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FOCUS

Fluorouracil, Oxaliplatin and Irinotecan : Use and Sequencing

A randomised trial to assess the role of irinotecan and oxaliplatin in advanced colorectal cancer

Colorectal Cancer Group

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CLINICAL PROTOCOL
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MRC COLORECTAL CANCER GROUP

A randomised trial to assess
the role of irinotecan and oxaliplatin in advanced colorectal cancer

This document describes a clinical trial, and provides information about procedures for entering patients. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial, but centres entering patients for the first time are advised to contact the MRC Clinical Trials Unit, to confirm details of the protocol in their possession.

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RANDOMISATIONS

Telephone the MRC Clinical Trials Unit on

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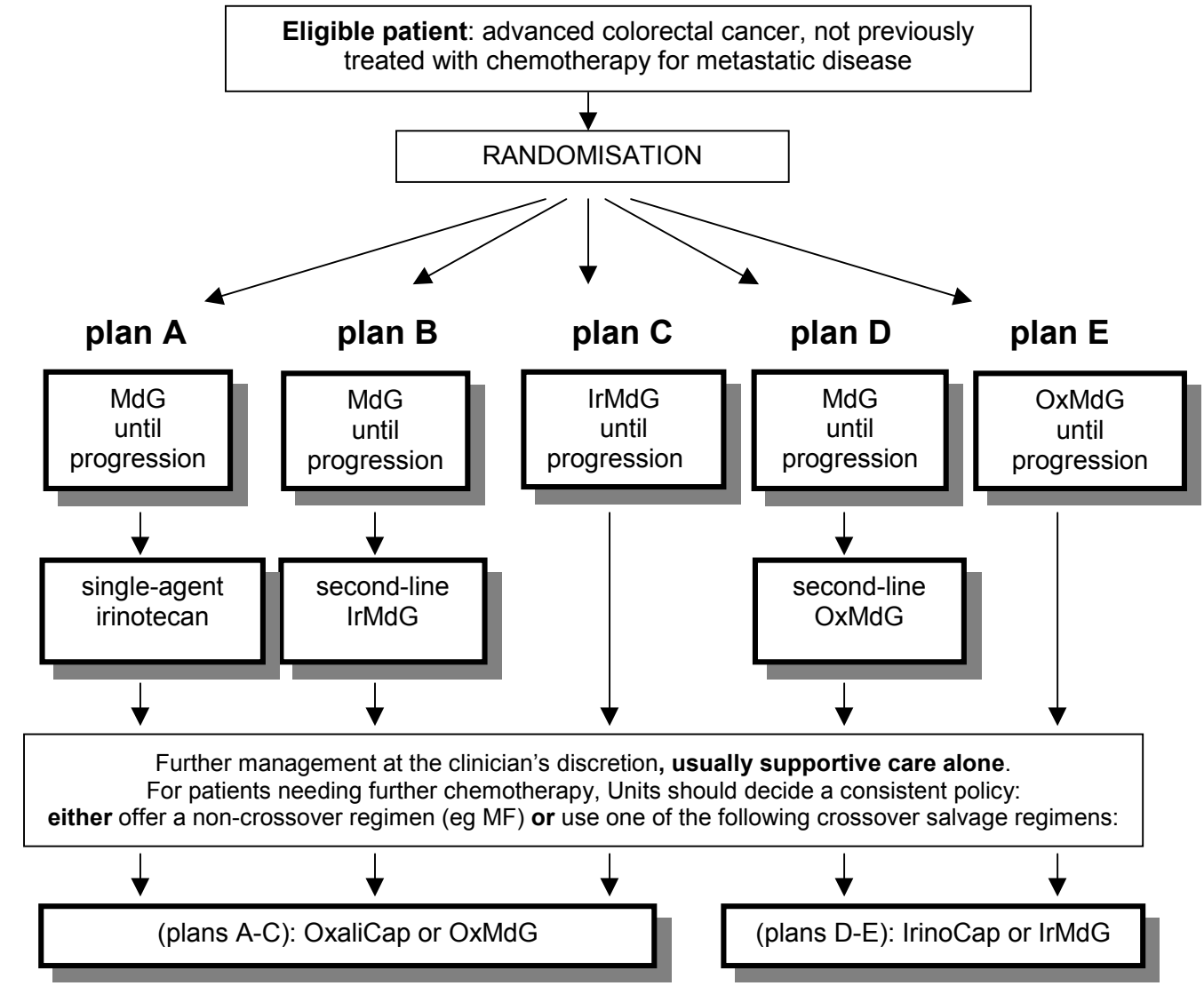
Between 0900 and 1700 hours, Monday to Friday

Contents

Trial Design



Abbreviations: *MdG – modified de Gramont 2-weekly 5FU/FA schedule*
IrMdG – modified de Gramont + irinotecan *IrinoCap – 2-weekly irinotean/capecitabine*
OxMdG – modified de Gramont + oxaliplatin *OxaliCap – 2-weekly oxaliplatin/capecitabine*
MF – PVI 5FU + mitomycin

Summary

2100 patients will be randomised. Selection criteria include: measurable advanced colorectal cancer; PS 0-2 and fit for any of the treatments; not previously treated with chemotherapy for metastatic disease; at least 6 months from last cycle of adjuvant chemotherapy; no previous oxaliplatin or irinotecan. Randomisation will be as shown in the flow diagram, with 1/3rd of patients in the control arm A and 1/6th in each of the experimental arms B-E. Principal endpoint is overall survival, with secondary endpoints PFS, response rate, quality of life and economic evaluation.

1. Introduction

Colorectal cancer

In the UK, our lifetime risk of developing colorectal cancer is 1 in 20. Around 31,000 cases are diagnosed annually, and over 18,000 patients die, making it the second commonest cause of cancer death. For patients with unresectable local or metastatic disease, either at the time of presentation or at relapse (collectively termed 'advanced disease'), the prognosis is poor. In previous UK trials for this indication, median survival has been under a year. The aim of treatment is therefore to improve both the duration and quality of the patients' remaining life.

For many years only one drug, 5-fluorouracil (5FU), had useful efficacy for this group of patients; but recently two newcomers have been introduced – irinotecan and oxaliplatin – with different mechanisms of action and non-cross resistance with 5FU. Most recently, combination schedules have been developed involving concurrent use of 5FU and a new drug. The FOCUS trial is assessing the role of these combinations.

5FU for advanced colorectal cancer

Several randomised controlled trials have shown that 5FU can significantly improve survival and quality of life of patients with advanced colorectal cancer, compared with supportive care alone *[COG,'97].* It is also known that the addition of folinic acid (FA) enhances the activity of 5FU in terms of response rate *[MAGC,'92]*, and that infusional 5FU regimens are more active than bolus regimens *[MAGC,'98].*

There is no universally accepted gold standard 5FU regimen. The 'Mayo' regimen – bolus 5FU and FA for 5 days each month – is recognised by the USA Food and Drug Administration (FDA) as a standard comparator for new drug evaluation. However, the Mayo regimen was clearly inferior in terms of response rate, time to progression and toxicity profile when compared with the 'de Gramont' (dG) regimen of FA plus injections and infusions of 5FU in a large randomised trial *[de Gramont,' 97].*

The MRC colorectal cancer group has been involved in developing optimum 5FU-based therapy. Most recently, our randomised trial of over 900 patients (CR06) compared three treatments, two 5FU-based regimens ('dG' described above, and the 'Lokich' in which patients receive a continuous infusion of 5FU via a pump) and another single agent thymidylate synthase inhibitor, raltitrexed. The preliminary results indicate that the dG regimen is the best, on balance, in terms of progression-free survival, safety, toxicity and quality of life *[Maughan,'99; Stephens,'99].* Its fortnightly intensive administration schedule and minimal myelotoxicity make dG a particularly good basis for combination therapy exploiting interactions with other drugs.

A modified version of dG ('MdG') has now been developed and tested. In dG, on two consecutive days, FA and bolus 5FU are followed by a 22-hour infusion of 5FU

[de Gramont,' 97]. In MdG, FA and bolus 5FU are given on day 1 only, followed by a higher dose 5FU infusion over 46 hours. This reduces drug, pharmacy and nursing costs, and, most importantly, makes outpatient treatment feasible for nearly all patients. A dose-escalation study involving 40 patients has confirmed the activity of this regimen and established the optimum dose *[Seymour,'98]*. The calculated 5FU plasma AUC is increased by approximately 20%, compared with standard dG. Although an MdG vs dG 'equivalence trial' (which would take several thousand patients) has never been performed, there is a strong consensus that MdG can be accepted as at least equivalent to dG as a suitable basis for future development.

Irinotecan and oxaliplatin: new drugs, different mechanisms

After many years with no new cytotoxic agents for colorectal cancer, there is now considerable interest in two new drugs, irinotecan (CPT-11, Campto) and oxaliplatin (L-OHP, Eloxatin). Both new drugs:

- have mechanisms unlike 5FU, and independent of thymidylate synthase
- often interact synergistically with 5FU *in vitro* *[Lavelle,'96, Raymond,'97]*
- may be given in combination with dG and MdG with tolerable additional toxicity
- are much more expensive than our previous drugs for colorectal cancer

Oxaliplatin

Oxaliplatin is an organo-platinum compound. Its dose-limiting toxicity is cumulative peripheral sensory neuropathy, which is usually reversible, but persists for more than 2 months after stopping in around 20% of cases.

Second-line: In non-randomised studies, adding oxaliplatin to dG resulted in objective response rates of 20-46% in patients who had disease progression on dG alone *[de Gramont,'97]*. Response rates for the addition of oxaliplatin to other 5FU regimens, or for second-line single agent oxaliplatin, are lower, at 10-11% *[Machover,'96, van Cutsem,'99].*

First-line combination: A randomised trial in 420 previously untreated patients compared dG versus dG + oxaliplatin ('Ox-dG'). Significant increases were seen in objective response rate (22% vs 49%) and progression-free survival (PFS) (median 28 wks vs 40 wks). The additional toxicity of 'Ox-dG' over dG was moderate, most commonly asymptomatic leucopenia and reversible sensory symptoms, and did not adversely affect quality of life *[de Gramont,2000; Seymour,'99]*. Overall survival was not significantly affected, though this was influenced by crossover (ie patients on the dG arm were allowed to receive Ox-dG on progression). A previous, smaller trial compared chronomodulated 5FU/FA ± oxaliplatin. Similar results were obtained, with markedly increased response rate and PFS but, again possibly due to the benefits of 'salvage' oxaliplatin in control arm patients, overall survival was no different *[Giacchetti, 2000]*.

Irinotecan

Irinotecan damages DNA through topoisomerase-1. It can cause acute cholinergic symptoms, delayed diarrhoea, myelosuppression and alopecia. In recent randomised trials, moderate to severe (WHO grade 3-4) diarrhoea was seen in 20% and leucopenia in 22% of patients *[Cunningham,'98; Rougier,'98]*.

Second-line: Two large randomised trials in 5FU-pretreated patients compared single-agent irinotecan 300-350 mg/m^2 every 21 days with, respectively, best supportive care *[Cunningham,'98]* and with 'second-line' 5FU schedules *[Rougier,'98]*. These trials reported statistically significant absolute survival advantages, of 22% (from 14% to 36%) and 13% (from 32% to 45%) at 1 year respectively, for patients receiving irinotecan. QL assessments did not cover the interval d1-14 after each irinotecan administration, but with this proviso patients on irinotecan had better QL on parameters apart from diarrhoea. Unlike oxaliplatin, irinotecan has mainly been used as a single agent; it is not known whether irinotecan-5FU combinations are of value for patients with 5FU-resistant disease.

First-line combination: Two recent randomised trials compared first line 5FU versus 5FU+irinotecan combination therapy. One compared dG versus dG-irinotecan; early results showed superior response rate and PFS, also a significant increase in overall survival *[Douillard,2000]*. The other compared the Mayo clinic 5FU/FA regimen with a weekly bolus 5FU/FA + irinotecan schedule, again showing improved response rate and PFS, but not overall survival *[Saltz, 2000].* In both trials, toxicity of the 5FU-irinotecan combinations was acceptable, no worse than that of single agent irinotecan, without detriment to QL.

To summarise

There is now good evidence for the efficacy of irinotecan and oxaliplatin in colorectal cancer. In both cases, they offer second-line activity in patients with disease progressing on 5FU. Alternatively, in both cases, a first-line combination with 5FU can produce longer disease control than 5FU alone. The efficacy of the two drugs, in either situation, appears similar (although the strength of clinical trials evidence available varies) and their toxicities, although significant, are manageable.

Unanswered questions and FOCUS

There are several outstanding questions about how to use these important new drugs to best effect for patients with advanced colorectal cancer.

- Combination chemotherapy or single-agent therapy?

