A Review of the Evidence for the Clinical and Cost Effectiveness of Capecitabine and Tegafur with Uracil for the Treatment of Metastatic Colorectal Cancer

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In order to share expertise on this work, we have set up a wider collaboration, InterTASC, with units in other regions. These are the Wessex Institute for Health Research and Development, Southampton University, The University of Birmingham Department of Public Health and Epidemiology, The Centre for Reviews and Dissemination, University of York.

CONTRIBUTIONS OF AUTHORS

Eva Kaltenthaler carried out the review of the background information and the clinical effectiveness review.

Sue Ward and Johanna Cowan carried out the cost effectiveness review.

Naomi Brewer undertook the electronic literature searches.

CONFLICTS OF INTEREST

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All responsibility for the contents of the report remains with the authors.

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The service evaluated in this review is the use of capecitabine and tegafur with uracil (UFT/LV) as first line treatments for patient with metastatic colorectal cancer.

Epidemiology

Colorectal cancer (cancers of the colon and rectum combined) accounts for 13% of all cancers in England and Wales and is the second most common cancer in the UK, after lung cancer. In 1997, 28,900 cases of colorectal cancer were diagnosed in England and Wales of which about two thirds were in the colon and one third in the rectum. Incidence increases with age. The median age of patients at diagnosis is just under 70 years of age.

Approximately 80% of patients with colorectal cancer undergo surgery and of these 40% will remain disease free in the long term. Approximately 20% of patients with colorectal cancer present with advanced disease and of these approximately 50% will have liver metastases. Median survival after diagnosis of metastatic disease is approximately six to nine months. Patients may have a variety of symptoms, both physical and psychological, which detract from their quality of life and often require hospital admission.

Colorectal cancer is a significant cause of premature mortality with 48% of deaths occurring in the under-75 age group. It is also a significant cause of morbidity. The main aims of treatment for patients with metastatic colorectal cancer are to relieve symptoms, increase survival and improve quality of life.

Number and Quality of Studies and Direction of Evidence

Two published randomised controlled trials (RCTs) of capecitabine, along with one separate report pooling data from the same two studies, met the inclusion criteria. These studies compared treatment with capecitabine to treatment with the Mayo clinic 5-fluorouracil (5-FU/LV) regimen. Duration of response, time to disease progression or death, time to treatment failure and overall survival were not found to be significantly different between the two treatments. Overall response rates, assessed by the investigator were significantly greater in both trials in the capecitabine group while overall response rates, as assessed by an independent review committee, were found to be significantly greater for the capecitabine group in one of the trials and pooled data. With regard to toxicity patients in the capecitabine group reported less diarrhoea, stomatitis, nausea and alopecia of all grades than those in the 5-FU/LV groups. Those in the capecitabine group also had significantly less grade 3/4 neutropenia and less frequent hospitalisation for adverse events. Hand-foot syndrome and grade 3 hyperbilirubinemia was significantly greater in the capecitabine group. Despite this improved toxicity profile, the reported health related quality of life did not differ significantly between the capecitabine and 5-FU/LV groups in either trial.

Two RCTs of treatment with UFT/LV met the inclusion criteria. One trial compared UFT/LV with the standard Mayo 5-FU/LV regimen while the other compared UFT/LV with a modification of the Mayo regimen. There were no significant differences with regard to overall response rates, duration of response or survival between UFT/LV and 5-FU/LV in either trial. Time to disease progression was significantly inferior for the UFT/LV group compared to the 5-FU/LV group in one study although there was no difference in time to disease progression between UFT/LV and 5-FU/LV in the second study. Treatment with UFT/LV was associated with significantly less diarrhoea, nausea/vomiting, mucositis, neutropenia and thrombocytopenia of all grades compared with 5-FU/LV in one study and fewer episodes of stomatitis/mucositis, neutropenia, thrombocytopenia and anaemia of any grade in the other study. With regard to grade 3/4 toxicity, mucositis, neutropenia, thrombocytopenia and anemia were significantly less frequent in the UFT/LV group in one study and grade 3/4 stomatits/mucositis and neutropenia were significantly less common in the second study. Significantly increased bilirubin was more common among UFT/LV patients than in those treated with 5-FU/LV in the first study. As with the capecitabine studies, despite this improved toxicity profile, reported health related quality of life did not differ significantly between the UFT/LV and 5-FU/LV groups in either trial.

Economic evidence reviewed in this analysis includes a pharmacoeconomic study of UFT costs in South America and two resource use studies, one relating to evidence from the Hoff capecitabine trial and the other to results from the UFT/LV trial by Carmichael. None of the evidence identified was directly applicable to the situation of England and Wales. Two sponsor submissions received by the National Institute for Clinical Excellence (NICE) from Roche and Bristol-Myers Squibb were also reviewed.

Summary of Benefits

There is good evidence to suggest that treatment with capecitabine improves overall response rates and has an improved adverse effect profile in comparison to 5-FU/LV treatment with the Mayo regimen, with the exception of hand-foot syndrome. There is no evidence comparing capecitabine with infusional 5-FU schedules such as the de Gramont or modified de Gramont regimens, both commonly used as standard treatment in the UK.

Time to disease progression or death after treatment with UFT/LV in one study appears to be shorter than after treatment with 5-FU/LV with the Mayo regimen. There is no evidence comparing UFT/LV with treatment with the de Gramont or modified de Gramont regimen. Treatment with UFT/LV appeared to have an improved adverse effect profile compared with 5-FU/LV treatment with the Mayo regimen.

Neither capecitabine nor UFT/LV appeared to improve health related quality of life. Information on patient preference was available for UFT/LV only from a small crossover trial. Patients appeared strongly to prefer treatment with UFT/LV over 5-FU/LV.

Costs

Costs were estimated through resource use data taken from the published trials and the

unpublished sponsor submissions. Unit costs were taken published sources, where available. The total cost of capecitabine and UFT/LV treatments were estimated at £2,111 and £3,375 respectively, compared with the total treatment cost for the Mayo regimen of £3,579. Cost estimates were also presented for the Modified de Gramont and inpatient de Gramont regimens. These were £ 3,684 and £ 6,155 respectively.

Cost-effectiveness

An economic evaluation was undertaken to compare the cost-effectiveness of capecitabine and UFT/LV with three intravenous 5-FU/LV regimens widely used in the UK: the Mayo, the Modified de Gramont regimen and the inpatient de Gramont regimen.

No survival advantage was shown in the RCTs of the oral drugs against the Mayo regimen. Cost minimisation analyses were therefore undertaken for both oral therapies against the Mayo regimen. Cost savings of capecitabine and UFT/LV over the Mayo regimen were estimated to be £1,461 and £209 respectively. Drug acquisition costs were higher for the oral therapies than for the Mayo regimen, but were offset by lower administration costs. Adverse event treatment costs were similar across the three regimens.

No direct evidence comparing either capecitabine or UFT/LV treatment with de Gramont regimens was identified and therefore an indirect comparison was undertaken for the purposes of economic evaluation. On the basis that no proven survival difference between the Mayo and the de Gramont regimens was identified, it was inferred that there was no survival difference between the oral drugs and the de Gramont regimens. Cost minimisation analyses of the oral therapies against the de Gramont regimens were performed. Cost savings of capecitabine and UFT/LV over the Modified de Gramont regimen were estimated to be £1,353 and £101 respectively. Cost savings of capecitabine and UFT/LV over the inpatient de Gramont regimen were estimated to be £4,123 and £2,870 respectively.

Cost effectiveness analyses were also undertaken, for illustrative purposes, to explore the impact of adopting an assumption of survival benefit of de Gramont regimens over the oral regimens. In addition infusional regimens have been shown to be more effective in terms of progression-free survival, tumour response and toxicity [19]. The impact of a potential difference in progression-free survival between the oral drugs and the infusional regimens was explored in terms of the impact on the cost per progression-free life year gained. The cost savings offered by the oral drugs, particularly in relation to MdG are not large. On the assumption that oral drugs compromise the progression-free survival of patients by an order of 1 to 2 months, oral drugs cannot necessarily be considered a cost effective option relative to the MdG regimen. Preliminary estimates are presented. However further direct evidence on the survival benefits and costs of oral therapies relative to infusional regimens is required

Conclusion

The results show that there are cost savings associated with the use of oral therapies. No survival difference has been proven between the oral drugs and the Mayo regimen. In addition no evidence of a survival difference between the Mayo regimen and the de Gramont regimens has been identified. However, improved progression-free survival and an improved adverse event profile have been shown for de Gramont regimen over the Mayo regimen and these need to be taken into consideration. These issues can only be indirectly addressed in the absence of direct randomised comparisons between the oral drugs and optimum infusional 5-FU regimens.

Need for Further Research

The following points have been identified as areas requiring further research:

- Quality of life data should be included in trials of colorectal cancer treatments. Well validated instruments should be used and this research should be conducted by independent researchers. It may be necessary to use more than one instrument in order to identify differences in quality of life and to identify the components of QoL that vary with different treatments.
- More research is needed to determine the place of effective oral treatments in the treatment of colorectal cancer. This should focus on when such treatments should be given alone and when they should be given in combination with other chemotherapeutic agents. Research is needed on the combination of oral agents with other chemotherapy agents (notably irinotecan and oxaliplatin) and novel agents.
- Some types of patients may benefit more from oral treatment than others. Research is needed to determine what safety mechanisms are needed in order to ensure compliance and the monitoring of adverse effects.
- The optimum duration of treatment needs to be determined for example, to disease progression, to response, to unacceptable toxicity or death. Intermittent treatment with a pause after 12 weeks for those with stable or responding disease also needs to be considered.
- The issue of patient preference must be given careful consideration in future trials and all trials should incorporate the measurement of patient preference.
- In order to make a precise estimate of the cost-effectiveness of capecitabine versus modified de Gramont treatment, a phase III comparative trial would be necessary to determine whether there was any survival advantage and to collate the necessary economic data. This would also give clinicians clear information on survival to present to patients who can then make an informed choice with regard to treatment.

LIST OF ABBREVIATIONS

5-FU	5-Fluorouracil
AIO	Arbeitsgemeinschaft Internische Onkologie
AUC	Area under the curve
BMS	Bristol-Myers Squibb
BNF	British National Formulary
Ci	continuous infusion
CI	Confidence interval
DARE	Database of Abstracts of Reviews of Effectiveness
DPD	dihydropyrimidine dehydrogenase
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
FA	Folinic acid (leucovorin, calcium folinate)
FDA	Food and Drug Administration
FLIC	Functional Living Index-Cancer
HEED	Health Economics Database
HRG	Health Resource Group
HTA	Health Technology Assessment
IRC	Independent Review Committee
ITT	intention to treat
IV	intravenous
LV	leucovorin (folinic acid, calcium folinate)
LYG	life-year gained
MdG	modified de Gramont
MRC	Medical Research Council
NCCTG	National Colorectal Cancer Treatment Group
NICE	National Institute of Clinical Excellence
NS	not significant
PSSRU	Personal and Social Services Research Unit
QoL	quality of life
UFT	Uftoral®

DEFINITION OF TERMS

Adjuvant chemotherapy: chemotherapy given after apparently curative surgery to increase the chance of cure.

Advanced disease: cancer which has spread either locally or to distant sites such that a curative complete resection cannot be performed.

Cost effectiveness: measures the net cost of providing a service as well as the outcomes obtained.

Cost minimisation: if health effects are known to be equal, only costs are analysed and the least costly alternative is chosen

Duration of response: period from first day of treatment until the date progressive disease was first noted.

Failure-free survival: the length of time from the start of treatment to either the first evidence of disease progression, unacceptable toxicity or death

First-line treatment: treatment of patients for advanced disease who have not previously received chemotherapy for advanced disease (but may have received previous adjuvant therapy)

Friction-cost method: a valuation of work time lost based on the assumption that in short period of illnesses (a friction period) the productivity losses associated with the loss of a single worker are less than the productivity of that worker had she/he been able to work.

Progression-free survival: the length of time from the start of treatment to either the first evidence of disease progression or death

Response rate: see Appendix 1

Second-line treatment: treatment of patients who have previously received chemotherapy for advanced disease

Time to progression: from date of randomisation to the first recorded observation of progressive disease or the occurrence of death from any cause

Time to treatment failure: as for time to disease progression but additionally including toxicity-related premature withdrawals, failure to return and treatment refusals as events

1. AIM OF THE REVIEW

The overall aim of this review is to evaluate the clinical and cost effectiveness of capecitabine and tegafur with uracil as first-line treatments for patients with metastatic colorectal cancer, as compared with 5-FU/FA regimens. It reviews these drugs in relation to their licensed indications. Capecitabine is indicated for first-line monotherapy for metastatic colorectal cancer. Tegafur with uracil is indicated for first-line treatment of metastatic colorectal cancer in combination with calcium folinate. This review does not consider the use of chemotherapy in an adjuvant setting nor the use of these drugs in combination with other chemotherapy agents or as second-line treatment.

The review focuses not only on differences between treatment in overall survival and disease progression rates as there is a need to consider changes in quality of life associated with new drug treatment. The review therefore includes any significant impacts that such treatments may have on health related quality of life.

