTU responsibilities.

10.a Definitions

The definitions of the EU Directive 2001/20/EC Article 2 based on ICH GCP apply in this trial protocol. These definitions are given in table 10.1.

Table 10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (or Investigator brochure) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • results in death • is life-threatening* • requires hospitalisation or prolongation of existing hospitalisation** • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect

Clarifications and Exceptions

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

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Trial-Specific Exceptions

Disease progression or death as a result of disease progression are not considered to be SAEs and should be reported on the Progress Report CRF.

The following situations that fulfill the definition of an SAE are excluded from expedited notification on an SAE form and should be reported on the Progress Form CRF.

- Elective hospitalisation and surgery for treatment of Colorectal Cancer or its complications.
- Elective hospitalisation to simplify treatment or procedures.
- Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment

10.b Institution/Investigator Responsibilities

All non-serious AEs/ARs, whether expected or not, should be recorded in the toxicity (symptoms) section of the Treatment form CRF and sent to the MRC CTU within one month of the form being due. SAEs/SARs should be notified to the MRC CTU as described below.

The severity (i.e. intensity) of all AEs/ARs (serious and non-serious) in this trial should be should be graded using Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (http://ctep.cancer.gov/reporting/index.html). *CTC toxicity, please refer to inside back cover of CRF booklet for main selected categories.*

A flowchart is given in appendix XVII, page 102, to help explain the notification procedures. Any questions concerning this process should be directed to the MRC CTU in the first instance.

10.c Investigator Assessment

(a) Seriousness

When an AE/AR occurs the investigator responsible for the care of the patient must first assess whether the event is **serious** using the definitions given in Table 10.1. If the event is serious and not exempt from expedited reporting, then an SAE form must be completed and the MRC CTU notified.

(b) Causality

The Investigator must assess the causality of all serious events/reactions in relation to the trial therapy using the definitions in Table 10.2. There are 5 categories: unrelated, unlikely, possible, probable and definitely related. If the causality assessment is unrelated or unlikely to be related the event is classified as a SAE. If the causality is assessed as either possible, probable or definitely related then the event is classified as a SAR.

Table 10.2 Definitions of causality

Relationship	Description	Event Type
Unrelated	There is no evidence of any causal relationship	SAE
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	SAE
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

(c) Expectedness

If the event is a SAR the Investigator must assess the expectedness of the event. Please see Appendix XVIII for a list of expected toxicities associated with the drugs being used in this trial. If a SAR is assessed as being unexpected it becomes a SUSAR.

(d) Notification

Investigators must notify the MRC CTU of all SAEs occurring from the time of randomisation until 30 days after the last protocol treatment administration. SARs and SUSARs must be notified to the MRC CTU indefinitely (i.e. no matter when they occur after randomisation).

Notification Procedure:

1. The SAE form must be completed by the Investigator (consultant named on the signature list and delegation of responsibilities log who is responsible for the patient's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator the form should be completed and signed by a member of the site trial team. The responsible investigator should subsequently check the SAE form, make changes as appropriate, sign and then re-fax to the MRC CTU as soon as possible. The initial report shall be followed by detailed, written reports as appropriate.

2. Send the SAE form by fax to the MRC CTU

   Fax Number: + 44 (0) 20 7670 4818

3. Follow-up: Patients must be followed-up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. Follow-up information should be noted on a further SAE form by ticking the box marked 'follow-up' and faxing to the MRC CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

4. Staff at the institution must **notify** their local research ethics committee (LREC) of the event (as per the institutions standard local procedure).

10.d MRC CTU Responsibilities

Medically qualified staff at the MRC CTU and/or the Chief Investigator (or a medically qualified delegate) will review all SAE reports received. The causality assessment given by the local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided in any subsequent reports.

The MRC CTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA and competent authorities of other

European member states and any other countries in which the trial is taking place) and the research ethics committees as appropriate.

The MRC CTU will also keep all investigators informed of any safety issues that arise during the course of the trial.

11 General Health and QoL Assessments

11.a Purpose and timing

- Oncologists usually base decisions whether to offer full-dose, reduced-dose or no chemotherapy on factors including performance status, co-morbidity and age.
  - In *FOCUS2*, an attempt is being made to assess treatment success in relation to objective criteria of general health and fitness at baseline. Therefore a comprehensive health assessment tool is applied before starting therapy.
- A major determinant of the "success" of palliative chemotherapy is its impact upon general health and quality of life, which are not necessarily reflected by response, progression-free survival and overall survival.
  - In *FOCUS2*, both physical and mental aspects of general health will be assessed at intervals during treatment, as outcome measures both for treatment comparison and for correlation with baseline fitness criteria.
  - The major assessment points will be at 14 weeks (i.e. 2 weeks after completing the first treatment course) and 24 weeks.

11.b Choice of Instruments

- The EORTC QLQ-C30 is a modular QoL tool used in previous MRC colorectal cancer trials (CR05, CR06 and *FOCUS*). However, for the purposes of this trial, more detailed information is required on certain aspects of QoL than the QLQ-C30 modules provides. Therefore, questions from QLQ-C30's global and symptom modules are used, but specialist tools have been chosen to replace several modules:
  - Activities of Daily Living (ADL) will be examined using the 24-point Nottingham IADL tool.[32]
  - Psychological risk and morbidity will be measured using the Hospital Anxiety and Depression Scale (HADS)
  - Satisfaction with treatment is addressed using additional questions previously used in MRC trials

- Physical fitness and co-morbidity: several components of physical fitness are being measured at baseline as they may contribute to "fitness for chemotherapy"
  - Nutrition: a mini-nutritional assessment (MNA).[33]
  - Mental state/cognition: a Mini-Mental State Examination (MMSE) is used to detect cognitive impairment.[34]
  - A timed 20-metre walk test.[35]
  - Medical Co-Morbidity: the Charlson co-morbidity score is a validated tool for quantifying co-morbidity in the geriatric population.[36]
- EuroQol (EQ-5D) is a widely used generic measure of health status which, through a valuation survey of 3,500 members of the public provides a link to health state preferences. This provides a route for calculating Quality-Adjusted Life-Years (QALY) for cost-effectiveness analysis.
- We have designated the above collection of QoL and physical fitness tools the "**Comprehensive Health Assessment – CHA**" (see page 86). These assessments have been validated in the geriatric literature[37,38] and have been applied in some European and American oncology units.[39,40]
- A shortened version of this assessment is used at the 14 and 24-week time points, designated the "**Limited Health Assessment – LHA**" (see page 94). This does not include the MMSE or Charlson co-morbidity score, so is quicker to administer.

11.c Administration of the CHA and LHA tools

- The CHA and LHA are administered in the outpatient clinic by the research nurse. CHA takes approximately 40 min and LHA approximately 20 min to administer.
  - One person in each centre must be nominated to take responsibility for the administration, collection and checking of the QL forms.
  - Both CHA and LHA consist of a nurse-administered section and a patient-completed questionnaire.
  - The patient-completed questionnaire should be completed by the patient in the clinic. The research nurse or data manager should be available to assist (eg with reading questions or marking responses) if the patient requires. This person should also check through the questionnaire after completion and ensure that all question have been answered, and that the patient ID and date are completed.
- The baseline (CHA) assessment may be performed at the same visit as consent and randomisation, and must be within 4 weeks prior to starting chemotherapy.
- A window of 3 weeks each side of target follow-up LHA is acceptable (i.e. 11-17 weeks for the 14 week LHA and 21-27 weeks for the 24 week LHA).
- Please note that, once randomised, all patients remain in the trial and the follow-up LHA data are required even if patients do not complete protocol treatment.

12 Follow-Up of Patients

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

12.a Stopping Trial Treatment

A patient may stop trial treatment for the following reasons:

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

The patient should however remain in the trial for the purposes of follow-up and data analysis.

12.b Moving

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

12.c Withdrawal of consent

If a patient explicitly states their wish not to contribute further data to the study, the MRC CTU should be informed in writing.

13 Trial Closure

For the purposes of regulatory requirements the end of the trial is defined as 12 weeks after the date of the last treatment visit for the last patient undergoing protocol treatment. However, this

will be followed by the non-interventional phase of long term follow-up, which will continue for a minimum of three years after entry of the last patient.

14 Economic evaluation

- The Health Economic evaluation in *FOCUS2* parallels that being performed in *FOCUS* (further details in appendix, page 100). Briefly, two analyses are planned:
  - Cost-consequences analysis: differential costs associated with each management strategy are presented alongside its clinical and Health-Related Quality of Life (HRQL) effects.
  - Cost-effectiveness analysis: differential costs associated with each treatment are related to benefits in terms of quality-adjusted life years (QALYs), and standard cost-effectiveness acceptability curves will be used to show the probability of one option being more cost-effective than the other.[41]

15 Molecular pathological research

Recent work has demonstrated the capacity for tumour molecular variables to be used to predict benefit from chemotherapy ("chemoprediction").[42] There may also be potential to predict either tumour response or excessive drug toxicity by examining normal tissue DNA for genetic polymorphisms in key enzymes in drug metabolic pathways ("pharmacogenetics").[43]

- In *FOCUS*, over 95% of patients have given separate consent for surplus pathological material to be used in research of this kind.[44] We will now extend this project to *FOCUS2*.
- Consenting patients' details of stored pathological samples are sent to the MRC CTU at the time of trial registration. Samples will then be retrieved direct from the pathology hospital by the MRC CTU.
- The MRC CTU will anonymise the samples and send them to the processing laboratory in Leeds. Sample preparation will include preparation of normal and tumour tissue microarrays (TMAs), RNA and DNA extraction.
- An anonymised 8ml blood sample will also be sent to Leeds for preparation of DNA for SNP analysis.
- The samples will be considered the property of the sponsor of the trial. Proposals for translational research projects involving the material will be considered by the TMG and presented to the independent TSC for approval.

16 Analysis plan and statistics

16.a Pilot stage

- 30 patients will be randomised into each arm (total 120) before analysis.
- Review of data by the IDMC will then be arranged. The IDMC will consider:
  - Toxicity: If grade 3 non-haematological or grade 4 haematological toxicity is observed in 10 or more of 30 patients in one arm, this would be evidence that the underlying serious toxicity rate for the regimen exceeds 19%.
  - Efficacy: All available efficacy data will be reviewed.
- The IDMC may recommend (a) proceeding to phase III with all 4 arms; (b) a further pilot phase, or (c) removal of one or more arms from the phase III study. In the case of (c), a revised phase III analysis plan would be required.

16.b Phase III stage

- If all arms are accepted into the phase III stage, a further 340 patients (85 per arm) will be randomised into the trial to give a total sample size of 460 patients, for the two main comparisons.
- The two main factorial trial comparisons are "+/- 1st-line oxaliplatin" ([D vs E]+[F vs G]) and "MdG vs Cap" ([D vs F]+[E vs G])
- +/- 1st-line oxaliplatin: The primary outcome measure is progression-free survival (PFS), defined as the interval from randomisation to first evidence of progression or any death.
  - The groups will be compared by intention-to-treat (ITT) using the Mantel-Cox version of the log-rank test.
  - The expected PFS in arms D and F is 50% at 6 months. The total of 460 patients will give 90% power to detect an improvement of 15% (from 50% to 65%) with combination therapy (2-sided 5% significance level, based on a log-rank test).
  - We will also compare the treatment hazard ratios in arms D and E in this trial with arms D and E of the main *FOCUS* trial to see if there is a consistent relative effect, using tests for interaction (chi-squared test for heterogeneity).
- MdG vs Cap": The primary outcome measure is quality of life (QoL).
  - The main QoL comparison is the difference in the change in symptom or subscale score from baseline to 14 weeks between groups, compared by ITT using the Mann-Whitney Test. Changes from baseline to 24 weeks will be a supplemental comparison.
  - In *FOCUS,* all patients receive initial infusional FU/FA, and 40% show improvement in overall QoL from baseline to 12 weeks. 100% compliance

with QoL questionnaires in this group of patients may be difficult to achieve, but even a poor rate of 56% (260 patients) would give 90% power to detect an improvement of 20% (from 40% to 60%) with capecitabine (2-sided, 5% significance level, based on chi-squared test).

- Please see section 5 for details of secondary outcome measures to be used

17 Trial Management

This trial is being undertaken in accordance with the MRC Guidelines for Good Clinical Practice in Clinical Trials (1998).[32] Collaborating investigators should be familiar with these guidelines, which are available from the MRC CTU or on the MRC website (http://www.mrc.ac.uk). Responsibilities of the trial personnel and committees are as follows:

- The **Chief Investigator** (PI) and the **MRC Clinical Trials Unit** (MRC CTU) are responsible for the day-to-day running of the trial as detailed in MRC GCP Guidelines. The CTU will in addition prepare data reports for the TSC and IDMC, including interim analyses, and will make safety and progress reports to the Multicentre Research Ethics Committee (MREC) and Medicines and Healthcare products Regulatory Agency (MHRA)
- The **Trial Management Group** (TMG) meets at least once every 6 months (but may convene more often or by other means) to advise the PI and MRC CTU in the promotion and running of the trial. TMG members include active trial investigators, members with specific interests (e.g. pharmacist; nurse; geriatrician; user representative).
- The **Trial Steering Committee** (TSC) is an independent committee providing overall supervision of the trial. It will meet at least annually, and will receive reports from the MRC CTU, PI and IDMC.
- The **Data Monitoring & Ethics Committee** (IDMC) is also independent. It will review the data at the completion of the pilot phase (see section 0). Thereafter it will meet at least annually, with interim analysis reports from the CTU, to give advice on continuing recruitment. A recommendation to discontinue recruitment (in all patients or in selected subgroups) will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDMC will make recommendations to the TSC as to the continuation of the trial.

18 Publication

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

All publications shall include a list of participants, and if there are named authors, these should include the Chief Investigator(s), Clinical Trial Manager(s), and Statistician(s) involved in the trial. If there are no named authors then a Writing Committee will be identified.

19 Patient confidentiality

Patient confidentiality will be respected at all times throughout this trial. The name of a patient will be collected at randomisation as this will be required for flagging purposes. However, on all subsequent forms and on any correspondence the patients trial number, initials and date of birth will be used. The MRC is registered with the Data Protection Act to hold this information on a confidential basis (DPA reference number G0027154).

Patients will not be named in any publications.

20 Regulatory and Ethics Approval

FOCUS 2 has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA). The CTA reference is **00316/007/001.**

20.a Ethical Considerations

This is a randomised controlled trial. Therefore neither the patient nor their physicians will be able to choose the patients' treatment. Treatment will be allocated randomly using a computer-

based algorithm. This is to ensure that the groups of patients receiving each of the different treatments are similar.

20.b Ethical Approval

The protocol has Main Research Ethics Committee (MREC) approval but the Local Research Ethics Committee (LREC) must approve each institution before patients are entered at that institution (Site Specific Assessment (SSA)).

The patient's consent to participate in the trial should be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. Patients should be given sufficient time after being given the trial patient information sheet to consider and discuss participation in the trial with friends and family. A contact number should be given to the patient should they wish to discuss any aspect of the trial. Following this, the randomising investigator should determine that the patient is fully informed of the trial and their participation, in accordance with ICH GCP guidelines. Patients should always be asked to sign a consent form. One copy should be given to the patient, one copy should be kept with patient's hospital notes and one copy should be kept in the local investigator's file. If the patient has provided their consent a copy of the consent form should also be sent to the MRC CTU.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the patient must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

A statement of MRC policy on ethical considerations in clinical trials of cancer therapy, including the question of informed consent, is available from the MRC Head Office web site (http://www.mrc.ac.uk). This may be used to give guidance to participating investigators and to accompany applications to LREC.

The MRC and NHS are not allowed to purchase advance insurance to cover indemnity because they are backed by the resources of the Treasury. MRC Head Office has issued this statement: *"MRC will give sympathetic consideration to claims for non-negligent harm suffered by a person as a result of trial or other work supported by MRC. This does not extend to liability for non-negligent harm arising from conventional treatment where this is one arm of a trial. MRC acts as its own insurer and does not provide cover for non-negligent harm in advance for participants in MRC-funded studies. Where studies are carried out in a hospital, the hospital continues to have*

a duty of care to a patient being treated within the hospital, whether or not the patient is participating in an MRC-supported study. MRC does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is a NHS Trust or not."

21 Monitoring and Quality Assurance

21.a Monitoring at MRC CTU

Data provided to the MRC CTU will be checked for missing or unusual values (range checks) and consistency over time. If missing or questionable data are identified, staff at the MRC CTU will request that the data be clarified. The exact procedures for data clarification and the amendment of CRFs will be described in the trial specific SOPs and instructions will be sent to all FOCUS 2 institutions as soon as they have been approved to participate in the trial. The MRC CTU will also send reminders for any overdue data.

21.b Direct Access to Data

Collaborating institutions should be aware that direct access to patient data by MRC CTU staff may be required for trial-related monitoring or audit. Patient consent for this will be obtained as part of the general trial consent process.

21.c Visits to Investigator Sites

Each institution **may** be visited at least once during the course of the FOCUS 2 trial.

The purpose of these visits is:

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

The MRC CTU will give the responsible investigator adequate notice of the monitoring visit to allow adequate time, space and staff for these visits. The standard operating procedures (SOP) for monitoring are available from the MRC CTU.

After the monitoring visit the monitor will complete a site visit report. This report will be circulated to the TMG for comment. Once the TMG have reviewed the report and agreed on any recommendations the monitor will finalise the report and send a copy to the Chief Investigator (PI) at the site. A copy will also be sent to the CI for the trial and another copy will be kept in the MRC CTU FOCUS 2 master file.

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Appendix I – The chemotherapy regimens

The *FOCUS2* MdG regimen

Day 1 of treatment schedule (14 day cycle)

time 0:00	iv bolus dexamethasone 8 mg
time 0:00 – 2:00	**l*-folinic acid 175mg (flat dose) iv infusion over 2 hours
time 2:00 – 2:05	5-fluorouracil 320 mg/m^2 iv bolus injection over 5 mins
time 2:05 – 48:00	5-fluorouracil 2240 mg/m^2 iv infusion over 46 hours
time 48:00	Disconnect pump; flush line (5 ml heparinised saline).

(*In the event that *l*-folinic acid is not available you may use 350mg *d,l*-folinic acid as an alternative.)

Oral antiemetics, etc (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

Emesis is insignificant with MdG, but dexamethasone is included for its possible contribution to the anticancer effect. For patients at high risk of steroid side effects (eg diabetics) or for those who develop toxicity attributable to steroids (eg dyspepsia; dysphoria; etc), the oral steroids should be omitted.