Current standard practice as advised by the National Institute for Clinical Excellence [NICE, '02] is to give single-agent 5FU (with folinic acid) followed when this fails, and if

patient fitness allows, by single-agent irinotecan. This is unusual: in most other solid cancers, active drugs are used in combination, an approach supported by tumour kinetic theory *[Goldie,'84].* However, as the trials to date have controlled only a single treatment episode, we do not know whether sequenced single agent therapy is inferior to combination chemotherapy in this disease. FOCUS addresses this question, with a standard arm of sequenced single-agent therapy, compared with experimental arms using combination chemotherapy.

- Combinations in first-line or second-line?

As well as the question of whether to use new drugs in combination schedules, the Oncologist must decide whether such schedules will be used 'up front' or reserved for second-line therapy. Until now, trials of first-line 5FU ± new drug have had variable degrees of unplanned crossover, but none has set out to examine a planned sequence of first-line then second-line therapy.

FOCUS addresses this question by comparing first-line combination treatment with planned second-line combination treatment on disease progression. The intention-to-treat analysis is important here, since the decision to keep a drug 'in reserve', although perhaps reducing toxicity, could potentially disadvantage some patients if, as a consequence, they never receive it.

- Irinotecan or oxaliplatin, or both in sequence?

In a recent French trial, patients were randomised to receive FU/FA plus either oxaliplatin ("FOLFOX") or irinotecan ("FOLFIRI") first-line, with planned crossover on progression [Tournigand 2001]. Both schedules produced a similar high response rate (>50%) in first-line, and overall survival exceeded 20 months in both arms. This raises interest in sequential therapy with both new drugs. But to date there have been no randomised trials, in patients who have failed 5FU and one new drug, comparing crossover to the other *versus* an alternative chemotherapy schedule or supportive care.

So to summarise the current situation (a) it remains important to determine which new drug provides better overall survival and quality of life, whether or not the other drug is also used at a later point in the treatment course; (b) unbalanced crossover (ie in one direction but not the other) would potentially confound this and the other FOCUS questions, but (c) accumulating evidence would support consideration of crossover therapy, although the survival benefit of this approach is hard to estimate. Therefore, after an initial "no-crossover" policy used during the first part of the trial, the FOCUS protocol has now been amended to introduce balanced crossover.

2. Aims

- The principal aim is to determine whether there is an advantage to the use of combination chemotherapy for colorectal cancer (IrMdG, OxMdG) compared with the standard approach of sequential single-agent therapy (MdG then irinotecan).
- In addition, the trial will determine whether combination therapy is best used in first-line management, or reserved for planned second-line treatment following progression on first-line single-agent MdG.
- Finally, the trial compares the efficacy and toxicity of an irinotecan-containing combination (IrMdG) *vs* the equivalent oxaliplatin-containing combination (OxMdG).
- In each case the comparison is initially one of overall survival duration, but a range of other endpoints are also being examined. These include progression-free survival, quality of life, safety, toxicity, patient acceptability and economic evaluation.

3. Design

An open, multicentre randomised trial, comparing five treatment plans (see page 1):

Plan A: (Reference treatment) First-line MdG. In the event of radiological or clinical disease progression, MdG is stopped and, if appropriate, patients receive second-line therapy with irinotecan (single-agent).

Plan B: First-line MdG. In the event of disease progression patients will, if appropriate, receive second-line therapy with IrMdG.

Plan C: First-line treatment with IrMdG.

Plan D: First-line MdG. In the event of disease progression patients will, if appropriate, receive second-line therapy with OxMdG.

Plan E: First-line treatment with OxMdG.

The randomisation is weighted, with 1/3rd patients in Plan A and 1/6th patients in each of the other four plans. The increased number of patients receiving the reference treatment maximises the statistical power of the trial.

4. Endpoints

Primary

- Overall survival (all causes of death)

Secondary

- Progression-free survival
- Objective response rates
- Quality of Life (to include palliation, toxicity, functional impairment)
- Economic evaluation

5. Trial entry

5a. Centre registration

Because of the relatively new status of both irinotecan and oxaliplatin, and the specialised demands of the new regimens on doctors, nurses and pharmacists, general minimum requirements, along with some specific staff experience, are required before an Oncology Centre/Unit can be registered for participation in FOCUS. The completed centre accreditation checklist applies to the expertise of the colorectal team. It is the experience of the whole team that is important.

- Patients must be under the care of a Consultant Medical or Clinical Oncologist.
- Treatment must be administered in a dedicated oncology facility where, in addition to specialist nursing and junior medical staff, the consultant medical or clinical oncologist is routinely on-site and available to discuss/assess patients prior to treatment.
- Defined arrangements must be in place for the management of acute complications. These may include admission to the dedicated facility at the Cancer Centre or Unit under the direct supervision of the consultant oncologist or haemato-oncology colleague, but should not include admission under the general medical or surgical service.
- Written policies for acute management of neutropenic sepsis, venous line complications and acute diarrhoea must be in place, and familiar to relevant staff including on-call staff and those answering telephone queries.
- Defined arrangements are required for nursing support and data collection.
- Familiarity with ambulatory venous infusion techniques: at least 10 patients should have been treated using PVI 5FU, out-patient De Gramont or equivalent ambulatory chemotherapy schedules, with audited results.

- Familiarity with oxaliplatin and irinotecan: at least three patients should have been treated with each of these drugs, using an approved regimen (single-agent irinotecan, Ir-dG, IrMdG, Ox-dG, OxMdG, etc), with audited results.

5b. Patient Selection

Inclusion criteria

- Histologically confirmed adenocarcinoma of the colon or rectum.
- Inoperable metastatic or locoregional disease (synchronous or recurrence).
- No previous chemotherapy for established metastatic disease (if adjuvant chemotherapy was given previously this may have included 5FU but not oxaliplatin or irinotecan, and must have been completed more than 6 months prior to trial entry. Adjuvant/neoadjuvant chemoradiation is considered equivalent to adjuvant chemotherapy).
- Measurable disease (see Appendix VI, RECIST classification).
- Bone marrow function: WBC >4 $x10^9$/l and platelet count >150 $x10^9$/l.
- Hepatobiliary function: serum bilirubin <1.25 x upper limit of normal (ULN) and ALP <5 x ULN.
- Renal function: estimated creatinine clearance (Cockroft method, Appendix III) >50ml/min, or measured GFR (EDTA or creatinine clearance) >50 ml/min..
- WHO performance status 0, 1 or 2 (see Appendix IV) and considered fit and able to undergo all possible treatments.
- For women of child-bearing potential, negative pregnancy test and adequate contraceptive precautions.

Exclusion criteria

- Concurrent uncontrolled medical illness, or other previous or current malignant disease likely to interfere with protocol treatments or comparisons.
- Partial or complete bowel obstruction.
- Age <18. There is no fixed upper age limit, but clinicians are advised to use particular caution in selection of elderly patients.
- Pre-existing neuropathy (> grade 1).
- Chronic diarrhoea or inflammatory bowel disease.
- Gilbert's syndrome or other congenital abnormality of biliary transport (eg Crigler-Najjar syndrome, Dubin-Johnson syndrome).
- Previous transplant surgery, requiring immunosuppressive therapy (due to interaction of cyclosporin-A with irinotecan).
- Unable to comply with QL assessment.

5c. Pre-randomisation evaluation

The following must be performed within 3 weeks prior to the planned start of treatment:

- History and examination; full blood count; biochemistry; renal function (see inclusion criteria); liver function (see inclusion criteria); CXR.
- Serum tumour marker: CEA and/or alternative.
- Measurement of disease. Use CT scanning unless the disease is better evaluated by an alternative imaging modality (eg MRI). CT/MRI scans must be performed within 4 weeks of the planned start of treatment.
- Ensure that the patient has completed the first Quality of Life questionnaire (EORTC QLQ-C30) before randomisation.
- Obtain patient's consent to participate in the trial (see Appendix VII for the patient information sheets and consent form).

5d. Randomisation

Randomisation will only be performed after confirmation that the patient is eligible, has given signed consent and has completed a baseline QL form. After pre-treatment evaluation please complete the first page of the Randomisation Form and telephone the MRC Clinical Trials Unit (9am – 5pm, Mon – Fri):

randomisation line: 020-7670-4777

Details will be taken and the patient will be allocated a treatment plan and trial number. At that point, please complete the remainder of the Randomisation Form and return it to the Clinical Trials Unit (by fax: 020-7670-4818). Once randomised, the patient remains in the trial, even if withdrawn from treatment, and full documentation is required.

6. Treatment

6a. Chemotherapy regimens

Details of the chemotherapy regimens used in this trial are given in Appendix I, along with dose adjustments for toxicity. All are intended as outpatient ambulatory treatment (although they may also be given as inpatient chemotherapy). Recommendations for ambulatory techniques are given in Appendix II.

It is the responsibility of the treating consultant to ensure that the treatment protocols are followed. In particular:

- Treatment should be started as soon as possible after randomisation, and within 3 weeks of the investigations which have been used for eligibility and disease evaluation. If there is a delay in obtaining permanent venous access, the first cycle may be delivered as an in-patient.
- The 2-week cycle should not be extended by more than 7 days except when a delay is indicated for toxicity, or for a planned treatment break (see below).
- dose modifications should be made in accordance with the protocol.
- care should be taken to monitor and react to changes in renal function, body surface area, etc, requiring dose adjustment during treatment.

For significantly obese patients (weight >1.15 x ideal body weight) please use 1.15 x ideal body weight when calculating surface area.

6b. Changes in renal and hepatic function

Renal and hepatic function at the time of initial registration/randomisation in FOCUS must be within the limits stated in the eligibility criteria (section 5b).

After trial entry, the following scheme is used for patients whose renal or hepatic function change at any point after randomisation, for example between randomisation and the start of treatment, between randomisation and progression from first to second line treatment, or during a treatment episode.

Note, however, that deteriorating organ function may be a sign of disease progression and require cessation or alteration in treatment; always discuss with the consultant oncologist.

	day 1 lab values	**Oxaliplatin dose**	**Irinotecan dose**	**5FU dose**
Renal function	*GFR ≥ 50 ml/min	full	full	full
	*GFR 30-49 ml/min	50%	full	full
	*GFR < 30 ml/min	omit oxaliplatin	50%	80%
Hepatic function	Bili ≤ 1.5x ULN **and** ALP ≤ 5x ULN	full	Full	full
	Bili 1.5-3x ULN **or** ALP > 5x ULN	full	50%	full
	**Bili > 3x ULN	50%	Omit irinotecan	50%

*GFR: the Cockroft formula (Appendix III) is used to estimate GFR on day 1 of each cycle and may be used for dose reduction. However, for patients with an estimate of <50 ml/min, a measured EDTA clearance (or 24 hour urinary creatinine clearance) should be obtained on at least one occasion, since the Cockroft formula frequently underestimates GFR in this patient population.

**Bili > 3x ULN. Note that significantly impaired hepatic function may be a sign of disease progression and require cessation of, or change in, treatment. Always discuss deteriorating organ function with the consultant oncologist responsible.

6c. Chemotherapy duration and breaks

Once chemotherapy is started:

- During the first 3 months: As far as possible, treatment should only be interrupted if necessary for toxicity, or stopped for disease progression/clinical deterioration.
- During the second 3 months: In patients with response or stable disease after 3 months, treatment continues for a further 3 months. During this period, an interruption of up to 4 weeks for holidays/patient choice is acceptable, at the clinician's discretion.

- After 6 months: For stable/responding patients, treatment may be stopped electively or continued according to clinician/patient choice. In either case, assessments including radiological assessment must continue at 3-month intervals (see section 7b).
- These rules also apply to planned second-line chemotherapy.

6d. The move from first- to second-line treatment

Patients in Plan A, B or D have a planned second-line treatment "in reserve". This should be started if disease progression occurs during or after MdG, and provided the patient is fit enough (see section 6e). Evidence for disease progression may be:

- Radiological: increase in size of lesions or appearance of new lesions compared with either the pretreatment scan or with the previous on-treatment scan.
- Clinical: new or deteriorating symptoms, signs or other clinical evidence clearly attributable to progression of cancer (not to drug toxicity), in the absence of objective evidence of a response to chemotherapy.
- A rising tumour marker is not, on its own, an indication to start second-line therapy. However if a patient has a > 2-fold increase in a tumour marker compared with baseline/nadir, then a further rise when repeated, this is strong supporting evidence for clinical progression.

Patients who respond to MdG, stop treatment electively after 6 or more months (see section 6c), and remain in stable remission for more than 12 weeks before progressing, may be either re-treated with MdG, or move directly on to the planned second-line option, at the discretion of the treating clinician.

6e. Fitness for planned second-line treatment

At the time of starting second-line treatment, the patient should be evaluated by the responsible oncologist for fitness for the planned treatment. Poor performance status (PS >2) is a relative contra-indication to second-line. Renal and hepatic function must be within the limits indicated in the table in section 6b, and any dose adjustment made as indicated.

Please also note:

- The disease must have been evaluated (eg CT scan) within the 4 weeks prior to starting second-line therapy so that response assessment will be possible.
- The patient must be given ample opportunity to ask further questions and receive information about the planned second-line treatment.
- If a 5FU dose-modification has been necessary during MdG alone, a proportional dose-reduction is made in the dose of 5FU in the IrMdG or OxMdG schedule (see Appendix I).