Progression-free survival is considered to be a particularly important outcome measure in relation to the treatment of metastatic colorectal cancer because disease progression may impair both physical and emotional health. However, progression may only become a problem when symptoms develop. Tumour response (see **Appendix 1**) does not necessarily correspond to subjective benefit in terms of quality of survival, and subjective improvement (a clinical response) is possible without an objective response. If survival advantage is only modest compared with that provided by alternative regimens, 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 clinical effectiveness of the two drugs in terms of disease progression rates, tumour response and time to treatment failure
2. to estimate their effects on overall survival, progression-free survival and quality-of-life adjusted survival
3. to evaluate their adverse-effect profiles and toxicities
4. to estimate the incremental cost effectiveness of the drugs in comparison to conventional therapy
5. to estimate the possible overall cost of these drugs in England and Wales

In undertaking to achieve the above aims the review also considers factors such as patient preference and compliance to treatment. Issues associated with routinely used IV agents will be considered, such as complications from catheter use.

2. BACKGROUND

2.1 DESCRIPTION OF UNDERLYING HEALTH PROBLEM

2.1.1 Epidemiology of colorectal cancer

Colorectal cancer (cancers of the colon and rectum combined) accounts for 13% of all cancers in England and Wales.[1] It is the second most common cancer in the UK after lung cancer. In 1997, 28,900 cases of colorectal cancer were diagnosed in England and Wales of which about two thirds were in the colon and one third were in the rectum.[1] Males are more frequently affected than females with an age-standardised male: female ratio of 1.5:1[1] although some studies suggest that incidence rates for males and females may be similar.[2] The incidence rate per 100,000 (all ages) is 53.5 for men and 36.7 for women.[3] Incidence increases continuously with age in both sexes for both colon and rectal cancers.[1] The median age of patients at diagnosis is just under 70 years.[4]

Risk factors for colorectal cancer are thought to include diets high in fats and animal proteins and low in fruit and vegetables and fibre. Other risk factors associated with developing colon cancer are lack of physical activity and family history of the disease. There is some evidence that colon cancer in women may be related to sex hormones or reproductive history. The risk of developing colorectal cancer is also raised for patients with one or more adenomatous polyps as occurs in familial adenomatous polposis and other hereditary conditions. The incidence of colorectal cancer is three to four times greater in developed countries than in developing countries.[1] At present there are no established screening services for the general population.[4]

Death rates for England and Wales for 1998 are illustrated in Table 1.

Table 1 Death Rates for Colorectal Cancer in England and Wales in 1998[5]

Age	0-44	45-64	65-74	75+	Total
Deaths	203	2783	4132	7866	14984
Rate per 100,000 population	0.6	23.0	93.9	202.3	28.6

Large differences in survival exist according to the stage of disease.[2] The overall 5-year survival rate in England is 35%, however within Britain, there is evidence of wide variations in treatment and outcomes.[3] Table 2 shows the Modified Dukes' Staging of Colorectal Cancer with five-year survival.

Table 2 Modified Dukes' Staging of Colorectal Cancer, with Five-year Survival*[3]

Dukes' Stage (modified)	Definition	Approximate frequency at diagnosis	5-year survival
A	Cancer localised within bowel wall	11%	83%
B	Cancer which penetrates the bowel wall	35%	64%
C	Cancer spread to the lymph nodes	26%	38%
D	Cancer with distant metastases (most often in the liver)	29%	3%

*Data from St. Vincent's Hospital, Dublin. These figures are illustrative only, since stage frequency and survival statistics vary between published series from different centres.

On average, patients survive for three years after diagnosis.[4] Median survival after diagnosis of metastatic disease is approximately six to nine months. The five-year survival rate for advanced colorectal cancer is lower than 5%.[6] Patients may develop a variety of symptoms during this time both physical and psychological.[7] In about 20% of cases of colorectal cancer, patients present with advanced disease and of these approximately 50% will have liver metastasis.[6]

2.1.2 Significance in Terms of Ill-health

Colorectal cancer is a significant cause of premature death with 48% of deaths occurring in the under-75 age group. It is also a significant cause of morbidity. When treating patients with metastatic colorectal cancer, the main aims of treatment are to relieve symptoms, increase survival and improve quality of life. Individual patient preferences for treatment are also important to consider.

There is some evidence that extended survival is not always associated with an overall improvement in quality of life. The treatments assessed in this report provide palliative care and offer no real chance of long-term survival. For this reason information regarding health-related quality of life, particularly that associated with treatment related toxicity will be given careful consideration. Since chemotherapy can cause disabling adverse effects, assessing quality of life outcomes is essential.

2.2 CURRENT SERVICE PROVISION

2.2.1 Current Service Provision

The NHS Executive document "Improving Outcomes in Colorectal Cancer" outlines current service provision for the diagnosis, treatment and follow-up of patients with colorectal cancer.[4] Approximately 80% of patients with colorectal cancer undergo surgery[3] and chemotherapy is used as an adjuvant treatment after surgery to improve survival.[3] About 50% of patients treated with curative surgery will go on to develop

advanced disease and of those with advanced disease 50% will present with liver metastasis.[6]

Once metastatic disease develops, curative treatment is rarely possible. Resection of liver metastases produces occasional cures in cases where there is no evidence of extra-hepatic disease and the position and size of the metastases is favourable; similarly resection of isolated lung metastases may be worthwhile. However for the large majority of patients, treatment is aimed at modest extension of survival with palliation of symptoms. In this situation, chemotherapy is the principle active treatment, although palliative radiotherapy and surgery have a role for some patients with localised symptoms.

There is clear evidence that chemotherapy improves survival and prolongs time to disease progression in patients with advanced colorectal cancer.[8,9,10] Chemotherapy delays the occurrence or progression of symptoms by about six months and improves symptoms, weight gain and functional performance in about 40% of patients.[6] However, patients must be sufficiently fit to receive chemotherapy. Referral patterns and treatment policies for patients with advanced colorectal cancer vary widely in the United Kingdom.[6]

5-Fluorouracil (5-FU) has been the main treatment for advanced colorectal cancer for over forty years, usually in combination with calcium folinate (calcium leucovorin, leucovorin, folinic acid). Fluorouracil is a prodrug which is converted intracellularly into metabolites that inhibit the enzyme thymidylate synthase. This prevents DNA synthesis and inhibits RNA and protein synthesis.[11] 5-fluorouracil is usually given as a bolus IV injection or via infusion as it has erratic oral bioavailability.[11] The addition of calcium folinate enhances response rates.[12]

Trials comparing chemotherapy given immediately on diagnosis of advanced or recurrent disease with chemotherapy for the palliation of symptoms have shown that early chemotherapy increases median survival and that symptom-free survival increases from a median of two months to ten months ($P<0.001$).[3]

2.2.2 5-FU regimens

A variety of 5-FU based regimens are currently in use in the United Kingdom. Details of these 5-FU regimens are listed in **Appendix 2**, mainly bolus injection or continuous infusion. Bolus regimens typically require frequent hospital visits. Continuous infusion regimens require placement of a venous access device, the use of a portable infusion pump and intravenous infusion supplies.[13] The use of infusional regimens is frequently associated with complications such as infections and thromboses,[14] while bleeding and pneumothorax occur rarely.

Internationally, the most commonly used bolus regimen is the so-called Mayo Clinic or National Colorectal Cancer Treatment Group (NCCTG) schedule and this is also the most frequently used comparator in clinical trials. It is not used as frequently in the UK as in

the past and its use as a comparator in clinical trials is a reflection of current practice in the US rather than in the UK.

A meta-analysis comparing continuous infusion of 5-FU with bolus administration found that continuous infusion administration was superior in terms of tumour response and resulted in a slight increase in overall survival.[15,16] The results of the meta-analysis are presented in detail in **Appendix 3**.

The three infusional regimens currently in use in the UK are the Lokich, the de Gramont and the modified de Gramont, with the de Gramont and modified de Gramont being more frequently used. A randomised trial comparing the de Gramont regimen with the Mayo bolus regimen found the de Gramont regimen to have significantly better response rates and progression-free survival than the Mayo regimen and equivalent median survival times.[17] Grade 3-4 toxicities also occurred in more patients in the Mayo regimen than in the de Gramont. The results of this trial are presented in detail in **Appendix 4**.

The de Gramont has been demonstrated to be equivalent to the Lokich infusional regimen in terms of survival, quality of life and response rates, although the Lokich regimen was associated with more central line complications and hand-foot syndrome[18] (palmar-plantar erythrodysasthesia) which causes unpleasant and painful reddening of the soles of the feet and palms of the hands.

Response rates, progression free survival and median overall survival for the de Gramont regimen have been reported in comparisons of this regimen with other treatment regimens.[19,20] The range of reported response rates, progression free survival and overall median survival for the de Gramont regimen from four studies are reported in **Appendix 5.** It is difficult to compare results of different studies for several reasons apart from the fact that they use different comparators. Some studies report intention to treat analyses while others use per protocol analyses. In one study, de Gramont[17] only included patients with measurable lesions in the response rate analyses in both arms of the trial. Some values have been assessed by the investigators themselves while others have used independent assessors. Finally, the studies were designed to use different primary outcome measures and are therefore not directly comparable. However, the figures reported in Appendix 5 give an overall picture of the range of values reported in these studies.

The de Gramont regimen is repeated every 14 days. It can be administered on an inpatient or outpatient basis. A modified de Gramont regimen has been developed whereby LV and bolus 5-FU are given only on the first day of treatment, followed by a higher dose 5-FU infusion over 46 hours. This requires the insertion of a central line as a day-case procedure, thus enabling 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 dose-escalation study was used to confirm the activity of this regimen and to establish the optimum dose.[21] 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 in-patient de Gramont regimen.[22] However,

for any regimen which uses indwelling venous lines, the line itself may present significant problems. For example, a report from the Royal Marsden Hospital has indicated that 11% of Hickman lines used for protracted venous infusion 5-FU have to be removed unplanned, most commonly because of superficial infection, pain, line slippage, septicaemia or thrombosis.[23]

Approximately 60% of patients who receive first-line 5-FU/LV therapy have a response or a period of stable disease. This is however temporary and drug resistance develops. About 40% of patients have disease that does not respond to 5-FU. Second-line treatments may then be used. Recently the National Institute of Clinical Excellence recommended that irinotecan monotherapy may be used as second line treatment for patients who have failed an established 5-FU containing treatment regimen.[24]

2.2.3 Combination therapies

Recently interest has centred on the possibility of combining drugs with different mechanisms to treat colorectal cancer. Several RCTs have demonstrated that combination chemotherapy with 5-FU/LV and either oxaliplatin or irinotecan produces a higher response rate, longer time to progression and in some cases better overall survival than 5-FU/LV alone.[21,20] A current MRC trial (CR08; FOCUS) is further examining these combinations, comparing their effect on overall survival and quality of life when used as routine first-line therapy for all patients, or as planned second-line therapy after an initial trial of 5-FU/LV alone. This trial is expected to report in 2004; meanwhile the National Institute of Clinical Excellence (NICE) has recommended that oxaliplatin/5-FU/LV should be considered for patients with metastases that are confined to the liver and may become respectable following treatment.[24]

2.2.4 Variation in services

Patterns for referral vary widely throughout the country. Performance status will have a bearing on whether or not a patient is eligible for chemotherapy. Those with a poor performance status (3 or 4 on the WHO Performance Scale) are not able to benefit from chemotherapy. Therefore many patients, particularly elderly patients, are managed in the primary care setting.

There is no clear evidence as to which 5-FU regimen is most frequently used in the UK. As the de Gramont regimen was recently found to be superior[17] to the Mayo regimen, more clinicians are now using this regimen or the modified de Gramont. Treatment regimen may also vary depending on where patients would like to be treated. As the de Gramont regimen is relatively expensive, some centres may not use it.[7]

2.2.5 Current Service Cost

The care and treatment of patients with colorectal cancer in the UK has been estimated to account for approximately 2% of all bed days and for between 10% and 20% of all palliative care provision.[25]

2.3 DESCRIPTION OF NEW INTERVENTION

Two new drugs, capecitabine and tegafur with uracil, have been proposed for first-line treatment of patients with metastatic colorectal cancer. They will be discussed separately below. Both drugs are administered orally.

2.3.1 Summary of Product Characteristics

(a)Capecitabine (Roche)
Capecitabine (*N*-[1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1.2-dihydro-2-oxo-4-pyrimidinyl]-m-pentyl carbamate; Ro 09-197) is a cytotoxic fluoropyrimidine carbamate. It is an oral 5-FU pro-drug with no anti-tumour activity itself.[26] It is metabolised in the body via three sequential enzyme steps to produce 5-FU within tumours. Capecitabine is preferentially activated in tumour tissue.[13]

The UK licence for capecitabine is held by Roche and it is marketed as Xeloda®. Xeloda® is available as blisters of film-coated tablets in two sizes: 60 x 150 mg (6 blisters of 10 tablets) and 120 x 500 mg (12 blisters of 10 tablets).

Xeloda® is indicated for first-line monotherapy of metastatic colorectal cancer. It is also used in the treatment of advanced or metastatic breast cancer.