Dose escalation to full-dose MdG

Schedule the patient for review by the treating consultant 6 weeks after starting treatment (start of cycle 4). A dose increase to full dose may be considered at that point. See page 16 for criteria for dose increase, but note especially that it is at the discretion of the treating consultant, not automatic.

Full dose MdG regimen: as above except:

time 2:00 – 2:05	5FU 400 mg/m^2 iv bolus injection over 5 minutes
time 2:05 – 48:00	5FU 2800 mg/m^2 iv infusion over 46 hours

Scheduled tests

- FBC and clinical assessment (NCI toxicity scores) should be performed on the day of starting each cycle, or within 3 days before, and the results available before starting.
- Biochemistry (including creatinine and bilirubin) is done at the same time as FBC; however it is acceptable to proceed with the current cycle based on the biochemistry results from the previous cycle.

Toxicity and dose reductions/delays

Haematological

- Check FBC on (or the day before) day 1 of each cycle. Delay 1 week if WBC < 3.0 x 10^9/l, granulocytes < 1.5 x 10^9/l or platelets < 100 x 10^9/l. Only treat when WBC and platelets are above these limits.
- If >1 delay, or 1 delay of ≥ 2 weeks occurs, reduce the 5FU doses (bolus and infusion) 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 clinician.

Stomatitis

- Routine mouthcare (eg 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.

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 from the previous cycle 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 5FU doses (bolus and infusion) by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.

Hand-foot syndrome (HFS)

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

DPD deficiency

- With any 5FU regimen, the occasional patient is encountered (approx 1-3%) who has markedly exaggerated toxicity due to reduced 5FU catabolism. If this occurs, await full recovery. Further treatment at much reduced 5FU dose (eg 50%) may be considered. Please discuss with one of the clinical coordinators.

Hepatic and renal function (see also appendix page 57)

- Bilirubin ≤ 3 x ULN and GFR > 30 ml/min are required for study entry. If bilirubin rises above 3x ULN or GFR falls below 30 ml/min during treatment, discuss with consultant as stopping chemotherapy may be indicated. If treatment is to continue, dose adjustment is required: refer to the table on page 57.

Cardiac and neurotoxicity

- These are uncommon but recognised 5FU side-effects.
- 5FU may provoke angina attacks or even MI in patients with ischaemic heart disease. Continued treatment with upgraded antianginal medication and reduced 5FU dose may be considered, alternatively consider non-5FU treatment off trial (eg raltitrexed).
- Neurotoxicity (most often cerebellar) is uncommon; again, consider changing to alternative treatment.

The *FOCUS2* OxMdG regimen

The same schedule is used, whether as first-line (Arm E) or second-line (Arm D). If used as second-line therapy, any 5FU reductions required during MdG should be carried through as proportionate reductions in this schedule.

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.

Day 1 of treatment schedule (14 day cycle)

	time 0:00	iv dexamethasone 8mg + granisetron 1-3 mg or equivalent
	time 0:00–2:00	*_l_-folinic acid 175mg (flat dose) iv infusion over 2 hours
plus:	time 0:00–2:00	oxaliplatin 68 mg/m^2 iv infusion over 2 hours
	time 2:00–2:05	5-fluorouracil 320 mg/m^2 iv bolus injection over 5 min
	time 2:05–48:00	5-fluorouracil 1920 mg/m^2 iv infusion over 46 hours
	time 48:00	Disconnect pump; flush line (5 ml heparinised saline).

(*In the event that *l*-folinic acid is not available you may use 350mg *d,l*-folinic acid as an alternative.)

Oral antiemetics, etc (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 (eg diabetics) or for those who develop toxicity attributable to steroids (eg dyspepsia; dysphoria; etc), the oral steroid should be omitted.

Dose escalation to full-dose OxMdG

Schedule the patient for review by the treating consultant 6 weeks after starting treatment (start of cycle 4). A dose increase to full dose may be considered at that point. See page 16 for criteria for dose increase, but note especially that it is at the discretion of the treating consultant, not automatic.

Full dose OxMdG regimen: as above except:

time 0:00 – 2:00	oxaliplatin 85 mg/m^2 iv infusion over 2 hours
time 2:00 – 2:05	5-fluorouracil 400 mg/m^2 iv bolus injection over 5 min
time 2:05 – 48:00	5-fluorouracil 2400 mg/m^2 iv infusion over 46 hours

Scheduled tests

- FBC and clinical assessment (NCI toxicity scores) should be performed on the day of starting each cycle, or within 3 days before, and the results available before starting.

- Biochemistry (including creatinine and bilirubin) is done at the same time as FBC; however it is acceptable to proceed with the current cycle based on the biochemistry results from the previous cycle.

Toxicity and dose adjustments for OxMdG

Haematological

- Check FBC on (or the day before) day 1 of each cycle. Delay 1 week if WBC < 3.0 x 10^9/l, granulocytes < 1.5 x 10^9/l or platelets < 75 x 10^9/l. Only treat when WBC and platelets are above these limits. Note the lower limit for the day 1 platelet count for this regimen.
- If >1 delay, or 1 delay of **≥** 2 weeks occurs, reduce oxaliplatin and 5FU (bolus + infusion) by 20%. Continue at the lower dose for subsequent cycles unless further toxicity occurs.
- If a further delay(s) for myelotoxicity occurs despite a 20% dose reduction, a further dose reduction may be made, at the discretion of the treating clinician.

Neurotoxicity

- Oxaliplatin commonly causes peripheral sensory symptoms, easily distinguishable from 5FU neurotoxicity, which is uncommon, and cerebellar.
- Many patients experience transient paraesthesia of hands and feet, or mild throat dysaesthesia, precipitated by cold and lasting several days after each oxaliplatin administration. They do not require treatment or dose reduction.
- If symptoms persist for 14 days (i.e. until the next cycle is due), and are associated with significant discomfort or loss of function (eg dropping objects), omit oxaliplatin and continue with MdG alone until fully recovered, then restart OxMdG.

Renal function (see also appendix page 57)

Oxaliplatin, like carboplatin, is not nephrotoxic but is renally cleared.

- Before starting, ensure patient fulfils eligibility for renal function. If Cockroft estimate GFR <50 ml/min, check GFR with EDTA clearance or equivalent. If GFR is in the range 30-49 ml/min, a 25% reduction in the dose of oxaliplatin is required (see page 57)
- Check serum creatinine at each treatment cycle. If this rises >25%, re-check EDTA clearance, and adjust doses according to the table on page 57.

Hepatobiliary function

- Bilirubin ≤ 3 x upper limit of normal is required for study entry. If bilirubin rises above this limit during treatment, discuss with consultant as stopping chemotherapy may be indicated. If treatment is to continue, a 50% dose reduction will be required; refer to table on page 57.

Stomatitis

- Routine mouthcare (eg 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.

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, initially with pyridoxine 50 mg tds by mouth. Topical corticosteroid may also 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 5FU catabolism. If this occurs, await full recovery. Further treatment at much reduced 5FU dose (eg 50%) may be considered. Please discuss with one of the clinical coordinators.
- 5FU may provoke angina attacks or even MI in patients with ischaemic heart disease. Continued treatment with upgraded antianginal medication and reduced 5FU dose may be considered, alternatively consider non-5FU treatment off trial (eg raltitrexed).

Allergic reactions to oxaliplatin

- Patients may develop acute hypersensitivity to oxaliplatin, usually only after several doses. During drug administration, the patient may develop rash, fever, swollen mouth or tongue, hypo- or hypertension and other signs/symptoms of hypersensitivity, although full-blown anaphylaxis is rare
- If acute hypersensitivity occurs, discontinue the infusion and treat with i.v. corticosteroid and antihistamine
- After full recovery, the patient may continue with MdG alone

Respiratory

- As with other platinum drugs, rare cases of acute interstitial lung disease or lung fibrosis have been reported with oxaliplatin. In the case of unexplained respiratory symptoms or signs, oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease.

The *FOCUS2* Cap regimen

Treatment schedule (21 day cycle)

day 1-15: Capecitabine 1000 mg/m^2 twice daily (28 doses total)

day 16-21: no treatment

Notes:

- The full treatment cycle consists of 28 doses taken 12-hourly. This starts with the evening dose on day 1 and ends with the morning dose on day 15.
- The dose is rounded to the nearest achievable dose using the table in appendix page 52. The same dose is taken morning and evening.
- patients are instructed to take capecitabine within 30 minutes after food, approximately 12 hourly (eg 8 am and 8pm)

Antiemetics, etc:

- Patients should be prescribed a p.r.n. oral antiemetic (eg metoclopramide 10 mg t.d.s.)

Dose escalation to full-dose Cap

Schedule the patient for review by the treating consultant 6 weeks after starting treatment (start of cycle 3). A dose increase to full dose may be considered at that point. See page 16 for criteria for dose increase, but note especially that it is at the discretion of the treating consultant, not automatic

Full dose Cap regimen:

day 1-15: Capecitabine 1250 mg/m^2 twice daily (28 doses total)

day 16-21: no treatment

Scheduled tests

- FBC and clinical assessment (NCI toxicity scores) should be performed on the day of starting each cycle, or within 3 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 transaminase).

Toxicity and dose reductions/delays

Haematological

- Check FBC on (or the day before) day 1 of each cycle. Delay 1 week if WBC < 3.0 x 10^9/l, granulocytes < 1.5 x 10^9/l or platelets < 100 x 10^9/l. Only treat when WBC and platelets are above these limits.
- If >1 delay, or 1 delay of ≥ 2 weeks occurs, reduce capecitabine 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 clinician.

General Non-Haematological Toxicities

- NCI grade 1 toxicity is managed symptomatically and does not usually require dose reduction or interruption
- For any toxicity of grade 2 or higher (eg diarrhoea, mucositis, vomiting) **stop capecitabine** and treat symptomatically until the toxicity has resolved to grade 0 or 1.
    - Note that 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 capecitabine after a pause for toxicity, use the following dose reduction scheme:
    - Grade 2 toxicity: resume at the same dose after first pause, but reduce to 75% of the previous dose if a second pause is required.
    - Grade 3 toxicity: resume at 75% of original dose
    - Grade 4 toxicity: discontinue permanently.
- If further toxicity of grade ≥2 occurs after a dose-reduction, the dose should either be reduced to 50% of the original dose, or stopped permanently, at the consultant's discretion.

Renal function (see also appendix page 57)

- Before starting, ensure patient fulfils eligibility for renal function. If Cockroft estimate GFR <50 ml/min, check GFR with EDTA clearance or equivalent. If GFR is in the range 30-49 ml/min, a 25% reduction in the dose of capecitabine is required (see page 57)
- Check serum creatinine at each treatment cycle. If this rises by >25%, re-check EDTA clearance, and adjust capecitabine doses according to the table on p 57.

Hepatobiliary function

- Capecitabine undergoes hepatic metabolism. In addition, patients on capecitabine may have temporary treatment-related elevation of transaminases; this requires interruption of treatment.
- Bilirubin ≤ 3 x ULN is required for study entry. If bilirubin rises above this limit during treatment, discuss with consultant as this may indicate disease progression. If treatment is to continue, refer to table on p 57.
- Transaminase (either AST or ALT) ≤ 2.5x ULN is required for study entry. An isolated rise in transaminase above this level during treatment is likely to be drug-related, and capecitabine should be interrupted until recovery (see page 57).

The *FOCUS2* OxCap regimen

The same schedule is used, whether as first-line (Arm G) or second-line (Arm F). If used as second-line therapy, if a capecitabine reduction was required during Cap this should be carried through as a proportionate reduction. 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.

Treatment schedule (21 day cycle)

day 1	iv bolus dexamethasone 8mg + granisetron 1-3mg or equivalent, then oxaliplatin 104 mg/m^2 iv infusion in 500 ml 5% dextrose iv infusion over 2 hours
day 1-15	capecitabine 800 mg/m^2 twice daily (28 doses total)
day 16-21	no treatment

Notes:

- 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
- 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.
- The capecitabine dose is rounded to the nearest achievable dose using the table on page 52. The same dose is taken morning and evening.
- Patients are instructed to take capecitabine within 30 minutes after food, approximately 12 hourly (eg 8 am and 8pm)

Oral antiemetics, etc:

- From 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 (eg diabetics) or for those who develop toxicity attributable to steroids (eg dyspepsia; dysphoria; etc), the oral steroid should be omitted.

Dose escalation to full-dose OxCap

Schedule the patient for review by the treating consultant 6 weeks after starting treatment (start of cycle 4). A dose increase to full dose may be considered at that point. See page 16 for criteria for dose increase, but note especially that it is at the discretion of the treating consultant, not automatic.

Full dose OxCap regimen, as above except:

day 1	oxaliplatin 130 mg/m^2 iv infusion over 2 hours
day 1-15	capecitabine 1000 mg/m^2 twice daily (28 doses total)

Scheduled tests

- FBC and clinical assessment (NCI toxicity scores) should be performed on the day of starting each cycle, or within 3 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 transaminase).

Toxicity and dose reductions/delays

Haematological

- Check FBC on (or the day before) day 1 of each cycle. Delay 1 week if WBC < 3.0 x 10^9/l, granulocytes < 1.5 x 10^9/l or platelets < 75 x 10^9/l. Only treat when WBC 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 clinician.

Non-haematological toxicities (excluding neurotoxicity – see below)

- Grade 1 toxicity is managed symptomatically and does not usually require dose reduction or interruption
- For any toxicity of grade 2 or higher (eg diarrhoea, mucositis, vomiting) **stop capecitabine** and treat symptomatically until the toxicity has resolved to grade 0 or 1.
    - Note that 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 OxCap 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 drugs to 75% of the previous doses if a second pause is required.
    - Grade 3 toxicity: resume at 75% of original doses (both drugs)
    - Grade 4 toxicity: discontinue permanently.
- If further toxicity of grade ≥2 occurs after a dose-reduction, the doses should either be reduced to 50% of the original dose, or stopped permanently, at the consultant's discretion.

Neurotoxicity

- Oxaliplatin commonly causes peripheral sensory symptoms.
- Many patients experience transient paraesthesia of hands and feet, or mild throat dysaesthesia, precipitated by cold and lasting several days after each oxaliplatin administration. This does not require treatment or dose reduction.

- If symptoms persist for 14 days (i.e. until the next cycle is due), and are associated with significant discomfort or loss of function (eg dropping objects), omit oxaliplatin and continue with capecitabine alone until fully recovered, then restart OxCap

Renal function (see also appendix page 57)

- Before starting, ensure patient fulfils eligibility for renal function. If Cockroft estimate GFR <50 ml/min, check GFR with EDTA clearance or equivalent. If GFR is in the range 30-49 ml/min, a 25% reduction in the doses of both capecitabine and oxaliplatin is required (see page 57).
- Check serum creatinine at each cycle. If this rises >25%, re-check EDTA clearance, and adjust oxaliplatin and capecitabine doses according to the table on page 57.

Hepatobiliary function

- Capecitabine undergoes hepatic metabolism. In addition, patients on capecitabine may have temporary treatment-related elevation of transaminases which require interruption of treatment.
- Bilirubin ≤ 3 x ULN is required for study entry. If bilirubin rises above this limit during treatment, discuss with consultant as this may indicate disease progression. If treatment is to continue, refer to table on p 57.
- Transaminase (either AST or ALT) ≤ 2.5x ULN is required for study entry. An isolated rise in transaminase above this limit during treatment is likely to be treatment-related, and capecitabine should be interrupted until recovery (see page 57).

Respiratory

- As with other platinum drugs, rare cases of acute interstitial lung disease or lung fibrosis have been reported with oxaliplatin. In the case of unexplained respiratory symptoms or signs, oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease.

Appendix II – Dose calculations and banding

Obese patients:

- Ideal body weight is calculated (Lorenz formula) as:
  - Men: IBW in kg = [height in cm minus 100] – [(height – 150) ÷ 4]
  - Women IBW in kg = [height in cm minus 100] – [(height – 150) ÷ 2]
- If a patient weighs more than 1.15x their IBW, use 1.15x IBW to calculate SA.
- Examples:
  - A man is 174 cm tall. His IBW is 174 – 100 – (24 ÷ 4) = **68 kg**. So if his actual weight is less than 78.2 kg (68 x 1.15), we use his actual weight to calculate SA, but if he weighs more than 78.2 kg, we use 78.2kg to calculate SA (which gives us **1.93 m^2**).
  - A woman is 174 cm tall, so her IBW is 74 – 12 = **62 kg**. So if she is over 71.3 kg, we use 71.3 kg to calculate SA (this gives us **1.85 m^2**)

Capecitabine dose banding

- First calculate the patient's surface area accurately to 2 decimal places.
- Calculate the **exact** (not rounded) target dose of capecitabine.
  - *For example, a patient on OxCap requiring 800 mg/m^2, who's S.A is 1.59 m^2, has an exact target dose of 1.59 x 800 = 1272 mg.*
- Use the table to find the rounded dose and the number of tablets per dose:

Exact Target Dose within range (mg)	Rounded Dose (mg)	Number of tablets per dose	
		500 mg +	150 mg
401 – 575	500	1	0
576 – 725	650	1	1
726 – 900	800	1	2
901 – 1075	1000	2	0
1076 – 1225	1150	2	1
1226 – 1400	1300	2	2
1401 – 1575	1500	3	0
1576 – 1725	1650	3	1
1726 – 1900	1800	3	2
1901 – 2075	2000	4	0
2076 – 2225	2150	4	1
2226 – 2400	2300	4	2
2401 – 2575	2500	5	0

- Complete the patient's diary sheet for the cycle, including the patient's name, the numbers of each tablet to take (at the top) and the day and date of each dose due (in the table). Give the diary sheet to the patient together with their tablets.

Fluorouracil dose banding

- As for capecitabine, first calculate the patient's surface area accurately to 2 decimal places, then calculate the exact target doses for the 5FU bolus and 46-hour infusion
    - *For example, a patient of 1.59m^2 receiving the OxMdG regimen without dose-adjustments would have target doses of 320 x 1.59 = 508.8 mg fluorouracil bolus and 1920 x 1.59 = 3052.8 mg fluorouracil infusion.*

- Bolus fluorouracil may then be rounded to the nearest 25 mg, and infusion fluorouracil may be rounded to the nearest 100 mg.
    - *So the patient in the above example would receive 500 mg bolus + 3100 mg infusion.*

Oxaliplatin dose banding

- As for capecitabine and fluorouracil, first calculate the patient's surface area accurately to 2 decimal places, then calculate the exact target dose.
    - *For example, the patient of 1.59m^2 receiving the OxMdG regimen without dose-adjustment would have a target dose of 68 x 1.59 = 108.12 mg*

- The round the oxaliplatin dose to the nearest 10mg
    - *So the patient in the above example would receive 110 mg oxaliplatin.*

Appendix III – Delivery of infusional treatment

The MdG and OxMdG regimens may be delivered in hospital but are intended as daycase/outpatient treatments. Investigators need to consider the following issues:

Venous access:

- Semi-permanent venous access is required, e.g.:
  - a single-lumen Hickman line
  - a peripheral long line (PICC, etc).
  - a subcutaneous implantable port (Portacath, Infu-KT, etc)

- Choices:
  - **use only single-lumen lines, not double** (double-lumen lines have a higher complication rate and are not required for MdG or OxMdG.
  - for Hickman lines, use right subclavian approach not left
  - if PICC lines are used, the non-return valve type is recommended.