7. Evaluations during treatment

7a. Every chemotherapy cycle

On the first day of each cycle (or the day before, depending on local arrangements):

- FBC, U&Es, LFTs. See schedule protocols (Appendix I) for critical values.
- Clinical history/examination.
- Any SAEs to be reported to Clinical Trials Unit immediately.
- Drug accountability returns to be completed by pharmacist.

7b. Every 3 months

- Repeat investigations for evaluable disease (usually CT scan) and tumour markers if raised. Ensure that CT scans are reported using RECIST response criteria with reference to the start of the current treatment episode.

  Note that patients having an elective break in treatment (see section 6c) continue to undergo 3-monthly assessment.

8. End of trial and salvage treatment

8a. 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.

8b. 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). In most cases this will involve stopping FOCUS trial treatment but, if appropriate, trial treatment may be continued after the other treatment.

8c. Further chemotherapy

When there is disease progression after first and second-line (plans A, B, D) or first-line combination (plans C, E) treatment within FOCUS, options of further chemo-therapy or purely symptomatic treatment may be considered.

During the first part of the FOCUS trial an “avoid crossover” policy was used. However, after review by the TMG, DMEC and TSC, and consultation with all

FOCUS collaborators, a "balanced crossover" policy has been adopted. Balanced crossover ensures that equal proportions of patients have access to crossover therapy regardless of their initial FOCUS drug allocation.

Under the balanced crossover policy, if a patient remains fit and willing to receive further chemotherapy after completion of the FOCUS plan, they should be considered for either OxaliCap or OxMdG (Plans A-C) or IrinoCap or IrMdG (Plans D-E) as indicated on page 1. If, in the opinion of the treating consultant, salvage chemotherapy is appropriate, this should then be discussed with the patient. Separate Patient Information Sheets are provided for use at this point (see Appendix VII). Patients receiving crossover salvage therapy continue the same FOCUS clinical and quality of life evaluation schedule, including SAE reporting.

Some units may wish to continue with the "avoid crossover" policy. In that case, an established non-crossover salvage regimen (eg MF *[Ross,'97]*, *[Chester,'99]*), or a phase II agent, should be nominated, which may be offered regardless of the previous FOCUS trial treatment. However, units adopting the "balanced crossover" are asked to use the protocol salvage therapy whenever salvage therapy is given, provided the patient meets the fitness requirements for these treatments. Specifically, collaborators are asked not to adopt different salvage policies for patients in different FOCUS arms.

Salvage chemotherapy should be considered if:

- there is evidence of disease progression during or within 12 weeks of the last protocol treatment
- and, in the opinion of the treating clinician, there would be no benefit from continuing or restarting their protocol treatment.

Under that circumstance, treatment options that should be discussed with the patient will include symptomatic care alone, and, when fitness allows, salvage chemotherapy.

Salvage chemotherapy should not be offered to patients of PS $\geq$3, or if life expectancy without treatment is <12 weeks. Severe renal or hepatic dysfunction is a contraindication, but mild dysfunction may be acceptable with appropriate dose adjustment (see Appendix 1).

9. Trial drug supplies

Cytotoxic drug supplies

Sanofi are providing free oxaliplatin for patients in Arm E. This supply will be separately identifiable, and may only be used to treat Arm E patients who are receiving first-line OxMdG. Documentary evidence of usage by pharmacies will be required for this stock.

Aventis are providing free irinotecan for patients in Arm C who were randomised up to 31.7.02, but not for patients randomised thereafter. Again, this supply is separately identifiable, may only be used to treat Arm C patients on IrMdG, and documentary evidence is required.

All other cytotoxic drug treatments must come from normal commercial stock. Pharmacists are of course free to negotiate the best possible deal on the basis of volume, etc, as with any other NHS purchase, but no specific trial discount is currently available. This applies to fluorouracil, irinotecan (for all except Arm C patients randomised up to 31.07.02), oxaliplatin (for all except Arm E patients) and capecitabine.

l-Folinic Acid

L-folinic acid is provided by Wyeth at a special trial price. To order call Wyeth Commercial Operations on 01628 414794/5 and quote "MRC FOCUS trial". Orders received by Wyeth will be reconciled with patient accrual numbers by centre.

Infusor Systems

Baxter Healthcare Ltd are supporting the trial by offering a range of preferential pricing and services to ensure effective running of the trial. For details contact the CTU.

Fresenius Kabi are also offering preferential pricing on their 48-hour pumps. For further details contact Cathy Connor on Tel: 01928 594237.

10. Assessments and forms

10a. Clinical forms

Specimen Case Record Forms (CRFs) are shown in Appendix IX. The following CRFs should be completed:

- Pre-treatment / randomisation form
- Treatment form – every 6 weeks while on FOCUS protocol treatment
- Progress report – every 12 weeks

Once randomised, all patients remain in the trial and clinical forms are required even if patients withdraw from treatment.

10b. Adverse events

An Adverse Event (AE) is the development of a new medical condition or the deterioration of a pre-existing condition (excluding unequivocal progression of disease) following or during treatment.

10c. Serious Adverse events

A Serious Adverse Event (SAE) is defined as one which is fatal, is life-threatening, causes or prolongs hospitalisation, causes disability or incapacity, requires medical intervention to prevent permanent impairment or damage, is a second primary cancer diagnosis, results from an overdose, or is a serious complication of the venous access device. If any of the above occur a SAE Form must be completed and faxed to the CTU immediately. (Fax 020 7670 4818)

If death occurs within 4 weeks of the most recent chemotherapy administration, consideration must be made, by the responsible consultant, of whether chemotherapy has caused or contributed to the death. Any death which is suspected of being related to trial treatment must be notified to the Clinical Trials Unit immediately.

11. Quality of Life

11a. QL timing

QL assessments will be performed at baseline (prior to randomisation) 6 weeks, 12 weeks and 12-weekly thereafter. The primary QL endpoints will be analysed at 12 weeks after randomisation.

11b. QL instrument and endpoints

The EORTC QLQ-C30 has been chosen. It has been used in previous MRC trials (CR05 and CR06). In addition, a small number of trial-specific questions have been added. The primary QL endpoints are palliation, toxicity, functional scales and global QL.

11c. Administration of the QL questionnaires

The initial QL questionnaire must be completed in the clinic before randomisation, and thereafter, in order to fit in with treatment schedules and protocol assessments. When the QL questionnaire coincides with a treatment cycle it should be completed in the clinic before treatment is given.

A window of 2 weeks around each follow-up QL assessment timepoint will be accepted. One person in each centre must be nominated to take responsibility for the administration, collection and checking of the QL forms. High levels of compliance throughout will be required in order to pick up cumulative toxicity and to assess duration of palliation.

The questionnaires should be completed by the patients without conferring with friends or relatives, and all questions should be answered even if the patient feels them to be irrelevant. Patients should always be asked to complete questionnaires even if they declined to complete a previous assessment.

An explanation for patients is given in Appendix VII and fuller details about QL administration are contained in separate MRC CTU guidelines. Please note that once randomised all patients remain in the trial and QL questionnaires are required even if patients do not complete protocol treatment.

12. Economic evaluation

The differential cost of the treatments will be related to their differential benefits in terms of quality adjusted life years (QALYS) (see Appendix VIII).

13. Associated molecular/pathological research

In the future it may be possible, using molecular assays, to select for individual patients the treatment most likely to benefit them, and conversely to avoid the use of ineffective drugs.

FOCUS provides an ideal setting for this research. We are working with British groups currently engaged in molecular pathology research to use this opportunity to study the molecular profile of patients entering FOCUS in order to construct and validate a model of chemoresponsiveness. Any additional studies requiring fresh tumour biopsy or FNA material will of course require separate ethical approval and consent.

14. Analysis plan

Intention-to-treat analysis will be carried out.

14a. Primary endpoint

Overall Survival (OS) is the interval from randomisation to death from any cause. Those still alive will be censored at the date last seen. The Kaplan-Meier method will be used to calculate the curves, and the Mantel-Cox version of the log-rank test to make treatment comparisons. Confidence intervals will be calculated for the corresponding hazard ratios.

14b. Secondary endpoints

Progression free survival (PFS), is the interval from randomisation to first evidence of progression or death from any cause. Surviving patients without progression will be censored at date last seen. The regimens will be compared (ITT) using the Mantel-Cox version of the log-rank test. Arms A, B and D all receive MdG alone as first-line treatment, so PFS should be equivalent in these arms.

Number of cycles. The regimens will be compared (using the Mann-Whitney U Test) in terms of the number of cycles of allocated protocol treatment received.

Objective response rate. The number of patients in each regimen achieving a partial or complete response at 12 weeks (using the standard WHO criteria, see Appendix VI) will be compared using the chi-squared test. Supplementary analyses will look at best response rates achieved with either first or second-line treatment.

Patient's assessment of Quality of Life. The primary QL hypothesis is that the combination regimens will more effectively palliate pre-treatment symptoms, but increase side effects. The main QL comparison will be the change in symptom or subscale score from baseline to 12 weeks, compared by ITT using the Mann-Whitney U Test. Supplementary analyses will look at the changes from baseline to other timepoints.

Economic Evaluation. Standard cost-effectiveness decision rules will be used to establish the most cost-effective option.

15. Statistical considerations

15a. Primary comparisons:

Standard vs first-line combination comparisons (A vs C, A vs E)

Standard vs planned second-line combination comparisons (A vs B, A vs D).

The estimated survival at 2 years for patients receiving dG in the MRC CR06 trial is 10%. With the additional effect of second-line irinotecan, we estimate survival in arm A at 2 years to be in the region of 15%. To show an improvement from 15% to 22.5% with any of the experimental first-line combination arms will require 1050 patients (700 in the reference arm, 350 in the experimental arm) with a 1-sided test, 80% power and 1% significance level. A 1-sided test has been chosen because there would be no interest in any new regimen that was worse than the reference arm. The 1% significance level has been chosen to make an allowance for the multiple comparisons. This number of patients would also give more than 80% power (1% significance, 2-sided test) to detect a 10% improvement from 15% to 25%.

15b. Secondary comparisons:

First-line vs second-line (B vs C, D vs E)

The estimated survival at 2 years for the patients receiving planned second-line combination treatment (plan B or D) is 15%. In order to show an increase in survival to 25% using first-line combination treatment (plan C or E) will require 700 patients (2-sided test, 85% power, 1% significance level). A 2-sided test has been chosen because there would be interest if the planned second-line treatment proved better than first-line, and the 1% significance level has been chosen to make an allowance for the multiple comparisons.

Head-to-head comparison of first-line irinotecan and oxaliplatin (C vs E)

We expect a small (<5%) survival difference between irinotecan and oxaliplatin but 700 patients will be insufficient to show this reliably. However, it is possible that larger differences (~10%) will be observed in terms of progression-free survival, and our 700 patients will allow such a difference to be reliably detected (2-sided test, 95% power, 1% significance level). The design of the trial will also allow the opportunity to combine arms to compare the 2 new drugs head-to-head (ie the 700 patients in arms B+C vs the 700 patients in arms D+E).

Progression free survival (A+B+D vs C, A+B+D vs E)

As patients on plans A, B and D all start treatment with MdG, it is possible to compare the PFS of MdG with IrMdG (plan C). The estimated PFS for MdG is 22.5% at 1 year, and 1750 patients (1400 in A+B+D vs 350 in C) will allow us to detect a difference of 7.5% (1% significance level, 80% power). This also applies to MdG vs OxMdG.

First-line vs second-line (B+D vs C+E)

Finally, it may be possible to combine the 2 first-line plans (plans C and E) and compare their survival with the 2 second-line plans (B+D). The 1400 patients in this comparison (700 B+D vs 700 C+E) will allow us to detect a difference of 7.5% - from 15% to 22.5% (2-sided test, 1% significance, 90% power)

16. Interim analysis; Data Monitoring & Ethics

Day-to-day running of the trial is the responsibility of the Clinical Trials Unit and Clinical Coordinators, working with a Trials Management Group (TMG), which meets at least twice yearly.

The independent Data Monitoring and Ethics Committee (DMEC) consists of two clinicians not entering patients in the trial, and an independent statistician. This DMEC meets at least once yearly; the exact frequency determined by accrual, progression and death rates. At their first meeting, the DMEC advised on the nature and frequency of subsequent interim analyses.

The trial is over-seen by an independent Trial Steering Committee (TSC), to whom the Clinical Trials Unit, Principle Investigator and DMEC report.

17. Publication

The results from different centres will be analysed together and published as soon as possible. Individual clinicians must not publish data concerning patients entered into the trial, which are directly relevant to questions posed by the trial, until after the Trial Management Group has published its report. Named authors for the definitive publication will include the clinical co-ordinators, statisticians, clinical trial managers and all collaborators contributing 10% or more of the patients. All other contributors will be acknowledged.

