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Rapid review

A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer

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A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer

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Contents

Glossary and list of abbreviations

Adjuvant chemotherapy	chemotherapy given at or around the time of curative surgery
AIO	Arbeitsgemeinschaft Internische Onkologie
AUC	area under the curve*
ASCO	American Society of Clinical Oncology
BNF	British National Formulary
BSC	best supportive care
CCTR	Cochrane Controlled Trials Register
CDSR	Cochrane Database of Systemic Reviews
CEA	carcinoembryonic antigen*
Chrono-modulated	delivered over a 24-hour period in varied quantities to correspond with biological rhythms, reduce toxicity and increase response rate
CI	confidence interval*
CRIB	Current Research in Britain (database)
Delayed diarrhoea	diarrhoea occurring more than 24 hours after drug administration
DRG	diagnosis-related group
ECOG	Eastern Cooperative Oncology Group*
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQoL-5 dimensions
FA	folinic acid
FDA	Food and Drug Administration (USA)
First-line treatment	treatment of patients who have not previously received chemotherapy for advanced disease
FOCUS	fluorouracil, oxaliplatin and irinotecan: use and sequencing (MRC trial)
FOLFIRI	irinotecan + FU/FA
FOLFOX	oxaliplatin + FU/FA
FU	fluorouracil
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HEED	Health Economics Database
HNPCC	hereditary non-polyposis colorectal cancer
ICRF	Imperial Cancer Research Fund
iv	intravenous*
LYG	life-years gained
MMC	mitomycin C*
MRC	Medical Research Council
NA	not applicable*
NIH	National Institutes of Health (USA)
NRR	National Research Register
OHE	Office of Health Economics
Progression-free survival	the length of time from randomisation to either the first evidence of disease progression or death
QALY	quality-adjusted life-year
QLQ	Quality of Life Questionnaire
QoL	quality of life

continued

continued

Q-TWiST	quality-adjusted time without symptoms or toxicity
RCT	randomised controlled trial
RSCL	Rotterdam Symptom Checklist
Rx	treatment regimen
ScHARR	School of Health and Related Research
SCI	Science Citation Index
SE	standard error*
Second-line treatment	treatment of patients who have previously received chemotherapy for advanced disease
VAT	value added tax

* Used only in tables, figures or appendices

Executive summary

Background

Description of proposed service

The service evaluated in this review is the use of irinotecan, oxaliplatin and raltitrexed, as both monotherapy and combination therapy, in the first- and second-line treatment of patients with advanced colorectal cancer.

Epidemiology

Colorectal (large bowel) cancer is the second most common cancer in the UK after lung cancer. In 1992, a total of 29,664 new cases were registered in England and Wales, an incidence of 56.6 per 100,000 population. Colorectal cancer is also the second most common cause of cancer death in the UK, causing almost 15,000 deaths in England and Wales in 1998. It affects men and women almost equally. Incidence rises sharply with age but is fairly evenly distributed across the social classes, and within the UK there is little age-specific geographic variation.

Advanced colorectal cancer has been defined as colorectal cancer that, at presentation or recurrence, is either metastatic or so locally advanced that surgical resection is unlikely to be carried out with curative intent. Around 29% of patients who present with colorectal cancer have distant metastases at the time of presentation. About 80% of patients diagnosed with colorectal cancer undergo surgery. Many have potentially good survival outcomes following surgery (with adjuvant chemotherapy in some cases), but over 50% of patients who have undergone surgery with apparently complete excision will eventually develop advanced disease and distant metastasis (typically presenting within 2 years of initial diagnosis). Median survival from diagnosis of metastatic disease is 6–9 months, and during this time patients may develop a wide range of physical and psychological symptoms, which detract from their quality of life and often require hospital admission.

Colorectal cancer is rare below 40 years of age, and 41% of patients are over the age of 75 years. Although 52% of deaths from colorectal cancer occur in the over-75 age group, colorectal cancer is nonetheless a significant cause of premature death as well as of morbidity. The aim of treatment in patients with advanced disease is to improve both the duration and quality of the patient's remaining life.

Objectives

The objectives of this review are:

1. to evaluate the relative clinical effectiveness of irinotecan, oxaliplatin and raltitrexed in terms of disease progression rates
2. to estimate their relative effect on overall survival and quality-of-life-adjusted survival
3. to evaluate their side-effect profiles
4. to estimate the incremental cost-effectiveness of the three drugs in comparison with conventional therapy
5. to estimate the overall cost associated with the use of these drugs in England and Wales.

Methods

A systematic review of the literature, involving a range of databases, was conducted. Full details are described in the main report.

Results

Number and quality of studies, and direction of evidence

Irinotecan

Six randomised controlled trials relating to the use of irinotecan as first-line treatment of advanced colorectal cancer were judged to have met the inclusion criteria. Only preliminary data were available for four of these, of which three had been published only in abstract form. The two completed studies found that the combination of irinotecan with fluorouracil and folinic acid (FU/FA) was associated with significantly longer median overall and progression-free survival than FU/FA alone. Irinotecan alone appeared comparable with FU/FA alone. However, irinotecan plus FU/FA was associated with a higher level of toxicity than FU/FA alone.

Seven studies relating to the use of irinotecan as second-line treatment of advanced colorectal

cancer were judged to have met the inclusion criteria. Full reports were available for only two of these; for the remainder, only preliminary data were available in abstract form. One of the two completed studies compared irinotecan with best supportive care (BSC), and the other compared it with FU/FA. Irinotecan was found to significantly increase median overall survival compared with FU/FA, although it did not increase median progression-free survival significantly. Irinotecan was associated with increased overall survival compared with BSC, but it is not clear to what extent this should be attributed specifically to irinotecan and to what extent to other factors. Irinotecan significantly increased pain-free survival and time to deterioration of performance status in comparison with BSC, but not in comparison with FU/FA. There is also some preliminary evidence that combination second-line irinotecan/FU/FA therapy may increase progression-free survival compared with FU/FA alone. As second-line treatment, irinotecan was again associated with a higher level of toxicity than FU/FA.

Oxaliplatin

Seven studies relating to the use of oxaliplatin as first-line treatment of advanced colorectal cancer were judged to have met the inclusion criteria. Of these, two studies compared only chronomodulated versus fixed-rate oxaliplatin plus FU/FA. Full reports were available for only two of the remaining studies; for the remainder, only preliminary data were available in abstract form. Oxaliplatin plus FU/FA was found to increase median progression-free survival compared with FU/FA alone. In both studies for which final results were available, so many patients received chemotherapy subsequent to the study medication that the impact of oxaliplatin on overall survival has been obscured. Oxaliplatin appeared to be associated with increased toxicity compared with FU/FA regimens.

Three studies relating to the use of oxaliplatin as second-line, or first- and second-line treatment of advanced colorectal cancer were judged to have met the inclusion criteria. Only preliminary results have been published, in abstract form, in relation to these studies. These preliminary results suggest that median progression-free survival may be longer in patients receiving oxaliplatin plus 5FU than in those receiving either 5FU or irinotecan monotherapy.

Raltitrexed

Four studies relating to the use of raltitrexed as first-line treatment of advanced colorectal cancer were judged to have met the inclusion criteria. Full reports were available for only two of these studies. When the results were statistically significant, raltitrexed was associated with shorter progression-free and overall survival than FU/FA. Although raltitrexed was associated with less toxicity than the Mayo bolus FU/FA regimen, it was associated with more deaths that were considered to be possibly treatment related.

Summary of benefits

There is good evidence to suggest that the use of a combination of irinotecan and FU/FA in the first-line treatment of advanced colorectal cancer can extend both median progression-free and overall survival by 2–3 months compared with either FU/FA alone or irinotecan alone, although at the cost of increased toxicity compared with FU/FA alone. As second-line treatment, irinotecan monotherapy appears to extend median progression-free survival by approximately 1 month and overall survival by approximately 2 months compared with FU/FA alone, again at the cost of increased toxicity. There is also some preliminary evidence to suggest that combination irinotecan/FU/FA therapy after FU/FA failure may extend median progression-free survival by approximately 2 months and overall survival by almost 3 months compared with FU/FA alone.

There is also good evidence to suggest that, when used as first-line therapy, the combination of oxaliplatin with an infusional FU/FA regimen extends median progression-free survival by 2–3 months compared with FU/FA alone, although again with increased toxicity. This combination may also prolong overall survival, although this is not clear because of the extensive use of second-line oxaliplatin in patients randomised to FU/FA alone, which would dilute the evidence of the efficacy of oxaliplatin in the oxaliplatin arm. In addition, the improved response rate achieved by the addition of oxaliplatin to FU/FA may enable larger numbers of patients to undergo potentially curative surgical resection of liver metastases. Preliminary data suggest that, as second-line treatment, oxaliplatin plus 5FU may extend median progression-free survival compared with either 5FU or irinotecan monotherapy.

In comparison with FU/FA, raltitrexed used as first-line therapy appears to reduce both progression-free and overall survival, and is associated with a higher mortality rate. Thus, there seems no advantage in using raltitrexed to treat advanced colorectal cancer in patients who

can tolerate FU/FA treatment, and further research is required to determine whether it has a role in the treatment of the patient group for whom it is licensed, namely those few patients with specific metabolic intolerance to 5FU who would not be too frail for 5FU treatment. This is a smaller patient group than AstraZeneca, in their submission to the National Institute for Clinical Excellence, suggest would benefit from raltitrexed.

Costs

The cost of treatment with 5FU and FA by the de Gramont infusional regimen is estimated to be £2500 per month when given on an inpatient basis or £1500 when given on an outpatient basis. The addition of oxaliplatin adds £800 per month to this regimen, and addition of irinotecan adds £1000. The Mayo 5FU regimen is less costly at £1100 per month. The cost of treatment with raltitrexed has been shown by one economic study[1] to be similar to that for the Mayo regimen (£781 for raltitrexed, £834 for Mayo), although these published costs of Mayo treatment are lower than the estimate calculated by the authors of this review. The estimated cost of second-line treatment with irinotecan as a single agent is £1800.

The estimation of the total costs per patient for any treatment is dependent on the mean treatment duration. For first-line treatment with irinotecan, this mean value is not known, so there is great uncertainty in the calculation of treatment costs.

Furthermore, in practice, treatments may be given to patients for limited periods. The estimates of additional treatment costs compared with 5FU are based on mean treatment times from the trials, except for first-line irinotecan.

Total treatment costs for oxaliplatin are £5330 greater than costs for inpatient treatment with the de Gramont FU/FA regimen. The same comparison for irinotecan shows an additional cost of £11,400. It should be noted that there is more uncertainty in the estimate for irinotecan than for oxaliplatin. The differences with the Mayo regimen are greater. The total cost of single-agent irinotecan for second-line treatment is less than that of 5FU by the de Gramont regimen. A bolus regimen (such as Mayo) is not normally appropriate for second-line treatment. However, not all patients who may be eligible for second-line treatment with irinotecan (approximately 65%) would currently receive 5FU. For these patients, the relevant comparison is with BSC. Assuming that BSC costs are the same for all patients (i.e. patients treated with irinotecan eventually incur the same BSC costs as patients having no second-line treatment), the additional cost of giving patients irinotecan is £7600.

Cost-effectiveness

The calculations of cost-effectiveness are based on progression-free survival, rather than survival, because when chemotherapy is given subsequent to the allocated first-line regimens, survival cannot be uniquely related to the allocated therapy. The use of progression-free survival in place of survival has considerable implications on the results of the economic analysis. Oxaliplatin shows greater improvement than irinotecan in progression-free survival, compared with 5FU, based on our analysis of the progression-free survival curves; however, no survival benefit has been shown in clinical trials with oxaliplatin, whereas it has with irinotecan. For second-line treatment (after which smaller proportions of patients had further chemotherapy compared with after first-line therapy), cost-effectiveness ratios were estimated on the basis of both progression-free survival and survival. The results of the two estimates are different.

The marginal cost per progression-free year for oxaliplatin compared with the de Gramont 5FU regimen is £23,000. The equivalent cost for irinotecan is £58,400. These figures are obviously dependent on the cost estimates that, as previously noted, are more uncertain for irinotecan than for oxaliplatin. Second-line treatment with irinotecan (single-agent therapy) is less expensive than the inpatient de Gramont regimen. If it is assumed that all treatments are given on an outpatient basis, the marginal cost per progression-free year is unchanged for oxaliplatin, £49,000 for irinotecan and £26,400 for second-line irinotecan.

For second-line treatment, the marginal cost per life-year gained (i.e. based on survival benefit) is zero when irinotecan is compared to inpatient treatment with the de Gramont regimen, £11,180 when compared to outpatient de Gramont, and between £17,700 and £28,200 when compared to BSC.

An illustrative analysis was undertaken to estimate the effect of taking quality of life into account. The assumptions are considered to be too uncertain to base conclusions on the results.

Because there is no benefit in either progression-free survival or survival when treatment with

raltitrexed is compared with 5FU, a cost-effectiveness analysis is not appropriate.

Conclusions

When used as first-line therapy, the combination of either irinotecan or oxaliplatin with an infusional FU/FA regimen appears to extend median progression-free survival by 2–3 months compared with FU/FA alone, although with increased toxicity; irinotecan has also been shown to extend overall survival. However, raltitrexed appears to reduce both progression-free and overall survival compared with FU/FA. When used as second-line treatment, irinotecan monotherapy appears to extend median progression-free survival by approximately 1 month and overall survival by approximately 2 months compared with FU/FA alone, again at the cost of increased toxicity. Preliminary data suggest that, as second-line treatment, oxaliplatin plus 5FU may extend median progression-free survival compared with either 5FU or irinotecan monotherapy.

Recommendations for research

Evidence is needed of the relative merits of irinotecan and oxaliplatin for patients with advanced colorectal cancer, the best time to introduce these drugs (as first- or second-line therapy), and whether both should routinely be offered to a single patient and, if so, in what order.

Randomised controlled trials are also required to explore:

- the relative efficacy of second-line 5FU plus mitomycin C versus irinotecan or oxaliplatin
- whether raltitrexed is beneficial compared with either BSC alone or other agents in patients with specific metabolic intolerance of 5FU
- the relative efficacy of different sequences of therapies
- the optimum duration of therapy (i.e. whether it should be continued to disease progression, death or unacceptable toxicity, or only until response, with or without consolidation)
- the relative efficacy of oxaliplatin and 5FU in patients with a family history of colorectal cancer caused by the *HNPCC* gene mutation.

Given the palliative objectives of therapy, research is required to address the issue of measuring quality of life in patients with terminal cancer.

Chapter 1

Aim of the review

The overall aim of this review is to evaluate the marginal clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed in both first- and second-line treatment of patients with advanced colorectal cancer, as compared with established treatments. The report reviews the use of these drugs in both monotherapy and combination therapy. It does not consider the use of chemotherapy adjuvant to potentially curative surgery.

There is a need to review changes in quality of life associated with new drug treatments for advanced cancer. It is desirable for extended survival to be associated with the maintenance of good quality of life. Progression-free survival is considered to be a particularly important outcome measure in relation to the treatment of advanced colorectal cancer because disease progression impairs both physical and emotional health. Tumour response (see appendix 1) does not necessarily correspond to subjective benefit in terms of the quality of survival, and subjective improvement (a clinical response) is possible without an objective response.

The review therefore focuses primarily on differences between treatments in terms of overall survival and disease progression, and also on any significant impacts that treatments may have on health-related quality of life. If survival advantage is only modest compared with that provided by alternative regimens or by best supportive care (BSC), disease-related symptoms and quality of life obviously become particularly relevant outcome measures.

The following objectives are therefore contained within the overall aim of the review:

1. to evaluate the relative clinical effectiveness of the three drugs in terms of disease progression rates
2. to estimate their relative effect, if any, on overall survival and quality-of-life-adjusted survival
3. to evaluate their side-effect profiles
4. to estimate the incremental cost-effectiveness of the three drugs in comparison with conventional therapy
5. to estimate the possible overall cost associated with the use of these drugs in England and Wales.

Chapter 2
Background

Description of underlying health problem

Epidemiology of colorectal cancer

Colorectal (large bowel) cancer is the second most common cancer in the UK after lung cancer. In 1992, a total of 29,664 new cases were registered in England and Wales, an incidence of 56.6 per 100,000 population.[2] Colorectal cancer is also the second most common cause of cancer death in the UK, causing almost 15,000 deaths in England and Wales in 1998.[3] This cancer affects men and women almost equally.[4] Thus, an average Health Authority with a population of approximately 500,000 could expect in the region of 280 new cases and 140 deaths a year.

The incidence of colorectal cancer rises sharply with age. It is rare below 40 years of age, and 41% of patients are over age 75 years.[5] This is illustrated by the death rates for England and Wales for 1998[3] (see *Table 1*).

The incidence of colorectal cancer is fairly evenly distributed across the social classes, and within the UK there is little age-specific geographic variation.[5]

Survival is related to the spread of the disease at diagnosis. Around 29% of patients who present with colorectal cancer have distant metastases at the time of presentation, and their outlook is poor[6] (see *Table 2*).

About 80% of patients diagnosed with colorectal cancer undergo surgery.[7] Many have potentially good survival outcomes following surgery (with adjuvant chemotherapy in some cases), but over 50% of those who have undergone surgery with apparently complete excision will eventually develop advanced disease and distant metastasis (typically presenting within 2 years of initial diagnosis). Median survival from diagnosis of metastatic disease is 6–9 months, and during this time patients may develop a wide range of physical and psychological symptoms that detract from their quality of life and often require hospital admission.[8]

The most frequent site of metastatic disease is the liver. In as many as 30–40% of patients with advanced disease, the liver may be the only site of spread. For these patients, surgery provides the only chance of a cure. Reported 5-year survival rates for resection of liver metastases range from 16% to 48%, considerably better than those for systemic chemotherapy; however, reported operative mortality rates range from 0% to 14%, and postoperative complications are common and often serious.[9]

Metastatic rectal cancers respond better to chemotherapy than metastatic colon cancers.

TABLE 1 *Death rates for colorectal cancer in England and Wales in 1998*[3]

	Death rates by age group (years)				
	0–44	**45–64**	**65–74**	**75+**	**Total**
Number of deaths	203	2783	4132	7866	14,984
Rate per 100,000 population	0.6	23.0	93.9	202.3	28.6

TABLE 2 *Modified Duke's staging of colorectal cancer, with 5-year survival*[6]

Duke's stage (modified)	Definition	Frequency at diagnosis	5-year survival
A	Cancer localised within bowel wall	11%	83%
B	Cancer that penetrates the bowel wall	35%	64%
C	Cancer spread to the lymph nodes	26%	38%
D	Cancer with distant metastases	29%	3%

Definition of advanced colorectal cancer

Advanced colorectal cancer has been defined as colorectal cancer that, at presentation or recurrence, is either metastatic or so locally advanced that surgical resection is unlikely to be carried out with curative intent.[10] This review will consider treatment in the following patient groups with advanced disease:

- those who have metastatic disease at initial diagnosis and those who develop metastatic disease more than 6 months after stopping adjuvant fluorouracil (5FU)-based therapy (i.e. 5FU naive)
- those who have developed metastatic disease while receiving or within 6 months of stopping adjuvant 5FU-based therapy and those who have metastatic disease that progresses either while receiving or within 12 weeks of stopping 5FU-based treatment (i.e. 5FU refractory).

Significance in terms of ill health

Although 52% of deaths from colorectal cancer occur in the over-75 age group, this cancer is a significant cause of premature death. It is also a significant cause of morbidity. The aim of treatment in patients with advanced disease is to improve both the duration and the quality of the patient's remaining life. Although poor WHO performance status (see appendix 2) is a contraindication to chemotherapy, age alone is not.

In particular, this review will not only focus on differences between treatments in overall survival and disease progression rates but also aim to include information on the significant impacts that such treatments may have on health-related quality of life. There is some evidence to suggest that extended survival is not always associated with an overall improvement in quality of life. This is particularly relevant in cases such as this, when treatments are purely palliative and have no real chance of achieving long-term survival.

Current service provision

The recent NHS Executive document 'Improving outcomes in colorectal cancer' summarises current service provision for diagnosis, treatment and follow-up of patients with colorectal cancer.[9] The only potential for long-term survival in patients with metastatic disease results from resection of liver metastases in cases in which there is no evidence of extra-hepatic disease and the position and size of the metastases are favourable. Some patients have also survived after resection of lung metastases, but such cases are rare.

Patients with metastatic disease who are sufficiently fit can be treated with systemic chemotherapy, typically 5FU with folinic acid (FA). Those with a WHO performance status greater than 2 would usually be deemed unsuitable for chemotherapy. In five randomised controlled trials (RCTs), 5FU-based chemotherapy given immediately on diagnosis of advanced or recurrent disease was compared with supportive care that reserved chemotherapy for the palliation of symptoms. The results showed that the former therapy increased median survival by 2–6 months (from a range of 5–9 months to a range of 7.5–14 months) and symptom-free survival from a median of 2 months to 10 months, without any adverse impact on quality of life.[9] This is a conservative estimate of the potential impact of chemotherapy because, in all five studies, suboptimal chemotherapy schedules were used and a proportion of the 'control' patients received chemotherapy.

Of the 5FU-based regimens, the 'de Gramont' infusional regimen has been demonstrated to be equivalent to both the Mayo bolus regimen[11] and the Lokich infusional regimen[12,13] in terms of survival, superior to the Mayo regimen in terms of progression-free survival and superior to both in relation to toxicity (for details of 5FU-based regimens, see appendix 3).

The de Gramont regimen is typically repeated every 14 days. It involves a 48-hour inpatient stay. However, a modified de Gramont regimen has been developed whereby FA and bolus 5FU are given only on the first day of treatment, followed by a higher-dose 5FU infusion over 46 hours. This modified regimen requires the insertion of a central line as a day-case procedure, but enables most patients to be treated as outpatients, spending half a day in the day unit and receiving a home visit from a district nurse for each course of treatment. A pilot study has indicated that this modified de Gramont regimen is associated with higher compliance, fewer treatment delays and significantly higher quality of life than the inpatient de Gramont regimen.[14] However, experience at the Royal Marsden Hospital (Sutton, UK) has indicated that 11% of Hickman lines used for protracted venous infusion of 5FU have to be removed unplanned, most commonly because of superficial infection, pain, line slippage, septicaemia or thrombosis.[15]

5FU does not have a cumulative dose limit, and in some countries it is standard practice to continue treatment until disease progression.[8] About 60% of patients with advanced colorectal cancer have either a response or a period of stable disease with

first-line 5FU-based therapy, but in all cases this is temporary because they develop resistance to the drug. The remaining 40% have disease that is refractory to 5FU. Both groups have a very poor prognosis. Second-line therapy is considered both for those patients who do not respond to first-line 5FU-based therapy ('primary non-responders') and for those who initially respond to such therapy but whose disease eventually but inevitably progresses. In some cases, disease resistant to bolus 5FU will respond to infusional 5FU, and this has led to the use of infusional 5FU regimens as second-line therapy, but response rates are usually low.[16]

Until recently, there was no accepted second-line treatment other than supportive care for patients who had failed to respond to, or whose disease had progressed after, a first-line 5FU-based treatment. However, since 1998, irinotecan with supportive care has become a standard second-line treatment for patients in Europe and North America.

Variation in services

It is not clear how many patients with advanced colorectal cancer in the UK currently receive 5FU-based therapy or, of those who do, how many receive each regimen. Not all patients with colorectal cancer ever see an oncologist. In the UK as a whole, only around 25% of patients with advanced colorectal cancer are referred to an oncology tertiary centre and assessed for chemotherapy; however, local referral patterns vary widely.[10] Patients with a performance status of 3 or 4 are unlikely to benefit from chemotherapy, and many elderly patients are managed by their general practitioner (GP) and geriatrician alone. However, a local audit carried out in Yorkshire, which found that 30–35% of patients who died of colorectal cancer had received chemotherapy for advanced disease, estimated that another 15% would have been able to benefit from such chemotherapy.

The most recent available evidence relating to the relative popularity of the various 5FU regimens derives from a postal questionnaire sent in 1994 to all UK clinical and medical oncologists and surgeons with an expressed interest in colorectal cancer. This survey found that, of respondents who regularly prescribed chemotherapy for metastatic colorectal cancer, 55% prescribed bolus/short infusion regimens, 46% prescribed 24- to 48-hour infusions, and 20% prescribed long-term infusions. In terms of treatment duration, 30% routinely stopped chemotherapy in these patients after only 3 months of treatment, 47% continued for 6 months, and 20% continued indefinitely until disease progression or unacceptable toxicity.[8] Following the publication of evidence of the superiority of the de Gramont regimen mentioned above, it is thought that the proportion of clinicians prescribing, and therefore of patients receiving, this regimen will have increased at the expense of regimens involving bolus/short infusions and long-term infusions, in particular the Mayo regimen. However, factors other than clinical efficacy alone may influence the choice of regimen: for example, the use of a bolus regimen may enable oncologists to treat patients close to home in peripheral clinics rather than at a distant cancer centre, while some centres do not use the de Gramont regimen because of its relatively high cost.[8]

Current service cost

Treatment and care for colorectal cancer have been estimated to account for approximately 2% of all bed-days and between 10% and 20% of palliative care provision in the UK.[5]

It has been estimated that, in 1996, £15 million was spent on medicines for colorectal cancer (including cytotoxic chemotherapy and other drugs) in the UK.[17]

Description of new intervention

Three new drugs (irinotecan, oxaliplatin and raltitrexed) have been proposed for the first- or second-line treatment of patients with advanced colorectal cancer. They will be discussed separately below.

Summary of product characteristics

Irinotecan (Aventis Pharma Ltd, West Malling, UK)

Irinotecan hydrochloride (CPT-11, Campto®) inhibits topoisomerase I, an enzyme that is essential for cell division, and thus kills cancer cells. Irinotecan was approved in France in May 1995 for the treatment of patients with inoperable advanced colorectal cancer who had previously been treated with adjuvant or palliative 5FU-based chemotherapy, and it was licensed in Japan in September 1995 for the treatment of patients with colorectal cancer. Following approval in the USA in June 1996, it has been approved in several other European countries, Canada, Australia and some Latin American countries.[18]

The UK licence for irinotecan is held by Aventis Pharma Ltd. It is marketed as Campto, in 20-mg/2-ml and 100-mg/5-ml concentrate for solution

for intravenous infusion. The wording of the licensed indication is:

> "Campto is indicated for the treatment of patients with advanced colorectal cancer:
>
> - in combination with 5-fluorouracil and folinic acid in patients without prior chemotherapy for advanced disease; and
> - as a single agent in patients who have failed an established 5-fluorouracil containing treatment regimen".[19]

It is contraindicated in patients with:

- chronic inflammatory bowel disease and/or bowel obstruction
- history of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients of Campto
- pregnancy and lactation
- bilirubin more than 1.5 times the upper limit of the normal range
- severe bone marrow failure
- WHO performance status of more than 2.

It is recommended for use only in adults.[19]

The recommended dose in first-line combination therapy is 180 mg/m^2 administered as an intravenous infusion every 2 weeks over 30–90 minutes, followed by FU/FA infusion, and the recommended dose in second-line monotherapy is 350 mg/m^2 as an intravenous infusion over 30–90 minutes every 3 weeks.[19]

Oxaliplatin (Sanofi Winthrop Ltd, Guildford, UK)

Oxaliplatin (L-OHP, Eloxatin®) is a stable, water-soluble platinum cytotoxic compound. It is licensed in the UK for the first-line treatment of metastatic colorectal cancer in combination with 5FU and FA in adult patients.[20] Neurotoxic side-effects (including sensory peripheral neuropathy) are dose-limiting.

Oxaliplatin is contraindicated in patients who:

- have a known history of hypersensitivity to oxaliplatin
- are breastfeeding
- have myelosuppression prior to starting the first course
- have a peripheral sensitive neuropathy with functional impairment prior to the first course
- have severely impaired renal function.[21]

The approved dose is 85 mg/m^2 every 2 weeks by intravenous infusion over 2–6 hours prior to the administration of FU/FA.[20]

Raltitrexed (AstraZeneca, London, UK)

Raltitrexed (Tomudex®, ZD 1694) is a thymidylate synthase inhibitor. It is marketed in 2-mg vials. It is licensed in the UK for:

> "the palliative treatment of advanced colorectal cancer where 5-fluorouracil and folinic acid based regimes are either not tolerated or inappropriate".[19]

Raltitrexed is contraindicated in:

- pregnant women, women who may become pregnant during treatment or women who are breastfeeding
- patients with severe renal impairment.[19]

It is recommended for use only in adults.

The approved dose is 3 mg/m^2 by 15-minute intravenous infusion, repeated every 3 weeks.[19]

Identification of patients

A computer model developed by Rhône-Poulenc Rorer (Antony, France) in collaboration with UK colorectal cancer specialists has estimated that 9–10% of patients presenting with colorectal cancer may be considered suitable for treatment with irinotecan after the failure of other therapies. However, this model takes into account only those patients who first present with advanced disease; it does not include the prevalent cases with Duke's stage C disease (cancer spread to the lymph nodes), 38% of whom could be expected to survive 5 years.[6] Thus, the demand for treatments is substantially greater than that derived from the number of patients who first present with advanced disease. Indeed, it could be argued that all patients who eventually die of colorectal cancer have the capacity to benefit from treatments for advanced disease, unless their health at the time of diagnosis is so poor that it contraindicates the use of such treatments.

Criteria for treatment

It is likely that the interventions reviewed here will be used mainly in people with a WHO performance status of less than 2 (for details of WHO performance status, see appendix 2).

It is anticipated that treatment with irinotecan and oxaliplatin will be delivered in dedicated oncology centres, and treatment with raltitrexed in dedicated oncology centres or units, with consultant oncologist supervision.

Degree of diffusion

Irinotecan is already in use as second-line treatment of advanced colorectal cancer, but the extent of that use is not known.

Chapter 3

Methods for reviewing effectiveness

Identification of studies

The search strategy aimed to identify all relevant papers relating to irinotecan, oxaliplatin or raltitrexed in the treatment of colorectal cancer. Keyword strategies were developed using key references retrieved through initial scoping searches. Search strategies included sensitive quality filters to limit results to clinical trials, reviews or economics studies. Date and language restrictions were not used. Searches of the following databases were undertaken: MEDLINE, EMBASE, Science Citation Index (SCI), Cochrane Database of Systematic Reviews (CDSR), Cochrane Controlled Trials Register (CENTRAL/CCTR), the NHS Centre for Reviews and Dissemination databases (DARE, NHS EED and HTA) and the Office of Health Economics (OHE) Health Economics Database (HEED). A search of the last 6 months of PubMed was undertaken to identify recent studies not yet indexed on MEDLINE. Abstracts of the American Society for Clinical Oncology (ASCO) for 1997–2000 were searched using the ASCO website.

In addition to searches of electronic bibliographic databases, further sources were consulted to identify current research and grey literature. The National Research Register (NRR), Medical Research Council (MRC) Clinical Trials Register, US National Institutes of Health (NIH) Clinical Trials Register and Current Research in Britain (CRIB) databases were searched. The publication lists and current research registers of health technology assessment and guideline-producing agencies as well as funding and regulatory bodies were consulted. Industry submissions and the reference lists of included studies were hand-searched, and citation searches using the SCI citation search facility were undertaken.

A further search for economic studies relating to the main comparators to the three drugs and to the various methods of drug administration was undertaken to inform the economic analysis carried out following the review of cost-effectiveness evidence.

Preliminary scoping searches were undertaken in September 2000. Full searches were undertaken in November 2000. Citation searches were undertaken in December 2000. Keyword strategies for MEDLINE may be found in appendix 4. Keyword strategies for all other databases are available.

Inclusion criteria

The titles and abstracts of the papers identified through the search process outlined above were assessed for relevance to the study question by two reviewers using the following criteria:

- **intervention**: irinotecan, oxaliplatin or raltitrexed, alone or in combination with other agents
- **comparators**: conventional 5FU-based treatment, irinotecan, oxaliplatin or raltitrexed, alone or in combination with other agents, or BSC (i.e. non-chemotherapy-based palliative care)
- **subjects**: human patients with colorectal cancer who:
  - are initially diagnosed with metastatic disease or
  - have developed metastatic disease after having received adjuvant 5FU-based therapy (first-line therapy) or
  - have proved resistant to previous 5FU treatment for metastatic disease
- **outcome measure(s)** to include at least one of the following:
  - survival rates
  - disease progression rates
  - health-related quality of life
  - adverse events
  - cost
- **methodology** to include at least one of the following:
  - systematic reviews
  - RCTs
  - economic evaluations.

Full copies were obtained of all those papers that appeared to be relevant or that could not be assessed on the basis of the abstract alone.

Quality assessment strategy

The methodological quality of RCTs was assessed using the Jadad scale, which addresses random-

isation, blinding, and the handling of withdrawals and dropouts.[22] In some cases, formal quality assessment was not possible because the trials had been published only in abstract form. No studies were therefore excluded on the basis of methodological quality.

Data extraction strategy

Data were extracted by one researcher and checked by a second, using customised data extraction forms; any disagreements were resolved by discussion.

The data extracted from the relevant studies will be presented separately for all three interventions, and for their use as first- and second-line therapy. If available, the following data will be reviewed in relation to each intervention:

- duration of treatment
- progression-free survival
- overall survival
- 1-year survival
- survival from diagnosis to death
- pain-free survival
- symptom-free survival
- time to deterioration of performance status
- time to weight loss of more than 5%
- response rates (see appendix 1)
- response duration
- treatment-related deaths
- grade 3–4 toxicities (see appendix 5)
- hospital admissions for severe adverse events
- cumulative number of hospital days for severe adverse events
- quality of life.

The most important outcome measures are survival, both overall and, because disease progression impairs both physical and mental health, progression-free. However, quality of life is also particularly important in this patient group, for whom chemotherapy is palliative, not curative. In this context, it is unfortunate that no studies provided information on grade 2 toxicities, although these are important in relation to quality of life.

In relation to response rates, it should be noted that patients who do not receive an objective tumour response but whose disease is stabilised by chemotherapy (the 'no change' category; see appendix 1) also derive symptomatic and survival advantages from chemotherapy.[10] However, tumour response is important in relation to the possibility of the resection of liver metastases.

Meta-analysis of trial results was felt to be inappropriate because of both the variety of irinotecan and oxaliplatin regimens used, and the variety of comparator regimens used with all three drugs. Moreover, it would not have been possible to undertake meta-analysis of survival data because typically these data were presented only as median survival times.

Chapter 4

Effectiveness results

In total, 23 trials have been identified that relate to the efficacy of irinotecan, oxaliplatin or raltitrexed.[23–45] The evidence from these trials is summarised below. Quality-of-life data are presented in this section, but the interpretation of such data is discussed in chapter 6 (see *Review of quality-of-life data*).

Irinotecan: quantity and quality of research available

Irinotecan has been licensed for use:

- in combination with 5FU and FA as first-line treatment
- as a single agent as second-line treatment.

Six RCTs have been identified that deal with the use of irinotecan as first-line treatment[31,33,37,39,43,44] and seven that study its use in second-line treatment.[23,24,28,40–42,45] The two uses will be reviewed separately.

Irinotecan as first-line treatment of advanced colorectal cancer

Information relating to the design and study populations of the six studies that deal with irinotecan as first-line treatment of advanced colorectal cancer is summarised in *Tables 3–6*.

These studies relate to four comparisons:

- irinotecan + FU/FA versus FU/FA alone[31,33,37,43]
- irinotecan + FU/FA versus irinotecan alone[43]
- irinotecan alone versus FU/FA alone[39,43]
- irinotecan + FU/FA (FOLFIRI) followed at progression by oxaliplatin + FU/FA (FOLFOX) versus FOLFOX followed at progression by FOLFIRI.[44]

It should be noted that irinotecan is not licensed in the UK for use as a single agent in the first-line treatment of patients with advanced colorectal cancer.

Two studies stated that they imposed an upper age limit of 75 years,[31,37] and a third appeared

TABLE 3 *Irinotecan as first-line treatment of advanced colorectal cancer: studies included in the review*

Study	Countries (no. of centres)	Recruitment dates	Comparison	Study type	Source of funding
Saltz *et al.*, 2000[43]	USA, Canada, Australia, New Zealand (71)	May 1996 to May 1998	Irinotecan + FU/FA vs either FU/FA or irinotecan alone	Open-label RCT	Pharmacia
Graeven *et al.*, 2000[33]	Europe	Not stated	Irinotecan + FU/FA vs FU/FA alone	RCT	Not stated
Douillard *et al.*, 2000[31]	Europe, Israel, South Africa	May 1997 to Feb 1998	Irinotecan + FU/FA vs FU/FA alone	Open-label RCT	Rhône-Poulenc Rorer
Maiello *et al.*, 2000[37]	Italy	Nov 1997 to Jan 1999	Irinotecan + FU/FA vs FU/FA alone	RCT	Not stated
Pozzo *et al.*, 1999[39]	Europe	Not stated	Irinotecan vs FU/FA alone	RCT	Not stated
Tournigand *et al.*, 2000[44]	Europe	Not stated	FOLFIRI followed at progression by FOLFOX vs FOLFOX followed at progression by FOLFIRI	RCT	Not stated

FOLFIRI, irinotecan + FU/FA; FOLFOX, oxaliplatin + FU/FA

TABLE 4 *Irinotecan as first-line treatment of advanced colorectal cancer: study design*

Study	Participants	Treatment groups (no. randomised)	Study procedure	Outcome measurements reported (when known, primary outcome measure in bold)	Comments
Saltz *et al.*, 2000[43]	Patients with histologically documented colorectal cancer and measurable metastatic disease, an ECOG performance status of 0–2 and adequate organ function, and who had not had pelvic irradiation or prior therapy for metastatic disease; adjuvant 5FU-based therapy was allowed if patients had remained free of disease for at least 1 year after its completion	Rx1: Irinotecan 125 mg/m^2 as a 90-minute iv infusion + FA 20 mg/m^2 as an iv bolus + 5FU 500 mg/m^2 as an iv bolus weekly for 4 weeks every 6 weeks (231) Rx2: Irinotecan 125 mg/m^2 as a 90-minute iv infusion weekly for 4 weeks every 6 weeks (226) Control: Mayo regimen (226)	Treatment given until disease progression, unacceptable adverse effects or withdrawal of consent by the patient. After first treatment, doses were adjusted to accommodate individual levels of tolerance	**Progression-free survival** Overall survival Response rate Quality of life	• Phase III study • Randomisation was stratified according to age (< 65 or ≥ 65 years), ECOG performance status (0 vs 1 or 2), interval from diagnosis to enrolment (< 6 vs ≥ 6 months) and history of adjuvant treatment with 5FU • Of the patients for whom follow-up data were available, 52% of those in the irinotecan + FU/FA group, 70% of those in the FU/FA group and 79% of those receiving irinotecan alone received additional chemotherapy after the study treatment ended; 56% of those in the FU/FA group received an irinotecan-based regimen following the study medication • Analysis was by intention to treat
Graeven *et al.*, 2000[33]	Patients with measurable metastatic colorectal cancer, no prior chemotherapy for advanced disease, performance status of 0–2, and normal marrow, hepatic and renal function	Rx1: Irinotecan 125 mg/m^2 + bolus 5FU 500 mg/m^2 + FA 20 mg/m^2 weekly for 4 weeks out of 6 weeks (33) Rx2: Irinotecan 350 mg/m^2 alternating with bolus 5FU 425 mg/m^2 + FA 20 mg/m^2 every 6 weeks (42) Control: Mayo regimen (42)		Response rate Tolerance	• Phase II study • Only preliminary results available, in abstract form • No survival data available
Douillard *et al.*, 2000[31]	Patients aged 18–75 years with histologically proven adenocarcinoma of the colon or rectum, WHO performance status of 2 or less, and life expectancy of more than 3 months, and who had no previous (other than adjuvant) chemotherapy, finished more than 6 months before randomisation	Rx: Irinotecan 80 mg/m^2 + 5FU 2300 mg/m^2 + FA 500 mg/m^2 weekly (54) or Irinotecan 180 mg/m^2 fortnightly with the de Gramont regimen (145) Control: AIO regimen (43) or de Gramont regimen (143)	Treatment was continued until disease progression, unacceptable adverse effects or withdrawal of consent. Doses of irinotecan and 5FU were lowered by 20% if severe toxic effects occurred	**Response rate** Time to progression Duration of response Time to treatment failure Overall survival Quality of life	• Phase III study • The two different irinotecan regimens were analysed together as one arm, as were the two FU/FA regimens • 39% of the irinotecan group and 58% of the non-irinotecan group received further chemotherapy; 31% of the non-irinotecan group subsequently received irinotecan; 16% of the irinotecan group and 13% of the non-irinotecan group received further treatment with oxaliplatin • Analysis was by intention to treat

continued

TABLE 4 contd *Irinotecan as first-line treatment of advanced colorectal cancer: study design*

Study	Participants	Treatment groups (no. randomised)	Study procedure	Outcome measurements reported (when known, primary outcome measure in bold)	Comments
Maiello *et al.*, 2000[37]	Patients aged 18–75 years with histologically confirmed and locally advanced measurable colorectal cancer, life expectancy of at least 3 months, ECOG performance status of 0–2, adequate bone marrow, renal and hepatic function, and who had not previously been treated for advanced disease; prior adjuvant chemotherapy was allowed if 1 year had elapsed since discontinuation of treatment	Rx: Irinotecan 180 mg/m^2 fortnightly with the de Gramont regimen (59) Control: de Gramont regimen (29)		Tumour response Response duration Time to progression Survival Toxicity	• Phase II study • Only preliminary data available because the study was ongoing at the time of publication; only 49 patients were evaluable (30 in the irinotecan and 19 in the non-irinotecan arm), and no survival data were available • Randomisation was stratified according to the presence or absence of hepatic disease, and by total tumour burden as "limited" or "extensive" disease using 10 cm^2 as the cut-off • About two-thirds of patients in the control arm subsequently received second-line therapy with regimens containing irinotecan or oxaliplatin • Analysis was by intention to treat
Pozzo *et al.*, 1999[39]	First-line patients with metastatic colorectal cancer	Rx: Irinotecan 350 mg/m^2 every 3 weeks (82) Control: Mayo regimen (77)		Tumour response Response duration Time to progression Survival Toxicity	• Phase II study • Only interim results available, in abstract form • After progression, patients with performance status ≤ 2 and good renal, liver and haematological functions were crossed over; however, the results published are before crossover
Tournigand *et al.*, 2000[44]	Previously untreated patients with unresectable metastatic colorectal cancer	Rx1: Irinotecan 180 mg/m^2 fortnightly + modified de Gramont regimen (FOLFIRI) followed at progression by oxaliplatin 100 mg/m^2 fortnightly with the same regimen (FOLFOX) (113) Rx2: FOLFOX followed at progression by FOLFIRI (113)		**Time to progression**	• Phase III study • Only interim results available, in abstract form

ECOG, Eastern Cooperative Oncology Group; Rx, treatment regimen; iv, intravenous; AIO, Arbeitsgemeinschaft Internische Onkologie

TABLE 5 *First-line irinotecan: characteristics of study populations*

Study	Median age, in years (range)	% male	WHO performance status (%)	Site of primary tumour (%)	No. of organs involved (%)	Sites of metastases (%)	Patients asymptomatic at study entry (%)	Median time from diagnosis to randomisation, in months (range)	Weight loss > 5% (%)
Saltz *et al.*, 2000[43]	Rx1: 62 (25–85) Rx2: 61 (30–87) Control: 61 (19–85)	Rx1: 65 Rx2: 64 Control: 54	Rx 1: 0: 39 1: 46 2: 15 Rx2: 0: 46 1: 46 2: 8 Control: 0: 41 1: 45 2: 13	Rx1: Colon: 81 Rectum: 16 Rx2: Colon: 84 Rectum: 14 Control: Colon: 85 Rectum: 15	Rx1: 1: 64 2: 26 > 2: 10 Rx2: 1: 62 2: 28 > 2: 9 Control: 1: 66 2: 23 > 2: 10	Rx1: Liver: 82 Rx2: Liver: 83 Control: Liver: 82	No data	Rx1: 1.9 (0.1–161) Rx2: 1.8 (0.1–185) Control: 1.7 (0.1–203)	No data
Graeven *et al.*, 2000[33]	No data	No data	Rx1: 0 + 1: 91 2: 9 Rx2: 0 + 1: 90 2:10 Control: 0 + 1: 95 2: 5	No data	No data	No data	No data	No data	No data
Douillard *et al.*, 2000[31]	Rx: 62 (27–75) Control: 59 (24–75)	Rx: 67 Control: 53	Rx: 0: 51.5 1: 41.9 2: 6.6 Control: 0: 51.3 1: 41.2 2: 7.5	Rectum said to be the primary site in more patients in the irinotecan group than in the FU/FA group	Rx: 1–2: 85.3 ≥ 3: 14.6 Control: 1–2: 90.9 ≥ 3: 9.1	Rx: Liver: 76.8 Lung: 26.3 Lymph nodes: 14.1 Peritoneum/ retroperitoneum: 10.1 Other: 23.7 Control: Liver: 79.7 Lung: 23.0 Lymph nodes: 12.8 Peritoneum/ retroperitoneum: 11.8 Other: 20.3	Rx: 52 Control: 49	No data	No data

continued

TABLE 5 contd *First-line irinotecan: characteristics of study populations*

Study	Median age, in years (range)	% male	WHO performance status (%)	Site of primary tumour (%)	No. of organs involved (%)	Sites of metastases (%)	Patients asymptomatic at study entry (%)	Median time from diagnosis to randomisation, in months (range)	Weight loss > 5% (%)
Maiello *et al.*, 2000[37]	Rx: 60 (33–75) Control: 61 (42–75)	Rx: 51 Control: 65	No data	Rx: Colon: 76 Rectum: 24 Control: Colon: 62 Rectum: 38	Rx: 1: 62 ≥ 2: 38 Control: 1: 85 ≥ 2: 15	Rx: Liver: 72 Lung: 25 Lymph node: 19 Control: Liver: 76 Lung: 15 Lymph node: 6	No data	No data	No data
Pozzo *et al.*, 1999[39]	Rx: 62 Control: 58	No data	Rx: 0: 53 Control: 0: 62	Rx: Colon: 64 Rectum: 36 Control: Colon: 57 Rectum: 43	Rx: ≥ 2: 44 Control: ≥ 2: 46	No data	No data	No data	No data
Tournigand *et al.*, 2000[44]	Rx1: 61 (29–75) Rx2: 64 (40–75)	Rx1: 58 Rx2: 70	Rx1: 0: 43 1: 40 2: 16 Rx2: 0: 46 1: 48 2: 6	No data	No data	No data	No data	No data	No data

TABLE 6 *Percentage of patients who had previously received adjuvant FU/FA treatment*

Study	% of patients who received specified treatment				
	Irinotecan + FU/FA	**Irinotecan alone**	**FU/FA alone**	**FOLFIRI**	**FOLFOX**
Saltz *et al.*, 2000[43]	11	10	8		
Graeven *et al.*, 2000[33]	No data		No data		
Douillard *et al.*, 2000[31]	26		24		
Maiello *et al.*, 2000[37]	No data		No data		
Pozzo *et al.*, 1999[39]		No data	No data		
Tournigand *et al.*, 2000[44]				No data	No data

to have imposed such a limit.[44] A fourth study included patients up to the age of 85 years.[43] The remaining two studies neither stated whether they imposed an upper age limit nor provided sufficient data to allow this to be inferred. However, because greater than 40% of new cases of colorectal cancer occur in patients over 75 years of age, at least three and possibly five of the six studies under-represent older patients.