The recommended dose is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to 2500 mg/ m^2 total daily dose) for 14 days followed by a seven day rest period.[27]

Xeloda® is contraindicated in patients with:

- a history of severe and unexpected reactions to fluoropyrimidine therapy
- known hypersensitivity to capecitabine, fluorouracil or any of the excipients
- known dihydropyrimidine dehydrogenase (DPD) deficiency
- pregnancy and lactation
- severe leucopenia, neutropenia or thrombocytopenia
- severe hepatic impairment
- severe renal impairment (creatinine clearance below 30 ml/min)
- treatment with sorivudine or its chemically related analogues, such as brivudine

(b) Tegafur with uracil (UFT) (Bristol-Myers Squibb Company)

Tegafur (FT; ftorafur; 1-[tetrahydro-2-furanyl]-5-fluorouracil) is a furanyl nucleoside analog of FudR.[28] Tegafur is a prodrug of fluorouracil and the addition of uracil inhibits the degradation of 5-fluorouracil. Early clinical trials of UFT were conducted in Japan,[29] where it has been licensed for use since 1983 and has been used to treat a variety of solid tumours.[30] The addition of leucovorin (calcium folinate) acts as a modulator and leads to an improvement in response rates.[28] although this has also been shown to increase toxicity.[31] UFT/LV has been approved for use in the European Union.[32]

The UK licence for UFT is held by Bristol-Myers Squibb and it is marketed as Uftoral®. Uftoral® is available as hard, white opaque capsules imprinted with the code TC434. Each capsule contains tegafur (100 mg) plus uracil (224 mg). Uftoral® is indicated as first-line treatment of metastatic colorectal cancer, in combination with calcium folinate in adults.

The recommended dose of Uftoral® is tegafur 300 mg/m^2 (with uracil 672 mg/ m^2) daily, combined with 90 mg/day oral calcium folinate, given in three divided doses (preferably every 8 hours) for 28 days with subsequent courses repeated after 7 day intervals giving a treatment cycle of 35 days.[27]

Uftoral® is contraindicated in patients who

- have a known hypersensitivity to 5-FU, tegafur, uracil or any of the excipients
- are pregnant or attempting to become pregnant
- are breastfeeding
- are adolescents, children or infants
- have severe hepatic impairment
- present with evidence of bone marrow suppression from previous radiotherapy or antineoplastic agents
- have a known deficiency of hepatic CYP2A6

2.3.2 Identification of patients

These treatments would only be suitable for patients able to self medicate or who live with someone able to undertake a supervisory role.

2.3.3 Criteria for treatment

These interventions, capecitabine and UFT/LV, would be used mainly by people with a WHO performance status of 2 or less (see **Appendix 6**).

These treatments would most likely be supplied in a dedicated oncology centres with consultant oncologist supervision. Support for home use of these drugs would be needed via a call centre or visits from trained nurses.

2.3.4 Degree of diffusion

Both capecitabine and UFT/LV are already in use as first-line treatment for metastatic colorectal cancer but the full extent of use is not known. The use of these drugs is frequently within the context of clinical trials. There is significant usage of these agents in private practise and some usage in NHS practise whenever a reason for avoidance of a central line can be substantiated.

3. EFFECTIVENESS

3.1 METHODS FOR REVIEWING EFFECTIVENESS

3.1.1 Identification of studies

The search strategy aimed to identify all literature relating to the clinical and cost effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer. The main searches were conducted in April and May 2002.

Fifteen electronic bibliographic databases were searched, covering biomedical, science, social science, health economic and grey literature. A list of databases is provided in **Appendix 7.1**.

In addition, the reference lists of relevant articles and sponsor submissions were hand-searched and various health services research related resources were consulted via the Internet. These included health economics and HTA organisations, guideline producing agencies, generic research and trials registers, and specialist sites. A list of these additional sources is given in **Appendix 7.2**. Citation searches were conducted on key papers and authors using the Science and Social Science Citation Index facilities.

A combination of free-text and thesaurus terms were used. 'Population' search terms (*e.g.* colorectal, colon, rectum, neoplasm, carcinoma, adenocarcinoma, *etc*.) were combined with 'intervention' terms (*e.g.* Capecitabine, Xeloda, Fluoropyrimidine, tegafur, uftoral, *etc*.). Three searches were performed in Medline, the first was the main Medline search, the second was for the epidemiology of colorectal cancer, and the third search was performed to identify further references specifically on the two 5-Fluorouracil regimens (de Gramont and Mayo Clinic). Copies of the search strategies used in the major databases are included in **Appendix 7.3**.

No language or date restrictions were applied to the searches. The search performed in Medline for the epidemiology of colorectal cancer was limited to 1990-present to ensure that only recent data were reviewed. No language or study/publication type restrictions were applied to the main searches. An economic evaluations filter was used in the main searches performed in Medline and Embase to assist with the identification of articles for the cost effectiveness aspect of the review (refer to **Appendix 7.4**).

3.1.2 Inclusion and exclusion criteria

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

Inclusion Criteria
Subjects: adults with metastatic colorectal cancer
Intervention: capecitabine or UFT/LV used alone as first-line treatment

Comparators: 5-FU/LV regimens for metastatic colorectal cancer
Outcome measures to include the following:

- survival rates
- progression-free survival
- tumour response
- time to treatment failure
- health-related quality of life
- adverse events
- patient preference
- compliance
- cost

Methodology, to include at least one of the following:

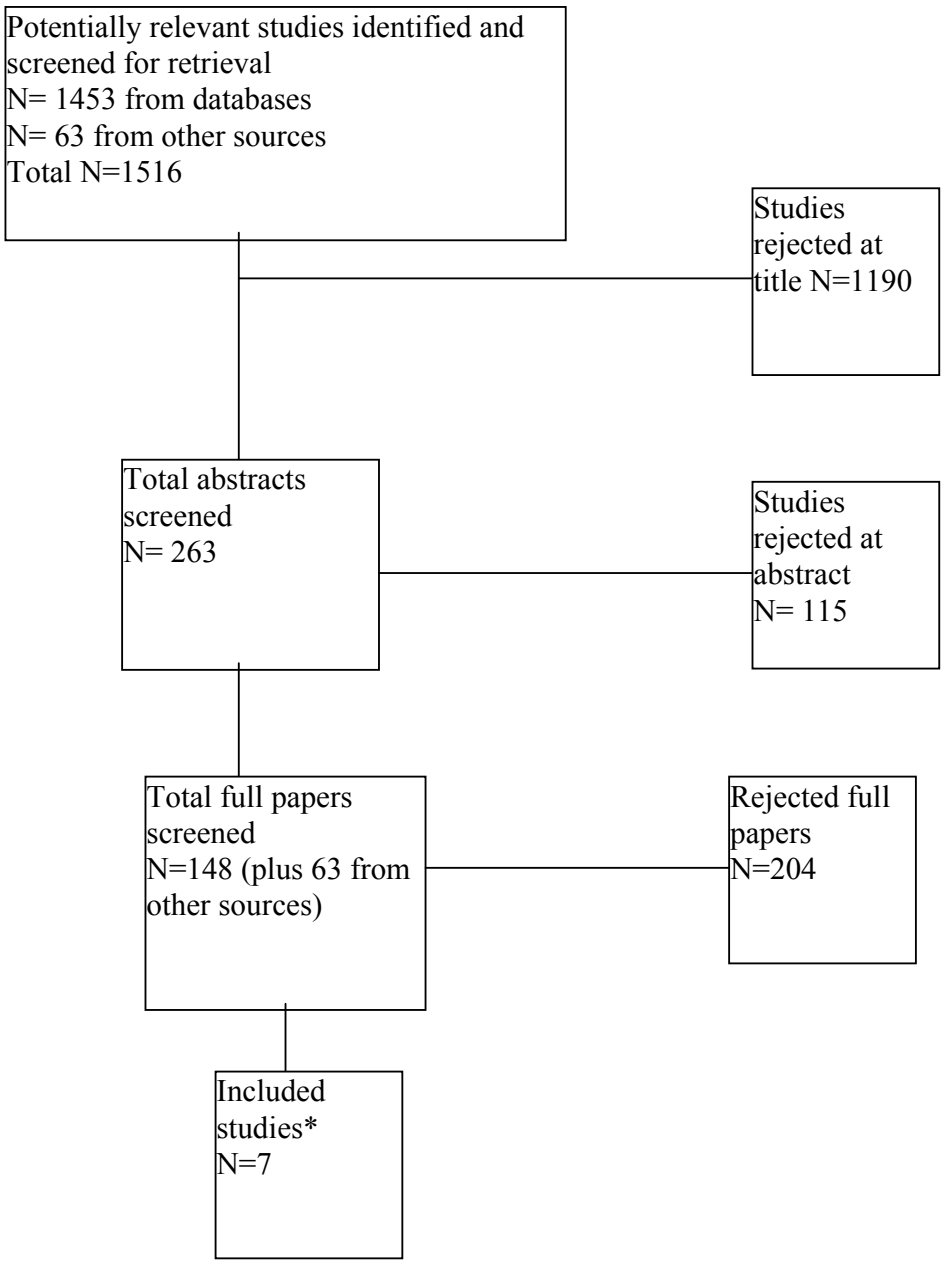
- systematic reviews or meta-analyses
- randomised controlled trials
- non-randomised studies (for outcomes where no data from randomised controlled trials are available)
- economic evaluations

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

Exclusion Criteria
Papers describing the use of chemotherapy in an adjuvant setting were excluded. Papers describing randomised phase II trials were excluded where phase III evidence was available.

Figure 1 shows a summary of study selection and exclusion.

Figure 1. Summary of flow of study selection and exclusion: clinical effectiveness



*These studies refer to papers of trials of capecitabine and UFT/LV. Other papers are included in this report dealing with background information, patient preference, quality of life and toxicity. Studies used in the cost effectiveness analysis are listed in chapter 4 of this review.

3.1.3 Quality assessment strategy

The randomised controlled trials were assessed for quality using the Jadad criteria.[33] Other criteria were used to assess the quality of the meta-analyses[34] and non-randomised studies.[35]

3.1.4 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 the two interventions. Where available, the following data will be reviewed in relation to each intervention:

- duration of treatment
- progression free survival
- overall survival
- tumour response rates
- time to progression or death
- duration of response
- treatment-related deaths
- grade 1-4 toxicities
- quality of life
- patient preference

No meta-analyses of the capecitabine trials were identified, although a study of pooled data was identified.[36] No meta-analyses of the UFT/LV trials were identified or undertaken. The two trials used different 5-FU regimens as well as different dosages of calcium folinate (leucovorin). Meta-analysis was therefore felt to be inappropriate.

3.1.4.1 Choice of outcomes

As described above, a variety of endpoints form part of the data extracted from the relevant trials in this review. Relevant endpoints in evaluating treatments for colorectal cancer include tumour response rates, progression free survival and overall survival. However it is not clear how these outcomes relate to each other and which if any are most important. In a meta-analysis of 25 randomised trials of first-line treatment comparing standard bolus 5-FU treatment with a variety of experimental fluoropyrimidines, the authors concluded that an increase in tumour response rates translated into an increase in overall survival. However, it was emphasised that knowledge that a treatment improves tumour response rates does not necessarily accurately predict benefit with regard to overall survival.[37]

In another study, Louvet et al[38] suggest that progression free survival, rather than overall survival is the most appropriate primary endpoint for interpreting effectiveness in studies of metastatic colorectal cancer treatments. They analysed data from 29 phase III trials

and found significant correlations between progression free survival and response rates, between response rates and overall survival and between progression free survival and overall survival. The strongest correlation was between response rates and progression free survival.

Progression free survival reflects the effectiveness of the first-line treatment while overall survival reflects the effectiveness of first-line treatment as well as any second-line treatment used. When comparing treatments where overall survival is equivalent, the use of other endpoints is even more important than treatments resulting in different survival times. These endpoints include response rates, time to disease progression, tolerability and patients' convenience.[39] Because of the uncertainties surrounding choice of outcome measure, all outcomes reported in the trials are included in this review.

3.2 RESULTS

Two large phase III RCTs[40,41] and one study of pooled data of capecitabine[36] were identified. The evidence from these trials is summarised below in section 3.2.1. No phase III RCTs of capecitabine were excluded from the review.

Two large phase III RCTs of UFT/LV were identified.[42,43] The results of these trials, together with supplementary information are summarised below in section 3.2.2. No phase III RCTs of UFT/LV were excluded from the review.

Information on quality of life and patient preference is presented separately within the relevant sections.

3.2.1 QUANTITY AND QUALITY OF RESEARCH AVAILABLE: CAPECITABINE

Capecitabine is licensed for use as first-line treatment as monotherapy for patients with metastatic colorectal cancer. It is also licensed for use in the treatment of advanced or metastatic breast cancer. This review will deal only with its use in the treatment of metastatic colorectal cancer.

Three studies have been identified which deal with the use of capecitabine as first-line treatment for metastatic colorectal cancer, two RCTs[40,41] and study of pooled data from these two RCTs.[36] The capecitabine studies included in this review are listed in Table 3.

These studies relate to comparisons between treatment with capecitabine and an IV 5-FU regimen (Mayo). The two RCTs[40,41] were designed with identical protocols to facilitate pooling of the data. The third study[36] shows the pooled data from these two trials.