18. Ethical considerations

The protocol has MREC approval but must be approved by the local ethics committee before patients are entered. 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. A suggested patient information leaflet and patient consent form are attached. A copy of the local ethics committee approval letter must be sent to the 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 patient's best interest. However the reasons for doing so should be recorded and the patient will remain within the trial for the purposes 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 Clinical Trials Unit. This may be used to give guidance to participating investigators and to accompany applications to the local ethics committee.

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Appendix I The chemotherapy regimens

The FOCUS trial regimens:

Salvage regimens:

The MdG regimen

Day 1 of treatment schedule (14 day cycle)

0:00	iv bolus dexamethasone 8 mg
0:00 - 2:00	*l*-folinic acid 175mg (flat dose) iv infusion over 2 hours
2:00 - 2:05	5-fluorouracil 400 mg/m^2 iv bolus injection over 5 minutes
2:05 - 48:00	5-fluorouracil 2800 mg/m^2 iv infusion over 46 hours
48:00	Disconnect pump and flush line (5 ml heparinised saline).

Please note that the bolus 5FU must be given as a 5 minute injection and not as a short 15 or 30 minute infusion.

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 the MdG regimen, and dexamethasone is not necessary as an antiemetic. However, it has been included in the schedule in order to correct for the possible contribution of dexamethasone to the anticancer effect in the combination regimens. For all the treatment regimens in this trial, dexamethasone should be reduced or omitted if patients develop significant toxicity attributable to steroids (eg dyspepsia; dysphoria; etc)

Toxicity and dose adjustments for MdG

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 $\geq$ 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.

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.
- Changes in treatment should be discussed with one of the clinical coordinators.

The IrMdG regimen

The same schedule is used, whether as first-line (Arm C), second-line (Arm B) or salvage crossover (Arms D and E) treatment. However, note that all 5FU dose reductions should be carried through to subsequent 5FU-containing regimens.

Day 1 of treatment schedule (14 day cycle)

0:00	iv bolus granisetron 3 mg (or equivalent)
	iv bolus dexamethasone 8 mg
0:00 - 0:30	Irinotecan 180 mg/m^2 iv infusion over 30 minutes in 250ml normal saline
0:30 - 2:30	*l*-folinic acid 175mg (flat dose) iv infusion over 2 hours
2:30 - 2:35	5-fluorouracil 400 mg/m^2 iv bolus injection over 5 minutes
2:35 -48:30	5-fluorouracil 2400 mg/m^2 iv infusion over 46 hours
48:30	Disconnect pump and flush line (5 ml heparinised saline).

Please note that the bolus 5FU must be given as a 5 minute injection, and not as a short 15 or 30 minute infusion

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
- Ensure patient has supplies of loperamide and ciprofloxacin, and knows how to use them.

The dose of dexamethasone may be adjusted at the discretion of the investigator in patients with side effects attributable to steroids.

Toxicity and dose adjustments for IrMdG

Acute cholinergic syndrome

- Irinotecan may provoke an acute cholinergic syndrome with diarrhoea, sweating, salivation, bradycardia, etc. This may start during the drug infusion or shortly after.
- If this occurs, give atropine sulphate 0.25 mg s/c immediately. Atropine should then be given prophylactically with subsequent cycles.

Haematological

- Myelotoxicity is commoner with IrMdG than with MdG.
- Check FBC on (or 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 $\geq$ 2 weeks occurs, reduce the irinotecan and 5FU (bolus and infusion) 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% dose reduction, a further dose reduction may be made, at the discretion of the treating clinician.

Diarrhoea

- Irinotecan may produce delayed diarrhoea which, if untreated, may become severe. Early intervention with high-dose loperamide is highly effective. Patients must be carefully instructed and given the written information sheet, telephone contact numbers and supplies of loperamide and ciprofloxacin. Care should be taken that out-of-hours staff answering patient queries are familiar with the protocol.
- Patients should start loperamide at the first loose stool: 4 mg, then 2 mg every 2 hours until 12 hours after the last loose stool (up to a maximum of 48 hours).
- If diarrhoea lasts > 24 hours, ciprofloxacin 500 mg bd should be added. If it lasts > 48 hours, or if the patient reports symptoms of dehydration, admit acutely for rehydration and further management (eg octreotide).
- After an episode of severe diarrhoea (grade 3-4), delay chemotherapy until full recovery then resume at 20% reduced doses of irinotecan and 5FU (bolus and infusion).
- If diarrhoea from the previous cycle, even if not severe, has not resolved by the time the next cycle is due, delay 1 week.

Hepatobiliary function

- Irinotecan and its metabolites are cleared by biliary excretion and patients with cholestasis have delayed clearance.
- LFTs should be checked before each treatment cycle. Patients with serum ALP >5 x ULN or serum bilirubin in the range 1.5-3 x ULN require a 50% dose reduction of irinotecan; patients with serum bilirubin >3 x ULN should not receive irinotecan (please refer to section 6b).

Hand-foot syndrome (HFS)

- This is a 5FU side effect. 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 (no need to reduce irinotecan).

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.

Cardiac and neurotoxicity

- 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.
- Neurotoxicity (cerebellar) is uncommon; consider changing to alternative treatment.
- Changes in treatment should be discussed with one of the clinical coordinators.

Renal function

- Patients with moderate renal impairment may receive irinotecan, but if GFR <30ml/min, the dose should be reduced by 50% (see section 6b).

The OxMdG regimen

The same schedule is used, whether as first-line (Arm E), second-line (Arm D) or salvage crossover (Arms A, B and C) treatment. However, note that all 5FU dose reductions should be carried through to subsequent 5FU-containing regimens.

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)

0:00	iv bolus granisetron 3 mg (or equivalent)
	iv bolus dexamethasone 8 mg
	flush line with 5% dextrose
0:00 – 2:00	*l*-folinic acid 175mg (flat) iv infusion, 2 hrs, 250 ml 5% dextrose concurrently with:
0.00 – 2:00	oxaliplatin 85 mg/m^2 iv infusion, 2 hrs, 250 ml 5% dextrose
2:00	flush line with 5% dextrose again.
2:00 - 2:05	5-fluorouracil 400 mg/m^2 iv bolus injection over 5 minutes
2:05 - 48:00	5-fluorouracil 2400 mg/m^2 iv infusion over 46 hours
48:00	Disconnect pump and flush line (5 ml heparinised saline).

Please note that the bolus 5FU must be given as a 5 minute injection and not as a short 15 or 30 minute infusion

Oral antiemetics (starting day 2):

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

The dose of dexamethasone may be adjusted at the discretion of the investigator in patients with side effects attributable to steroids.

Toxicity and dose adjustments for OxMdG

Haematological

- myelotoxicity is more frequent with OxMdG than with MdG.
- 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. The lower limit for the day one platelet count for this regimen is due to the possible occurrence of mild thrombocytopenia after a number of cycles of OxMdG.
- If >1 delay, or 1 delay of ≥ 2 weeks occurs, reduce the oxaliplatin and 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% 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, and some experience dysaesthesia in the throat. These symptoms are precipitated by cold and last from a few hours to a few 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 from the regimen and continue with MdG alone until fully recovered, then restart OxMdG.

Renal function

- Oxaliplatin, like carboplatin, is not nephrotoxic but is renally cleared.
- Before starting oxaliplatin, ensure patient fulfils eligibility for renal function in Section 5b (arm E patients) or section 6b (Arm D patients).
- During treatment serum creatinine should be checked during each treatment cycle. If this rises >25%, re-check measured renal function (EDTA clearance). If GFR is 30-49 ml/min, give oxaliplatin at 50% dose. If GFR falls below 30 ml/min omit oxaliplatin from regimen. This is outlined in section 6b.

Hepatobiliary function

- Oxaliplatin is not principally cleared by the liver, but there is evidence of delayed clearance in patients with marked hepatic dysfunction. For this reason oxaliplatin should be reduced in patients with serum bilirubin >3 x ULN (please see section 6b).

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

- The occasional patient (approx 0.5%) develops acute hypersensitivity to oxaliplatin, usually after more than 6 cycles have been administered. During drug administration, the patient may develop rash, fever, swollen mouth or tongue, hypo- or hypertension and other signs/symptoms of hypersensitivity. This rarely develops to full-blown anaphylaxis, even with repeated treatment
- If acute hypersensitivity occurs, discontinue the infusion and treat with i.v. corticosteroid and antihistamine
- After full recovery, the patient may continue with FA and 5FU
- At the clinician's discretion, the patient may be rechallenged with oxaliplatin at the next cycle. In this case, premedication is recommended as follows:

Dexamethasone 4mg p.o. 6 hourly starting 24 hours pre-treatment, + 8mg i.v. 30 minutes pre-dose

Chlorpheniramine 10mg (or equivalent) + ranitidine 50mg (or equivalent) i.v. 30 minutes pre-dose

Single-agent irinotecan

The second-line option for patients in the control arm (A) is standard single-agent irinotecan, as described in the drug product information sheets. The irinotecan dose recommended is 350 mg/m^2 every 21 days for patients < 70 years and of WHO performance status 0 or 1. For patients > 70 years, or at any age of performance status 2, a lower dose (300 mg/m^2) should be used.

Day 1 of treatment schedule (21 day cycle)

0:00	iv bolus granisetron 3 mg (or equivalent)
	iv bolus dexamethasone 8 mg
0:00 – 1:30	iv infusion irinotecan 350 mg/m^2 (or 300 mg/m^2 – see above) in 250 ml normal saline over 90 minutes (may be reduced to 30 minutes after the first cycle if well tolerated).

Oral antiemetics (starting day 2):

- Dexamethasone 4 mg tds x 1 day; 4 mg bd x 1 day; 4 mg od x 1 day.
- Domperidone or metoclopramide prn
- Ensure patient has supplies of loperamide and ciprofloxacin, and instructions for use.

Toxicity and dose adjustments

Acute cholinergic syndrome

- Irinotecan may provoke an acute cholinergic syndrome with diarrhoea, sweating, salivation, bradycardia, etc. This may start during the drug infusion or shortly after.
- If this occurs, give atropine sulphate 0.25 mg s/c immediately. Atropine should then be given prophylactically with subsequent cycles.

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 $\geq$2 weeks occurs, reduce the irinotecan dose 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% dose reduction, a further dose reduction may be made, at the discretion of the treating clinician.

Diarrhoea

- Irinotecan may produce delayed diarrhoea which, if untreated, may become severe. Early intervention with high-dose loperamide is highly effective for this side effect.
- Patients receiving irinotecan should be carefully instructed about this side effect, given the written information sheet (see Appendix VII), telephone contact numbers and supplies of loperamide and ciprofloxacin. Care should be taken that out-of-hours staff answering patient queries are familiar with the protocol.
- Patients should start loperamide at the first loose stool: 4 mg, then 2 mg every 2 hours until 12 hours after the last loose stool (up to a maximum of 48 hours).
- If diarrhoea lasts > 24 hours, ciprofloxacin 500 mg bd should be added. If it lasts > 48 hours, or if the patient reports symptoms of dehydration, he/she should be admitted acutely for rehydration and further management (eg octreotide)
- After an episode of severe diarrhoea (eg. requiring admission), delay until full recovery then resume at 20% reduced dose irinotecan.
- If diarrhoea from the previous cycle, even if not severe, has not resolved by the time the next cycle is due, delay 1 week.

Hepatobiliary function

- Irinotecan and its metabolites are cleared by biliary excretion and patients with cholestasis have delayed clearance.
- LFTs should be checked before each treatment cycle. Patients with serum ALP >5 x ULN or serum bilirubin in the range 1.5-3 x ULN require a 50% dose reduction of irinotecan; patients with serum bilirubin >3 x ULN should not receive irinotecan (please refer to section 6b).

Renal function

- Patients with moderate renal impairment may receive irinotecan, but if GFR <30ml/min, the dose should be reduced by 50% (see section 6b).

The OxaliCap Regimen

OxaliCap is recommended as a salvage regimen for patients who have been treated under FOCUS plan A, B or C, and so have already received 5FU/LV and irinotecan, either in sequence or in combination. Treatment is given in two-week cycles as follows:

Day 1: **Oxaliplatin 85 mg/m^2** (i.v. infusion over 2 hours, in 250ml 5% dextrose). Antiemetics: granisetron 3mg i.v. plus dexamethasone 4 mg i.v. or equivalents

Day 1 – 9: **Oral Capecitabine 800 mg/m^2 twice daily** to the nearest 150 mg. First dose at end of oxaliplatin infusion; thereafter, at 9am and 9pm each day, within 30 min after ingestion of food and swallowed with water.

Days 10 – 14: No treatment

Starting doses

- Patients who required 5FU dose reduction during previous FOCUS treatment should have a proportionately reduced dose of capecitabine. Eg, a patient who required a 20% 5FU reduction starts with capecitabine at 640 mg/m^2 b.d.
- Mild-moderate renal impairment (GFR 30-49 ml/min): reduce oxaliplatin dose by 50% and reduce capecitabine dose by 25% (these reductions on top of any other dose reductions). Patients with severe renal impairment (GFR <30 ml/min) should not receive OxaliCap.
- ALP >5 x ULN, and/or bilirubin in the range 1.6 – 3 x ULN: reduce both drugs by 25% (these reductions on top of any other dose reductions). Patients with severe hepatic impairment (bilirubin > 3x ULN) should not receive OxaliCap.