In four of the studies, there was a reasonable balance between treatment arms in terms of performance status. However, in one study, the proportion of patients with a performance status of 0 favoured the control arm,[39] and in another, the proportion of patients with a performance status of 2 favoured the arm that did not receive irinotecan until after disease progression.[44] Overall survival data were not available for either of these studies.

Only one study provided information indicating that the treatment arms were balanced in relation to the site of the primary tumour.[43] Two studies gave no information,[33,44] while in two of the remaining three studies, the rectum was more common than the colon in the control arm.[37,39] In the third study, the rectum was said to be more common in the irinotecan arm, but this was not quantified[31] (see *Table 5*).

In those studies that provided the relevant information, patients who had previously received adjuvant FU/FA treatment were evenly distributed among treatment arms (see *Table 6*).

The doses of irinotecan used in the studies varied. Two studies administered 125 mg/m^2 of irinotecan per week for 4 out of 6 weeks,[33,43] but one of these studies also had a second irinotecan arm with patients taking a dose of 350 mg/m^2 every 12 weeks.[33] Another two studies administered 180 mg/m^2 fortnightly.[37,44] The fifth study administered 350 mg/m^2 of irinotecan every 3 weeks.[39] Finally, one study used both a fortnightly 180-mg/m^2 dose and a weekly 80-mg/m^2 dose.[31]

Number and type of studies excluded

No studies that appeared to meet the inclusion criteria were subsequently excluded from the review.

Quality of studies, characteristics of studies and evidence rating

Three of the above studies were large, multicentre Phase III trials;[31,43,44] however, only interim results were available for one of these.[44] The remainder were smaller Phase II trials. It was possible to assess the methodological quality of only the three trials for which full reports were available. Of these, one trial[43] scored 0 and two trials[31,37] scored 2 on the Jadad scale. None of the studies were reported to have been blinded, and some were specifically open-label, which may have influenced the quality-of-life ratings.

Assessment of effectiveness: irinotecan as first-line treatment

Critical review and synthesis of information

Although one study used two different regimens for both irinotecan and FU/FA, for most analyses the authors pooled the results to compare the irinotecan group with the non-irinotecan group.[31]

In those studies for which data were available, median duration of treatment ranged from a maximum of 25 weeks to a minimum of 18 weeks in the irinotecan/FU/FA arm and a maximum of 21 weeks to a minimum of 12 weeks for FU/FA alone (see *Table 7*).

In all studies that compared irinotecan plus FU/FA with FU/FA alone, and for which results were available,[31,43] median time to progression was longer in the irinotecan group, although this was not statistically significant in the smaller

TABLE 7 *Median duration of treatment*

Study	Median duration of treatment				
	Irinotecan + FU/FA	**Irinotecan alone**	**FU/FA alone**	**FOLFIRI**	**FOLFOX**
Saltz *et al.*, 2000[43]	5.5 months	3.9 months	4.1 months		
Graeven *et al.*, 2000[33]	Rx1: 3 cycles (18 weeks) Rx2: 2 cycles (24 weeks)		3 cycles (12 weeks)		
Douillard *et al.*, 2000[31]	Weekly regimen: 24 weeks Biweekly (every 2 weeks) regimen: 25 weeks		Weekly regimen: 21 weeks Biweekly (every 2 weeks) regimen: 18 weeks		
Maiello *et al.*, 2000[37]	No data		No data		
Pozzo *et al.*, 1999[39]		No data	No data		
Tournigand *et al.*, 2000[44]				No data	No data

Phase II study.[37] One of the Phase III studies found that time to progression in the group receiving single-agent irinotecan was virtually identical to that in the FU/FA group,[43] although in a smaller Phase II trial, irinotecan alone was associated with a significantly longer time to progression than FU/FA alone[39] (see *Table 8*).

In the two Phase III studies that compared irinotecan plus FU/FA with FU/FA alone, and for which results were available, median overall survival was significantly longer in the irinotecan/FU/FA group,[31,43] although a smaller Phase II study found no significant difference between the two groups.[37] Single-agent irinotecan was associated with an overall survival comparable with that achieved using FU/FA alone[43] (see *Table 9*).

The evidence relating to the impact of irinotecan on 1-year survival is not conclusive (see *Table 10*).

None of the studies provided information about time from randomisation to pain onset (in patients pain-free at baseline), time from randomisation

TABLE 8 *Median time from randomisation to progression, in months*

Study	Median time from randomisation to progression, in months (range)					*p*-value
	Irinotecan + FU/FA	**Irinotecan alone**	**FU/FA alone**	**FOLFIRI**	**FOLFOX**	
Saltz *et al.*, 2000[43]	7.0	4.2	4.3			0.004*
Graeven *et al.*, 2000[33]	No data		No data			
Douillard *et al.*, 2000[31]	6.7 (0–13.8+)		4.4 (0–11.8)			< 0.001
Maiello *et al.*, 2000[37]	6 (1–22)		5 (1–18)			Not stated
Pozzo *et al.*, 1999[39]		6.4 (0.7–11.6+)	3.9 (1.2–9.8)			0.03
Tournigand *et al.*, 2000[44]				No data	No data	

* *Irinotecan + FU/FA vs FU/FA alone*

TABLE 9 *Median overall survival: time from randomisation to death, in months*

Study	Median time from randomisation to death, in months (range)					*p*-value
	Irinotecan + FU/FA	Irinotecan alone	FU/FA alone	FOLFIRI	FOLFOX	
Saltz *et al.*, 2000[43]	14.8	12.0	12.6			0.04*
Graeven *et al.*, 2000[33]	No data		No data			
Douillard *et al.*, 2000[31]	17.4 (0.4–28.4+)		14.1 (0.5–27.6+)			0.031
Maiello *et al.*, 2000[37]	14 (1.5–27+)		15 (5–26.5+)			Not stated
Pozzo *et al.*, 1999[39]		No data	No data			
Tournigand *et al.*, 2000[44]				No data	No data	

* *Irinotecan + FU/FA vs FU/FA alone*

TABLE 10 *Survival rates at 1 year*

Study	Survival rate at 1 year (%)					*p*-value
	Irinotecan + FU/FA	Irinotecan alone	FU/FA alone	FOLFIRI	FOLFOX	
Saltz *et al.*, 2000[43]	No data	No data	No data			
Graeven *et al.*, 2000[33]	No data		No data			
Douillard *et al.*, 2000[31]	69		59			Not stated
Maiello *et al.*, 2000[37]	62		65			
Pozzo *et al.*, 1999[39]		No data	No data			
Tournigand *et al.*, 2000[44]				No data	No data	

to the onset of tumour-related symptoms (in patients symptom-free at baseline) or time from randomisation to weight loss of more than 5% relative to baseline. Only one study provided information about the median time from randomisation to deterioration of performance status: this time was significantly longer in the group receiving irinotecan plus FU/FA than in the group receiving FU/FA alone (11.2 vs 9.9 months, $p = 0.046$).[31]

All the studies found that response rates were higher in patients receiving irinotecan plus FU/FA than in those receiving FU/FA alone. Although the results relating to irinotecan alone were not consistent, the larger Phase III trial showed that response rates for irinotecan alone were slightly lower than for FU/FA alone, and significantly lower than for irinotecan plus FU/FA. The interim results indicate little difference between the FOLFIRI and FOLFOX regimens in terms of response rates (see *Table 11*).

Only one study provided information about the median time to response onset: this time was 8.9 weeks (range, 4.7–25.4 weeks) in the irinotecan/FU/FA group and 11.4 weeks (range, 5.3–29.6 weeks) in the FU/FA group.[31] However,

TABLE 11 *Response rates: percentage of patients*

Study	% of patients responding to treatment regimen (95% CI)					*p*-value
	Irinotecan + FU/FA	Irinotecan alone	FU/FA alone	FOLFIRI	FOLFOX	
Saltz *et al.*, 2000[43]	39	18	21			< 0.001*
Graeven *et al.*, 2000[33]	Rx1: 47 Rx2: 39		24			
Douillard *et al.*, 2000[31]	35		22			0.005
Maiello *et al.*, 2000[37]	40		18			0.014
Pozzo *et al.*, 1999[39]		15.4 (7.6 to 26.5)	9.9 (4.1 to 19.3)			
Tournigand *et al.*, 2000[44]				63	60	

CI, confidence interval

* *Irinotecan + FU/FA vs FU/FA alone*

TABLE 12 *Median response duration*

Study	Median response duration (months)					*p*-value
	Irinotecan + FU/FA	Irinotecan alone	FU/FA alone	FOLFIRI	FOLFOX	
Saltz *et al.*, 2000[43]	≈ 9	≈ 9	≈ 9			
Graeven *et al.*, 2000[33]	No data		No data			
Douillard *et al.*, 2000[31]	9.3 (95% CI, 2.8 to 13.1)		8.8 (95% CI, 3.7 to 11.8)			
Maiello *et al.*, 2000[37]	10		9			
Pozzo *et al.*, 1999[39]		7.0 (range, 1.3–11.5+)	5.6 (range, 1.4–9.8)			0.015
Tournigand *et al.*, 2000[44]				No data	No data	

with one exception, the duration of the response was similar in each group; when the durations differed significantly, irinotecan alone was associated with a longer duration of response than FU/FA alone[39] (see *Table 12*).

Only two studies provided information relating to the proportion of patients who received additional chemotherapy subsequent to the study medication (see *Table 13*). In both cases, the proportion was high, particularly in the non-irinotecan arm. In one study, 56% of the non-irinotecan group received irinotecan, while fewer than 5% in any group received oxaliplatin or other investigational agents.[43] In the other study, 31% of the non-irinotecan group received irinotecan, and 16% of the irinotecan group and 13% of the non-irinotecan group received oxaliplatin.[31] It is clear that this level of crossover will have affected the ability of the studies to detect differences in survival, toxicity and quality of life due to the use of irinotecan.

Adverse effects of the intervention

Few studies provided information on the number of deaths that could be attributed to the study treatment (see *Table 14*). However, it may be implicit in those studies providing no such data

TABLE 13 *Percentage of patients receiving subsequent chemotherapy*

Study	% of patients receiving subsequent chemotherapy				
	Irinotecan + FU/FA	**Irinotecan alone**	**FU/FA alone**	**FOLFIRI**	**FOLFOX**
Saltz *et al.*, 2000[43]	52	79	70		
Graeven *et al.*, 2000[33]	No data		No data		
Douillard *et al.*, 2000[31]	39		58		
Maiello *et al.*, 2000[37]	No data		No data		
Pozzo *et al.*, 1999[39]		No data	No data		
Tournigand *et al.*, 2000[44]				No data	No data

TABLE 14 *Treatment-related deaths*

Study	Treatment-related deaths (%)				
	Irinotecan + FU/FA	**Irinotecan alone**	**FU/FA alone**	**FOLFIRI**	**FOLFOX**
Saltz *et al.*, 2000[43]	0.9	0.9	1.4		
Graeven *et al.*, 2000[33]	No data		No data		
Douillard *et al.*, 2000[31]	No data		No data		
Maiello *et al.*, 2000[37]	0		0		
Pozzo *et al.*, 1999[39]		No data	No data		
Tournigand *et al.*, 2000[44]				No data	No data

that no treatment-related deaths had occurred, at least at the time of publication.

None of the studies provided information on the overall proportion of patients suffering at least one grade 3–4 adverse event. However, all provided separate information on a number of toxic effects. Data relating to some of the most frequently experienced of these are summarised below.

Irinotecan was generally associated with a higher prevalence of grade 3–4 diarrhoea and vomiting than FU/FA alone, although in no case was this stated to have reached statistical significance (see *Tables 15* and *16*).

TABLE 15 *Percentage of patients suffering grade 3–4 diarrhoea*

Study	% of patients suffering grade 3–4 diarrhoea					*p*-value
	Irinotecan + FU/FA	**Irinotecan alone**	**FU/FA alone**	**FOLFIRI**	**FOLFOX**	
Saltz *et al.*, 2000[43]	23	31	13			
Graeven *et al.*, 2000[33]	Rx1: 6 Rx2: 22		19			
Douillard *et al.*, 2000[31]	44.4		25.6			0.055
Maiello *et al.*, 2000[37]	7		3			
Pozzo *et al.*, 1999[39]		25	9			
Tournigand *et al.*, 2000[44]				9	8	

TABLE 16 *Percentage of patients suffering from grade 3–4 vomiting*

Study	% of patients suffering from grade 3–4 vomiting					*p*-value
	Irinotecan + FU/FA	Irinotecan alone	FU/FA alone	FOLFIRI	FOLFOX	
Saltz *et al.*, 2000[43]	9.7	12.1	4.1			
Graeven *et al.*, 2000[33]	No data		No data			
Douillard *et al.*, 2000[31]	11.1		4.7			0.25
Maiello *et al.*, 2000[37]	6*		0*			
Pozzo *et al.*, 1999[39]		9	7			
Tournigand *et al.*, 2000[44]				13*	4*	

* *Includes patients suffering nausea*

TABLE 17 *Percentage of patients suffering from grade 3–4 mucositis*

Study	% of patients suffering from grade 3–4 mucositis					*p*-value
	Irinotecan + FU/FA	Irinotecan alone	FU/FA alone	FOLFIRI	FOLFOX	
Saltz *et al.*, 2000[43]	2.2	2.2	16.9			
Graeven *et al.*, 2000[33]	No data		No data			
Douillard *et al.*, 2000[31]	0		2.3			0.26
Maiello *et al.*, 2000[37]	2		0			
Pozzo *et al.*, 1999[39]		No data	No data			
Tournigand *et al.*, 2000[44]				10	1	

In contrast, the prevalence of grade 3–4 mucositis was generally lower in patients receiving irinotecan than in those receiving FU/FA alone (see *Table 17*).

One study found that the prevalence of stomatitis was higher (at 10%) in patients receiving FU/FA alone than in those receiving either of two irinotecan regimens (with treatment regimen 1 [Rx1], 0%; with Rx2, 7%).[33]

There seems no predictable difference between the groups in terms of the prevalence of grade 3–4 neutropenia (see *Table 18*). In one study,[43] the high proportion of patients receiving FU/FA (whether alone or in combination with irinotecan) who suffered such neutropenia seems to be attributable to the use of a bolus regimen.

Only one study provided separate information on the prevalence of grade 4 toxicities.[43] These were substantially less common than grade 3/4 toxicities, and in most instances, the difference between patients receiving irinotecan plus FU/FA and those receiving FU/FA alone was less marked (see *Table 19*). This study used as a comparator the Mayo FU/FA regimen, which is more toxic than the de Gramont regimen, and thus a lower prevalence of grade 4 toxicities could be expected in patients receiving an optimum FU/FA regimen.

TABLE 18 *Percentage of patients suffering from grade 3–4 neutropenia*

Study	% of patients suffering from grade 3–4 neutropenia					*p*-value
	Irinotecan + FU/FA	Irinotecan alone	FU/FA alone	FOLFIRI	FOLFOX	
Saltz *et al.*, 2000[43]	53.8	31.4	66.2			
Graeven *et al.*, 2000[33]	No data		No data			
Douillard *et al.*, 2000[31]	28.8		2.4			0.001
Maiello *et al.*, 2000[37]	10		6			
Pozzo *et al.*, 1999[39]		41	42			
Tournigand *et al.*, 2000[44]				26	43	

TABLE 19 *Percentage of patients suffering from grade 4 toxicities*[43]

Toxicity	% of patients suffering from grade 4 toxicities		
	Irinotecan + FU/FA	Irinotecan alone	FU/FA alone
Diarrhoea	7.6	12.6	7.3
Vomiting	4.4	6.3	1.4
Mucositis	0	0.4	2.3
Neutropenia	24.0	12.1	42.5

None of the studies provided information about the number of patients admitted to hospital for serious adverse events or the number of days that they spent there.

Overall, therefore, the combination of irinotecan and FU/FA appears more toxic than FU/FA alone.

Quality of life

Two studies measured quality of life: one study[31] used the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, and the other[43] used the EORL QLQ version 2. Both studies assessed quality of life at the beginning of each treatment cycle, when the memory of adverse events can be assumed to be at its weakest. One study provided no information about the number of patients who completed the questionnaire, and this study found no significant difference in quality of life between irinotecan plus FU/FA and the Mayo regimen groups.[43] In the other study,[31] response rates were 62% in the irinotecan group and 59% in the control group. When missing data for death, progressive disease or grade 3–4 adverse events were taken into account, quality of life was significantly better in the irinotecan group, and definitive deterioration in the quality of life was stated to occur consistently later in this group.[31]

Although therapy with irinotecan plus FU/FA is associated with more adverse effects than treatment with FU/FA alone, the available evidence suggests that this does not impact adversely on quality of life.

Summary and conclusions of the evidence on irinotecan in the first-line treatment of advanced colorectal cancer

Only two studies[31,37] chose as their comparator the de Gramont regimen. In one of these, although the majority of patients in the control arm received the de Gramont regimen, a minority received the Arbeitsgemeinschaft Internische Onkologie (AIO) regimen,[31] which is also an infusional regimen (see appendix 3 for details). Three studies used the Mayo regimen[39,43] or another bolus regimen.[33] The final study compared combination irinotecan/FU/FA therapy (followed at disease progression by combination oxaliplatin/FU/FA therapy) with combination oxaliplatin/FU/FA

(followed at disease progression by combination irinotecan/FU/FA therapy).[44]

The outcome measures used by the studies were appropriate. However, only preliminary data were available for some studies,[33,39,44] and in these cases, overall survival data were not available. Two studies for which only preliminary data were available did not provide data on time to progression.

Only one study is known to have included patients over the age of 75 years,[43] and only two studies[43,44] are known to have included more than 10% of patients with a performance status of 2. There is therefore some uncertainty regarding the generalisability of the results to the wider population of patients with advanced colorectal cancer. With this caveat, despite the potential reduction of the differences between the treatment groups occasioned by the use of chemotherapy subsequent to the study medication, the data suggest that a combination of irinotecan and FU/FA in the first-line treatment of advanced colorectal cancer can extend both progression-free and median overall survival by 2–3 months, compared with either FU/FA alone or irinotecan alone, although at the cost of increased toxicity. These survival differences are significant, despite the fact that the use of salvage chemotherapy will have affected the ability of the studies to detect differences in overall survival attributable to the use of irinotecan. Irinotecan alone appeared comparable with FU/FA alone in terms of effect on survival.

Irinotecan as second-line treatment of advanced colorectal cancer

Information relating to the design and study populations of the seven studies that deal with irinotecan as second-line treatment of advanced colorectal cancer is summarised in *Tables 20–23*.

The included studies relate to eight relevant comparisons:

- irinotecan alone versus BSC[28]
- irinotecan alone versus 5FU[23]
- irinotecan alone versus FU/FA[41]
- irinotecan alone versus oxaliplatin + FU/FA[23]
- irinotecan + FU/FA versus FU/FA alone[42]
- irinotecan + FU/FA versus oxaliplatin + FU/FA[40]
- irinotecan + oxaliplatin versus an alternated combination of irinotecan + FU/FA and oxaliplatin + FU/FA[24]
- irinotecan + mitomycin C versus oxaliplatin + mitomycin C.[45]

In one study, the interventions were used as both first- and second-line treatments.[40]

TABLE 20 *Irinotecan as second-line treatment of advanced colorectal cancer: studies included in the review*

Study	Countries (no. of centres)	Recruitment dates	Comparison	Study type	Source of funding
Cunningham *et al.*, 1998[28]	Europe (48)[18]	Sep 1995 to Jun 1997[18]	Irinotecan + BSC vs BSC alone	Open-label RCT	Rhône-Poulenc Rorer
Rougier *et al.*, 1998[41]	Europe (46)	Oct 1995 to Jul 1997	Irinotecan vs FU/FA (three regimens)	Open-label RCT	Rhône-Poulenc Rorer
Adenis *et al.*, 2000[23]	France	Not stated	Irinotecan vs either 5FU alone or oxaliplatin + 5FU	RCT	Not stated
Rougier *et al.*, 1999[42]	Europe	Not stated	Irinotecan + FU/FA (two regimens) vs FU/FA alone	RCT	Not stated
Recchia *et al.*, 2000[40]	Italy	Not stated	Irinotecan + FU/FA vs oxaliplatin + FU/FA	RCT	Not stated
Becouarn *et al.*, 1999[24]	France	Jul 1997 onward	Irinotecan + oxaliplatin vs alternated combination of irinotecan + FU/FA and oxaliplatin + FU/FA	RCT	Not stated
Ulrich-Pur *et al.*, 1999[45]	Austria	Not stated	Irinotecan + MMC vs oxaliplatin + MMC	RCT	Not stated

MMC, mitomycin C

TABLE 21 *Irinotecan as second-line treatment of advanced colorectal cancer: study design*

Study	Participants	Treatment groups (no. randomised)	Study procedure	Outcome measurements reported (when known, primary outcome measure in bold)	Comments
Cunningham *et al.*, 1998[28]	Patients aged 18–75 years with histologically proven metastatic colorectal cancer and WHO performance status of 0–2, who had disease progression (assessed either by two imaging procedures or by an increase in CEA) either while on 5FU or within 6 months of the last dose of a 5FU-based regimen, and who had had one adjuvant and/or no more than two palliative 5FU-based regimens, and had not been previously treated with topoisomerase I inhibitors	Rx: Irinotecan 350 mg/m^2 (300 mg/m^2 in patients aged ≥ 70 years or with WHO performance status of 2) as a 90-minute iv infusion once every 3 weeks + BSC (189) Control: BSC alone (90)	4-week washout from last course of radiotherapy or chemotherapy, then treatment	**Overall survival** Performance status Body weight Tumour-related symptoms Quality of life	• Phase III study • 28 patients (31%) in the supportive care group received chemotherapy (21 patients received 5FU, nine received other drugs, and one received irinotecan) • Analysis was by intention to treat
Rougier *et al.*, 1998[41]	Patients aged 18–75 years with histologically proven progressive metastatic adenocarcinoma of the colon or rectum, and WHO performance status of 2 or less, and who had disease progression (assessed either by two imaging procedures or by an increase in CEA) either while on 5FU or within 3 months of the last dose of a 5FU-based regimen; one previous 5FU-based regimen was permitted, either adjuvant only or for metastatic disease (with or without previous adjuvant therapy), but previous treatment with oxaliplatin or raltitrexed was not allowed	Rx: Irinotecan 350 mg/m^2 (300 mg/m^2 in patients aged ≥ 70 years or with WHO performance status of 2) as a 90-minute iv infusion once every 3 weeks (133) Control: FU/FA (de Gramont, Lokich or AIO regimen) (134)	4-week washout from last course of chemotherapy (6 weeks for nitrosoureas or mitomycin), then treatment was continued until the disease progressed, unacceptable toxicity developed or the patient refused to continue treatment	**Overall survival** Progression-free survival Tumour response Pain-free survival Performance status Symptoms Tolerance Quality of life Weight loss	• Phase III study • Randomisation was stratified by centre and performance status using a minimisation procedure • There was a significant difference at baseline in the percentage of patients with hyperleukocytosis, although mean white blood cell counts were similar in both groups[41] • Analysis was by intention to treat, but 11 patients were excluded (six from irinotecan group and five from non-irinotecan group) who did not receive the study medication[18]
Adenis *et al.*, 2000[23]	Patients aged 18–75 years with previously treated, measurable inoperable metastatic colorectal cancer, progression on 5FU/raltitrexed, no neuropathy and performance status ≤ 2	Rx1: Irinotecan 350 mg/m^2 every 3 weeks (17) Rx2: Oxaliplatin 130 mg/m^2 every 3 weeks + Lokich regimen for 7/9 weeks (49) Control: Lokich regimen for 7/9 weeks (19)	In oxaliplatin arm, 5FU dose was reduced to 250 mg/m^2/day in cases of gastrointestinal toxicity	**Objective response rate** Safety Progression-free survival Overall survival	• Phase II/III study • Only preliminary data available, in abstract form • Recruitment stopped at 87 patients because of low accrual due to availability of oxaliplatin as first-line therapy

continued

TABLE 21 contd *Irinotecan as second-line treatment of advanced colorectal cancer: study design*

Study	Participants	Treatment groups (no. randomised)	Study procedure	Outcome measurements reported (when known, primary outcome measure in bold)	Comments
Rougier *et al.*, 1999[42]	Patients with metastatic colorectal cancer and prior 5FU failure	Rx: Irinotecan 180 mg/m^2 fortnightly + de Gramont regimen or Irinotecan 80 mg/m^2 + 5FU 2.3 g/m^2 as a 24-hour continuous infusion + FA weekly x 6 every 7 weeks (199) Control: "the same regimen of FU/FA alone" (188)	No data	Response rate Time to progression Survival Safety	• Only preliminary results available, in abstract form • It is not clear why two different irinotecan regimens were grouped together or which FU/FA regimen is meant by "the same regimen"
Recchia *et al.*, 2000[40]	Chemotherapy-naive and FU/FA-resistant patients with metastatic colorectal cancer	Rx: Irinotecan 90 mg/m^2 followed by de Gramont regimen for 2 consecutive days every 15 days, with crossover to oxaliplatin at progression (21) Control: Oxaliplatin 50 mg/m^2 followed by de Gramont regimen for 2 consecutive days every 15 days, with crossover to irinotecan at progression (21)	No data	Response Toxicity Progression-free survival Overall survival	• Phase II study • Only interim data available, in abstract form
Becouarn *et al.*, 1999[24]	Patients with advanced colorectal cancer, measurable disease and WHO performance status of 0–2, who had disease progression either while on 5FU or within 6 months of 5FU treatment, and who had had no more than one palliative 5FU-based regimen	Rx: Irinotecan 180 mg/m^2 + de Gramont regimen alternated with oxaliplatin 85 mg/m^2 + de Gramont regimen Control: Oxaliplatin 85 mg/m^2 + irinotecan 200 mg/m^2 every 3 weeks	Doses of irinotecan and 5FU were reduced if severe toxic effects occurred	Response rate Time to progression Safety	• Phase II study • Only interim results available, in abstract form • 62 of 72 planned patients enrolled; distribution between groups not given • Results relate to 22 evaluable patients in alternating irinotecan/oxaliplatin + FU/FA arm and 19 patients in irinotecan + oxaliplatin arm
Ulrich-Pur *et al.*, 1999[45]	Patients with advanced colorectal cancer who had received prior palliative 5FU-based chemotherapy	Rx: Irinotecan 120 mg/m^2 on days 1 and 15 + MMC 8 mg/m^2 on day 1 Control: Oxaliplatin 85 mg/m^2 on days 1 and 15 + MMC 8 mg/m^2 on day 1	In both arms, treatment courses were repeated every 4 weeks	Treatment response Time to progression Overall survival Toxicity	• Phase II study • Only interim results available, in abstract form

CEA, carcinoembryonic antigen

TABLE 22 *Second-line irinotecan: characteristics of study populations*

Study	Median age, in years (range)	% male	WHO performance status (%)	Site of primary tumour (%)	No. of organs involved (%)	Sites of metastases (%)	Patients asymptomatic at study entry (%)	Median time from diagnosis to randomisation (months)	Weight loss > 5% (%)
Cunningham *et al.*, 1998[18,28]	Rx: 59 (22–75) Control: 62 (34–75)	Rx: 68 Control: 58	Rx: 0: 47 1: 39 2: 14 Control: 0: 31 1: 46 2: 23	Rx: Right colon: 21 Left colon: 32 Rectum: 40 Rectosigmoid: 5 Control: Right colon: 20 Left colon: 30 Rectum: 42 Rectosigmoid: 5	Rx: 1: 43 2: 40 ≥ 3: 17 Control: 1: 47 2: 34 ≥ 3: 19	Rx: Liver: 80 Lung: 37 Abdominal mass: 19 Lymph nodes: 7 Peritoneum: 7 Control: Liver: 77 Lung: 30 Abdominal mass: 30 Lymph nodes: 10 Peritoneum: 10	Rx: 31 Control: 23	Rx: 19.3 Control: 17[18]	Rx: 7 Control: 11
Rougier *et al.*, 1998[18,41]	Rx: 58 (30–75) Control: 58 (25–75)	Rx: 57 Control: 65	Rx: 0: 58 1: 35 2: 8 Control: 0: 54 1: 43 2: 3	Rx: Right colon: 21 Left colon: 35 Rectum: 42 Rectosigmoid: 1 Control: Right colon: 22 Left colon: 40 Rectum: 37 Rectosigmoid: 1	Rx: 1: 48 2: 34 ≥ 3: 18 Control: 1: 47 2: 36 ≥ 3: 18	Rx: Liver: 79 Lung: 35 Abdominal mass/ lymph nodes: 20 Peritoneum: 15 Other: 24 Control: Liver: 76 Lung: 41 Abdominal mass/ lymph nodes: 20 Peritoneum: 10 Other: 23	Rx: 53 Control: 52	Rx: 15.7 Control: 15.4[18]	
Adenis *et al.*, 2000[23]	No data	No data	No data	No data	No data	No data	No data	No data	No data
Rougier *et al.*, 1999[42]	Rx: 62 Control: 59	No data	Rx: 0: 52 Control: 0: 51	Rx: Colon: 55 Rectum: 45 Control: Colon: 65 Rectum: 35	Rx: ≥ 2: 38 Control: ≥ 2: 37	No data	No data	No data	No data

continued

TABLE 22 contd *Second-line irinotecan: characteristics of study populations*

Study	Median age, in years (range)	% male	WHO performance status (%)	Site of primary tumour (%)	No. of organs involved (%)	Sites of metastases (%)	Patients asymptomatic at study entry (%)	Median time from diagnosis to randomisation (months)	Weight loss > 5% (%)
Recchia *et al.*, 2000[40]	59	62	No data	No data	No data	No data	No data	No data	No data
Becouarn *et al.*, 1999[24]	Rx: 64 Control: 62	No data	No data	No data	No data	No data	No data	No data	No data
Ulrich-Pur *et al.*, 1999[45]	No data	No data	No data	No data	No data	No data	No data	No data	No data

TABLE 23 *Nature of previous treatment: percentage of patients*

	Cunningham *et al.*, 1998[47]		Rougier *et al.*, 1998[47]	
	Irinotecan	**BSC alone**	**Irinotecan**	**FU/FA**
	% of patients			
Prior 5FU, adjuvant only	10	17	13	15
One palliative line	66	58	87	85
Two or more palliative lines	24	26	–	–
Progression while on 5FU	70	63	58	68
Progression within 3 months of last 5FU	27	36	39	23
Last 5FU regimen bolus	31	26	65	60
Last 5FU regimen infusional	69	75	34	38
	Months			
Median time from progression to randomisation	1	1	0.9	0.9

It should be noted that irinotecan is not licensed in the UK for use in combination with FU/FA, oxaliplatin or mitomycin C in the second-line treatment of patients with advanced colorectal cancer.

Some of the data tabulated below were not available in journal publications but were derived from the US Food and Drug Administration (FDA) medical and statistical reviews of material submitted by the sponsors of the drug in their application for full approval in the USA. These reviews have been published on the FDA website.[18,46]

Two studies imposed an upper age limit of 75 years.[28,41] A further four studies did not state whether they imposed an upper age limit. No information is available relating to the fifth study.[45] Thus, older patients were under-represented in at least two and possibly all seven studies.

In addition, two studies[28,41] stated that they excluded patients with bulky disease (> 50% hepatic involvement, > 25% lung involvement or abdominal mass ≥ 10 cm), presence or history of central nervous system metastases, or unresolved bowel obstruction or diarrhoea. According to the FDA medical review, they also excluded patients with a past or current history of neoplasm other than colorectal carcinoma, curatively treated non-melanoma skin cancer or *in situ* carcinoma of the cervix.[18]

In two of the studies that provided this information, the treatment arms appeared to be balanced in terms of performance status. However, in the comparison of irinotecan with BSC alone, the difference between the groups at baseline in terms of WHO performance status clearly gave rise to bias favouring the intervention group.[28] Although the investigators dealt with this by using multivariate analysis and by stratifying the results according to performance status, there is still the potential for significant residual confounding. As no adjusted measure of relative or absolute risk was provided, it is not possible to tell how much better the irinotecan group fared overall.[6]

In those studies that provided the relevant information, the treatment arms also seem balanced in terms of the site of the primary tumour, with the possible exception of one study in which the control group contained a higher proportion of patients with a primary colon cancer than the intervention group.[42]

In two studies (Rougier and co-workers, and Cunningham and colleagues), the hospitals contributing patients are known to represent both university centres and large and small community hospitals, suggesting that the results might well be generalisable in this respect.[47]

Only three studies provided information on the nature of the previous treatment that patients had received. Two of these studies provided information broken down by treatment arm (see *Table 23*), but the third, which used oxaliplatin/FU/FA or irinotecan/FU/FA as first- or second-line treatment, stated only that seven patients (17%) were chemotherapy-naive and did not attribute them to treatment arms.[40]

The doses of irinotecan used in the studies varied. One study administered 120 mg/m^2 of irinotecan fortnightly.[45] Another two studies administered 180 mg/m^2 fortnightly.[24,40] A further three studies administered 350 mg/m^2 of irinotecan every 3 weeks.[23,28,41] Finally, one study used both a fortnightly 180-mg/m^2 dose and a weekly 80-mg/m^2 dose.[42]

Number and type of studies excluded

No studies that appeared to meet the inclusion criteria were subsequently excluded from the review.

Quality of studies, characteristics of studies and evidence rating

Two studies[28,41] were stated to be and a third[42] appeared to be large, multicentre Phase III trials. Another was a small Phase II/III study.[23] The remainder were small Phase II studies. It was possible to assess the methodological quality of only the two trials for which full reports were available. Of these, one study[41] scored 0 and the other[28] scored 2 on the Jadad scale.

None of the studies were reported to have been blinded, and two were specified to be open-label. This lack of blinding may have influenced the quality-of-life ratings.

Assessment of effectiveness: irinotecan as second-line treatment

Critical review and synthesis of information

For studies that provided this information, the median duration of treatment ranged from a maximum of 17 weeks to a minimum of 9 weeks for irinotecan alone, compared with 11 weeks for FU/FA alone (see *Table 24*).

In both studies that compared irinotecan (with or without FU/FA) with FU/FA alone, the median time to progression was longer in the irinotecan group.[41,42] This difference was statistically significant in only one study, in which the treatment arms were unbalanced in terms of the location of the primary tumour, favouring the irinotecan arm[42] (see *Table 25*). However, in the other study, it was noted that, at first tumour assessment (usually 9–12 weeks), disease progression was significantly more common in the FU/FA group (56.2%) than in the irinotecan group (36.4%; $p = 0.002$).[41]

Similarly, in both studies that compared irinotecan (with or without FU/FA) with FU/FA alone, median overall survival was significantly longer in the irinotecan group,[41,42] although again it should be noted that, in one of these,[42] the imbalance between treatment arms in relation to the location of the primary tumour favoured the irinotecan arm. In the study that used three FU/FA regimens as comparators, overall survival was said to be similar for all three regimens.[41] In the study that compared irinotecan with BSC, median overall survival was also longer in the irinotecan group[28] (see *Table 26*).

In the two studies that provided this information, 1-year survival was also better in the irinotecan groups than in the non-irinotecan groups (see *Table 27*).

Information on median survival from diagnosis to death was available for two studies. In both cases, median survival was significantly longer in the irinotecan group (see *Table 28*).

Two studies provided information about the median time from randomisation to pain onset in patients who were pain-free at baseline (see *Table 29*). Both studies found that pain-free survival was longer in the irinotecan group, and in the comparison with BSC, the difference between treatment groups was statistically significant. Although the robustness of these data has been questioned on the grounds that patient follow-up was not at equal intervals between the treatment arms and that the data were collected retrospectively,[18] it is supported by the evidence relating to analgesic use (see *Table 30*).

The same two studies provided information about the median time from randomisation to onset of tumour-related symptoms in patients who were symptom-free at baseline (see *Table 31*). Although in both cases this time was longer in the irinotecan group, in neither study was the difference statistically significant. However, it has been pointed out that, in the comparison with BSC, symptoms likely to be tumour related were identified retrospectively, and the investigators had difficulty in reporting symptoms that could be both tumour related and drug related.[18]

Again, the same two studies provided information about the median time from randomisation to deterioration of performance status (see *Table 32*). Of these, only the comparison with BSC showed a statistically significant advantage for irinotecan. As performance status was evaluated prospectively, in this case the results may truly represent a clinical benefit in the intervention arm.[18]

The same two studies also provided information about the median time from randomisation to weight loss of more than 5% relative to baseline (see *Table 33*). Again, only the comparison with

TABLE 24 *Median duration of treatment*

Study	Median duration of treatment (range)											*p*-value
	IR + FU/FA	IR alone	IR/OX + FU/FA	IR + OX	IR + MMC	OX + 5FU	OX + FU/FA	OX + MMC	FU/FA	5FU alone	BSC alone	
Cunningham *et al.*, 1998[28]		4.1 months (0.7–12.6 months)									NA	
Rougier *et al.*, 1998[41,46]		4.2 months							2.8 months			0.035
Adenis *et al.*, 2000[23]		3 3-week cycles				6 3-week cycles				4 cycles		
Rougier *et al.*, 1999[42]	No data								No data			
Recchia *et al.*, 2000[40]	No data						No data					
Becouarn *et al.*, 1999[24]			7.0 months	4.8 months								
Ulrich-Pur *et al.*, 1999[45]					No data			No data				

IR, irinotecan; OX, oxaliplatin; NA, not applicable

TABLE 25 *Median time from randomisation to progression, in months*

Study	Median time from randomisation to progression, in months (range)											*p*-value
	IR + FU/FA	IR alone	IR/OX + FU/FA	IR + OX	IR + MMC	OX + 5FU	OX + FU/FA	OX + MMC	FU/FA	5FU alone	BSC alone	
Cunningham *et al.*, 1998[28]		No data									No data	
Rougier *et al.*, 1998[41,46]		4.2 (0.9–14.2)							2.9 (0.8–12.8)			0.30
Adenis *et al.*, 2000[23]		2.0				5.1				3.5		
Rougier *et al.*, 1999[42]	6.7								4.4			< 0.001
Recchia *et al.*, 2000[40]	6.6						5.3					Not stated
Becouarn *et al.*, 1999[24]			7.0	4.8								
Ulrich-Pur *et al.*, 1999[45]					No data			No data				

IR, irinotecan; OX, oxaliplatin

TABLE 26 *Median overall survival: time from randomisation to death, in months*

Study	Median time from randomisation to death, in months (range)										*p*-value
	IR + FU/FA	IR alone	IR/OX + FU/FA	IR + OX	IR + MMC	OX + 5FU	OX + FU/FA	OX + MMC	FU/FA	5FU alone	BSC alone	
Cunningham *et al.*, 1998[28]		9.2									6.5	0.0001
Rougier *et al.*, 1998[41,46]		10.8 (1.2–18.7)							8.5 (0.8–20.9)			0.035
Adenis *et al.*, 2000[23]		No data				No data				No data		
Rougier *et al.*, 1999[42]	16.8								14.0			0.029
Recchia *et al.*, 2000[40]	No data						No data					
Becouarn *et al.*, 1999[24]			No data	No data								
Ulrich-Pur *et al.*, 1999[45]					No data			No data				

IR, irinotecan; OX, oxaliplatin

TABLE 27 *Survival rates at 1 year*

Study	Survival rate at 1 year (%)										
	IR + FU/FA	IR alone	IR/OX + FU/FA	IR + OX	IR + MMC	OX + 5FU	OX + FU/FA	OX + MMC	FU/FA	5FU alone	BSC alone
Cunningham *et al.*, 1998[28]		36									14
Rougier *et al.*, 1998[41,46]		45							32		
Adenis *et al.*, 2000[23]		No data				No data				No data	
Rougier *et al.*, 1999[42]	No data								No data		
Recchia *et al.*, 2000[40]	No data						No data				
Becouarn *et al.*, 1999[24]			No data	No data							
Ulrich-Pur *et al.*, 1999[45]					No data			No data			

IR, irinotecan; OX, oxaliplatin

TABLE 28 *Median survival from diagnosis to death, in months*

Study	Median survival from diagnosis to death, in months (95% CI)			*p*-value
	IR alone	FU/FA	BSC alone	
Cunningham *et al.*, 1998 (reported by the FDA)[18]	33.8 (28.7 to 36.6)		26.6 (21.6 to 31.6)	0.008
Rougier *et al.*, 1998 (reported by the FDA)[18]	33.6 (28.3 to 40.4)	27.0 (23.9 to 30.7)		0.007

IR, irinotecan

TABLE 29 *Median time from randomisation to pain onset in patients who were pain-free at baseline, in months*

Study	Median time from randomisation to pain onset in patients pain-free at baseline, in months (range)											*p*-value
	IR + FU/FA	IR alone	IR/OX + FU/FA	IR + OX	IR + MMC	OX + 5FU	OX + FU/FA	OX + MMC	FU/FA	5FU alone	BSC alone	
Cunningham *et al.*, 1998[28]		6.9									2.0	0.003
Rougier *et al.*, 1998[41,46]		10.3 (0.4–15.6)							8.5 (0.2–16.4)			0.059
Adenis *et al.*, 2000[23]		No data				No data				No data		
Rougier *et al.*, 1999[42]	No data								No data			
Recchia *et al.*, 2000[40]	No data						No data					
Becouarn *et al.*, 1999[24]			No data	No data								
Ulrich-Pur *et al.*, 1999[45]					No data			No data				

IR, irinotecan; OX, oxaliplatin

TABLE 30 *Percentage of patients taking analgesics who did not take analgesics at baseline*

Study	% of patients taking analgesics who did not take analgesics at baseline					
	IR alone		FU/FA		BSC alone	
	Opioids	Non-opioids	Opioids	Non-opioids	Opioids	Non-opioids
Cunningham *et al.*, 1998 (reported by the FDA)[46] (at week 20)	13.5	17.6			33.3	28.6
Rougier *et al.*, 1998 (reported by the FDA)[46] (at week 18)	6.2	6.2	11.1	12.3		

IR, irinotecan

TABLE 31 *Median time from randomisation to onset of tumour-related symptoms in patients who were symptom-free at baseline, in months*

Study	Median time from randomisation to onset of tumour-related symptoms in patients symptom-free at baseline (months)											*p*-value
	IR + FU/FA	IR alone	IR/OX + FU/FA	IR + OX	IR + MMC	OX + 5FU	OX + FU/FA	OX + MMC	FU/FA	5FU alone	BSC alone	
Cunningham *et al.*, 1998[28]		5.9									4.1	0.2
Rougier *et al.*, 1998[41,46]		8.1							7.0			0.23
Adenis *et al.*, 2000[23]		No data				No data				No data		
Rougier *et al.*, 1999[42]	No data								No data			
Recchia *et al.*, 2000[40]	No data						No data					
Becouarn *et al.*, 1999[24]			No data	No data								
Ulrich-Pur *et al.*, 1999[45]					No data			No data				

IR, irinotecan; OX, oxaliplatin

TABLE 32 *Median time from randomisation to deterioration of performance status, in months*

Study	Median time from randomisation to deterioration of performance status (months)											*p*-value
	IR + FU/FA	IR alone	IR/OX + FU/FA	IR + OX	IR + MMC	OX + 5FU	OX + FU/FA	OX + MMC	FU/FA	5FU alone	BSC alone	
Cunningham *et al.*, 1998[28]		5.7									3.3	< 0.001
Rougier *et al.*, 1998[41,46]		6.4							5.1			0.18
Adenis *et al.*, 2000[23]		No data				No data				No data		
Rougier *et al.*, 1999[42]	No data								No data			
Recchia *et al.*, 2000[40]	No data						No data					
Becouarn *et al.*, 1999[24]			No data	No data								
Ulrich-Pur *et al.*, 1999[45]					No data			No data				

IR, irinotecan; OX, oxaliplatin

TABLE 33 *Median time from randomisation to weight loss of more than 5% relative to baseline, in months*

Study	Median time from randomisation to weight loss of more than 5% relative to baseline (months)											*p*-value
	IR + FU/FA	IR alone	IR/OX + FU/FA	IR + OX	IR + MMC	OX + 5FU	OX + FU/FA	OX + MMC	FU/FA	5FU alone	BSC alone	
Cunningham *et al.*, 1998[28]		6.4									4.2	0.018
Rougier *et al.*, 1998[41,46]		8.9							7.4			0.22
Adenis *et al.*, 2000[23]		No data				No data				No data		
Rougier *et al.*, 1999[42]	No data								No data			
Recchia *et al.*, 2000[40]	No data						No data					
Becouarn *et al.*, 1999[24]			No data	No data								
Ulrich-Pur *et al.*, 1999[45]					No data			No data				

IR, irinotecan; OX, oxaliplatin

BSC showed a statistically significant difference between treatment groups. However, it is not clear how this result should be interpreted. Changes in weight may or may not be a true indication of clinical benefit, because unwanted weight gain from ascites and/or oedema is very common in these patients, while weight loss may be due to factors such as overzealous diuresis, dehydration from nausea, vomiting or diarrhoea, and poor hydration.[18]

Several studies provided information relating to response rates, which were higher in regimens that included irinotecan than in those that contained only 5FU or FU/FA. However, in two studies, oxaliplatin plus 5FU or FU/FA produced higher response rates than irinotecan either alone or with FU/FA[23,40] (see *Table 34*).