- Management
  - local protocol for insertion and management of the venous line is required
  - nominated staff for insertion and management of lines
  - written information for GPs and community nurses

- Flushing
  - subcutaneous ports (eg PortaCath) do not need flushing between treatments.
  - Hickman and PICC lines require weekly flushing.
  - district nurse, carer, or district nurse should perform the weekly between-treatment flush.

- Anticoagulation:

  Following the recent WARP study Warfarin anti-coagulation is no longer recommended as routine. Centres are advised to follow their own local policy on anti-coagulation

Infusion pumps

- Suitable pumps for this study are:
  - elastomeric balloon infusors (eg Baxter 'LV5')
  - battery-powered electrical pumps (eg Walkmed).
- It is important that staff including out-of-hours on-call staff are familiar with the types of pump being used in the unit.
- Note that with elastomeric pumps, flow-rates through PICC lines may be less consistent than through Hickman lines. Pumps should be allowed to complete before disconnecting, even if this takes a little longer than the intended 46 hours.

Liason with community services

- Good communication with general practitioners and community nursing teams is particularly important. District nurses should be invited to attend the chemotherapy unit to learn the procedure for disconnecting chemotherapy pumps at the end of the 46-hour infusion. Written nursing protocols for care of the venous lines and pumps should be prepared for this purpose.

In-patient delivery via a peripheral vein

- Occasionally it is necessary to give MdG or OxMdG as an inpatient via a peripheral vein, eg:
  - for the first cycle if there is a waiting-list for permanent venous access insertion
  - if venous access has had to be removed because of a complication
- In this instance, the 46-hour infusion of 5FU should be divided into two 23-hour infusions, each given in 1 litre normal saline.
- Repeated treatment administration in this way may lead to discolouration and pain over the arm veins and is not recommended. A head pad is recommended during the oxaliplatin infusion if OxMdG is being given (see OxCap protocol p 49)
- Never use a peripheral vein cannula for ambulatory home chemotherapy, or to administer concentrated 5FU intended for central venous line use.

Appendix IV - Cockroft & Gault Formula

- The estimated GFR is given by:

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

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

- This formula usually under-estimates GFR by 10-30% compared with EDTA or measured 24-hour creatinine clearance, so is used in this trial as a screening test.
  - A Cockroft/Gault estimate of >50 ml/min is accepted as evidence of adequate renal function
  - Patients with a Cockcroft/Gault estimate of < 50 ml/min prior to randomisation should have formal GFR measurement with EDTA or 24 urinary creatinine, which must be within the normal range. The corrected EDTA clearance should be greater than 50ml/min
  - After the start of treatment, if the Cockroft/Gault estimate falls by >25% from baseline, to below 50 ml/min, the formal EDTA measurement should be re-checked.

Appendix V – Renal & hepatic function

		Oxaliplatin dose	Capecitabine dose	5FU dose
Renal function	GFR ≥ 50 ml/min	full	full	full
	GFR 30–49 ml/min	reduce by 25%	reduce by 25%	full
	GFR < 30 ml/min	do not give	do not give	reduce by 25%
Hepatic function	Bili ≤ 3x ULN and AST/ALT ≤ 2.5x ULN	full	full	full
	AST or ALT > 2.5 x ULN	full	withhold until recovery	full
	Bili > 3x ULN	reduce by 50%	reduce by 50%	reduce by 50%

Notes:

- Organ function at the time of enrolment must meet the eligibility criteria (see page 15), ie GFR > 30 ml/min, bilirubin ≤ 3 x ULN and transaminase ≤ 2.5 x ULN (use either AST or ALT – it is not necessary to measure both).

- Note that patients with measured GFR in the range 30-49 ml/ml may enter *FOCUS2*, but if randomised to receive oxaliplatin and/or capecitabine these drugs are given at 25% reduced dose (as per table).

- If renal or renal or hepatic function changes at any point after randomisation, use the table above. **Deteriorating organ function may be a sign of disease progression, so always discuss with the consultant oncologist.**
  - Use the more conservative guideline. Eg, for a patient with Bili >3x ULN ***and*** ALT > 2.5x ULN, withhold capecitabine.

- GFR: see notes on page 56 for the use of Cockroft formula to estimate GFR. For patients with a Cockroft estimate <50 ml/min, a measured EDTA clearance (or 24 hour urinary creatinine clearance) should be obtained on at least one occasion, and this value takes precedence over the Cockroft estimate

Appendix VI – WHO performance status

Clinical Performance Status

0 Able to carry out all normal activity without restriction.

1 Restricted in physically strenuous activity but ambulatory and able to carry out light work.

2 Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.

3 Capable only of limited self-care; confined to bed or chair more than 50% of waking hours.

4 Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

Appendix VII – RECIST response definitions

- RECIST (Response Evaluation Criteria In Solid Tumours) has now superseded the old WHO response criteria for solid tumours.
- The key differences are:
  - instead of measuring lesions in 2 dimensions it is now only necessary to measure the longest diameter.
  - disease is classified as measurable or not measurable but the term evaluable is no longer used

Measurable disease:

- Disease is measurable if there is at least one measurable target lesion. Target lesions should be selected on the basis of size and suitability for repeat measurement, up to a maximum of 5 measurable lesions per organ, and up to a maximum of 10 lesions in total. These should be representative of all involved organs.
- Target lesion must be accurately measurable in at least 1 dimension, with the longest diameter ≥20 mm (or ≥10 mm with spiral CT scan). If the lesion is smaller than this then it is classed as non-measurable.
- Measurements must be taken as close as possible to the beginning of treatment and never more than 4 weeks before the start of treatment. Target lesions should be assessed by CT, MRI or CXR, not by clinical assessment alone. The same imaging modality should be used throughout for any given patient.
  - When intra-venous contrast agents are given with CT, it is important to measure hepatic lesions in the same vascular phase on subsequent examinations
  - If MRI is used than the same sequence (eg T1 or T2 weighted images) in the same anatomical plane should be used.
- Add the longest diameters of the target lesions and report this as the **baseline sum longest diameter.** This will be used as a reference by which the tumour response will be measured.

Response definitions:

- **Complete response (CR)**: disappearance of all lesions (ie all evidence of disease, not just the target lesions) determined by 2 observations not less than 2 weeks apart (in *FOCUS2* the 12-week assessment should be used as the confirmatory assessment; there is no need for additional confirmatory scans.

- **Partial response (PR)**: ≥30% decrease in the sum of longest diameters of target lesions compared to baseline, with response or stable disease observed in non-target lesions, and no new lesions
- **Stable disease (SD)**: neither sufficient shrinkage to qualify for response or sufficient increase to qualify for progressive disease in target lesions, with response or stable disease observed in non-target lesions, and no new lesions
- **Progressive disease (PD)**: ≥20% increase in the sum of longest diameters of target lesions compared to smallest sum longest diameter recorded, or unequivocal progression of non-target lesions, or appearance of new lesions.

Reminder:

- Response is judged against baseline, but progression is judged against the smallest recorded score.

Example:

Month	0	3	6	9	12
Measurement (mm)	100	90	50	55	65
Classification	baseline	SD	PR	PR	PD

References:

Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumours. J Natl Cancer Inst 2000, 92, 205-216

Gehan EA and Tefft MC. Will there be resistance to the RECIST (Response Evaluation Criteria in Solid Tumours)? J Natl Cancer Inst 2000, 92, 179-181

Appendix VIII – NCI Common Toxicity Criteria (v3.0)

Toxicity	0	1	2	3	4	5
NAUSEA	None	Loss of appetitie without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated < 24hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥ 24hrs	Life-threatening consequences	Death
VOMITING	None	1 episode in 24 hours	2-5 episodes in 24 hours; IV fluids indicated < 24hrs	≥ 6 episodes in 24 hours; IV fluids, or TPN indicated ≥ 24hrs	Life-threatening consequences	Death
ANOREXIA	None	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition; IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALOPECIA	Normal	Thinning or patchy	Complete	-	-	-
HAND-FOOT SKIN REACTION	None	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, oedema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain, interfering with function	-	-
PAIN	None	Mild pain not interfering with function	Moderate pain: pain or analgesics interfering with function, but not interfering with ADL	Severe pain: pain or analgesics severely interfering with ADL	Disabling	-
STOMATITIS	None	Minimal discomfort, intervention not indicated	Symptomatic, medical intervention indicated but not interfering with ADL	Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
DIARRHOEA (patients without colostomy)	None	Increase of <4 stools/day over baseline	Increase of 4-6 stools/day over baseline; IV fluids indicated < 24hrs	Increase of ≥ 7 stools/day; incontinence; IV fluids ≥ 24hrs; hospitilisation	Life-threatening consequences (e.g., haemodynamic collapse)	Death
DIARRHOEA (patients with a colostomy)	None	Mild increase in ostimy output compared with baseline	Moderate increase in ostomy output compared with basleine, not interfering with ADL	Severe increase in ostomy output compared to baseline, interfering with ADL	Life-threatening consequences (e.g., haemodynamic collapse)	Death
LETHARGY	None	Mild fatigue over baseline	Moderate or causing difficulty performing some activities	Severe fatigue interfering with ADL	Disabling	-
HAEMO-GLOBIN	Within normal limits	10.0g/dl - normal	8.0 - 9.9g/dl	6.5 - 7.9g/dl	<6.5g/dl	Death
PLATELETS	Within normal limits	$75x10^9/1$ - normal	50 - $74x10^9/1$	25 – $49x10^9/1$	<$25x10^9/1$	Death
WBC	Within normal limits	$3.0x10^9/1$- normal	2.0 - $2.9x10^9/1$	1.0 - $1.9x10^9/1$	<$1.0x10^9/1$	Death
NEUTROPHILS	Within normal limits	$1.5x10^9/l$ – normal	1.0 - $1.4x10^9/1$	0.5 - $0.9x10^9/1$	<$0.5x10^9/1$	Death
SENSORY NEUROPATHY	Normal	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
MOTOR NEUROPATHY	Normal	Asymptomatic; weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk indicated	Life-threatening; disabling (e.g., paralysis)	Death

These are selected categories. For full list see http://ctep.cancer.gov/reporting/ctc.html

Appendix IX: Patient Information Sheets

(Version 1.1 – August 2003)

The written information accompanying *FOCUS2* has been organised in separate sections as follows:

- A General Patient Information Sheet for use prior to randomisation. This describes the reason for the research, the design of the trial and a brief outline of the treatments which the patient may receive. It also covers important general issues such as alternative options, withdrawing from the research, indemnity, confidentiality, and access to pathological material.
- Four regimen-specific Patient Information Sheets, covering each of the four chemotherapy regimens used in the trial. The relevant sheet(s) should be given to the patient after randomisation, before treatment starts (or at the point of starting second-line treatment if appropriate). These include more detailed information about possible unwanted effects and safety instructions such as what to do in the event of diarrhoea or fever. Some patients may wish to receive all four regimen-specific information sheets to read before making a decision about randomisation, but this is not mandatory.
- Quality of Life: There is a separate Patient Information Sheet to accompany the quality of life questionnaires.

Each information sheet is provided in a standard 11-point format and also a large-print format. Please ensure your patient receives the appropriate format.

We are conscious of the need to provide concise, readable information for the *FOCUS2* trial population whilst complying with COREC guidelines. The following notes refer to COREC "Guidelines for Researchers – Patient Information Sheet":

- For clarity, the COREC sections 6-10 have been reorganised in the paragraphs "How is the research done?" through to "How is my condition monitored?"
- Standard statements about pregnancy, contraception and breast-feeding (COREC section 11) are not included, since *FOCUS2* is unlikely to include any women of childbearing potential. In the event of such a patient being entered into *FOCUS2*, it is the responsibility of the clinician to give this advice, as for any standard chemotherapy schedule.
- COREC section 13 has been incorporated with section 11 in our paragraph "What are the potential disadvantages and risks of taking part?"
- COREC section 17 has been omitted; this information is contained in "What are the possible benefits of taking part?" and "Confidentiality"

Delete this line, then print on Hospital headed paper

General Information Sheet

FOCUS2: Drug treatment for bowel cancer: making the best choices when a milder treatment is needed

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

You have been invited to take part in a research study called "FOCUS2". Before you decide whether to accept, we would like to explain why the research is being done and what it will 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 time to decide whether or not you wish to take part.

What is the purpose of the study?

If cancer cannot be removed by surgery, anti-cancer drugs ("chemotherapy") are sometimes helpful. Chemotherapy does not completely cure bowel cancer, but it can shrink or control it for a period, so on average patients who receive it live longer, and with fewer symptoms. But chemotherapy today is far from perfect: it does not help everyone, and it can produce unwanted effects as well as benefits. So we are always seeking new treatments to help more patients, to control the cancer for longer, or to cause fewer side-effects.

New cancer treatments are usually tested first in the youngest or fittest patients. After those initial trials, the new treatment is often found to be useful for patients of all ages, or for people whose illness has made them less fit. However, in that circumstance doctors usually prescribe a lower dose of drugs, to reduce the risk of unwanted effects.

So the *FOCUS2* trial is especially designed for patients when, for one reason or another, their specialist feels that full-dose chemotherapy would not be advisable. It uses some of the most promising new chemotherapy treatments developed in the past decade, but given at a slightly reduced dose, with the aim of avoiding side-effects.

FOCUS2 will help us to answer two questions. It will let us compare two ways of giving chemotherapy: one in tablet form, the other directly into a vein using a portable pump. Also, it will show whether it is helpful to have an extra chemotherapy drug added to treatment from the start, or whether it is better to keep that extra drug in reserve to use at a later date.

Why have I been chosen?

Nearly 500 patients will be taking part in *FOCUS2* in the UK. Your specialist will have invited you to consider it if you have a form of bowel cancer that is not amenable to an operation, and if he/she feels there is a good chance that you could benefit from chemotherapy treatment. *FOCUS2* involves relatively gentle treatments, so this study is recommended if your specialist feels that maximum-dose chemotherapy would not be in your best interests.

Do I have to take part?

No, *FOCUS2* is entirely voluntary. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form, but you are still free to withdraw at any time and without giving a reason. If you decide not to take part, or if you take part then decide to withdraw later, this will not affect the standard of care you receive.

How is the research done?

An important part of this research is to carefully measure how fit you are before starting. To help do this, we would like to ask you a series of questions about your health and activities. We will also ask you some standard memory-test questions, and will time your walking over a short distance. This "baseline" assessment will take about 40 minutes and is required before we start any treatment.

After that, the best way of weighing up the advantages and disadvantages of the different treatments is in a randomised trial. 'Randomised' means that a computer will allocate you, purely by chance, to receive one of the four treatments. Neither your doctor nor you yourself will choose which treatment you receive. In this way, a fair comparison can be made, and at the end of the trial we will know for sure if there are any true differences between the effectiveness or side-effects of the treatments.

During your treatment you will have periodic scans and other checks to monitor your progress. We will also want to ask about changes in your general health and activities, so after 12 weeks of treatment we will perform a shorter version of the baseline assessment, lasting about 20 minutes, and then at three monthly intervals a five-minute questionnaire will be requested.

What is the standard treatment?

The National Institute for Clinical Excellence (NICE) has looked at the different treatments available for bowel cancer, and recommended some standard options for the initial treatment of bowel cancer. In *FOCUS2*, two of the four treatments being tested are standard treatments as recommended by NICE:

- **Cap** is a tablet treatment. It involves taking some tablets (trade name Xeloda) twice per day for two weeks, followed by one week off. After that you come back to the hospital for a check-up, then repeat the same cycle.
- **MdG** treatment is given intravenously (into the bloodstream). A thin plastic tube is fitted into a vein in your arm or chest, and stays in place for around 3 months. The treatment is given through this tube using a drip for two hours in the day-unit,

followed by a small portable pump (about the size of a can of drink), which you take home. A nurse disconnects the pump 48 hours later, usually at your home. This treatment is repeated once each fortnight.

What are the new treatments?

Half the patients who take part in *FOCUS2* start using one of the standard treatments (either Cap or MdG), but the other half receive a new treatment, which consists of a standard treatment plus another anti-cancer drug called **Ox** (short for oxaliplatin). We call these new treatments OxCap and OxMdG.

- **OxCap** involves a "drip" on the first day of treatment. For this, a thin plastic needle is placed into a vein on your hand or arm; the drip takes about two hours. Then you have some tablets to take twice a day for 2 weeks followed by one week off. After that you come back to the hospital for a check-up, then repeat the same cycle.
- **OxMdG** takes the same form as MdG. A thin plastic tube is fitted into a vein in your arm or chest and stays in place for around 3 months. The treatment is given through this tube using a drip for two hours, followed by a small portable pump (about the size of a can of drink), which you take home. It is disconnected 2 days later. This treatment is repeated once each fortnight.

How long does treatment go on?

The initial treatment period is 12 weeks. Half-way through that time you will be seen by the doctor in the clinic and, depending on any side-effects you have had, the dose of chemotherapy may be increased or reduced. At the end of the 12 weeks you will have a scan and will see the doctor again to assess how things have gone.

If the initial 12 weeks of treatment has controlled or shrunk the cancer and not caused severe side effects, it can be helpful to have more of the same treatment in the future, usually after a break. Your doctor will discuss this with you. Some patients have several courses of 12 weeks, with breaks in between.

The aim of treatment is to control your cancer and help you feel well for as long as possible. If at any stage you would be better helped by an alternative treatment (eg surgery or radiotherapy), your doctor can offer it.

What if the treatment doesn't help?

Unfortunately, not everybody benefits from chemotherapy and, even at its best, chemotherapy does not control bowel cancer indefinitely. If your cancer starts to grow despite the chemotherapy, your doctor will discuss further treatment options.

Sometimes it is better not to have further chemotherapy, but sometimes it is worthwhile trying a different sort (we call this "second-line" treatment). In *FOCUS2*, if you have started with one of the standard treatments (Cap or MdG), it may be possible to use the corresponding "Ox" treatment (OxCap or OxMdG) as second-line treatment. Another option, which may be considered after any of the *FOCUS2* treatments, is to receive a different drug called irinotecan. Your specialist will advise you on these options at the time.