Dose increases

- Patients tolerating OxaliCap for 3 cycles with no toxicity of grade >2 may be considered for an increase in capecitabine dose up to a maximum of 1000 mg/m^2 twice daily

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

Dexamethasone may be adjusted or omitted at the discretion of the investigator in patients with side effects attributable to steroids.

Management of toxicity

The following is intended as a guide. All dose adjustments should be discussed with the treating consultant.

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 oxaliplatin and capecitabine 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% dose reduction, a further dose reduction may be made, at the discretion of the treating clinician.

Stomatitis

- Routine mouth-care (eg Corsadyl, nystatin) is recommended.
- For mild stomatitis use sucralfate suspension 4-6 x daily prn.
- If mouth ulcers recur despite this, reduce the doses of both drugs by 20%.

Diarrhoea

- Patients should be instructed to interrupt oral capecitabine treatment if diarrhoea develops at home.
- 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 capecitabine doses by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.

Hand-foot syndrome (HFS)

- Treat symptomatically, with moisturising creams. Topical steroids may also help.
- If HFS is still a problem, reduce the capecitabine dose by 20%.
- Pyridoxine is not proven to be of benefit for capecitabine-induced HFS.

Neurotoxicity

- Oxaliplatin commonly causes peripheral sensory symptoms.
- Many patients experience transient paraesthesia of hands and feet, and some experience dysaesthesia in the throat. These symptoms are precipitated by cold and last from a few hours to a few 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. Capecitabine may be continued at the clinician's discretion.

Allergic reactions to oxaliplatin

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

The IrinoCap Regimen

IrinoCap is recommended as a salvage regimen for patients who have been treated under FOCUS plan D or E, and so have already received 5FU/LV and oxaliplatin, either as first-or second-line therapy. Treatment is given in two-week cycles as follows:

Day 1: **Irinotecan 180 mg/m^2** (i.v. infusion over 30 minutes, 250ml saline). Antiemetics: granisetron 3mg i.v. plus dexamethasone 4 mg i.v. or equivalents.

Day 1 – 9: **Oral Capecitabine 800 mg/m^2 twice daily** to the nearest 150 mg. First dose at end of irinotecan infusion; thereafter, at 9am and 9pm each day, within 30 min after ingestion of food, and swallowed with water.

Days 10 – 14: No treatment

Starting doses

- Patients who required 5FU dose reduction during previous FOCUS treatment should have a proportionately reduced dose of capecitabine. Eg, a patient who required a 20% 5FU reduction during their OxMdG starts with capecitabine at 640 mg/m^2 b.d.
- Mild-moderate renal impairment (GFR 30-49 ml/min): reduce capecitabine dose by 25% (this reduction on top of any other dose reductions). Patients with severe renal impairment (GFR <30 ml/min) should not receive IrinoCap.
- ALP >5 x ULN, and/or bilirubin in the range 1.6 – 3 x ULN: reduce irinotecan by 50% and capecitabine by 25%. Patients with severe hepatic impairment (bilirubin > 3x upper limit normal) should not receive IrinoCap.

Dose increases

- Patients tolerating IrinoCap for 3 cycles with no toxicity of grade >2 may be considered for an increase in capecitabine dose up to a maximum of 1000 mg/m^2 twice daily

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
- Ensure patient has supplies of loperamide and ciprofloxacin, and knows how to use them.

Dexamethasone may be adjusted or omitted at the discretion of the investigator in patients with side effects attributable to steroids.

Management of toxicity

The following is intended as a guide. All dose adjustments should be discussed with the treating consultant.

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 irinotecan and capecitabine 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% dose reduction, a further dose reduction may be made, at the discretion of the treating clinician.

Stomatitis

- Routine mouth-care (eg Corsadyl, nystatin) is recommended. For mild stomatitis use sucralfate suspension 4-6 x daily prn. If mouth ulcers recur despite this, reduce the doses of both drugs by 20%.

Diarrhoea

- Patients should be instructed to interrupt oral capecitabine treatment if diarrhoea develops at home. Otherwise, diarrhoea is managed as in the IrMdG schedule, i.e.:
- Start loperamide at the first loose stool: 4 mg, then 2 mg every 2 hours until 12 hours after the last loose stool (up to a maximum of 48 hours).
- If diarrhoea lasts > 24 hours, ciprofloxacin 500 mg bd should be added. If it lasts > 48 hours, or if the patient reports symptoms of dehydration, he/she should be admitted acutely for rehydration and further management (eg octreotide)
- After an episode of severe diarrhoea (eg. grade 3), delay until full recovery then resume at 20% reduced dose of both drugs.
- If diarrhoea from the previous cycle, even if not severe, has not resolved by the time the next cycle is due, delay 1 week..

Hand-foot syndrome (HFS)

- Treat symptomatically, with moisturising creams. Topical steroids may also help.
- If HFS is still a problem, reduce the capecitabine dose by 20%.
- Pyridoxine is not proven to be of benefit for capecitabine-induced HFS.

The MF Regimen: Mitomycin + Protracted Venous 5FU

The MF regimen may be given as a non-crossover option for patients who require further chemotherapy after completing the trial programme. Clinicians are recommended to refer to *Ross et al, Annals Oncol 8:995-1001, 1997,* which gives a full description of this regimen.

Patients who have already required a 5FU dose reduction during the MdG, OxMdG or IrMdG regimens should receive a reduced dose of 5FU (250 mg/m^2). The patient should have normal renal function (serum creatinine within normal limits), bilirubin < 1.5 x normal and adequate blood count without evidence of red cell fragmentation, before starting this regimen and before each dose of mitomycin.

Day 1 of treatment schedule (42 day cycle)

Antiemetics:	Not routinely needed
day 1	Mitomycin, 7 mg/m^2 (max 14 mg) bolus iv injection
days 1-42	5-fluorouracil 300 mg/m^2/24hours continuous iv infusion

Maximum 4 cycles (total mitomycin dose 28 mg/m^2, max 56 mg)

Toxicity and dose adjustments

There is a potential problem if this regimen is started within a short time interval of cessation of 'IrMdG' or 'OxMdG' regimens. This is because intracellular poly-glutamated folinic acid may persist for several weeks and cause enhanced 5FU toxicity. It is recommended that patients starting the MF regimen within 2 months of the most recent MdG-based treatment should initially receive 200mg/m^2 5FU and, if well-tolerated, the dose increased by 50mg/m^2 every 2 weeks until the full dose is reached.

Stomatitis

- Routine mouthcare (eg corsadyl, nystatin) is recommended. For mild stomatitis use sucralfate suspension 4-6 x daily prn.
- If ≥ grade 2 stomatitis occurs despite this, interrupt 5FU infusion until recovered then resume with the dose reduced by 50 mg/m^2/day (if grade 2) or 100 mg/m^2/day (if grade >2).

Diarrhoea

- For mild diarrhoea, use loperamide 2-4 mg qds and/or codeine phosphate 30-60 mg qds.
- If ≥ grade 2 diarrhoea occurs despite this, interrupt 5FU infusion until recovered then resume with the dose reduced by 50 mg/m^2/day (if grade 2) or 100 mg/m^2/day (if grade >2).

Haemolytic Uraemic Syndrome (HUS)

- This is extremely rare at the dose of mitomycin used in this protocol, but important to be aware of as it is avoidable, but usually fatal if it occurs.
- Check serum creatinine is within normal range before starting and before each dose of mitomycin (if abnormal, do not give mitomycin)
- Check biochemistry and FBC including manual film before each dose of mitomycin. Only give mitomycin provided: creatinine within normal range; bilirubin <30 μmol/l; WBC >3.0 x 10^9/l; granulocytes >1.5 x 10^9/l; platelets >100 x 10^9/l and no red blood cell fragmentation seen.
- If early HUS is suspected (eg. red blood cell fragmentation) give no further mitomycin and treat with prednisolone 40 mg od x 7 days.
- Do not exceed the recommended cumulative maximum dose of mitomycin.

Haematological

- If WBC < 3.0 x 10^9/l, granulocytes < 1.5 x 10^9/l or platelets < 100 x 10^9/l, delay mitomycin for 1 week (but continue 5FU). If still not recovered, delay further 5 weeks.
- If a grade 3-4 neutropenic fever occurs, stop 5FU until recovery, then resume, but omit further mitomycin

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, stop 5FU until recovery then resume with 50 mg/m^2/day dose reduction.

Appendix II Delivery of treatment

The MdG, OxMdG and IrMdG regimens may be delivered in hospital with conventional drip apparatus, but are intended as daycase/outpatient treatments. Investigators who are not already set up for outpatient infusional therapy need to consider the following issues:

Venous access

Semi-permanent venous access is required. Commonly used methods include:

- subcutaneous implantable ports (Portacath, Infu-KT, etc)
- Hickman lines (single-lumen preferred)
- peripheral long lines (PICC, etc).

A defined local protocol for insertion and management of the venous line is required, with identified responsible nursing staff. The right subclavain vein approach gives a lower incidence of complications than left-sided lines and should be used for preference. Fully implantable ports do not need flushing between treatments. Hickman and PICC lines require weekly flushing. The patient, carer, or district nurse should perform the weekly between-treatment flush. If PICC lines are used, the non-return valve type is recommended.

Single or double-lumen lines?

Single-lumen lines are satisfactory for this trial. There is good documented evidence of lower complication rates for single compared with double-lumen lines. Oxaliplatin and folinic acid may be given concurrently through a single-lumen line provided the line is fitted with a y connector at the entry point and the drugs are diluted as specified in this protocol.

Prophylactic anticoagulation

All indwelling venous lines carry a risk of thrombosis. Prophylactic anticoagulation is recommended unless the patient has a contraindication. Options include:

- Warfarin 1 mg od flat rate
- Warfarin adjusted to give INR 1.5-2.0
- Full anticoagulation (INR 2.0-3.0)

There is no firm evidence at present to favour one or other of these policies. Clinicians should adhere to local policy or contribute to a trial. The certain randomisation of the WARP trial is comparing these policies (Contact: CRC Unit, Birmingham, tel: 0121 414 7974, email: a.young@bham.ac.uk).

Infusion pumps

The regimens include a 46-hour infusion of 5FU. This may be delivered using any suitable portable pump device. Most commonly used are:

- battery-powered electrical pumps (eg Walkmed).
- elastomeric balloon infusors (eg Baxter 'LV5').

It is important that staff including out-of-hours on-call staff are familiar with the types of pump being used in the unit.

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.

Appendix III Cockroft and 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 IV 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 V Common Toxicity Criteria

Toxicity	0	1	2	3	4
NAUSEA	None	Able to eat	Oral intake significantly decreased	No significant intake, requiring iv fluids	-
VOMITING	None	1 episode in 24 hours	2-5 episodes in 24 hours	≥ 6 episodes in 24 hours, or need for iv fluids	Requiring parenteral nutrition, or physiologic consequences requiring intensive care: haemodynamic collapse
ANOREXIA	None	Loss of appetite	Oral intake significantly decreased	Requiring iv fluids	Requiring feeding tube or parenteral nutrition
ALOPECIA	Normal	Mild hair loss	Pronounced hair loss	-	-
HAND-FOOT SKIN REACTION	None	Skin changes or dermatitis without pain (e.g., erythema, peeling)	Skin changes with pain, not interfering with function	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 activities of daily living	Severe pain: pain or analgesics severely interfering with activities of daily living	Disabling
STOMATITIS	None	Painless ulcers, erythema or mild soreness	Painful erythema, oedema, or ulcers but can eat or swallow	Painful erythema, oedema, or ulcers requiring iv hydration	Severe ulceration or requires parenteral or enteral nutritional support or prophylactic ntubation
DIARRHOEA (patients without colostomy)	None	Increase of <4 stools/day over pre-treatment	Increase of 4-6 stools/day, or nocturnal stools	Increase of ≥ 7 stools/day, or incontinence; or need for parenteral support for dehydration	Physiologic consequences requiring intensive care, or haemodynamic collapse
DIARRHOEA (patients with a colostomy)	None	Mild increase in loose, watery colostomy output compared with pre-treatment	Moderate increase in loose, watery colostomy output compared with pre-treatment, but not interfering with normal activity	Severe increase in loose, watery colostomy output compared with pre-treatment, interfering with normal activity	Physiologic consequences requiring intensive care, or haemodynamic collapse
LETHARGY	None	Increased fatigue over baseline, but not altering normal activities	Moderate (decrease in performance status by 1 level) or causing difficulty performing some activities	Severe (decrease in performance status by ≥ 2 levels), or loss of ability to perform some activities	Bedridden or disabling
HAEMOGLOBIN	Within normal limits	10.0g/dl - normal	8.0 - 9.9g/dl	6.5 - 7.9g/dl	<6.5g/dl
PLATELETS	Within normal limits	$75x10^9/1$ - normal	50 - $74x10^9/1$	10 – $49x10^9/1$	<$10x10^9/1$
WHITE BLOOD COUNT	Within normal limits	$3.0x10^9/1$- normal	2.0 - $2.9x10^9/1$	1.0 - $1.9x10^9/1$	<$1.0x10^9/1$
NEUTROPHILS	Within normal limits	$1.5x10^9/l$ – normal	1.0 - $1.4x10^9/1$	0.5 - $0.9x10^9/1$	<$0.5x10^9/1$
SENSORY NEUROPATHY	Normal	Loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	Sensory loss or paresthesia interfering with activities of daily living	Permanent sensory loss that interferes with function
MOTOR NEUROPATHY	Normal	Subjective weakness but no objective findings	Mild objective weakness interfering with function, but not interfering with activities of daily living	Objective weakness interfering with activities of daily living	Paralysis

Appendix VI Response Definitions

The RECIST criteria

Some tumour types tend not to produce well defined, bi-dimensionally, easily measurable lesions (e.g. ovarian cancer) which make the assessment of response according to the WHO criteria difficult.