No data were available regarding time to onset of response or response duration.

Information on the proportion of patients who received chemotherapy subsequent to the study intervention was available in relation to two studies. In the Cunningham study, 21% of the irinotecan group were said to have received subsequent chemotherapy with a 5FU regimen or another drug other than irinotecan, while 31% of the BSC arm received chemotherapy with either a 5FU regimen, another drug or, in one case, irinotecan.[28] However, the FDA review provided different figures, stating that 30% of the irinotecan arm received subsequent therapies compared with only 7% of the control arm ($p = 0.0001$). According to the FDA review, 21% of patients in the intervention arm received chemotherapy subsequent to the trial intervention, 8% received radiation therapy, and 0.5% underwent surgery; in the control arm, 6% of patients received chemotherapy, 1% received radiation, and none underwent surgery. The median survival of patients in the irinotecan group who received subsequent therapies was 11.7 months ($n = 32$) compared with 9.2 months for the group as a whole; however, the contribution of subsequent therapy to this prolongation of survival is not clear.[18]

In the Rougier study, 1998 (reported by the FDA),[46] 2% of patients in the intervention arm and 5% in the control arm received radiation therapy; 9% of patients in the intervention arm and 6% in the control arm received heparin or low-molecular-weight derivatives such as fraxiparin and fragmin. Because of the small number of patients involved and the equal distribution between treatment arms, the effect of these therapies on survival was thought by the FDA medical reviewer to be probably insignificant.[18]

Adverse effects

Only three studies provided information on deaths that could be attributed to study treatment (see *Table 35*). In one case, the figure in the table may be an underestimate: the FDA medical reviewer considered four deaths (2.1%) in the intervention arm of the Cunningham study to be definitely, possibly or probably treatment related,[18] compared with the two reported by the investigators.[28] Although in one study[23] a high percentage of patients suffered death related to treatment with irinotecan alone, the actual figures are small (two individuals) and thus not necessarily a reliable indicator of toxicity.

Irinotecan was associated with more grade 3–4 toxicity than either BSC or FU/FA alone. In the latter case, the difference between treatment groups was stated to be statistically significant (see *Table 36*). One study that did not provide data on the proportion of patients suffering grade 3–4 adverse events stated that there were substantially more severe adverse events requiring dose reductions (40% vs 11%) and early discontinuations (27% vs 11%) in the irinotecan arm than in the oxaliplatin arm, respectively.[45]

Irinotecan was generally associated with a higher prevalence of grade 3–4 diarrhoea than either BSC or FU/FA alone (see *Table 37*). Data relating to grade 4 diarrhoea alone were available for only two studies: in the Cunningham study, this adverse event affected 7% of the irinotecan group and 3% of the control group, and in the Rougier study (1998), it affected 6% of the irinotecan group and 2% of the control group.[18]

Irinotecan was also generally associated with a higher prevalence of grade 3–4 vomiting than either BSC or FU/FA alone (see *Table 38*).

However, there seemed no consistent difference between treatment groups in relation to the prevalence of grade 3–4 mucositis (see *Table 39*).

Irinotecan was associated with a substantial increase in the prevalence of grade 3–4 neutropenia compared with BSC or FU/FA alone (see *Table 40*).

There was no evidence of any significant difference between irinotecan and non-irinotecan groups in terms of the proportion of patients admitted to hospital for serious adverse events or the

TABLE 34 *Response rates: percentage of patients*

Study	% of patients responding to treatment regimen (95% CI)											*p*-value
	IR + FU/FA	IR alone	IR/OX + FU/FA	IR + OX	IR + MMC	OX + 5FU	OX + FU/FA	OX + MMC	FU/FA	5FU alone	BSC alone	
Cunningham *et al.*, 1998[28]		No data									No data	
Rougier *et al.*, 1998[41,46]		4.5* 10.5†							0.7* 4.4†			
Adenis *et al.*, 2000[23]		17.6				36.7				5.3		
Rougier *et al.*, 1999[42]	41								23			< 0.001
Recchia *et al.*, 2000[40]	22						33					
Becouarn *et al.*, 1999[24]			14*	21*								
Ulrich-Pur *et al.*, 1999[45]					23.3 (9.9 to 42.3)			18.5 (6.3 to 38.1)				

IR, irinotecan; OX, oxaliplatin

* *Partial*

† *Unconfirmed partial/minor*

TABLE 35 *Treatment-related deaths*

Study	Treatment-related deaths (%)										
	IR + FU/FA	IR alone	IR/OX + FU/FA	IR + OX	IR + MMC	OX + 5FU	OX + FU/FA	OX + MMC	FU/FA	5FU alone	BSC alone
Cunningham *et al.*, 1998[28]		1.1									0
Rougier *et al.*, 1998[41,46]		0							0.7		
Adenis *et al.*, 2000[23]		12				0				0	
Rougier *et al.*, 1999[42]	No data								No data		
Recchia *et al.*, 2000[40]											
Becouarn *et al.*, 1999[24]			No data	No data							
Ulrich-Pur *et al.*, 1999[45]					No data			No data			

IR, irinotecan; OX, oxaliplatin

TABLE 36 *Toxicity: percentage of patients suffering at least one grade 3–4 adverse event*

Study	% of patients suffering at least one grade 3–4 adverse event											*p*-value
	IR + FU/FA	IR alone	IR/OX + FU/FA	IR + OX	IR + MMC	OX + 5FU	OX + FU/FA	OX + MMC	FU/FA	5FU alone	BSC alone	
Cunningham *et al.*, 1998[28]		79									67	
Rougier *et al.*, 1998[41,46]		69							54			0.013
Adenis *et al.*, 2000[23]		No data				No data				No data		
Rougier *et al.*, 1999[42]	No data								No data			
Recchia *et al.*, 2000[40]	No data						No data					
Becouarn *et al.*, 1999[24]			No data	No data								
Ulrich-Pur *et al.*, 1999[45]					No data			No data				

IR, irinotecan; OX, oxaliplatin

TABLE 37 *Percentage of patients suffering grade 3–4 diarrhoea*

Study	% of patients suffering grade 3–4 diarrhoea											*p*-value
	IR + FU/FA	IR alone	IR/OX + FU/FA	IR + OX	IR + MMC	OX + 5FU	OX + FU/FA	OX + MMC	FU/FA	5FU alone	BSC alone	
Cunningham *et al.*, 1998[28]		22									6	
Rougier *et al.*, 1998[41,46]		22							11			
Adenis *et al.*, 2000[23]		12				43				5		
Rougier *et al.*, 1999[42]	22								10			
Recchia *et al.*, 2000[40]	12*						10*					Not stated
Becouarn *et al.*, 1999[24]			13	5								
Ulrich-Pur *et al.*, 1999[45]					53			No data				

IR, irinotecan; OX, oxaliplatin

* *Grade 3 only*

TABLE 38 *Percentage of patients suffering from grade 3–4 vomiting*

Study	% of patients suffering from grade 3–4 vomiting										
	IR + FU/FA	**IR alone**	**IR/OX + FU/FA**	**IR + OX**	**IR + MMC**	**OX + 5FU**	**OX + FU/FA**	**OX + MMC**	**FU/FA**	**5FU alone**	**BSC alone**
Cunningham *et al.*, 1998[28]		14									8
Rougier *et al.*, 1998[41,46]		14							5		
Adenis *et al.*, 2000[23]		6				6				0	
Rougier *et al.*, 1999[42]	No data								No data		
Recchia *et al.*, 2000[40]	No data						No data				
Becouarn *et al.*, 1999[24]			3*	10*							
Ulrich-Pur *et al.*, 1999[45]					No data			No data			

IR, irinotecan; OX, oxaliplatin

* *Includes nausea*

TABLE 39 *Percentage of patients suffering from grade 3–4 mucositis*

Study	% of patients suffering from grade 3–4 mucositis										
	IR + FU/FA	**IR alone**	**IR/OX + FU/FA**	**IR + OX**	**IR + MMC**	**OX + 5FU**	**OX + FU/FA**	**OX + MMC**	**FU/FA**	**5FU alone**	**BSC alone**
Cunningham *et al.*, 1998[28]		2									1
Rougier *et al.*, 1998[41,46]		2							5		
Adenis *et al.*, 2000[23]		0				10				26	
Rougier *et al.*, 1999[42]	No data								No data		
Recchia *et al.*, 2000[40]	No data						No data				
Becouarn *et al.*, 1999[24]			No data	No data							
Ulrich-Pur *et al.*, 1999[45]					No data			No data			

IR, irinotecan; OX, oxaliplatin

TABLE 40 *Percentage of patients suffering from grade 3–4 neutropenia*

Study	% of patients suffering from grade 3–4 neutropenia											*p*-value
	IR + FU/FA	**IR alone**	**IR/OX + FU/FA**	**IR + OX**	**IR + MMC**	**OX + 5FU**	**OX + FU/FA**	**OX + MMC**	**FU/FA**	**5FU alone**	**BSC alone**	
Cunningham *et al.*, 1998[28]		22									0	
Rougier *et al.*, 1998[41,46]		14							2			
Adenis *et al.*, 2000[23]		No data				No data				No data		
Rougier *et al.*, 1999[42]	42								11			
Recchia *et al.*, 2000[40]	25						29					Not stated
Becouarn *et al.*, 1999[24]			33	30								
Ulrich-Pur *et al.*, 1999[45]					No data			No data				

IR, irinotecan; OX, oxaliplatin

cumulative number of hospital days occasioned by such adverse events (see *Tables 41* and *42*).

Overall, therefore, irinotecan monotherapy appears more toxic than FU/FA.

Quality of life

Three studies reported on quality of life. Two used the EORTC QLQ-C30,[28,41] and the third did not state what instrument was used.[42]

One study administered the EORTC QLQ-C30 at baseline, 3 weeks and 6 weeks, then every two visits up to 1 year, and every 6 weeks after treatment stopped. Compliance was 67% in the irinotecan group and 70% in the FU/FA group. The investigators reported that quality of life was similar in the irinotecan and FU/FA groups, with the exception of nausea and vomiting ($p = 0.007$) and diarrhoea ($p = 0.03$), which favoured FU/FA.[41] However, the FDA medical reviewer also found significant advantages favouring the FU/FA arm in relation to cognitive functioning, physical functioning and financial impact.[18] Deterioration in quality of life (defined as a more than 50% decrease from baseline score) was said to occur significantly later in the irinotecan group.[48]

The second study administered the EORTC QLQ-C30 at baseline, 3 weeks and 6 weeks, and then every 6 weeks. Compliance in both groups was about 80% at the beginning of the study, decreasing during the course of the study to about 50%.[28] The FDA medical reviewer found significant advantages favouring the intervention arm in relation to physical functioning, role functioning, cognitive functioning, social function, fatigue, pain, dyspnoea, appetite loss and constipation, but significant advantages favouring the control (BSC) arm in relation to diarrhoea.[18] However, the estimated linear trends for four out of six subscales of the QLQ-C30 were noticeably different for those patients who dropped out on or before the third course of treatment and those who completed at least one course after the third course.[46]

The FDA statistical reviewer felt that the statistical methods used in both the above studies to control for type I error (rejection of the null hypothesis when it is true) and to deal with missing data were not appropriate.[46]

The third study reported that a better quality of life was maintained during chemotherapy in the irinotecan group.[42]

The available quality-of-life evidence is not straightforward but may perhaps favour irinotecan, even though this drug appears more toxic than FU/FA.

Summary and conclusions of the evidence on irinotecan as second-line therapy for advanced colorectal cancer

One of the studies reviewed here had as its comparator BSC alone, defined as "the best care available as judged by the attending physician, according to institutional standards for each centre". This care included antibiotics, analgesics, transfusions, corticosteroids or any other symptomatic therapy except irinotecan or other topoisomerase I inhibitors, as well as access to psychotherapy, and localised radiation therapy to alleviate symptoms, provided that the total dose delivered was in the palliative range. This care was also given to patients in the irinotecan arm.[28]

Three studies used as their comparator 5FU or FU/FA regimens alone. In one of these studies, the comparator arm included three different infusional regimens.[41] The second study compared irinotecan with 5FU alone,[23] and the third compared two different irinotecan/FU/FA regimens with the same FU/FA regimens alone.[42] Concern has been expressed in relation to the first of these studies, regarding the acceptability of the control arm as a single homogeneous arm, given that the different FU/FA regimens may have different efficacy and safety profiles and that the study was not designed or powered for subgroup comparisons.[18]

Two studies compared irinotecan (alone or with FU/FA) with oxaliplatin plus FU/FA.[23,40] In the remaining studies, combinations of irinotecan with another agent (oxaliplatin, mitomycin C) were compared with regimens that included oxaliplatin.[24,45]

In one of the above studies, 38% of the FU/FA arm had already received, and progressed on or shortly after receiving, infusional FU/FA.[41] The control treatment of infusional FU/FA was therefore unlikely to be effective in this group.

The Cunningham and Rougier studies both had adequate power to reliably detect a 15% difference between the two groups in 1-year survival. In both studies, factors predictive of poor prognosis were generally well balanced across treatments. Although poor performance status was more common in the BSC arm of the Cunningham study, any effect of this on survival outcome

TABLE 41 *Percentage of patients admitted to hospital for serious adverse events*

Study	% of patients admitted to hospital for serious adverse events										
	IR + FU/FA	IR alone	IR/OX + FU/FA	IR + OX	IR + MMC	OX + 5FU	OX + FU/FA	OX + MMC	FU/FA	5FU alone	BSC alone
Cunningham *et al.*, 1998[28]		72									63
Rougier *et al.*, 1998[41,46]		41							39		
Adenis *et al.*, 2000[23]		No data				No data				No data	
Rougier *et al.*, 1999[42]	No data								No data		
Recchia *et al.*, 2000[40]	No data						No data				
Becouarn *et al.*, 1999[24]			No data	No data							
Ulrich-Pur *et al.*, 1999[45]					No data			No data			

IR, irinotecan; OX, oxaliplatin

TABLE 42 *Median cumulative number of hospital days for serious adverse events*

Study	Median cumulative no. of hospital days for serious adverse events (range)										
	IR + FU/FA	IR alone	IR/OX + FU/FA	IR + OX	IR + MMC	OX + 5FU	OX + FU/FA	OX + MMC	FU/FA	5FU alone	BSC alone
Cunningham *et al.*, 1998[28]		15 (1–168)									11 (2–87)
Rougier *et al.*, 1998[41,46]		23							22		
Adenis *et al.*, 2000[23]		No data				No data				No data	
Rougier *et al.*, 1999[42]	No data								No data		
Recchia *et al.*, 2000[40]	No data						No data				
Becouarn *et al.*, 1999[24]			No data	No data							
Ulrich-Pur *et al.*, 1999[45]					No data			No data			

IR, irinotecan; OX, oxaliplatin

would have been effectively excluded in the analysis by stepwise multiple regression.[47]

Four studies did not appear to include quality of life among their outcome measures.[23,24,40,45] One study unfortunately did not provide data on progression-free survival.[28]

The FDA medical reviewer considered that the Rougier and Cunningham studies appeared adequate and well controlled in relation to the evaluation of survival. However, in relation to end-points of clinical benefit such as pain-free survival and symptom-free survival, the variations in the frequency of patient visits, patient compliance, symptom reporting and investigator evaluations were felt to be such that comparability of results between treatment arms was weak.[18] In addition, it was felt that, in both studies, the censoring of patients for data analysis may have disadvantaged the irinotecan arm relative to the control arm.[18]

No studies of irinotecan as second-line therapy are known to have included patients over the age of 75 years. Only two studies provided information on the proportion of patients with a performance status of 2,[28,41] and in one of these,[41] this figure is substantially lower than in the other study and seems very low for this patient group. Thus, there is some uncertainty regarding the generalisability of the results of these studies to the wider population of patients with advanced colorectal cancer in need of second-line therapy. However, with this caveat, there is good evidence to suggest that, in selected patients, irinotecan monotherapy extends median overall survival after FU/FA failure by approximately 2 months, compared with FU/FA alone, although at the cost of increased toxicity and without significant extension of progression-free survival. There is also preliminary evidence to suggest that combination irinotecan/FU/FA therapy after FU/FA failure may extend median progression-free survival by approximately 2 months and median overall survival by almost 3 months, compared with FU/FA alone; however, the quality of this evidence cannot be assessed because the study has been reported only in abstract form.

In the study that compared irinotecan with BSC alone, the imbalance in terms of baseline performance status and the lack of clarity regarding the proportion of patients in the treatment arms receiving subsequent therapies[28] are such that it is not clear whether the survival benefit associated with irinotecan is due to that drug alone or to the total package of therapies, or possibly even to underlying patient characteristics that determined their receipt of subsequent therapies.

Irinotecan significantly increased pain-free survival and time to deterioration of performance status in comparison with BSC, but not in comparison with FU/FA.

Evidence for irinotecan in the first- and second-line treatment of advanced colorectal cancer

As noted above, there are good data to suggest that, in the first-line treatment of advanced colorectal cancer in patients aged 75 years and under with a performance status of 2 or below, combination irinotecan therapy is more effective than either FU/FA or irinotecan alone in extending median progression-free and overall survival, although this combination therapy is also associated with more toxicity than FU/FA alone. However, the role of subsequent therapies in relation to survival benefit is unknown. The data also indicate that, in this patient group, irinotecan, either alone or in combination with FU/FA, is more effective than FU/FA alone in extending overall survival after FU/FA failure. In both first- and second-line treatment, irinotecan appears to extend median overall survival by 2–3 months.

With the possible exception of asthenia, the toxicities associated with irinotecan (e.g. neutropenia, anaemia, nausea, vomiting and alopecia) are generally similar to those associated with other cytostatic agents. However, as both first- and second-line therapy, irinotecan is associated with a higher incidence of diarrhoea than the comparator regimens. Delayed diarrhoea associated with irinotecan can be severe and even potentially life-threatening.[49] Although it can be reduced or even suppressed using high doses of loperamide, many patients experience severe delayed diarrhoea refractory to loperamide, and this adverse effect has a significant impact on their quality of life and ability to complete treatment. It is particularly problematic for elderly patients with reduced mobility.[50] European studies have suggested that patients who are at increased risk of irinotecan-induced delayed diarrhoea and neutropenia include those in poor condition (performance status > 2) with bulky disease, pretreatment leucocytosis or prior abdominopelvic irradiation, or with initially increased levels of bilirubin more than 1.5 times normal, and those aged over 65 years.[49] Indeed, the product specification states that irinotecan is contraindicated in some of these conditions, though not in the elderly[19] (see *Summary of product characteristics* in chapter 2). However, American studies have

produced inconsistent results in relation to the predictive value of age.[51]

Oxaliplatin: quantity and quality of research available

Oxaliplatin has been licensed for the first-line treatment of metastatic colorectal cancer in combination with 5FU and FA.

Seven RCTs have been identified that deal with its use as first-line treatment,[25,27,30,32,35,36,44] two of which study its use as second-line treatment,[23,24] and one of which studies its use primarily as second-line treatment.[40] First- and second-line treatment will be reviewed separately.

Oxaliplatin as first-line treatment of advanced colorectal cancer

Information relating to the design and study populations of the seven studies that deal with oxaliplatin as first-line treatment of advanced colorectal cancer is summarised in *Tables 43–46*.

These studies relate to four comparisons:

- oxaliplatin + FU/FA versus FU/FA alone[25,30, 32]
- oxaliplatin + FU/FA followed by irinotecan + FU/FA versus irinotecan + FU/FA followed by oxaliplatin + FU/FA[44]
- oxaliplatin + FU/FA versus oxaliplatin alone[27]
- chronomodulated oxaliplatin + FU/FA versus fixed-rate infusion of oxaliplatin + FU/FA.[35,36]

All these studies use oxaliplatin in accordance with the UK licence.

One study did not provide any information on patient characteristics subdivided by treatment group. However, taken overall, the median age of 62 years (range, 27–75 years) was comparable with that in the other studies, but a higher proportion of patients (70%) were male.[25]

Four studies imposed an upper age limit of 75 years,[25,32,35,36] and two more studies appeared to do so.[25,44] The seventh study included patients aged 76 years.[30] Thus, all the studies under-represent

TABLE 43 *Oxaliplatin as first-line treatment of advanced colorectal cancer: studies included in the review*

Study	Countries (no. of centres)	Recruitment dates	Comparison	Study type	Source of funding
Giacchetti *et al.*, 2000[32]	France, Italy, Belgium (15)	Jun 1994 to Mar 1996	Oxaliplatin + chrono-modulated FU/FA vs chronomodulated FU/FA alone	Open-label RCT	Debiopharm SA; Université Paris Sud; Association Internationale pour la Recherche sur le Temps Biologiques et la Chronotherapie International
de Gramont *et al.*, 2000[30]	Europe, Israel (35)	Aug 1995 to Jul 1997	Oxaliplatin + FU/FA vs FU/FA alone	RCT	Debiopharm SA
Buechele *et al.*, 2000[25]	Germany	Not stated	Oxaliplatin + infusional FU/FA vs bolus FU/FA (Mayo regimen)	RCT	Not stated
Tournigand *et al.*, 2000[44]	Europe	Not stated	FOLFOX followed at progression by FOLFIRI vs FOLFIRI followed at progression by FOLFOX	RCT	Not stated
Zori Comba *et al.*, 1999[27]	Argentina	Not stated	Oxaliplatin + FU/FA vs oxaliplatin alone	RCT	Not stated
Levi *et al.*, 1994[35]	France, Italy, Belgium (7)	May 1990 to May 1991	Chronomodulated oxaliplatin + FU/FA vs fixed-rate infusion of oxaliplatin + FU/FA	Partially blinded RCT	Not stated
Levi *et al.*, 1997[36]	Europe	May 1991 to Feb 1993	Chronomodulated oxaliplatin + FU/FA vs fixed-rate infusion of oxaliplatin + FU/FA	RCT	Debiopharm; Centre National de la Recherche Scientifique, Paris; Association Internationale pour la Recherche sur le Temps Biologiques et la Chronotherapie International

TABLE 44 *Oxaliplatin as first-line treatment of advanced colorectal cancer: study design*

Study	Participants	Treatment groups (no. randomised)	Study procedure	Outcome measurements reported (when known, primary outcome measure in bold)	Comments
Giacchetti *et al.*, 2000[32]	Patients aged 75 years or under with histologically proven colorectal carcinoma, bi-dimensionally measurable metastatic lesions with one diameter of at least 20 mm, WHO performance status of 2 or less, adequate bone marrow, renal and hepatic function, and no previous chemotherapy or radiotherapy for metastatic disease; if prior adjuvant chemotherapy had been given, it had to be completed for at least 6 months	Rx: 5-day course of chronomodulated 5FU 700 mg/m^2/day and FA 300 mg/m^2/day, plus oxaliplatin 125 mg/m^2 as a continuous 6-hour iv infusion on day 1 (100) Control: 5-day course of chronomodulated 5FU 700 mg/m^2/day and FA 300 mg/m^2/day (100)	Each course was repeated every 21 days. Doses were reduced when necessary because of toxicity. Patients continued on treatment until disease progression, toxicity, refusal or death; treatment was also discontinued if a complete, partial or minor response allowed the complete surgical resection of metastases	**Tumour response** Toxicity Progression-free survival Overall survival	• Phase II/III study • Randomisation by centre by blocks of four patients allowed the possibility of selection bias • After treatment failure, patients in the non-oxaliplatin arm could receive oxaliplatin, and patients in both arms could receive a three-drug schedule different from that tested in the study; thus, 57% of patients in the non-oxaliplatin arm eventually received oxaliplatin in addition to their 5FU regimen • Analysis was by intention to treat
de Gramont *et al.*, 2000[30]	Patients with adenocarcinoma of the colon or rectum, unresectable metastases, at least one bi-dimensionally measurable lesion of at least 2 cm, adequate bone marrow, renal and hepatic function, WHO performance status of 0–2 and ability to complete quality-of-life questionnaires; if prior adjuvant chemotherapy had been given, it had to be completed for at least 6 months	Rx: Fortnightly de Gramont regimen + oxaliplatin 85 mg/m^2 on day 1 only + routine antiemetic prophylaxis (210) Control: Fortnightly de Gramont regimen (210)	Treatment was continued until disease progression, unacceptable adverse effects or patient chose to discontinue treatment	**Progression-free survival** Tumour response Overall survival Quality of life	• Phase III study • Randomisation was stratified by centre, performance status and number of metastatic sites, using a minimisation procedure • Crossover from the non-oxaliplatin to the oxaliplatin arm was allowed, provided disease progression was documented • 58% of the oxaliplatin group and 61% of the non-oxaliplatin group received post-study chemotherapy: 37% of the non-oxaliplatin arm received oxaliplatin and/or irinotecan (28%, oxaliplatin; 20%, irinotecan), and 30% of the oxaliplatin arm received irinotecan • Analysis was by intention to treat
Buechele *et al.*, 2000[25]	Untreated patients with metastatic colorectal cancer and measurable disease	Rx: Oxaliplatin 50 mg/m^2 + FA 500 mg/m^2 and infusional 5FU 2000 mg/m^2 weekly Control: Bolus FU/FA (Mayo regimen)	No data	Efficacy Progression-free survival Toxicity	• Phase III study • Only preliminary data available, in abstract form

continued

TABLE 44 contd *Oxaliplatin as first-line treatment of advanced colorectal cancer: study design*

Study	Participants	Treatment groups (no. randomised)	Study procedure	Outcome measurements reported (when known, primary outcome measure in bold)	Comments
Tournigand *et al.*, 2000[44]	Previously untreated patients with unresectable metastatic colorectal cancer	Rx: Oxaliplatin 100 mg/m^2 fortnightly + modified de Gramont regimen (FOLFOX) followed at progression by irinotecan 180 mg/m^2 fortnightly with the same regimen (FOLFIRI) (113) Control: FOLFIRI followed at progression by FOLFOX (113)	No data	**Time to progression**	• Phase III study • Only interim results available, in abstract form
Zori Comba *et al.*, 1999[27]	Chemotherapy-naive patients with metastatic colorectal cancer	Rx1: Bimonthly oxaliplatin 85 mg/m^2 + Mayo regimen Rx2: Bimonthly oxaliplatin 85 mg/m^2	Treatment continued until disease progression	Efficacy	• Phase II study • Only interim results available, in abstract form
Levi *et al.*, 1994[35]	Patients aged 75 years or under with biopsy-proven adenocarcinoma of colorectal origin, measurable recurrent or metastatic disease, WHO performance status of 2 or less, life expectancy greater than 1 month, and no previous chemotherapy or radiotherapy for metastatic disease; patients who had received prior adjuvant or neoadjuvant chemotherapy and/or radiotherapy were eligible for the study if they had a disease-free period of at least 6 months after treatment completion	Rx: 5-day course of chronomodulated 5FU 600 mg/m^2/day, FA 300 mg/m^2/day and oxaliplatin 20 mg/m^2 (45) Control: 5-day course of flat-rate 5FU 600 mg/m^2/day, FA 300 mg/m^2/day and oxaliplatin 20 mg/m^2 (47)	Each course was repeated after a 16-day interval. In the absence of toxicity greater than WHO grade 1, the daily doses of 5FU and oxaliplatin were increased to 700 mg/m^2 and 25 mg/m^2, respectively; if toxicity was greater than grade 3, the dose reduction was 100 mg/m^2/day for 5FU and/or 5 mg/m^2/day for oxaliplatin, depending on the type of toxic symptom	**Tumour response** Toxicity Progression-free survival Overall survival	• Patients and nursing staff were blinded to treatment allocation, but the main investigator at each centre was not blinded • Four patients crossed over between the 4th and 11th course of treatment from flat-rate to chronomodulated FU/FA • Analysis was by intention to treat

continued

TABLE 44 contd *Oxaliplatin as first-line treatment of advanced colorectal cancer: study design*

Study	Participants	Treatment groups (no. randomised)	Study procedure	Outcome measurements reported (when known, primary outcome measure in bold)	Comments
Levi *et al.*, 1997[36]	Patients aged 75 years or under with biopsy-proven adenocarcinoma of colorectal origin, measurable recurrent or metastatic disease, WHO performance status of 2 or less, life expectancy greater than 1 month, and no previous chemotherapy or radiotherapy for metastatic disease; patients who had received prior adjuvant or neoadjuvant chemotherapy and/or radiotherapy were eligible for the study if they had a disease-free period of at least 6 months after treatment completion	Rx: 5-day course of chronomodulated 5FU 600 mg/m^2/day, FA 300 mg/m^2/day and oxaliplatin 20 mg/m^2 (93) Control: 5-day course of flat-rate 5FU 600 mg/m^2/day, FA 300 mg/m^2/day and oxaliplatin 20 mg/m^2 (93)	Each course was repeated after a 16-day interval. In the absence of toxicity greater than WHO grade 1, the daily doses of 5FU and oxaliplatin were increased to 700 mg/m^2 and 25 mg/m^2, respectively; if toxicity was greater than grade 3, the dose reduction was 100 mg/m^2/day for 5FU and/or 5 mg/m^2/day for oxaliplatin, depending on the type of toxic symptom	**Tumour response** Toxicity Progression-free survival Overall survival	• Patients and nursing staff were blinded to treatment allocation, but the main investigator at each centre was not blinded • 22 (24%) patients in the flat-rate group received chronomodulated FU/FA, either from the start of treatment or after maximum-response assessment to avoid excessive toxic effects • Analysis was by intention to treat

older patients. One study had a higher proportion than the others of patients with a performance status of 0.[32]

In several studies, there were some imbalances between the treatment arms despite randomisation. In one study, the proportion of patients with a performance status of 2 favoured the arm that received FOLFOX as its primary treatment,[44] and in another study, the proportion of patients with a performance status of 1 or 2 was higher in the arm receiving flat-rate therapy than in that receiving chronomodulated therapy.[35] In four of the studies,[27,30,32,36] there was a reasonable balance between treatment arms in terms of performance status. The remaining study provided no data.[25]

In one study, more patients in the oxaliplatin arm than in the FU/FA arm had primary rectal cancer. Also, twice as many patients in the FU/FA arm as in the oxaliplatin arm had received 5FU-based adjuvant chemotherapy, and half as many patients in the FU/FA arm had normal carcinoembryonic antigen levels as in the oxaliplatin arm; these two differences were statistically significant ($p = 0.013$ and 0.03, respectively; see *Table 46*).[32] In a second study, there was a substantial difference in the number of patients with metastases that had recurred after previous surgical removal: 25% of patients receiving chronomodulated therapy but only 8% of those receiving flat-rate therapy had such metastases ($p < 0.005$).[36] In a third study, over twice as many patients in the group receiving oxaliplatin plus FU/FA had primary rectal cancer as in the group receiving oxaliplatin alone.[27] In a fourth study, the control group had a higher proportion of patients with primary rectal cancer and a lower proportion with more than one organ involved[35] (see *Table 45*).

The doses of oxaliplatin used in the studies varied. One study administered 125 mg/m^2 of oxaliplatin every 3 weeks.[32] Another two studies administered 85 mg/m^2 of the drug fortnightly.[27,30] A fourth administered 50 mg/m^2 weekly.[25] A fifth study administered 100 mg/m^2 of oxaliplatin every 4 weeks,[44] and the last two administered 100 mg/m^2 every 16 days.[35,36]

Number and type of studies excluded

No studies that appeared to meet the inclusion criteria were subsequently excluded from the review.

TABLE 45 *First-line oxaliplatin: characteristics of study populations*

Study	Median age, in years (range)	% male	WHO performance status (%)	Site of primary tumour (%)	No. of organs involved (%)	Sites of metastases (%)	Patients asymptomatic at study entry (%)	Median time from diagnosis to randomisation, in months (range)	Weight loss > 5% (%)
Giacchetti *et al.*, 2000[32]	Rx: 61 (31–75) Control: 61 (29–74)	Rx: 66 Control: 64	Rx: 0: 69 1: 20 2: 11 Control: 0: 66 1: 27 2: 7	Rx: Colon: 66 Rectum: 34 Control: Colon: 77 Rectum: 23	Rx: 1: 50 2: 34 ≥ 3: 16 Control: 1: 48 2: 37 ≥ 3: 15	Rx: Liver: 88 Lung: 35 Other: 24 Control: Liver: 86 Lung: 37 Other: 24	No data	No data	No data
de Gramont *et al.*, 2000[30]	Rx: 63 (20–76) Control: 63 (22–76)	Rx: 61 Control: 58	Rx: 0: 43 1: 46 2: 11 Control: 0: 49 1: 42 2: 10	Rx: Colon: 72 Rectum: 28 Multiple/ unspecified: 0 Control: Colon: 70 Rectum: 29 Multiple/ unspecified: 1	Rx: 1: 43 ≥ 2: 57 Control: 1: 40 ≥ 2: 60	Rx: Liver: 87 Lung: 23 Other: 12 Control: Liver: 82 Lung: 30 Other: 11	No data	No data	No data
Buechele *et al.*, 2000[25]	62 (27–75)	70	No data	No data	No data	No data	No data	No data	No data
Tournigand *et al.*, 2000[44]	Rx1: 61 (29–75) Rx2: 64 (40–75)	Rx1: 58 Rx2: 70	Rx1: 0: 43 1: 40 2: 16 Rx2: 0: 46 1: 48 2: 6	No data	No data	No data	No data	No data	No data

continued

TABLE 45 contd *First-line oxaliplatin: characteristics of study populations*

Study	Median age, in years (range)	% male	WHO performance status (%)	Site of primary tumour (%)	No. of organs involved (%)	Sites of metastases (%)	Patients asymptomatic at study entry (%)	Median time from diagnosis to randomisation, in months (range)	Weight loss > 5% (%)
Zori Comba *et al.*, 1999[27]	Rx1: 62 (46–75) Rx2: 62 (36–75)	No data	Rx1: 0: 44 1: 50 2: 6 Rx2: 0: 46 1: 51 2: 3	Rx1: Colon: 69 Rectum: 31 Rx2: Colon: 86 Rectum: 14	Rx1: 1: 44 2: 42 ≥ 3: 14 Rx2: 1: 46 2: 51 ≥ 3: 3	No data	No data	No data	No data
Levi *et al.*, 1994[35]	Rx1: 60 (31–73) Rx2: 60 (34–73)	Rx1: 44 Rx2: 57	Rx1: 0: 42 1: 51 2: 7 Rx2: 0: 30 1: 57 2: 13	Rx1: Colon: 76 Rectum: 24 Rx2: Colon: 64 Rectum: 36	Rx1: 1: 49 ≥ 2: 51 Rx2: 1: 57 ≥ 2: 43	Rx1: Liver: 88 Lung: 44 Rx2: Liver: 85 Lung: 23	No data	No data	No data
Levi *et al.*, 1997[36]	Rx1: 61 (22–75) Rx2: 61 (29–75)	Rx1: 56 Rx2: 65	Rx1: 0: 53 1: 32 2: 15 Rx2: 0: 54 1: 37 2: 10	Rx1: Colon: 68 Rectum: 32 Rx2: Colon: 71 Rectum: 29	Rx1: 1: 60 2: 31 ≥ 3: 9 Rx2: 1: 59 2: 32 ≥ 3: 9	Rx1: Liver: 82 Lung: 31 Rx2: Liver: 81 Lung: 41	No data	No data	Rx1: 20 Rx2: 13

TABLE 46 *Percentage of patients who had received prior adjuvant chemotherapy*

Study	% of patients who had received prior adjuvant chemotherapy						
	Chrono-modulated oxaliplatin + FU/FA	**Flat-rate oxaliplatin + FU/FA**	**Oxaliplatin alone**	**Chrono-modulated FU/FA**	**Flat-rate FU/FA**	**FOLFIRI**	**FOLFOX**
Giacchetti *et al.*, 2000[32]	10			23			
de Gramont *et al.*, 2000[30]		20.0			20.5		
Buechele *et al.*, 2000[25]		No data			No data		
Tournigand *et al.*, 2000[44]						No data	No data
Zori Comba *et al.*, 1999[27]		13.9	28.6				
Levi *et al.*, 1994[35]	11	6					
Levi *et al.*, 1997[36]	14	13					

Quality of studies, characteristics of studies and evidence rating

Three of the above studies were Phase III studies;[25,30,44] however, only interim results were available for two of these.[25,44] A fourth study was a fairly large, multicentre Phase II/III study.[32] A fifth study was a small, multicentre Phase II study.[27] It was not stated whether the remaining two studies were Phase II or Phase III studies. It was possible to assess the methodological quality of only the four trials for which full reports were available. Of these, one study[30] scored 0, and three studies[32,35,36] scored 2 on the Jadad scale.

Assessment of effectiveness: oxaliplatin as first-line treatment

Critical review and synthesis of information

Only one study provided information on the median duration of treatment. This median duration was 8 courses (24 weeks) in the oxaliplatin arm, and 6 courses (18 weeks) in the arm receiving FU/FA alone; in both cases, the range of treatment duration was 1–15 courses (3–45 weeks).[32]

In both studies that compared oxaliplatin plus FU/FA with FU/FA alone, and for which results were available,[30,32] time to progression was significantly longer in the oxaliplatin group than in the control group (see *Table 47*).

However, median overall survival was longer in the oxaliplatin group in only one study,[30] and in that case, the difference between the groups was not statistically significant (see *Table 48*). The investigators admit that the other study for which such data are available was inadequately powered to validate differences in overall survival.[32] One study suggested that the use of a chronomodulated rather than a flat-rate regimen conferred a survival

TABLE 47 *Median time from randomisation to progression, in months*

Study	Median time from randomisation to progression, in months (range)							*p*-value
	Chrono-modulated OX + FU/FA	**Flat-rate OX + FU/FA**	**OX alone**	**Chrono-modulated FU/FA**	**Flat-rate FU/FA**	**FOLFIRI**	**FOLFOX**	
Giacchetti *et al.*, 2000[32]	8.7 (7.4–9.2)			6.1 (4.0–7.4)				0.048
de Gramont *et al.*, 2000[30]		8.2*			6.0*			0.003
Buechele *et al.*, 2000[25]		No data			No data			
Tournigand *et al.*, 2000[44]						No data	No data	
Zori Comba *et al.*, 1999[27]		No data	No data					
Levi *et al.*, 1994[35]	11	8						0.19
Levi *et al.*, 1997[36]	9.8	7.9						0.20

OX, oxaliplatin

* *According to external review*

TABLE 48 *Median overall survival: time from randomisation to death, in months*

Study	Median time from randomisation to death, in months (range)							*p*-value
	Chrono-modulated OX + FU/FA	Flat-rate OX + FU/FA	OX alone	Chrono-modulated FU/FA	Flat-rate FU/FA	FOLFIRI	FOLFOX	
Giacchetti *et al.*, 2000[32]	19.4 (15.4–23.4)			19.9 (14.0–25.7)				Not stated
de Gramont *et al.*, 2000[30]		16.2			14.7			0.12
Buechele *et al.*, 2000[25]		No data			No data			
Tournigand *et al.*, 2000[44]						No data	No data	
Zori Comba *et al.*, 1999[27]		No data	No data					
Levi *et al.*, 1994[35]	19	14.9						0.03
Levi *et al.*, 1997[36]	15.9	16.9						0.46

OX, oxaliplatin

TABLE 49 *Survival rates at 1, 2 and 3 years*

Study	Survival rate (%)			
	Chronomodulated oxaliplatin + FU/FA	Flat-rate oxaliplatin + FU/FA	Chronomodulated FU/FA	Flat-rate FU/FA
de Gramont *et al.*, 2000[30] (at 1 year)		69		61
Giacchetti *et al.*, 2000[32] (at 2 years)	37		45	
Giacchetti *et al.*, 2000[32] (at 3 years)	23.5		30	
Levi *et al.*, 1997[36] (estimated survival at 3 years)	22	21		

advantage,[35] but the other study that compared these regimens did not produce a statistically significant result.[36]

Only one study provided information relating to 1-year survival, which was 69% in the oxaliplatin arm and 61% in the FU/FA arm.[30] However, another study provided information relating to survival at 2 and 3 years,[32] and a third study provided estimated survival rates at 3 years[36] (see *Table 49*). In the study that compared oxaliplatin plus FU/FA with FU/FA alone, 2- and 3-year survival rates were higher in the FU/FA group.[32]

No data were available relating to median pain-free survival in patients pain-free at baseline, median symptom-free survival in patients symptom-free at baseline, median time from randomisation to deterioration of performance status, or median survival without weight loss of more than 5% relative to baseline.