Unwanted effects of treatment

As well as its benefits, chemotherapy can produce unwanted effects. Some patients get no side effects, but it is helpful to be forewarned of some of the things that **could possibly** happen:

- **Cap:** some patients find that their bowel movements become looser, and this may develop into diarrhoea. Cap may also sometimes cause nausea or vomiting (feeling or being sick), tiredness, and soreness of the mouth or altered taste. It can affect the skin, particularly on the hands and feet, which can become tingly, sore, red or flaky.
- **MdG**: MdG can cause mild nausea, diarrhoea and some tiredness for a few days after each treatment. MdG may also produce some soreness of the hands, feet or mouth. If you are on MdG you need a "line" – that is, a thin tube which stays in one of the veins in your arm or chest. Usually these lines cause no problems, but occasionally one can trigger an infection or blockage.
- **OxCap:** this is similar to Cap, and can produce the same side-effects. However, the extra drug (Ox) can give some additional side-effects. Some patients experience pain in the arm while the Ox drip is running, although if you are affected this is usually helped by a heat-pad. Ox often causes pins and needles or numbness, mainly in the hands and feet and usually caused by exposure to cold, for a few days after each treatment; occasionally this can become more persistent.
- **OxMdG:** this is similar to MdG and can produce the same side-effects. However, the extra drug (Ox) often causes pins and needles or numbness, mainly in the hands and feet and usually caused by exposure to cold, for a few days after each treatment; occasionally this can become more persistent.
- **Any of the chemotherapy treatments** 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.

Also, any of the treatments may cause temporary thinning of your hair (although this is usually mild enough to pass unnoticed by other people).

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.

Separate, more detailed information about each of the treatments is available on request

As with any cancer treatment, your doctors and nurses aim to ensure that any risks are kept to a minimum,. However, this research trial does not have special compensation arrangements. If you were to be 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 are available to you.

How is my condition monitored?

Your progress will be monitored carefully. Each time you come to the hospital for treatment (every 2 or 3 weeks), you will be asked about any side effects you have experienced and will have a blood test. Please tell us about any problems, as we can often help. We are interested in how you are feeling emotionally as well as physically, and you will be asked to complete a confidential 'Quality of Life' questionnaire at regular intervals.

About 12 weeks after starting treatment you will have a scan and any other tests necessary to determine what has happened to the cancer. This will help your specialist and you to decide on further treatment. Further scans may be necessary at intervals after that.

What are the possible disadvantages and risks of taking part?

We anticipate that all the treatments used in *FOCUS2* will prove at least as good as the best standard treatment available to patients not participating in trials, however we cannot be 100% certain that is the case. Similarly, we anticipate but cannot guarantee that the risks and side-effects of the *FOCUS2* treatments will be no greater than standard therapy.

An independent committee reviews the results of the trial on an ongoing basis so that if any of the treatments turns out to be substantially worse than the others that would be detected as soon as possible and the trial stopped. This committee also reviews information from other relevant trials around the world emerging during the course of *FOCUS2*.

What are the possible benefits of taking part?

We hope that participation in *FOCUS2* will help you by providing the best available treatment for your cancer. We also hope that the information gained from the trial will be helpful in guiding doctors in the treatment of patients in the future with a similar condition to yours.

Will my taking part be kept confidential?

If you decide to participate in *FOCUS2*, information about you will be passed to the Medical Research Council Clinical Trials Unit. Information leaving the hospital will have your name and address removed so that you cannot be recognised from it. 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. In the event that you lose touch with your hospital doctor, we will register your name with the Office of National Statistics (ONS). This is so we can check your health status after the trial has closed. When the trial is complete the results will be published in a medical journal, but no individual patients will be identified.

Additional research

If you have had surgery, specimens from your cancer will have been stored in the hospital pathology laboratory. If you take part in the *FOCUS2* trial, we would like to request your permission to retrieve some of that stored material in the future, for bowel cancer research. This research is based in UK Universities but may involve collaboration with commercial companies or other institutions. It 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. We would also like your permission to take a blood sample of 10 mls (about two teaspoons-full) which will be used to help this research. 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. These studies will not affect your treatment in any way, and you are free to withhold this permission without affecting your participation in *FOCUS2* or your relationship with your doctor.

Who has organised, reviewed and funded the research?

This research is organised by the National Cancer Research Institute, funded jointly by Cancer Research UK and the NHS, and is being run together with the UK Medical Research

Council Clinical Trials Unit. The research has been reviewed by those organisations, and also by an independent NHS Research Ethics Committee.

Further information

There is an information sheet with some further details about each of the types of chemotherapy used in this trial. You will be given the appropriate one at the time of starting treatment, but if you would like to see all of them at this point please ask.

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 CancerBACUP, an independent patient advisory group (freephone : 0800 800 1234; address: 3 Bath Place, Rivington Street, London, EC2A 3DR; web site www.cancerbacup.org).

Your contact telephone numbers:

……

Delete this line, then print on Hospital headed paper

FOCUS2: Drug treatment for bowel cancer: making the best choices when a milder treatment is needed

MdG Information Sheet

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

This sheet gives some information about the chemotherapy you will be receiving. 'MdG' is short for 'Modified de Gramont'. It is named after a Professor de Gramont, who devised a method of giving chemotherapy in this way. We have modified his method - hence the name.

How is the treatment given?

MdG chemotherapy is given each fortnight. The treatment starts with a two hour drip, into a vein, of a vitamin called folinic acid. This is followed by an injection of the chemotherapy drug, fluorouracil. The injection, also into the vein, takes about five minutes.

After that, you receive more fluorouracil, this time given very slowly into the vein, over the next 46 hours. There are several different methods of doing this and your doctor or nurse will discuss with you the way that suits you best. It is possible that you will need to stay in hospital, but more usually it is done at home, using a small portable pump.

Depending upon which method is used, you may 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 can stay in for the duration of your treatment. You may also be asked to take a tablet called warfarin, to reduce the risk of a blood clot forming on the tube in your vein

Will MdG chemotherapy have unwanted effects?

Any chemotherapy can cause side effects. For most patients the side effects of MdG are mild, and some have no side effects at all. However, you may find it helpful to be forewarned about some of the side effects that **could** occur.

- MdG 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 the MdG 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.
- In the longer term, usually after more than one cycle of treatment, your hands and feet may become rather tingly or sore, with redness or dryness of the skin.

Other complications

If you have had a tube fitted for receiving chemotherapy at home, there is a possibility of a problem related to the tube. If you notice any problems such as redness, pain or discharge around the tube, or swelling of one arm, please speak to the doctor or nurse as soon as possible.

Rare side-effects

Very rarely, MdG chemotherapy can cause heart palpitations, chest pain (angina), or poor co-ordination. It is most unlikely that you will be affected, but if you suspect you have one of these problems, please discuss it with your oncology doctor or nurse.

And finally:

If you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering attacks or severe diarrhoea, please telephone immediately for advice from your hospital team. You may need to be admitted to the Oncology Unit

Your contact numbers are:

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Delete this line, then print on Hospital headed paper

FOCUS2: Drug treatment for bowel cancer: making the best choices when a milder treatment is needed

OxMdG Information Sheet

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

This sheet gives some information about the chemotherapy you will be receiving. 'OxMdG' is short for 'Oxaliplatin plus Modified de Gramont'. Oxaliplatin (Ox for short) is a chemotherapy injection treatment. Modified de Gramont is a different chemotherapy treatment that was devised by a Professor de Gramont. We have modified his method - hence the name.

How is the treatment given?

OxMdG chemotherapy is given each fortnight. The treatment starts with a two hour drip, into a vein, of the Ox chemotherapy, plus a vitamin called folinic acid. This is followed by an injection of another chemotherapy drug, fluorouracil. The injection takes about five minutes.

After that, you receive more fluorouracil, this time given very slowly into the vein, over the next 46 hours. There are several different methods of doing this and your doctor or nurse will discuss with you the way that suits you best. It is possible that you will need to stay in hospital, but more usually it is done at home, using a small portable pump.

Depending upon which method is used, you may 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 can stay in for the duration of your treatment. You may also be asked to take a tablet called warfarin, to reduce the risk of a blood clot forming on the tube in your vein.

Will OxMdG chemotherapy have unwanted effects?

Any chemotherapy can cause side effects. For most patients the side effects of OxMdG are mild, and some have no side effects at all. However, you may find it helpful to be forewarned about some of the side effects that **could** occur.

- For a few hours or days after starting treatment, you may feel pins & 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.
- After several treatments, the pins & needles sensation might become more troublesome, or develop into persistent numbness of the fingers and toes. Please tell the doctor and nurse if this happens as it may be necessary to adjust your treatment
- Just occasionally, people can become allergic to Ox, though usually only after several treatments. If, while the Ox drip is running, you develop palpitations, an itchy rash, wheezing or a swollen tongue, please tell the nurses immediately.
- OxMdG 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.
- In the longer term (after several cycles of treatment), your hands and feet may become rather tingly or sore, with redness or dryness of the skin.

Other complications

If you have had a tube fitted for receiving chemotherapy at home, there is a possibility of a problem related to the tube. If you notice any problems such as redness, pain or discharge around the tube, or swelling of one arm, please speak to the doctor or nurse as soon as possible.

Rare side-effects

Very rarely, OxMdG chemotherapy can cause heart palpitations, chest pain (angina), or poor co-ordination. It is most unlikely that you will be affected, but if you suspect you have one of these problems, please discuss it with your oncology doctor or nurse.

And finally:

If you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering attacks or severe diarrhoea, please telephone immediately for advice from your hospital team. You may need to be admitted to the Oncology Unit

Your contact numbers are:

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Delete this line, then print on Hospital headed paper

***FOCUS2*: Drug treatment for bowel cancer: making the best choices when a milder treatment is needed**

Cap Information Sheet

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

This sheet gives some information about the chemotherapy you will be receiving. 'Cap' is short for 'Capecitabine', which is a tablet-form chemotherapy drug. Cap is also known by its trade name, "Xeloda".

How is the treatment taken?

Cap is taken as a course of tablets, each morning and evening for two weeks, followed by a one-week rest period with no Cap tablets. We call the whole three-week period (two weeks on and one week off) one "**cycle**" of Cap chemotherapy.

The dose of tablets is prescribed by your specialist, based on your body size and other factors. Different patients need different doses. The tablets come in two sizes, large (500 mg) and small (150 mg). The hospital pharmacist will work out how many large and small tablets you should take to give you the right dose, and will dispense one full cycle at a time (i.e. 14 days = 28 doses). If you take your first dose of Cap on the evening after your hospital appointment, the last dose of the cycle will be due on the morning 2 weeks later.

Take your dose of Cap tablets twice a day, approximately twelve hours apart (for example 8 a.m. and 8 p.m). Try to stick to the same time each day, give-or-take two hours. It is best not to take Cap on an empty stomach, so have something to eat during the half-hour before your tablets are due. Swallow the tablets with water; they may be crushed if you find them too large to swallow whole.

How will I remember?

Everybody finds it difficult to remember to take tablets sometimes. When you start each cycle of Cap you will be given a diary sheet with a space for each dose you are due. Please keep the sheet with your tablets, and make a note of the time you take each dose.

If you forget a dose but remember it within the next 6 hours, take it then and mark the time on the sheet. If you forget a dose completely, just write "forgot" in the box for that dose. Do not try to squeeze in extra doses the next day, and do not add on any missed doses at the end of the course, during your week's rest from treatment.

What about my other medications?

Most other medications (though not all) can be taken safely alongside Cap tablets. If you are on regular medications, please make sure your specialist knows about them before you start your Cap treatment so that they can be checked.

After starting your Cap treatment, if any new medication is required it is important that the doctor prescribing it knows you are on Cap.

It is particularly important to tell your specialist about any of the following medications: warfarin, allopurinol, phenytoin, sorivudine, brivudine.

Are there any other precautions?

Please keep your Cap tablets well away from children, and do not let them become mixed up with anybody else's tablets. If there are any left over at the end of a cycle (for example if you forgot a dose, or missed some doses because of illness) please bring these along to your next hospital appointment and return them to the nurse or pharmacist along with your diary sheet – do not throw them away or store them at home.

Will Cap chemotherapy have unwanted effects?

Any chemotherapy can cause side effects. For most patients the side effects of Cap are mild, and some have no side effects at all. However, you may find it helpful to be forewarned about some of the side effects that **could** occur.

- Cap 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 stop taking your Cap tablets** and telephone the hospital for advice.
- Some patients find they feel a little sick, 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 stop taking your Cap tablets** and 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, **stop taking your Cap tablets** and telephone the hospital for advice.
- Some people feel more tired than usual during Cap treatment. There is no easy answer to this, but you may find it helps to set aside a rest period in the middle of each day.
- In the longer term, usually after more than one cycle of treatment, your hands and feet may become rather tingly or sore, with redness or dryness of the skin. If you get pain, swelling, blistering or peeling of the skin, **please stop taking your Cap tablets** and telephone the hospital for advice.

If you have to stop taking your Cap tablets for any of these reasons, please make a note on the diary sheet. Do not add on the missed doses at the end of the course.

It is important to stop taking the Cap tablets if the side effects become troublesome. Some patients worry that this might reduce the effectiveness of the treatment, but research has shown this is not the case.

Rare side-effects

Very rarely, Cap chemotherapy can cause heart palpitations, chest pain (angina), or poor co-ordination. It is most unlikely that you will be affected, but if you suspect you have one of these problems, please discuss it with your oncology doctor or nurse.

And finally:

If you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering attacks or severe diarrhoea, please telephone immediately for advice from your hospital team. You may need to be admitted to the Oncology Unit

Your contact numbers are:

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Delete this line, then print on Hospital headed paper

FOCUS2: Drug treatment for bowel cancer: making the best choices when a milder treatment is needed

OxCap Information Sheet

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

This sheet gives some information about the chemotherapy you will be receiving. 'OxCap' is short for 'Oxaliplatin plus Capecitabine'; these are the names of the two chemotherapy drugs you will be receiving. Oxaliplatin is an injection, and is also known by the trade name Eloxatin. Capecitabine is a tablet and is also known by the trade name Xeloda.

How is the treatment given?

OxCap treatment starts with a drip treatment, done at the hospital. For this, a nurse or doctor will fit a small plastic needle called a "cannula" into one of the veins in your hand or arm. Then a drip containing the Ox treatment will be connected to the cannula. It takes about 2 hours for this to run in, then the cannula is removed and you will be able to go home.

At home, you will have a course of Cap tablets to take each morning and evening for two weeks, followed by a one-week rest period with no Cap tablets. We call the whole three-week period (the drip treatment, plus two weeks of tablets and one week off) one "**cycle**" of OxCap chemotherapy.

The dose of tablets is prescribed by your specialist, based on your body size and other factors. Different patients need different doses. The tablets come in two sizes, large (500 mg) and small (150 mg). The hospital pharmacist will work out how many large and small tablets you should take to give you the right dose, and will dispense one full cycle at a time (i.e. 14 days = 28 doses). You should take your first dose of Cap on the evening after your Ox drip treatment at the hospital; the last dose of the cycle will be due on the morning 2 weeks later.

Take your dose of Cap tablets twice a day, approximately twelve hours apart (for example 8 a.m. and 8 p.m). Try to stick to the same time each day, give-or-take two hours. It is best not to take Cap on an empty stomach, so have something to eat during the half-hour before your tablets are due. Swallow the tablets with water; they may be crushed if you find them too large to swallow whole.

How will I remember the tablets?

Everybody finds it difficult to remember to take tablets sometmes! When you start each cycle of OxCap you will be given a diary sheet with a space for each dose you are due. Please keep the sheet with your tablets, and make a note of the time you take each dose.

If you forget a dose but remember it within the next 6 hours, take it then and mark the time on the sheet. If you forget a dose completely, just write "forgot" in the box for that dose. Do not try to squeeze in extra doses the next day, and do not add on any missed doses at the end of the course, during your week's rest from treatment.

What about my other medications?

Most other medications (though not all) can be taken safely alongside OxCap treatment. If you are on regular medications, please make sure your specialist knows about them before you start your treatment so that they can be checked.

After starting your OxCap treatment, if any new medication is required it is important that the doctor prescribing it knows you are on OxCap.

It is particularly important to tell your specialist about any of the following medications: warfarin, allopurinol, phenytoin, sorivudine, brivudine.

Are there any other precautions?

Please keep your Cap tablets well away from children, and do not let them become mixed up with anybody else's tablets. If there are any left over at the end of a cycle (for example if you forgot a dose, or missed some doses because of illness) please bring these along to your next hospital appointment and return them to the nurse or pharmacist along with your diary sheet – do not throw them away or store them at home.

Will OxCap chemotherapy have unwanted effects?

Any chemotherapy can cause side effects. For most patients the side effects of OxCap are mild, and some have no side effects at all. However, you may find it helpful to be forewarned about some of the side effects that **could** occur.

- Some people fell discomfort or pain up their arm during the 2 hours that the Ox drip is running. If you are affected please tell the nurse on the chemotherapy unit straight away: this symptom can usually be relieved by placing a warm pad over the arm.
- For a few hours or days after the Ox treatment, you may feel pins & 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.
- After several treatments, the pins & needles sensation might become more troublesome, or develop into persistent numbness of the fingers and toes. Please tell the doctor and nurse if this happens as it may be necessary to adjust your treatment
- Just occasionally, people can become allergic to Ox, though usually only after several treatments. If, while the Ox drip is running, you develop palpitations, an itchy rash, wheezing or a swollen tongue, please tell the nurses immediately.
- OxCap 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 stop taking your Cap tablets** and telephone the hospital for advice.
- Some patients feel sick, particularly during the first few days. 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 stop taking your Cap tablets** and 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, **stop taking your Cap tablets** and telephone the hospital for advice.
- Some people feel more tired than usual during OxCap treatment. There is no easy answer to this, but you may find it helps to set aside a rest period in the middle of each day.
- In the longer term, usually after more than one cycle of treatment, your hands and feet may become rather tingly or sore, with redness or dryness of the skin. If you get pain, swelling or blistering/peeling of the skin, **please stop taking your Cap tablets** and telephone the hospital for advice

If you have to stop taking your Cap tablets for any of these reasons, please make a note on the diary sheet. Do not add on the missed doses at the end of the course.

It is important to stop taking the Cap tablets if the side effects become troublesome. Some patients worry that this might reduce the effectiveness of the treatment, but research has shown this is not the case.