Recently Therasse et al (JNCI 2000) have published an update of the WHO guidelines for evaluating response in solid tumours, called RECIST – Response Evaluation Criteria in Solid Tumours.

These new guidelines aim to eliminate some of the problems highlighted by the use of the WHO criteria, including variation between research groups of a) the methods for integrating change in size of measurable and 'evaluable' lesions into response assessments, b) the minimum number and lesion size to be recorded and c) the definition of progressive disease – based either on a change in one lesion or in the overall tumour load.

A comparison of the new RECIST guidelines against the original WHO criteria in over 4600 patients showed no major differences in the response or progression rates (Gehan and Tefft, JNCI 2000). However as the new guidelines are simpler to implement, quicker to perform, and have clarified a number of aspects, it seems appropriate to incorporate them into the FOCUS trial.

The key difference with the new guidelines, is that instead of measuring the lesion in 2 dimensions (longest dimension and dimension at right angles to the longest dimension) it is now only necessary to measure the longest diameter. To compensate for the fact that a uni-dimension is used (rather than a product of 2 measurements) a proportional adjustment has been made for the change required for response and progression as explained below.

All measurements should be recorded in metric notation by the use of a ruler or callipers. The same method of assessment and the same technique should be used to characterise each identified lesion at baseline and during follow-up.

Notes:

- Disease is divided into 'target' and 'non-target' lesions, the term evaluable is no longer used.
- Lesions should be assessed by CT, MRI or chest radiograph (CXR) rather than by clinical assessment alone, when measurable disease is present.
- When intra-venous contrast agents are given with spiral CT, both the arterial and portal venous phases of enhancement of the liver can be demonstrated. Contrast enhancement and phase of enhancement have a significant effect on ap

parent size of liver metastases, so it is important to measure hepatic lesions in the same vascular phase on subsequent examinations.

- The same imaging modality should be used throughout for any given patients and if MRI is used than the same sequence (eg T1 or T2 weighted images) in the same anatomical plane should be used.]

Baseline:

- **Measurable lesions:** Lesions are classed as accurately measurable in at least 1 dimension, with the longest diameter ≥20 mm with conventional techniques, 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**: Target lesions should be selected on the basis of size and suitability for repeat measurement. Select 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. Sum 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.
- **Non-target lesions**: All other lesions should be noted.

Response definitions:

- **Complete response**: disappearance of all target and non-target lesions (ie all evidence of disease, not just the lesions being measured) determined by 2 observations not less than 2 weeks apart. In FOCUS regular assessments are scheduled 12–weekly. This 12-week assessment should be used as the confirmatory assessment; there is no need for additional confirmatory assessments.
- **Partial response**: ≥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**: 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**: ≥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.

Important reminder:

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

Example:

Month	0	1	2	3	4
Measurement (mm)	100	90	50	55	65
Classification	base-line	stable	partial	partial	progres-sive

Interpretation:

Month 1 - stable disease as neither ≥30% decrease or ≥20% increase from baseline

Month 2 - partial response as ≥30% decrease from baseline

Month 3 - partial response as still ≥30% decrease from baseline. It is not progression as it is not ≥20% increase from smallest total (50mm at month 2)

Month 4 - progressive disease as ≥20% increase from smallest total

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 VII: Patient Information Sheets

This is a relatively complex trial with several different trial treatments, each requiring a certain amount of specific patient information. Clearly there is a danger of 'information overload' or, conversely, over-simplification. For this reason, the written information accompanying the trial has been organised in separate sections as follows:

- The 'general' Patient Information Sheet is intended 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.
- There are then several regimen-specific Patient Information Sheets. The relevant sheet(s) should be given to the patient after randomisation, before treatment starts. 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 these before making a decision about randomisation, but this is not mandatory.
- There is a separate Patient Information Sheet to accompany the quality of life questionnaires.

CancerBACUP Booklets

In addition to these loose-leaf sheets, CancerBACUP have produced an A5-sized bound booklet "*Understanding the FOCUS trial",* which includes most of this information, plus more general information on bowel cancer and cross-references to other information sources. This is highly recommended. To order a supply please contact the MRC Clinical Trials Unit, or CancerBACUP. Please note that the booklets were printed before developing the balanced crossover regimen so do not include information on this aspect of the trial.

The MRC 'FOCUS' Trial of Chemotherapy for Bowel Cancer

General Information Sheet

You have been asked to consider taking part in a clinical trial called "FOCUS". Over 2000 patients will be taking part in FOCUS, in many hospitals across the UK, over several years. Participation is entirely voluntary. Your doctor will explain to you the best standard treatment available, which you will be offered if you decide not to participate in FOCUS.

What is chemotherapy?

When cancer is not completely removable by surgery, 'chemotherapy' – drugs which aim to kill cancer cells – may be given. Although it does not completely cure bowel cancer, chemotherapy can shrink or control it for a period. On average, patients who receive chemotherapy live longer, with fewer symptoms, than those who do not.

Why is this research being done?

Unfortunately chemotherapy does not help every patient, and it can produce unwanted effects as well as benefits. So we are always seeking treatments which can help a higher proportion of patients, carry on working for longer, and cause fewer unwanted effects. In the FOCUS trial, we are looking at two new chemotherapy treatments.

How is the research done?

The best way of weighing up the advantages and disadvantages of these different treatments is in a randomised trial. 'Randomised' means that a computer will allocate you randomly (as if by a roll of the dice) to receive the 'standard treatment' or one of the new treatments being tested. 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 be able to tell reliably if there are any true differences between the treatments.

What is standard treatment?

The most commonly used chemotherapy for bowel cancer is called '5FU'. In this trial you receive 5FU together with a vitamin called folinic acid as a 'drip' into a vein, for 48 hours each fortnight. In many hospitals, by using a small portable pump, most of that 48 hours can be spent at home. This is called the 'modified de Gramont' method, or 'MdG' for short.

If MdG is ineffective, or if it helps at first then stops working, it may be helpful to try a different chemotherapy. This is called 'second-line treatment'. Because not every patient benefits from second-line treatment, your doctor will make a careful assessment of your general health at the time, before recommending it. The most commonly used second-line treatment is called 'irinotecan', and is given as a drip over 1½ hours every 3 weeks. The policy of giving MdG initially, then considering irinotecan second-line treatment in the future, is regarded by many doctors as a standard treatment for your condition.

What are the new treatments?

Sometimes, rather than having a single chemotherapy drug at a time, it can be worthwhile having two drugs concurrently. This is called **'combination chemotherapy**'. Combination chemotherapy is used routinely for many other cancers, but it's a relatively new idea for patients with bowel cancer. In the FOCUS trial, we are testing whether it gives better long-term results than standard treatment.

We are testing two different combination chemotherapies. One consists of irinotecan plus MdG, so we call it **'IrMdG'** for short. The other uses a different drug, 'oxaliplatin', instead of irinotecan, so it is called **'OxMdG'**. In the FOCUS trial, these are being compared with standard treatment. We are also finding out whether combination chemotherapy is better used from the start, or kept in reserve for 'second-line' treatment.

Which treatment might I receive if I take part?

If you take part in FOCUS, the computer will randomly allocate you to a 'treatment plan'. One third of patients are allocated standard treatment, which we have called plan A. The other two thirds are allocated to one of four new plans which we have called B, C, D and E.

A is the "standard treatment" plan. Your treatment will start with MdG. If the cancer starts to grow despite the MdG treatment, your doctor will assess your general condition and consider recommending a course of standard irinotecan.

B also starts with the standard MdG treatment, the same as plan A. However, on plan B if the cancer starts to grow despite the MdG treatment, your doctor will consider, instead of irinotecan alone, a course of the new combination treatment IrMdG.

C uses the new combination treatment, IrMdG, from the very start of your treatment.

D starts with the standard MdG treatment, the same as plan A. But on plan D, if the cancer starts to grow, your doctor considers the new combination treatment OxMdG.

E uses the new combination treatment, OxMdG, from the very start of your treatment.

Whichever you receive, the aim of chemotherapy 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. Unfortunately, even at its best, chemotherapy may not control bowel cancer indefinitely. If your cancer starts to grow despite the full treatment plan, your doctor will discuss further treatment options.

What if I change my mind?

If, after deciding to take part, you change your mind, you can withdraw from the trial at any time. This will not affect your relationship with the doctors and nurses, or your subsequent care, in any way.

Unwanted effects of treatment

As well as its benefits, chemotherapy can also produce some unwanted effects. The unwanted effects of the chemotherapy schedules in the FOCUS trial are summarised here. Some separate information sheets, with more details, are available on request.

MdG: The side effects of MdG are usually mild: nausea, diarrhoea and some tiredness for a few days after each treatment. After some months you may get sore hands and feet, or irritation in the mouth, eyes or nose. Hair loss is rare. A few people are extra-sensitive to MdG chemotherapy and have more exaggerated side effects; if this happens, it is usually possible to continue with effective treatment using a lower dose.

Irinotecan: Unwanted effects can vary from very mild to quite severe. On the day of treatment, you may notice sweating, nausea or diarrhoea, but this can usually be stopped by an injection. Between treatments, the main side effect is diarrhoea, though tablets can usually stop this. Other problems may include tiredness, nausea, sickness and a low white blood cell count (this temporarily increases susceptibility to infections). Hair loss is common with irinotecan, though your hair re-grows when irinotecan is stopped.

IrMdG: this can, in some patients, cause diarrhoea, sweating and nausea or vomiting. About half of patients on IrMdG experience noticeable thinning of the hair. As with irinotecan alone, IrMdG can affect the white blood cell count, which in turn could temporarily make you more vulnerable to infections.

OxMdG: this may also, for some patients, cause diarrhoea, nausea or sickness. Quite commonly, a temporary tingling sensation in the hands or throat can occur after treatment, usually just for a few days but occasionally for longer. OxMdG may also affect your white blood cell count. Hair loss is not common.

What happens during the chemotherapy?

Chemotherapy is given over a 48-hour period each fortnight. Depending on the facilities available at your hospital, you may stay in hospital for 2 nights on a 'drip' into one of the veins in your arm or, more likely, have the treatment at home using a portable pump. For pump treatment at home, you will need to be fitted with a thin tube ('cannula') in the arm, shoulder or chest. This tube leads into one of the veins in your chest and is what the chemotherapy pump is attached to. You will still need to attend the hospital for a day each fortnight, but you will not need to stay as an in-patient.

While you are having chemotherapy, your progress will be monitored carefully. You will be asked about any side effects you have experienced and will have a blood test once a fortnight. Please tell us about any problems, as it is often possible to deal with them. As part of the research, we would like to know how you are feeling, both physically and emotionally. To collect this information, you will be asked to complete a 'Quality of Life' questionnaire at regular intervals. These are treated confidentially.

When does chemotherapy stop?

About every 12 weeks, your doctor will assess what effect your chemotherapy is having on the cancer, usually using a CT scan, and will decide with you whether to continue or stop the treatment. Treatment will normally continue for 6 months, sometimes even longer, provided it is controlling the cancer and not causing too many side effects. If the cancer starts to enlarge during a course of chemotherapy your doctor will stop that treatment and advise on the best course of action.

How will this trial help patients in the future?

This trial will enable us to compare the effects of these different treatment plans on how long people live, their unwanted effects and how they rate their quality of life during the treatment. This will give important information about how best to treat future patients.

Confidentiality and safety

If you decide to participate in FOCUS, information will be collected by the Medical Research Council Clinical Trials Unit. Your GP will be informed, but otherwise all information about you and your treatment will remain strictly confidential. No individual patients will be identified when the results of the trial are published. The trial is being reviewed at regular intervals by an expert committee. This is so that if one of the treatment plans turns out to be substantially better or worse than the others, the trial can be stopped early.

