Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study involved patients with advanced colorectal cancer who were given one of the three following chemotherapy treatments.

1. De Gramont regimen, i.e. dl-folinic acid 100 mg/m2 (in the effectiveness study this is given as 200 mg/m2), 5-fluorouracil (5FU) bolus 400 mg/m2 and infusion 600 mg/m2 day 1 and 2, q4ld.

2. Lokich regimen, i.e. a protracted venous infusion of 5FU 300 mg/m2 per day; or

3. Raltitrexed (3 mg/m2 intravenously q21d) for an initial period of 12 weeks.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with advanced metastatic colorectal carcinoma for whom palliative chemotherapy was the only remaining treatment option.

Setting
The setting was secondary and primary care. The economic study was carried out in the UK.

Dates to which data relate
The dates to which the effectiveness evidence related were reported elsewhere (Maughan et al., see Other Publications of Related Interest). The patients were recruited between May 1996 and July 1998, and were assessed 12 weeks after starting treatment. The dates to which the resource use related were the same as those for the effectiveness evidence. The price year was 1998 to 1999.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on a sub-sample of the patients used in the effectiveness study.

Study sample
Power calculations were reported in the parent study. These determined that the minimum number of patients in the trial should be 840. A total of 905 patients were reported to have been initially enrolled in the trial and were randomised to one of the treatment arms. Six patients were then deemed to be ineligible, 584 received the prescribed treatment for 12 weeks (though 162 had cycles delayed or doses modified), 208 had the treatment stopped prematurely, and 29 received no protocol treatment. At 12 weeks, 167 patients were not assessed and 121 had died. Patients with histologically confirmed adenocarcinoma of the colon or rectum and locally advanced or metastatic disease were eligible. If the patients had already received systematic chemotherapy, it had to have been FU-based adjuvant therapy completed more than 6 months before trial entry. All patients had to have adequate bone-marrow and renal function and a World Health Organisation (WHO) performance status of 0, 1 or 2. All patients gave written informed consent.

Study design
This was a multi-centre randomised controlled trial. The patients were randomly assigned to one of the study regimens by a telephone call to the MRC Clinical Trials Unit, and were stratified for clinical status of disease and WHO performance status. The effectiveness study carried on monitoring patients after 12 weeks of treatment, whereas the cost study was concerned only with the results at 12 weeks after treatment. At 12 weeks, 784 patients were still alive. A total of 764 patients completed questionnaires at baseline. There were 335 patients who completed questionnaires at baseline, at 6 weeks and at 12 weeks, and 481 patients who completed questionnaires at 6 and 12 weeks.

Analysis of effectiveness
The basis of the analysis was intention to treat. The following health outcomes were measured:

overall survival,

progression-free survival,

the response rate,

treatment-related deaths,

toxicity, and

quality of life measures (QLQ-C30 of the European Organisation for Research and Treatment of Cancer, six pre-tested trial-specific questions, and the 14-item hospital and anxiety and depression scale).

Effectiveness results
At 12 weeks, of the 303 patients initially assigned to the de Gramont regime, 51 were not assessed, 39 died, 60 were suffering from progressive disease and 153 were stable or responding.

Out of the 301 initially assigned to the Lokich regime, 65 were not assessed, 32 were dead, 66 were suffering from progressive disease, and 138 were stable or responding.

Out of the 301 initially assigned to raltitrexed, 51 were not assessed, 50 were dead, 68 were suffering from progressive disease, and 132 were stable or responding.

Overall survival and response were not very different between the three regimens. However, the raltitrexed regimen produced significantly more treatment-related deaths (18 compared with 21 in the whole trial), (p=0.0002 compared with de Gramont and p=0.0006 compared with Lokich).

In terms of toxicity and quality of life measures, the de Gramont regimen was only worse than the Lokich regimen in terms of neutropenia. Otherwise, it was better in terms of pain, problems with eating, and soreness of the hands and feet.

Raltitrexed was worse than the other two regimens in most areas (palliation, appetite, emotional functioning). In
addition, it was worse than the Lokich regimen in terms of fatigue, nausea or vomiting, and constipation.

Compared with raltitrexed, the de Gramont regimen was worse in terms of diarrhoea and hands and feet problems. The Lokich regimen was worse in terms of eating problems and hands and feet problems.

No significant differences were found in terms of depression, but the Lokich regimen came out significantly better in terms of anxiety, \((p=0.005)\).

Patients in the raltitrexed group found their treatment less acceptable than those in the other two groups, and significantly less worthwhile than the de Gramont regimen, \((p=0.026)\). The results were presented in detail elsewhere (Maughan et al., see Other Publications of Related Interest).

**Clinical conclusions**
Raltitrexed produced more treatment-related deaths and a lower quality of life than the de Gramont and Lokich regimens. The de Gramont regimen was better than the Lokich regimen in terms of quality of life.

**Measure of benefits used in the economic analysis**
No summary benefit measure was used since the authors conducted a cost-consequences analysis.

**Direct costs**
No discounting was carried out, which was appropriate given that the costs were incurred over a 12-week period. The quantities and the costs of most resources were analysed separately. The costs were calculated for the drugs, pharmacy staff, nursing, use of pump, Hickman line, inpatient costs, general practitioner (GP) visits, district nurse visits, specialist nurse visits, and patients' expenses. The drug costs were taken from the British National Formulary 1998. GP and district nurse visits were taken from Netten et al. (see Other Publications of Related Interest). The costs of inpatient stays, investigations, materials and disposables were provided by the Finance Department of one of the centres participating in the trial. The price year used was 1998 to 1999.