Table 3. Capecitabine studies included in the review

Study	Study site	Comparators, dosage and procedure	Type of study	Numbers randomised	Funding
Hoff et al, 2001[40]	61 centres in USA, Canada, Brazil and Mexico	Capecitabine 1,250 mg/m^2 twice daily in 3-week cycles (2 weeks of treatment followed by a 1 week rest period). 5-FU/LV in Mayo clinic regimen: rapid IV injection of 20 mg/m^2 LV followed by an iv bolus injection of 425 mg/m^2 5-FU daily, days 1 to 5 every 4 weeks.	Open label, phase III RCT	Capecitabine n=302 5-FU/LV n=303	Hoffman-LaRoche
Van Cutsem, 2001[41]	59 centres in Europe, Australia, New Zealand, Taiwan and Israel	Capecitabine 1,250 mg/m^2 twice daily in 3-week cycles (2 weeks of treatment followed by a 1 week rest period). 5-FU/LV in Mayo clinic regimen: rapid iv injection of 20 mg/m^2 LV followed by an iv bolus injection of 425 mg/m^2 5-FU daily, days 1 to 5 every 4 weeks.	Open label, phase III RCT	Capecitabine n=301 5-FU/LV n=301	Hoffman-LaRoche
Twelves, 2002[36]	120 centres (Pooled results of above two trials)	As above	Pooled data from above two phase III trials	Capecitabine n= 603 5-FU/LV n= 604	Not reported

3.2.1.1 Study characteristics of included capecitabine studies

Tables 4 and 5 illustrate study design and patient details respectively. As stated previously the RCTs were designed to identical protocols. Therefore the inclusion/exclusion criteria, outlined in Table 4 were identical. Both RCTs were adequately powered to demonstrate at least equivalence in overall response rates. Apart from alkaline phosphatase levels in the Hoff study,[40] there was baseline comparability between the two groups in both RCTs. Baseline levels of serum alkaline phosphatase were significantly elevated in the capecitabine group compared to the 5-FU/LV group, indicating that the 5-FU/LV patients were of an inherently better prognosis.

Table 5 describes the patient details of the capecitabine studies. For information on the Karnofsky performance score see Appendix 6. The primary tumour site was the colon in the majority of patients treated with either capecitabine or 5-FU/LV and the most common site of metastasis was the liver.

Table 4. Study design: capecitabine

Study	Length of study	Inclusion criteria	Exclusion criteria	Power calculation	Baseline comparability
Hoff et al, 2001[40]	Assessments performed up to 30 weeks for most patients and 48 weeks for those receiving prolonged therapy.	Patients with advanced or metastatic disease and no previous chemotherapy for metastatic disease. Adjuvant chemotherapy completed at least 6 months before trial enrolment; histological or cytological confirmation of colorectal adenocarcinoma was required as well as at least one bidimensionally measurable indicator lesion that had not been irradiated; at least 18 years of age; Karnofsky performance status ≥ 70%; life expectance of at least 3 months	Pregnancy or lactation, hypersensitivity to 5-FU or had previous severe reaction to fluoropyrimidines, history of other cancer within previous 5 years (except for cured basal cell carcinoma of the skin or in situ cervical carcinoma), experimental drugs or radiotherapy within 4 weeks before enrolment or not fully recovered from recent major surgery; patients with organ allografts; CNS involvement of their disease, neurological or psychiatric disorders to interfere with treatment compliance, significant cardiac disease or MI in last 12 months; serious uncontrolled infections; malabsorption syndrome, lack of physical integrity of the upper gastrointestinal tract; abnormalities in neutrophils, platelets, serum creatinine or serum bilirubin, ALT, AST or alkaline phosphatase (5 times upper normal limit for ALT, AST and alkaline phosphatase allowed for those with liver metastes and 10 times alkaline phosphatase for patients with bone metasteses).	Sample size was sufficient to achieve 80% power to demonstrate at least equivalence in overall response rates`	Yes apart from serum alkaline phosphatase concentrations at baseline (significantly higher in capecitabine group compared to 5-FU/LV group, $p<0.0025$)
Van Cutsem, 2001[41]	As above	As above	As above	As above	Yes
Twelves 2002[36]	As above	As above	As above	As above	Yes

Table 5. Patient details: capecitabine **Study**

	Sex (M/F)	Age	Performance score	Primary site	Sites of metastasis
Hoff et al, 2001[40]	Capecitabine: 181/121 5-FU/LV: 197/106	*Median (range)* Capecitabine 64.0 (23-86) 5-FU/LV 63.0 (24-87)	*Karnofsky performance score* **Cap** **5-FU/LV** Mean 88.3 88.5 SD 10.0 9.8 Median 90 90 Range 70-100 70-100	*Site of primary tumour (%)* **Cap** **5-FU/LV** Colon 222 (73.5) 232 (76.6) Rectal 79 (26.2) 70 (23.1)	*Metastatic sites at baseline* **Cap** **5-FU/LV** Liver 232 225 Lymph nodes 116 123 Lung 107 107 Peritoneum 41 46 Soft tissue 30 28 Other 94 103
Van Cutsem, 2001[41]	Capecitabine 57%/43% 5-FU/LV 57%/43%	*Median (range)* Capecitabine 64.0 (29-84) 5-FU/LV 63.5 (36-86)	*Karnofsky performance score* **Cap** **5-FU/LV** Mean 89.7 89.6 SD 9.7 9.7 Median 90 90 Range 70-100 70-100	*Site of primary tumour %* **Cap** **5-FU/LV** Colon 66.1 65.1 Rectal 33.6 34.9	*Metastatic sites at baseline* **Cap** **5-FU/LV** Liver 230 238 Lymph nodes 82 88 Lung 89 89 Peritoneum 37 40 Soft tissue 27 28 Other 40 54
Twelves 2002[36]	Capecitabine 60%/40% 5-FU/LV 61%/39%	*Median (range)* Capecitabine 64 (23-86) 5FU/LV 63 (24-87)	*Karnofsky performance status (%) mean (range)* Capecitabine 89 (70-100) 5-FU/LV 89 (70-100)	*Site of primary tumour %* **Cap** **5-FU/LV** Colon/rectal cancer (%) 70/30 71/29	*Predominant metastatic sites at baseline* **Cap** **5-FU/LV** Liver (%) 77 77 Lung (%) 12 14

Cap=capecitabine

3.2.1.2 Study quality of included capecitabine studies

Table 6 shows the study quality of the two capecitabine RCTs. The Jadad criteria were used to assess the quality of the RCTs.[33] The Jadad criteria consist of three categories: randomisation (including method to generate the sequence of randomisation and whether or not the method was appropriate), double blinding and description of withdrawals and dropouts. The maximum number of possible points is five. The Jadad score of both RCTs was 3, indicating that the studies were of moderate quality. Neither study was double blinded which resulted in loss of points according to these criteria. However, blinding would be virtually impossible when comparing an oral drug with a bolus 5-FU regimen, as mode of delivery is different for the two treatments. The problem of blinding was partly overcome in these studies by the use of an Independent Review Committee to assess response rates.

The pooled data report[36] included the two RCTs. As they were designed using identical protocols, pooling was an appropriate method of synthesis. The trials were of identical size giving them equal weight. Meta-analysis techniques were not used in the synthesis so it is not appropriate to assess the quality of the study as if it were a meta-analysis but rather as a large RCT. In this case, the pooled data would receive a 3 according to the add criteria, again indicating moderate quality.

Table 6. Trial Quality Assessment: capecitabine

Study	Randomised/method	Blinding/appropriate method	Description of withdrawals and dropouts	Jadad score
Hoff et al, 2001[40]	Yes, computer generated randomisation code	Open label trial, so patients were not blinded to treatment. An Independent Review Committee were blinded to clinical condition of the patient and investigator's assessment and assessed tumour responses solely on the basis of X-ray or scan imaging.	Withdrawals and dropouts well described	3/5
Van Cutsem, 2001[41]	Yes, computer-assisted randomisation centre	As above	Withdrawals and dropouts well described	3/5

3.2.1.3 Assessment of effectiveness of capecitabine

Outcomes for the capecitabine trials are listed in Table 7 and results in Table 8.
Primary outcomes in both trials were tumour response rates and secondary outcomes included time to response, duration of response, time to disease progression and overall survival. Analyses of efficacy were based on all patients randomised, indicating an intention to treat analysis.

Tumour response rates
Information on the definition of response rates can be found in Appendix 1. Both the Hoff [40] and Van Cutsem[41] studies had tumour response rates as a primary outcome. Both studies reported response rates as measured by the study investigator and by an Independent Review Committee (IRC), a panel of radiologists who were blinded to study treatment, clinical condition of the patient and investigator's assessment.

In the Hoff study,[40] overall response rates for the capecitabine group were significantly greater than the 5-FU/LV group when assessed by investigator or by the IRC. Overall response rates were 24.8% (CI: 20.1% to 30.1%) for capecitabine and 15.5% (CI: 11.6% to 20.1%) for 5-FU/LV (p=0.005) when assessed by investigator. When assessed by the IRC, overall response rates were 25.8% (CI: 21.0% to 31.2%) for capecitabine and 11.6% (CI: 8.2% to 15.7%) for 5-FU/LV (p=0.0001).

In the Van Cutsem study,[41] investigator assessed overall response rates were significant for capecitabine at 26.6% (CI: 21.7% to 32.0%) compared with 5-FU/LV at 17.9% (CI: 13.8% to 22.8%) (p=0.013). However, in the IRC assessed group response rates were 18.9% (CI: 14.7% to 23.8%) for capecitabine compared with 15.0% (CI: 11.1% to 19.5%) for the 5-FU/LV group (not significant) (NS).

In the Twelves study,[36] data from the above two studies were pooled. Investigator assessed overall response rates were significantly better for the capecitabine arm (25.7% compared with the 5-FU/LV arm (16.7%) (p<0.0002). Overall response rates assessed by the IRC were also significantly better for the capecitabine arm (22.4%) compared to 13.2% for the 5-FU/LV group (13.2%) (p<0.0001). Confidence intervals were not reported.

Duration of response
Both the Hoff [40] and the Van Cutsem[41] reported no significant difference in mean duration of response between the capecitabine and 5-FU/LV groups. In the Hoff study,[40] median duration of response (CR and PR) was 9.1 months in the capecitabine group (54 events) and 9.5 months in the 5-FU/LV group (30 events) (p=0.37). In the Van Cutsem study,[41] median duration of response in responding patients (PR or CR) was 7.2 months in the capecitabine group and 9.4 months in the 5-FU/LV group (p=0.17). Duration of response was not reported by Twelves.[36]

Time to disease progression or death
All three studies[40,41,36] report no significant differences in time to disease progression or death between the capecitabine and 5-FU/LV groups. For the Hoff study,[40] median time to disease progression or death was 4.3 (95% CI: 4.1-5.1) months for the capecitabine group and 4.7 (95% CI: 4.3-5.5) months for the 5-FU/LV group. The Van Custem study[41] reported median time to disease progression or death for the capecitabine group as 5.2 months and 4.7 months for the 5-FU/LV group.

Time to treatment failure in the three studies was also not significantly different between the capecitabine and 5-FU/LV groups. In the Hoff study [40], the capecitabine group had a time to treatment failure of 4.1 months and 3.1 months for the 5-FU/LV group while the Van Custem study [41] had a time to treatment failure of 4.2 months for the capecitabine group and 4.0 months for the 5-FU/LV group.

Survival
Median overall survival was equivalent for the capecitabine and 5-FU/LV groups in all three studies.[40,41,36] Values were 12.5 and 13.3 months respectively for the Hoff study,[40] 13.2 and 12.1 months respectively for the Van Cutsem study[41] and 12.9 and 12.8 months respectively for the Twelves pooled data report.[36]

Secondary Chemotherapy
No information was given for either trial or the pooled data regarding cross over to other treatments nor information concerning the addition of other chemotherapeutic agents.

Table 7. Outcomes: Capecitabine

Study	ITT analysis	Primary endpoints	Secondary endpoints	Duration of treatment
Hoff et al, 2001[40]	Yes, analyses of efficacy were based on all randomised patients	Tumour response rate	Time to response, duration of response, time to disease progression, time to treatment failure, overall survival and quality of life (results presented separately)	Capecitabine: mean daily dose corresponded to 80% of the scheduled dose and mean duration of treatment was 4.3 months. 5-FU/LV: mean daily dose corresponded to 86% of the scheduled dose and mean duration of treatment was 4.6 months.
Van Cutsem, 2001[41]	Yes, analyses of efficacy were based on all randomised patients	Tumour response rate	Time to response, duration of response, time to disease progression, time to treatment failure, overall survival and quality of life (results presented separately)	Capecitabine: median dose per cycle was 82-100% of that planned; median duration of treatment was 147 days. 5-FU/LV: median dose per cycle was between 95-100% of that planned and median duration of treatment was 140 days.
Twelves 2002[36]	Yes	Tumour response rate	Time to response, time to disease progression, overall survival and time to treatment failure.	Not reported