Objective response rates were significantly higher in those groups receiving oxaliplatin plus FU/FA than in those receiving either FU/FA or oxaliplatin alone. Two studies indicated that chronomodulated therapy was more effective in terms of objective response rates than flat-rate therapy (see *Table 50*).

Only one study provided information about the median time to response onset, which was shorter in the group receiving oxaliplatin plus FU/FA than in the group receiving FU/FA alone (9 vs 12 weeks). Duration of response was similar in both arms (45.1 vs 46.1 weeks).[30] Another study provided information about the median time to best response, which was 5 months in the oxaliplatin/FU/FA arm and 6 months in the FU/FA arm.[32]

Only two studies provided information on the proportion of patients who received chemotherapy subsequent to the study medication (see *Table 51*). In one study, 57 patients (57%) in the FU/FA arm for whom treatment failed were given oxaliplatin in addition to the FU/FA regimen.[32] In another study, 58.1% of patients in the intervention arm and 60.5% of those in the control arm received poststudy chemotherapy; 57.1% of those in the

TABLE 50 *Objective response rates: percentage of patients*

Study	% of patients responding to treatment regimen (95% CI)							*p*-value
	Chrono-modulated OX + FU/FA	Flat-rate OX + FU/FA	OX alone	Chrono-modulated FU/FA	Flat-rate FU/FA	FOLFIRI	FOLFOX	
Giacchetti *et al.*, 2000[32]	34* (24 to 44)			12* (6 to 20)				< 0.001
de Gramont *et al.*, 2000[30]		50.0† (46.1 to 54.9)			21.9† (17.9 to 25.9)			0.0001
Buechele *et al.*, 2000[25]		No data			No data			
Tournigand *et al.*, 2000[44]						63	60	
Zori Comba *et al.*, 1999[27]		34*	7*					0.012
Levi *et al.*, 1994[35]	53 (38 to 68)	32 (18 to 46)						0.38
Levi *et al.*, 1997[36]	51	29						0.003

OX, oxaliplatin

* *As assessed by external review*

† *Confirmed*

TABLE 51 *Percentage of patients receiving subsequent chemotherapy*

Study	% of patients receiving subsequent chemotherapy						
	Chrono-modulated OX + FU/FA	Flat-rate OX + FU/FA	OX alone	Chrono-modulated FU/FA	Flat-rate FU/FA	FOLFIRI	FOLFOX
Giacchetti *et al.*, 2000[32]	No data			57			
de Gramont *et al.*, 2000[30]		58.1			60.5		
Buechele *et al.*, 2000[25]		No data			No data		
Tournigand *et al.*, 2000[44]						No data	No data
Zori Comba *et al.*, 1999[27]		No data	No data				
Levi *et al.*, 1994[35]	No data	No data					
Levi *et al.*, 1997[36]	No data	No data					

OX, oxaliplatin

control arm received poststudy chemotherapy with oxaliplatin (27.6%) and/or irinotecan (20%), while 29.5% of those in the intervention arm received poststudy irinotecan. Overall survival in patients who did not receive poststudy oxaliplatin or irinotecan was 14.8 months in the oxaliplatin group and 12.2 months in the non-oxaliplatin group ($p = 0.04$), but as the investigators note, these are selected groups.[30] In a third study, 24% of patients receiving flat-rate oxaliplatin plus FU/FA received chronomodulated therapy either from the start of treatment (two patients) or after maximum-response assessment to avoid excessive toxicity (20 patients).[36] All these factors complicate interpretation of the study results.

Adverse effects

Few studies provided information on deaths that could be attributed to the study treatment (see *Table 52*). However, it may be implicit in those studies that provided no such data that no treatment-related deaths had occurred, at least by the time of publication.

None of the studies provided information relating to the overall percentage of patients suffering at least one grade 3–4 adverse event. However, in one study, grade 4 toxicity was said to have occurred in three times as many patients in the flat-rate group as in the chronomodulated therapy group (31% vs 10%, respectively; $p = 0.001$).[36]

One large Phase III study found that oxaliplatin plus the de Gramont regimen was associated with a significantly higher prevalence of grade 3–4 diarrhoea than the de Gramont regimen alone; in this study, grade 4 diarrhoea was found in 3.3% of the oxaliplatin arm and 1.5% of the control arm.[30] However, interim results from a smaller Phase III study suggest that oxaliplatin plus an infusional

TABLE 52 *Treatment-related deaths*

Study	Treatment-related deaths (%)						
	Chrono-modulated OX + FU/FA	Flat-rate OX + FU/FA	OX alone	Chrono-modulated FU/FA	Flat-rate FU/FA	FOLFIRI	FOLFOX
Giacchetti *et al.*, 2000[32]	1			1			
de Gramont *et al.*, 2000[30]		0.5			0		
Buechele *et al.*, 2000[25]		No data			No data		
Tournigand *et al.*, 2000[44]						No data	No data
Zori Comba *et al.*, 1999[27]		No data	No data				
Levi *et al.*, 1994[35]	0	0					
Levi *et al.*, 1997[36]	No data	No data					

OX, oxaliplatin

TABLE 53 *Percentage of patients suffering grade 3–4 diarrhoea*

Study	% of patients suffering grade 3–4 diarrhoea							*p*-value
	Chrono-modulated OX + FU/FA	Flat-rate OX + FU/FA	OX alone	Chrono-modulated FU/FA	Flat-rate FU/FA	FOLFIRI	FOLFOX	
Giacchetti *et al.*, 2000[32]	43			5				0.001
de Gramont *et al.*, 2000[30]		11.9			5.3			0.015
Buechele *et al.*, 2000[25]		5			9			
Tournigand *et al.*, 2000[44]						9	8	
Zori Comba *et al.*, 1999[27]		18*	0*					0.005
Levi *et al.*, 1994[35]	24	20						Not stated
Levi *et al.*, 1997[36]	29†	35†						Not stated

OX, oxaliplatin
* *Grade not specified*
† *WHO-modified grade 3–4*

FU/FA regimen may be associated with a lower incidence of grade 3–4 diarrhoea than the Mayo regimen alone.[25] A small Phase II study found that oxaliplatin plus the Mayo regimen was associated with significantly more diarrhoea than oxaliplatin alone[27] (see *Table 53*).

Oxaliplatin plus FU/FA was associated with a higher prevalence of grade 3–4 vomiting than either oxaliplatin or FU/FA alone; however, this difference was statistically significant in only one case[32] (see *Table 54*).

There was no significant difference in the prevalence of grade 3–4 mucositis between groups that received oxaliplatin and those that did not (see *Table 55*). However, in one study, five times as many patients who received flat-rate oxaliplatin/FU/FA treatment suffered stomatitis as those who received chronomodulated treatment (89% vs 18%, respectively; $p < 0.0001$).[35]

A large Phase III study found a statistically significant difference between groups in terms of the prevalence of grade 3–4 neutropenia, which was significantly higher in the oxaliplatin arm[30] (see *Table 56*).

Few studies provided information on the prevalence of grade 3–4 peripheral neuropathy. However, in those that did (including a large Phase III study[30]), such neuropathy was more common in patients who received oxaliplatin than in those who did not (see *Table 57*).

Few studies provided information on the number of patients admitted to hospital for serious adverse events. Such data as are available do not demonstrate a statistically significant difference between patients who did and those who did not receive oxaliplatin, but indicate that a substantially higher proportion of those receiving flat-rate treatment were hospitalised compared

TABLE 54 *Percentage of patients suffering from grade 3–4 vomiting*

Study	% of patients suffering from grade 3–4 vomiting							*p*-value
	Chrono-modulated OX + FU/FA	Flat-rate OX + FU/FA	OX alone	Chrono-modulated FU/FA	Flat-rate FU/FA	FOLFIRI	FOLFOX	
Giacchetti *et al.*, 2000[32]	25*			2*				0.001
de Gramont *et al.*, 2000[30]		5.8			2			0.43
Buechele *et al.*, 2000[25]		2			1			
Tournigand *et al.*, 2000[44]						13*	4*	
Zori Comba *et al.*, 1999[27]		7*	1.4*					Not stated
Levi *et al.*, 1994[35]	24*	9*						0.05
Levi *et al.*, 1997[36]	24†	25†						Not stated

OX, oxaliplatin

* *Nausea/vomiting*

† *WHO-modified grade 3–4*

TABLE 55 *Percentage of patients suffering from grade 3–4 mucositis*

Study	% of patients suffering from grade 3–4 mucositis							*p*-value
	Chrono-modulated OX + FU/FA	Flat-rate OX + FU/FA	OX alone	Chrono-modulated FU/FA	Flat-rate FU/FA	FOLFIRI	FOLFOX	
Giacchetti *et al.*, 2000[32]	10			4				0.09
de Gramont *et al.*, 2000[30]		5.8			1.5			0.19
Buechele *et al.*, 2000[25]		1			4			
Tournigand *et al.*, 2000[44]						No data	No data	
Zori Comba *et al.*, 1999[27]		No data	No data					
Levi *et al.*, 1994[35]	No data	No data						
Levi *et al.*, 1997[36]	14	76						0.0001

OX, oxaliplatin

TABLE 56 *Percentage of patients suffering from grade 3–4 neutropenia*

Study	% of patients suffering from grade 3–4 neutropenia							*p*-value
	Chrono-modulated OX + FU/FA	Flat-rate OX + FU/FA	OX alone	Chrono-modulated FU/FA	Flat-rate FU/FA	FOLFIRI	FOLFOX	
Giacchetti *et al.*, 2000[32]	2			1				0.555
de Gramont *et al.*, 2000[30]		39.7			5.3			< 0.001
Buechele *et al.*, 2000[25]		0.3			2.2			
Tournigand *et al.*, 2000[44]						25	37	
Zori Comba *et al.*, 1999[27]		4.2	0					Not stated
Levi *et al.*, 1994[35]	No data	No data						
Levi *et al.*, 1997[36]	3	8						Not stated

OX, oxaliplatin

TABLE 57 *Percentage of patients suffering from grade 3–4 peripheral neuropathy*

Study	% of patients suffering from grade 3–4 peripheral neuropathy							*p*-value
	Chrono-modulated OX + FU/FA	Flat-rate OX + FU/FA	OX alone	Chrono-modulated FU/FA	Flat-rate FU/FA	FOLFIRI	FOLFOX	
Giacchetti *et al.*, 2000[32]	No data			No data				
de Gramont *et al.*, 2000[30]		18.2			0			< 0.001
Buechele *et al.*, 2000[25]		4			0			
Tournigand *et al.*, 2000[44]						No data	29[†]	
Zori Comba *et al.*, 1999[27]		No data	No data					
Levi *et al.*, 1994[35]	0	0						
Levi *et al.*, 1997[36]	16[*]	31[*]						0.01

OX, oxaliplatin
[*] *WHO-modified grade 2–3*
[†] *Grade 3 sensory neuropathy*

TABLE 58 *Percentage of patients admitted to hospital for serious adverse events*

Study	% of patients admitted to hospital for serious adverse events							*p*-value
	Chrono-modulated OX + FU/FA	Flat-rate OX + FU/FA	OX alone	Chrono-modulated FU/FA	Flat-rate FU/FA	FOLFIRI	FOLFOX	
Giacchetti *et al.*, 2000[32]	11			3				< 0.1
de Gramont *et al.*, 2000[30]		No data			No data			
Buechele *et al.*, 2000[25]		No data			No data			
Tournigand *et al.*, 2000[44]						No data	No data	
Zori Comba *et al.*, 1999[27]		No data	No data					
Levi *et al.*, 1994[35]	No data	No data						
Levi *et al.*, 1997[36]	10	31						0.001

OX, oxaliplatin

with those receiving chronomodulated treatment (see *Table 58*).

None of the studies provided information about the number of days patients spent in hospital for serious adverse events.

Overall, therefore, the use of oxaliplatin generally appears to be associated with increased gastrointestinal toxicity, neutropenia and peripheral neuropathy, compared with FU/FA regimens.

Quality of life

Only one study[30] reported on quality of life, which was measured using the EORTC QLQ-C30 every fourth treatment cycle. In this study, 85% of patients in the intervention arm and 82% in the control arm participated in the quality-of-life study. Participation gradually declined to 39% overall after 8 months but remained well balanced between the groups.[52] There was no statistically significant difference between groups in median quality-of-life scores, despite the increased incidence of 5FU-related side-effects and specific peripheral neurotoxicity in the oxaliplatin arm.[30]

Summary and conclusions of the evidence on oxaliplatin in the first-line treatment of advanced colorectal cancer

Only one study chose as its comparator the de Gramont regimen;[30] another study used a chronomodulated infusional regimen,[32] and a third used the Mayo regimen.[25] One study compared alternating irinotecan and oxaliplatin plus a modified de Gramont regimen,[44] and another compared oxaliplatin plus the Mayo regimen with oxaliplatin alone.[27] The remaining two studies compared oxaliplatin plus chronomodulated FU/FA with oxaliplatin plus flat-rate FU/FA.[35,36]

As noted above (see *Assessment of effectiveness: oxaliplatin as first-line treatment* on page 47), one study that had tumour response as its primary outcome measure was stated to be inadequately powered to validate differences in overall survival.[32]

The outcome measures used for all studies were generally appropriate, However, only preliminary results were available for three studies,[25,27,44] and survival data were not available for these studies. It was also disappointing that only one study included quality of life in its reported outcome measures, given its importance in relation to this patient group.

Only one study included patients over the age of 75 years, and even then the oldest patients were only aged 76 years.[30] Only three studies included more than 10% of patients with a performance status of 2.[30,36,44] There is thus some uncertainty regarding the generalisability of the results to the wider population of patients with advanced colorectal cancer. However, there is good evidence to suggest that, in this population, the combination of oxaliplatin with an infusional FU/FA regimen, when used as first-line therapy, extends median progression-free survival by 2–3 months, although at the expense of increased toxicity. Oxaliplatin may also extend overall survival, although this is not clear because of the extent of the use of salvage oxaliplatin in patients randomised to FU/FA alone, which would dilute the evidence of the effectiveness of oxaliplatin in the oxaliplatin arm. However, it would certainly be unusual if improvements in the response rate did not translate into extended survival. In addition, oxaliplatin therapy may enable larger numbers of patients to undergo potentially curative surgical resection of liver metastases. Thus, in one study, 32 patients in the oxaliplatin plus FU/FA arm were able to undergo such surgery, compared with 21 patients in the FU/FA alone arm, although the macroscopic complete resection rate was comparable (21 vs 17 patients, respectively).[32]

There is no evidence that the use of chronomodulated rather than flat-rate delivery confers a significant advantage in terms of progression-free survival, nor is there any evidence to support the use of oxaliplatin monotherapy as first-line therapy.

Oxaliplatin as second-line treatment of advanced colorectal cancer

Information relating to the design and study populations of the three studies that deal with oxaliplatin as second-line treatment of advanced colorectal cancer is summarised in *Tables 59–61.*

The included studies relate to four relevant comparisons:

- oxaliplatin + 5FU versus 5FU alone as second-line treatment[23]
- oxaliplatin + 5FU versus irinotecan alone as second-line treatment[23]
- oxaliplatin + FU/FA versus irinotecan + FU/FA as first- or second-line treatment[40]
- irinotecan + oxaliplatin versus an alternated combination of irinotecan + FU/FA and oxaliplatin + FU/FA as second-line treatment.[24]

In one study, the interventions were used as both first- and second-line treatments.[40]

It should be noted that oxaliplatin is not licensed in the UK for use in the second-line treatment of patients with advanced colorectal cancer.

None of the studies provided information regarding their inclusion criteria, and none provided sufficient information relating to patient characteristics to indicate whether the treatment arms were evenly balanced.

In the study that used oxaliplatin/FU/FA or irinotecan/FU/FA as first- or second-line treatment, seven patients (17%) were chemotherapy-naive; their allocation to treatment arms was not given.[40]

TABLE 59 *Oxaliplatin as second-line treatment of advanced colorectal cancer: studies included in the review*

Study	Countries	Recruitment dates	Comparison	Study type	Source of funding
Adenis *et al.*, 2000[23]	France	Not stated	Oxaliplatin + 5FU vs either 5FU or irinotecan	RCT	Not stated
Recchia *et al.*, 2000[40]	Italy	Not stated	Oxaliplatin + FU/FA vs irinotecan + FU/FA	RCT	Not stated
Becouarn *et al.*, 1999[24]	France	Jul 1997 onward	Irinotecan + oxaliplatin vs alternated combination of irinotecan + FU/FA/ oxaliplatin + FU/FA	RCT	Not stated

TABLE 60 *Oxaliplatin as second-line treatment of advanced colorectal cancer: study design*

Study	Participants	Treatment groups (no. randomised)	Study procedure	Outcome measurements reported (when known, primary outcome measure in bold)	Comments
Adenis *et al.*, 2000[23]	Patients aged 18–75 years with previously treated, measurable inoperable metastatic colorectal cancer, and who had progression while on 5FU/raltitrexed, no neuropathy and performance status of 2 or less	Rx1: Oxaliplatin 130 mg/m^2 every 3 weeks + the Lokich regimen for 7/9 weeks (49) Control 1: Lokich regimen for 7/9 weeks (19) Control 2: Irinotecan 350 mg/m^2 every 3 weeks (17)	In oxaliplatin arm, the 5FU dose was reduced to 250 mg/m^2/day in cases of gastrointestinal toxicity	**Objective response rate** Safety Progression-free survival Overall survival	• Phase II/III study • Only interim results available, in abstract form • Only preliminary data available • Recruitment stopped at 87 patients because of low accrual due to availability of oxaliplatin as first-line therapy
Recchia *et al.*, 2000[40]	Chemotherapy-naive and FU/FA-resistant patients with metastatic colorectal cancer	Rx1: Oxaliplatin 50 mg/m^2 followed by the de Gramont regimen for 2 consecutive days every 15 days, with crossover to irinotecan at progression (21) Rx2: Irinotecan 90 mg/m^2 followed by the de Gramont regimen for 2 consecutive days every 15 days, with crossover to oxaliplatin at progression (21)	No data	Response Toxicity Progression-free survival Overall survival	• Phase II study • Only interim results available, in abstract form
Becouarn *et al.*, 1999[24]	Patients with advanced colorectal cancer, measurable disease and WHO performance status of 0–2, who had disease progression either while on 5FU or within 6 months of 5FU treatment, and who had had no more than one palliative 5FU-based regimen	Rx1: Irinotecan 180 mg/m^2 + the de Gramont regimen alternated with oxaliplatin 85 mg/m^2 + the de Gramont regimen Rx2: Oxaliplatin 85 mg/m^2 + irinotecan 200 mg/m^2 every 3 weeks		Response rate Time to progression Safety	• Phase II study • Only interim results available, in abstract form • 62 of 72 planned patients enrolled; distribution between groups not given • Results relate to 22 evaluable patients in the alternating irinotecan/ oxaliplatin + FU/FA arm and 19 in the irinotecan + oxaliplatin arm

TABLE 61 *Second-line oxaliplatin: characteristics of study populations*

Study	Median age (years)	% male	WHO performance status (%)	Site of primary tumour (%)	No. of organs involved (%)	Sites of metastases (%)	Patients asymptomatic at study entry (%)	Median time from diagnosis to randomisation, in months (range)	Weight loss > 5% (%)
Adenis *et al.*, 2000[23]	No data	No data	No data	No data	No data	No data	No data	No data	No data
Recchia *et al.*, 2000[40]	59	62	No data	No data	No data	No data	No data	No data	No data
Becouarn *et al.*, 1999[24]	Rx: 64 Control: 62	No data	No data	No data	No data	No data	No data	No data	No data

Number and type of studies excluded

No relevant studies were excluded.

Quality of studies, characteristics of studies and evidence rating

The only studies of oxaliplatin as second-line treatment of advanced colorectal cancer were small Phase II trials[24,40] or Phase II/III trials.[23] None of these trials could be assessed in terms of their methodological quality because all were available only in abstract form.

Assessment of effectiveness: oxaliplatin as second-line treatment

Critical review and synthesis of information

Only one study provided information on the median duration of treatment, which was 6 cycles (18 weeks) in the oxaliplatin/5FU arm, 3 cycles (9 weeks) in the arm receiving irinotecan alone and 4 cycles (12 weeks) in the arm receiving 5FU alone.[23]

Median time to progression appeared longer in patients receiving oxaliplatin plus 5FU than in those receiving either irinotecan alone or 5FU alone.[23] Similarly, the addition of FU/FA to oxaliplatin and irinotecan appeared to extend progression-free survival.[24] However, there was no significant difference between oxaliplatin plus FU/FA and irinotecan plus FU/FA[40] (see *Table 62*).

No data were available relating to overall survival, 1-year survival, pain-free survival, symptom-free survival, progression-free survival or survival without weight loss of more than 5% from baseline.

Response rates were higher in patients receiving oxaliplatin with 5FU regimens than in those receiving either irinotecan-based regimens or 5FU alone, although in one case it was stated that this difference was not statistically significant (see *Table 63*).

No data were available relating to time to onset of response, response duration or the percentage of patients who received chemotherapy subsequent to the study medication.

Adverse effects

Only one of the studies provided information on deaths that could be attributed to the study treatment. In that study, 12% of patients receiving irinotecan alone and none of those receiving oxaliplatin plus 5FU suffered possible treatment-related deaths.[23]

No information was available relating to the overall percentage of patients suffering at least one grade 3–4 adverse event.

The different treatment groups varied in the extent to which they suffered grade 3–4 diarrhoea.

TABLE 62 *Median time from randomisation to progression, in months*

Study	Median time from randomisation to progression (months)							*p*-value
	OX + 5FU	OX + FU/FA	OX/IR + FU/FA	OX + IR	IR alone	IR + FU/FA	5FU alone	
Adenis *et al.*, 2000[23]	5.1				2.0		3.5	
Recchia *et al.*, 2000[40]		5.3				6.6		Not stated
Becouarn *et al.*, 1999[24]			7.0	4.8				

OX, oxaliplatin; IR, irinotecan

TABLE 63 *Response rates: percentage of patients*

Study	% of patients responding to treatment regimen							*p*-value
	OX + 5FU	OX + FU/FA	OX/IR + FU/FA	OX + IR	IR alone	IR + FU/FA	5FU alone	
Adenis *et al.*, 2000[23]	36.7				17.6		5.3	
Recchia *et al.*, 2000[40]		33				22		Not stated
Becouarn *et al.*, 1999[24]			14	21				

OX, oxaliplatin; IR, irinotecan

One study showed a substantial difference between patients receiving oxaliplatin with 5FU and those receiving either 5FU or irinotecan alone[23] (see *Table 64*).

The results do not suggest that oxaliplatin increases the risk of grade 3–4 vomiting (see *Table 65*).

Only one study provided information about the percentage of patients suffering from grade 3–4 mucositis, which was highest (26%) in the group receiving 5FU alone (vs 10% in the oxaliplatin/5FU group and 0% in the group receiving irinotecan alone).[23]

There was no evidence that oxaliplatin was associated with an increased prevalence of grade 3–4 neutropenia (see *Table 66*).

Only one study provided information on neurosensory toxicity, which was measured using a specific scale. Such toxicity was suffered by 20% of patients receiving oxaliplatin plus 5FU, compared with none receiving either irinotecan alone or 5FU alone.[23]

No data were available relating to the percentage of patients admitted to hospital for serious adverse events or the cumulative number of hospital days for serious adverse events.

TABLE 64 *Percentage of patients suffering grade 3–4 diarrhoea*

Study	% of patients suffering grade 3–4 diarrhoea							*p*-value
	OX + 5FU	OX + FU/FA	OX/IR + FU/FA	OX + IR	IR alone	IR + FU/FA	5FU alone	
Adenis *et al.*, 2000[23]	43				12		5	
Recchia *et al.*, 2000[40]		10*				12*		Not stated
Becouarn *et al.*, 1999[24]			13	5				

OX, oxaliplatin; IR, irinotecan
* *Grade 3 only*

TABLE 65 *Percentage of patients suffering from grade 3–4 vomiting*

Study	% of patients suffering from grade 3–4 vomiting						
	OX + 5FU	OX + FU/FA	OX/IR + FU/FA	OX + IR	IR alone	IR + FU/FA	5FU alone
Adenis *et al.*, 2000[23]	6				6		0
Recchia *et al.*, 2000[40]		No data				No data	
Becouarn *et al.*, 1999[24]			3*	10*			

OX, oxaliplatin; IR, irinotecan
* *Includes nausea*

TABLE 66 *Percentage of patients suffering from grade 3–4 neutropenia*

Study	% of patients suffering from grade 3–4 neutropenia							*p*-value
	OX + 5FU	OX + FU/FA	OX/IR + FU/FA	OX + IR	IR alone	IR + FU/FA	5FU alone	
Adenis *et al.*, 2000[23]	No data				No data		No data	
Recchia *et al.*, 2000[40]		29				25		Not stated
Becouarn *et al.*, 1999[24]			33	30				

OX, oxaliplatin; IR, irinotecan

Although the main acute side-effects of oxaliplatin are nausea, vomiting and diarrhoea, the dose-limiting toxicity is cumulative peripheral sensory neuropathy, which is usually reversible but which persists for more than 2 months after stopping treatment in about 20% of cases.[53] Only interim results were available for the use of oxaliplatin in second-line treatment, and they did not provide sufficient data to assess the impact of such neuropathy in these studies.

Quality of life

No data were available relating to the quality of life associated with the use of oxaliplatin as second-line treatment of advanced colorectal cancer.

Summary and conclusions of the evidence on oxaliplatin in the second-line treatment of advanced colorectal cancer

All three studies compared different oxaliplatin regimens with different comparator regimens (see *Table 60*). In each case, an infusional 5FU regimen was used.

It is disappointing that none of these studies included quality of life as one of their outcome measures.

Only preliminary data were available for all three studies, and thus few results are available for discussion. As no information is available relating to the inclusion criteria used by the three studies, the generalisability of any results is not clear. Such data as are available suggest that the use of oxaliplatin plus 5FU may extend median progression-free survival compared with either 5FU or irinotecan alone (see *Table 62*). However, further evidence is required before a definitive conclusion can be reached about the use of oxaliplatin as second-line treatment for the general population of patients with advanced colorectal cancer. In the meantime, oxaliplatin is a potential alternative to irinotecan when that drug is relatively contraindicated, for example, in patients who have undergone pelvic radiotherapy or who have subacute bowel obstruction (Cunningham D, Royal Marsden Hospital, Sutton: personal communication, 2000).

Evidence for oxaliplatin in the first- and second-line treatment of advanced colorectal cancer

There is good evidence that, in the first-line treatment of advanced colorectal cancer, oxaliplatin plus FU/FA extends median progression-free survival by 2–3 months compared with FU/FA alone, although at the expense of increased toxicity; it seems probable that this combination therapy may also extend overall survival. Preliminary data suggest that oxaliplatin plus 5FU may also extend progression-free survival when used as second-line treatment.

Raltitrexed: quantity and quality of research available

Raltitrexed has been licensed for the palliative treatment of advanced colorectal cancer.

Four relevant RCTs have been identified.[29,34,38,54] Three deal with raltitrexed as first-line therapy; in the fourth study report, it is not stated whether raltitrexed is used as first- or second-line therapy.[38]

Information relating to the design and study populations of the four studies that deal with raltitrexed as first-line treatment of advanced colorectal cancer is summarised in *Tables 67–70*.[29,34,38,54,55]

All the included studies compared raltitrexed with an FU/FA regimen. As these are randomised studies with FU/FA as their comparator, they clearly do not comply with the UK licence for raltitrexed, which states that the drug should be used only in patients for whom FU/FA regimens are either not tolerated or inappropriate.[19]

TABLE 67 *Raltitrexed for advanced colorectal cancer: studies included in the review*

Study	Countries (no. of centres)	Recruitment dates	Comparison	Study type	Source of funding
Study 3 Cunningham *et al.*, 1996[29]	Europe, South Africa, Australasia[55]	Nov 1993 to Jun 1994	Raltitrexed vs FU/FA	RCT	Zeneca Pharmaceuticals
Study 10 Pazdur & Vincent, 1997[38]	North America	Not stated	Raltitrexed (two doses) vs FU/FA	RCT	Not stated
Study 12 Harper, 1997[54]	Europe, South Africa, Australasia[55]	Jul 1995 to Feb 1996	Raltitrexed vs FU/FA	Open RCT	Zeneca Pharmaceuticals
MRC trial CR06 Ledermann *et al.*, 1999[34]	UK (45)	May 1996 to Jul 1998[12]	Raltitrexed vs FU/FA or 5FU alone	RCT	Zeneca Pharmaceuticals

TABLE 68 *Raltitrexed for advanced colorectal cancer: study design*

Study	Participants	Treatment groups (no. randomised)	Study procedure	Outcome measurements reported (when known, primary outcome measure in bold)	Comments
Study 3 Cunningham *et al.*, 1996[29]	Patients aged 18 years and over with advanced recurrent metastatic adenocarcinoma of the colon or rectum, with at least one measurable or evaluable lesion, and a WHO performance status of 2 or less, who had not received adjuvant chemotherapy within the previous year, were not receiving folic acid, had no other malignancies or serious illnesses, and no evidence of significant renal or hepatic insufficiency	Rx: Raltitrexed 3 mg/m^2 once every 3 weeks (233) Control: Mayo regimen (216)	All treatments were continued until disease progression or unacceptable toxicity	**Time to progression** Objective response rate Toxicity Quality of life	• Phase III • Crossover between treatments was not permitted • Analysis was by intention to treat
Study 10 Pazdur & Vincent, 1997[38]	Patients with advanced colorectal cancer	Rx1: Raltitrexed 3 mg/m^2 every 3 weeks (217) Rx2: Raltitrexed 4 mg/m^2 (32) Control: Mayo regimen (210)		Objective response rate Survival Time to disease progression Toxicity	• Phase III study • The 4-mg/m^2 arm was closed down prematurely following three therapy-related deaths, and the intention-to-treat analysis was carried out on the remaining two arms
Study 12 Cocconi *et al.*, 1998[26]	Patients aged 18 years and over with advanced recurrent or metastatic adenocarcinoma of the colon or rectum, with at least one measurable or evaluable lesion, and a WHO performance status of 2 or less, who had not received prior systemic cytotoxic therapy for advanced disease, or adjuvant cytotoxic chemotherapy within the previous 12 months, had no other malignancies (except adequately treated carcinoma in situ of the cervix or basal or squamous cell cancer of the skin) or serious illnesses, and no evidence of significant renal or hepatic insufficiency	Rx: Raltitrexed 3 mg/m^2 every 3 weeks (247) Control: Machover regimen (248)	Therapy continued until disease progression or unacceptable toxicity, or until the investigator decided the patient was no longer benefiting from the treatment or the patient chose to discontinue treatment Dose escalation was permitted in relation to 5FU only	**Time to disease progression** Objective response rate Survival Drug tolerability Palliative benefits Quality of life	• Phase III study • After trial therapy, patients were treated at the investigators' discretion, but no patient who received 5FU was given raltitrexed • Analysis was by intention to treat
MRC trial CR06 Maughan *et al.*, 1999[12] Ledermann *et al.*, 1999[34]	Patients with recurrent or metastatic colorectal cancer, a life expectancy of more than 3 months and a WHO performance status of 0–2	Rx: Raltitrexed 3 mg/m^2 every 3 weeks (301) Control 1: de Gramont regimen (303) Control 2: Lokich regimen (301)		**Survival** Quality of life Response rate	

TABLE 69 *Raltitrexed: characteristics of study populations*

Study	Median age, in years (range)	% male	WHO performance status (%)	Site of primary tumour (%)	No. of organs involved (%)	Sites of metastases (%)	Patients asymptomatic at study entry (%)	Median time from diagnosis to randomisation, in months (range)	Weight loss > 5% (%)
Study 3 Cunningham *et al.*, 1996[29]	Rx: 61 (27–82) Control: 61 (27–80)	Rx: 60 Control: 59	Rx: 0: 45 1: 44 2: 10 Control: 0: 39 1: 49 2: 12	Rx: Colon: 59 Rectum: 40 Unknown: 0 Control: Colon: 68 Rectum: 32 Unknown: 0	No data	Rx: Liver: 78 Lung: 25 Lymph nodes: 20 Control: Liver: 77 Lung: 29 Lymph nodes: 19	No data	No data	No data
Study 10 Cunningham, 1998[55]	Rx: 61 Control: 62	Rx: 62 Control: 56	Rx: 0–1: 90 Control: 0–1: 90	Rx: Colon: 79 Rectum: 20 Control: Colon: 80 Rectum: 20	No data	No data	No data	No data	No data
Study 12 Cocconi *et al.*, 1998[26]	Rx: 60 (23–79) Control: 62 (36–83)	Rx: 62 Control: 66	Rx: 0: 49 1: 41 2: 10 Control: 0: 43 1: 50 2: 7	Rx: Colon: 65 Rectum: 35 Control: Colon: 67 Rectum: 33	No data	Rx: Liver: 77 Lung: 27 Lymph nodes: 23 Control: Liver: 77 Lung: 30 Lymph nodes: 23	No data	No data	No data
MRC trial CR06 Maughan *et al.*, 1999[12] Ledermann *et al.*, 1999[34]	63*	66	0: 33 1: 44 2: 22	No data	No data	No data	No data	No data	No data

* *Median age*

TABLE 70 *Percentage of patients who had received prior adjuvant 5FU*

Study	% of patients who had received prior adjuvant 5FU			
	Raltitrexed 4 mg/m^2	**Raltitrexed 3 mg/m^2**	**FU/FA**	**5FU alone**
Study 3 Cunningham *et al.*, 1996[29]		5	5	
Study 10 Pazdur & Vincent, 1997[38]	No data	No data	No data	
Study 12 Cocconi *et al.*, 1998[26]		11.7	12.9	
MRC trial CR06 Maughan *et al.*, 1999[12]		No data	No data	No data

At least two[29,54] and possibly all of the studies did not impose upper age restrictions; as may be seen, two studies included patients over the age of 80 years.[26,29] Thus, the populations of these studies seem similar in age to the wider population of patients with advanced colorectal cancer.

In three of the studies, 90% or more of patients had a performance status of 0–1,[26,29,55] and in the fourth study, 22% of patients had a performance status of 2.[12] Thus, this last study seems more representative than the others of patients with advanced colorectal cancer.

In one of the studies, there seemed some imbalance in terms of the proportion of patients in each arm in whom the rectum was the site of the primary tumour.[29] Because metastatic rectal cancers respond better to chemotherapy than metastatic colon cancers, this imbalance would favour the raltitrexed arm.

In those studies that provided the relevant information, patients who had previously received adjuvant FU/FA treatment were evenly distributed among treatment arms (see *Table 70*).

All the studies used the same dose of raltitrexed (3 mg/m^2). One study also initially used a higher dose (4 mg/m^2), but this arm was prematurely closed down following therapy-related deaths.[54]

Number and type of studies excluded

No studies that appeared to meet the inclusion criteria were subsequently excluded from the review.

Quality of studies, characteristics of studies and evidence rating

All four studies were large, multicentre Phase III studies. It was possible to assess the methodological quality of only the three trials for which full reports were available. Of these, two studies[26,29] scored 0, and one study[56] was marked in confidence so the score is not presented here. None of the studies were reported to have been blinded, and some were specifically open-label, which may have influenced the quality-of-life ratings.

Assessment of effectiveness: raltitrexed

Critical review and synthesis of information

In those studies for which data were available, the median duration of treatment ranged from a maximum of 15 weeks to a minimum of 12 weeks in the raltitrexed arm, with a maximum of 22 weeks for FU/FA (see *Table 71*).

In all three studies that produced a statistically significant result, the median time from randomisation to disease progression was longer in the FU/FA group than in the raltitrexed group (see *Table 72*).[12,26,38,57] In one case, the investigators suggested that this result may have been influenced by the fact that the assessments for time to progression took place every 3 weeks for the raltitrexed group and every 5 weeks for the FU/FA group, and thus progression would have been identified earlier in the raltitrexed group.[26] In this study, median postprogression survival duration was slightly longer in the raltitrexed group (7.1 months) than in the control group (6.4 months), regardless of second-line treatment.[26]

Median overall survival was longer in the FU/FA arm, although the difference between treatment arms reached statistical significance in only one study[38] (see *Table 73*). It has been suggested that this result may be due to the much longer duration of treatment in the FU/FA arm; in this study, the shorter duration

TABLE 71 *Median duration of treatment, in weeks*

Study	Median duration of treatment (weeks)			
	Raltitrexed 4 mg/m^2	**Raltitrexed 3 mg/m^2**	**FU/FA**	**5FU alone**
Study 3 Cunningham *et al.*, 1996[29]		15.2	15.0	
Study 10 Cunningham, 1998[55]	No data	12.1	22.3	
Study 12 Cocconi *et al.*, 1998[26]		12.7	16.9	
MRC trial CR06		*	*	*

* *Data not available for publication*

TABLE 72 *Median time from randomisation to progression, in months*

Study	Median time from randomisation to progression (months)				***p*-value**
	Raltitrexed 4 mg/m^2	**Raltitrexed 3 mg/m^2**	**FU/FA**	**5FU alone**	
Study 3 Cunningham *et al.*, 1996[29]		4.7	3.6		0.61
Study 10 Pazdur & Vincent, 1997[38] AstraZeneca, 2000[57]	No data	3.1	5.3		< 0.0001
Study 12 Cocconi *et al.*, 1998[26]		3.9	5.1		< 0.005
MRC trial CR06 Maughan *et al.*, 1999[12]		5	6	No data	0.03

TABLE 73 *Median overall survival: time from randomisation to death, in months*

Study	Time from randomisation to death (months)				***p*-value**
	Raltitrexed 4 mg/m^2	**Raltitrexed 3 mg/m^2**	**FU/FA**	**5FU alone**	
Study 3 Cunningham, 1998[55]		10.1	10.2		0.42
Study 10 Pazdur & Vincent, 1997[38]	No data	9.7	12.7		< 0.0109
Study 12 Cunningham, 1998[55]		10.9	12.3		0.197
MRC trial CR06 Ledermann *et al.*, 1999[34]		10	10	10	

of treatment in the raltitrexed arm was attributed to unconscious bias on the part of the investigators, probably arising from the termination of the 4-mg/m^2 raltitrexed arm because of unacceptable toxicity.[55] However, it should be remembered that, in the remaining studies (which, like study 10, were large studies), overall survival was shorter in the raltitrexed arm, although this was not statistically significant.

None of the studies provided information relating to median time from randomisation to pain onset, onset of tumour-related symptoms, deterioration of performance status or weight loss of more than 5% relative to baseline.

None of the studies demonstrated any statistically significant difference in response rates (see *Table 74*).

TABLE 74 *Objective response rates: percentage of patients*

Study	% of patients responding to treatment regimen				*p*-value
	Raltitrexed 4 mg/m^2	Raltitrexed 3 mg/m^2	FU/FA	5FU alone	
Study 3 Cunningham *et al.*, 1996[29] Cunningham, 1998[55]		19.3	16.7		0.48
Study 10 Cunningham, 1998[55]	No data	14.3	15.2		0.597
Study 12 Harper, 1997[54]		18.6	18.1		0.90
MRC trial CR06 Maughan *et al.*, 1999[12]		20	24	26	

No information was provided relating to time to response onset, duration of response or the proportion of patients receiving subsequent chemotherapy.

Adverse effects

Raltitrexed was associated with more deaths than either FU/FA or 5FU (see *Table 75*). In one study, the number of deaths in the group receiving 4 mg/m^2 of raltitrexed was such that this arm of the study was terminated.[38] The industry submission claims that the majority of drug-related deaths associated with raltitrexed in these trials have occurred as a result of failure to carry out dose modification in response to inadequate renal function or toxicity, as specified in the clinical trial protocol or prescribing information.[57] However, the manufacturer does not make it clear why they expect patient monitoring and dose modification in accordance with the drug protocol to be more thorough in normal practice than in the trials.

Only one study reported data relating to the prevalence of grade 3–4 adverse events.[58] This study reported very high toxicity for FU/FA (see *Table 76*) and used the Mayo regimen.[58] Unfortunately, published data comparing the percentages of patients in each arm who suffered at least one grade 3–4 adverse event are not available for the remaining three studies,[26,34,38] one of which used infusional FU/FA regimens as comparators.[34]

One study gave data relating to the prevalence of serious adverse events attributed to treatment: 18% in the raltitrexed arm, 3% in the de Gramont arm and 12% in the Lokich arm, with most of the events in the last group due to Hickman line complications.[12]

In those studies that used a bolus 5FU regimen, the prevalence of grade 3–4 diarrhoea was either lower or the same in the raltitrexed arm, compared with the FU/FA arm (see *Table 77*).

Raltitrexed was associated with a higher, or at best equal, prevalence of grade 3–4 nausea and vomiting compared with FU/FA (see *Table 78*).

TABLE 75 *Possible treatment-related deaths*

Study	Possible treatment-related deaths (%)			
	Raltitrexed 4 mg/m^2	Raltitrexed 3 mg/m^2	FU/FA	5FU alone
Study 3 Cunningham *et al.*, 1996[29]		3.6	2.8	
Study 10 Pazdur & Vincent, 1997[38]	9.4	No data	No data	
Study 12 Cocconi *et al.*, 1998[26]		1.6	1.2	
MRC trial CR06 Maughan *et al.*, 1999[12]		4*	0*	0*

* *Preliminary data*

TABLE 76 *Toxicity: percentage of patients suffering at least one grade 3–4 adverse event*

Study	% of patients suffering at least one grade 3–4 adverse event				*p*-value
	Raltitrexed 4 mg/m^2	Raltitrexed 3 mg/m^2	FU/FA	5FU alone	
Study 3 Kerr, 1995[58]		5.9	36.3		< 0.001
Study 10 Pazdur & Vincent, 1997[38]	No data	No data	No data		
Study 12 Cocconi *et al.*, 1998[26]		No data	No data		
MRC trial CR06 Ledermann *et al.*, 1999[34]		*	*	*	

* *Data not available for publication*

TABLE 77 *Percentage of patients suffering grade 3–4 diarrhoea*

Study	% of patients suffering grade 3–4 diarrhoea				*p*-value
	Raltitrexed 4 mg/m^2	Raltitrexed 3 mg/m^2	FU/FA	5FU alone	
Study 3 Cunningham *et al.*, 1996[29]		14	14		0.890
Study 10 Pazdur & Vincent, 1997[38]	No data	10	13		
Study 12 Cocconi *et al.*, 1998[26]		10	19		
MRC trial CR06		*	*	*	

* *Data not available for publication*

TABLE 78 *Percentage of patients suffering grade 3–4 nausea and vomiting*

Study	% of patients suffering grade 3–4 nausea and vomiting				*p*-value
	Raltitrexed 4 mg/m^2	Raltitrexed 3 mg/m^2	FU/FA	5FU alone	
Study 3 Cunningham *et al.*, 1996[29]		13	9		0.288
Study 10 Pazdur & Vincent, 1997[38]	No data	13	8		
Study 12 Cocconi *et al.*, 1998[26]		9	9		
MRC trial CR06		*	*	*	

* *Data not available for publication*

Raltitrexed was associated with a significantly lower prevalence of grade 3–4 mucositis than bolus 5FU regimens (see *Table 79*).

The data relating to the prevalence of grade 3–4 neutropenia suggest that raltitrexed is less toxic in terms of neutropenia than the Mayo regimen (see *Table 80*).

Raltitrexed was associated with a lower prevalence of grade 3–4 leucopenia than the Mayo regimen (see *Table 81*). Unfortunately, no data were available to allow comparison with infusional regimens.