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 FOCUS trial, we would like to

request your permission to retrieve some of that stored material in the future, for bowel cancer research. The research involves extracting DNA or other chemicals from the tumour to see whether it is possible to predict which patients will benefit most from each treatment. All such work is anonymous: your specimens will be identified by a code number, not your name, and neither you nor your relatives will be identified or contacted. These studies will not affect your treatment in any way, and you are free to withhold this permission without affecting your participation in FOCUS or your relationship with your doctor.

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:

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The MRC 'FOCUS' Trial of Chemotherapy for Bowel Cancer

Information for patients receiving MdG chemotherapy

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, '5FU'. The injection, also into the vein, takes about five minutes.

After that, you receive more 5FU, 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 there are also ways of doing it at home, using a 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 warfarin, a tablet which reduces the tendency of blood to form clots.

Unwanted effects of chemotherapy

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

Some people feel more tired than usual for a few days. You may notice a change in taste for certain foods, or soreness in the mouth; also a more frequent bowel habit. Some patients find they feel a little sick, although actual vomiting is unusual. In the longer term, usually after several months of treatment, your hands and feet may become rather dry or sore, and you may have some hayfever-like symptoms such as a runny nose or sore eyes.

All these side effects, if mild, can usually be treated easily. Therefore, if they occur please discuss them with your medical team. If medication has been tried but the side effects persist, it is usually possible to get rid of them by slightly reducing the dose of chemotherapy. This does not compromise the effectiveness of treatment.

Hair loss is uncommon on MdG, however some people do notice hair thinning after several months of treatment. If you are affected, please discuss this with your nurse or doctor.

Rare side-effects

Just occasionally, we meet someone who is unusually sensitive to the effects of 5FU chemotherapy, and the side effects described above occur more quickly and severely than for others. The reason for this is an unusual metabolism which means that the 5FU stays in the bloodstream for longer after it has been given. If this happens, treatment is stopped until the problems have resolved, and it is then usually possible to restart at a lower dose. This does not compromise the effectiveness of treatment.

Very rarely, chemotherapy can cause heart palpitations, chest pain, 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 doctor.

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.

Finally, if you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering fits or severe diarrhoea, please seek advice immediately, either from your hospital team or from your GP.

Your contact numbers are:

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The MRC 'FOCUS' Trial of Chemotherapy for Bowel Cancer

Information for patients receiving single-agent irinotecan

This sheet gives some information about the chemotherapy you will be receiving. It is called irinotecan, but you may also hear it referred to by its trade name "Campto" or by its chemical name, "CPT-11"

How is the treatment given?

Irinotecan is given once every 3 weeks, usually in the chemotherapy day-unit or outpatient department. The treatment starts with an anti-sickness injection, then the irinotecan is given by a 1-2 hour 'drip', into a vein. If you have already had a "cannula" fitted for your MdG chemotherapy, this may be used for the irinotecan infusion; alternatively treatment can be given using a small needle placed into a vein on the back of the hand or arm each time.

When you leave the hospital you will have some tablets to take home including anti-diarrhoea tablets and antibiotics, only to be used if you develop diarrhoea (see below).

Unwanted effects of chemotherapy

You may find it helpful to be forewarned about some of the things which could occur, but bear in mind that most patients will not experience many of these.

During the first couple of hours after starting the chemotherapy infusion you may notice sweating or watering eyes, and feel stomach cramps or have a bout of diarrhoea. If you are affected, tell the nurse on the chemotherapy unit: these symptoms are easily stopped by an injection. If this happens to you, you may receive the injection in advance for future treatments. If the symptoms occur after you have got home from the hospital, during the 24 hours after your irinotecan infusion, rest quietly and telephone the ward for advice.

Occasionally, more severe diarrhoea occurs, usually 1-2 weeks after the treatment. If left untreated this could be dangerous, but it usually responds well to prompt treatment. If you have diarrhoea (except within the first 24 hours after the irinotecan infusion):

- take 2 of the loperamide tablets provided, immediately after the first liquid stool, then another tablet every two hours until 12 hours *after* the diarrhoea has stopped.
- drink plenty of water, fizzy drinks or soups for as long as the diarrhoea lasts.

- if the diarrhoea hasn't settled within 24 hours, you should contact the hospital. You will be asked to start a course of an antibiotic called ciprofloxacin. However, if the diarrhoea is severe, or if you can't drink plenty or if you also have a temperature, you may need to be admitted for a period of observation.

Other side-effects

Some people feel more tired than usual for a few days. You may notice a change in taste for certain foods, or soreness in the mouth. Some patients find they feel sick, although actual vomiting is unusual.

If you are affected please talk to your oncology team. Medications can be tried to combat these unwanted effects. If they persist, it is usually possible to get rid of them by slightly reducing the dose of chemotherapy, without compromising its effectiveness.

It is likely that your hair will thin out during this treatment, and perhaps fall out completely. Please talk this through with your oncology nurses who will be able to help you cope. Hair loss is temporary – it will grow back when irinotecan treatment stops.

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.

Finally, if you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering fits or severe diarrhoea, please seek advice immediately, either from your hospital team or from your GP.

Your contact numbers are:

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The MRC 'FOCUS' Trial of Chemotherapy for Bowel Cancer

Information for patients receiving IrMdG chemotherapy

This sheet gives some information about the chemotherapy you will be receiving. 'IrMdG' is short for 'Irinotecan + 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 and added a new drug, irinotecan - hence the name.

How is the treatment given?

IrMdG chemotherapy is given each fortnight. The treatment starts with an anti-sickness injection then a 2-3 hour 'drip', into a vein, of a chemotherapy drug (irinotecan) and a vitamin (FA). This is followed by an injection of the chemotherapy drug, '5FU'. The injection, also into the vein, takes about five minutes.

After that, you receive more 5FU, 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 there are also ways of doing it at home, using a 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 warfarin, a tablet which reduces the risk of blood clots.

Unwanted effects of chemotherapy

For most patients the side effects of IrMdG are only mild. However, you may find it helpful to be forewarned about some of the things which could occur.

During the first couple of hours of the chemotherapy you may notice sweating or watering eyes, and feel stomach cramps or have a bout of diarrhoea. If you are affected, tell the nurse on the chemotherapy unit: these symptoms are easily stopped by an injection. If this happens to you, you may receive the injection in advance for future treatments. If the symptoms occur after you have got home from the hospital, during the 24 hours after your irinotecan infusion, rest quietly and telephone the ward for advice.

Occasionally, more severe diarrhoea can occur as a side effect of IrMdG chemotherapy. If left untreated this could be dangerous, but it usually responds well

to prompt treatment. If you have diarrhoea (except within the first 24 hours after the irinotecan infusion):

- take 2 of the loperamide tablets provided, immediately after the first liquid stool, then another tablet every two hours until 12 hours *after* the diarrhoea has stopped.
- drink plenty of water, fizzy drinks or soups for as long as the diarrhoea lasts.
- if the diarrhoea hasn't settled within 24 hours, you should contact the hospital. You will be asked to start a course of an antibiotic called ciprofloxacin. However, if thediarrhoea is severe, or if you can't drink plenty or if you also have a temperature, you may need to be admitted for a period of observation.

Other side-effects

Some people feel more tired than usual for a few days. You may notice a change in taste for certain foods, or soreness in the mouth. Some patients find they feel sick, although actual vomiting is unusual. In the longer term, usually after several months of treatment, your hands and feet may become rather dry or sore, and you may have some hayfever-like symptoms such as a runny nose or sore eyes.

All these side-effects can be helped by medication, so if you are affected please talk to your oncology team. If medication has been tried but the side effects persist, it is usually possible to get rid of them by slightly reducing the dose of chemotherapy. This does not compromise the effectiveness of treatment.

It is possible, though not inevitable, that your hair will thin during this treatment. If you find that you are losing hair, talk it through with your oncology nurses who will be able to help you cope. Hair loss, if it occurs, is temporary – it will grow back when IrMdG treatment stops.

Rare side-effects

Just occasionally, we meet someone who is unusually sensitive to the effects of 5FU chemotherapy, and the side effects described above occur more quickly and severely than for others. The reason for this is an unusual metabolism which means that the 5FU stays in the bloodstream for longer after it has been given. If this happens, treatment is stopped until the problems have resolved, and it is then usually possible to restart at a lower dose. This does not compromise the effectiveness of treatment.

Very rarely, chemotherapy can cause heart palpitations, chest pain, 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 doctor.

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.

Finally, if you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering fits or severe diarrhoea, please seek advice immediately, either from your hospital team or from your GP.

Your contact numbers are:

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The MRC 'FOCUS' Trial of Chemotherapy for Bowel Cancer

Information for patients receiving OxMdG chemotherapy

This sheet gives some information about the chemotherapy you will be receiving. 'OxMdG' is short for 'Oxaliplatin + 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 and added a new drug, oxaliplatin - hence the name.

How is the treatment given?

OxMdG chemotherapy is given each fortnight. The treatment starts with an anti-sickness injection then a 2 hour 'drip', into a vein, of a chemotherapy drug (oxaliplatin) and a vitamin (FA). This is followed by an injection of the chemotherapy drug, '5FU'. The injection, also into the vein, takes about five minutes.

After that, you receive more 5FU, 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 there are also ways of doing it at home, using a 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 warfarin, a tablet which reduces the risk of blood clots.

Unwanted effects of chemotherapy

For most patients the side effects of OxMdG are only mild. However, you may find it helpful to be forewarned about some of the things which could occur.

You may find that during the first few days of each chemotherapy cycle you are more than usually sensitive to cold. Picking up cold objects or putting your hands into cold water may cause tingling feelings, and stepping out into cold air may give a tight sensation in the throat. This is quite normal and not harmful. If affected, you may wish to wear gloves and avoid cold places for the periods when you are affected.

After several months of treatment, some patients find that the temporary tingling sensations, instead of lasting just a few hours or days, persist for longer. As a general rule, if this symptom persists right through the 2 weeks until your next treatment is due, and especially you have numbness as well as tingling, it is time to

drop one of the drugs (oxaliplatin) from the chemotherapy. Please ensure you discuss this with your doctors if you are affected.

Other side-effects

Some people feel more tired than usual for a few days after chemotherapy. You may notice a change in taste for certain foods, or soreness in the mouth; also a more frequent bowel habit. Some patients find they feel sick, although actual vomiting is unusual. In the longer term, usually after several months of treatment, your hands and feet may become rather dry or sore, and you may have some hayfever-like symptoms such as a runny nose or sore eyes.

All these side-effects can be helped by medication, so if you are affected please talk to your medical team. If medication has been tried but the side effects persist, it is usually possible to get rid of them by slightly reducing the dose of chemotherapy. This does not compromise the effectiveness of treatment.

Hair loss is uncommon on OxMdG, but some people do notice hair thinning after several months of treatment. If you are affected, please discuss this with your nurse or doctor.

Rare side-effects

Just occasionally, we meet someone who is unusually sensitive to the effects of 5FU chemotherapy, and the side effects described above occur more quickly and severely than for others. The reason for this is an unusual metabolism which means that the 5FU stays in the bloodstream for longer after it has been given. If this happens, treatment is stopped until the problems have resolved, and it is then usually possible to restart at a lower dose. This does not compromise the effectiveness of treatment.

Very rarely, chemotherapy can cause heart palpitations, chest pain, 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 doctor.

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.

Finally, if you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering fits or severe diarrhoea, please seek advice immediately, either from your hospital team or from your GP.

Your contact numbers are:

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MRC 'FOCUS' Trial: Chemotherapy for Bowel Cancer

Further Treatment after FOCUS

General Information Sheet

Some time ago you kindly agreed to participate in FOCUS. This is a large research trial in which over two thousand patients are receiving different schedules and sequences of anti-cancer drugs, so that we can determine which is the best treatment for the future. Best, that is, both in terms of keeping cancer under control for as long as possible and keeping side-effects to a minimum.

FOCUS treatment often controls cancer well, but unfortunately not indefinitely, and there comes a time when further chemotherapy on the FOCUS treatment plan would not be helpful. If you have reached that time in your treatment, your doctor will have discussed with you the options that are open to you.

- Usually, one option is to stop chemotherapy altogether. Many patients find this a positive step, and feel it allows them to concentrate on keeping any symptoms they have under control, and making the very most of their time with their family and friends.
- Sometimes, alternative medical treatments may be helpful. These may include conventional treatments such as surgery or radiotherapy, unproven research treatments, or alternative therapies. Your doctor can advise you about these options.
- Sometimes it can be worthwhile considering further chemotherapy. This is sometimes a difficult decision since, as you will know from experience, chemotherapy treatments can have unwanted effects as well as benefits. It is therefore important to weigh up the pro's and con's before deciding. That is what this information sheet is about.

Further chemotherapy

As part of your FOCUS treatment you will have received a chemotherapy treatment called "5FU and folinic acid" (this is also known as "MdG"). You will also have received a new chemotherapy drug, either "irinotecan" or "oxaliplatin". The government's "National Institute for Clinical Excellence" (NICE) have recently reviewed these new drugs and confirmed that both are active treatments for bowel cancer.