Table 8. Results: Capecitabine

Study	Response rate	Duration of response	Median time to disease progression or death	Survival
Hoff et al, 2001[40]	*Response rates (%)* **Capecitabine** (n=302) **5-FU/LV** (n=303) *Investigator* Overall response, CR or PR 75 (24.8) 47 (15.5)† CR 3 (1.0) 3 (1.0) PR 72 (23.8) 44 (14.5) Stable disease 146 (48.3) 158 (52.1) PD 57 (18.9) 59 (19.5) Missing post-baseline 22 (7.3) 38 (12.5) † p=0.005 *IRC* Overall response, CR or PR 78 (25.8) 35 (11.6)* CR 1 (0.3) 1 (0.3) PR 77 (25.5) 34 (11.2) Stable disease 148 (49.0) 181 (59.7) PD 43 (14.2) 36 (11.9) Missing post-baseline 30 (9.9) 49 (16.2) *χ^2 test showed the response rate for capecitabine to be significantly greater than that achieved with 5-FU/LV (p=0.0001)	Median duration of response (CR and PR) was 9.1 months in the capecitabine group (54 events) and 9.5 months in the 5-FU/LV group (30 events) (p=0.37).	*Median time to disease progression or death* Capecitabine 4.3 (95% CI: 4.1-5.1) months (269 events) 5-FU/LV 4.7 (95% CI: 4.3-5.5) months (271 events) (p=0.72, log-rank test) Hazard ratio was 1.03 (95% CI: 0.87-1.22) *Time to treatment failure* Capecitabine: 4.1 months (227 events) 5-FU/LV: 3.1 months (280 events) p=0.19, log-rank test; Hazard ratio 0.90 (95% CI:0.76-1.06)	*Median overall survival* Capecitabine 12.5 (95% CI: 10.5-14.2) months (260 events) 5-FU/LV 13.3 (95% CI: 12.0-14.6) months (273 events) p=0.97, log-rank test) Hazard ratio was 1.00 (95% CI: 0.84-1.18)
Van Cutsem, 2001(2207}	*Response rates (%)* **Capecitabine** (n=301) **5-FU/LV** (n=301) *Investigator* Overall response, CR or PR 26.6% 17.9%* p=0.013	Median duration of response in responding patients (PR or CR) was 7.2 months in the capecitabine group and 9.4 months in the 5-FU/LV group (p=0.17)	*Median time to disease progression or death* Capecitabine 5.2 months 5-FU/LV 4.7 months (log-rank p=0.65) Hazard ratio: 0.96 (95% CI:	*Median overall survival* Capecitabine 13.2 months 5-FU/LV 12.1 months Hazards ratio: 0.92 (95% CI: 0.78-1.09) (log-rank p=0.33)

Study	Response rate	Duration of response	Median time to disease progression or death	Survival
	IRC Overall response, CR or PR 57 (18.9) 45 (15.0) CR 1 (0.3) 2 (0.7) PR 56 (18.6) 43 (14.3) Stable disease 171 (56.8) 167 (55.5) PD 38 (12.6) 51 (16.9) Missing post-baseline 33 (11.0) 38 (12.6)		0.81-1.14) *Time to treatment failure* Capecitabine 4.2 months 5-FU/LV 4.0 months (log-rank p= 0.89)	
Twelves 2002[36]	*Response rates (%)* **Capecitabine** (n=603) **5-FU/LV** (n=604) *Investigator* PR + CR (%) 25.7 16.7 ($p<0.0002$) Stable disease (%) 47.8 52.2 *IRC* PR + CR (%) 22.4 13.2 ($p<0.0001$) Stable disease (%) 52.9 57.6 Both overall response rates were significantly higher in favour of capecitabine using two-sided χ^2 test with Schouten correction	Not reported	*Median time to disease progression or death* Capecitabine 4.6 months (95% CI: 4.3-5.3) 5-FU/LV 4.7 months (95% CI: 4.3-5.4) *Median time to treatment failure* Capecitabine 4.2 months 5-FU/LV 3.6 months Median time to response 1.7 months for capecitabine and 2.4 months for 5-FU/LV	*Median overall survival* Capecitabine 12.9 months (95% CI: 12.0-14.0) † 5-FU/LV 12.8 months (95% CI: 11.8-14.0) †; (hazard ratio= 0.96, 95% CI: 0.85-1.08); log rank p=0.48† † Confidence intervals and log rank p value from Hoff et al [44]

IRC= Independent review committee, PR=partial response, CR= complete response;

3.2.1.4 Toxicity

Toxicity in the form of Grade 3 and 4 adverse reactions are listed in Table 9. For information on toxicity grading, see **Appendix 8**.

The Hoff [40] study reports that patients in the capecitabine group had significantly lower incidence of any grade of diarrhoea, stomatitis, nausea and alopecia compared with the 5-FU/LV group ($p<0.0002$). The patients in the capecitabine group had a significantly higher incidence of hand-foot syndrome (palmar-plantar erythrodysesthesia) compared to the 5-FU/LV group. With regard to grade 3 toxicities, stomatitis (15.3% vs. 3%) and neutropenia (values not reported) were significantly more frequent in the 5-FU/LV group ($p<0.0001$). Grade 3 hand-foot syndrome (18.1% vs. 0.7%) ($p<0.00001$) and grade 3/4 hyperbilirubinemia were more frequently reported in the capecitabine group than in the 5-FU/LV group. Fewer patients in the capecitabine group required hospitalisation for treatment related toxicity than those in the 5-FU/LV group (11.4% vs. 20.4%) ($p=0.003$).

Van Cutsem,[41] also reported significantly less stomatitis and alopecia of any grade in the capecitabine group compared with the 5-FU/LV group ($p<0.00001$). Hand-foot syndrome was again more frequent in the capecitabine group ($p<0.00001$). The capecitabine group had a lower incidence of grade 3/4 stomatitis (1% vs. 13%) and neutropenia (values not reported) ($p<0.00001$) but greater incidence of grade 3 hand-foot syndrome (16.2% vs. 0.3%) ($p<0.00001$) and uncomplicated grade 3/4 hyperbilirubinemia ($p<0.0001$). Patients in the capecitabine group had fewer hospitalisations due to adverse effects compared to the 5-FU/LV group (11.8% vs. 15.7%) (p value not reported).

The Twelves study,[36] which pools data from the above two trials, reports significantly lower incidence of diarrhoea, stomatitis, nausea and alopecia in the capecitabine group compared with the 5-FU/LV group. Grade 3/4 neutropenia also occurred more frequently in the 5-FU/LV group. Hand-foot syndrome and grade 3 hyperbilirubinemia occurred more frequently in the capecitabine group. Hospitalisation for adverse events was significantly less frequent in the capecitabine group compared with the 5-FU/LV group (11.6% vs. 18%) ($p=0.002$). Treatment related mortality was 1% for each group.

Table 9. Toxicity: Capecitabine

<table>
<tr><th>Study</th><th>Types of side effects</th><th>Treatment related deaths</th></tr>
<tr><td>Hoff et al, 2001[40]</td><td>
Patients with grade 3 and 4 adverse reactions related to treatment; number (%)
<table>
<tr><th></th><th colspan="2">Capecitabine (n=299)</th><th colspan="2">5-FU/LV (n=294)</th></tr>
<tr><th></th><th>Grade 3</th><th>Grade 4</th><th>Grade 3</th><th>Grade 4</th></tr>
<tr><td>All reactions</td><td>121 (40.5)</td><td>8 (2.7)</td><td>105 (35.7)</td><td>14 (4.8)</td></tr>
<tr><td>Total no. events</td><td>199</td><td>10</td><td>190</td><td>19</td></tr>
<tr><td>Diarrhoea</td><td>41 (13.7)</td><td>5 (1.7)</td><td>33 (11.2)</td><td>8 (2.7)</td></tr>
<tr><td>Hand-foot syndrome</td><td>54 (18.1)</td><td>NA</td><td>2 (0.7)</td><td>NA</td></tr>
<tr><td>Stomatitis</td><td>9 (3.0)</td><td>0</td><td>45 (15.3)</td><td>2 (0.7)</td></tr>
<tr><td>Vomiting</td><td>10 (3.3)</td><td>1 (0.3)</td><td>13 (4.4)</td><td>1 (0.3)</td></tr>
<tr><td>Dehydration</td><td>6 (2.0)</td><td>1 (0.3)</td><td>10 (3.4)</td><td>1 (0.3)</td></tr>
<tr><td>Sepsis</td><td>0</td><td>0</td><td>1 (0.3)</td><td>1 (0.3)</td></tr>
<tr><td>Myocardial infarction</td><td>0</td><td>0</td><td>0</td><td>1 (0.3)</td></tr>
<tr><td>Sudden death</td><td>0</td><td>1 (0.3)</td><td>0</td><td>0</td></tr>
<tr><td>Pneumonia</td><td>0</td><td>1 (0.3)</td><td>0</td><td>1 (0.3)</td></tr>
<tr><td>Septicemia</td><td>0</td><td>1 (0.3)</td><td>0</td><td>0</td></tr>
<tr><td>Viral infection</td><td>0</td><td>0</td><td>0</td><td>1 (0.3)</td></tr>
<tr><td>Renal failure</td><td>0</td><td>0</td><td>0</td><td>1 (0.3)</td></tr>
<tr><td>Respiratory distress</td><td>0</td><td>0</td><td>0</td><td>1 (0.3)</td></tr>
<tr><td>Drug toxicity NOS</td><td>0</td><td>0</td><td>0</td><td>1 (0.3)</td></tr>
</table>
NOS= not otherwise specified; NA= not applicable; an adverse reaction is listed if it was reported at grade 3 in ≥ 5% of patients or grade 4 in any patient.

Adverse Reactions requiring hospitalisation; number (%)
<table>
<tr><th></th><th>Capecitabine (n=299)</th><th>5-FU/LV (n=294)</th></tr>
<tr><td>Total patients hospitalised*</td><td>34 (11.4)</td><td>60 (20.4)</td></tr>
<tr><td>Dehydration</td><td>8 (2.7)</td><td>9 (3.1)</td></tr>
<tr><td>Diarrhoea</td><td>12 (4.0)</td><td>8 (2.7)</td></tr>
<tr><td>Infection</td><td>1 (0.3)</td><td>2 (0.7)</td></tr>
<tr><td>Nausea</td><td>0</td><td>1 (0.3)</td></tr>
<tr><td>Neutropenia</td><td>0</td><td>4 (1.4)</td></tr>
<tr><td>Neutropenic fever</td><td>0</td><td>10 (3.4)</td></tr>
<tr><td>Sepsis</td><td>0</td><td>1 (0.3)</td></tr>
<tr><td>Stomatitis</td><td>0</td><td>10 (3.4)</td></tr>
<tr><td>Vomiting</td><td>3 (1.0)</td><td>5 (1.7)</td></tr>
</table>
</td><td>Capecitabine: 3 patients died due to treatment-related adverse reactions (one each from gastrointestinal haemorrhage, pneumonia, and death of unknown cause).

5-FU/LV: two patients died due to treatment related adverse reactions (one sepsis and one upper respiratory tract infection)</td></tr>
</table>

Study	Types of side effects	Treatment related deaths
	Other 12 (4.0) 12 (4.1) *patients could be hospitalised more than once for different adverse events. Lower overall incidence and later onset of grade 3 or 4 adverse reactions with capecitabine throughout the entire treatment period (p=0.0037, log-rank test) with the difference particularly pronounced during the first 4 to 5 month. Fewer patients in the capecitabine group required hospitalisation for adverse reactions than 5-FU/LV group (p=0.003).	
Van Cutsem, 2001[41]	*Patients with grade 3 and 4 adverse reactions related to treatment; number (%)* **Capecitabine (n=297)** **5-FU/LV (n=299)** **Grade 3** **Grade 4** **Grade 3** **Grade 4** Diarrhoea 28 (9.4) 4 (1.3) 28 (9.4) 3 (1.0) Hand-foot syndrome 48 (16.2) NA 1 (0.3) NA Stomatitis 3 (1.0) 1 (0.3) 39 (13.0) 1 (0.3) Sepsis 0 1 (0.3) 5 (1.7) 2 (0.7) Deep venous thrombosis 4 (1.3) 1 (0.3) 0 0 Neutropenic fever 0 0 2 (0.7) 1 (0.3) NA=not applicable, an adverse reaction is listed if reported at grade 3 in > 5% of patients in at least one of the treatment groups and all adverse grade 3 or 4 reactions reported in ≥ 1% of the patients with at least one grade 4 adverse event. *Adverse Reactions requiring hospitalisation; number (%)* **Capecitabine (n=297)** **5-FU/LV (n=299)** All adverse reactions 35 (11.8) 47 (15.7) Dehydration 5 (1.7) 0 Diarrhoea 13 (4.4) 14 (4.7) Hand-foot syndrome 2 (0.7) 0 Infection 0 4 (1.3) Neutropenia 1 (0.3) 2 (0.7) Sepsis 1 (0.3) 6 (2.0) Stomatitis 1 (0.3) 11 (3.7) Vomiting 1 (0.3) 1 (0.3) Other 14 (4.7) 11 (3.7)	Capecitabine: 3 patients died due to treatment-related adverse reactions (one each from gastrointestinal necrosis, pulmonary embolism and myocardial infarction). 5-FU/LF: four patients died due to treatment related adverse reactions (cardiac failure, renal tubular necrosis, sepsis and enterocolitis)
Twelves 2002[36]	Significantly lower (p<0.001) incidence of diarrhoea (48% vs. 58%), stomatitis (24% vs. 62%), nausea (38% vs. 47%) and alopecia (6% vs. 21%) for capecitabine compared with 5-FU/LV. Incidence of vomiting and fatigue was similar in both treatment groups. Hand-foot syndrome (all grades) was the only adverse event to	Treatment related mortality was 1% in each group.

Study	Types of side effects	Treatment related deaths
	occur more frequently with capecitabine than 5-FU/LV. Hand-foot syndrome led to hospitalisation (0.3%) or withdrawal from treatment (1.7%) infrequently. Grade 3/4 stomatitis occurred in 2% of capecitabine patients but 15% of 5-FU/LV patients ($p<0.0001$). Grade 3 or 4 neutropenia was significantly more common in the 5-FU/LV group compared with capecitabine (21.1% vs. 2.2%). Hyperbilirubinemia was higher in capecitabine group with a higher percentage in the capecitabine group developing total bilirubin levels >1.5 and ≤ 3 times the upper limit of normal (grade 3: 18.3% for capecitabine vs. 3.3% for 5-FU/LV, $p<0.0001$; Grade 4 hyperbilirubinemia there were similar rates in both groups (4.5% vs. 2.5%, $p=0.07$). Hospitalisation for treatment related adverse events was significantly less frequent in the capecitabine group compared with the 5-FU/LV group (11.6% vs. 18.0%, $p=0.0002$)	

3.2.1.5 Health related quality of life

Quality of life was assessed in both RCTs of capecitabine although this data has not been published. Quality of life data was reported in the Roche sponsor submission to NICE.[45] No published health related quality of life studies for capecitabine were identified in the literature searches. Both of the RCTs[40,41] measured QoL using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). The results showed that there was no significant difference in global quality of life between the capecitabine and 5-FU/LV groups in either trial. The quality of life data are presented in more detail in section 4.2.3.