In one study, the prevalence of severe asthenia was higher in the raltitrexed arm than in the FU/FA arm (18% vs 10%, respectively).[38]

TABLE 79 *Percentage of patients suffering from grade 3–4 mucositis*

Study	% of patients suffering from grade 3–4 mucositis				*p*-value
	Raltitrexed 4 mg/m^2	**Raltitrexed 3 mg/m^2**	**FU/FA**	**5FU alone**	
Study 3 Cunningham *et al.*, 1996[29]		2	22		< 0.0001
Study 10 Pazdur & Vincent, 1997[38]	No data	3	10		
Study 12 Cocconi *et al.*, 1998[26]		2	16		< 0.001
MRC trial CR06 Maughan *et al.*, 1999[12]		No data	No data	No data	

TABLE 80 *Percentage of patients suffering from grade 3–4 neutropenia*

Study	% of patients suffering from grade 3–4 neutropenia			
	Raltitrexed 4 mg/m^2	**Raltitrexed 3 mg/m^2**	**FU/FA**	**5FU alone**
Study 3 Kerr, 1995[58]		10	26	
Study 10 Pazdur & Vincent, 1997[38]	No data	No data	No data	
Study 12 Cocconi *et al.*, 1998[26]		No data	No data	
MRC trial CR06		*	*	*

* *Data not available for publication*

TABLE 81 *Percentage of patients suffering from grade 3–4 leucopenia*

Study	% of patients suffering from grade 3–4 leucopenia			
	Raltitrexed 4 mg/m^2	**Raltitrexed 3 mg/m^2**	**FU/FA**	**5FU alone**
Study 3 Cunningham *et al.*, 1996[29]		14	30	
Study 10 Pazdur & Vincent, 1997[38]	No data	18	41	
Study 12 Cocconi *et al.*, 1998[26]		6	13	
MRC trial CR06 Maughan *et al.*, 1999[12]		No data	No data	No data

No information was provided on the number of patients admitted to hospital for serious adverse events, or the cumulative number of hospital days for serious adverse events.

Raltitrexed appears more toxic than FU/FA, being associated with more deaths and shorter survival. The available evidence relating to the prevalence of grade 3–4 adverse events suggests that raltitrexed is associated with a prevalence of such events that is lower compared with the Mayo regimen.

Quality of life

Three studies measured quality of life, each using different tools.

In one study, patients completed the EORTC QLQ-C30 at study entry and every 12 weeks

thereafter until disease progression. The only significant difference reported in quality of life between the two groups was the greater impact of nausea and vomiting in patients treated with raltitrexed. The investigators attribute the failure to demonstrate a significant quality-of-life advantage for raltitrexed to a number of factors.

- Patients in the raltitrexed group were more likely than those in the FU/FA group to complete the questionnaire at the time of drug administration.
- The questionnaire assessed the impact on quality of life of toxicity symptoms more often associated with raltitrexed than with FU/FA treatment.
- The largest difference in the frequency of grade 3 and 4 events between the two treatment arms was seen after the first cycle of raltitrexed, and the questionnaire was not administered until after that point, so the main differences would not have been recorded.
- Only 55% of the raltitrexed group and 57% of the control group provided usable quality-of-life data.[29]

While possibly true, these post hoc attempts to claim a higher quality of life for patients in the raltitrexed group are unattractive. The first factor could certainly have been avoided had thought been given to the timing of the questionnaire, and the second suggests that more thought should have been given to the choice of a suitable instrument. The third factor's relevance to patients in relation to treatment that could extend for over 22 weeks is unclear. It should also be noted that this study compared raltitrexed with the Mayo regimen, which is associated with higher toxicity than the de Gramont regimen, and that therefore the quality of life associated with raltitrexed is likely to be appreciably lower than that associated with the optimum 5FU-based regimen.

In another study, quality of life was assessed prior to treatment, and then at weeks 2, 5, 10 and 15 using the Rotterdam Symptom Checklist (RSCL) and the EQ-5D.[26,60] Instrument completion rates were between 90% at baseline and 64% up to week 20.[60] Raltitrexed was found to maintain quality of life significantly better than the Machover regimen during the first treatment cycle, and up to week 10 of treatment was said to be associated with significantly fewer toxicity-related symptoms.[60] However, at weeks 5, 10 and 15, there was no difference between the groups in any dimension in either questionnaire.[57]

In a third study, quality of life was assessed at baseline and at regular intervals thereafter using EORTC QLQ-C30 (with additional trial-specific questions), and the Hospital Anxiety and Depression Scale (HADS). Patients who completed a 12-week form tended to have better baseline quality of life than those who did not. Patients on raltitrexed reported worse quality of life than those on the de Gramont regimen in terms of toxicity (nausea and vomiting [$p = 0.008$] and loss of appetite [$p = 0.004$]), role functioning ($p = 0.02$) and global quality of life ($p = 0.04$); the regimens were not significantly different in terms of palliation of pain, relief of anxiety, or improved physical or social functioning. None of the regimens improved fatigue or depression.[12]

It would thus appear that the quality of life of patients receiving raltitrexed was no better than that of patients receiving bolus 5FU-based regimens, and worse than the quality of life of those receiving the de Gramont infusional regimen.

Summary and conclusions of the evidence on raltitrexed in the treatment of advanced colorectal cancer

Only one study[12] chose as one of its comparators the de Gramont regimen; this study had a third arm receiving the Lokich regimen. Two studies used the Mayo regimen,[38,61] and the fourth study used the Machover regimen.[54]

The outcome measures used by the studies were appropriate, although one study did not measure quality of life.[38] However, only limited data were available.

At least two studies and possibly all four studies included patients over the age of 75 years, and one study included over 20% of patients with a performance status of 2.[12] The results therefore appear generalisable to the wider population of patients with advanced colorectal cancer.

The data indicate that, in the treatment of advanced colorectal cancer, raltitrexed was associated with a shorter time to disease progression and shorter overall survival when compared with FU/FA. It was associated with less toxicity than bolus 5FU regimens, but with more deaths considered to be possibly treatment related than any 5FU-based regimen.

Any case for using raltitrexed in the treatment of advanced colorectal cancer therefore rests on whether it can be demonstrated to lead to improved outcomes in patients with specific metabolic intolerance of 5FU leading to neuropathy or cardiac spasm, and who would not be

too frail for 5FU treatment. Such patients are likely to be very few in number because, generally, patients who are not suitable for treatment with 5FU have too many co-morbidities to be suitable for any chemotherapy, including raltitrexed. However, if feasible, an RCT would be required to demonstrate the utility of raltitrexed compared with BSC, irinotecan alone or oxaliplatin alone in this patient group.

It has also been suggested that raltitrexed has a role on the basis that patients with advanced colorectal cancer considered, hypothetically, that they would find its side-effect profile preferable to that of the Mayo regimen, to which raltitrexed was claimed to be similar in efficacy, and its administration attributes preferable to those of the Mayo, de Gramont and Lokich regimens, assuming that raltitrexed had comparable efficacy.[62] However, as noted above, raltitrexed appears less effective than FU/FA in terms of overall and progression-free survival, and is associated with a higher toxicity-related death rate. Thus, the use of raltitrexed for reasons of patient convenience should be weighed carefully against the associated risks.

Summary of the evidence on irinotecan, oxaliplatin and raltitrexed in the treatment of advanced colorectal cancer

The available evidence suggests that a combination of irinotecan and FU/FA in the first-line treatment of advanced colorectal cancer can extend both median progression-free and overall survival by 2–3 months, compared with either FU/FA alone or irinotecan alone. However, the effects of subsequent therapy on overall survival are unknown. Irinotecan monotherapy may also extend median overall survival after FU/FA failure by approximately 2 months, compared with FU/FA alone, and may extend median progression-free survival by a little over a month. However, irinotecan is also associated with more toxicity than FU/FA alone. There is also some preliminary evidence to suggest that combination irinotecan/FU/FA therapy after FU/FA failure may extend median progression-free survival by approximately 2 months and overall survival by almost 3 months, compared with FU/FA alone.

There is also good evidence to suggest that, when used as first-line therapy, the combination of oxaliplatin with an infusional FU/FA regimen extends median progression-free survival by 2–3 months, although at the expense of increased toxicity. Survival benefit was not demonstrated, but this may be a factor of trial design. In addition, oxaliplatin therapy may enable larger numbers of patients to undergo potentially curative surgical resection of liver metastases. However, there is no evidence to support the use of oxaliplatin monotherapy as first-line therapy.

Such preliminary data as are available suggest that the use of oxaliplatin plus 5FU as second-line treatment may extend progression-free survival, compared with either 5FU or irinotecan alone. However, further evidence is required before a definitive conclusion can be reached.

While it is difficult to compare across trials, the improvement in median progression-free survival (over 5FU) for both irinotecan and oxaliplatin as first-line treatment is similar at 2–3 months. Only irinotecan has shown a significant survival benefit, but as previously noted, it is impossible to relate this finding uniquely to first-line therapy due to the non-randomised use of second-line treatment. In second-line therapy, only irinotecan as a single agent has shown improved progression-free and overall survival. There is currently insufficient evidence relating to second-line combination therapies.

The available evidence suggests that, when used as first-line therapy, raltitrexed reduces both progression-free survival and overall survival in comparison with FU/FA, and that it is associated with a higher mortality rate. Thus, there seems no advantage in using raltitrexed in the treatment of advanced colorectal cancer, except in those few patients with specific metabolic intolerance of 5FU who would not be too frail for 5FU treatment.

Chapter 5

Methods for economic analysis

Overview

This chapter includes reviews of the published economic literature, company submissions and quality-of-life data from the clinical trials, as well as our own analysis of the costs and cost-effectiveness of the different treatments. The latter analysis was undertaken because the economic evidence was incomplete and not always comparable between studies.

The methods used for all parts of the economic review are described in the text below, which also includes an overview of the possible benefit measures that could be used in the analysis, explaining the reason why progression-free survival was used as the principal benefit measure.

The results, including the review of the literature and our own analysis, are presented in chapter 6, entitled *Results of economic analysis* (page 77).

Little clinical and no published economic evidence was identified concerning patients with liver-only metastases, for whom the increased response rates of the new treatments may offer increased potential for liver resection and increased survival. Liver resection rates are lower in the UK than in Europe, so there may be potential for increased resection, even with existing treatments.

Identification of studies

A literature search was carried out with the aim of identifying all economic studies of treatment with the three drugs, treatment with different 5FU regimens and BSC, as described in the section entitled *Identification of studies* in chapter 3. The search strategy is shown in appendix 4. The following studies were identified:

- **irinotecan in combination with 5FU**
  - one prospective study of a clinical trial, reported in abstract only
- **irinotecan alone as second-line treatment**
  - two economic studies and one resource use study, all based on a mixture of prospective and estimated data from a single clinical trial
- **oxaliplatin**
  - no published studies identified
- **raltitrexed**
  - two retrospective analyses of case-note data from a single clinical trial
  - one study based on a retrospective case-note analysis at a single hospital
  - one prospective economic study not yet published, the results of which are therefore confidential.

In addition to the published studies, Aventis provided an economic model in their submission, and Sanofi carried out an economic analysis using unpublished data from the de Gramont trial for oxaliplatin. AstraZeneca refers to the published studies of raltitrexed in their submission.

All the studies are reviewed in chapter 6. The 'Guidelines for authors and peer reviewers of economic submissions to the *BMJ*' (by Drummond and Jefferson for the *BMJ* Economic Evaluation Working Party)[63] have been used to assess the economic papers. Note that these guidelines serve as a checklist for the methods and reporting of economic studies, but are not a formal scoring system. They have been interpreted with this particular study in mind, which is a different perspective from that of a journal. For this analysis, it is the quality and relevance of the economic studies that are of real interest; less important is the presentation of the results.

It will be seen from the reviews in chapter 6 that the different studies include different cost elements, cover different (sometimes unspecified) time periods and use different measures of benefit. For this reason, our own economic analysis was undertaken with the aim of achieving comparable cost-effectiveness estimates for the different treatments.

Review of possible benefit measures

There are different possible benefit measures that could be used in the economic analysis. The advantages and disadvantages of each will be reviewed to explain the reasoning behind the benefit measure chosen.

Quality of life

The purpose of chemotherapy for advanced metastatic disease is as much for palliation of symptoms as for relatively small survival benefits. Therefore, it is essential to ensure that the burden of treatment does not negate the palliative and survival benefits. Many of the recent studies have used the well-validated EORTC QLQ-C30 cancer-specific quality-of-life questionnaire. However, the difficulty of obtaining good-quality data on quality of life from seriously ill patients, in particular the possibility of bias due to non-random censoring of data (discussed more fully in chapter 6 in *Summary of evidence from economic studies*), makes the data difficult to interpret.

Note that utility values have not been measured in any of the clinical trials. One study that assessed utility values for patients with colorectal cancer (independently of a clinical trial) will be discussed.

Survival

Survival is a clearly unambiguous and highly relevant clinical measure. Median survival based on Kaplan–Meier curves is consistently reported across all clinical trials. However, there are two difficulties in the use of median survival.

The first difficulty is with regard to the median as the measure of survival. The median certainly has the benefit of simplicity and avoids having to make any explicit assumptions about the survival distributions. However, there is an implicit assumption about the relative shapes of the two curves, and this does not necessarily reflect the actual survival difference between treatments. The true difference is the area between the survival curves. However, this difference is not as easily measured. It can be simply estimated from survival curves using the trapezoidal rule, but because the curves are usually incomplete (censored), they need to be projected in order to be able to estimate the total area between the survival curves. Both methods (trapezoids and curve fitting to allow projection) were used to estimate survival benefits in studies for which survival curves have been published. See appendix 6 for details of the methodology. It should be noted that all the other studies that calculate a cost-effectiveness ratio use the median measure.

The second issue with respect to many of the trials included in this review is the problem of crossover between treatments. Once patients had progressed on their allocated therapy, some received further therapy with a different agent. *Table 82* shows the proportion of patients who had further chemotherapy, and the agent, where indicated.

It is clear that, with only one exception, in all first-line trials for which data were provided, over 50% of patients went on to have further chemotherapy after progression on their initial allocated therapy, and in one study, as many as 79% of patients in one treatment arm received further chemotherapy. It is equally clear that the survival benefit of the first-line allocated therapy cannot be estimated from the survival differences shown, because the effect of the second-line therapy is unknown. When differences in survival between treatment with a new agent and the control have been shown, one interpretation is that it reflects the benefit of earlier treatment with the more active agent.

Survival is therefore a measure of sequential chemotherapy regimens, and the influence of the initial allocated therapy on overall survival is difficult to ascertain. Because the survival of patients in the different control arms cannot be uniquely related to their allocated therapy, progression-free survival will be used as the primary measure of benefit, despite the recognised problems with this measure, as discussed below.

Progression-free survival

Progression-free survival has been related to improved utility, reduced hospital stays and improved quality of life.[64] The theme of these studies in general is that patients who do not respond to treatment, but whose disease is stabilised, derive benefit from chemotherapy. The relationship with survival is debated (see discussion below in *Response* section). Median differences in progression-free survival are reported in many trials. The comments made in the previous section (*Survival*) about the median apply equally to the measure of progression-free survival. An analysis similar to that described for survival was carried out on progression-free survival curves, when plots were available. In general, these are the same studies for which survival plots are shown. It should be noted, however, that the determination of patient progression is not a completely objective measure, and the estimated length of progression-free time may be affected by the frequency of check-ups.

Response

Perhaps because of the difficulties discussed above in the measurement of survival, there is debate as to what extent response is an indicator of survival benefit. Buyse and co-workers[65] carried out an analysis with the aim of identifying the relation-

TABLE 82 *Percentage of patients receiving further chemotherapy*

Trial	Treatment	% of patients receiving further chemotherapy	% of whom received irinotecan	% of whom received oxaliplatin
Oxaliplatin, first-line				
de Gramont *et al.*, 2000[30]	Oxaliplatin + 5FU (de Gramont)	58	29.5	
	5FU (de Gramont)	61	20	27.6
Giacchetti *et al.*, 2000[32]	Oxaliplatin + 5FU (chronomodulated)	Some*		
	5FU (chronomodulated)	Some*		57
Irinotecan, first-line				
Douillard *et al.*, 2000[31]	Irinotecan + 5FU (de Gramont)	39		15.7
	5FU (de Gramont)	58	31	12.8
Saltz *et al.*, 2000[43]	Irinotecan + 5FU	52		< 5
	5FU (Mayo)	70		< 5
	Irinotecan only	79		< 5
Irinotecan, second-line				
Rougier *et al.*, 1998[41]	Irinotecan			
	5FU (various regimens)			
Cunningham *et al.*, 1998[28]	Irinotecan†	21		
	BSC†	31	1	
	Irinotecan‡	21		
	BSC‡	31	1	

* *An unspecified number of patients had a three-drug schedule different to that tested in the study (i.e. not oxaliplatin + FU + FA)*
† *Patients with performance status < 2*
‡ *Patients with performance status = 2*

ship. Using patient-level data from several trials of different 5FU regimens, they found response to be highly and significantly predictive of survival, when comparing hazard ratios at several different times from 1 to 12 months. However, they also found that for individual trials, only 38% of the variation in survival rates could be explained by the variation in response rates.

Economic analysis methods

This discussion of economic analysis methods will be divided into three sections:

- *Estimation of net costs*
- *Measurement of survival and progression-free survival benefits*
- *Estimation of quality-adjusted life-years (QALYs).*

Estimation of net costs

In addition to the review of existing cost-effectiveness evidence, an analysis was undertaken to estimate the marginal cost-effectiveness of irinotecan in combination with 5FU and oxaliplatin in combination with 5FU, both compared with 5FU alone in the first-line treatment of colorectal cancer. As previously stated, there is reasonable evidence of the costs of raltitrexed treatment compared with the Mayo 5FU regimen.

Also estimated was the cost-effectiveness of irinotecan for second-line treatment compared with BSC alone.

Ideally, the cost-effectiveness of giving sequential treatments (i.e. based on lifetime costs and benefits) to patients would be included in the analysis. However, there are such scant data available on the second-line treatment given to patients after failure of first-line treatment in the clinical trials that an estimate could not be made.

In order to calculate treatment costs, data from the published economic studies were used. The source and values of the different resource and cost estimates are shown in *Table 83*.[1,16,66] It should be noted that, because not all the studies from which cost data were taken showed the resource use on which the cost estimates were based, we have had to use the quoted costs (inflated as necessary to the year 2000), rather than basing costs on resource use.

TABLE 83 *Unit/monthly costs*

Item	No./person per month	Source of number	Unit cost (£)	Cost/month (£)	Source of cost	Year
Line insertion			250		Iveson *et al.*, 1999[16]	1996/1997
Chemotherapy	See *Table 84*				BNF	Sep 2000
Pump			62		Iveson *et al.*, 1999[16]	1999
Inpatient day (medical oncology)			356		Netten *et al.*, 1999[66]	1999
Outpatient (medical oncology)			109		Netten *et al.*, 1999[66]	1999
Adverse events						
Hospital days/month (low estimate)	0.38	Henry *et al.*, 1999[61] (de Gramont)	299.91	113.42	Netten *et al.*, 1999[66]	1999
Hospital days/month (high estimate)	1.00	Iveson *et al.*, 1999[16]	257.54	257.54	Netten *et al.*, 1999[66]	1999
Drug costs/month				9.70	Kerr & O'Connor, 1999[1]	1997
Tests/month (high estimate)				65.00	Kerr & O'Connor, 1999[1]	1997
Tests/month (low estimate)				3.16	Iveson *et al.*, 1999[16]	1996/1997
Clinician consultations/month				79.81	Iveson *et al.*, 1999[16]	1996/1997
Primary care/month (low estimate)				1.14	Kerr & O'Connor, 1999[1]	1997
Primary care/month (high estimate)				10.42	Iveson *et al.*, 1999[16]	1996/1997

Using these estimates, the cost of treating patients while on chemotherapy, but excluding the cost of chemotherapy and its administration, ranges from £154.77 to £383.26. The greatest component cost is for hospitalisations. Three studies that included data on this are Schmitt and co-workers,[67] a retrospective case-note study by Henry and colleagues,[61] and data from the de Gramont trial[30] included in the Sanofi submission (unpublished).[21] The average number of hospital days per patient was estimated from the latter study (see appendix 7).

The average number of days per patient while on treatment was almost identical for the data from Henry and colleagues[61] and Sanofi[21] (0.37 and 0.38 days, respectively). Schmitt and co-workers[67] reported 1.2 and 0.8 days for irinotecan and 5FU, respectively (combined data, 1.0 days), although the difference is not significant. A value of 0.38 days is used for a low estimate of costs and 1.0 days for a high estimate. Both Schmitt and co-workers[67] and Sanofi[21] provided a split of hospital days between specialties. These values have been used to calculate an average cost per hospital day. The data from Henry and colleagues relate to the stable state, which includes both treatment time and time in remission.

It should be noted that, because the resource estimates used for all items (except for chemotherapy and its administration) are common across all treatments, the analysis will not be sensitive to possible differences between them in, for example, treatment-related admissions. In the Henry[61] study, however, there were as many symptom-related hospital days as toxicity-related days (admittedly very small numbers). Thus, there would need to be fairly large differences in toxicity-related admissions to have a large effect on the total days, although different palliative effects may also affect admissions. It is also noteworthy that the costs of chemotherapy and its administration for regimens based on de Gramont far exceed other costs.

The cost of chemotherapy and its administration is the dominant cost. While it is relatively simple to calculate the cost of a cycle of treatment given according to protocol, the lack of information in some trial reports regarding the mean number of

cycles given, or mean treatment times, makes the calculation of total chemotherapy costs uncertain. *Table 84* shows the information available from different trials on the duration and intensity of treatment.

The 'estimated mean' treatment duration is based on the mean number of cycles multiplied by the interval between cycles. Because cycles may be omitted, the mean treatment duration calculated may underestimate the total time over which treatment is given (see *Irinotecan, single agent, as second-line treatment* below). For costing chemotherapy itself, the mean number of cycles is the measure required, but other costs will depend on the actual time over which treatment is given.

The only consistent treatment duration specified in all trials is the median. For costing, it is the mean that is required. The median is not necessarily a good estimate of the mean and may lie either side of it, as can be seen from *Table 84*. In some instances, the mean number of treatment cycles was provided or could be derived, but for first-line treatment with irinotecan, no indication of mean treatment cycles or treatment duration was available. Because the costs of chemotherapy dominate the economic analysis, the analysis is based on three treatment scenarios around different estimates of treatment duration.

Scenario 1

This scenario is based on median treatment duration for chemotherapy and low other costs (see *Table 83*).

While the basis of costing the different chemotherapy regimens is the same across all treatments, the comparability of the results depends on how good an estimate of the mean the median treatment time is. For oxaliplatin, the median treatment times are similar to the mean, but for 5FU the median appears to be an underestimate. For irinotecan with 5FU, there is no comparator.

Scenario 2

The absolute maximum treatment duration is until disease progression.

TABLE 84 *Duration and intensity of chemotherapy treatments*

Study	Treatment	Treatment duration (months)			Mean no. of treatment cycles	Time to progression (months)	% dose intensity	
		Median	Mean	Estimated mean			Novel drug	5FU
Oxaliplatin, first-line								
de Gramont *et al.*, 2000[30]	Oxaliplatin + de Gramont regimen	5.5		5.4	11.7	10.01	73	76
	de Gramont regimen	5.1		5.4	11.6	7.2		89
Giacchetti *et al.*, 2000[32]	Oxaliplatin + de Gramont regimen	5.53		5.37	7.76	10.22		
	de Gramont regimen	4.15		5.04	7.28	8.36		
Irinotecan, first-line								
Douillard *et al.*, 2000[31] (biweekly regimen)	Irinotecan + de Gramont regimen	5.7				7.8	93	92
	de Gramont regimen	4.15				5.5		96
Saltz *et al.*, 2000[43]	Irinotecan + Mayo regimen	5.5				7.4	72	71
	Mayo regimen	4.1				5.7		86
Irinotecan, second-line								
Rougier *et al.*, 1998[41]	Irinotecan	4.2	4.7	4.15	6	5.16	> 90	> 90
	de Gramont regimen	2.8		3.14	6.8	4.18		> 90

This maximum treatment duration is the basis of this scenario, together with high 'other costs', which obviously will produce a high estimate. Because treatment in all trials was given until disease progression, unless a patient suffered from severe toxic effects (or withdrew consent), the validity of this estimate depends on the proportion of patients who stopped treatment prior to progression. *Table 84* shows that, for oxaliplatin, which has cumulative toxic effects, the mean treatment time is almost half the mean time to progression, but this is not true for 5FU treatment, nor for irinotecan administered as a single agent.

Scenario 3 (baseline)
When mean treatment duration was available, this value has been used. In the absence of mean treatment times for irinotecan in combination with 5FU (and its control arm), an average of the median treatment time and time to progression has been used. There is no way of assessing whether this is a reasonable estimate or not. For the 5FU cohorts, this estimate results in treatment times that are slightly less than those for the 5FU cohorts in the oxaliplatin trials (4.83 and 4.9 months, compared with 5.4 and 5.04 months, respectively). A mean of high and low other costs was used.

For all scenarios, the costs of chemotherapy drugs have been based on protocol, reduced to take into account the reported dose intensities, as shown in *Table 84*. The costs of chemotherapy drugs have been taken from the BNF and estimated based on the costs of the cheapest vial size. Value added tax (VAT) is charged on drugs so has been added to the drug costs.

The costs of patients after termination of treatment, but prior to progression, have been estimated as being the same as for patients on chemotherapy, excluding the costs of chemotherapy and its administration. The average costs have been used, except in the case of hospitalisation, for which the lower estimate of hospital days was used. This estimate yields a cost per month of time in remission of £253.

Measurement of survival and progression-free survival benefits

As previously discussed (see *Survival* on page 70), while all studies reported median survival benefit, and most also reported median progression-free survival, the difference between medians is not necessarily representative of the survival (or progression-free survival) difference between two treatments. The true difference is the area between the survival curves. This difference was estimated both for survival and for progression-free survival curves using the method of trapezoids (limited to the extent of the published curves) and by fitting theoretical curves, to allow projection.

In order to undertake this analysis, the published graphs were scanned into digitising software that allows data points to be easily read off the curves. From these data, the areas under the curves at 3, 6 and 12 months were estimated using the trapezoidal rule. Three commonly used curves in survival analysis (the exponential, Weibull and Gompertz) were fitted to the data using a least-squares minimisation procedure in Excel software. The sum of square deviations, maximum deviation, and comparison of actual and predicted areas at 3, 6 and 12 months were used to assess the appropriateness of the fitted curves. Further details of the methodology are described in appendix 6.

The availability of survival curves limits this analysis to a subset of the trials, although this includes all the large, multicentre trials.

The analysis was undertaken for both survival and progression-free survival curves, but as previously discussed, the principal measure used in the economic analysis is progression-free survival.

However, for second-line treatment with irinotecan, there is no indication that patients in the Rougier trial[41] comparing irinotecan with 5FU had further chemotherapy other than their allocated treatment. An estimate of the marginal cost per life-year gained (LYG) of irinotecan compared with 5FU will be made. This estimate is equivalent to the economic study by Iveson and co-workers.[16]

Currently, not all patients are offered second-line therapy. For these patients, the relevant comparator is BSC. In order to estimate the marginal cost-effectiveness of irinotecan compared with BSC, the parameters shown in *Table 85* were used. Progression-free survival for first-line therapy with 5FU was estimated from the control arms of the trials by Douillard and co-workers[31] and Saltz and colleagues.[43] The parameters for second-line therapy were derived from Rougier and co-workers.[41] It is assumed that only 65% of patients will be suitable for/receive second-line therapy, estimated on the basis of trial reports (see *Table 82*). The total survival of 16 months resulting from this estimate fits between the mean survival reported by Saltz and colleagues[43] and Douillard and co-workers[31] for patients starting on 5FU therapy alone. It is assumed that the patients treated only with 5FU

TABLE 85 *Parameters for the estimation of the cost-effectiveness of irinotecan compared with 5FU for second-line treatment*

Study	Treatment	Regimen	Progression-free survival (months)	Proportion of patients	Actual progression-free survival (months)
Saltz *et al.*, 2000[43] Douillard *et al.*, 2000[31]	5FU, first-line	Mayo or de Gramont	5.5	1	5.5
Rougier *et al.*, 1998[41]	Irinotecan, second-line	As in Rougier *et al.*, 1998[41]	5.16	0.65	3.354
Rougier *et al.*, 1998[41]	BSC, second-line		7.13	1	7.13
Total					15.984

survive for the same amount of time after finishing their first-line therapy as patients do after terminating second-line therapy. The resulting total survival is 12.6 months. For the estimation of the marginal cost-effectiveness of second-line treatment of irinotecan compared with BSC, it is only the additional progression-free survival that matters (and the cost of treatment), because first-line treatment and BSC are assumed to be the same for both cohorts. However, the full scenario assumptions are shown to illustrate the resulting assumed survival for both cohorts, based on the previous assumptions.

It is noteworthy that the assumed survival benefit of 5.16 months for patients receiving irinotecan, compared with no irinotecan, is considerably greater than that shown by Cunningham and coworkers[28] (3.23 months for patients with performance status < 2). However, in the Cunningham trial, 31% of patients allocated to no chemotherapy eventually had some, although only 1% had irinotecan; 21% of patients allocated to irinotecan also had further chemotherapy. For both cohorts, the proportion of patients given further chemotherapy with a drug other than 5FU or irinotecan was 9%. As a high estimate of cost-effectiveness, the Cunningham trial's survival benefit will be used (i.e. 0.65 × 3.23 months = 2.1 months), leaving treatment costs the same.

Estimation of quality-adjusted life-years (QALYs)

None of the clinical trials measured utility values. However, one study was identified that assessed utility values for patients with advanced colorectal cancer. It will be briefly reviewed with regard to the application of the results in this study.

Petrou and Campbell, 1997,[64] 'Stabilisation in colorectal cancer'

Descriptions of 23 health states representative of those for colorectal cancer, including responding, stabilised and progressive disease, with and without toxic side-effects of treatment, were drawn up by a panel of experts. Thirty nurses, all experienced in the care of colorectal cancer patients, were used as proxies for patients, to estimate the utilities of the various health states using the standard gamble technique. The results (median utility score) are presented only for health states free of toxic effects, with some discussion of the effect of toxicities on reducing the utility values of them. The results are compared with a 'similar' (unpublished) Italian study (see *Table 86*).

TABLE 86 *Utility scores for colorectal cancer states, without toxic effects of chemotherapy*

Health state	UK score	Italian score
Best possible health (by definition)	100	100
Partial response	100	100
Stable disease	95	95
Progressive disease	57.5	45
Terminal disease	10	5
Worst possible health: death (by definition)	0	0

Some aspects of the methodology and reporting are not clear, as exemplified by the following questions.

- Were all nurses asked to value all health states (a huge task), and how consistent were the results? No measure of variation around the median scores is shown.
- Who comprised the expert panel that drew up the health state descriptions, and what were the descriptions? Only one example description is shown. It is not clear how severe the toxic effects were assumed to be (e.g. on the WHO scale grade 1–4).
- How was 'best possible health' defined? How were the patient proxies (nurses)

presented with the questions; for example, were they asked to imagine they were in the health state?
- Why are the full results for all 23 health states not reported?

Apart from these concerns, the main practical difficulty in applying the results is not having utility values for states that include toxic effects, and not knowing for how many days toxic effects affected patients.

In order to estimate the effect of adjusting progression-free survival for quality of life, the following assumptions will be made.

All days in hospital, whether for chemotherapy (including outpatient administration), toxic effects or disease symptoms, count as zero. The value of zero is arbitrary and is tested in a sensitivity analysis using the value 0.5. The hospital days for chemotherapy are known (based on protocol), and the high and low estimates of additional hospital days per month for stable disease (1.0 and 0.38 days, respectively) are used.

The remaining days are multiplied by the QALY value of 0.95 shown by Petrou and Campbell[64] for stable disease. This method ignores the period of time that some patients benefit from response. This proportion of time is difficult to estimate, and as progression-free survival has a QALY rating of 0.95 (compared with 1.0 for response), adjusting for this time is likely to have only a small effect on the result.

The method outlined above has similarities to the quality-adjusted time without symptoms or toxicity (Q-TWiST) method described by Gelber and colleagues.[68]

Chapter 6

Results of economic analysis

The results are presented in the following sections:

- *Assessment of economic studies relating to irinotecan, oxaliplatin and raltitrexed*
- *Summary of evidence from economic studies*
- *Review of quality-of-life data*
- *Survival and progression-free survival benefits*
- *Estimate of quality-of-life-adjusted progression-free survival*
- *Costs of treatment*
- *Estimation of cost-effectiveness of treatments*
- *Summary of results of economic analysis.*

Assessment of economic studies relating to irinotecan, oxaliplatin and raltitrexed

Irinotecan combined with 5FU as first-line treatment

Cunningham and co-workers, 2000,[69] ASCO abstract

In this study, the cost-effectiveness of irinotecan in combination with 5FU was compared with the cost-effectiveness of 5FU alone, both administered by the de Gramont regimen. The results of the clinical trial have been reported by Douillard and colleagues.[31] The study takes a UK NHS perspective. As only an abstract is available, the methods used are incompletely described, and there is insufficient detail to assess the quality of the study. The cost (assumed marginal) per LYG of the combined treatment is reported to be £16,015 (1997–1999 cost data), based on an analysis of a UK subset of the complete (European) trial data.

Irinotecan, single agent, as second-line treatment

There are two economic studies and one report of resource consumption for the single trial reported by Rougier and colleagues,[41] which compared irinotecan against three different infusional 5FU regimens.

Iveson and co-workers, 1999,[16] European Journal of Cancer *(irinotecan)*

The economic study takes a UK NHS purchasers' viewpoint and is based principally on resource use data collected during the trial. Exceptions to this are estimates of the costs of chemotherapy, which are based on the trial protocol and the costs of administering the drugs, for which resource use estimates are made based on usual administration modes in the UK.

The reported total costs per patient for treatment with irinotecan (1996/1997–1998) are £8253, compared with £6791 for the de Gramont regimen and £5983 for Lokich. Using the median survival benefit of irinotecan over 5FU treatment (0.19 years) reported by Rougier and colleagues,[41] the marginal cost per LYG is £7695 for irinotecan compared with the de Gramont regimen and £11947 compared with Lokich.

However, the cost-effectiveness results reported by Iveson and co-workers[16] need to be interpreted with caution for the following reasons.

1. It is not clear over what time period the costs have been collected, only that they are not lifetime costs. An estimate of lifetime cost-effectiveness is given, but the assumptions and methodology are not described. However, Schmitt[67] has confirmed (Schmitt C, MDS Pharma Services, France: personal communication, 2000) that the analysis was based on his resource analysis (see points 3 and 4 below). The baseline calculation of cost-effectiveness based on costs over a fixed time period that is less than lifetime is likely to bias the result in favour of irinotecan, due to the survival advantage of patients treated with the drug. This is illustrated by the marginal cost per LYG lifetime estimate shown of irinotecan compared with the de Gramont regimen: £10,104, which is £2409 more than the baseline estimate. There is still a possibility of bias in favour of irinotecan for the lifetime estimate, which was based on average hospital usage during and after treatment for the two trial arms. There is some evidence[61] that patients have high hospital usage in the terminal phase. With more patients on irinotecan surviving the time period over which costs were estimated, bias may have been introduced into the estimates of average number of hospital days. However, the graph of cumulative hospital days presented by Schmitt and co-workers[67] does not suggest this was an important effect.

2. There is some lack of consistency with the year of costing, varying from 1996 (GP/nurse consultations) to 1998 (drug costs). This inconsistency is unlikely to have a significant effect on the result. Of potentially more importance is the omission of pharmacy staff costs for the preparation of the chemotherapy drugs. A cost saving for this cost element has been demonstrated for raltitrexed when compared with 5FU given with FA, as in the de Gramont regimen (Summerhayes and colleagues[70]). As a single-agent treatment, this is likely to be true for irinotecan also.
3. Other points that are not discussed in the Iveson paper,[16] but which are clarified elsewhere, include the omission of drug costs for treatment of complications and how differences in practice across Europe may have affected resource use. The results of Kerr and O'Connor,[1] comparing the monthly treatment costs of raltitrexed and 5FU, show that the drug costs for treating adverse events comprised less than 2% of total costs in both treatment arms. Regarding variation in resource use between countries, Schmitt and co-workers[67] reported that an analysis of hospitalisation for diarrhoea found "apparent greater variability between centres in the same country than between countries".
4. There is very little sensitivity analysis. Some variation around the central estimate of LYGs as a result of irinotecan treatment is essential. There is also no sensitivity analysis around resource use. The confidence limits around the number of hospital days for the treatment of complications shown by Schmitt and co-workers[67] suggest the difference between the two treatment arms was not significant. If the same average number of hospital days is assumed for both treatment arms, the additional cost of irinotecan treatment over the de Gramont regimen would increase to £2000.
5. In practice, only a minority of patients would receive second-line 5FU therapy, perhaps in the order of 20%. From this perspective, the Cunningham trial,[28] which compared irinotecan with BSC, is more relevant. Unfortunately, there is no economic study of the trial.

Levy-Piedbois and colleagues, 2000[71]

The paper by Levy-Piedbois and colleagues[71] is also based on the clinical results and resource use data collected in the Rougier[41] study. However, the viewpoint is from a French hospital perspective, with the resulting costs converted to US$. This perspective is less relevant to this review, but the paper will be briefly discussed, and differences with the Iveson[16] study, both in methodology and results, will be highlighted.

As with Iveson and co-workers,[16] it is unclear for what period of time resource data were collected, although two statements are made concerning this. One states that "costs were computed over the total duration of patient survival, or three year follow-up", while the other contradictory statement is "overall survival and costs were estimated from the time of randomisation until the death of the patient, or last visit." In fact, both statements are cast into doubt because some of the resource quantities quoted (e.g. the total hospital days per patient after termination of chemotherapy) are the same as those quoted by Schmitt and co-workers,[67] who stated a maximum 16-month follow-up. The confusion over the time horizon for resource use makes the results difficult to interpret.

Levy-Piedbois and colleagues[71] found irinotecan to be more expensive than all three 5FU regimens, whereas Iveson and co-workers[16] found irinotecan to be less expensive than the AIO 5FU regimen, whether the latter was provided on an inpatient or outpatient basis. Unfortunately, Levy-Piedbois and colleagues[71] did not detail all resources and unit costs, but often showed only aggregated costs. However, one main difference with the Iveson study[16] may be deduced, which may account for the slightly different result.

Table 87 compares the drug cost of 5FU therapy (including FA) relative to irinotecan for one cycle of treatment in the Iveson[16] and Levy-Piedbois[71] studies.

TABLE 87 *Drug cost per cycle relative to irinotecan*

Treatment regimen	Drug cost/cycle (£)	
	Iveson *et al.*, 1999[16]	Levy-Piedbois *et al.*, 2000[71]
Irinotecan	1	1
de Gramont	0.327	0.015
Lokich	0.072	0.013
AIO	0.718	0.083

The table shows that the drug cost of 5FU therapy relative to irinotecan is considerably less in France than in England. This difference will tend to make irinotecan less cost-effective in France, all other parameters being equal. It should be noted, however, that the Iveson study's[16] drug costs took into account dose reductions, whereas

Levy-Piedbois and colleagues[71] calculated costs according to protocol, but the effect of this on the relative costs of the therapies is small.

There are also differences in approach between the Levy-Piedbois[71] and Iveson[16] analyses. The effects of these differences on the result are difficult to ascertain.

Levy-Piedbois and colleagues[71] used time and motion surveys to estimate the resources required for drug administration, whereas Iveson and co-workers[16] used standard inpatient/outpatient consultation costs. Unfortunately, the Levy-Piedbois report[71] presents only the resulting costs, and not the underlying staff time data, so the data cannot be used. For inpatient episodes during chemotherapy, Levy-Piedbois and colleagues[71] used diagnosis-related group (DRG) costs per episode, rather than counting and costing hospital days as Iveson and co-workers[16] did. The Levy-Piedbois method[71] seems contrary because length of stay is likely to be the most important determinant of episode cost, and the information is available – all the more so because cost per day was used as the basis of costing hospital stays after termination of chemotherapy.

Unlike the Iveson paper,[16] a sensitivity analysis of the effect of variation around the central estimate of survival gain on cost-effectiveness was attempted by Levy-Piedbois and colleagues.[71] However, because no confidence limits were available from the Rougier study,[41] a "reasonable range" had to be estimated. The analysis shows that the calculated cost-effectiveness is very sensitive to the survival gain, over the estimated limits.

Schmitt and co-workers, 1999[67]

The paper by Schmitt and co-workers[67] details some of the resources used to treat patients in the trial, but is not an economic study because no attempt has been made to cost the resources. This paper is of interest, however, in aiding the interpretation of the two economic studies. In particular, it is the only paper that makes a clear statement as to the time horizon of the collection of resource data (median, 10 months; maximum, 16 months) and the method used to take into account censoring of data. Schmitt has confirmed that the Iveson analysis[16] was based on his work (Schmitt C, MDS Pharma Services, France: personal communication, 2000).

The Schmitt paper[67] also presents data on actual resource use for the administration of chemotherapy, which show that for all treatment modalities there was a range of settings (inpatient, day case and outpatient). The trial took place in several different European countries, and the treatment setting may have been determined as much by usual practice as clinical considerations.

Aventis Pharma industry submission, 2000[72]

Aventis Pharma have included a model of treatment for advanced metastatic disease, which follows patients through first- and second-line treatments to death. Alternative treatments included are first-line treatment with irinotecan or oxaliplatin in combination with 5FU, and 5FU alone by the de Gramont regimen. It is assumed a proportion of patients have second-line therapy with either 5FU or single-agent irinotecan. The model treatment and adverse event probabilities are described as being based on a meta-analysis of trial data for irinotecan and oxaliplatin. What is unclear, however, is the source of many of the parameters used in the model. It is assumed that all patients receive chemotherapy for 6 weeks, after which they are assessed as to whether or not they are responding to treatment, or are stable. It is assumed that those not responding have no further first-line therapy, while the responders and stabilised patients continue on therapy for differing times. Subsequent to therapy, patients have a period of time in remission (not on therapy, but stable). At progression, a proportion of patients (60%) go on to second-line therapy with either 5FU or single-agent irinotecan. This means that the quoted cost-effectiveness ratio was based on the assumption that 30% of patients who receive second-line therapy have irinotecan in the baseline scenario. Resource consumption has been estimated for patients on therapy, in remission and on BSC, as well as for each toxic event. For second-line therapy the costs have been taken from the Iveson study.[16]

The results of this model are unreliable for several reasons. The most important of these is that errors were made in the calculation of the treatment times used in the model for irinotecan, oxaliplatin and 5FU. Re-analysis of the Aventis calculations shows that, in the model, the mean treatment time for irinotecan was underestimated by 7 weeks, and those for oxaliplatin and 5FU were overestimated by 3 and 2 weeks, respectively. These errors have a significant effect on the relative treatment costs of the different treatment cohorts. A summary of the periods of time that patients spend in each state for each treatment cohort used in the model has been calculated from the underlying parameters used in the model. The difference between 'total survival' and 'model survival' represents the error in the estimation. The time periods used in the model are shown in *Table 88*. Similar data from the main trials are shown in *Table 89*.

The trial data suggest that patients on irinotecan spent only 15–20% of stable time in remission (no chemotherapy, so the least expensive state), whereas in the model remission represents around 50% of stable time.

It should be noted that the published studies gave median times, and as previously explained, it is uncertain whether the median is a good estimate of the mean. The mean treatment times are required for costing.