Rare side-effects

Very rarely, OxCap chemotherapy can cause heart palpitations, chest pain (angina), or poor co-ordination. It is most unlikely that you will be affected, but if you suspect you have one of these problems, please discuss it with your oncology doctor or nurse.

And finally:

If you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering attacks or severe diarrhoea, please telephone immediately for advice from your hospital team. You may need to be admitted to the Oncology Unit

Your contact numbers are:

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Delete this line, then print on Hospital headed paper

***FOCUS2*: Drug treatment for bowel cancer: making the best choices when a milder treatment is needed**

Patient Diary Card

(for patients on Cap or OxCap treatment)

The dose and date information on this sheet must be completed by the pharmacist or research nurse before handing to the patient

Patient initials_____ Trial number_____

Cycle number: ☐ First day of cycle: / / Capecitabine dose: mg

Dear Patient,

Please use the chart on the other side of this sheet of paper to keep a record of your capecitabine (Xeloda) tablets as you take them. The dose which you have been prescribed for this cycle should be taken every 12 hours for two weeks, followed by one week with no capecitabine.

Each dose of is made up of ☐ tablet(s) of 500mg, plus ☐ tablet(s) of 150 mg.

Have something to eat during the 30 minutes before each dose is due, then take it with water. Try to remember to take the tablets regularly every 12 hours, but if you are late just take them as soon as you remember and record the time on the sheet. If you forget a dose completely, or if you miss a dose because you are unwell, record this on the sheet and **do not try to make it up at the end.**

The possible side-effects of your chemotherapy, how to deal with them, and who to phone if problems arise, are detailed in an information sheet which you will have been given at the start of this course of chemotherapy. This sheet is called: "**Cap Information Sheet**" or "**OxCap Information Sheet**". If you have not received it, or would like another copy, please ask the nurse for one today.

Remember, if you develop diarrhoea, a high temperature, or any other severe side-effect it may be necessary to stop taking the capecitabine tablets. Please phone your 24-hour telephone advice number if this happens.

	Date (Research nurse or pharmacist to complete this column)	**Morning dose:** time taken	**Evening dose:** time taken
d1		**No morning dose this day**	
d2			
d3			
d4			
d5			
d6			
d7			
d8			
d9			
d10			
d11			
d12			
d13			
d14			
d15			**No evening dose this day**
d16		**No tablets due on these days**	
d17			
d18			
d19			
d20			
d21			
d22			

Your notes and comments:

Your next hospital appointment is due on:……Time……..……

Please bring this sheet with you on that day, along with any unused capecitabine tablets.

affix patient ID sticker

(Reprint this form on headed paper)

Patient Identification Number for this trial:……

CONSENT FORM

Date: August 2003 Version 1.1

Title of Project:

***FOCUS2*: Drug treatment for bowel cancer: making the best choices when a milder treatment is needed**

Name of Researcher:……

Please initial boxes:

1. I confirm that I have read and understand the information sheet (dated .....version .....) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Medical Research Council where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I give permission for my name to be registered with the Office of National Statistics (ONS) should I lose contact with my hospital doctor. I give permission for information about my health status to be obtained from the ONS by the Medical Research Council if necessary. ☐

5. I give permission for a sample of my blood, and for any stored pathological specimens, to be used for future bowel cancer research. (If you do not wish to give this permission, do not initial the box – you can still participate in the trial). ☐

I agree to take part in the above study

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

(1 copy for patient; 1 for researcher; 1 to be kept with hospital notes)

Appendix XII - GP letter

. Delete this line and print on hospital headed notepaper

Affix patient's identification label here

Date:……

Dear Doctor

The above patient is participating in *FOCUS2*, a randomised clinical trial of palliative chemotherapy for colorectal cancer. *FOCUS2* is a National Cancer Research Institute (NCRI) trial, jointly funded by the MRC and Cancer Research UK, and is being run through the MRC Clinical Trials Unit. It uses chemotherapy at 80% of full standard dose, and is particularly intended for patients who would not normally be offered full-dose combination chemotherapy, for example because of advanced age or borderline performance status.

Patients entering the trial are randomised between four treatment plans. They receive initial treatment with either capecitabine alone ("Cap"), capecitabine plus oxaliplatin ("OxCap"), 5FU and folinic acid ("MdG"), or oxaliplatin, 5FU and folinic acid ("OxMdG"). Patients who have been randomised to one of the two arms which do not include oxaliplatin may receive this drug at a later date, if this is considered in their best interests.

Enclosed with this letter is a copy of the information which has been supplied to the patient about this trial. This includes a general information sheet with details of the randomisation, etc., and a separate sheet giving some details of the specific treatment to which your patient has been randomised.

As with any chemotherapy schedule, there is a possibility of myelosuppression, and therefore of neutropenic sepsis. Should your patient develop a fever and/or other signs of sepsis at any point during their treatment, they have been advised to contact the hospital urgently as hospital review, full blood count and possible admission may be indicated.

The preferred hospital for admission for management of chemotherapy complications is

……..., where the on-call admitting officer may be contacted on

the following telephone number……

For non-urgent queries concerning the patient's treatment, would you please contact the consultant oncologist or registrar, as detailed on the accompanying correspondence.

Yours faithfully,

Appendix XIII Baseline Comprehensive Health Assessment

FOCUS2 Trial

Baseline Comprehensive Health Assessment (CHA)

Notes for Research Nurse/Data Manager:

This baseline health assessment is an indispensable part of the *FOCUS2* trial. It must be completed **after** obtaining the patient's consent, but **before** telephoning the MRC CTU to register and randomise the patient. The CHA is in two parts, (a) a nurse-administered assessment of physical parameters, mental state and medical history, and (b) a patient-completed questionnaire dealing with various aspects of quality of life. **Randomisation will not be performed until both parts of the CHA have been completed.**

CHA Nurse-Administered Section:

For this section of the CHA, you need a quiet, private environment where the patient can answer questions without feeling pressurised or "on trial". Ensure the patient is comfortable and not hungry, thirsty or in need of the toilet or analgesia. Hearing aids, if used, should be working. The patient may have a carer present, but if so ask them not to answer questions on the patient's behalf. If an interpreter is required, use a professional interpreter in preference to a relative.

You will need: a blank sheet of paper; scales and a measure for height and weight; a tape measure for arm circumference. This assessment includes a timed 20-metre walk. For this, a straight 20-metre distance should be marked out, for example in the clinic corridor, and you will need a watch or stopwatch.

Patient initials	**Date form completed**	**Trial N^{o}. (complete after registering)**

Section P – Physical tests

P.1) **height in cm:**	P.2) **weight in kg:**	P.3) **right arm circumference in cm** (midway between elbow and shoulder):

P.4) **approximate weight change in past 3 months:**

Ask the patient if they are aware of having lost or gained weight:

☐ don't know

☐ weight loss. If so, how much? Approx ……..kg (½ stone = 3 kg)

☐ weight gain If so, how much? Approx ……..kg (½ stone = 3 kg)

P.5) **timed 20-metre walk.** Use an unobstructed straight 20-metre distance (this should be marked off, for example, in the clinic corridor). Ask the patient to walk as fast as they can without running, starting at the start line and continuing for a few steps beyond the finish line. If they normally use a walking stick or frame, this should be used. Gentle support (e.g. holding elbow) may be given.

Did the patient walk 20 metres? Yes ☐ No ☐

If yes, time taken in seconds: ……..seconds

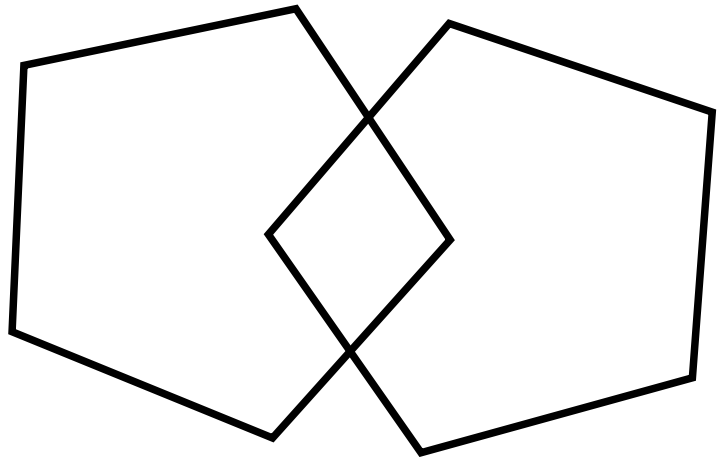
If no, give reason: ☐ declined test
☐ unable to walk

Section M (Mini-Mental State Examination)

Introduce this section with something along the lines of: ***"Please don't be offended, but I'd like to ask you a few memory test questions now."*** Then ask the patient the following questions (exact words in **bold**) clearly and score the patient's answers.

M.1) **"What day of the week is it?"** (must be exact to score as correct)	☐ correct	☐ incorrect
M.2) **"What is the date today?"** (must be exact to score as correct)	☐ correct	☐ incorrect
M.3) **"What is the month?"** (must be exact to score as correct)	☐ correct	☐ incorrect
M.4) **"What is the season?"** ("spring" acceptable for Mar – Jun; "summer" for Jun – Sep; "autumn" for Sep – Dec, and "winter" for Dec – Mar inclusive)	☐ correct	☐ incorrect
M.5) **"What is the year?"** (must be exact to score as correct)	☐ correct	☐ incorrect
M.6) **"Where are we now?"** (must be correct but may need clarification)	☐ correct	☐ incorrect
M.7) **"What floor are we on?"** ("upstairs"/"downstairs" is acceptable)	☐ correct	☐ incorrect
M.8) **"In which town are we?"** (accept only the correct answer)	☐ correct	☐ incorrect
M.9) **"In which county [or district] are we?"** (accept any correct answer)	☐ correct	☐ incorrect
M.10) **"In which country are we?"** (accept any correct answer)	☐ correct	☐ incorrect
M.11-13) **"I am going to name three objects, After I have finished saying all three, please repeat them. Remember what they are because I am going to ask you to name them again in a few minutes: Apple…. Table…. Penny"** (may repeat up to 5 times)	Apple: ☐ Table: ☐ Penny: ☐ correct	☐ ☐ ☐ incorrect
M.14) **"Now please take 7 away from 100"** (only "93" scores correct)	☐ correct	☐ incorrect
M.15) **"Now take 7 away from the number you get"** (score correct if difference is 7, even if previous answer was wrong)	☐ correct	☐ incorrect
M.16-18) **"Now keep going until I ask you to stop"** (score each correct if difference is 7, even if previous answer was wrong)	first: ☐ second: ☐ third: ☐ correct	☐ ☐ ☐ incorrect
M.19-21) **"What were the three words I asked you to repeat a little while ago?"** (there should be no prompting)	Apple: ☐ Table: ☐ Penny: ☐ correct	☐ ☐ ☐ incorrect

M.22) **"What is this?"** (show a pencil)	☐ correct ☐ incorrect
M.23) **"What is this?"** (show a watch)	☐ correct ☐ incorrect
M.24) **"I am going to say something and I would like you to repeat it after me: NO IFS, ANDS OR BUTS"** (read this only once)	☐ correct ☐ incorrect
M.25-27) **"I am going to ask you to carry out some actions. Please listen to the whole command before trying: Take this piece of paper, fold it in half and put it on the floor"** (offer a sheet of paper)	take paper: ☐ ☐ fold in half: ☐ ☐ put on floor ☐ ☐ correct incorrect
M.28) **"Please do this"** (close your eyes)	☐ correct ☐ incorrect
M.29) **"Please write a sentence of your choice on this piece of paper"** (grammar and spelling not important; accept any sentence with a subject (real or implied) and verb. "Help" or "Go away" are acceptable)	☐ correct ☐ incorrect
M.30) "**Copy this drawing on a piece of paper"** (show the patient the following drawing. To score correct, they must draw two intersecting pentagons, and the intersection should be a diamond shape)	☐ correct ☐ incorrect



Section C (Charlson Co-Morbidity Index)

This section is completed from the medical notes, although it is helpful to do so whilst the patient is still present so that you can clarify any missing data (using lay terms). Record whether there is a past or current history of any of the following medical conditions (if in doubt, consult the doctor responsible):

C.1) Myocardial infarct *History of medically documented myocardial infarction*	☐ present ☐ absent
C.2) Congestive heart failure Symptomatic CHF with response to specific treatment	☐ present ☐ absent
C.3) Peripheral vascular disease *Intermittent claudication, peripheral arterial bypass for insufficiency, gangrene, acute arterial insufficiency, untreated aneurysm (≥6cm)*	☐ present ☐ absent
C.4) Cerebrovascular disease (except hemiplegia) *History of TIA, or CVA with no or minor sequellae*	☐ present ☐ absent
C.5) Dementia *Chronic cognitive deficit*	☐ present ☐ absent
C.6) Chronic pulmonary disease *Symptomatic dyspnoe due to chronic respiratory conditions (including asthma)*	☐ present ☐ absent

C.7) Connective tissue disease *SLE, polymyositis, mixed CTD, polymyalgia rheumatica, moderate to severe RA.*	☐ present	☐ absent
C.8) Ulcer disease *Patients who have required treatment for PUD*	☐ present	☐ absent
C.9) Mild liver disease *Cirrhosis without PHT, chronic hepatitis*	☐ present	☐ absent
C.10) Diabetes (without complications) *Diabetes with medication*	☐ present	☐ absent
C.11) Diabetes with end organ damage *Retinopathy, neuropathy, nephropathy*	☐ present	☐ absent
C.12) Hemiplegia *Hemiplegia or paraplegia*	☐ present	☐ absent
C.13) Moderate or severe renal disease *Creatinine > 265 umol/l, dialysis, transplantation, uraemic syndrome*	☐ present	☐ absent
C.14) 2nd Solid tumour (non metastatic) *Initially treated in the last 5 years. Excl non-melanomatous skin ca, and in situ cervical ca.*	☐ present	☐ absent
C.15) Leukaemia *CML, CLL, AML, ALL, PV*	☐ present	☐ absent
C.16) Lymphoma, Multiple myeloma *Non Hodgkin's Lymphoma (NHL), Hodgkins, Waldenstrom, multiple myeloma*	☐ present	☐ absent
C.17) Moderate or severe liver disease *Cirrhosis with PHT =/- variceal bleeding*	☐ present	☐ absent
C.18) 2nd Metastatic solid tumour	☐ present	☐ absent
C.19) AIDS *AIDS and AIDS related complex*	☐ present	☐ absent

NB Now please go back and check that patient ID and date are completed at the top of this form, then ask the patient to complete the patient questionnaire section of the CHA.

CHA Patient Questionnaire Section:

This section of the CHA is a patient-completed questionnaire. Please ensure the patient has a relaxed, private environment such as a clinic room, **not a public waiting area**. Ensure they are comfortable and not hungry, thirsty or in need of the toilet or analgesia. The patient may have a carer present, but if so ask them not to answer questions on the patient's behalf. If an interpreter is required, use a professional interpreter rather than a relative, if possible.

Some patients will require help reading or interpreting the questions, or ticking the response boxes. The research nurse or data manager should offer to sit with the patient and help if they wish, but if so should not change the patient's initial "gut reaction" responses. **When the patient has finished, the research nurse or data manager should look through the questionnaire before the patient leaves, check that there are no missing or unclear answers and check that the patient ID and date are complete.**

Dear Patient,

As part of our research into finding the best chemotherapy for your condition, we'd like to ask you some questions about your activities, symptoms and feelings. Would you please go through this questionnaire and, for each question, tick the answer that fits most closely, even if it is not exact. If there are questions you cannot answer, please ask the nurse for help (or, if you would prefer, the nurse can sit with you and read out all the questions).

Thank you!

Your initials	/ / **Today's Date**	**Trial N°. (Nurse to complete)**

First, some questions about what activities you can manage currently:

A.1) Do you walk around outside?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.2) Do you climb stairs?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.3) Do you get in and out of the car?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.4) Do you walk over uneven ground?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.5) Do you cross roads?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.6) Do you travel on public transport?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.8) Do you manage to feed yourself?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.9) Do you manage to make yourself a hot drink?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.10) Do you take hot drinks from one room to another?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.11) Do you do the washing up?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.12) Do you make yourself a hot snack?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.14) Do you manage your own money when you are out?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily

A.15) Do you wash small items of clothing?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.16) Do you do your own shopping?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.17) Do you do a full clothes wash?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.19) Do you read newspapers or books?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.20) Do you use the telephone?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.21) Do you write letters?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.22) Do you go out socially?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.23) Do you manage our own garden?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.24) Do you drive a car?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily

E.1) Over the past **6 weeks** how many times has your GP visited you?	☐ not at all	or: How many times?:……
E.2) Over the past **6 weeks** how many times have you visited your GP?	☐ not at all	or: How many times?:……
E.3) Over the past **6 weeks** how often have you been visited by a district nurse?	☐ not at all	or: How many times?:……
E.4) Over the past **6 weeks,** have you been visited by a MacMillan nurse?	☐ not at all	or: How many times?:……

E.5) Which best describes your mobility **today**?	☐ I have no problems walking about	☐ I have some problems walking about	☐ I am confined to bed
E.6) Which best describes your self-care **today**?	☐ I have no problems with self care	☐ I have some problems washing or dressing	☐ I am unable to wash or dress myself
E.7) Which best describes your activities **today**?	☐ I have no problems performing my usual activities	☐ I have some problems performing my usual activities	☐ I am unable to perform my usual activities
E.8) Do you have any pain **today**?	☐ I have no pain or discomfort	☐ I have some pain or discomfort	☐ I have extreme pain or discomfort
E.9) Which best describes your mood **today**?	☐ I am not anxious or depressed	☐ I am moderately anxious or depressed	☐ I am extremely anxious or depressed

Now some questions about your symptoms over the past week.