**Statistical analysis of costs**
The costs were treated stochastically. The sample of patients participating in the cost study was analysed to ensure there was no significant difference between their health status, type of chemotherapy and way in which the chemotherapy was administered, from the patients in the larger effectiveness study. When there was variation in the costs, the standard deviation (SD) was given.

**Indirect Costs**
The carers’ time was calculated. The cost of the carers’ time was calculated using the average hourly wage taken from the Office for National Statistics, 1999.

**Currency**
UK pounds sterling (

**Sensitivity analysis**
The authors investigated whether changing the grade of nurse from E to either D or H would have a significant effect.

The effect on costs of delivering de Gramont either on an inpatient basis, or always as an outpatient, was investigated.

The effect of changing from Hickman lines in the delivery of the Lokich regimen to peripherally implanted central catheters, was calculated.
Also, the effect of Lokich patients being trained to change the pump themselves, rather than attending hospital to get it changed, was analysed.

The costs that were taken from the Finance Department of one of the centres were halved and doubled to see whether there was any effect on the outcome.

**Estimated benefits used in the economic analysis**

See the 'Effectiveness Results' section. The side effects were taken into account in the effectiveness results.

**Cost results**

The total costs for the de Gramont regimen were 5,051 (SD 1,910).

The total costs for the Lokich regimen were 2,576 (SD 1,711).

The total costs for raltitrexed were 2,616(SD 991).

The difference was significant between the de Gramont and Lokich regimens, (p=0.003), and between the de Gramont regimen and raltitrexed, (p=0.005). The difference between the Lokich regimen and raltitrexed was not significant.

The costs were calculated for 12 weeks of treatment. The costs of adverse effects were included.

**Synthesis of costs and benefits**

Not applicable. The sensitivity analysis of the costs showed that the ranking of the three regimens in terms of the costs was not significantly affected by the sensitivity analyses.

**Authors’ conclusions**

The side-effects and reduced quality of life of patients taking raltitrexed mean that it is inferior to the other two treatments. The de Gramont regimen, as administered in the study, is better than the Lokich regimen in terms of central line complications and minor adverse events. A shift towards more outpatient administration of the de Gramont regimen reduces the costs but increases the possibilities of central line complications. Overall, the authors recommend Lokich as the best value for money, as it is significantly cheaper than de Gramont but not significantly worse than de Gramont in terms of efficacy, side effects and quality of life.

**CRD COMMENTARY - Selection of comparators**

The selection of the comparators was justified as all three chemotherapy regimens are widely used for patients with metastatic colorectal cancer. You should determine if these alternatives are relevant for your own setting.

**Validity of estimate of measure of effectiveness**

The source of the effectiveness data, the randomised clinical trial in Maughan et al. (see Other Publications of Related Interest) was appropriate, and the study sample was representative of the study population. The baseline characteristics of the patients on the trial were given in the parent study, but no statistical test was carried out to show the comparability of the three groups. Although power calculations were carried out to determine the size of the trial, quite a large number of patients were not assessed. In the end, the number of assessed patients was less than the target trial size. The different measures of effectiveness were all appropriate, and there was a thorough attempt in the effectiveness study to take into account all the effects on the patients' lives. The authors tried, informally, to summarise the different quality of life and toxicity outcomes. It may have been more helpful to have listed them separately, as different patients will react differently to the relative importance of different outcomes.
Validity of estimate of measure of benefit
There was no summary measure of benefit as the authors used a cost-consequences approach.

Validity of estimate of costs
The authors made a good attempt to include all the costs, taking into account the time given up by the carers and the patients' expenses. They carried out thorough tests to check that the sample of patients whose costs were calculated were representative of all the patients in the trial. Whenever possible, the authors gave the quantities separately from prices. In addition, they carried out sensitivity and statistical analyses on key quantities to check the robustness of their results. The price date was given. The authors also carried out a sensitivity analysis on the prices that they had used from one of the hospitals.

Other issues
The authors compared their results with those of other studies, but they did not discuss the generalisability of their results to other countries. There was a discrepancy between the dosage in the de Gramont regimen between the current paper (100 mg/m2 dl-folinic acid) and the effectiveness paper (200 mg/m2 dl-folinic acid).

Implications of the study
The authors recommend that the Lokich regimen should be used for the kind of patients studied in this trial since it is half as expensive as de Gramont and, although raltitrexed is similar in terms of costs, it has more toxic effects and provides a worse quality of life. The authors did not think that the de Gramont regimen was clearly superior to the Lokich regimen, despite its lower toxicity effects.

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The economic sub-study was funded by Zeneca Pharma.

Bibliographic details
Hale J P, Cohen D R, Maughan T S, Stephens R J. Costs and consequences of different chemotherapy regimens in metastatic colorectal cancer. British Journal of Cancer 2002; 86(11): 1684-1690

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Other publications of related interest
Maughan TS, et al. A multicentre randomised trial comparing survival, palliation and quality of life for 3 chemotherapy regimens (de Gramont, Lokich and ralitrexed) in metastatic colorectal cancer. Lancet 2002;359:1555-63.

Netten A, Dennett J, Knight J. Unit costs of Health and Social Care PSSRU. Canterbury: University of Kent; 1998.

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Antineoplastic Agents /economics /therapeutic use; Colorectal Neoplasms /drug therapy /economics /pathology; Costs and Cost Analysis; Female; Great Britain; Humans; Male; Middle Aged; Neoplasm Metastasis; Sensitivity and Specificity; Treatment Outcome