Another issue relates to the assumptions that are made in comparing treatment with irinotecan to that with oxaliplatin. There are no fully reported trials comparing the two treatments, and therefore scenarios have to be devised on which to base the analysis. The sensitivity analysis does not cover the full range of assumptions that are made. In particular, the scenario devised is driven by survival. Because no significant difference in survival has been shown for oxaliplatin over 5FU, the scenario used assumes that survival is the same. In fact, survival for both arms of both oxaliplatin trials is much greater than the 12.69 months assumed in the Aventis scenario. This means that the oxaliplatin trial time has to be compressed to fit the time assumed in the model. The approach adopted is that the additional time has all been taken from 'remission time'; it is assumed that

TABLE 88 *Mean time (months) spent in different states, according to the Aventis model*

Treatment	First-line treatment duration (months)	Time in remission (months)	Time to progression (months)	Second-line treatment duration (months)	Time in BSC (months)	Time in second-line chemotherapy/ BSC (months)	Total survival time (months)	Model survival time (months)
Irinotecan + de Gramont regimen	3.7	4.41	8.11	2.51	4.95	7.46	15.57	15.58
Oxaliplatin + de Gramont regimen	3.3	2.45	5.75	2.34	4.95	7.29	13.04	12.69
de Gramont regimen	3.7	1.58	5.28	2.51	4.95	7.46	12.74	12.69

TABLE 89 *Median time (months) spent in different states, according to the trials*

Study	Treatment	First-line treatment duration (months)	Time in remission (months)	Time to progression (months)	Second-line treatment duration (months)	Time in BSC (months)	Time in second-line chemotherapy/ BSC (months)	Total survival time (months)
Oxaliplatin, first-line								
de Gramont *et al.*, 2000[30]	Oxaliplatin + de Gramont regimen	5.5	2.7	8.2			8.0	16.2
	de Gramont regimen	5.1	0.9	6.0			8.7	14.7
Giacchetti *et al.*, 2000[32]	Oxaliplatin + de Gramont regimen	5.53	3.17	8.7			10.7	19.4
	de Gramont regimen	4.15	1.95	6.1			13.8	19.9
Irinotecan, first-line								
Douillard *et al.*, 2000[31] (weekly regimen)	Irinotecan + de Gramont regimen	5.5	1.2	6.7			10.7	17.4
	de Gramont regimen	4.8	–0.4	4.4			9.7	14.1
Douillard *et al.*, 2000[31] (biweekly regimen)	Irinotecan + de Gramont regimen	5.7	1.0	6.7			10.7	17.4
	de Gramont regimen	4.15	0.25	4.4			9.7	14.1
Saltz *et al.*, 2000[43]	Irinotecan + Mayo regimen	5.5	1.5	7.0			7.8	14.8
	Mayo regimen	4.1	0.2	4.3			8.3	12.6
Irinotecan, second-line								
Rougier *et al.*, 1998[41]	Irinotecan				4.2	6.6	10.8	
	de Gramont regimen				2.8	5.7	8.5	
Cunningham *et al.*, 1998[28]	Irinotecan				4.1		9.2	
	BSC						6.5	

treatment times are as they were in the trials (but overestimated, as discussed above). This is one possible scenario (and that most favourable to irinotecan), but there are several others, the simplest of which would be to decrease treatment times for oxaliplatin in proportion to the progression-free survival time assumed. As discussed in chapter 4, the effect of second-line treatments on the survival of patients in these trials is unknown and makes the attribution of survival benefits to first-line therapy uncertain.

Additionally, there are computational errors in the model that result in miscalculation of both first- and second-line chemotherapy costs. However, the effect on the result is small.

Oxaliplatin

No published economic studies were identified.

Sanofi-Synthelabo Ltd sponsor submission, 2000[21]

Two economic analyses are presented in the submission from Sanofi-Synthelabo Ltd. The first, comparing first-line treatment with 5FU (with and without oxaliplatin), is based on data from the de Gramont trial.[30] The second compares the cost-effectiveness of oxaliplatin and irinotecan (both in combination with 5FU) with 5FU alone, using the Douillard publication[31] as the source of data on irinotecan treatment. Both analyses used median differences in progression-free years as the benefit measure.

In the first analysis, the only resource data available were for chemotherapy drugs and the number of patient days in hospital. These have been shown by other studies to be the greatest costs, together with the costs of administration. The latter have been ignored, however, on the basis that they are common to both treatment arms. This is only valid if the mean number of treatment cycles for each cohort is the same. Using the total chemotherapy costs and costs per cycle presented in the Sanofi submission, the number of cycles in the cohorts were calculated to be 11.7 for oxaliplatin and 11.6 for 5FU, in fact identical. However, the costs of patients in remission (after stopping chemotherapy, but prior to progression), which will be greater for oxaliplatin, have been ignored. The central estimate of the marginal cost per progression-free year comparing the combination of oxaliplatin with 5FU to 5FU alone (by de Gramont) is £24,991, with a range of £20,546–29,435, depending on costs. The median difference in progression-free years is used (2.8 months), but our analysis suggests that this is similar to the total progression-free survival difference of 2.9 months. A sensitivity analysis on the benefit (progression-free years) was conducted, the results of which gave a range of marginal cost-effectiveness per progression-free year of £16,740–107,651.

In the second analysis, comparison of the cost-effectiveness ratios of oxaliplatin versus 5FU and irinotecan, and also versus 5FU alone, was based on chemotherapy drug costs only. No data were available to calculate the number of hospital days from the Douillard trial.[31]

Raltitrexed, single agent, as first-line treatment

Kerr and O'Connor, 1999,[1] Journal of Medical Economics *(raltitrexed)*

The study by Kerr and O'Connor[1] was based on the clinical trial reported by Cunningham and co-workers,[29] in which raltitrexed was compared with 5FU (Mayo regimen) for the primary treatment of advanced colorectal cancer. The trial showed similar survival for both treatment arms, and benefits with raltitrexed treatment for reduction in severe (WHO grades 3 and 4) toxic events. This economic study assumed the clinical benefit to be equal and therefore adopted a cost-minimisation approach. Resource information was collected retrospectively from the trial data, with the exception of pharmacy charges, which were based on a time and motion study reported by Summerhayes and colleagues.[70]

The study shows that the cost per month of treatment with raltitrexed is similar to that of 5FU administered by the Mayo regimen, presumably comparing average resource use while patients were still on chemotherapy. The study included the costs of drug therapy for adverse events (from the Elliott report,[73] based on the same clinical study) and pharmacy charges (from the Summerhayes time and motion study[70]), which have been omitted in some other studies. According to Kerr and O'Connor,[1] the costs for adverse events and pharmacy charges comprise, respectively, less than 1% and 1.6% (for raltitrexed vs 5FU, respectively), and 2% and 9% (for raltitrexed vs 5FU). These values suggest that drug therapies for adverse events may be insignificant and can be omitted, whereas the pharmacy charges are more important and should be included.

The study includes all the relevant costs, and problems of censoring of data (not discussed) may be minimal if the study is restricted to the treatment period only, and with survival in the two treatment arms being equal. The study report is missing only details of resources used, the results being presented only as average costs per month.

It should be noted that the relevance of the study is limited to comparison with the Mayo regimen. This regimen has been shown in a meta-analysis[74] to have greater haematological toxicity than infusional regimens such as de Gramont, which is more usual in the UK.

Groener and colleagues, 1999[75]

The economic study by Groener and colleagues[75] was also based on the Cunningham trial,[29] but used Dutch estimates of unit costs. This study differs from Kerr and O'Connor[1] in including patient travel costs; although, as the viewpoint is not stated, it is not clear whether this is because in The Netherlands the travel costs are borne by the hospital, or whether a societal viewpoint is intended. As with Kerr and O'Connor,[1] the total costs per patient (over an unspecified time frame) are similar for the two treatment arms.

Ross and co-workers, 1996,[76] European Journal of Cancer

The study by Ross and co-workers[76] was based on a retrospective analysis of patient case notes at the Royal Marsden Hospital. All the patients had advanced colorectal cancer and were on primary chemotherapy. Only patients on raltitrexed were part of a clinical trial: the patients included in the analysis were selected on the basis of the availability of complete patient notes. The comparability of the baseline characteristics of the patients in the different treatment arms is not known, apart from gender. Differences may have led to bias in the reported results. The cost of monthly treatment for patients on 5FU by the Mayo (bolus), de Gramont or Lokich (infusional) regimens, and those on raltitrexed were compared. All hospital costs were included, with the exception of pharmacy costs. The mean, median or range of time that information for each patient was collected is not stated in the report. There were 31 patients in each group, except for Mayo, which had 23 patients. The summarised results are shown in *Table 90*.

TABLE 90 *Mean treatment costs per month (1994/1995)*

Treatment	Mean cost (£)	95% CI
Mayo (bolus 5FU)	954	649 to 1259
de Gramont (infusional 5FU)	2029	1715 to 2342
Pump (infusional 5FU)	1208	660 to 1755
Raltitrexed	1257	1017 to 1497
Adjusted raltitrexed*	1118	876 to 1360

* *Outpatient visits adjusted to exclude those assumed to be for trial protocol purposes only*

AstraZeneca industry submission, 2000[57]

No additional economic data are shown in the AstraZeneca submission. The results of Ross and co-workers[76] and Summerhayes and colleagues[70] are presented.

Summary of evidence from economic studies

There is more evidence on the costs of treatment with raltitrexed compared to 5FU than for the other treatments. The study by Kerr and O'Connor,[1] which included all the relevant treatment elements, shows that treatment with raltitrexed costs the same as 5FU treatment with the Mayo regimen for the first-line treatment of advanced colorectal cancer.

Because there is no clinical benefit from treatment with raltitrexed compared to 5FU, cost-effectiveness analysis is not appropriate. No further analysis was undertaken for raltitrexed.

There is less good evidence on the costs of first-line treatment with irinotecan in combination with 5FU and FA. Cunningham and co-workers[69] presented the results of a cost-effectiveness analysis for irinotecan, but in abstract form only, so nothing is known about the methodology. The Sanofi submission[21] presents an analysis for oxaliplatin first-line treatment, based on the chemotherapy drug costs and hospitalisations only. For this trial, it appears that the mean number of treatment cycles in each treatment arm were the same, and therefore other costs (assumed to be the same) can be ignored when considering differences in cost and marginal cost-effectiveness between the two treatments. The total costs of each treatment, however, are unknown.

As with the clinical evidence, the only economic studies specifically for second-line treatment are for irinotecan, given alone. The study by Iveson and co-workers[16] has some shortcomings, but the lifetime estimate of the marginal cost per progression-free year of irinotecan, compared with 5FU (de Gramont regimen), of £10,104 is likely to indicate the order of magnitude of the cost-effectiveness ratio. This ratio is also based on the median survival difference.

The differences in approach and presentation of results of the various studies make comparisons between the treatments impossible. *Table 91* summarises the costing elements included and the results presented from the economic studies.

TABLE 91 *Summary of economic and resource data available*

	Rougier *et al.*, 1998[41]	**Cunningham *et al.*, 1996[29]**	**Case note**	**Industry submissions**	
Economic study	Iveson *et al.*, 1999[16]	Kerr & O'Connor, 1999[1]	Ross *et al.*, 1996[76]	Sanofi, 2000[21]	Aventis, 2000[72]
Treatment regimens	Irinotecan 5FU (de Gramont) 5FU (Lokich) 5FU (AIO)	Raltitrexed 5FU (Mayo)	Raltitrexed 5FU (de Gramont) 5FU (Lokich)	Oxaliplatin	Irinotecan
Chemotherapy drug costs	*	*	*	*	*
Pharmacy charges		*			
Administration costs	*	*	*		*
Hospital days	*	*	*	*	*
Consultations	*	Outpatient and GP	*		*
Drug treatments		*	*	*	*
Tests		*	*		
Costing year	1996/1997–1998	1997	1994, 1995	1999/2000	1999/2000
Data presented					
Unit costs	Some	Some	Some	*	*
Resources	Some			*	*
Results presented					
Monthly costs		*	*	*	*
Total treatment costs	*			*	*
Costs by category	*	*	*	*	*
Time period	Maximum of 16 months, including treatment and follow-up	While on treatment?	While on treatment?	Treatment	Lifetime

* *Costs included*

It is apparent that the different studies exclude different resource items. Even when the same resource item is included in several studies, the method of estimation is not always consistent between studies. Most studies do not detail resources and costs separately, which limits the availability of resource information that can be derived from them. Results too are presented differently: cost per month and cost per treatment course are common. The results of the studies are therefore not all comparable.

For this reason, our own economic analysis was undertaken, to estimate the costs and benefits of treatment with irinotecan or oxaliplatin, both in combination with 5FU and FA, and compared to treatment with FU and FA. For second-line treatment, irinotecan is compared to FU and FA, and to BSC. No further analysis was undertaken for raltitrexed.

Review of quality-of-life data

Many of the more recent trials have included a validated measure of quality of life, most usually the EORTC QLQ-C30. This cancer-specific quality-of-life measure includes five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, nausea and vomiting, and pain), six individual items and a general quality-of-life question. Additional questions specific to colorectal cancer have been developed (EORTC QLQ-C38), but this development is too recent to have been included in any of the

published trials. Other quality-of-life measures that have been used are the RSCL and the EQ-5D.

The trials that have included a quality-of-life measure are shown in *Table 92*.

Many of the quality-of-life studies are reported only briefly, with limited detail both of methods and results. Few refer to the problems of interpretation of the data, which is particularly difficult for these patients, for the following reasons.

Firstly, the timing of the questionnaire in relation to the chemotherapy regimen is likely to influence the results. The EORTC questionnaire, for example, asks patients to assess their well-being over the previous week. Using the same frequency of questionnaire for different treatment regimens may favour one arm over another. Even the comparison of the quality of life of patients undergoing chemotherapy with the same administration frequency, but with different drugs, may be difficult if the time profiles of the toxic effects are very different.

Secondly, there is evidence from some trials that censoring of the quality-of-life data is not random, an effect known as 'informative censoring'. This means that completion rates are not independent of the quality-of-life state of the patient, and the results may be biased. For example, van Cutsem and Blijham[48] reported that completion rates for patients still on treatment (i.e. with responding or stable disease) were 86%, compared with 26% for patients who were no longer on treatment, mainly due to their disease having progressed. Only one study[31] used imputation methods to deal with the effect.

Irinotecan as first-line treatment

Saltz and co-workers, 2000[43]

In the paper by Saltz and co-workers,[43] quality of life is reported only for the two treatment arms including 5FU. There was no significant difference in mean change in (global) health score between the treatments with and without irinotecan. For patients whose treatment included irinotecan, there was significantly less deterioration for some symptom and function subscales: fatigue, anorexia, pain and role functioning. The other analyses were not significant.

Douillard and colleagues, 2000[31]

In the Douillard study,[31] informative dropout was allowed for by using two alternative imputation methods. However, the reporting of results comparing quality of life between the two treatment arms is ambiguous.

According to the report, "QoL [quality of life] did not differ significantly between groups. When missing data for death, progressive disease, or grade 3–4 adverse events were taken into account with the two imputation methods, results were biased in favour of the no-irinotecan group. The analysis of variance on QoL showed significantly better quality of life in the irinotecan group after the first imputation method used ($p = 0.03$). The same trend was seen with the second imputation method."

Deterioration in quality of life occurred consistently, but not significantly later for patients treated with irinotecan, for a deterioration from baseline score of 5%, 10%, 20% and 30%.

Irinotecan as second-line treatment

Cunningham and co-workers, 2000,[29] and Cunningham, 1999[77]

The mean global quality-of-life scores were consistently and significantly higher for patients on irinotecan, compared with those receiving BSC only. For all symptoms, the mean worst scores were significantly worse for BSC only, except nausea and vomiting and insomnia, for which the difference was non-significant, as well as diarrhoea, which was significantly worse in the irinotecan arm. Again, when compared on mean worst score, the functioning scores all significantly favoured irinotecan, except for emotional functioning, for which the benefit was non-significant.

Rougier and colleagues, 1998,[41] and van Cutsem and Blijham, 1999[48]

According to the reports by Rougier and colleagues[41] and van Cutsem and Blijham,[48] no significant difference was found in mean global quality-of-life scores between the two treatment arms, although patients in the irinotecan cohort had a significantly longer time to a 50% deterioration in global health score from baseline. Analysis of the mean worst scores showed a significant benefit for patients treated with a 5FU regimen only for nausea and vomiting and for diarrhoea, the other differences being non-significant.

It is noteworthy that the FDA reviewed both the above trials.[18] On the quality-of-life analysis, they were particularly concerned with the possibility of informative dropout, as previously discussed. They re-analysed the original data for three of the subscales considered to be the most clinically relevant: physical functioning, pain, and nausea and vomiting. Contrary to the original analyses, they found evidence that patients treated with irinotecan had **less** nausea and vomiting than the

TABLE 92 *Summary of data on quality of life from clinical trials*

Study	Source of data on quality of life	Measure	Treatments	Questionnaire frequency	Completion rate	Control for informative dropout
Irinotecan, first-line						
Saltz *et al.*, 2000[43]	Trial	EORTC version 2	Irinotecan weekly for 4 weeks, with 2-week break	6 weeks	Not stated	No
			5FU (Mayo)	4 weeks		
			Irinotecan + 5FU	6 weeks		
Douillard *et al.*, 2000[31]	Trial	EORTC QLQ-C30	Irinotecan + 5FU (de Gramont or AIO)	Before each cycle, every 6–7 weeks	62%	Yes, two imputation methods used and results compared
			5FU (de Gramont or AIO)		59%	
Irinotecan, second-line						
Cunningham *et al.*, 1998[29]	Trial Also Cunningham, 1999[77]	EORTC QLQ-C30	Irinotecan	Baseline, 3 and 6 weeks, then every 6–8 weeks	80% at start, then declining to 50% compliance	No
			BSC		Decreased more rapidly in BSC group	
Rougier *et al.*, 1998[41]	Trial Also van Cutsem & Blijham, 1999[48]	EORTC QLQ-C30	Irinotecan every 3 weeks	Baseline, 3 and 6 weeks, then every two visits	67%	No
			5FU (three different regimens)		70%	
Oxaliplatin						
de Gramont *et al.*, 2000[30]	Trial	EORTC QLQ-C30	5FU (de Gramont) every 2 weeks	Baseline and every 4th cycle (i.e. 8 weeks)	83.6% participated, then declining to 39% after 8 months	No
			Oxaliplatin every 2 weeks			
Raltitrexed						
Study 12 Cocconi *et al.*, 1998[26]	Trial	RSCL EQ-5D	Raltitrexed every 3 weeks	Baseline and weeks 2, 5, 10 and 15	Baseline: 85% Subsequently: 75%	Adjusted for intermittent missing values
			5FU (Machover) for 5 consecutive days every 4 weeks			
	Also Anderson & Palmer, 1998[78]				60%	No, but discussed
Study 3 Cunningham *et al.*, 1996[29]	Trial	EORTC	Raltitrexed every 3 weeks	Baseline and every 12 weeks	Baseline: 97% Week 12: 99% of patients still in study	Adjusted for intermittent missing values
			5FU (Mayo) daily for 5 days, every 4 weeks for three courses, then every 5 weeks			
	Also Anderson & Palmer, 1998[78]				Baseline: 94% Week 12: 95% of patients still in study	No, but discussed
MRC CR06 trial Stephens *et al.*, 1999[13]		EORTC QLQ-C30 HADS Trial-specific measure	Raltitrexed			
			5FU de Gramont			
			Lokich			

control arm, while admitting that this conflicted with the known toxicity of irinotecan. They also reported that their results on the other two subscales were also not consistent with the original analysis. The report concludes, "This reviewer had difficulty supporting the claim that there is evidence of QoL improvements in general in patients on CPT-11 [irinotecan]". It should be noted, however, that there are inconsistencies in the reporting of the FDA analysis, which makes it difficult to ascertain exactly what some of their results were.

Conclusions: irinotecan

Irinotecan: first-line therapy

Although the trial reported by Douillard and colleagues[31] is the only quality-of-life study reviewed to have used imputation methods to take into account dropouts, the description of the results is ambiguous. Saltz and co-workers[43] found less deterioration in some symptom subscales and the role functioning subscale for patients treated with irinotecan, but gave no indication of completion rates for either trial arm. The results are inconclusive.

Irinotecan: second-line therapy

Cunningham[29,77] reported significantly better mean global quality of life and also significantly better worst scores across most symptom and functional scales for patients treated with irinotecan, compared to BSC, with compliance decreasing more rapidly in the BSC cohort than for irinotecan. The quality-of-life comparison of irinotecan and 5FU showed no significant differences in mean global scores, but a significant increase in time to a 50% deterioration in global health status. However, the FDA's re-analysis of the data from both trials raised concerns about the reported results because of the presence of informative dropout, and type I errors due to the number of quality-of-life subscales were not controlled for. They considered the results to be inconclusive, while not ruling out the possibility of quality-of-life benefits from irinotecan.

Oxaliplatin

As shown in *Table 92*, only one published study on oxaliplatin reported on quality of life.[30] Based on the EORTC QLQ-C30, median quality-of-life scores were reported to be similar for the two treatment arms (5FU by the de Gramont regimen, with and without the addition of oxaliplatin). Selective results of the functional and symptom scales were reported at weeks 8 and 16 of treatment. Improved emotional functioning was reported by patients in both treatment arms. Patients whose treatment did not include oxaliplatin had diminished insomnia, improved general condition and, at one measurement point, reduced pain, compared with baseline. Patients treated with oxaliplatin had worsening nausea and vomiting and, at one measurement point, improved appetite. There was a significant difference between the treatment arms in the time to deterioration of global health (20% and 40%), in favour of those treated with oxaliplatin. However, because no mention was made of adjustments for informative censoring, the result may be biased.

Conclusions: oxaliplatin

There is no evidence of quality of life being substantially affected by the addition of oxaliplatin to 5FU treatment. It is likely that the apparent longer time to deterioration in global health status of patients whose treatment includes oxaliplatin reflects the increased time to progression and possible (non-significant) survival benefit.

Raltitrexed

Cunningham and co-workers, 2000[29] (study 3)

In the study by Cunningham and co-workers,[29] no significant difference was found between the two treatment arms, except for increased nausea and vomiting in patients in the raltitrexed arm at week 12. Anderson and Palmer[78] commented that the questionnaire had been administered too late to detect initial toxic adverse events in patients starting chemotherapy, and that the EORTC questionnaire did not capture all toxic effects, including mucositis.

Cocconi and colleagues, 1998[26] (study 12)

According to the study by Cocconi and colleagues,[26] based on the RSCL scale, raltitrexed was favoured at week 2 on all four dimensions, three significantly. Subsequently, there were no significant differences between the treatments. Similarly, the EQ-5D showed some significant benefits for raltitrexed at week 2. No significant benefits were reported at later measurement times, except when the toxicity-related symptoms (part of the physical symptom dimension) were analysed separately: 5FU showed significantly worse toxicity for weeks 2, 5 and 10 ($p = 0.0001$).

Stephens and co-workers, 1999[13] (MRC trial CR06)

In the MRC multicentre trial CR06,[13] some trial-specific questions were added to the standard EORTC questions, and the HADS was also used.

Patients receiving raltitrexed reported worse quality of life than those receiving the de Gramont regimen in terms of toxicity (nausea and vomiting [$p = 0.008$] and lack of appetite [$p = 0.004$]), role functioning ($p = 0.02$) and global quality of life ($p = 0.04$). The regimens were not significantly different in terms of palliation of pain, relief of

anxiety, or improved physical and social functioning. None of the regimens improved fatigue or depression.[13]

Conclusions: raltitrexed

There is evidence from the Cocconi study[26] that raltitrexed may offer better quality of life for patients at initiation of chemotherapy (measured at week 2) and some benefit in reduced toxicity until week 10, when compared with a bolus (Mayo) 5FU regimen. However, the same was not demonstrated when raltitrexed was compared with infusional 5FU regimens in the MRC CR06 trial.[13] There are two main differences that may have led to the contrasting result. Firstly, meta-analysis of infusional versus bolus 5FU regimens[74] showed infusional regimens to be less toxic (haematologically) than bolus regimens, although hand–foot syndrome is more common with infusional regimens. Secondly, the benefit in quality of life of raltitrexed over bolus 5FU was shown principally only early after the start of chemotherapy (2 weeks). Raltitrexed trial study 3[29] also showed no quality-of-life benefit of raltitrexed compared to bolus 5FU, with quality of life measured first (after baseline) at 12 weeks. None of the studies controlled for informative dropout, although it is discussed by Anderson and Palmer.[78]

Overall conclusions on quality of life

The difficulty in analysis of quality-of-life data in the presence of informative dropout makes it difficult to draw conclusions from the quality-of-life data. In many quality-of-life analyses, the researchers did not appear to have considered whether or how it may have affected their analyses. The FDA analysis that attempted to control for this difficulty came up with a non-intuitive result: that irinotecan, which is known to cause nausea and vomiting, had a better quality-of-life score on this symptom scale than either control arm. The FDA analysis demonstrates how difficult it is to analyse and interpret quality-of-life data from patients in these trials.

However, while it is difficult to demonstrate improvements in quality of life from the new treatments, there is also no evidence to suggest that they have a detrimental effect on patients' quality of life.

Other benefits

Raltitrexed

AstraZeneca[57] presented the results of an Australian willingness-to-pay study. Oncology nurses were used to value the raltitrexed and Mayo (bolus 5FU) regimens using both contingent valuation and conjoint analysis. The nurses were presented with descriptions of the regimens, including administration schedule and side-effects. The contingent valuation showed they were willing to pay an additional cost of £122 per cycle for raltitrexed, and conjoint analysis showed that 92% would pay an additional £72, increasing to £270 for 39% of subjects. It should be noted firstly that the comparison was with the Mayo regimen, which as previously noted has worse haematological toxicities than infusional 5FU regimens (although less prevalent hand–foot syndrome), and secondly that the comparison relates to perceived rather than actual benefits.

Survival and progression-free survival benefits

Survival benefit

Of the three curves fitted to the survival benefit data, it was found in all cases that the Weibull curve gave a reasonable fit, except for the subset of patients in the Cunningham trial[28] with performance status of 2, for which the number of patients was small (21 patients receiving BSC alone and 26 patients receiving irinotecan). All curve parameters are detailed in appendix 6. An example of the survival curves, with the fitted Weibull curves, is shown in *Figure 1*.

The results of the survival analysis are shown in *Table 93*. The survival benefit estimated from the survival curves is shown at 3, 6 and 12 months (arbitrary time points, in general within the published data) and the estimated total difference from the fitted Weibull curve. For comparison, the median difference is also shown.

The estimated survival benefit is sometimes less and sometimes more than the median, depending on the survival distributions compared.

Progression-free survival benefit

The curves for progression-free survival benefit were fitted as for survival, and the Weibull curve was also found to give the best fit to the data. Parameters are also shown in appendix 6.

There is of course a degree of uncertainty in all the estimates of benefit. This uncertainty will arise from the trial results themselves and from the projected total estimated benefit. Only one study (de Gramont and co-workers[30]) provided some confidence limits at selected points. Another, Saltz and colleagues,[43] gave the number of patients at selected time points, allowing estimation of confidence intervals at those time points using the method described by Altman.[79] These confidence intervals were used to estimate extreme upper

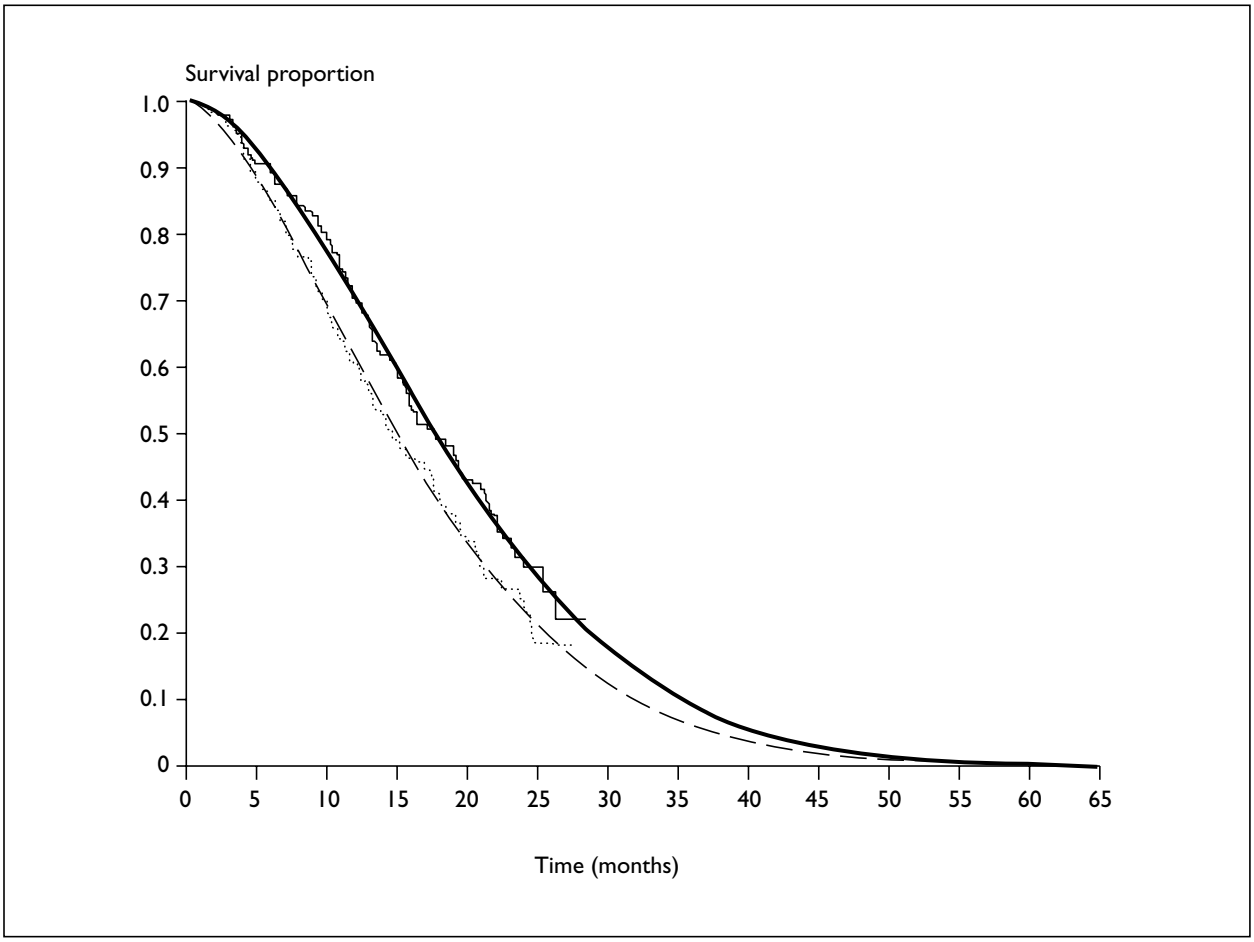

FIGURE 1 *Survival curves for two treatment arms from Douillard and co-workers,[31] with fitted Weibull curves (——, irinotecan data points; ——, irinotecan Weibull curve fit; ·····, de Gramont regimen data points; — — —, de Gramont regimen Weibull curve fit)*

TABLE 93 *Survival benefit estimated from the areas between survival curves*

Study	Trial arms		Survival difference (months) at:				Median difference (months)	*p*-value
	Treatment	Control	3 months	6 months	12 months	Total		
Oxaliplatin, first-line								
de Gramont *et al.*, 2000[30]	Oxaliplatin + 5FU (de Gramont)	5FU (de Gramont)	0.1	0.33	0.85	1.98	1.5	0.12
Giacchetti *et al.*, 2000[32]	Oxaliplatin + 5FU (chronomodulated)	5FU (chronomodulated)					–0.5	
Irinotecan, first-line								
Douillard *et al.*, 2000[31]	Irinotecan + 5FU (de Gramont)	5FU (de Gramont)	0.01	0.07	0.58	2.55	3.3	0.031
Saltz *et al.*, 2000[43]	Irinotecan + 5FU	5FU (Mayo)	0.00	–0.01	0.02	2.82	2.2	0.04
Irinotecan, second-line								
Rougier *et al.*, 1998[41]	Irinotecan	5FU (various regimens)	–0.04	0.09	0.88	2.31	2.3	0.035
Cunningham *et al.*, 1998[28]	Irinotecan*	BSC	–0.01	0.22	1.55	3.23	Not stated	
	Irinotecan†	BSC	–0.09	0.51	1.10	1.61	Not stated	

* *Patients with performance status < 2*
† *Patients with performance status = 2*

and lower bounds on the difference between the treatment cohorts in progression-free survival. The maximum survival benefit was estimated from the upper limit of progression-free survival for the novel treatment and the lower limit on progression-free survival for the control treatment, and vice versa for the minimum benefit estimate.

For de Gramont and co-workers,[30] this gave a range of progression-free survival benefit of 0.96–4.53 months (central estimate, 2.77 months; see *Table 94*), and for Saltz and colleagues,[43] the benefit was 0–4.07 months (central estimate, 1.69 months). The Sanofi submission[21] also presents an estimate for the range of progression-free survival benefit from the de Gramont trial of 0.65–4.18 months, which is similar to our estimate.

Given these wide bounds and the fact that the Weibull curve gave a clearly superior fit to the data than the other fitted curves, sensitivity analysis was not undertaken using the other fitted curves.

Table 95 summarises the estimated average number of months patients spent in a stable/response (progression-free) state, months after allocated treatment, and total survival, all estimated from the published survival curves.

Estimate of quality-of-life-adjusted progression-free survival

For oxaliplatin and irinotecan given by the de Gramont as first-line treatment, quality-of-life adjustment reduces the estimate of progression-free survival by 5.4–6.5% for oxaliplatin and by 10.7–19.2% for irinotecan (see *Table 96*). The effect of the quality-of-life adjustment is greater for irinotecan than oxaliplatin because treatment time is a higher proportion of total time for irinotecan, and it has been assumed that days of chemotherapy are valued lower than non-treatment days. This is also the reason why, for the comparison of irinotecan with the Mayo regimen, the estimated progression-free survival benefit is actually increased by quality-of-life adjustment. The Mayo regimen involves 5 days of chemotherapy every fortnight.

For second-line treatment, the QALY estimates ranged from 0.95 to 1.33 months, a considerable reduction on the unadjusted time of 2.3 months. Patients receiving irinotecan were treated for a mean of 4.2 months, compared with only 2.8 months for 5FU, and had less time in remission than 5FU patients. Thus, reducing the utility of treatment days had a greater proportionate effect on patients receiving irinotecan than on those receiving 5FU. Remission time (stable without treatment, i.e. highest QALY) was also less for irinotecan than for 5FU.

Costs of treatment

Monthly treatment costs

The calculated monthly treatment costs are shown in *Table 97*. Because the comparator regimens vary slightly, the estimated costs for each of them are also included.

TABLE 94 *Progression-free survival benefit estimated from the areas between curves*

Study	Trial arms		Survival difference (months) at:				Median difference (months)	*p*-value
	Treatment	Control	3 months	6 months	12 months	Total		
Oxaliplatin, first-line								
de Gramont *et al.*, 2000[30]	Oxaliplatin + 5FU (de Gramont)	5FU (de Gramont)	0.18	0.68	1.73	2.77	2.2	0.003
Giacchetti *et al.*, 2000[32]	Oxaliplatin + 5FU (chronomodulated)	5FU (chronomodulated)	0.27	0.99	1.85	1.86	2.6	0.048
Irinotecan, first-line								
Douillard *et al.*, 2000[31]	Irinotecan + 5FU (de Gramont)	5FU (de Gramont)	0.20	0.61	1.63	2.34	2.3	< 0.001
Saltz *et al.*, 2000[43]	Irinotecan + 5FU	5FU (Mayo)	0.06	0.53	1.20	1.69	2.7	0.004
Irinotecan, second-line								
Rougier *et al.*, 1998[41]	Irinotecan	5FU (various regimens)	0.09	0.41	0.81	0.98	1.3	0.3
Cunningham *et al.*, 1998[28]	Irinotecan	BSC	No data					

TABLE 95 *Time in progression-free and progressive states*

Study	Treatment	Progression-free disease (months)	Progressive disease (months)	Total survival (months)	Progression-free survival benefit (months)	Survival benefit (months)
Oxaliplatin, first-line						
de Gramont *et al.*, 2000[30]	Oxaliplatin + 5FU (de Gramont)	10.01	9.54	19.55	2.77	1.98
	5FU (de Gramont)	7.24	10.33	17.57		
Giacchetti *et al.*, 2000[32]	Oxaliplatin + 5FU (chronomodulated)	10.22	16.43	26.65	1.86	3.95
	5FU (chronomodulated)	8.36	14.33	22.7		
Irinotecan, first-line						
Douillard *et al.*, 2000[31]	Irinotecan + 5FU (de Gramont)	7.80	11.72	19.52	2.34	2.55
	5FU (de Gramont)	5.46	11.51	16.97		
Saltz *et al.*, 2000[43]	Irinotecan + 5FU	7.43	10.22	17.65	1.69	2.82
	5FU (Mayo)	5.74	9.09	14.83		
	Irinotecan only	5.62	10.50	16.12		
Irinotecan, second-line						
Rougier *et al.*, 1998[41]	Irinotecan	5.16	7.13	12.28	0.98	2.31
	5FU (various regimens)	4.18	5.80	9.97		
Cunningham *et al.*, 1998[28]	Irinotecan*			11.38		3.23
	BSC*			8.15		
	Irinotecan†			6.89		1.61
	BSC†			5.28		

* *Patients with performance status < 2*
† *Patients with performance status = 2*

TABLE 96 *Effect of quality-of-life adjustment on progression-free survival for various treatment scenarios*

Study	Treatment	Progression-free survival (months)	Quality-of-life-adjusted progression-free survival (months) for scenario				Difference in quality-of-life-adjusted progression-free survival (months) for scenario				
			1	2	3	4	Baseline	1	2	3	4
Oxaliplatin, first-line											
de Gramont *et al.*, 2000[30]	Oxaliplatin + de Gramont regimen	10.01	8.66	8.47	9.11	9.02	2.77	2.60	2.54	2.62	2.59
	de Gramont regimen	7.24	6.06	5.92	6.49	6.42					
Irinotecan, first-line											
Douillard *et al.*, 2000[31] (biweekly regimen)	Irinotecan + de Gramont regimen	7.80	6.41	6.25	6.93	6.86	2.34	1.94	1.89	2.09	2.06
	de Gramont regimen	5.46	4.47	4.36	4.85	4.80					
Saltz *et al.*, 2000[43]	Irinotecan + 5FU/FA	7.43	6.39	6.24	6.74	6.67	1.69	1.83	1.80	1.71	1.70
	Mayo regimen	5.74	4.56	4.44	5.03	4.98					

Baseline: no quality-of-life adjustment
Scenario 1: hospital days = 0, number of hospital days per month = treatment + 0.38
Scenario 2: hospital days = 0, number of hospital days per month = treatment + 1.0
Scenario 3: hospital days = 0.5, number of hospital days per month = treatment + 0.38
Scenario 4: hospital days = 0.5, number of hospital days per month = treatment + 1.0

The baseline monthly cost of treatment with the de Gramont regimen is estimated to be £2400–2600, with a central estimate of £2500 for inpatient administration, but only £1500 for the central estimate of outpatient administration. The baseline assumption for all treatments based on the de Gramont regimen is that they are administered on an inpatient basis. However, in some centres, this regimen may be given in an outpatient setting. When chemotherapy is administered on this basis, a central line has to be inserted into each patient prior to treatment, and the cost of a pump has been included for every cycle. When outpatient administration of the de Gramont regimen is

TABLE 97 *Monthly costs of treatment for various scenarios*

Study	Treatment	Scenario monthly cost (£)			
		1	2	3 (baseline)	Outpatient
Oxaliplatin, first-line					
de Gramont *et al.*, 2000[30]	Oxaliplatin + de Gramont regimen	3199	3435	3317	2357
	de Gramont regimen	2348	2584	2466	1506
Irinotecan, first-line					
Douillard *et al.*, 2000[31] (biweekly regimen)	Irinotecan + de Gramont regimen	3348	4206	3466	2507
	de Gramont regimen	2388	2624	2506	1547
Saltz *et al.*, 2000[43]	Irinotecan + 5FU/FA	1315	1567	1441	1441
	Mayo regimen	967	1245	1106	1106
Irinotecan, second-line					
Rougier *et al.*, 1998[41]	Irinotecan	1660	1883	1771	1771
	de Gramont regimen	2410	2646	2528	1569

Scenario 1: median chemotherapy duration, low other costs
Scenario 2: chemotherapy while stabilised, high other costs
Scenario 3 (baseline): mean chemotherapy duration (except irinotecan, for which the mean of scenarios 1 and 2 was used), average other costs
For more details of scenarios, see Estimation of net costs *section on page 71*

assumed, the cost of treatment with single-agent irinotecan is £202 more per month than with de Gramont.

These costs are based on average medical oncology costs per day for inpatient and day-case treatment, which is a crude estimate. This estimate may exaggerate the difference between inpatient and outpatient costs.

The Aventis model, which also costs de Gramont treatment on an inpatient basis, estimates the cost per month to be £2822 (for corrected version, see *Assessment of economic studies relating to irinotecan, oxaliplatin and raltitrexed* on page 77). The costs from Iveson and co-workers[16] are not directly comparable, because their report shows only total treatment costs, which include an element of BSC post-treatment. If the total costs are divided by treatment time, the cost per month of the de Gramont regimen is £2164. This study assumes outpatient administration of de Gramont.

The difference in costs between the Saltz irinotecan regimen[43] and the Douillard regimen[31] is that, in the Saltz trial, the FU and FA were given as an intravenous bolus 1 day a week for 4 weeks in 6. The Douillard regimen effectively adds irinotecan to the biweekly de Gramont regimen, in which an infusion of FU and FA is given over 2 days. It has been assumed that the Saltz regimen is given on an outpatient basis, as is the comparator Mayo regimen. The outpatient costs are therefore equal to the baseline scenario.

The Giacchetti regimen[32] was not costed. It used chronomodulated administration of the chemotherapy agents, which is not a usual mode of delivery. Similarly, the costs of the weekly regimen used by Douillard are not shown, because the biweekly regimen is more usual.

Total treatment costs

The difficulty in calculating differences in the total costs of the new therapies compared with 5FU is the assumed times for which treatment is given. While in clinical trials treatment is usually continued until progression (unless treatment is stopped due to toxic effects), in practice the optimal treatment time is unknown. Seymour and co-workers' survey[8] of the clinical management of metastatic colorectal cancer showed varying clinical practice. Of the 198 responding hospital consultants (including clinical and medical oncologists, and surgeons with an interest in colorectal cancer), only 20% continued treatment indefinitely until progression, while 30% limited treatment to about 3 months, and 47% limited it to 6 months. *Table 98* shows the mean treatment times, given different assumptions about maximum treatment times and assuming treatment until progression. These times are likely to represent overestimates because treatment may be stopped earlier due to toxic effects. The final column entitled 'Unlimited' provides the mean treatment times, in other words, the length of time patients receive treatment until toxicity or progression.

The values in *Table 99* show the difference in total costs of treatment, including a new combination

TABLE 98 *Effective treatment times for different maximum treatment assumptions*

Study	Treatment	Mean effective treatment time (months)		
		Limit of 3 months	Limit of 6 months	Unlimited
Oxaliplatin, first-line				
de Gramont *et al.*, 2000[30]	Oxaliplatin + 5FU (de Gramont)	2.86	5.21	5.4
	5FU (de Gramont)	2.69	4.57	5.4
Giacchetti *et al.*, 2000[32]	Oxaliplatin + 5FU (chronomodulated)	2.84	5.15	5.37
	5FU (chronomodulated)	2.51	4.25	5.04
Irinotecan, first-line				
Douillard *et al.*, 2000[31]	Irinotecan + 5FU (de Gramont)	2.68	4.60	6.75*
	5FU (de Gramont)	2.48	3.94	4.83*
Saltz *et al.*, 2000[43]	Irinotecan + 5FU	2.71	4.64	6.45*
	5FU (Mayo)	2.51	4.04	4.9*
Irinotecan, second-line				
Rougier *et al.*, 1998[41]	Irinotecan	2.52	3.96	4.15
	5FU (various regimens)	2.40	3.55	3.14

* *No mean treatment time available, so value included is the average of the median and time to progression*

TABLE 99 *Additional treatment costs for differing maximum treatment durations*

Study	Treatment	Additional cost (£)		
		Limit of 3 months	Limit of 6 months	Unlimited
Oxaliplatin, first-line				
de Gramont *et al.*, 2000[30]	Oxaliplatin + de Gramont regimen de Gramont regimen	2,866	6,014	5,328
Irinotecan, first-line				
Douillard *et al.*, 2000[31] (biweekly regimen)	Irinotecan + de Gramont regimen de Gramont regimen	3,086	6,085	11,400
Saltz *et al.*, 2000[43]	Irinotecan + 5FU/FA Mayo regimen	1,131	2,227	3,913
Irinotecan, second-line				
Rougier *et al.*, 1998[41]	Irinotecan de Gramont regimen	–1,604	–1,954	–597

therapy with 5FU (plus FA) compared to 5FU (plus FA) alone.