During the past week…

Q.8) …were you short of breath?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.9) …have you had pain?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.10) …did you need to rest?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.11) …have you had trouble sleeping?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

Q.12) …have you felt weak?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.13) …have you lacked appetite?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.14) …have you felt nauseated?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.15) …have you vomited?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.16) …have you been constipated?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.17) …have you had diarrhoea?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.18) …were you tired?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.31)…have you had a dry and/or sore mouth?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.32)…have you had problems eating or drinking because of a sore mouth?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.33)…have you had soreness or redness of your hands or feet?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.34) …have you had difficulty handling small objects (eg buttons or zips)?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.35) …have you lost any hair?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

Q.36) …if you have a colostomy, have you had trouble with it (soreness of skin, increased frequency, leakage)?	☐ not applicable	☐ not at all	☐ a little	☐ quite a bit	☐ very much

G.1) How was your **overall health** during the past week? *(put a circle round the score)*	**1** Very poor	**2**	**3**	**4**	**5**	**6**	**7** Excellent
G.2) And how was your **overall quality of life** during the past week?	**1** Very poor	**2**	**3**	**4**	**5**	**6**	**7** Excellent

Finally, please answer these questions about your feelings. For each statement please mark the box which best describes how you have been feeling over the past week:

H.1) "I feel tense or 'wound up'…"	☐ most of the time	☐ a lot of the time	☐ time-to-time, occasionally	☐ not at all
H.2) "I still enjoy the things I used to enjoy…"	☐ definitely as much	☐ not quite so much	☐ only a little	☐ hardly at all
H.3) "I get a sort of frightened feeling as if something awful is about to happen…"	☐ very definitely and quite badly	☐ yes, but not too badly	☐ a little but it doesn't worry me	☐ not at all
H.4) "I can laugh and see the funny side of things…"	☐ as much as I always could	☐ not quite so much now	☐ definitely not so much now	☐ not at all

H.5) "Worrying thoughts go through my mind…"	☐ a great deal of the time	☐ a lot of the time	☐ time to time but not too often	☐ only occasionally
H.6) "I feel cheerful…"	☐ not at all	☐ not often	☐ sometimes	☐ most of the time
H.7) "I can sit at ease and feel relaxed…"	☐ definitely	☐ usually	☐ not often	☐ not at all
H.8) "I feel as if I am slowed down…"	☐ nearly all the time	☐ very often	☐ sometimes	☐ not at all
H.9) "I get a sort of frightened feeling like 'butterflies' in the stomach…"	☐ not at all	☐ occasionally	☐ quite often	☐ very often
H.10) "I have lost interest in my appearance…"	☐ definitely	☐ I take less care than I should	☐ I may not take quite as much care	☐ I take just as much care as ever
H.11) "I feel restless as if I have to be on the move…"	☐ very much indeed	☐ quite a lot	☐ not very much	☐ not at all
H.12) "I look forward with enjoyment to things…"	☐ as much as I ever did	☐ rather less than I used to	☐ definitely less than I used to	☐ hardly at all
H.13) "I get sudden feelings of panic…"	☐ very often indeed	☐ quite often	☐ not very often	☐ not at all
H.14) "I can enjoy a good book or radio or TV programme…"	☐ often	☐ sometimes	☐ not often	☐ very seldom

Many thanks for helping us by filling in this questionnaire. Please now hand it to the research nurse. You may feel that you wish to discuss some of the issues which it has raised – please feel free to do so.

Appendix XIV Limited Health Assessment (LHA)

FOCUS2 Trial

Limited Health Assessment (LHA)

Notes for Research Nurse/Data Manager:

This health assessment, along with the baseline CHA, is an indispensable part of the *FOCUS2* trial. It is completed once after the first 12 weeks of chemotherapy (during week 12-14), and once again 6 months after trial entry. These forms will provide some of the most important data for the trial. Like the CHA, the LHA is in two sections, (a) a nurse-administered assessment of physical parameters, and (b) a patient-completed questionnaire dealing with various aspects of quality of life.

LHA Nurse-Administered Section:

You will need: scales and a measure for height and weight; a tape measure for arm circumference. This assessment includes a timed 20-metre walk. For this, a straight 20-metre distance should be marked out, for example in the clinic corridor, and you will need a watch or stopwatch.

Patient initials	**Date form completed**	**Trial N°.**

Section P – Physical tests

P.1) **height in cm:**	P.2) **weight in kg:**	P.3) **right arm circumference in cm** (midway between elbow and shoulder):

P.4) **approximate weight change in past 3 months:**

Ask the patient if they are aware of having lost or gained weight:

☐ don't know

☐ weight loss. If so, how much? Approx ……..kg (½ stone = 3 kg)

☐ weight gain If so, how much? Approx ……..kg (½ stone = 3 kg)

P.5) **timed 20-metre walk.** Use an unobstructed straight 20-metre distance (this should be marked off, for example, in the clinic corridor). Ask the patient to walk as fast as they can without running, starting at the start line and continuing for a few steps beyond the finish line. If they normally use a walking stick or frame, this should be used. Gentle support (e.g. holding elbow) may be given.

Did the patient walk 20 metres? Yes ☐ No ☐

If yes, time taken in seconds: ……..seconds

If no, give reason: ☐ declined test

☐ unable to walk

LHA Patient Questionnaire Section:

This section of the LHA is a patient-completed questionnaire. Please ensure the patient has a relaxed, private environment such as a clinic room, **not a public waiting area**. Ensure they are comfortable and not hungry, thirsty or in need of the toilet or analgesia. The patient may have a carer present, but if so ask them not to answer questions on the patient's behalf. If an interpreter is required, use a professional interpreter rather than a relative, if possible.

Some patients will require help reading or interpreting the questions, or ticking the response boxes. The research nurse or data manager should offer to sit with the patient and help if they wish, but if so should not change the patient's initial "gut reaction" responses. **When the patient has finished, the research nurse or data manager should look through the questionnaire before the patient leaves, check that there are no missing or unclear answers and check that the patient ID and date are complete.**

Dear Patient,

As part of our research into finding the best chemotherapy for your condition, we would like to ask you the same questions that we did at the start of your treatment, about your activities, symptoms and feelings. For each question, tick the answer which fits most closely, even if it is not exact. If there are questions you cannot answer, please ask the nurse for help (or, if you would prefer, the nurse can sit with you and read out all the questions).

Thank you!

Your initials	**Today's Date** / /	**Trial N^{o}. (Nurse to complete)**

First, some questions about what activities you can manage currently:

A.1) Do you walk around outside?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.2) Do you climb stairs?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.3) Do you get in and out of the car?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.4) Do you walk over uneven ground?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.5) Do you cross roads?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.6) Do you travel on public transport?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.8) Do you manage to feed yourself?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.9) Do you manage to make yourself a hot drink?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.10) Do you take hot drinks from one room to another?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.11) Do you do the washing up?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.12) Do you make yourself a hot snack?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily

A.14) Do you manage your own money when you are out?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.15) Do you wash small items of clothing?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.16) Do you do your own shopping?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.17) Do you do a full clothes wash?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.19) Do you read newspapers or books?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.20) Do you use the telephone?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.21) Do you write letters?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.22) Do you go out socially?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.23) Do you manage our own garden?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily
A.24) Do you drive a car?	☐ not at all	☐ with help	☐ alone with difficulty	☐ alone easily

E.1) Over the past **6 weeks** how many times has your GP visited you?	☐ not at all	or: How many times?:……
E.2) Over the past **6 weeks** how many times have you visited your GP?	☐ not at all	or: How many times?:……
E.3) Over the past **6 weeks** how often have you been visited by a district nurse?	☐ not at all	or: How many times?:……
E.4) Over the past **6 weeks,** have you been visited by a MacMillan nurse?	☐ not at all	or: How many times?:……

E.5) Which best describes your mobility **today**?	☐ I have no problems walking about	☐ I have some problems walking about	☐ I am confined to bed
E.6) Which best describes your self-care **today**?	☐ I have no problems with self care	☐ I have some problems washing or dressing	☐ I am unable to wash or dress myself
E.7) Which best describes your activities **today**?	☐ I have no problems performing my usual activities	☐ I have some problems performing my usual activities	☐ I am unable to perform my usual activities
E.8) Do you have any pain **today**?	☐ I have no pain or discomfort	☐ I have some pain or discomfort	☐ I have extreme pain or discomfort
E.9) Which best describes your mood **today**?	☐ I am not anxious or depressed	☐ I am moderately anxious or depressed	☐ I am extremely anxious or depressed

Now some questions about your symptoms. Over the past week….

Q.8) …were you short of breath?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.9) …have you had pain?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.10) …did you need to rest?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.11) …have you had trouble sleeping?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

Q.12) …have you felt weak?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.13) …have you lacked appetite?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.14) …have you felt nauseated?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.15) …have you vomited?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.16) …have you been constipated?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.17) …have you had diarrhoea?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.18) …were you tired?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.31)…have you had a dry and/or sore mouth?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.32)…have you had problems eating or drinking because of a sore mouth?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.33)…have you had soreness or redness of your hands or feet?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.34) …have you had difficulty handling small objects (eg buttons or zips)?	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.35) …have you lost any hair?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

Q.36) If you have a colostomy, have you had trouble with it (soreness of skin, increased frequency, leakage)?	☐ not applicable	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.37) …how much has your chemotherapy treatment interfered with your normal daily activities?	☐ not applicable	☐ not at all	☐ a little	☐ quite a bit	☐ very much
Q.38) **Since you started chemotherapy,** how worthwhile do you think your treatment has been?	☐ not applicable	☐ not at all	☐ a little	☐ quite a bit	☐ very much

G.1) How was your **overall health** during the past week? *(put a circle round the score)*	**1** **2** **3** **4** **5** **6** **7** Very poor … Excellent
G.2) And how was your **overall quality of life** during the past week?	**1** **2** **3** **4** **5** **6** **7** Very poor … Excellent

Finally, please answer these questions about your feelings. For each statement please mark the box which best describes how you have been feeling over the past week:

H.1) "I feel tense or 'wound up'…"	☐ most of the time	☐ a lot of the time	☐ time-to-time, occasionally	☐ not at all
H.2) "I still enjoy the things I used to enjoy…"	☐ definitely as much	☐ not quite so much	☐ only a little	☐ hardly at all
H.3) "I get a sort of frightened feeling as if something awful is about to happen…"	☐ very definitely and quite badly	☐ yes, but not too badly	☐ a little but it doesn't worry me	☐ not at all

H.4) "I can laugh and see the funny side of things…"	☐ as much as I always could	☐ not quite so much now	☐ definitely not so much now	☐ not at all
H.5) "Worrying thoughts go through my mind…"	☐ a great deal of the time	☐ a lot of the time	☐ time to time but not too often	☐ only occasionally
H.6) "I feel cheerful…"	☐ not at all	☐ not often	☐ sometimes	☐ most of the time
H.7) "I can sit at ease and feel relaxed…"	☐ definitely	☐ usually	☐ not often	☐ not at all
H.8) "I feel as if I am slowed down…"	☐ nearly all the time	☐ very often	☐ sometimes	☐ not at all
H.9) "I get a sort of frightened feeling like 'butterflies' in the stomach…"	☐ not at all	☐ occasionally	☐ quite often	☐ very often
H.10) "I have lost interest in my appearance…"	☐ definitely	☐ I take less care than I should	☐ I may not take quite as much care	☐ I take just as much care as ever
H.11) "I feel restless as if I have to be on the move…"	☐ very much indeed	☐ quite a lot	☐ not very much	☐ not at all
H.12) "I look forward with enjoyment to things…"	☐ as much as I ever did	☐ rather less than I used to	☐ definitely less than I used to	☐ hardly at all
H.13) "I get sudden feelings of panic…"	☐ very often indeed	☐ quite often	☐ not very often	☐ not at all
H.14) "I can enjoy a good book or radio or TV programme…"	☐ often	☐ sometimes	☐ not often	☐ very seldom

Many thanks for helping us by filling in this questionnaire. Please now hand it to the research nurse. You may feel that you wish to discuss some of the issues which it has raised – please feel free to do so.

Appendix XV EQ-5D Questionnaire

FOCUS2 trial: - EQ-5D Questionnaire

Notes for Research Nurse/Data Manager:

This questionnaire is administered 9 months after randomisation (i.e. 3 months after the last LHA), and every 3 months thereafter. It may be administered during an outpatient visit, or alternatively by telephone if the patient is not due to attend out-patients at the time it is due.

Patient's initials	/ / **Today's Date**	**Trial N°. (Nurse to complete)**

E.1) Over the past **6 weeks** how many times has your GP visited you?	☐ not at all	or: How many times?:……
E.2) Over the past **6 weeks** how many times have you visited your GP?	☐ not at all	or: How many times?:……
E.3) Over the past **6 weeks** how often have you been visited by a district nurse?	☐ not at all	or: How many times?:……
E.4) Over the past **6 weeks,** have you been visited by a MacMillan nurse?	☐ not at all	or: How many times?:……

E.5) Which best describes your mobility **today**?	☐ I have no problems walking about	☐ I have some problems walking about	☐ I am confined to bed
E.6) Which best describes your self-care **today**?	☐ I have no problems with self care	☐ I have some problems washing or dressing	☐ I am unable to wash or dress myself
E.7) Which best describes your activities **today**?	☐ I have no problems performing my usual activities	☐ I have some problems performing my usual activities	☐ I am unable to perform my usual activities
E.8) Do you have any pain **today**?	☐ I have no pain or discomfort	☐ I have some pain or discomfort	☐ I have extreme pain or discomfort
E.9) Which best describes your mood **today**?	☐ I am not anxious or depressed	☐ I am moderately anxious or depressed	☐ I am extremely anxious or depressed

Appendix XVI – Economic evaluation

1. Overview

The economic evaluation will take the form of a cost-consequences analysis and of a cost-effectiveness analysis. In the former, the differential resource use and cost of the alternative management strategies will be presented alongside the range of clinical and health-related quality of life (HRQL) effects. In the latter, the differential cost of the alternative treatments will be related to their differential benefits in terms of quality-adjusted life years (QALYs), and standard cost-effectiveness acceptability curves will be used to show the probability of one option being more cost-effective than the other.

2. Estimating costs

All significant resource consumption that is expected to differ between treatment options will be estimated within the study regardless of who eventually incurs the cost; that is, the study will take a societal perspective on costs. Resource use measurement during the trial will be divided into four components: hospital; NHS non-hospital; patient travel costs and patient productivity costs. These are dealt with in turn below.

2.1 Hospital resource use

Within the trial, hospital resource use data will be collected on all patients entering the trial. These will be collected using case record forms completed at clinical review at 6 weeks, 3 months, 6 months, 9 months and 12 months. Some visits to and stays in hospital may relate to non-study hospitals. To ensure that data on this form of resource use are captured, a questionnaire will be administered to patients as part of the CHA and LHA assessments at baseline, 12-14 weeks and 21-27 weeks.

These resources will be valued in monetary terms using unit costs representative of UK practice at the time of analysis. For drugs, this will be based on British National Formulary prices. For hospital procedure and hotel costs, unit costs will if available, be based on NHS Reference Costs. Otherwise, they will be estimated from a sample of UK centres randomising patients into the trial.

2.2 NHS non-hospital resource use

Patients' use of community-based NHS (and complementary health) services will be collected from patients in the form of a short questionnaire administered at 6 weeks, 3 months, 6 months, 9 months and 12 months. The resources will include visits to and from a GP or district nurse. Costing of community-based resources will be based on published unit costs[2]. Other services will be costed using data available at the point of analysis.

2.3 Patient travel costs

Patients' travel costs will be estimated using a cost per hospital visit and multiplying that cost by the number of occasions each patient visits hospital. In order to cost a given visit to

hospital for each patient, a short questionnaire will be administered at baseline to all patients. This will collect information on the typical mode(s) of transport, distance and time of journeys to hospital, and whether the patient had a companion. Based on these data, patients' travel costs will be based on published unit costs for travel[3].

The questionnaire will also collect information to cost the time patients and any companions allocate to the visit. Time will be valued using an average national wage rate with sensitivity analysis used to explore the implications of valuing the time of patients who are not in employment differently from those that are in employment.

2.4 Patient productivity costs

The number of days during which patients are unable to undertake their usual activities because of illness will be established at the various points of follow-up. In addition, it will be necessary to ask patients at baseline what their usual activity is. Productivity costs will be estimated using the average national wage rate, with sensitivity analysis used to explore the implications of valuing lost days of patients who are not employment differently from those who are in employment.

3. Measuring effects

The clinical trial is estimating a range of clinical and HRQL effects in trial patients. The purpose of the economic evaluation will be to set these in context of the resource costs incurred in achieving them. In the cost-consequences analysis, these effects will be presented alongside the cost data in disaggregated form. A cost-effectiveness analysis will relate differential cost to an aggregated measure of effect in the form of a quality-adjusted life-year (QALY).

4. Analysis

All resource use data will be valued in monetary terms as described above such that each patient has a cost over the period of follow-up. A full stochastic analysis will be undertaken to allow for sample variation in resource use and effect data. Methods are altering quickly in this area and, by the time of the analysis, 'best practice' may have altered markedly from today. If such an analysis were to be undertaken now, the general methods would be as follows.

4.1 Cost-consequences analysis

In the cost-consequences analysis (i.e. disaggregated analysis), resource use, cost and effect data will be described using standard descriptive statistics.

Allowance will have to be made – both for the costs and effects – for censored data due to differential follow-up and the fact that it is unlikely that all patients would have died at the point of analysis. For effects, these methods are clear and established using standard methods of survival analysis. For costs, methods have recently been suggested for handling censored data[5].

Although cost data are likely to be heavily skewed, it is important that means are reported as this is the relevant statistic for decision makers. Parametric methods or non-parametric bootstrapping will be used as appropriate.

4.2 Cost-effectiveness analysis

For the cost-effectiveness analysis, two analyses will be undertaken (one taking a health care system perspective on costs, the other a societal perspective) . QALYs will be the measure of effectiveness.

A QALY profile will be estimated for each patient based on their survival duration weighted by their responses to the EQ-5D HRQL questionnaire, which generates a single index value for health at each point of follow-up[6]. The profiles will assume a straight-line relationship between the index value at time t and the value at time t+1. The number of QALYs they experience during the period of follow-up in the trial will be the area under the QALY profile.