3.2.1.6 Patient preference

None of the three studies[40,41,36] reported information on patient preference.

3.2.1.7 Conclusions on effectiveness of capecitabine

Two trials were identified[40,41] that compared capecitabine with 5-FU/LV administered via the Mayo regimen. An additional study was identified[36] that pooled the data from these two trials. No studies were identified that compared capecitabine treatment with the de Gramont or modified de Gramont 5-FU/LV regimens, both commonly used regimens in the UK.

One study[41] reported only investigator assessed overall response rates to be significantly greater in the capecitabine group compared with the 5-FU/LV group. The other trial[40] and the pooled data both found that investigator assessed and IRC assessed overall response rates were significantly greater in the capecitabine group compared with the 5-FU/LV group.

Duration of response, time to disease progression or death, time to treatment failure and overall survival were not found to be significantly different between the capecitabine groups and the 5-FU/LV groups in the two trials and in the pooled data.

With regard to toxicity, patients in the capecitabine groups reported less diarrhoea, stomatitis, nausea and alopecia of all grades than those in the 5-FU/LV groups. Those in the capecitabine group also had significantly less grade 3/4 neutropenia and less frequent hospitalisation for adverse events. Hand-foot syndrome and grade 3 hyperbilirubinemia was significantly greater in the capecitabine group.

3.2.2 QUANTITY AND QUALITY OF RESEARCH AVAILABLE: UFT/LV

Tegafur plus uracil administered with folinic acid (UFT/LV) is licensed for use in the UK as first-line treatment of metastatic colorectal cancer. Two phase III RCTs of UFT/LV were identified (011 and 012). Information on these studies was obtained from a variety

of sources. Both studies have been published in abstract form[42] and only very recently (September 2002) have the full reports of these studies been published.[46,47,43]

Both studies relate to comparison of UFT/LV with bolus 5-FU. The first, study 011[46] (n=816) compared UFT/LV with the Mayo regimen. The second, study 012[47](n=380) compared UFT/LV with a modification of the Mayo regimen, where treatment was repeated every 35 days as opposed to the standard 28 days in the Mayo regimen. This non-standard variation of the Mayo regimen is a less dose intensive regimen and has not been tested for efficacy.

The two trials also differ in that study 011 (n=816)[46] used different dosages of leucovorin for patients in the United States and non-U.S. patients. Patients in the U.S. received 75 mg/day and those in other countries received 90 mg/d. In study 012 (n=380)[47] all patients received 90mg/d of leucovorin.

The UFT/LV studies included in this review are listed in Table 10.

Table 10. UFT/LV studies included in the review

Study	Study site	Comparators, dosage and procedure	Type of study	Numbers randomised	Funding
Douillard et al[46] **Study 011**	85 sites in the US, Canada, Europe and Israel	UFT (300mg/m^2/d) given orally with Leucovorin (LV) (75 or 90 mg/d) given orally for 28 days every 35 days. [Patients in the US received 75 mg/day and those in other countries received 90 mg/d]. 5-FU (425 mg/m^2/d) and LV (20 mg/m^2/d) given by iv for 5 days *every 28 days* (Mayo Clinic regimen) for the first two cycles and repeated at intervals of 4-5 weeks.	Open label, phase III RCT	UFT/LV: 409 5-FU/LV: 407	Bristol-Myers Squibb
Carmichael et al[47] **Study 012**	47 sites in Canada, Europe, Israel, Australia, New Zealand	Oral UFT 300 mg/ m^2/d and LV (90 mg/d) both administered for 28 days every 35 days IV 5-FU (425 mg/ m^2/d) and LV (20 mg/ m^2/d both given by iv for 5 days *every 35 days* (not standard Mayo regimen).	Open label, phase III RCT	380 patients randomised to study (190 for each treatment)	Bristol-Myers Squibb

3.2.2.1 Study characteristics of included UFT/LV studies

Tables 11 and 12 show the study characteristics of the two included UFT/LV trials.
Inclusion and exclusion criteria were similar although there were some differences, notably that study 012 [47] had an upper age limit of 75 years.

The Douillard study (study 011)[46] was adequately powered to demonstrate equivalence as non-inferiority of survival while the Carmichael study (study 012) [47] was adequately powered to determine time to progression.

Baseline comparability was reported and no significant differences between the UFT/LV and 5-FU/LV groups were reported in either of the studies apart from differences in baseline quality of life in the Carmichael study.[47]

No information on the primary tumour site was presented for either study. The most common site of metastases was the liver in both studies.

Table 11. Study design: UFT/LV

Study	Length of study	Inclusion criteria	Exclusion criteria	Power calculation	Baseline comparability
Douillard et al[46] **Study 011**	Recruitment between June 1995 and August 1997	Previously untreated metastatic colorectal cancer with evaluable or measurable disease; adequate bone marrow (absolute granulocyte count ≥ 2000/mm^3, platelets ≥ 100,000/mm^3); liver (bilirubin normal) and renal function (creatinine normal); age ≥ 18 years; unsuitable for definitive surgical resection, prior adjuvant chemotherapy completed more than six months prior to enrolment	Unstable medical conditions; concurrent serious infections, an oncological emergency on presentation; history of malignant neoplasms other than skin cancer or in situ carcinoma of the cervix	Study designed with 80% power to show equivalence of UFT/LV with 5-FU/LV as non-inferiority of survival.	No significant differences reported in baseline characteristics between treatment groups.
Carmichael et al[47] **Study 012**	Recruitment between May 1996 and July 1997	Histologically confirmed metastatic colorectal adenocarcinoma with bidimensionally measurable disease or evaluable disease located outside previously irradiated fields (all measurements ≥ 1.5 cm); between 18 and 75 years; completed any prior colorectal adjuvant treatment at least 6 months prior to	Concurrent uncontrolled medical disorders or prior malignancies	Sample size gave study 80% power to detect a hazard ratio of 1.40 between the two treatments with regard to time to progression	No significant differences reported in baseline characteristics between treatment groups apart from differences in baseline quality of life.

Study	Length of study	Inclusion criteria	Exclusion criteria	Power calculation	Baseline comparability
		enrolment; granulocyte count ≥ 2,000/mm^3; platelet count ≥ 100,000/ mm^3; total bilirubin ≤ 1.5 x upper limit of normal; Eastern Cooperative Oncology Group 0-2.			

Table 12. Patient details: UFT/LV

Study	Sex (M/F)	Age	Performance score	Primary site	Sites of metastasis
Douillard et al[46] **Study 011**	UFT/LV: 249/160 5-FU/LV: 245/162	*Median (range)* UFT/LV: 64 (29-88) 5-FU/LV: 64 (22-90)	*Eastern Cooperative Oncology Group (ECOG) (%) Performance Status* **UFT/LV** **5-FU/LV** 0 45 43 1 48 49 2 7 8	Not reported	*Extent of disease (%)* **UFT/LV** **5-FU/LV** Liver 325 (79) 237 (80) Lymph node/soft tissue- in primary area 120 (29) 124 (30) Lymph node/soft tissue- outside primary area 23 (6) 18 (4) Lung 113 (28) 115 (28) Visceral, other 29 (7) 30 (7) Intestine 15 (4) 35 (9) Ascites 5 (1) 9 (2) Bone 7 (2) 1 (<1) Pleural effusion 2 (<1) 4 (1) Not reported 0 (0) 1 (<1)
Carmichael et al[47] **Study 012**	UFT/LV: 128/62 5-FU/LV: 122/68	*Median (range)* UFT/LV: 61 (30-77) 5-FU/LV: 62 (29-81)	*Eastern Cooperative Oncology Group (ECOG) (%) Performance Status* **UFT/LV** **5-FU/LV** 0 39 33 1 47 56 2 14 11	Not reported	*Extent of disease (%)* **UFT/LV** **5-FU/LV** Liver 149 (78) 146 (77) Lymph node/soft tissue-in primary area 64 (34) 65 (34) Outside primary area 17 (9) 14 (7) Lung 58 (31) 55 (29) Visceral, other 12 (6) 8 (4) Intestine 28 (15) 21 (11) Ascites 4 (2) 8 (4) Bone 2 (1) 9 (5)

Study	Sex (M/F)	Age	Performance score	Primary site	Sites of metastasis
					Pleural effusion 6 (3) 4 (2) Not reported 2 (1) 2 (1)

3.2.2.2 Study quality of included UFT/LV studies

The Jadad criteria were used to assess the quality of the RCTs.[33] The Jadad criteria consist of three categories: randomisation (including method to generate the sequence of randomisation and whether or not the method was appropriate), double blinding and description of withdrawals and dropouts. The maximum number of possible points is five. The Jadad score of both RCTs was 3, indicating moderate quality. Neither study was double blinded which resulted in loss of points according to these criteria. However, blinding would be virtually impossible when comparing an oral drug with a bolus 5-FU regimen, as mode of delivery is different for the two treatments. There was no independent assessment of response rates in either study. Table 13 describes the quality of the two UFT/LV studies.

Table 13. Trial Quality Assessment: UFT/LV

Study	Randomised/method	Blinding/appropriate method	Description of withdrawals and dropouts	Jadad score
Douillard et al [46] **Study 011**	RCT, secure remote centralised randomisation procedure	Open label trial, no blinding reported	Withdrawals and dropouts clearly described	3/5
Carmichael et al [47] **Study 012**	RCT, secure remote centralised randomisation procedure	Open label study, no blinding reported	Withdrawals and dropouts clearly described	3/5

3.2.2.3 Assessment of effectiveness of UFT/LV

Table 14 describes the outcomes used in the UFT/LV studies and Table 15 shows the results. The Douillard study[46] (study 011) used overall survival as the primary endpoint while the Carmichael study[47] (study 012) used time to disease progression as the primary endpoint.

Tumour response rates
In both studies there was no significant differences between the UFT/LV group and the 5-FU/LV group with regard to overall tumour response rates. Response rates were assessed by the sponsor's physician and an internal review was conducted. In the Douillard study,[46] overall response rates were 11.7% for the UFT/LV group and 14.5% for the 5-FU/LV group while in the Carmichael study,[47] overall response rates were 10.5% for the UFT/LV group and 9.0% for the 5-FU/LV group.

Duration of response
Both studies reported no significant differences with regard to duration or response although actual values were not reported for either study.[48]

Time to disease progression or death
In Douillard study,[46] time to disease progression was significantly greater in the 5-FU/LV group compared to the UFT/LV group 3.8 months vs. 3.5 months (p=0.01). The actual difference was therefore 0.3 of a month (10 days) and the confidence intervals overlap. There was no significant difference in time to disease progression in the Carmichael study[47] between the UFT/LV and the 5-FU/LV groups, which reported figures of 3.4 months and 3.3 months respectively.

Survival
There were no significant differences in median survival time between the UFT/LV group and the 5-FU/LV group for either study.[46,47] Median survival in the Douillard study (study 011)[46] was 12.4 months in the UFT/LV group and 13.4 months in the 5-FU/LV group, while in the Carmichael study (study 012),[47] median survival was 12.2 in the UFT/LV group and 10.3 months in the 5-FU/LV group.

Additional analysis on survival was reported by Benner[49] showing survival for study 011 to be worse in U.S. study sites.[49] As stated previously, the U.S. sites in study 011 used a different dosage of leucovorin compared with the non-U.S. sites, which could potentially be responsible for the difference in survival. No U.S. sites were included in study 012, in which all UFT/LV patients received the same dosage of LV.

Secondary chemotherapy
In the Douillard study,[46] secondary chemotherapy was administered to 52% of patients in the UFT/LV group and 50% in the 5-FU/LV group, although data on type of drugs was not collected. In the Carmichael study[47] 41% of patients in the UFT/LV group and 39%

in the 5-FU/LV group received secondary chemotherapy including fluoropyrimidines, irinotecan and oxaliplatin.