As previously discussed, the values at 3 and 6 months take into account the proportion of patients who stop chemotherapy due to progression, but not those that stop chemotherapy due to toxic effects, because the latter is unknown. Failure to consider withdrawal due to toxicity is likely to have a greater effect on the 6-month figures than on those for 3 months. The fact that, for oxaliplatin, the 'unlimited' figure is less than the 6-month figure is an indication of the magnitude of this effect for this treatment.

The values at 3 and 6 months also do not take into account possible differences in costs of time in remission, because these are unknown.

The 'unlimited' figures for first-line irinotecan are more uncertain than for other treatments because the mean treatment times are unknown, so the estimates are based on the average of the median treatment times and time to progression.

It is unknown how the clinical benefits are affected by restricting treatment to a limited time period. When information is available, it appears that the mean treatment duration is around 5 months for first-line treatment and possibly less for second-line treatment.

Each of the novel treatments has been compared to the 5FU control arm used in the particular trial. These include the de Gramont regimen, with a monthly cost of treatment of around £2500, and the bolus Mayo regimen, with a considerably lower

monthly cost of £1100. Obviously, if irinotecan or oxaliplatin with 5FU by the de Gramont regimen is compared with the Mayo 5FU regimen, rather than de Gramont, the additional cost of treatment per month is increased by £1400.

Estimate of costs to NHS

Mortality from colorectal cancer is approximately 15,000 annually in England and Wales. A recent audit in Yorkshire suggested that only 30–35% of patients who die of colorectal cancer have received chemotherapy. That percentage indicates that the total number of patients currently undergoing chemotherapy per year is around 5000, which is the basis of the total costs shown below, except for second-line irinotecan. For this treatment, the estimate of total additional cost is based on only 65% of patients who received first-line therapy subsequently receiving second-line therapy, which is 3250 patients. The estimate of 65% is based on the trial reports of the proportion of patients receiving second-line therapy (see *Table 82*).

There is greater uncertainty in the 'unlimited' estimates (based on mean treatment times) for irinotecan (first-line) than oxaliplatin, because the mean treatment time is not known for irinotecan.

The new treatments have been compared with the comparator used in the clinical trial. Because the Mayo regimen costs £1400 less per month than the de Gramont regimen, the comparison of irinotecan with this regimen will obviously be more favourable than when compared with the de Gramont regimen.

Table 100 shows only the costs to the NHS of alternative first- or second-line therapies. The availability of new treatments means there are more treatment options and the possibility of more lines of treatment for each patient. As explained earlier (see *Review of possible benefit measures* on page 69), there are very few data about sequential treatments. Irinotecan and oxaliplatin in combination with 5FU are not yet licensed for second-line treatment in the UK. However, irinotecan as second-line single-agent treatment is cheaper than the de Gramont regimen when the latter is given on an inpatient basis.

Estimation of cost-effectiveness of treatments

The estimated marginal costs per progression-free year of the novel treatments compared with 5FU are shown in *Table 101*, for the different cost scenarios.

The costs per progression-free year for first-line irinotecan with the de Gramont regimen are considerably higher than for oxaliplatin, even for scenario 1, which uses median treatment durations. One difference is that, for the Douillard regimen, the median treatment duration for 5FU was only 4.15 months, compared with 5.1 months for the de Gramont trial of oxaliplatin. While the actual trial comparator is considered the more valid, it may be due to chance that the two treatment durations differ. Confidence limits for the treatment times are not known. To test the effect, the marginal cost per progression-free year was calculated for irinotecan, with the costs of the comparator 5FU treatment based on treatment lasting 5.1 months. The marginal cost per progression-free year for irinotecan compared with 5FU, based on scenario 1, is reduced from £47,989 to £37,955.

Another difference between oxaliplatin and irinotecan is that, for oxaliplatin, the estimated

TABLE 100 *Additional costs to NHS of new therapies for differing maximum treatment durations*

Study	Treatment	Additional cost (£)		
		Limit of 3 months	Limit of 6 months	Unlimited
Oxaliplatin, first-line				
de Gramont *et al.*, 2000[30]	Oxaliplatin + de Gramont regimen de Gramont regimen	14,331,000	30,069,000	26,640,000
Irinotecan, first-line				
Douillard *et al.*, 2000[31] (biweekly regimen)	Irinotecan + de Gramont regimen de Gramont regimen	15,431,000	30,423,000	57,000,000
Saltz *et al.*, 2000[43]	Irinotecan + 5FU/FA Mayo regimen	5,654,000	11,135,000	19,566,000
Irinotecan, second-line				
Rougier *et al.*, 1998[41]	Irinotecan de Gramont regimen	–5,213,000	–6,351,000	–1,940,000

TABLE 101 *Additional costs per progression-free year for different cost scenarios*

Study	Treatment	Additional cost (£) for scenario			
		1	2	3 (baseline)	Outpatient
Oxaliplatin, first-line					
de Gramont *et al.*, 2000[30]	Oxaliplatin + de Gramont regimen de Gramont regimen	27,039	67,856	23,047	23,047
Irinotecan, first-line					
Douillard *et al.*, 2000[31] (biweekly regimen)	Irinotecan + de Gramont regimen de Gramont regimen	47,989	94,713	58,424	48,956
Saltz *et al.*, 2000[43]	Irinotecan + 5FU/FA Mayo regimen	23,720	31,919	27,763	–
Irinotecan, second-line					
Rougier *et al.*, 1998[41]	Irinotecan de Gramont regimen	1,416	*	*	26,416

Scenario 1: median chemotherapy duration, low other costs
Scenario 2: chemotherapy while stabilised, high other costs
Scenario 3 (baseline): mean chemotherapy duration (except irinotecan, for which the mean of scenarios 1 and 2 was used), average other costs
For more details of scenarios, see Estimation of net costs *section on page 71*
* *Dominated*

progression-free survival benefit based on the analysis of the progression-free survival curves is considerably higher (2.77 months) than the median estimate (2.2 months), whereas for irinotecan they are similar (mean, 2.34 months; median, 2.2 months). Although the median is not an ideal estimate of the progression-free survival benefit, there is also uncertainty in the estimation of the mean survival benefit based on the projection of the progression-free survival curves. As a sensitivity analysis, the marginal cost per progression-free year for oxaliplatin compared with 5FU was calculated based on median progression-free survival difference. This increases the baseline estimate from £23,047 to £28,096, which is similar to the value of £26,665 calculated by Sanofi. The estimate is still lower than that for irinotecan.

The costs per progression-free year are less for the bolus (Saltz) regimen than for the de Gramont regimen. Not only is the regimen itself less costly, but the comparator, the Mayo regimen, is also less expensive than de Gramont 5FU therapy. It is difficult to estimate the marginal cost per progression-free year of the irinotecan and oxaliplatin de Gramont regimens compared with the Mayo regimen, particularly because in the de Gramont trial[30] of oxaliplatin the mean progression-free survival of patients on FU and FA alone was 7.2 months, compared with 5.7 months for patients on the Mayo regimen in the Saltz trial.[43] This suggests that using the difference in progression-free survival of cohorts between trials is likely to produce misleading results. Another approach is to use the progression-free survival benefit shown in each trial, with the Mayo regimen used as baseline. However, bolus regimens (such as Mayo) have been shown to have a small, but significant reduction in survival compared with infusional regimens such as de Gramont, which suggests some further adjustment. Also, if overall progression-free survival is assumed to be less than that in a trial, what assumptions should be made about treatment times? For these reasons, an estimate has not been made of the marginal cost per progression-free year of new therapies given by the de Gramont regimen, using the Mayo regimen as baseline.

The effect of assuming that the de Gramont regimen is provided on an outpatient basis is small for the first-line treatments, because both treatment arms are similarly affected. In particular, the difference for de Gramont with or without oxaliplatin is zero because the mean treatment times are the same. The effect on the second-line comparison of irinotecan with 5FU by the de Gramont regimen is much greater, because outpatient de Gramont is estimated to cost less than irinotecan. The additional cost per progression-free year changes from being negative to £26,416. Although the difference in monthly cost between irinotecan (as a single agent) and outpatient de Gramont regimen is only £202 per month, patients on irinotecan received more cycles of treatment. It should be noted that the estimates

of cost-effectiveness of second-line treatment with irinotecan compared to 5FU shown in *Table 101* are not comparable with the results of Iveson and co-workers,[16] because analysis is based on progression-free survival, whereas Iveson's analysis is based on survival. The difference in progression-free survival is only 0.08 years, compared with 0.19 years for survival. Using the costs from our analysis, the estimated marginal cost per LYG (baseline estimate) when irinotecan is compared with outpatient de Gramont (as for Iveson and co-workers[16]) is £11,183, which is higher than the Iveson main reported result of £7695 (1996–1998 costs) but not dissimilar to the lifetime estimate of £10,104, which is considered to be the more valid.

An analysis was also undertaken for two lines of therapy, with LYGs as the benefit measure. On the basis of second-line therapy with irinotecan alone after 5FU therapy, compared with BSC after 5FU treatment failure, the estimated marginal cost-effectiveness ratio is estimated to be between £17,687 and £28,249 per LYG. The low estimate is based on the assumption that the progression-free survival time of patients given irinotecan in the Rougier trial[41] translates to additional survival compared with patients on BSC alone, and the high estimate is based on the additional survival of patients treated with irinotecan compared to BSC, but with 31% of patients eventually receiving chemotherapy. Both estimates are based on the baseline cost scenario.

The results of the extreme sensitivity analysis on the difference in progression-free survival between oxaliplatin and 5FU versus irinotecan and 5FU are shown in *Table 102*.

These results show that the marginal cost-effectiveness of the treatments is highly sensitive to the progression-free survival benefit, although as previously noted these are extreme values.

The reason for the high sensitivity is that the relatively small progression-free survival differences between the new treatments and 5FU are on the order of only 2–3 months, combined with additional costs of a few thousand pounds sterling.

For the Saltz trial,[43] the minimum extreme benefit is negative (i.e. progression-free survival was better with 5FU than irinotecan), although log rank tests were reported showing a significant benefit of irinotecan over 5FU. The result of 'infinite' (see *Table 102*) therefore demonstrates the limitation of the methodology in estimating limits of benefit, rather than the lack of significant results in the Saltz trial.

Table 103 shows the effect of adjusting progression-free survival for quality of life. The effect on the marginal cost per progression-free year is a small increase for oxaliplatin; treatment times for oxaliplatin and 5FU are the same. The effect is much larger for irinotecan by the de Gramont regimen, but it must be noted that the treatment times are subject to considerably more uncertainty than for oxaliplatin. For the comparison of irinotecan with the Mayo regimen, adjustment for quality of life slightly decreases the marginal cost per progression-free year. This is because the Mayo regimen involves several days of chemotherapy per week, and it has been assumed that treatment days have lower utility than other days.

This analysis should be regarded as illustrative of the possible effects of adjusting for quality of life using the assumptions described, but is too uncertain to use to draw conclusions about the different treatments.

No trials of three-agent therapies for second-line treatment have been fully reported, which makes their cost-effectiveness impossible to assess.

TABLE 102 *Sensitivity analysis on progression-free survival*

Treatment A	Treatment B	Additional cost (£)	Progression-free survival for treatment A (months)	Progression-free survival for treatment B (months)	Progression-free survival difference (months)	Additional cost per progression-free year (£)
Oxaliplatin + de Gramont regimen	de Gramont regimen	5328	10.61	6.08	4.53	14,107
Oxaliplatin + de Gramont regimen	de Gramont regimen	5328	8.58	7.62	0.96	66,410
Irinotecan + 5FU/FA	Mayo regimen	3913	8.69	4.62	4.07	11,544
Irinotecan + 5FU/FA	Mayo regimen	3913	6.25	6.78	–0.54	Infinite

TABLE 103 *Marginal costs per quality-adjusted progression-free life-years for various treatment scenarios*

Study	Treatment	Additional cost (£)	Difference in quality-of-life-adjusted progression-free survival (months) for scenario					Quality-of-life-adjusted marginal cost-effectiveness ratio (£) for scenario				
			Baseline	1	2	3	4	Baseline	1	2	3	4
Oxaliplatin, first-line												
de Gramont *et al.*, 2000[30]	Oxaliplatin + de Gramont regimen de Gramont regimen	5,328	2.77	2.60	2.54	2.62	2.59	23,047	24,595	25,122	24,437	24,680
Irinotecan, first-line												
Douillard *et al.*, 2000[31] (biweekly regimen)	Irinotecan + de Gramont regimen de Gramont regimen	11,400	2.34	1.94	1.89	2.09	2.06	58,424	70,681	72,404	65,555	66,248
Saltz *et al.*, 2000[43]	Irinotecan + 5FU/FA Mayo regimen	3,913	1.69	1.83	1.80	1.71	1.70	27,763	25,614	26,087	27,406	27,661

Baseline: no quality-of-life adjustment
Scenario 1: hospital days = 0, number of hospital days per month = treatment + 0.38
Scenario 2: hospital days = 0, number of hospital days per month = treatment + 1.0
Scenario 3: hospital days = 0.5, number of hospital days per month = treatment + 0.38
Scenario 4: hospital days = 0.5, number of hospital days per month = treatment + 1.0

Summary of results of economic analysis

Costs

The cost of treatment with 5FU and FA by the de Gramont regimen is estimated to be £2500 per month when given on an inpatient basis or £1500 on an outpatient basis. The addition of oxaliplatin adds £800 per month to this regimen, and the addition of irinotecan adds £1000. The Mayo 5FU regimen is less costly at £1100 per month. The cost of treatment with raltitrexed has been shown by Kerr and O'Connor[1] to be similar to that for the Mayo regimen (£781 for raltitrexed, £834 for Mayo), although Kerr and O'Connor's costs of Mayo treatment are lower than our estimate. The cost of second-line treatment with irinotecan as a single agent is £1780.

The estimation of the total costs per patient for any treatment is dependent on the mean treatment duration. For first-line treatment with irinotecan, this is not known, so there is great uncertainty in the estimation of treatment costs.

Furthermore, in practice, treatments may be given to patients for limited periods. The estimates of additional treatment costs, compared with the cost of 5FU, are based on mean treatment times obtained from the trial reports, except for first-line irinotecan.

Total treatment costs for oxaliplatin are £5300 greater than inpatient treatment with the de Gramont regimen. The same comparison for irinotecan is an additional cost of £11,400. The differences with the Mayo regimen are greater. The total cost of single-agent irinotecan for second-line treatment is less than 5FU by the de Gramont regimen. A bolus regimen (such as Mayo) is not normally appropriate second-line treatment. However, not all patients who may be eligible for second-line treatment with irinotecan (approximately 65%) would currently receive 5FU. For these patients, the relevant comparison is BSC. Assuming that BSC costs are the same for all patients (i.e. patients treated with irinotecan eventually incur the same BSC costs as patients having no second-line treatment), the additional cost of giving patients irinotecan is £7600.

Cost-effectiveness

The calculations of cost-effectiveness are based on progression-free survival, rather than survival, because chemotherapy subsequent to the allocated first-line regimens means that survival cannot be uniquely related to the allocated therapy. The use of progression-free survival in place of survival has considerable implications on the results of the economic analysis. Compared with 5FU, oxaliplatin shows greater improvement in progression-free survival than irinotecan, based on our analysis of the progression-free survival curves; however, no survival benefit over 5FU has been shown in clinical trials with oxaliplatin, whereas it has with irinotecan. Estimates for second-line treatment (when lower proportions of patients had further chemotherapy) on both progression-free survival and survival show different results.

The marginal cost per progression-free year for oxaliplatin compared with 5FU by the de Gramont regimen is £23,000. The same figure for irinotecan is £58,400. Second-line treatment with irinotecan (single-agent therapy) is less expensive than the inpatient de Gramont regimen. If it is assumed that all treatments are given on an outpatient basis, the marginal cost per progression-free year is unchanged for oxaliplatin, £49,000 for irinotecan and £26,400 for second-line irinotecan.

For second-line treatment, the marginal cost per LYG (i.e. based on survival benefit) is zero when irinotecan is compared with inpatient treatment with the de Gramont regimen, £11,200 when compared with outpatient de Gramont, and between £17,700 and £28,200 when compared with BSC.

An illustrative analysis was undertaken to estimate the effect of taking quality of life into account. The assumptions are considered to be too uncertain to base conclusions on the results.

Chapter 7
Discussion

Main results

The studies summarised above suggest that both irinotecan and oxaliplatin, combined with an optimum FU/FA regimen as first-line treatment of advanced colorectal cancer, can extend progression-free survival by a median of 2–3 months, compared with FU/FA alone. Because of the manner in which the studies were carried out, the impact of these first-line therapies on overall survival is less clear. Thus, in reviewing the results of these studies, while ideally overall survival would have been the most important outcome measure, more emphasis has been laid on progression-free survival than would otherwise have been done. However, even though the relationship between progression-free survival and overall survival is unclear, progression-free survival is valid as an outcome measure because disease progression impairs physical and mental health. The significance of tumour response as an outcome measure is more uncertain: subjective benefit does not necessarily correspond to tumour response, but such response is important in terms of the possibility of the resection of liver metastases.

As noted in the evidence review in chapter 4, many of the studies reported that irinotecan and oxaliplatin are associated with a higher toxicity, but also with higher quality of life, than the comparator regimens. The problems of measuring quality of life in this patient group have been discussed in the *Review of quality-of-life data* (page 83). However, if these results are valid, they presumably reflect a situation in which the symptoms caused by metastatic disease may have a greater detrimental impact on quality of life than the side-effects of chemotherapy, and improvement in those symptoms as a result of chemotherapy may outweigh the detrimental effects of that chemotherapy.

The quality of those studies that provided enough information to allow assessment appears low. This assessment result is a product of our use of the Jadad scale, which requires studies to be blinded and which scores only three aspects of study design and implementation: randomisation, blinding and description of withdrawals/dropouts. Because two points out of five are allocated for blinding, and one further point can be subtracted for failure to blind appropriately, this instrument is therefore inflexible in the scoring of studies for which blinding is impossible or not desirable.

Assumptions, limitations and uncertainties

No studies have included patients with a performance status greater than 2. This is not problematic, because patients with such a performance status would generally not be deemed suitable for chemotherapy. However, it could be argued that, in most of the studies reviewed here, the proportion of patients with a performance status of 0 is higher and the proportion with a performance status of 2 is lower than might generally be the case, and that the results obtained might therefore be more favourable than would be seen in actual clinical practice.

Few studies have included patients aged over 75 years. Any studies that use 75 years as their upper age limit will exclude half the population of patients with advanced colorectal cancer, some of whom may be suitable for chemotherapy. There is therefore little evidence as to the performance of the study interventions in older patients.

Cost and benefit assumptions in the economic analysis

There is considerable uncertainty in the economic analysis, the sources of which are explained.

Costs

For irinotecan first-line therapy, the mean treatment durations are unknown, with only the median available. The median may lie either side of the mean. Other than the median, the only other information regarding treatment times is mean time to progression. As patients are given treatment until progression, unless withdrawn earlier due to toxic effects, this duration represents the maximum treatment time (average for cohort). For oxaliplatin, the median treatment time is close to the mean and considerably less than the mean time to progression, but patients treated with oxaliplatin are known to develop

cumulative toxicities from the drug, which limit treatment times. For 5FU, the median treatment times are slightly less than the mean, but the mean treatment times comprise a higher proportion of the time until progression. For the baseline scenario, the irinotecan treatment duration is calculated as the mean of the median and maximum (time to progression). As a sensitivity analysis, all treatments are costed on the basis of median treatment durations (scenario 1).

There were few data on the costs of treating adverse events, which include hospitalisations, clinician consultations and primary care. Therefore, the same unit costs per month have been used for all treatments. Of these, hospitalisations are the most important, and a sensitivity analysis was done based on two different estimates. However, as the costs per month are the same for all treatments, their effect on cost differences is small. There of course may be differences between treatments.

Chemotherapy regimens based on de Gramont have been costed on both an inpatient and outpatient basis using average medical oncology costs per day for each. Both inpatient and outpatient administration methods are used in the UK. Costs based on average specialty inpatient and outpatient costs for the same treatment may exaggerate the difference in the administration methods, because it seems likely that the cost of treatment will be above the mean outpatient cost and less than the mean inpatient cost. If this is the case, it means that inpatient costs are exaggerated and outpatient costs underestimated. This discrepancy is not so important when two inpatient or outpatient regimens are compared, but when single-agent irinotecan (outpatient) is compared with 5FU (inpatient), it makes a large difference, as demonstrated by the effect on cost-effectiveness when outpatient treatment with 5FU is assumed rather than inpatient.

Benefits

Due to the lack of good evidence relating survival differences between first-line treatments to those treatments, progression-free survival was used as the main benefit measure. Progression-free survival is in itself of some benefit to patients in terms of reduced hospitalisations and improved quality of life, but the relationship with survival is unclear.

The median is not necessarily a good estimate of the difference between two survival (or progression-free survival) curves. The total survival (or progression-free survival) difference between curves was estimated by fitting Weibull curves to the published data. While in most cases they gave a good fit to the data, there is obviously uncertainty in the projected total survival benefit.

The trial data are themselves subject to uncertainty. For two trials, one of oxaliplatin and the other of irinotecan, both as first-line treatment, it was possible to estimate confidence limits on the progression-free survival curves and hence calculate extreme limits to the estimated progression-free survival benefit. It must be noted that these limits are 'extreme': for both drugs, there is another trial that, although using different regimens in both treatment arms, suggests similar benefit, well within the extreme limits calculated. For oxaliplatin, the extreme limits on progression-free survival benefit are 0.96–4.53 months (central estimate, 2.77 months). For irinotecan, the extreme limits are 0–4.07 months (central estimate, 1.69 months).

There is no trial evidence on utility values. The values from a study using nurses as proxy subjects were employed, but values were available only for states excluding toxic effects. No data were available from the trials as to the number of days that patients suffered from adverse events in any case. Progression-free survival years were adjusted for quality of life using the utility values from the study, and by making assumptions (subject to sensitivity analysis) as to the loss of utility due to treatment days and days in hospital for adverse events. These estimations give only some indication of how consideration of utility may affect estimated benefits, and do not differentiate well between different treatments. They are shown for illustrative purposes only.

Implications for other parties

Sculpher and co-workers[80] report an analysis of the travel costs of patients and their carers for patients treated with raltitrexed and 5FU. This report shows that many patients were accompanied by carers when having chemotherapy treatment, and that between 79% (raltitrexed) and 85% (5FU) of carers took time off from work or household duties to do this. On this basis, the number and duration of hospital visits are obviously going to affect the burden on carers. However, there are obviously other aspects of carer burden that also need to be considered.

Chapter 8
Conclusions

There is good evidence to suggest that the use of a combination of irinotecan and FU/FA in the first-line treatment of advanced colorectal cancer can extend both median progression-free and overall survival by 2–3 months, compared with either FU/FA alone or irinotecan alone, although at the cost of increased toxicity compared with FU/FA alone. However, the effect of subsequent therapy on overall survival is not known. As second-line treatment, irinotecan monotherapy appears to extend median progression-free survival by approximately 1 month and overall survival by approximately 2 months, compared with FU/FA alone, again at the cost of increased toxicity. There is also some preliminary evidence to suggest that combination irinotecan/FU/FA therapy after FU/FA failure may extend progression-free survival by approximately 2 months and overall survival by almost 3 months, compared with FU/FA alone.

The estimated marginal cost per progression-free year of irinotecan compared with 5FU ranges from £38,000 to £94,700, with a central estimate of £58,400. Irinotecan given as a single-agent treatment as second-line treatment is less expensive than inpatient treatment with 5FU, although it is possible that the total costs of second-line treatment may increase because more patients may be suitable for treatment with irinotecan. Previously these patients would have received BSC.

There is also good evidence to suggest that, when used as first-line therapy, the combination of oxaliplatin with an infusional FU/FA regimen extends median progression-free survival by 2–3 months, although again with increased toxicity. This combination may also prolong overall survival, although this is not clear because of the extensive use of salvage oxaliplatin in patients randomised to FU/FA alone, which would dilute the evidence of effectiveness of oxaliplatin in the oxaliplatin arm. In addition, the improved response rate achieved by the addition of oxaliplatin to FU/FA may enable larger numbers of patients to undergo potentially curative surgical resection of liver metastases. Preliminary data suggest that, as second-line treatment, oxaliplatin plus 5FU may extend median progression-free survival compared with either 5FU or irinotecan monotherapy.

The estimated marginal cost per progression-free year of oxaliplatin compared with 5FU ranges from £23,000 to £67,900, with a baseline estimate of £23,000.

In comparison with FU/FA, raltitrexed, when used as first-line therapy, appears to reduce both progression-free and overall survival, and is associated with a higher mortality rate. Thus, there seems no advantage in using it to treat advanced colorectal cancer in patients who can tolerate FU/FA treatment. Further research is required to determine whether it has a role in the treatment of the patient group for whom it is licensed, namely those few patients with specific metabolic intolerance to 5FU who would not be too frail for 5FU treatment. This is a smaller patient population than that suggested for raltitrexed by AstraZeneca in their submission.[57]

The cost of treatment with raltitrexed is similar to that of the Mayo 5FU regimen, which itself is less costly than the de Gramont regimen.

The quality-of-life data are ambiguous. Although many of the more recent trials have included measurement of quality of life, most often using the EORTC QLQ-C30 instrument, the difficulty of analysis of quality-of-life data in the presence of informative dropout makes it challenging to draw conclusions from the data. In many quality-of-life analyses, the researchers did not appear to have considered whether or how this difficulty may have affected their analyses. The FDA analysis[18] that attempted to control for it came up with a non-intuitive result: that irinotecan, which is known to cause nausea and vomiting, had a better quality-of-life score on this symptom scale than either control arm. The FDA analysis demonstrates how difficult it is to analyse and interpret quality-of-life data from patients in these trials.

Factors relevant to the NHS

The available evidence suggests that, currently, about 30% of patients who die of colorectal cancer receive chemotherapy for advanced disease and that another 15% have the capacity to benefit from such chemotherapy. The majority of those who

receive chemotherapy presumably receive a 5FU-based regimen, probably in most cases the de Gramont infusional regimen. If chemotherapy is extended to all those patients who have a capacity to benefit from it, expenditure thus has the potential to increase by 50%, even before the introduction of the new agents.

The introduction of the new therapies is not likely to significantly increase the pool of patients who could benefit from treatment. However, it would increase the treatment options for the current pool of patients and would potentially increase the number of lines of therapy that they may receive. Combination first-line therapies with irinotecan and oxaliplatin have been licensed for use in the UK. Combination second-line therapies are unlicensed at present but are currently the subject of clinical trials, and it is possible that they will gain approval in the future.

The new therapies also have further resource implications inasmuch as they appear to increase the number of patients suitable for potentially curative resection of liver metastases. However, liver resection rates are low in this country compared with some other European countries, so some of the potential benefit of the improved response rates of the new therapies may not be realised unless this situation changes.

Recommendations for research

As has been mentioned, there are several questions in relation to which further research is required. Several of these questions are being addressed in ongoing trials, while no information regarding relevant research has been found in relation to others.

Ongoing trials

No published data was identified relating to ongoing trials.

The ongoing large-scale MRC CR08 FOCUS (fluorouracil, oxaliplatin and irinotecan: use and sequencing) randomised trial[53] is likely to report in summer 2004. It compares the following treatment plans:

- modified de Gramont regimen until progression, followed if appropriate by single-agent irinotecan
- modified de Gramont regimen until progression, followed if appropriate by combination irinotecan/modified de Gramont
- combination irinotecan/modified de Gramont regimen until progression
- modified de Gramont regimen until progression, followed if appropriate by combination oxaliplatin/modified de Gramont
- combination oxaliplatin/modified de Gramont regimen until progression.

Management subsequent to these treatment plans is at the clinician's discretion, but it is anticipated that this will usually be supportive care alone. If further chemotherapy is required, protracted venous infusion of 5FU plus mitomycin is recommended.[53]

This MRC study will allow direct comparison of:

- first-line combination irinotecan therapy versus first-line combination oxaliplatin therapy
- first-line combination irinotecan therapy versus the modified de Gramont regimen alone
- first-line combination oxaliplatin therapy versus the modified de Gramont regimen alone
- irinotecan versus oxaliplatin as part of second-line therapy
- second-line single-agent irinotecan versus second-line combination schedules.

The study does not allow comparison of first-line irinotecan combination therapy followed by second-line oxaliplatin combination therapy with either first-line oxaliplatin combination therapy followed by second-line irinotecan combination therapy or with any of the other permutations included in the study.

The ongoing large-scale North American Intergroup 3C trial is comparing first-line irinotecan plus FU/FA with first-line oxaliplatin plus FU/FA, and with the combination of irinotecan plus oxaliplatin.[21]

Further research

RCTs are required to explore:

- the relative efficacy of second-line 5FU plus mitomycin C versus irinotecan or oxaliplatin
- whether raltitrexed is beneficial compared with either BSC alone or irinotecan alone in patients with specific metabolic intolerance of 5FU
- the relative efficacy of different sequences of therapies
- the optimum duration of therapy (i.e. whether therapy should be continued to disease progression, death or unacceptable toxicity, or only until response, with or without consolidation)
- the relative efficacy of oxaliplatin and 5FU in

patients with a family history of colorectal cancer caused by the *HNPCC* (hereditary non-polyposis colorectal cancer) gene mutation.

Given the palliative objectives of therapy, research is required to address the issue of measuring quality of life in patients with terminal cancer.

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References

1. Kerr D, O'Connor KM. An economic comparison of the net clinical benefit and treatment costs of raltitrexed and 5-fluorouracil + leucovorin (Mayo regimen) in advanced colorectal cancer. *Journal of Medical Economics* 1999;**2**:123–32.

2. Office for National Statistics. Cancer statistics registrations: registrations of cancer diagnosed in 1992, England and Wales. London: Stationery Office; 1998. Series MB1; No.: 25.

3. Office for National Statistics. Mortality statistics: cause: review of the Registrar General on deaths by cause, sex and age, in England and Wales, 1998. London: Stationery Office; 2000. Series DH2; No.: 25.

4. Boyle P, Langman JS. ABC of colorectal cancer: epidemiology. *BMJ* 2000;**321**:805–8.

5. Mountney L, Sanderson H, Harris J. Colorectal cancer. In: Stevens A, Raftery J, editors. Health care needs assessment. Oxford: Radcliffe Medical Press; 1993. p. 379–410.

6. Smithies A, Stein K. Irinotecan as second line chemotherapy in colorectal cancer. Southampton: University of Southampton, Wessex Institute for Health Research and Development; 1999. DEC Report No.: 97.

7. The management of colorectal cancer. *Effective Health Care* 1997;**3**:1–12.

8. Seymour MT, Stenning SP, Cassidy J. Attitudes and practice in the management of metastatic colorectal cancer in Britain. Colorectal Cancer Working Party of the UK Medical Research Council. *Clinical Oncology (Royal College of Radiologists)* 1997;**9**:248–51.

9. NHS Executive. Improving outcomes in colorectal cancer: the research evidence. Leeds: NHS Executive; 2000.

10. Young A, Rea D. ABC of colorectal cancer: treatment of advanced disease. *BMJ* 2000;**321**:1278–80.

11. de Gramont A, Bosset J, Milan C, Rougier P, Bouche O, Etienne PL, *et al.* Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. *Journal of Clinical Oncology* 1997;**15**:808–15.

12. Maughan TS, James RD, Kerr D, McArdle C, Ledermann JA, Seymour M, *et al.* Preliminary results of a multicentre randomised trial comparing 3 chemotherapy regimens (de Gramont, Lokich and raltitrexed) in metastatic colorectal cancer. Colorectal Cancer Working Party of the UK Medical Research Council. *ASCO OnLine* 1999. No.: 1007. URL: http://www.asco.org/prof/me/html/99abstracts/m_toc.htm

13. Stephens RJ, Hopwood P, Johnston C, Maughan TS. The value of quality of life (QL) outcomes in comparing 3 chemotherapy regimens (de Gramont, Lokich and raltitrexed) in a multicentre randomised trial of metastatic colorectal cancer. Colorectal Cancer Working Party of the UK Medical Research Council. *ASCO OnLine* 1999. No.: 2220. URL: http://www.asco.org/prof/me/html/99abstracts/m_toc.htm

14. Rowe M, James R. A prospective comparison of inpatient versus outpatient de Gramont therapy: using quality of life, acceptability and response measures: a pilot study [abstract no. 227]. *European Journal of Cancer* 1999;**35**:S73.

15. Scase A, Ross P, Cunningham D, Norman A, Prendiville J, Webb A, *et al.* The Royal Marsden Hospital experience with raltitrexed ('Tomudex') and its comparison with protracted venous infusion 5-fluorouracil, and bolus 5-fluorouracil. *GI Cancer* 1998;**2**:267–75.

16. Iveson TJ, Hickish T, Schmitt C, van Cutsem E. Irinotecan in second-line treatment of metastatic colorectal cancer: improved survival and cost-effect compared with infusional 5-FU. *European Journal of Cancer* 1999;**35**:1796–804.

17. Association of the British Pharmaceutical Industry. The value of medicines: bowel and breast cancer. London: ABPI; 1997.

18. US Food and Drug Administration. Camptosar (irinotecan): medical review. [Accessed 2000 Nov 15]. URL: http://www.fda.gov/cder/approval/main.htm

19. Electronic medicines compendium (eMC). [Accessed 2000 Oct 30]. URL: http://emc.vhn.net/

20. UK Drug Information Pharmacists Group. Oxaliplatin. [Accessed 2000 Oct 30]. URL: http://www.ukdipg.org.uk/

21. Sanofi-Synthelabo Ltd. Clinical and cost effectiveness of oxaliplatin (Eloxatin®) in the treatment of metastatic colorectal cancer. Sponsor submission to the National Institute for Clinical Excellence. 2000.

22. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996;**17**:1–12.

23. Adenis A, Douillard JY, Lacroix H, Dufour P, Tubiana N, Berger C, *et al.* Randomized phase II–III trial of oxaliplatin (OXA) with 5-fluorouracil (5FU) continuous infusion (CI) versus a control arm with either 5FU or irinotecan (CPT11) in previously treated metastatic colorectal cancer (MCRC) patients (Pts). *ASCO OnLine* 2000. No.: 1088. URL: http://www.asco.org/prof/me/html/00abstracts/m_toc.htm

24. Becouarn Y, Mousseau M, Gamelin E, Coudert B, Marceau-suissa J, Bekradda M. CPT-11 and L-OHP combination versus alternated combination of LV5FU2 + CPT-11/LV5FU2 + L-OHP in 5-FU resistant advanced colorectal cancer (CRC): preliminary results. *European Journal of Cancer* 1999;**35**:S71.

25. Buechele T, Kroening H, Reichardt P, Clemens M, Hirschmann WD, Freier W, *et al.* Bolus 5-fluorouracil (5-FU)/folinic acid (FA) (Mayo Clinic) versus weekly, high-dose 24h 5-FU infusion + FA plus oxaliplatin (LOPH) in advanced colorectal cancer (CRC). A randomized phase III study. *ASCO OnLine* 2000. No.: 984. URL: http://www.asco.org/prof/me/html/00abstracts/m_toc.htm

26. Cocconi G, Cunningham D, van Cutsem E, Francois E, Gustavsson B, van Hazel G, *et al.* Open, randomized, multicenter trial of raltitrexed versus fluorouracil plus high-dose leucovorin in patients with advanced colorectal cancer. Tomudex Colorectal Cancer Study Group. *Journal of Clinical Oncology* 1998;**16**:2943–52.

27. Zori Comba A, Blajman C, Richardet E, Vilanova M, Cóppola F, Van Kooten M, *et al.* Bimonthly oxaliplatin (L-OHP) with (A) or without (B) fluorouracil (FU) and leucovorin (FA): proven evidence of synergism in a phase II randomised trial. *ASCO OnLine* 1999. No.: 953. URL: http://www.asco.org/prof/me/html/99abstracts/m_toc.htm

28. Cunningham D, Pyrhonen S, James RD, Punt CJ, Hickish TF, Heikkila R, *et al.* Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998;**352**:1413–18.

29. Cunningham D, Zalcberg JR, Rath U, Oliver I, van Cutsem E, Svensson C, *et al.* Final results of a randomised trial comparing 'Tomudex' (raltitrexed) with 5-fluorouracil plus leucovorin in advanced colorectal cancer. 'Tomudex' Colorectal Cancer Study Group. *Annals of Oncology* 1996;**7**:961–5.

30. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, *et al.* Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *Journal of Clinical Oncology* 2000;**18**:2938–47.

31. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, *et al.* Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial [published erratum appears in *Lancet* 2000;**355**:1372]. *Lancet* 2000;**355**:1041–7.

32. Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, *et al.* Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil–leucovorin as first-line treatment of metastatic colorectal cancer. *Journal of Clinical Oncology* 2000;**18**:136–47.

33. Graeven U, Ridwelski K, Manns M, Espana P, Borner M, Carlson G, *et al.* Irinotecan (CPT-11) with bolus 5-fluorouracil (5-FU) and folinic acid (FA) in patients (Pts) with previously untreated metastatic colorectal cancer (MCRC): an active and safe regimen. *ASCO OnLine* 2000. No.: 952. URL: http://www.asco.org/prof/me/html/00abstracts/m_toc.htm

34. Ledermann JA, Maughan TS, James RD, Kerr D, McArdle C, Seymour M, *et al.* Preliminary results of a multicentre randomised trial comparing 3 chemotherapy regimens (de Gramont, Lokich and Raltitrexed) in metastatic colorectal cancer [abstract no. 4.10]. *British Journal of Cancer* 1999;**80**(Suppl 2):20.

35. Levi FA, Zidani R, Vannetzel JM, Perpoint B, Focan C, Faggiuolo R, *et al.* Chronomodulated versus fixed-infusion-rate delivery of ambulatory chemotherapy with oxaliplatin, fluorouracil, and folinic acid (leucovorin) in patients with colorectal cancer metastases: a randomized multi-institutional trial. *Journal of the National Cancer Institute* 1994;**86**:1608–17.

36. Levi F, Zidani R, Misset JL. Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. International Organization for Cancer Chronotherapy. *Lancet* 1997;**350**:680–6.

37. Maiello E, Gebbia V, Giuliani F, Paoletti G, Gebbia N, Cigolari S, *et al.* 5-fluorouracil and folinic acid with or without CPT-11 in advanced colorectal cancer patients: a multicentre randomised phase II study of the Southern Italy Oncology Group. *Annals of Oncology* 2000;**11**:1045–51.

38. Pazdur R, Vincent M. Raltitrexed (Tomudex®) versus 5-fluorouracil and leucovorin (5-FU + LV) in patients with advanced colorectal cancer (ACC): results of a randomized, multicenter, North American trial. *ASCO OnLine* 1997. No.: 801. URL: http://www.asco.org/

39. Pozzo C, Pyrhonen S, Bodrogi I, Szanto J, Kamica-Mlodkowska H, Starkammar H, *et al.* A randomized phase II trial assessing irinotecan (IRI) and 5FU/folinic acid (LV), 'Mayo regimen', in first line palliative chemotherapy patients (pts) with metastatic colorectal cancer (MCRC) [abstract no. 213]. *European Journal of Cancer* 1999;**35** (Suppl 4):S70.

40. Recchia F, De Filippis S, Rosselli M, Saggio G, Pompili PL, Rea S. Randomized phase II study of oxaliplatin (OX) or CPT-11 (CPT) combined with bimonthly leucovorin (L) and 5-fluorouracil (5-FU) in metastatic colorectal cancer (MCC). Preliminary report. *ASCO OnLine* 2000. No.: 1049. URL: http://www.asco.org/prof/me/html/00abstracts/m_toc.htm

41. Rougier P, van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, *et al.* Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 1998;**352**:1407–12.

42. Rougier P, Cunningham D, Roth AD, Germa JR, James RD, Karasek P, *et al.* Irinotecan (Iri) in combination with high-dose infusional (HDI) 5FU/FA either weekly or bi-weekly: evidence of survival advantage and quality of life (QoL) improvement in metastatic colorectal cancer (MCRC) [abstract no. 206]. *European Journal of Cancer* 1999;**35**(Suppl 4):S68.

43. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *New England Journal of Medicine* 2000;**343**:905–14.

44. Tournigand C, Louvet C, Andre T, Achille E, Lledo G, Flesch M, *et al.* FOLFIRI followed by FOLFOX or FOLFOX followed by FOLFIRI in metastatic colorectal cancer: which is the best sequence? Safety and preliminary efficacy results of a randomized phase III study. *ASCO OnLine* 2000. No.: 949. URL: http://www.asco.org/prof/me/html/00abstracts/m_toc.htm

45. Ulrich-Pur H, Brugger S, Kornek GV, Fiebiger W, Haider K, Kwasny W, *et al.* Randomized phase II study of CPT-11 plus mitomycin C versus oxaliplatin plus mitomycin C in previously treated patients with advanced colorectal cancer (ACC) [abstract no. 225]. *European Journal of Cancer* 1999;**35** (Suppl 4):S72.

46. US Food and Drug Administration. Camptosar (irinotecan): statistical review(s). [Accessed 2000 Dec 7]. URL: http://www.fda.gov/cder/approval/main.htm

47. Wilke HJ. Comparing irinotecan with best supportive care and infusional 5-fluorouracil: a critical evaluation of the results of two randomized phase III trials. *Seminars in Oncology* 1999;**26**:21–3.

48. van Cutsem E, Blijham GH. Irinotecan versus infusional 5-fluorouracil: a phase III study in metastatic colorectal cancer following failure on first-line 5-fluorouracil. V302 Study Group. *Seminars in Oncology* 1999;**26**:13–20.

49. Nikolic-Tomasevic Z, Jelic S, Popov I, Radosavljevic D. Irinotecan as second-line treatment in metastatic colorectal cancer: dilemmas regarding patient selection and toxicity prediction. *Journal of Chemotherapy* 2000;**12**:244–51.

50. Kornblau S, Benson AB, Catalano R, Champlin RE, Engelking C, Field M, *et al.* Management of cancer treatment-related diarrhea: issues and therapeutic strategies. *Journal of Pain and Symptom Management* 2000;**19**:118–29.

51. Hecht JR. Gastrointestinal toxicity of irinotecan. *Oncology (Huntington)* 1998;**12**:72–8.

52. Seymour MT, Tabah-Fisch I, Homerin M. Quality of life (QoL) in advanced colorectal cancer (ACC): a comparison of QoL during bolus plus infusion 5FU/leucovorin (LV5FU2) with or without oxaliplatin. *ASCO OnLine* 1999. No.: 901. URL: http://www.asco.org/prof/me/html/99abstracts/m_toc.htm

53. Medical Research Council Colorectal Cancer Group. FOCUS (fluorouracil, oxaliplatin and irinotecan: use and sequencing). A randomised trial to assess the role of irinotecan and oxaliplatin in advanced colorectal cancer. CR08 clinical protocol (version 4). 2000 Feb.

54. Harper P. Advanced colorectal cancer (ACC): results from the latest raltitrexed Tomudex® (raltitrexed) comparative study. *ASCO OnLine* 1997. No.: 802. URL: http://www.asco.org/

55. Cunningham D. Mature results from three large controlled studies with raltitrexed ('Tomudex'). *British Journal of Cancer* 1998;**77**:15–21.

56. Maughan TS, James RD, Kerr D, Ledermann JA, McArdle C, Seymour MT, *et al.* A multicentre randomised trial comparing survival, palliation and quality of life for 3 chemotherapy regimens (de Gramont, Lokich and Raltitrexed) in metastatic colorectal cancer. Unpublished 2000.

57. AstraZeneca. The clinical and cost effectiveness of irinotecan, oxaliplatin and raltitrexed – drugs for colorectal cancer. Submission of evidence relating to raltitrexed (Tomudex®). 2000.

58. Kerr D. 'Tomudex' (ZD 1694), a new direct and specific thymidylate synthase inhibitor, has resource saving implications in the management of colorectal cancer. *Quality of Life Research* 1995;**4**:576.