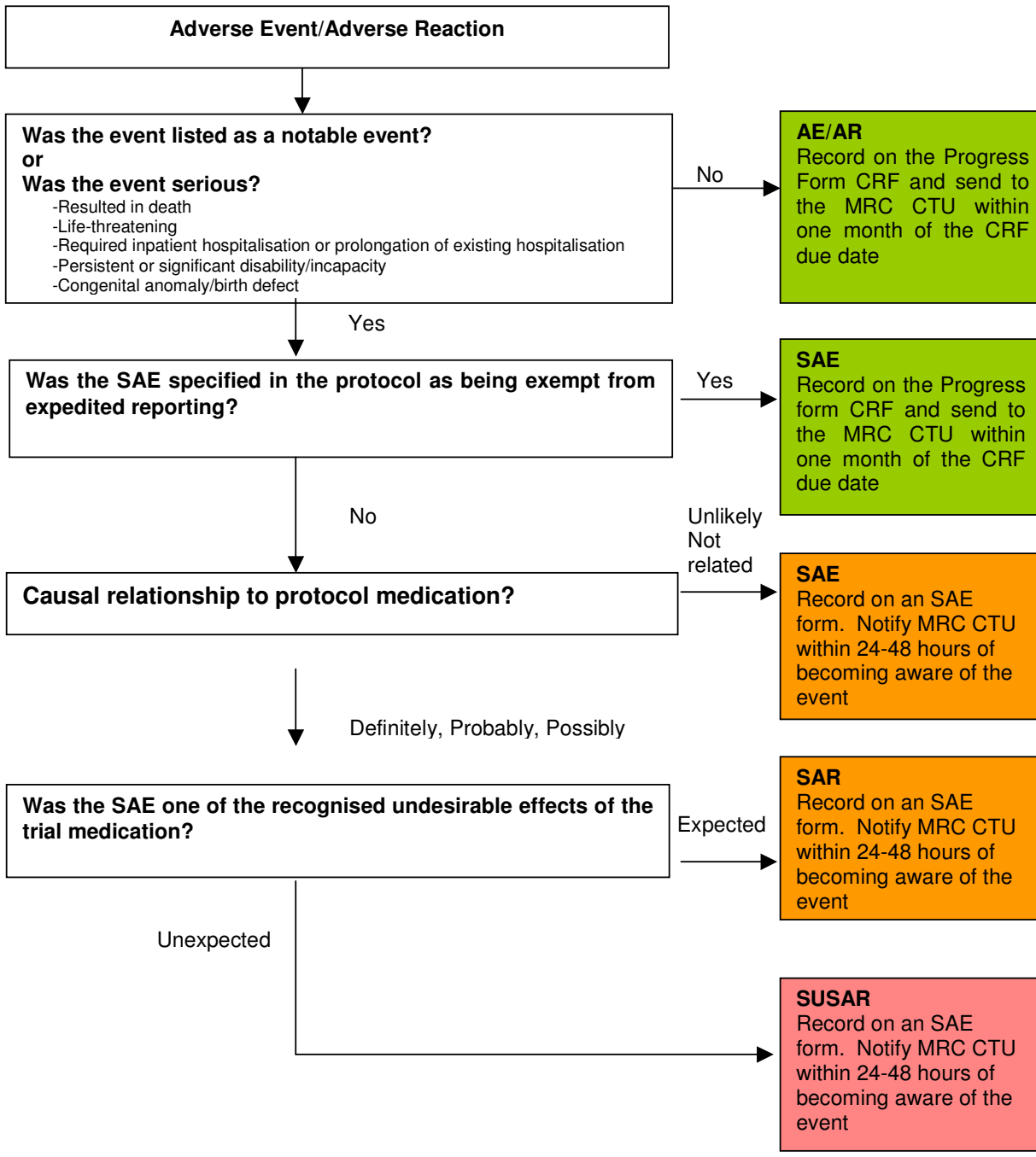
In the primary analysis only data collected in the trial will be used in the analysis; in other words, the estimate of QALYs for each group is likely to reflect the fact that some patients are still alive after the year's follow-up (i.e. the survival curve is truncated and survival techniques will be used to estimate QALYs).

As a secondary analysis, extrapolation techniques will be used to estimate the final portion of the curve so as to provide a full estimate of differential life expectancy. A range of extrapolation techniques exists, with currently no consensus as to the best. The methodological literature will be monitored.

Cost-effectiveness acceptability curves will be used to facilitate a measure of uncertainty around cost-effectiveness estimates[1]. These curves show the probability of one form of management being more cost-effective than the other assuming alternative levels of the maximum amount decision-makers are willing to pay for an extra QALY.

Sensitivity analysis will be used to consider the importance of sources of uncertainty other than sample variation (e.g. unit costs, discount rates, cost perspective). Multiple regression techniques will be employed to provide as precise a measure of cost-effectiveness as possible and to undertake sub-group analysis using baseline patient characteristics which will be defined in advance in the analysis plan.

Appendix XVII Summary of Safety Reporting



CRF: Case report form
SAE: Serious adverse event
SPC: Summary of product characteristics
IB: Investigator's brochure
SAR: Serious adverse reaction
SUSAR: Suspected unexpected serious adverse reaction

Appendix XVIII - Expected Toxicities

Toxicities/side effects that have previously occurred and are listed in the SPC are listed here. Please record all side effects on the treatment/toxicity or progress report and follow-up form. These will not have to be reported to the MHRA but will be collected as toxicity is an endpoint of the trial. If the outcome of the side effect is serious, the SAE form in the CRF booklet should also be completed. Any toxicity not described below, i.e. a toxicity that is unexpected, will be reported as a SUSAR.

Toxicity	**5-Fluorouracil**	**Capecitabine**	**Oxaliplatin**
Haemapoeitic:			
Anaemia	✓	✓	✓
Febrile neutropenia	✓		✓
Grade 3 or 4 lab abnormalities (according to CTC v3.0)	✓	✓	✓
Leukopenia	✓		
Neutropenia	✓	✓	✓
Thrombocytopenia	✓	✓	✓
Gastrointestinal:			
Abdominal pain	✓	✓	✓
Constipation		✓	✓
Diarrhoea	✓	✓	✓
Dry mouth	✓	✓	
Dyspepsia	✓	✓	✓
Flatulence		✓	
Loose stools	✓	✓	
Nausea	✓	✓	✓
Oral pain	✓	✓	
Stomatitis / mucositis	✓	✓	✓
Taste disturbance	✓	✓	✓

Toxicity	5-Fluorouracil	Capecitabine	Oxaliplatin
Gastrointestinal (contd):			
Upper abdominal pain	✓	✓	
Vomiting	✓	✓	✓
Neurotoxicity:			
Acute neurosensory manifestations			✓
Dizziness	✓	✓	
Dysarthria (rare)			✓
Headache		✓	✓
Hyperaesthesia		✓	✓
Hypoaesthesia		✓	✓
Insomnia		✓	
Ototoxicity (uncommon)			✓
Paraesthesia	✓	✓	✓
Pharyngolaryngeal dysaesthesia			✓
Sensory peripheral neuropathy characterised by dysaesthesia and/or paraesthesia of the extremities with or without cramps, often triggered by the cold			✓
Biochemistry:			
Grade 3 or 4 alkaline phosphatase (CTC v3.0)		✓	✓
Grade 3 or 4 ALT (CTC v3.0)			✓
Grade 3 or 4 AST (CTC v3.0)			✓
Grade 3 or 4 bilirubin increase (CTC v3.0)	✓	✓	✓
Cardiovascular:			
Lower limb oedema		✓	
Angina	✓	✓	
Cutaneous:			
Alopecia	✓	✓	✓

Toxicity	5-Fluorouracil	Capecitabine	Oxaliplatin
Dermatitis	✓	✓	
Dry skin	✓	✓	
Cutaneous (contd.):			
Exfoliative dermatitis	✓	✓	
Hand-foot syndrome or palmar-plantar erythrodysaesthaesia	✓	✓	
Localised exfoliation	✓	✓	
Nail disorders	✓	✓	
Pigmentation disorder	✓	✓	
Pruritic rash	✓	✓	
Pruritis		✓	
Rash erythematous	✓	✓	
Skin discolouration	✓	✓	
Skin fissures		✓	
Skin hyperpigmentation	✓	✓	
Respiratory effects:			
Pulmonary fibrosis (rare)			✓
General undesirable effects:			
Anorexia	✓	✓	✓
Arthralgia		✓	✓
Asthenia	✓	✓	✓
Back pain		✓	✓
Conjunctivitis	✓	✓	✓
Cough vertigo		✓	
Deafness (rare)			✓
Decreased appetite	✓	✓	
Dehydration	✓	✓	
Toxicity	**5-Fluorouracil**	**Capecitabine**	**Oxaliplatin**

Depression		✓	✓
Disturbance of renal function			✓
Dyspnoea		✓	✓
Dysuria			✓
Epistaxis	✓	✓	✓
General undesirable effects (contd.):			
Eye irritation	✓	✓	
Fatigue	✓	✓	✓
Fever	✓		✓
Haematuria			✓
Haemorrhage (rectum, nose)			✓
Increased lacrimation	✓	✓	
Infection	✓		✓
Lethargy	✓	✓	
Malaise	✓	✓	
Micturition, abnormal frequency			✓
Myalgia		✓	
Pain in limb		✓	
Pyrexia	✓	✓	
Rigors	✓	✓	
Weakness	✓	✓	
Weight decrease	✓	✓	✓
Weight increase	✓		✓

Appendix XX – Case Record Forms

Patient's Trial Number ☐☐☐☐

MRC Medical Research Council

FOCUS2

CR09 Drug Treatment for Bowel Cancer: Making the best choices when a milder treatment is needed

Randomisation and Pretreatment Form

Patient's initials _____ Clinician _____

Hospital _____ Date of birth ☐☐ ☐☐ ☐☐ (d m y)

NHS No: _____ Patient's home postcode _____

Hospital No: _____ Sex male ☐ female ☐

Eligibility Criteria see protocol for details

	Yes	No
1. Histologically confirmed adenocarcinoma of the colon or rectum **or** clinical/radiological evidence of colorectal cancer with adenocarcinoma cytology/histology from a metastatic site	☐	☒
2. Adequate bone marrow function (WBC >4 x10^9/l, platelet count >150 x10^9/l), test performed within last 7 days	☐	☒
3. Adequate hepatobiliary function (Serum bilirubin <3 x ULN and transaminase <2.5 x ULN)), test performed within last 7 days	☐	☒
4. Adequate renal function (Estimated creatinine clearance (Cockcroft method) >50ml/min **or** Measured GFR (EDTA)>30ml/min, test performed within last 7 days	☐	☒
5. Fit and able to undergo all possible treatments	☐	☒
6. No concurrent, uncontrolled illness or other previous or current malignant disease likely to interfere with the protocol treatments or comparisons	☐	☒
7. Measurable disease (RECIST criteria)	☐	☒

Written informed consent obtained Yes ☐ No ☒

Has Comprehensive Health Assessment (CHA) been completed? Yes ☐ No ☒

WHO performance status 0 ☐ 1 ☐ 2 ☐ 3 ☒ 4 ☒ not eligible

0 = Able to carry out normal activity

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 waking hours

3 = Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

4 = Completely disabled; cannot carry on any self-care; totally confined to bed or chair

Current status:

Primary Tumour

1 ☐ Resected 2 ☐ Unresected/unresectable 3 ☐ Local recurrence

Metastases Yes ☐ No ☐

If yes, Liver Yes ☐ No ☐ Lung Yes ☐ No ☐

Nodes Yes ☐ No ☐ Peritoneum Yes ☐ No ☐

Other (specify) _____

Please state the main reason(s) why this patient has entered FOCUS2 in preference to a full-dose chemotherapy protocol (tick as many as apply):

Borderline performance status ☐ Advanced Age ☐ Borderline renal/hepatic function ☐

General medical co-morbidity ☐ Patient choice ☐ Other ☐ specify _____

Now telephone the Cancer Group, MRC Clinical Trials Unit on: **020 7670 4777 Monday to Friday** between 0900 and 1700 hours to randomise the patient

Patient's Trial Number ☐☐☐☐

FOCUS2

Randomisation and Pretreatment Form

After randomisation, please complete the following Pretreatment details

Allocated Treatment

Trial Number ☐☐☐☐ Date of Randomisation ☐☐ ☐☐ ☐☐ (d m y)

(Please write this number on the CHA form and then post to the CTU)

D. MdG → OxMdG ☐ E. OxMdG ☐

F. Cap → OxCap ☐ G. OxCap ☐

Primary disease

Date of primary tumour diagnosis ☐☐ ☐☐ ☐☐ (d m y)

Site of the patients primary tumour:

Please specify:

Rectum ☐ Descending colon ☐ Ascending colon ☐

Sigmoid colon ☐ Transverse colon ☐ Caecum ☐

Metastatic disease

Metastatic disease: Yes ☐ No ☐ If yes, date of diagnosis ☐☐ ☐☐ ☐☐ (d m y)

Has patient received previous treatment for metastases?

Radiotherapy Yes ☐ No ☐ If **yes**,date completed ☐☐ ☐☐ ☐☐ (d m y)

Surgery Yes ☐ No ☐ If **yes**, date of surgery ☐☐ ☐☐ ☐☐ (d m y)

Please confirm no previous systemic chemotherapy for metastatic disease ☐ **(please tick)**

Symptoms

Record current CTC grade (0 - 4) *(see inside back cover - Common Toxicity Criteria) record 9 if not known*

Nausea ☐ Vomiting ☐ Anorexia ☐ Alopecia ☐

Pain ☐ Stomatitis ☐ Diarrhoea ☐ Lethargy ☐

Other ☐ Specify _____

Baseline assessment of disease (RECIST criteria) Date of assessment: ☐☐ ☐☐ ☐☐ (d m y)

Investigations used: CT scan

other ☐ specify _____

Result: Baseline sum of longest diameters ☐☐☐ mm **No. of lesions measured:** ☐

Patient's Trial Number

FOCUS2

Randomisation and Pretreatment Form

Has patient given permission for use of a blood sample and stored pathological material for research? Yes ☐ No ☐

If yes, please complete Pathology/Blood sample form and arrange for the blood sample to be sent to the reference laboratory.

Date test performed (must be within 7 days prior to randomisation)

Bone marrow function

WBC ☐☐.☐ 10^9/l Platelets ☐☐☐ 10^9/l ☐☐ ☐☐ ☐☐ (d m y)

Hepatobiliary function

Serum bilirubin ☐☐☐ µmol/l Alkaline phosphatase ☐☐☐ IU ☐☐ ☐☐ ☐☐ (d m y)

Transaminase (AST or ALT) ☐☐☐ IU
(Please circle parameter measured)

Renal function

Estimated creatinine clearance ☐☐☐ ml/min **OR** Measured GFR ☐☐☐ ml/min ☐☐ ☐☐ ☐☐ (d m y)

Albumin level ☐☐☐ g/dl ☐☐ ☐☐ ☐☐ (d m y)

Does this patient have a raised tumour marker? Yes ☐ No ☐ Results not back yet ☐

If yes, marker ☐☐☐☐ value ☐☐☐☐ ☐☐ ☐☐ ☐☐ (d m y)

What will be the patients usual travel arrangements from home to hospital (one-way) for chemotherapy? (Tick more than one type of transport if necessary)

		Approx distance (miles)
Own car	☐	☐☐☐
Bus	☐	☐☐☐
Taxi/hospital car	☐	☐☐☐
Walk	☐	☐☐☐
Train	☐	☐☐☐
Ambulance	☐	☐☐☐
Other Please specify	☐ _____	☐☐☐
Approximate time of one-way journey		☐☐☐

Will the patient normally be accompanied to hospital by a friend or relative?

Yes ☐ No ☐

Form completed by: _____ Date ☐☐ ☐☐ ☐☐ (d m y)

Please fax completed form immediately to:
CR09 Trial, Cancer Division, MRC Clinical Trials Unit, 222 Euston Road, London, NW1 2DA
Fax: 020 7670 4818

MRC Medical Research Council
CR09

Drug Treatment for Bowel Cancer: Making the best choices when a milder treatment is needed

FOCUS2

Pathology/Blood Sample Form

Patient's Initials _____ Trial No. ☐☐☐☐

Clinician _____

Hospital _____

When consenting for FOCUS2, did this patient give consent for the use of a blood sample and stored pathological specimens for future bowel cancer research?

Yes ☐ No ☐

If no, please return this form to the CTU with no further details completed.
If yes, please complete the following details

Primary Bowel Cancer Histology:

Resection ☐ Biopsy (only required if no resection ☐ No resection or biopsy ☐

Path Lab No _____ Date ☐☐ ☐☐ ☐☐ (d m y)

Path Hospital _____

Address _____

Metastases Histology:

Has this patient had a biopsy/resection or metastatic site(s)

No ☐ Yes ☐ If yes pleae complete

Path Lab No _____ Date ☐☐ ☐☐ ☐☐ (d m y)

Path Hospital _____

Address _____

Blood Sample for DNA analysis:

Take 8ml blood in EDTA (one 10ml EDTA tube, or two 4ml tubes).

The tube(s) should be clearly marked with the date and the patient's trial number and initials **but not the patients name.**

Seal the tube(s) in a plastic bag with plenty of padding to prevent breakage (Jiffy bag or padded plastic/cardboard box).

Include a photocopy of this form in the package and mark the envelope "Diagnostic Specimens".