Table 14. Outcomes: UFT/LV trials

Study	ITT analysis	Primary endpoints	Secondary endpoints	Duration of treatment
Douillard et al[46] **Study 011**	Analyses of efficacy are based on data from all randomised patients	Survival	Response rate; time to disease progression	*Median duration of treatment in weeks (range)* UFT/LV: 16.6 weeks (0.7-120) 5-FU/LV: 16.7 (0.7-69.4) *Mean percentage of planned dose* UFT/LV: 92.6% 5-FU/LV: 85.1%
Carmichael[47] **Study 012**	Analyses of efficacy are based on data from all randomised patients	Time to disease progression	Response rates, median survival	*Median duration of treatment in weeks (range)* UFT/LV: 17.2 (1.3-51.1) 5-FU/LV: 15.1 (0.3-67.1) *Mean percentage of planned dose* UFT/LV: 91.8% 5-FU/LV: 98.4%

Table 15: Results: UFT/LV trials

Study	Response rate	Duration of response	Median time to disease progression or death	Survival
Douillard et al[46] **Study 011**	*Response rates* **UFT/LV** (n=409) **5-FU/LV** (n=407) Total tumour response n(%) 48 (11.7) 59 (14.5) CR 8 (2) 8 (2) PR 40 (10) 51 (13) Stable disease 148 (36) 168 (41) Progressive disease 167 (41) 130 (32) Unevaluable 46 (11) 50 (12) Toxicity/early death % 21 21 Not assessed 19 15 Never treated 4 10 Other 2 4	No significant differences between treatment arms with regard to duration of response; values not reported.	3.5 months (95% CI: 3.0-4.4 months) for UFT/LV and 3.8 months for 5-FU/LV (95% CI: 3.6-5.0) (p=0.01, stratified log rank)	*Median survival* 12.4 months (95% CI: 11.2-13.6 months) for UFT/LV group and 13.4 months (95% CI: 11.6-15.4 months) for 5-FU/LV group (NS) Hazard ratio for 5-FU/LV over UFT/LV was 0.964 (95% CI: 0.826-1.125); Benner [49] for the FDA states that the HR for survival is uncertain because the survival curves cross at 24 months. The FDA believes that the highest lower bound that can be supported is approximately 0.80.
Carmichael[47] **Study 012**	*Response rates* **UFT/LV** (n=190) **5-FU/LV** (n=190) Total tumour response n (%) 20 (10.5) 17 (9) CR 2 (1) 2 (1) PR 18 (9) 15 (8) Stable disease 65 (34) 71 (37) Progressive disease 81 (43) 83 (44) Unevaluable	No significant differences between treatment arms with regard to duration of response; values not reported.	3.4 months (95% CI: 2.6-3.8 months) for UFT/LV and 3.3 months (95% CI: 2.5-3.7 months) for 5-FU/LV (p=0.591)	*Median survival* 12.2 months (95%CI: 10.4-13.8) median survival time for UFT/LV and 10.3 months (95% CI: 8.2-13.0) for 5-FU/LV (p=0.682) Hazard ratio for 5-FU/LV over UFT/LV was 1.14 (95% CI: 0.92-1.42)

Study	Response rate	Duration of response	Median time to disease progression or death	Survival
	24 (13) 19 (10) Toxicity/early death % 11 4 Not assessed 2 4 Never treated 3 4 Other 8 7			

3.2.2.4 Toxicity

Table 16 shows the toxicity results for the UFT/LV trials (see Appendix 8 for Toxicity Criteria). In the Douillard study,[46] UFT/LV was associated with significantly less diarrhoea, nausea/vomiting, mucositis, neutropenia and thrombocytopenia than 5-FU/LV for all grades. Grade 3-4 toxicity was also found less commonly with UFT/LV than with 5-FU/LV for mucositis (1% vs. 20%), neutropenia (1% vs. 56%), thrombocytopenia 0% vs. 2%) and anaemia (3% vs. 7%). Increased bilirubin, without other liver function abnormalities was significantly more common in UFT/LV patients than those treated with 5-FU/LV (39% vs. 22%) ($p<0.001$). No data were reported regarding amount of hospitalisation due to treatment related adverse effects.

In the Carmichael study,[47] UFT/LV treatment resulted in significantly fewer episodes of stomatitis/ mucositis, neutropenia, thrombocytopenia and anaemia of any grade than 5-FU/LV treatment. With regard to grade 3/4 adverse events, UFT/LV treatment resulted in significantly less stomatitis/mucositis (2% vs. 16%) and neutropenia (3% vs. 31%). A total of 127 patients were hospitalised during the study, 59 (31%) in the UFT/LV group and 68 (37%) in the 5-FU/LV group. Reasons for hospitalisation were not reported apart for five patients, all in the 5-FU/LV group who were hospitalised for febrile neutropenia.

Table 16. Toxicity for UFT/LV trials

Study	Types of side effects							Treatment related deaths
Douillard et al[46] **Study 011**		**Any (CTC Grades 1-4)**			**Severe (CTC Grades 3 and 4)**			A total of 65 patients died within 30 days of last administration of treatment drug, 10% in UFT/LV group and 6% in 5-FU/LV group. In the UFT/LV group, 7% died due to the disease alone and 3% due to other causes including cardiac arrest, pulmonary embolism, aspiration pneumonitis, lactic acidosis and disease/toxicity. In the 5-FU/LV group, 3% died due to disease alone, 1 died due to 5-FU/LV toxicity and the rest other causes including cardiac and/or respiratory arrest, pulmonary embolism and myocardial infarction.
		UFT/LV	**5-FU/LV**		**UFT/LV**	**5-FU/LV**		
		N (%)	**N (%)**	**p value**	**N (%)**	**N (%)**	**p value**	
	Diarrhoea	27 (67)	299 (76)	0.006	86 (21)	63 (16)	ns	
	Nausea/vomiting	27 (67)	296 (75)	0.020	53 (13)	39 (10)	ns	
	Mucositis	97 (24)	297 (75)	<0.00	6 (1)	76 (20)	<0.00	
	Neutropenia	52 (13)	302 (77)	<0.00	3 (1)	219 (56)	<0.00	
	Thrombocytopenia	84 (21)	123 (31)	<0.00	0 (0)	8 (2)	0.003	
	Anaemia	33 (83)	343 (87)	ns	13 (3)	26 (7)	0.032	
Carmichael[47] **Study 012**		**Any (CTC Grades 1-4)**			**Severe (CTC Grades 3 and 4)**			10% of patients in the UFT/LV arm died within 30 days of treatment and 9% in the 5-FU/LV. In the UFT/LV group death was due to disease in all cases. In the 5-FU/LV arm death was due to toxicity (Partly or entirely) in 4 patients, disease in 10 patients, disease and iatrogenic haematemesis and melena in 1 patient, disease and myocardial infarction in 1 patient and haemorrhage and hypovolemic shock in 1 patient.
		UFT/LV	**5-FU/LV**		**UFT/LV**	**5-FU/LV**		
		N (%)	**N (%)**	**p value**	**N (%)**	**N (%)**	**p value**	
	Diarrhoea	102 (54)	111 (60)	ns	33 (18)	21 (11)	ns	
	Nausea/vomiting	106 (56)	108 (58)	ns	17 (9)	17 (9)	ns	
	Stomatitis/mucositis	34 (18)	102 (55)	<0.001	3 (2)	29 (16)	<0.001	
	Neutropenia	21 (11)	120 (67)	<0.001	5 (3)	55 (31)	<0.001	
	Thrombocytopenia	33 (18)	50 (28)	0.025	1 (1)	4 (2)	ns	
	Anaemia	143 (76)	160 (89)	0.002	9 (5)	7 (4)	ns	
	UFT/LV treatment resulted in fewer episodes of febrile neutropenia (p<0.001) and documented infection (p=0.40)							

3.2.2.5 Health related quality of life

Health related quality of life for UFT/LV has been included in both studies.[46,47] In the Douillard study[46] quality of life was measured using the Functional Living Index-Cancer (FLIC) and in the Carmichael study,[47] using EORTC QLQ-C30. No significant differences in quality of life were found between the two treatment groups in either study. These data is presented in more detail in section 4.2.3.

Quality of life was also measured in an unpublished preliminary report (study CA 146-075). This trial was an open label, phase II randomised, non-comparative study to evaluate health related quality of life, patient preference and healthcare resource use. These data are presented in the sponsor submission[48] only and used the EORTC QLQ-C30 to measure health related quality of life at baseline and every week during the first course of therapy. Patients were treated with UFT (300 mg/m^2/d) and LV (90mg/d) administered for 28 days every 35 days (n=137) or 5-FU (425 mg/ m^2/d) and LV (20 mg/ m^2/d) IV for 5 days repeated every 4 weeks for two cycles then every 35 days (n=65). Preliminary data from this trial shows scores for functional and symptom scales to be either improved or unchanged from baseline in the UFT/LV group over time but worse in the 5-FU/LV group. Symptom scores on diarrhoea worsened for both treatment groups. No information is given regarding the actual values or significance.

3.2.2.6 Patient preference

Borner,[50] reports a crossover trial of 37 patients with advanced colorectal cancer. Patients received UFT 300 mg/m^2/d plus LV 90 mg/ m^2/d for 28 days every 5 weeks or iv FU 425 mg/ m^2/d plus LV 20 mg/ m^2/d for 5 days every 4 weeks. Patients were crossed-over to the other treatment regimen for the second treatment cycle. Patients were asked to complete a therapy preference questionnaire prior to the first and after the second treatment cycle. 36 patients were included in the trial (one was excluded due to elevated serum bilirubin) and of these, 31 completed the questionnaire. Of those who completed the questionnaire, 84% preferred the UFT/LV regimen. Reasons for preference of the UFT/LV regimen included being able to take medication at home, less stomatitis and diarrhoea and being able to use a tablet instead of an injection.

3.2.2.7 Conclusions on the effectiveness of UFT/LV

Two trials of UFT/LV[46,47] were identified in the literature searches both comparing UFT/LV with 5-FU/LV treatment, one using the standard Mayo regimen and once using a modification of the Mayo regimen. No studies were identified that compared UFT/LV treatment with the de Gramont or modified de Gramont 5-FU/LV regimens, both in common use in the UK.

The two UFT/LV trials are not comparable for three main reasons. First the comparator in the Douillard study[46] was the standard Mayo 5-FU/LV regimen while the comparator in the Carmichael study[47] as stated above was a modification of the Mayo 5-FU/LV regimen that has not yet been tested for efficacy. Secondly, the Douillard study [46] used

two different doses of leucovorin, depending on the study site, while the Carmichael study[47] used only one dosage. Finally the primary outcome measures differ in that the Douillard study[46] used survival and the Carmichael study[47]used time to disease progression as primary outcome measures.

There were no significant differences with regard to overall response rates, duration of response or survival between UFT/LV and 5-FU/LV in either trial. Time to disease progression was significantly inferior for the UFT/LV group compared to the 5-FU/LV group in the Douillard study (study 011).[46] There was no difference in time to disease progression between the two groups in the Carmichael study (study 012),[47] although this possibly due to the use of a non-standard Mayo regimen. The use of this less dose intensive regimen would make it less effective thereby obscuring any deficit in the effectiveness of UFT/LV. It is worth noting that survival in the 5-FU/LV group was much lower in this study (10.3 months) than in the Douillard study[46] (13.4 months) while the UFT/LV survival was similar in the two studies (12.4 months and 12.2 months).

With regard to toxicity, in the Douillard study[46](study 011), UFT/LV was associated with significantly less diarrhoea, nausea/vomiting, mucositis, neutropenia and thrombocytopenia than 5-FU/LV for all grades and mucositis, neutropenia, thrombocytopenia and anaemia for grades 3/4. Increased bilirubin, without other liver function abnormalities was significantly more common in UFT/LV patients than those treated with 5-FU/LV ($p<0.001$). No data were reported regarding amount of hospitalisation due to treatment related adverse effects.

In the Carmichael study[47] (study 012), UFT/LV treatment resulted in significantly fewer episodes of stomatitis/ mucositis, neutropenia, thrombocytopenia and anaemia of any grade. With regard to grade 3/4 adverse events, UFT/LV treatment resulted in significantly less stomatitis/mucositis and neutropenia.

4. ECONOMIC ANALYSIS

4.1 OVERVIEW

In this chapter the published economic literature is reviewed, along with the economic analyses included as part of the sponsor submissions from Roche (Capecitabine)[45] and Bristol Myers Squibb (UFT/LV)[48] In addition we have undertaken our own economic evaluation.

4.2 IDENTIFICATION OF STUDIES

Studies were identified through a systematic search of medical databases, as detailed in Section 3. Two economic evaluations by Murad et al.,[51,52] were found, based on the same South American study comparing UFT with 5-FU. Two resource use studies were also identified: one relating to medical resource use in the two capecitabine trials[53] and one to resource use in the Carmichael UFT/LV trial.[54] No published cost-effectiveness evaluations were found for capecitabine.

In addition to the published studies an economic evaluation was included as part of the sponsor submissions from Roche[45] and Bristol Myers Squibb.[48]

4.2.1 Review of existing economic evidence

4.2.1.1 Murad et al., 1997 [52],[51]

An economic evaluation was undertaken of the treatment of patients with colorectal cancer in Brazil and Argentina. This study estimated the total cost of a course of treatment over 18 months with UFT/LV compared to a course of treatment of 5-FU. The treatment regimen of 5-FU was not given. Therapeutic equivalence was assumed. The study used a modified Delphi technique with a panel composed of three physicians from Brazil and three from Argentina. Costs were divided into four categories: pre-chemotherapy care, chemotherapy cycles, chemotherapy follow-up and adverse event management. Cost per life year gained (LYG) was not estimated.

The results were divided by country and by chemotherapy for metastatic disease or adjuvant chemotherapy. The treatment cost in US$ for metastatic colorectal cancer in Brazil was $10,179 (£6,454) for UFT and $10,491 (£6,652) for 5-FU. The savings incurred through use of UFT treatment were $312 (£198). In Argentina, the treatment cost was $12,369 (£7,483) for UFT and $13,557 (£8,596) for 5-FU. The savings incurred through UFT treatment were $1,188 (£753). The cost savings came mainly in the area of adverse event management. All other cost areas were fairly similar. In Brazil, the pre-chemotherapy cost favoured UFT, but all other cost areas (excepting adverse events) favoured 5-FU. In Argentina, all cost areas favoured UFT. A Monte Carlo sensitivity

analysis gave a range of cost savings between $250 (£159) and $410 (£260) for Brazil, and $1,500 (£951) and $875 (£555) for Argentina. The authors of this study concluded that there was an economic advantage for oral UFT over 5-FU in the treatment of colorectal cancer in Brazil and Argentina.