59. Reference deleted.

60. Anderson H. Quality of life advantages demonstrated for patients receiving Tomudex compared with those receiving 5-fluorouracil plus leucovorin (5 FU+LV) in the treatment of advanced colorectal cancer (ACC) [abstract no. 1099]. Proceedings of the European Cancer Conference; 1997 Sep 14–18; Hamburg, Germany.

61. Henry B, Becouarn Y, Aussage P. Clinical benefits of stabilisation with second line chemotherapy in patients with metastatic colorectal cancer. *Critical Reviews in Oncology–Hematology* 1999;**32**:145–54.

62. Young A, Topham C, Moore J, Turner J, Wardle J, Downes M, *et al.* A patient preference study comparing raltitrexed ('Tomudex') and bolus or infusional 5-fluorouracil regimens in advanced colorectal cancer: influence of side-effects and administration attributes. *European Journal of Cancer Care* 1999;**8**:154–61.

63. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the *BMJ*. *BMJ* 1996;**313**:275–83.

64. Petrou S, Campbell N. Stabilisation in colorectal cancer. *International Journal of Palliative Nursing* 1997;**3**:275–80.

65. Buyse M, Thirion P, Carlson RW, Burzykowski T, Molenberghs G, Piedbois P. Relation between tumour response to first-line chemotherapy and survival in advanced colorectal cancer: a meta-analysis. *Lancet* 2000;**356**:373–8.

66. Netten A, Dennett J, Knight J. Unit costs of health and social care. Canterbury: Personal Social Services Research Unit (PSSRU); 1999.

67. Schmitt C, Blijham G, Jolain B, Rougier P, van Cutsem E. Medical care consumption in a phase III trial comparing irinotecan with infusional 5-fluorouracil (5-FU) in patients with metastatic colorectal cancer after 5-FU failure. *Anti-Cancer Drugs* 1999;**10**:617–23.

68. Gelber RD, Goldhirsch A, Cole BF, Wieand HS, Schroeder G, Krook JE. A quality adjusted time without symptoms or toxicity (Q-TWiST) analysis of adjuvant radiation therapy and chemotherapy for resectable rectal cancer. *Journal of the National Cancer Institute* 1996;**88**:1039–45.

69. Cunningham D, Falk S, Jackson DL. Irinotecan and infusional 5-fluorouracil as first line treatment of metastatic colorectal cancer: improved survival and cost-effective compared with infusional 5-FU. *ASCO OnLine* 2000. No.: 980. URL: http://www.asco.org/prof/me/html/00abstracts/m_toc.htm

70. Summerhayes M, Wanklyn SJ, Shakespeare RA, Lovell J. Reduced pharmacy resource utilization associated with raltitrexed treatment of advanced colorectal cancer. *Journal of Oncology Pharmacy Practice* 1997;**3**:24–30.

71. Levy-Piedbois C, Durand-Zaleski I, Juhel H, Schmitt C, Bellanger A, Piedbois P. Cost-effectiveness of second-line treatment with irinotecan or infusional 5-fluorouracil in metastatic colorectal cancer. *Annals of Oncology* 2000;**11**:157–61.

72. Aventis Pharma. National Institute for Clinical Excellence: Campto (irinotecan HCl trihydrate) in advanced colorectal cancer. Sponsor submission to NICE. 2000.

73. Elliott R. An analysis of drug costs in the management of chemotherapy-related side effects in advanced colorectal cancer. A comparison between raltitrexed ('Tomudex') and 5-fluorouracil plus folinic acid. *Journal of Oncology Pharmacy Practice* 1996;**2**:186–90.

74. The Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *Journal of Clinical Oncology* 1998;**16**:301–8.

75. Groener MG, van Ineveld BM, Byttebier G, van Hout BA, Rutten FF. An economic evaluation of Tomudex (raltitrexed) and 5-fluorouracil plus leucovorin in advanced colorectal cancer. *Anti-Cancer Drugs* 1999;**10**:283–8.

76. Ross P, Heron J, Cunningham D. Cost of treating advanced colorectal cancer: a retrospective comparison of treatment regimens. *European Journal of Cancer* 1996;**32A**:S13–17.

77. Cunningham D. Setting a new standard – irinotecan (Campto) in the second-line therapy of colorectal cancer: final results of two phase III studies and implications for clinical practice. *Seminars in Oncology* 1999;**26**:1–5.

78. Anderson H, Palmer MK. Measuring quality of life: impact of chemotherapy for advanced colorectal cancer. Experience from two recent large phase III trials. *British Journal of Cancer* 1998;**77** (Suppl 2):9–14.

79. Altman DG. Practical statistics for medical research. London: Chapman & Hall; 1991.

80. Sculpher M, Palmer MK, Heyes A. Costs incurred by patients undergoing advanced colorectal cancer therapy – a comparison of raltitrexed and fluorouracil plus folinic acid. *Pharmacoeconomics* 2000;**17**:361–70.

81. Schmoll HJ, Buechele T, Grothey A, Dempke W. Where do we stand with 5-fluorouracil? *Seminars in Oncology* 1999;**26**:589–605.

Appendix 1

WHO criteria for evaluation of response[6]

Bidimensionally or unidimensionally measurable disease.

Complete response

Disappearance of all known disease, determined by two observations not less than 4 weeks apart.

Partial response

In the case of bidimensionally measurable disease, decrease by at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions, as determined by two observations not less than 4 weeks apart.

For unidimensionally measurable disease, decrease by at least 50% in the sum of the largest diameters of all lesions, as determined by two observations not less than 4 weeks apart.

It is not necessary for all lesions to have regressed to qualify for partial response, but no lesion should have progressed and no lesion should appear. Serial evidence of appreciable change must be obtained and available for subsequent review. The assessment must be objective.

Minor response

In the case of bidimensionally measurable disease, decrease by at least 25% but less than 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions, as determined by two observations not less than 4 weeks apart.

For unidimensionally measurable disease, decrease by at least 25% but less than 50% in the sum of the largest diameters of all lesions, as determined by two observations not less than 4 weeks apart.

It is not necessary for all lesions to have regressed to qualify for minor response, but no lesion should have progressed and no lesion should appear. Serial evidence of appreciable change must be obtained and available for subsequent review. The assessment must be objective.

No change

For bidimensionally measurable disease, less than 25% decrease and less than 25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions.

For unidimensionally measurable disease, less than 25% decrease and less than 25% increase in the sum of the diameter of all lesions.

No new lesions should appear.

Progressive disease

Greater than 25% increase in the size of at least one bidimensionally or unidimensionally measurable lesion (in comparison with the measurements at nadir), or appearance of a new lesion. The occurrence of pleural effusion or ascites is also considered as progressive if this is substantiated by positive cytology.

Appendix 2

WHO scale for performance status[6]

0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework and office work)
2	Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 3

5FU-based treatment regimens referred to in the text

Regimen	Schedule
Bolus 5FU	
Machover	5FU (400 mg/m^2/day) + FA (200 mg/m^2/day) for 5 consecutive days every 4 weeks[26]
Mayo	5FU (425 mg/m^2/day) + FA (20 mg/m^2/day) for 5 days every 4 weeks
Roswell Park	5FU (300 mg/m^2 escalating to 750 mg/m^2) given in the middle of a 2-hour infusion of FA (500 mg/m^2) once a week for a minimum of 6 weeks and, in the case of response, until progression (maximum of 1 year)[81]
Infusional 5FU	
AIO	2-hour infusion of FA (500 mg/m^2) followed by 24-hour infusion of 5FU (2600 mg/m^2) weekly for 6 weeks
de Gramont	2-hour infusion of FA (200 mg/m^2) + bolus 5FU (400 mg/m^2) followed by a 22-hour infusion of 5FU (600 mg/m^2) on days 1 and 2 of each fortnight[11]
Modified de Gramont	FA (200 mg/m^2) + bolus 5FU (400 mg/m^2) followed by a 46-hour infusion of 5FU (2400–3000 mg/m^2) fortnightly[44]
Lokich	5FU (250–300 mg/m^2) as prolonged continuous intravenous infusion until progression/toxicity

Appendix 4

Literature search

MEDLINE search strategies (OVID BioMed 1966 to Nov 2000)

Effectiveness search

1 irinotecan.af.
2 100286-90-6.rn.
3 cpt 11.af.
4 cpt11.af.
5 campto.af.
6 camptosar.af.
7 oxaliplatin.af.
8 63121-00-6.rn.
9 l ohp.af.
10 eloxatin.af.
11 raltitrexed.af.
12 tomudex.af.
13 ici d1694.af.
14 ici d 1694.af.
15 112887-68-0.rn.
16 zd1694.af.
17 zd 1694.af.
18 or/1–17
19 exp Colorectal neoplasms/
20 Neoplasms/
21 Carcinoma/
22 Adenocarcinoma/
23 or/20-22
24 Colonic diseases/
25 Rectal diseases/
26 exp Colon/
27 exp Rectum/
28 or/24–27
29 23 and 28
30 (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
31 (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
32 (neoplasm$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
33 (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
34 (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
35 (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
36 (tumour$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
37 (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
38 or/30–37
39 19 or 29 or 38
40 18 and 39
41 randomized controlled trial.pt.
42 controlled clinical trial.pt.
43 Randomized controlled trials/
44 Random allocation/
45 Double-blind method/
46 Single-blind method/
47 or/41–46
48 clinical trial.pt.
49 exp Clinical trials/
50 (clin$ adj25 trial$).tw.
51 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw.
52 Placebos/
53 placebo$.tw.
54 random$.tw.
55 Research design/
56 or/48–55
57 "comparative study"/
58 exp evaluation studies/
59 Follow-up studies/
60 Prospective studies/
61 (control$ or prospectiv$ or volunteer$).tw.
62 or/57–61
63 47 or 56 or 62
64 "animal"/
65 "human"/
66 64 not 65
67 63 not 66
68 Meta-analysis/
69 exp review literature/
70 (meta analy$ or metaanaly$).tw.
71 meta analysis.pt.
72 review academic.pt.
73 review literature.pt.
74 letter.pt.
75 review of reported cases.pt.
76 historical article.pt.
77 review multicase.pt.
78 or/68–73
79 or/74–77
80 78 not 79
81 "human"/
82 "animal"/
83 82 not 80
84 80 not 83
85 Economics/
86 exp "Costs and cost analysis"/
87 Economic value of life/

88 exp Economics, hospital/
89 exp Economics, medical/
90 Economics, nursing/
91 exp models, economic/
92 Economics, pharmaceutical/
93 exp "Fees and charges"/
94 exp Budgets/
95 ec.fs.
96 (cost or costs or costed or costly or costing$).tw.
97 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
98 Quality-adjusted life years/
99 (QALY or QALYs).af.

Appendix 5

National Cancer Institute common toxicity criteria[6]

	Toxicity grade				
	0	**1**	**2**	**3**	**4**
White blood cell count	> 4.0	3.0–3.9	2.0–2.9	1.0–1.9	< 1.0
Infection	None	Mild	Moderate	Severe	Life-threatening
Nausea	None	Able to eat reasonable intake	Intake significantly decreased but can eat	No significant intake	
Vomiting	None	1 episode in 24 hours	2–5 episodes in 24 hours	6–10 episodes in 24 hours	> 10 episodes in 24 hours or **requiring** parenteral support
Diarrhoea	None	Increase of 2–3 stools/day	Increase of 4–6 stools/day or nocturnal stools or moderate cramping	Increase of 7–9 stools/day or incontinence or severe cramping	Increase of > 10 stools/day or grossly bloody diarrhoea or need for parenteral support
Stomatitis	None	Painless ulcers, erythema or mild soreness	Painful erythema, oedema or ulcers, but can eat	Painful erythema, oedema or ulcers, and cannot eat	**Requires** parenteral or enteral support

Appendix 6

Curve-fitting method and results

Analysis of published survival curves can be used to conduct a marginal cost-effectiveness analysis in which two treatments are compared with each other in terms of cost per LYG.

Mean survival is a better indication of survival gain than median because it indicates the overall survival time experienced by the cohort. The mean is derived by determining the total area under a curve. The area between survival curves therefore indicates the difference in survival experienced by the two groups (*Figure 2*).

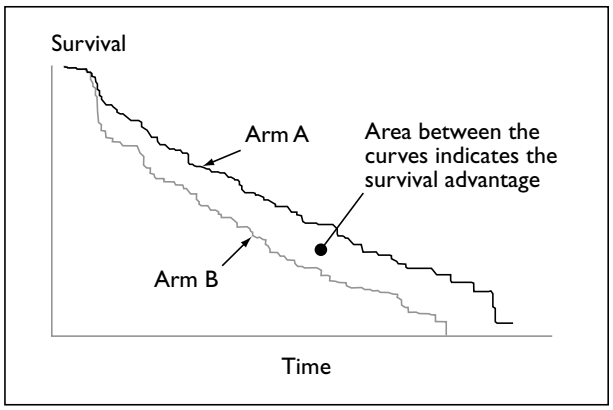

FIGURE 2 *Area between survival curves: an indicator of the difference in survival between two treatment arms*

To calculate the area, all the Kaplan–Meier curves were extrapolated using software designed to replicate published survival graphs. The trapezoidal rule, a simple numerical integration technique, was then used to calculate the area. Areas were calculated at 3, 6 and 12 months and at total survival end-points.

The trapezoidal rule looks at values at two incremental time steps and takes the average, then multiplies by the increase in time to calculate strips of areas (*Figure 3*). These areas are then summed to calculate the overall area under the curve (AUC). Though simple, the technique is well established as an accurate method with which to calculate areas under curves.

Because in some trials the time horizons end while patients are still alive, there is a clear argument that patient benefit beyond the reported limit should also be considered. Mathematical

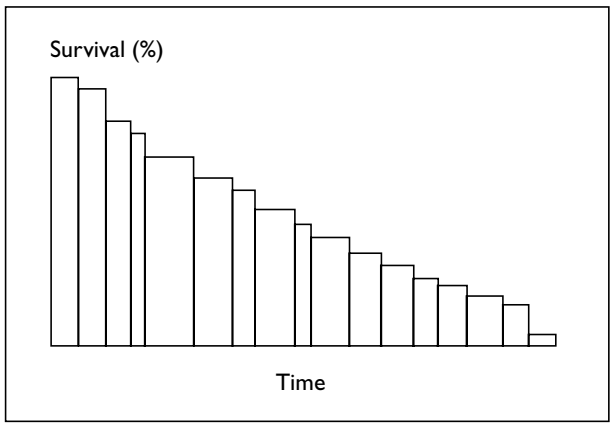

FIGURE 3 *Trapezoidal rule: the average of two incremental time steps is multiplied by the increase in time to calculate strips of areas, which are then summed to calculate the overall area under the curve (AUC)*

curves have been fitted to the extrapolated data to predict the overall survival. A suitable curve was chosen after three types of curves were fitted by minimising the sum of the least-squares method. In most cases, the Weibull curve was the most suitable. *Table 104* shows the results from all the published graphs.

The total AUC was estimated as the sum of the area directly measured within the trial (i.e. the area from zero time to the last time point of the follow-up) plus the extrapolated tail (i.e. the area from the last point of follow-up until infinity), as shown in *Figure 4*.

The Weibull curve is fitted using the formula:
$y = 1 - e^{-(x/\beta)^{\alpha}}$, where $\alpha, \beta > 0$
The exponential curve is fitted using the formula:
$y = 1 - e^{-\lambda x}$, where $\lambda > 0$
The Gompertz curve is fitted using the formula:
$y = s^x g^{c^x}$, where $0 < s, g < 1$ and $c > 1$.

Confidence intervals

It was possible to calculate CIs for the time to progression curves in the Saltz trial[43] because the number at risk was reported at 3-monthly time steps on the curves.

If p is the survival proportion, taken from the data points on the graph, and r is the number

TABLE 104 *Results of different models fitted to published survival curves*

Study	de Gramont et al., 2000[30]				Cunningham *et al.*, 1998[28]				Saltz *et al.*, 2000[43]					
Drug	**LV5FU2**	**LV5FU2 + oxaliplatin**	**LV5FU2 + oxaliplatin**	**LV5FU2**	**Irinotecan + BSC**	**BSC**	**Irinotecan + BSC**	**BSC**	**Irinotecan, fluorouracil, leucovorin**	**Fluorouracil, leucovorin**	**Irinotecan only**	**Irinotecan, fluorouracil, leucovorin**	**Fluorouracil, leucovorin**	**Irinotecan only**
Curve type	**Survival**	**Survival**	**Time to progression**	**Time to progression**	**Performance status > 2**	**Performance status > 2**	**Survival**	**Survival**	**Survival**	**Survival**	**Survival**	**Time to progression**	**Time to progression**	**Time to progression**
Data points														
AUC	19.127	16.840	9.953	7.245	6.679	5.578	10.579	8.285	16.810	14.281	15.479	7.195	5.739	5.619
Last data point	0.195	0.061	0.079	0.036	0.084	0.084	0.202	0.082	0.128	0.043	0.024	0.056	0.028	0.048
Last time point	37.962	37.966	23.927	23.928	18.601	18.601	18.036	19.383	40.999	34.723	38.924	18.013	18.028	18.042
3 months	2.981	2.876	2.870	2.689	2.574	2.659	2.913	2.920	2.855	2.853	2.870	2.683	2.626	2.562
6 months	5.852	5.520	5.247	4.571	4.292	3.785	5.455	5.231	5.342	5.348	5.450	4.595	4.060	3.986
12 months	10.697	9.849	8.189	6.457	5.939	4.839	8.946	7.394	9.291	9.269	9.402	6.594	5.390	5.229
Weibull														
Alpha	1.557	1.412	1.559	1.348	1.175	1.084	1.730	1.718	1.221	1.416	1.253	1.379	1.223	1.199
Beta	21.746	19.299	11.139	7.891	7.288	5.449	12.769	9.144	18.846	16.295	17.319	8.132	6.130	5.970
Sum of least squares	41451.467	16867.947	9684.526	4073.669	15973.682	104916.859	1785.719	23258.132	10271.844	8432.761	21737.153	9574.995	12540.438	10267.497
Maximum least square	104.962	28.150	25.220	24.907	67.070	346.481	15.218	57.984	27.176	13.502	39.183	42.004	59.911	66.941
AUC 0 > last point	18.694	16.852	9.843	7.184	6.634	5.173	10.574	8.068	16.709	14.396	15.441	7.216	5.639	5.518
AUC tail	0.855	0.714	0.169	0.054	0.260	0.111	0.807	0.085	0.942	0.430	0.679	0.213	0.100	0.099
Total AUC	19.548	17.567	10.012	7.238	6.893	5.284	11.381	8.153	17.651	14.826	16.120	7.430	5.738	5.618
3 months	2.957	2.922	2.863	2.689	2.572	2.367	2.922	2.853	2.870	2.899	2.866	2.713	2.512	2.485
6 months	5.706	5.558	5.210	4.569	4.281	3.712	5.459	5.078	5.390	5.448	5.359	4.643	4.036	3.968
12 months	10.356	9.826	8.168	6.451	6.006	4.848	8.943	7.406	9.397	9.351	9.231	6.605	5.321	5.210
Exponential														
Lambda	0.044	0.051	0.091	0.132	0.139	0.184	0.070	0.109	0.053	0.062	0.058	0.125	0.167	0.171
Sum of least squares	234526.913	132592.218	140669.274	57679.386	29162.810	107818.497	121976.350	184681.115	48666.550	125476.776	74723.855	61164.747	33421.977	26320.469
Maximum least square	232.409	146.497	202.711	108.765	89.458	426.807	168.680	473.306	56.572	115.304	125.854	101.958	173.761	172.914
AUC 0 > last point	18.567	16.737	9.768	7.254	6.631	5.242	10.265	8.052	16.719	14.191	15.458	7.138	5.679	5.559
AUC tail	4.278	2.764	1.275	0.334	0.547	0.186	4.101	1.116	2.130	1.842	1.800	0.845	0.304	0.274
Total AUC	22.845	19.501	11.043	7.588	7.178	5.428	14.366	9.169	18.849	16.032	17.258	7.983	5.983	5.833
3 months	2.821	2.790	2.635	2.485	2.459	2.311	2.716	2.566	2.782	2.744	2.762	2.508	2.365	2.351
6 months	5.288	5.174	4.635	4.151	4.071	3.634	4.911	4.408	5.147	5.013	5.076	4.223	3.792	3.751
12 months	9.353	8.972	7.321	6.030	5.831	4.834	8.140	6.695	8.886	8.454	8.655	6.210	5.179	5.089
Gompertz														
Model parameter *s*	0.957	0.958	0.946	0.906	0.878	0.832	0.965	0.947	0.950	0.945	0.949	0.913	0.856	0.851
Model parameter *g*	1.000	1.000	0.975	0.983	0.994	1.000	0.979	0.970	1.000	1.000	0.995	0.982	0.997	0.996
Model parameter *c*	1.471	1.470	1.241	1.322	1.296	1.456	1.271	1.327	1.419	1.469	1.152	1.327	1.437	1.379
Sum of least squares	234526.913	162965.989	70177.257	26975.621	26136.849	107818.497	28283.659	103945.413	38986.102	57138.467	54667.516	21491.245	26692.469	23338.719
Maximum least square	232.421	171.953	74.049	76.307	96.848	426.808	97.248	181.152	163.058	65.998	92.069	72.318	155.400	161.515
AUC 0 > last point	18.567	17.408	9.476	6.874	6.593	5.242	10.371	7.699	16.099	13.890	15.235	7.024	5.601	5.496
AUC tail	4.278	0.000	0.002	0.000	0.091	0.186	0.171	0.000	0.000	0.000	0.111	0.008	0.007	0.017
Total AUC	22.845	17.408	9.478	6.874	6.684	5.428	10.542	7.699	16.099	13.890	15.346	7.033	5.608	5.513
3 months	2.821	2.824	2.673	2.536	2.469	2.311	2.767	2.650	2.789	2.769	2.769	2.559	2.390	2.367
6 months	5.288	5.300	4.853	4.349	4.117	3.634	5.165	4.760	5.171	5.099	5.121	4.426	3.865	3.802
12 months	9.353	9.394	7.888	6.367	5.909	4.834	8.756	7.256	8.965	8.729	8.823	6.535	5.276	5.152

continued

TABLE 104 contd *Results of different models fitted to published survival curves*

Study	Giacchetti *et al.*, 2000[32]				Rougier *et al.*, 1998[41]				Douillard *et al.*, 2000[31]			
Drug	Irinotecan group	Non-Irinotecan group	Irinotecan group	Non-Irinotecan group	Irinotecan + BSC	Fluorouracil by continuous infusion	Irinotecan + BSC	Fluorouracil by continuous infusion	Irinotecan group	Non-Irinotecan group	Irinotecan group	Non-Irinotecan group
Curve type	Survival	Survival	Time to progression	Time to progression	Survival	Survival	Time to progression	Time to progression	Survival	Survival	Time to progression	Time to progression
Data points												
AUC	25.030	23.075	10.580	8.275	11.239	9.550	5.154	4.232	17.657	15.609	6.983	5.104
Last data point	0.132	0.082	0.029	0.011	0.223	0.181	0.035	0.024	0.223	0.183	0.049	0.053
Last time point	55.805	54.578	35.585	35.995	18.677	17.637	14.180	12.841	28.366	27.673	13.790	11.796
3 months	2.932	2.963	2.880	2.611	2.943	2.982	2.591	2.503	2.974	2.968	2.686	2.488
6 months	5.728	5.811	5.296	4.304	5.495	5.405	3.989	3.575	5.748	5.681	4.577	3.966
12 months	10.521	10.914	8.148	6.295	9.185	8.309	5.024	4.212	10.618	10.038	6.730	5.104
Weibull												
Alpha	1.195	1.448	1.463	0.980	1.679	1.628	1.343	1.364	1.730	1.558	1.281	1.219
Beta	28.373	25.027	11.286	8.289	13.756	11.143	5.617	4.564	21.901	18.878	8.417	5.823
Sum of least squares	24457.509	56830.062	35078.254	23619.791	4469.959	15581.350	12751.179	24931.072	4216.394	4050.828	11800.056	11205.771
Maximum least square	43.732	64.483	79.083	181.586	18.574	59.014	91.749	171.631	10.422	11.190	135.004	101.462
AUC 0 > last point	24.626	22.185	10.191	8.233	11.208	9.420	5.056	4.132	17.667	15.566	6.986	5.083
AUC tail	2.029	0.511	0.030	0.129	1.076	0.555	0.099	0.046	1.852	1.403	0.812	0.373
Total AUC	26.655	22.696	10.221	8.362	12.285	9.975	5.156	4.178	19.519	16.969	7.797	5.456
3 months	2.918	2.954	2.841	2.510	2.925	2.879	2.523	2.402	2.975	2.944	2.685	2.482
6 months	5.602	5.711	5.150	4.250	5.492	5.260	3.965	3.550	5.782	5.635	4.604	3.940
12 months	10.259	10.485	8.105	6.320	9.170	8.249	4.968	4.125	10.609	10.007	6.677	5.112
Exponential												
Lambda	0.034	0.037	0.092	0.120	0.064	0.083	0.182	0.226	0.039	0.049	0.116	0.172
Sum of least squares	52206.684	190203.562	154505.165	23968.083	111693.698	128704.563	49245.116	62211.221	172120.653	132745.088	33123.915	24551.487
Maximum least square	108.590	264.547	283.012	165.758	139.975	356.417	309.675	485.493	187.044	144.581	271.708	226.621
AUC 0 > last point	25.206	23.352	10.487	8.215	10.904	9.221	5.068	4.174	17.150	15.192	6.881	5.037
AUC tail	4.034	3.215	0.429	0.110	4.761	2.756	0.425	0.253	8.251	5.287	1.760	0.772
Total AUC	29.240	26.567	10.916	8.325	15.665	11.977	5.492	4.426	25.401	20.479	8.641	5.809
3 months	2.863	2.848	2.631	2.526	2.739	2.662	2.317	2.184	2.840	2.800	2.542	2.349
6 months	5.442	5.385	4.622	4.281	4.992	4.726	3.654	3.288	5.358	5.211	4.331	3.745
12 months	9.883	9.685	7.283	6.358	8.389	7.583	4.876	4.133	9.589	9.094	6.488	5.074
Gompertz												
Model parameter *s*	0.967	0.963	0.935	0.887	0.965	0.948	0.856	0.823	0.980	0.958	0.906	0.859
Model parameter *g*	1.000	1.000	0.982	1.000	0.981	0.984	0.992	0.995	0.982	1.000	0.998	0.997
Model parameter *c*	1.340	1.472	1.218	1.191	1.257	1.297	1.497	1.731	1.163	1.470	1.571	1.641
Sum of least squares	52207.064	190203.563	120678.230	23968.083	34491.786	67565.947	35617.619	45869.297	35367.478	71759.572	9221.542	13143.855
Maximum least square	108.490	264.558	154.492	165.760	84.003	204.222	254.662	390.556	51.990	113.639	72.938	187.927
AUC 0 > last point	25.211	23.351	9.770	8.215	11.017	9.247	4.980	4.067	17.377	15.231	6.919	5.035
AUC tail	4.037	3.215	0.000	0.110	0.269	0.117	0.006	0.000	0.464	0.090	0.104	0.051
Total AUC	29.247	26.566	9.770	8.325	11.286	9.364	4.986	4.067	17.842	15.320	7.024	5.085
3 months	2.863	2.848	2.656	2.526	2.779	2.712	2.367	2.251	2.854	2.822	2.593	2.397
6 months	5.442	5.385	4.774	4.281	5.204	4.947	3.792	3.441	5.495	5.293	4.489	3.871
12 months	9.883	9.685	7.718	6.358	8.949	8.058	4.920	4.066	10.148	9.366	6.670	5.045

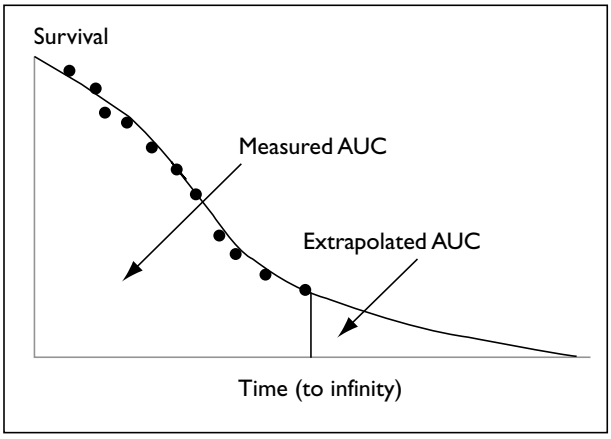

FIGURE 4 *Total AUC: estimated as the sum of the AUC directly measured within the trial (from zero through the last follow-up time point), plus the extrapolated tail of the AUC (from the last point of follow-up until infinity)*

at risk reported at time points on the graph, the standard error (SE) is:

$$\text{SE}\ (p) = p\sqrt{\frac{(1-p)}{r}}$$

Assuming that p will have approximately normal sampling distribution, the 95% CI can be calculated for p as:

$$p \pm 1.96\ \text{SE}(p)$$

Weibull curves (*Figures 5* and *6*) were then fitted to the interval end-points to estimate the curves at the CI limits.

Corresponding AUC estimates produced the values in *Tables 105* and *106*.

TABLE 105 *CI values based on the AUC estimates for the time to progression curves from Saltz and co-workers*[43]

Treatment	Central estimate	95% CI
Irinotecan + Mayo regimen	7.20	6.25 to 8.69
Mayo regimen	5.74	4.62 to 6.78

TABLE 106 *CI values based on the AUC estimates for the time to progression curves from de Gramont and colleagues*[30]

Treatment	Central estimate	95% CI
Oxaliplatin + de Gramont regimen	9.95	8.58 to 10.61
de Gramont regimen	7.25	6.08 to 7.62

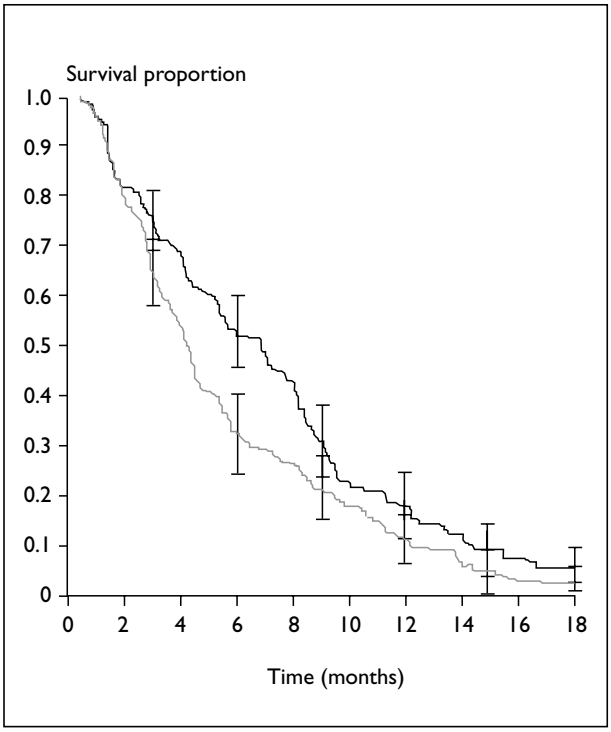

FIGURE 5 *Calculated 95% CIs for the time to progression curve for two treatment arms from Saltz and co-workers*[43] *(——, irinotecan plus Mayo regimen; ——, Mayo regimen)*

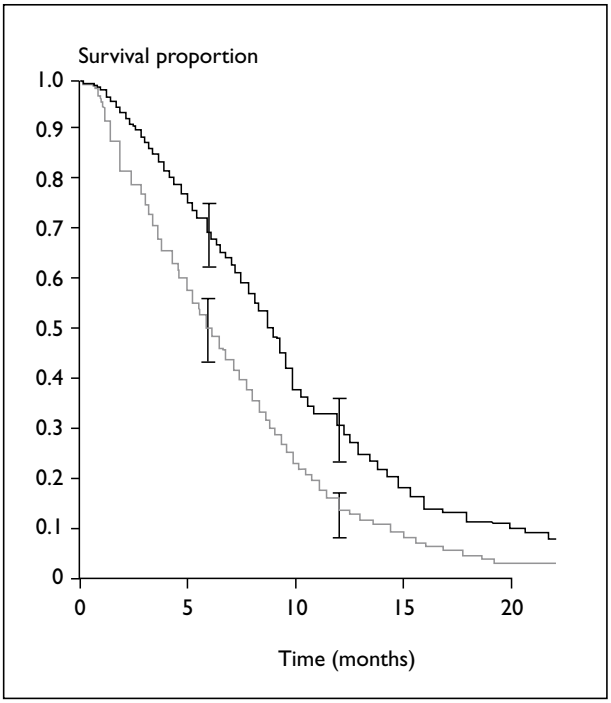

FIGURE 6 *Calculated 95% CIs for the time to progression curve for two treatment arms from de Gramont and colleagues*[30] *(——, de Gramont regimen; ——, de Gramont regimen plus oxaliplatin)*

Appendix 7

Costing assumptions

Inflation

All costs (*Table 107*) were inflated to the year 2000 using the Hospital and Community Health Service cost index until 1999, and the gross domestic product from 1999 to 2000.

Line insertion

The cost of line insertion was taken from Iveson and co-workers.[16] It was estimated assuming a half day of inpatient stay (costed for 1996/1997), doctor time and a chest X-ray. The cost was inflated to the year 2000 costs.

Pump

The cost of a pump was taken from Iveson and co-workers.[16] The weekly cost was estimated and includes the cost of pharmacist time.

Pharmacy costs

The pharmacy costs, including preparative time, labour, disposables and drug wastage, were taken from Summerhayes and colleagues.[70] High and low estimates are given for the pharmacy costs of the de Gramont, Mayo and raltitrexed regimens, depending on whether the drug is made up individually or in a batch. For the baseline cost estimate, an average is determined. It is assumed that the cost of oxaliplatin and irinotecan will be the same as that of raltitrexed. Therefore, the cost of the de Gramont regimen with either oxaliplatin or irinotecan is assumed to be the cost of the de Gramont regimen plus the cost of raltitrexed.

Administration costs

The costs of inpatient days and outpatient attendances were taken from Netten and co-workers.[66] The values are calculated from 1996/1997 costs. It is assumed that these costs include nursing time for the administration of chemotherapy. It should be noted that no costs are detailed for a medical oncology day case. When this cost was estimated by calculating the proportional cost of a generic day case (£66) compared with a generic inpatient day (£222) applied to the cost of a medical oncology inpatient day (£356), the resulting cost was £5 less than the cost of a medical oncology outpatient (£109). It was therefore assumed to be the same cost as an outpatient attendance.

Resource per cycle was assumed as follows:

- de Gramont regimen — 2 inpatient days
- Mayo regimen — 5 outpatient days
- raltitrexed — 1 outpatient day
- irinotecan plus 5FU (bolus) — 1 day attendance
- irinotecan plus 5FU (de Gramont regimen) — 2 inpatient days* (as de Gramont)
- oxaliplatin plus 5FU — 2 inpatient days (as de Gramont)
- irinotecan alone — 1 day attendance (as in Iveson and co-workers[16]).

Hospital admissions for adverse events

Three studies included data on hospitalisations: Schmitt and co-workers,[67] a retrospective case note study by Henry and colleagues,[61] and data from the de Gramont trial[30] that were included in the Sanofi submission.[21] The average number of hospital days per patient was estimated from the latter study, based on the estimated mean treatment time (from progression-free survival curve analysis).

The average number of days per patient while on treatment was almost identical for Henry and colleagues[61] and our estimate based on data from the de Gramont trial[30] (0.37 and 0.38 days, respectively). Schmitt and co-workers[67] reported 1.2 and 0.8 days for irinotecan and 5FU, respec-

* Also assumed in the Aventis submission[72]

TABLE 107 *Breakdown of treatment costs*

Drug	**Mayo regimen**		**de Gramont regimen**				**de Gramont regimen**		**de Gramont regimen**	
Study	**Saltz *et al.*, 2000[43]**		**Douillard *et al.*, 2000[31]**				**de Gramont *et al.*, 2000[30]**		**Rougier *et al.*, 1998[41]**	
Description of cycle	**Daily for 5 days every 4 weeks**		**Once weekly (unusual cycle)**		**Irinotecan with 5FU on day 1, then calcium folinate on days 1 and 2 every 2 weeks**		**Two consecutive days every 2 weeks**		**Two consecutive days every 2 weeks**	
Weeks in cycle	**4**		**1**		**2**		**2**		**2**	
Drugs in regimen	**5FU**	**FA**	**5FU**	**FA**	**5FU**	**FA**	**FA**	**5FU**	**FA**	**5FU**
Chemotherapy costs										
Dose/cycle (mg/m^2)	2125	100	2600	500	2000	400	400	2000	400	2000
Total dose/cycle (mg)	3718.75	175	4550	875	3500	700	700	3500	700	3500
Cost/cycle	£55.93	£53.45	£68.43	£267.25	£52.64	£213.80	£213.80	£52.64	£213.80	£52.64
Total cost/cycle	£109.38		£335.69		£266.44		£266.44		£266.44	
Protocol chemo-therapy cost/month	£118.49		£1454.53		£577.25		£577.25		£577.25	
Actual chemo-therapy cost/month	£101.90		£1309.07		£554.16		£513.75		£576.33	
Other costs			**Inpatient**	**Outpatient**	**Inpatient**	**Outpatient**	**Inpatient**	**Outpatient**	**Inpatient**	**Outpatient**
Inpatient days	£0.00		£1580.73	£0.00	£1580.73	£0.00	£1580.73	£0.00	£1580.73	£0.00
Outpatients days	£605.37		£0.00	£484.29	£0.00	£484.29	£0.00	£484.29	£0.00	£484.29
Pump	£0.00		£0.00	£275.49	£0.00	£137.74	£0.00	£137.74	£0.00	£137.74
Line insertion	£0.00		£0.00	£263.80	£0.00	£263.80	£0.00	£263.80	£0.00	£263.80
Drug costs	£10.24		£10.24		£10.24		£10.24		£10.24	
Consultations	£84.22		£84.22		£84.22		£84.22		£84.22	
	Low	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Low**	**High**
Adverse event	£116.31	£264.09	£116.31	£264.09	£116.31	£264.09	£116.31	£264.09	£116.31	£264.09
Tests	£3.33	£68.59	£3.33	£68.59	£3.33	£68.59	£3.33	£68.59	£3.33	£68.59
Primary care	£1.20	£10.99	£1.20	£10.99	£1.20	£10.99	£1.20	£10.99	£1.20	£10.99
Pharmacy costs	£44.58	£100.02	£37.04	£50.30	£37.04	£50.30	£37.04	£50.30	£37.04	£50.30
Low/high monthly costs	£967.15	£1245.41	£3143.14	£3379.22	£2388.23	£2624.31	£2347.82	£2583.90	£2410.40	£2646.48
Baseline monthly cost	£1106.28		£3261.18		£2506.27		£2465.86		£2528.44	
With de Gramont regimen given as outpatient (if relevant)			£2439.24		£1546.58		£1506.17		£1568.75	

continued

TABLE 107 contd *Breakdown of treatment costs*

Drug	OX + de Gramont regimen			IR + de Gramont regimen						IR + Mayo regimen			IR	
Study	de Gramont *et al.*, 2000[30]			Douillard *et al.*, 2000[31]						Saltz *et al.*, 2000[43]			Rougier *et al.*, 1998[41]	
Description of cycle	Two consecutive days every 2 weeks			Once weekly			IR with 5FU on day 1, then calcium folinate on days 1 and 2			Weekly for 4 weeks every 6 weeks			Once every 3 weeks days	
Weeks in cycle	2			1			2			6			3	
Drugs in regimen	OX	FA	5FU	IR	5FU	FA	IR	5FU	FA	IR	FA	5FU	IR	
Chemotherapy costs														
Dose/cycle (mg/m^2)	85	400	2000	80	2300	500	180	2000	400	500	80	2000	350	
Total dose/cycle (mg)	148.75	700	3500	140	4025	875	315	3500	700	875	140	3500	612.5	
Cost/cycle	£576.78	£213.80	£52.64	£213.85	£60.54	£267.25	£480.16	£52.64	£213.80	£1336.56	£42.76	£52.64	£935.59	
Total cost/cycle		£843.22			£541.64			£747.61			£1431.96		£935.59	
Protocol chemo-therapy cost/month		£1862.06			£2346.93			£1619.69			£1034.12		£1351.31	
Actual chemo-therapy cost/month		£1350.91			£1910.28			£1500.54			£743.93		£1278.38	
Other costs	**Inpatient**	**Outpatient**		**Inpatient**	**Outpatient**		**Inpatient**	**Outpatient**						
Inpatient days	£1580.73	£0.00		£1580.73	£0.00		£1580.73	£0.00			£0.00		£0.00	
Outpatients days	£0.00	£484.29		£0.00	£484.29		£0.00	£484.29			£322.88		£161.43	
Pump	£0.00	£137.74		£0.00	£275.49		£0.00	£137.74			£0.00		£0.00	
Line insertion	£0.00	£263.80		£0.00	£263.80		£0.00	£263.80			£0.00		£0.00	
Drug costs		£10.24			£10.24			£10.24			£10.24		£10.24	
Consultations		£84.22			£84.22			£84.22			£84.22		£84.22	
	Low	**High**		**Low**	**High**		**Low**	**High**		**Low**	**High**		**Low**	**High**
Adverse event	£116.31	£264.09		£116.31	£264.09		£116.31	£264.09		£116.31	£264.09		£116.31	£264.09
Tests	£3.33	£68.59		£3.33	£68.59		£3.33	£68.59		£3.33	£68.59		£3.33	£68.59
Primary care	£1.20	£10.99		£1.20	£10.99		£1.20	£10.99		£1.20	£10.99		£1.20	£10.99
Pharmacy costs	£50.75	£64.01		£50.75	£64.01		£50.75	£64.01		£32.92	£62.49		£4.57	£4.57
Low/high monthly costs	£3198.69	£3434.78		£3758.06	£4753.92		£3348.32	£4206.44		£1315.04	£1567.43		£1659.69	£1882.51
Baseline monthly cost		£3316.74			£3876.10			£3466.36			£1441.23		£1771.10	
With de Gramont regimen given as outpatient (if relevant)		£2357.04			£3054.15			£2506.67						

OX, oxaliplatin; IR, irinotecan

tively, although the difference is not significant. Sensitivity analysis was used to establish the effect of using the two different estimates. Both Schmitt and co-workers[67] and Sanofi[21] gave a split of hospital days between specialties. These values have been used to calculate an average cost per hospital day. The proportions are shown in *Table 108*.

Drug costs

Drug costs were estimated from Kerr and O'Connor,[1] taking an average of the raltitrexed and 5FU costs.

Cost of tests

Two estimates of the cost of tests were made. The first, from Kerr and O'Connor,[1] was calculated as the mean of the costs for the two treatment arms. Iveson and co-workers[16] showed the total costs of treatment, including beyond progression. The estimate was calculated from the mean cost of tests, divided by the mean treatment time. For this reason, it may be an overestimate.

Clinician consultations

The only data for which consultations were identified separately from chemotherapy administration are in the report by Iveson and co-workers.[16] The estimate was made as for tests and therefore will suffer from the same possible overestimation.

Primary care costs

Primary care costs were estimated from Kerr and O'Connor[1] and from Iveson and co-workers,[16] as previously described.

TABLE 108 *Average cost per hospital day based on proportions of days covered by various specialties*

Department	Proportion of hospital days, by specialty						Cost/hospital day
	Schmitt *et al.*, 1999[67]			de Gramont *et al.*, 2000[30]			Netten *et al.*, 1999[66]
	Irinotecan (*n* = 127)	5FU (*n* = 129)	Average	Oxaliplatin + 5FU (*n* = 210)	5FU (*n* = 210)	Average	
Medicine	51.5%	58.9%	55.2%	41.4%	15.1%	28.2%	£222
Oncology	21.7%	10.1%	15.9%	28.2%	47.6%	37.9%	£356
Surgery	19.3%	16.2%	17.8%	28.0%	32.7%	30.3%	£301
ICU	0.4%	0.4%	0.4%	2.5%	4.6%	3.5%	£359
Other	7.0%	14.2%	10.6%	0.0%	0.0%	0.0%	£222
Average cost			£257.54			£299.91	

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We look forward to hearing from you.

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