Post using normal first class mail to:

FOCUS 2 Trial Sample Laboratory
University of Leeds Molecular Pathology Department
Algernon Firth Building
Leeds General Infimary, Leeds LS2 9JT

Confirm blood sample has been sent to laboratory ☐

Date sent ☐☐ ☐☐ ☐☐ (d m y)

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6-week Early Assessment Form

Please complete post 2-cycles of a Capecitabine-containing regimen or post 3-cycles MdG-containing regimen

Patient's initials _____ Trial No ☐☐☐☐

Clinician _____ Trial Arm: D ☐ E ☐ F ☐ G ☐

Hospital _____

Date of assessment: ☐☐ ☐☐ ☐☐ (d m y)

Was a decision made to increase the patient's dose of chemotherapy? Yes ☐ No ☐

If No:

1. No/minimal toxicity so far, but dose not increased ☐
2. Significant toxicity therefore dose not increased ☐

Decision made by: .....
(CONSULTANT/SPR)

.....
(PLEASE PRINT NAME)

Please return completed form to:
CR09 Trial, Cancer Division, MRC Clinical Trials Unit, 222 Euston Road, London, NW1 2DA

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Treatment and Toxicity Form

Please complete at 6-weekly intervals when on FOCUS2 chemotherapy (complete one column for each cycle of chemotherapy. Return after 3 cycles if on MdG containing regimen or after 2 cycles if on a capecitabine containing regimen)

Patient's initials _____ Trial No ☐☐☐☐

Clinician _____ Patient's date of birth: ☐☐ (d) ☐☐ (m) ☐☐ (y)

Hospital _____ Current chemotherapy regime: _____

Trial Arm: D ☐ E ☐ F ☐ G ☐ _____

Date of cycle start: (d m y)	☐☐ ☐☐ ☐☐	☐☐ ☐☐ ☐☐	☐☐ ☐☐ ☐☐
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 clearance	☐☐☐ ml/min	☐☐☐ ml/min	☐☐☐ ml/min
Measured GFR or	☐☐☐ ml/min	☐☐☐ ml/min	☐☐☐ ml/min
Chemotherapy given as:	☐ I/P ☐ OP/ day case	☐ I/P ☐ OP/ day case	☐ I/P ☐ OP/ day case

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

5FU- bolus	☐☐☐ mg	☐☐☐ mg	☐☐☐ mg
5FU - infusion	☐☐☐☐ mg	☐☐☐☐ mg	☐☐☐☐ mg
Oxaliplatin	☐☐☐ mg	☐☐☐ mg	☐☐☐ mg
Dose of Capecitabine prescribed	☐☐☐☐ mg	☐☐☐☐ mg	
How many of these Capecitabine tablets were returned unused at the end of this cycle	☐ 500mg ☐ 150mg	☐ 500mg ☐ 150mg	
Cycle delayed* (code below)	☐	☐	☐
Dose(s) modified* (code below)	☐	☐	☐

*specify major reason(s) for dose delay(s)/ modification(s)

0 = No dose/delay modification
1 = Allergic reaction
2 = Haematological
3 = Stomatitis
4 = Diarrhoea
5 = Hand foot syndrome
6 = Hospital administrative
7 = Patient choice
8 = Cardiac dysfunction
9 = Neurotoxicity
10 = Hepatobiliary dysfunction
11 = Renal dysfunction
12 = Capecitabine non-compliance
13 = Other, specify (including combination of reasons):

Toxicity

(Before returning please record worst toxicity (v3.0) experienced in this six week period):

Nausea	☐	Vomiting	☐	Anorexia	☐	Alopecia	☐	Pain	☐
Stomatitis	☐	Diarrhoea	☐	Lethargy	☐	Platelets	☐	Haemoglobin	☐
WBC	☐	Neutrophils	☐	Peripheral neuropathy	☐			Hand-foot syndrome	☐
Vein pain	☐	Other	☐	Specify	☐	_____			

Form completed by: _____ Date ☐☐ (d) ☐☐ (m) ☐☐ (y)

Please return completed form to:

CR09 Trial, Cancer Division, MRC Clinical Trials Unit, 222 Euston Road, London, NW1 2DA

MRC Medical Research Council **FOCUS2**

Drug Treatment for Bowel Cancer: Making the best choices when a milder treatment is needed

CR09

3-Month Progress Report Form

Please complete at 12-14 weeks after randomisation after the patient's disease has been assessed

Patient's initials _____ Trial No. ☐☐☐☐

Clinician _____ Trial Arm: D ☐ E ☐ F ☐ G ☐

Hospital _____

Date of this assessment: ☐☐ ☐☐ ☐☐ (d m y) Please ensure all treatment and toxicity forms have been returned

Section A - Summary of FOCUS2 chemotherapy received so far:

No. of first-line cycles of MdG ☐ Cap ☐ OxMdG ☐ OxCap ☐

No. of second-line cycles of OxMdG ☐ OxCap ☐

Section B - Non FOCUS2 anticancer treatment

Has patient received any other anticancer treatment? No ☐ Yes ☐

If **Yes**: other chemotherapy ☐ radiotherapy ☐ surgery ☐ other ☐

give details of non-FOCUS2 treatment _____

Section C - Current WHO performance status

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐

Section D - Serious Adverse Events

Has the patient experienced any serious adverse events? No ☐ Yes ☐

If yes, has an SAE form been completed? If not, please complete and fax it immediately to the MRC Clinical Trials Unit (Fax 020 7670 4818)

Section E - Time in Hospital

Since starting FOCUS2 treatment

How many nights has the patient spent in hospital?

ICU ☐ HDU ☐ General/acute ☐ In patient chemotherapy ☐

How many days has the patient attended hospital as an:

Outpatient ☐ Day Case ☐

Section F - Assessment of response/progression

Date of assessment: ☐☐ ☐☐ ☐☐ Not assessed ☐ reason _____

Investigations used: clinical ☐ Xray ☐ US ☐ MRI ☐ CT scan ☐ tumour markers ☐

other ☐ specify _____

Result:

Assessment of measurable disease (use RECIST criteria): Sum of longest diameters ☐☐☐ mm No. of lesions measured ☐

Complete response ☐ Partial response ☐ Stable disease ☐ Progressive disease ☐

FOCUS2

3-Month Progress Report Form

Trial No. ☐☐☐☐

Section G continued

If progressive disease: date of progression ☐☐ ☐☐ ☐☐ (d m y)

If response/progression is based purely on clinical grounds, give details of signs and symptoms

_____

Treatment benefit assessment (see protocol P.13)

Treatment benefit ☐ (Break treatment for now, plan to resume same regimen at a later date)

No treatment benefit ☐ (Stop current treatment. If in arm D or F consider starting 2nd-line)

Is patient going to have a treatment break? Yes ☐ No ☐

If Yes, is break due to: Stable/disease response ☐ Unacceptable toxicity ☐

Other ☐ Details ☐ _____

Section H - Survival status

Has patient died? No ☐ Yes ☐ If yes give date of death ☐☐ ☐☐ ☐☐ (d m y)

Disease related ☐ Treatment related ☐* Other ☐ please specify _____

*If yes, please ensure SAE has been recorded.

Section I - LHA

Has the Limited Health Assessment been completed? No ☐ Yes ☐

If **no**, give reasons: _____

Albumin level ☐ g/dl Date test performed ☐☐ ☐☐ ☐☐ (d m y)

Section K - Comments

Form completed by: _____ Date ☐☐ ☐☐ ☐☐ (d m y)

Please return completed form to:

CR09 Trial, Cancer Division, MRC Clinical Trials Unit, 222 Euston Road, London, NW1 2DA

MRC Medical Research Council

FOCUS2

CR09 Drug Treatment for Bowel Cancer: Making the best choices when a milder treatment is needed

6- Month Progress Report Form

Please complete 6 months after randomisation after the patient's disease has been assessed

Patient's initials _____ Trial No. ☐☐☐☐

Clinician _____ Patient's date of birth: ☐☐ (d) ☐☐ (m) ☐☐ (y)

Hospital _____ Trial Arm: D ☐ E ☐ F ☐ G ☐

Date of this assessment: ☐☐ (d) ☐☐ (m) ☐☐ (y)

Section A - Summary of FOCUS2 chemotherapy received so far:

No. of first-line cycles of MdG ☐ Cap ☐ OxMdG ☐ Oxali Cap ☐

No. of second-line cycles of OxMdG ☐ Oxali Cap ☐

FOCUS2 treatment over the past 12 weeks:

☐ Yes, patient has received FOCUS2 chemotherapy (please ensure the Treatment and Toxicity forms covering these treatments are completed)

☐ No, patient has been on a planned treatment break, but more FOCUS2 chemotherapy may be given in the future

☐ No, patient has not received or is planned for further FOCUS2 chemotherapy

Section B - Non FOCUS2 anticancer treatment

Has patient received any other anticancer treatment since last form completed? No ☐ Yes ☐

If **Yes**: salvage chemotherapy ☐ radiotherapy ☐ surgery ☐ other ☐

give details of non-FOCUS2 treatment _____

Section C - Symptoms

Record worst CTC grade (v3) experienced *(see inside back cover)* since last form completed (record 9 if not known)

Nausea ☐ Vomiting ☐ Anorexia ☐ Alopecia ☐ Pain ☐

Stomatitis ☐ Diarrhoea ☐ Lethargy ☐ Platelets ☐ Haemoglobin ☐

WBC ☐ Neutrophils ☐ Peripheral neuropathy ☐ Hand-foot syndrome ☐

Vein pain ☐ Other ☐ Specify ☐ _____

Section D - Current WHO performance status

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐

Section E - Serious Adverse Events

Has the patient experienced any serious adverse events? No ☐ Yes ☐

If yes, has an SAE form been completed? If not, please complete and fax it immediately to the MRC Clinical Trials Unit (Fax no. 020 7670 4818)

Section F - Time in Hospital

Since the last assessment (previous 12 weeks)

How many nights has the patient spent in hospital?

ICU ☐ HDU ☐ General/acute ☐ In patient chemotherapy ☐

How many days has the patient attended hospital as an: Outpatient ☐ Day Case ☐

FOCUS2

6- Month Progress Report Form

Trial No. ☐☐☐☐

Section G - Assessment of response/progression

Date of assessment: ☐☐ (d) ☐☐ (m) ☐☐ (y) Not assessed ☐ reason _____

Investigations used: clinical ☐ Xray ☐ US ☐ MRI ☐ CT scan ☐ tumour markers ☐

other ☐ specify _____

Result:

Assessment of measurable disease (use RECIST criteria): Sum of longest diameters ☐☐☐ mm No. of lesions measured ☐

Complete response ☐ Partial response ☐ Stable disease ☐ Progressive disease ☐

If response/progression is based purely on clinical grounds, give details of signs and symptoms

_____

Section H -Summary of response so far:

Not progressed ☐ Date of progression during treatment break ☐☐ (d) ☐☐ (m) ☐☐ (y)

Date of progression on first-line ☐☐ (d) ☐☐ (m) ☐☐ (y) Date of progression on second-line ☐☐ (d) ☐☐ (m) ☐☐ (y)

Section I - Survival status

Has patient died? No ☐ Yes ☐ If yes give date of death ☐☐ (d) ☐☐ (m) ☐☐ (y)

Disease related ☐ Treatment related ☐* Other ☐ please specify _____

*If yes, please ensure SAE has been recorded.

Section J - LHA

Has the 6 month Limited Health Assessment been completed? No ☐ Yes ☐

If **no**, give reasons: _____

Albumin level ☐☐☐ g/dl Date test performed ☐☐ (d) ☐☐ (m) ☐☐ (y)

Section K - Comments

Form completed by: _____ Date ☐☐ (d) ☐☐ (m) ☐☐ (y)

Please note in your trial diary that the next Progress Form for this patient is due in a further 12 weeks on: Date ☐☐ (d) ☐☐ (m) ☐☐ (y)

Please return completed form to:

CR09 Trial, Cancer Division, MRC Clinical Trials Unit, 222 Euston Road, London, NW1 2DA

MRC Medical Research Council
CR09

FOCUS2

Drug Treatment for Bowel Cancer: Making the best choices when a milder treatment is needed

Follow-up Progress Report Form

Please complete 9 months after randomisation then 3 monthly thereafter

Patient's initials _____ Trial No. ☐☐☐☐

Clinician _____ Hospital _____

Date of assessment: ☐☐ ☐☐ ☐☐ (d m y)

Section A - Summary of FOCUS2 chemotherapy received so far:

No. of first-line cycles of MdG ☐ Cap ☐ OxMdG ☐ Oxali Cap ☐

No. of second-line cycles of OxMdG ☐ Oxali Cap ☐

FOCUS2 treatment over the past 12 weeks:

☐ Yes, patient has received FOCUS2 chemotherapy (please ensure the Treatment forms covering these treatments are completed)

☐ No, patient has been on a planned treatment break, but more FOCUS2 chemotherapy may be given in the future

☐ No, patient has not received or is planned for further FOCUS2 chemotherapy

Section B - Non FOCUS2 anticancer treatment

Has patient received any other anticancer treatment since last form completed? No ☐ Yes ☐

If **Yes**: salvage chemotherapy ☐ radiotherapy ☐ surgery ☐ other ☐

give details of non-FOCUS2 treatment _____

Section C - Symptoms

Record worst CTC grade (v3) experienced *(see inside back cover)* since last form completed (record 9 if not known)

Nausea ☐ Vomiting ☐ Anorexia ☐ Alopecia ☐ Pain ☐

Stomatitis ☐ Diarrhoea ☐ Lethargy ☐ Platelets ☐ Haemoglobin ☐

WBC ☐ Neutrophils ☐ Peripheral neuropathy ☐ Hand-foot syndrome ☐

Vein pain ☐ Other ☐ Specify ☐ _____

Section D - Current WHO performance status

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐

Section E - Serious Adverse Events

Has the patient experienced any serious adverse events? No ☐ Yes ☐

If yes, has an SAE form been completed? If not, please complete and fax it immediately to the MRC Clinical Trials Unit (Fax no. 020 7670 4818)

Section F - Time in Hospital

Since the last assessment (previous 12 weeks)

How many nights has the patient spent in hospital?

ICU ☐ HDU ☐ General/acute ☐ In patient chemotherapy ☐

How many days has the patient attended hospital as an: Outpatient ☐ Day Case ☐

FOCUS2

Follow-up Progress Report Form

Trial No. ☐☐☐☐

Section G - Assessment of response/progression

Date of assessment: ☐☐ (d) ☐☐ (m) ☐☐ (y) Not assessed ☐ reason _____

Investigations used: clinical ☐ Xray ☐ US ☐ MRI ☐ CT scan ☐ tumour markers ☐

other ☐ specify _____

Result:

Assessment of measurable disease (use RECIST criteria): Sum of longest diameters ☐☐☐ mm

Complete response ☐ Partial response ☐ Stable disease ☐ Progressive disease ☐

If response/progression is based purely on clinical grounds, give details of signs and symptoms

_____

Section H -Summary of response so far:

Not progressed ☐

Date of progression on first-line ☐☐ (d) ☐☐ (m) ☐☐ (y)

Date of progression on second-line ☐☐ (d) ☐☐ (m) ☐☐ (y)

Section I - Current status

Has patient died? No ☐ Yes ☐ If yes give date of death ☐☐ (d) ☐☐ (m) ☐☐ (y)

Disease related ☐ Treatment related ☐* Other ☐ please specify _____

*If yes, please ensure SAE has been recorded.

Section J - EQ-SD

Has the EQ-SD been completed? No ☐ Yes ☐

If **no**, give reasons: _____

Section K - Comments

Form completed by: _____ Date ☐☐ (d) ☐☐ (m) ☐☐ (y)

Please note in your trial diay that the next Progress Form for this patient is due in a further 12 weeks on: Date ☐☐ (d) ☐☐ (m) ☐☐ (y)

Please return completed form to:

CR09 Trial, Cancer Division, MRC Clinical Trials Unit, 222 Euston Road, London, NW1 2DA

MRC Clinical Trials Unit

Drug treatment for bowel cancer: making the best choices when a milder treatment is needed
SERIOUS ADVERSE EVENT REPORTING FORM

FOCUS 2

Page 1 of 2

EudraCT Number: 2004-004821-88

Please fax to 020 7670 4818 within 24 hours of notification of event FAO: <Trial> Trial Manager

1 Patient's initials | 2 Date of birth (d m y) | 3 Patient's ID No.

4 Hospital No. ..... | 5 Responsible clinician ..... | 6 Institution .....

Report date (7) (d m y)

Type of report (8) 1 = First, 2 = Follow-up

Trial arm (9) 1=D (MdG -> OxMdG), 2=E (OxMdG), 3=F (Cap ->OxCap), 4=G (OxCap)

Sex (10) 1 = Male, 2 = Female

Height (11) cm

Weight (12) kg

Why was the event serious? (13)
1 = Resulted in death
2 = Life-threatening
3 = Required inpatient hospitalisation or prolongation of existing hospitalisation
4 = Persistent or significant disability/incapacity
5 = Congenital anomaly/birth defect

Where did SAE take place? (14)
1 = Hospital
2 = Out-patient clinic
3 = Home
4 = Nursing home
5 = Other, specify.....

(15) Describe serious adverse event *(include symptoms, body site and relevant lab tests and any treatments received. Continue on a separate sheet if necessary).*

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Details of SAE

(16) Serious adverse event name: (Code using the short name of the adverse event from CTCAEv3.0).	(17) Grade (CTCAEv3.0 grade at time of assessment)	(18) Date of onset dd / mm / yyyy	(19) Date resolved dd / mm / yyyy	(20) SAE Status 1 = Resolved, 2 = Resolved with sequelae, 3 = Persisting, 4 = Worsened, 5 = Fatal	(21) Causal relationship to treatment 1 = Definitely, 2 = Probably, 3 = Possibly, 4 = Unlikely, 5 = Not related	(22) Expectedness* 1 = Expected, 2 = Unexpected

** Was the event one of the recognised undesirable effects of the trial medication?*

Trial medications

Date of most recent <chemotherapy/medication> given (23) (d m y)

Was the most recent cycle of <chemotherapy/medication> given at protocol dose (24) 0 = No, specify ..... 1 = Yes

Cycle Number (25)

(26) Trial drugs. Give generic name of most relevant protocol drugs given.	(27) Total Daily Dose/unit	(28) Start Date dd / mm / yyyy	(29) Ongoing Therapy 0 = No 1 = Yes	(30) End Date dd / mm / yyyy	(31) Causal relationship to SAE 1 = Definitely, 2 = Probably, 3 = Possibly, 4 = Unlikely, 5 = Not related	(32) Action taken 0 = None, 1 = Dose reduction, 2 = Treatment delayed, 3 = Treatment reduced and delayed, 4 = Treatment stopped
Oxaliplatin						
Capecitabine						
5FU						

FOCUS 2
EudraCT Number: 2004-004821-88

Patient ID No. ☐☐☐☐☐

33 **Other information to facilitate assessment**
(include: medical history, drug or alcohol abuse, family history, findings from special investigation).

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.....

Was this event expected in view of the patient's clinical history?

34 ☐ 0 = No
1 = Yes

Other treatments *(include concomitant medication, radiotherapy, surgery, palliative care, continue on seperate sheet if necessary)*

35 Treatment Give generic name of most relevant drugs/treatments given. Exclude any therapy given for management of SAE.	36 Total Daily Dose/unit	37 Route of administration 1 = Oral 2 = Intravenous 3 = Subcutaneous 4 = Other	38 Start Date dd / mm / yyyy	39 Ongoing Therapy 0 = No 1 = Yes	40 End Date dd / mm / yyyy	41 Causal relationship to SAE 1 = Definitely 2 = Probably 3 = Possibly 4 = Unlikely 5 = Not related	42 Action taken 0 =None 1 =Dose reduction 2 =Treatment delayed 3 =Treatment reduced and delayed 4 =Treatment stopped

43 **Additional information:**

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Signed by Clinician _____ **Contact telephone no** _____
(Authorised person)

Print name _____ **Date of completion** ☐☐ ☐☐ ☐☐☐☐ (d m y)

Clinical Trials Unit use only

MRC CTU staff

44 *Event No.* ☐☐☐☐☐☐☐☐

45 *MedDRA code:* ☐☐☐☐☐☐☐☐

46 *SUSAR* ☐ *7 day report* ☐ *15 day report* ☐

47 *SAR* ☐

48 *SAE* ☐

49 *Date sent to the MHRA and MREC* ☐☐ ☐☐ ☐☐☐☐ (d m y)

50 *Comments:*

.....

51 *SAE complete/ready to file* ☐

Form checked by MRC CTU staff (Signature)

_____

☐☐ ☐☐ ☐☐☐☐ (d m y)

Clinical Reviewer

52 *Was SAE drug related?* *Yes* ☐ *No* ☐

53 *Was event unexpected?* *Yes* ☐ *No* ☐

54 *Was the event a SUSAR?* *Yes* ☐ *No* ☐

55 *Comments:*

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Form checked by Clinical Reviewer (Signature)

_____

☐☐ ☐☐ ☐☐☐☐ (d m y)