If you decide to go ahead with further chemotherapy after FOCUS, the treatment you will be offered will contain whichever of these new drugs you have not already received. In addition, you may receive another drug called capecitabine. Capecitabine is similar to the 5FU which you have already received, except that

while 5FU had to be given intravenously using a slow pump, capecitabine is given in tablet form. This means that it is not essential to have a Hickman line or PICC line. Alternatively, you may receive your oxaliplatin or irinotecan together with 5FU in the same way as you did before – your doctor will explain which of these treatments he or she recommends.

The new tablet-based treatments are called “OxaliCap” and “IrinoCap” for short. So if you have already had irinotecan as part of your FOCUS treatment, you would now receive OxaliCap; if you have already received oxaliplatin in FOCUS, you would now receive IrinoCap. You will be given an extra information sheet explaining the practicalities and side-effects of the one which applies to you.

Whichever you receive, the aim of chemotherapy 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, radiotherapy, or different chemotherapy drugs), your doctor can offer it.

What if I change my mind?

At any time, before or during chemotherapy, you can change your mind and stop the treatment. This will not affect your relationship with the doctors or nurses, or your subsequent care, in any way.

Is this research?

Yes. Oxaliplatin, irinotecan and capecitabine are all well-established drugs, licensed by the government and with many thousands of patients' experience worldwide. However, we still need to find out more. In particular, we need to know how helpful these treatments are in patients who have already had chemotherapy, as you have, and we need to know the best doses and schedules to use. Given your experience, we would be very interested to know from you how you rate the side-effects and convenience of this treatment compared with the treatment you have already received in FOCUS.

How is the research done?

First, your doctor will need to confirm from blood tests and an examination that it is safe and sensible to go ahead with this new treatment. You may need a scan or other test to measure your cancer so that the treatment’s effect can be measured. Then you will receive chemotherapy, which takes the form of a 2-week treatment cycle.

While you are having chemotherapy, your progress will be monitored carefully. You will be asked about any side effects you have experienced and will have a blood test once a fortnight. Please tell us about any problems, as it is often possible to deal with them. As part of the research, we would like to know how you are feeling, both physically and emotionally. To collect this information, as during the FOCUS trial,

you will be asked to complete a 'Quality of Life' questionnaire at regular intervals. These are treated confidentially.

When does chemotherapy stop?

After about 12 weeks (6 treatment cycles). At that point, your doctor will assess what effect your chemotherapy has had on the cancer, usually using a CT scan, in the same way as during your FOCUS treatment. In some cases it may be worthwhile repeating the same treatment course at a later date. If the cancer starts to enlarge during a course of chemotherapy your doctor will stop that treatment and advise on the best course of action.

Confidentiality and safety

If you decide to participate, information will be collected by the Medical Research Council Clinical Trials Unit. Your GP will be informed, but otherwise all information about you and your treatment will remain strictly confidential. No individual patients will be identified when the results of the trial are published. The trial is being reviewed at regular intervals by an expert committee. This is so that the side-effects and results of the treatment can be compared with other treatments which may be available, to ensure that it is correct for us to continue.

Further information

There is another information sheet with some further details about the chemotherapy schedule – OxaliCap or IrinoCap – which you will receive if you decide to go ahead with further chemotherapy. Please ask for this if you have not yet received it.

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:

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The MRC 'FOCUS' Trial of Chemotherapy for Bowel Cancer

Information for patients receiving OxaliCap chemotherapy

This sheet gives some information about the chemotherapy you will be receiving. 'OxaliCap' is short for 'Oxaliplatin + Capecitabine'. These are the names of the two chemotherapy drugs which you will be receiving.

How is the treatment given?

OxaliCap chemotherapy is given on a fortnightly cycle, rather like the treatment you first received in the FOCUS trial. The treatment starts with an anti-sickness injection then a 2 hour drip into a vein: this is the oxaliplatin chemotherapy. Soon after that, you will be asked to take some tablets, which are the second chemotherapy drug, capecitabine. The exact dose of capecitabine is calculated to suit your size and your previous tolerance of chemotherapy, and this may involve taking several tablets of different sizes.

After that, you will be able to go home. Before going to bed that night you will take a second dose of capecitabine. Then at 9am and 9pm for the next eight days you will have further doses of capecitabine (making nine days treatment in all). After that there will be 5 free days without any capecitabine tablets to take, before you return to the hospital to start the next treatment cycle.

You will be asked to record each dose of capecitabine that you take on a diary card, including a note of any doses which you miss out, and return any unused tablets when you next come for treatment.

Unwanted effects of chemotherapy

For most patients the side effects of OxaliCap are only mild. However, you may find it helpful to be forewarned about some of the things which could occur.

You may find that during the first few days of each chemotherapy cycle you are more than usually sensitive to cold. Picking up cold objects or putting your hands into cold water may cause tingling feelings, and stepping out into cold air may give a tight sensation in the throat. This is quite normal and not harmful. If affected, you may wish to wear gloves and avoid cold places for the periods when you are affected.

After several months of treatment, some patients find that the temporary tingling sensations, instead of lasting just a few hours or days, persist for longer. As a general rule, if this symptom persists right through the 2 weeks until your next treatment is due, or if you have numbness or pain as well as tingling, it is time to

drop one of the drugs (oxaliplatin) from the chemotherapy. Please ensure you discuss this with your doctors if you are affected.

The other common side-effect of OxaliCap is redness or soreness of the hands and feet. This may have happened with your previous chemotherapy, but is rather more common with OxaliCap. If affected please discuss this side-effect with your chemotherapy nurse and doctor, who can advise on skin creams and, if necessary, adjust the dose of chemotherapy tablets. Sometimes, as well as the effects on the hands and feet, patients may develop a rash on other parts of the body, or some hayfever-like symptoms such as a runny nose or sore eyes – again, please tell us if you are affected.

Other side-effects

Some people feel more tired than usual for a few days after chemotherapy. You may notice a change in taste for certain foods, or soreness in the mouth; also a more frequent bowel habit or some bouts of diarrhoea. Some patients find they feel sick, although actual vomiting is unusual. You will be provided with a mouthwash and some anti-sickness and anti-diarrhoea tablets to use if required. If you develop mouth ulcers, vomiting or watery diarrhoea, please **stop your capecitabine tablets** as well as using the remedies provided, then talk the situation through with your medical team.

Hair loss is uncommon on OxaliCap. If you have already lost hair with your previous chemotherapy, you may find it growing back during this treatment.

Finally, if you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering fits or severe diarrhoea, please seek advice immediately, either from your hospital team or from your GP.

Your contact numbers are:

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The MRC 'FOCUS' Trial of Chemotherapy for Bowel Cancer

Information for patients receiving IrinoCap chemotherapy

This sheet gives some information about the chemotherapy you will be receiving. 'IrinoCap' is short for 'Irinotecan + Capecitabine'. These are the names of the two chemotherapy drugs which you will be receiving.

How is the treatment given?

IrinoCap chemotherapy is given on a fortnightly cycle, rather like the treatment you first received in the FOCUS trial. The treatment starts with an anti-sickness injection then a half-hour drip into a vein: this is the irinotecan chemotherapy. Soon after that, you will be asked to take some tablets, which are the second chemotherapy drug, capecitabine. The exact dose of capecitabine is calculated to suit your size and your previous tolerance of chemotherapy, and this may involve taking several tablets of different sizes.

After that, you will be able to go home. Before going to bed that night you will take a second dose of capecitabine. Then at 9am and 9pm for the next eight days you will have further doses of capecitabine (making nine days treatment in all). After that there will be 5 free days without any capecitabine tablets to take, before you return to the hospital to start the next treatment cycle.

You will be asked to record each dose of capecitabine that you take on a diary card, including a note of any doses which you miss out, and return any unused tablets when you next come for treatment.

Unwanted effects of chemotherapy

For most patients the side effects of IrinoCap are only mild. However, you may find it helpful to be forewarned about some of the things which could occur.

During the first couple of hours after starting chemotherapy you may notice sweating or watering eyes, and feel stomach cramps or have a bout of diarrhoea. If you are affected, tell the nurse on the chemotherapy unit: these symptoms are easily stopped by an injection. If this happens to you, you may receive the injection in advance for future treatments. If the symptoms occur after you have got home from the hospital, rest quietly and telephone the ward for advice.

Diarrhoea (watery stools). Occasionally diarrhoea may develop several days after starting chemotherapy, and if this happens it must be treated promptly. If you develop diarrhoea please follow these instructions:

- at the first liquid stool, take 2 loperamide tablets, then take another one tablet every 2 hours and carry on until 12 hours after the diarrhoea has stopped.
- If you are still taking the capecitabine tablets, STOP THEM.
- Drink plenty of extra drinks, to replace the fluid you are loosing.
- If the diarrhoea continues for more than 24 hours, or if you begin to feel dizzy, weak or otherwise ill, phone the hospital for advice (the contact numbers are on this sheet). It may be necessary to come into hospital for treatment.

Only re-start the capecitabine if the diarrhoea stops completely for at least 24 hours. Do not add on doses at the end of the time when you would normally have stopped taking capecitabine. This is because it important that you have had the full five days rest from chemotherapy before the next cycle of treatment starts. Bring any unused tablets back with you when you next come to the hospital.

Other side-effects The other common side-effect of IrinoCap is redness or soreness of the hands and feet. This may have happened with your previous chemotherapy, but is rather more common with IrinoCap. If affected please discuss this side-effect with your chemotherapy nurse and doctor, who can advise on skin creams and, if necessary, adjust the dose of chemotherapy tablets. Sometimes, as well as the effects on the hands and feet, patients may develop a rash on other parts of the body, or some hayfever-like symptoms such as a runny nose or sore eyes – again, please tell us if you are affected.

Some people feel more tired than usual for a few days after chemotherapy. You may notice a change in taste for certain foods, or soreness in the mouth. Some patients find they feel sick, although actual vomiting is unusual. You will be provided with a mouthwash and some anti-sickness tablets to use if required. If you develop mouth ulcers or vomiting please **stop your capecitabine tablets** as well as using the remedies provided, then talk the situation through with your medical team.

Hair loss is slightly commoner with IrinoCap than with your previous chemotherapy. If you are affected, please talk it through with your chemotherapy nurse.

Finally, if you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering fits or severe diarrhoea, please seek advice immediately, either from your hospital team or from your GP.

Your contact numbers are:

The MRC 'FOCUS' Trial of Chemotherapy for Bowel Cancer

Quality of Life Questionnaires – an explanation

About your questionnaires

We are concerned to find out more about how patients feel both physically and emotionally, during and after different treatments. In order to collect this information, brief questionnaires have been designed that can be completed by patients themselves. We would like you to complete questionnaires before, during and after your treatment.

The questionnaires ask you how you have been feeling during the past week and are designed to assess your day-to-day wellbeing, as well as to monitor any side effects you may be experiencing. Your questionnaires will be sent to the Medical Research Council where they will be treated in confidence and analysed together with those from patients in other hospitals, to help plan future treatments.

We enquire about a wide range of symptoms as the questionnaires are designed for use in many different areas of research, but please feel free to discuss any symptoms or concerns with your doctor.

Completing the questionnaires

If possible, complete the questionnaires on your own. Please make sure the correct date is written at the top of the questionnaire before you start. Try to answer all the questions but do not spend too much time thinking about each answer, as your first response is likely to be more accurate. If a question is not applicable to you, please write alongside 'not applicable' or 'N/A', but do not leave any question blank.

When you attend hospital for the first time, you will be asked to complete a questionnaire. We would like you to complete further questionnaires at 6 weeks, 12 weeks and then once every 12 weeks, when you come to hospital for an assessment. If you are not given a questionnaire to complete, please remind your doctor. You can, of course, decline to complete a questionnaire at any time without affecting your relationship with your doctor.

Thank you for your help.

Patient Consent form

COLORECTAL CANCER TRIAL (FOCUS)

Patient name_____

Address_____

_____

I have received an explanation of the trial and read the information sheet and understand:

- ☐ what the trial involves
- ☐ that if I decide not to participate my future treatment will not be affected in any way
- ☐ that I may withdraw from the trial at any time.
- ☐ I give permission for access to any stored pathological specimens for future bowel cancer research. If you do not wish to give this permission you can still participate in the trial.

I agree to take part in the trial.

Signature_____ Date _____

I have been present while the trial has been explained to the patient and have witnessed his/her consent to take part.

Signature_____ Date _____

Clinician's signature _____ Date _____

Appendix VIII 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[1].

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 short questionnaire will be administered to patients at the time intervals detailed above.

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 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].

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. For costs, methods have recently been suggested for using survival analysis[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. Recent methodological work has argued that the use of bootstrapping should be employed to test the parametric assumptions underlying the presentation of means and standard deviations.

4.2 Cost-effectiveness analysis

For the cost-effectiveness analysis, a health care system perspective will be taken on costs (i.e. only costs incurred by the health service will be included), and 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.

Bootstrapping and cost-effectiveness acceptability curves will be used to facilitate a measure of variability 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).

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