A number of issues make this study difficult to apply to the UK context. This study was not based on an RCT, but rather on a panel of physicians attempting to simulate a real-world situation, as experienced in their practices. It was not clear whether data were collected retrospectively or prospectively. No information was given on which resources were actually used in the cost calculations, and whether the treatment regimens were relevant to the UK setting. Also, the small number of physicians on the panel means that treatment options, particularly in the treatment of adverse effects, will be biased towards the preferences of these physicians. The study noted that an improved adverse effect profile could have a positive effect on quality of life, but no quality of life data were collected. The authors concluded that prospective economic research and quality of life evaluations are needed to assess the economic impact of UFT treatment.

4.2.1.2 Ollendorf, 1999 [54]

This article studied the use of inpatient and outpatient services in an international phase III trial comparing UFT with LV to 5-FU with LV[43] in patients with metastatic colorectal cancer. In this trial, 5-FU/LV was given according to a modified Mayo regimen with doses of 425mg/m^2 daily for five days every five weeks. All hospital and nursing home admissions were recorded, including hospitalisations for febrile neutropenia, infection, tumour progression, drug toxicity and transfusion. Drug administration data were not collected. Outpatient services included GP consultations, hospitals, private nurses, physiotherapists and home help visits.

The number of hospitalisations recorded was higher among the 5-FU/LV group than the UFT/LV group, as was the total number of days in hospital. No difference was observed between the groups in use of outpatient services. Among patients who were employed at baseline, fewer UFT/LV patients missed work due to illness than 5-FU/LV patients, and the mean number of days of work lost was lower in the UFT/LV group. The author concluded that UFT with LV may be associated with reductions in the use of inpatient services and work loss due to illness among patients with metastatic colorectal cancer.

This study is useful but limited. It gives volumes of resources used, but formal hypothesis testing was not undertaken as the study was not adequately powered to detect potentially important differences between treatment groups in the measures of interest, and the comparator regimen was not standard. Also, many other resources used over a course of treatment are not mentioned in this study, and no benefits were calculated.

4.2.1.3 Twelves et al., 2001 [53]

This article analysed the resource use of 602 patients with advanced or metastatic colorectal cancer in an international trial comparing capecitabine treatment with Mayo regimen 5-FU/LV treatment.[41] Data were collected on hospital visits required for drug administration, hospital admissions, and drugs and unscheduled consultations with physicians for the treatment of adverse effects. Treatment related resource use included clinic visits, both number and duration, and chemotherapy agents. Resource use related to adverse event management included consultations, hospitalisation days and treatments for the management of adverse effects.

The number of hospital visits per patient for drug administration was 2109 for capecitabine patients and 7625 for 5-FU/LV patients. The number of hospital days for adverse event management was 368 for capecitabine patients and 477 for 5-FU/LV patients. The number of consultations for the treatment of adverse events was similar between the two arms. Drug use for the management of adverse events was analysed with emphasis on expensive drugs that are likely to be economically important. An increased quantity of expensive drugs were required for the treatment of adverse events stemming from 5-FU/LV treatment compared to capecitabine treatment, where the most common side effect is hand-foot syndrome, which were treated with inexpensive creams. No estimation of benefit was made in this study.

The authors concluded that capecitabine in comparison with 5-FU/LV leads to a reduction in medical resource use as well as improved response rate and tolerability, and that the data support capecitabine as the preferred fluoropyrimidine-based regimen for the treatment of advanced colorectal cancer.

This study is not a cost-effectiveness analysis and does not calculate costs or cost per LYG. However it is useful because the resource use is likely to be similar to that of the UK, and UK prices combined with international resource use would give a good estimate of likely UK costs.

4.2.1.4 Roche Sponsor Submission[45]

An unpublished sponsor submission received from Roche used the Van Cutsem[41] and Hoff [40] evidence in their calculations. They made no mention of any other studies in terms of cost-effectiveness. The submission included an economic evaluation of first line treatment with capecitabine for patients with advanced colorectal cancer. This evaluation is reviewed below.

The Roche sponsor submission presents the hypothesis that "capecitabine as a monotherapy treatment in advanced colorectal cancer is at least cost-effective, but most likely cost-saving compared to Mayo regimen using the England and Wales perspective."[45] Roche used outcome and resource use data from the Van Cutsem and Hoff trials, which were funded by Roche. Roche were involved as sponsors of the work and therefore have access to data that were not available to ScHARR.

Cost estimates

Their costing took an NHS perspective, using a time horizon spanning from start of treatment until progression of the disease (4-5 months). Therefore, drug costs and administration were assumed to be incurred during this short time period, and costs were not discounted. Costs incurred after disease progression were not included.

Drug doses were assumed to be the same as those used in the clinical trials: capecitabine 1,250 mg/m^2 twice daily for 14 days every three weeks, as licensed and recommended in the Summary of Product Characteristics; and infusional 5-FU/LV given by the Mayo regimen of calcium folinate 20mg/m^2 followed by 5-FU 425 mg/m^2 for 5 days every four weeks. All doses were based on an average patient of 1.7 m^2. Mayo regimen 5-FU/LV may be considered a suitable comparator, since it is one of the many intravenous regimens used widely in the UK. Costs of calcium folinate and infusional 5-FU, as well as capecitabine, were the same as those on the British National Formulary website (BNF No. 43).[55] Calcium folinate (LV) costs were not discounted, although they are known to be in practice.

The cost of administration was only calculated for Mayo regimen. The only administration costs presented were the additional number of hospital visits incurred by patients on the Mayo regimen. Doctor and nurse time and the cost of infusions were not included for either treatment regimen, which means that the calculated administration cost of capecitabine was zero. Five hospital outpatient visits were assumed per cycle for most patients, with a small proportion of trial participants who required overnight visits for infusion assigned the cost of an inpatient day. We disagree with this method, since based on consultation with clinicians we have assumed that patients undergoing capecitabine treatment will have at least one scheduled consultation with a specialist each cycle, to discuss their treatment and any adverse effects they might be experiencing and receive their new prescription. The number of scheduled consultations would likely be higher for capecitabine patients than for Mayo patients, since the cycle is shorter and adverse events would have to be monitored more carefully. Therefore the non-hospitalisation costs of administration are unlikely to be equivalent, and should have been calculated for both arms.

The cost of adverse event related hospitalisations was calculated using the average number of hospitalisations per patient and the cost of an inpatient hospital day from Netten et al.[61] This cost was similar across both arms of the study (£434 for capecitabine treatment and £503 for Mayo regimen). Unit costs and resource use were not presented in the sponsor report, but were available in the spreadsheet document that accompanied the submission. Costs were also calculated for unscheduled physician consultations related to adverse events (£39 for capecitabine and £28 for Mayo) and the drug costs of treating adverse events (£166 for capecitabine and £681 for Mayo). There were errors in the spreadsheet calculations of these drug costs, however, and the numbers should have been lower for both arms.

Return transportation ambulance costs (£333) were included for a proportion of Mayo patients as established by a survey conducted by Roche. No transportation costs were included for capecitabine patients since no administration costs were assumed.

The total cost over the cost horizon used in the analysis was £2,713 for capecitabine treatment and £4,979 for Mayo regimen treatment. The main differences came in the areas of drug cost, which favoured Mayo, administration, which favoured capecitabine, and the cost of drug therapy for the treatment of adverse events, which favoured capecitabine. The cost of capecitabine itself accounted for the majority of the capecitabine treatment cost. Administration made up the largest proportion of Mayo regimen costs. Treatment time was similar across both treatment arms, so duration of treatment did not contribute substantially to the cost difference.

Table 17: Costs used in Roche Model

Component of health care utilisation:	Capecitabine	Mayo regimen	Net Cost Savings
Hospital use	£434	£503	£68
Infusion Administration (hospitalisation only)	£0	£2,707	£2,707
Transportation to hospital for treatment	£0	£333	£333
Drug therapy	£2,072	£725	-£1,347
Treating adverse events	£166	£681	£515
Physician consultations	£39	£28	-£11
Total costs	£2,713	£4,979	£2,266

Outcomes

It seems that the intention was to use survival, progression-free survival and quality-adjusted survival as outcomes, however since the survival difference was negligible, a cost-minimisation analysis was performed instead. Outcome results were used from the trials mentioned above.[40,41] Although capecitabine patients experienced a higher response rate, there was no statistical difference in time to progression or overall survival, so therapeutic equivalence was assumed.

Cost minimisation analysis

The incremental cost of Mayo regimen over capecitabine, according to the Roche analysis, is £2,266. Therefore use of capecitabine presents a cost saving to the NHS. The authors conclude that capecitabine is dominant over the Mayo regimen due to an improved side effect profile and more convenient administration.

Sensitivity analysis

The main savings of capecitabine lie in the areas of administration and adverse events. Since capecitabine is unlikely to be administered intravenously and 5-FU/LV cannot be administered orally, the administration costs were not tested in the sensitivity analysis. Therefore the sensitivity analysis only dealt with variation in adverse event rates. Three extreme scenarios were tested, one in which neither arm experienced any side effects, one

in which capecitabine patients did, but Mayo patients did not, and one in which Mayo patients did, but capecitabine patients did not. In every scenario, capecitabine was cost saving, showing that adverse event rates, although they contribute to the cost difference, do not change the advantage of capecitabine over Mayo.

A threshold analysis was performed to find the maximum average cost of a visit to the hospital for Mayo administration. The authors found that this cost would be £17, and concluded that since this low cost was impossible to achieve, capecitabine was clearly cost saving.

No sensitivity analysis was performed for the cost of either drug, despite the fact that this cost makes up a large proportion of total treatment costs, and discounts are frequently given to hospital pharmacies on the cost of calcium folinate.

Discussion of Roche economic evaluation

Although the published paper on resource use based on the capecitabine trials was well constructed and comprehensive, the cost analysis included in the sponsor submission was too brief and included errors and omissions.

Although the comparator chosen was suitable, many different intravenous 5-FU regimens are used in the UK, and it would be useful for comparison to see the cost savings of capecitabine over other commonly used regimens. The time horizon of time to progression seems suitable, since there is no evidence on which treatment might be used as second-line therapy after capecitabine treatment, or what proportion of patients would receive any second-line treatment.

The decision to perform a cost-minimisation analysis was reasonable, since there was no difference in survival outcomes. The cost calculations themselves, however, were of poor quality. No resource use data or unit costs were given in the report, and the explanations of how the costs had been categorised and collected were unclear. The sensitivity analysis did not test enough variables to show that the cost of capecitabine was robust.

No mention of quality of life was made in the economic evaluation, despite the fact that QoL data had been collected from the trials by a well-validated method. The results of the postal survey conducted by Roche on society preferences were presented, however. The authors concluded that the survey demonstrated a societal preference for a description of capecitabine treatment over a description of Mayo treatment. The preference results for other kinds of treatment were not presented.

Despite these deficiencies, however, the cost differences are small, and it is unlikely that in any case capecitabine would become more expensive than Mayo regimen unless the drug price were to be raised substantially. Therefore the errors do not impact the authors' conclusion that capecitabine provides a cost-saving option with therapeutic equivalence to Mayo regimen 5-FU.

4.2.1.5 Bristol Myers Squibb Sponsor Submission[48]

The unpublished sponsor submission from Bristol-Myers Squibb (BMS)[48] reviewed the South American study by Murad et al, as well as cost analyses by Avon, Somerset, Wiltshire Cancer Services (November 2000) and Devon and Cornwall Cancer Services (March 1999) and a NICE rapid review of Irinotecan, Oxaliplatin and Raltitrexed for the treatment of Advanced Colorectal Cancer.[24] It also included a brief summary of an economic evaluation commissioned by BMS comparing UFT/LV with intravenous 5-FU/LV treatment. This economic evaluation used a Markov model over a five-year time horizon to estimate costs of treatment with 5-FU/LV and UFT/LV. The model included first and second-line chemotherapy costs, costs of palliative care, treatment of adverse events, hospitalisations not due to adverse events and monitoring. The results showed a minor cost saving in favour of UFT/LV (£289 per patient), with the majority of savings arising from decreased hospitalisation costs for administration.

The submission also included two economic evaluations of UFT/LV as a first-line treatment for advanced colorectal cancer, one based on each of the studies funded by BMS: Douillard et al[46,42] and Carmichael et al.[43] The trials each used different infusional 5-FU/LV regimens, one with a 4-week cycle and one with a 5-week cycle. The authors chose to present the 5-week cycle trial[43] in the main body of the report, despite an irregular administration schedule and a smaller patient population. The reasoning is that because UFT/LV is given on a 5-week cycle the difference in cycle lengths between the two treatment arms has the potential to affect the relative number of cycles received and therefore the costs. Also, a number of patients in the Douillard study[46] received a reduced calcium folinate dose. Although different resource use was recorded in the two trials due to different trial protocols, the main cost areas of drug costs and administration were included in both trials, so the total cost-effectiveness should be similar.

Cost estimates

The costing took an NHS perspective with a time horizon lasting the same length as treatment time on the trials, since costs were based on actual resource utilisation data from the trials. Since treatment times were less than one year and costs incurred outside of treatment were not counted, no costs were discounted.

Drug costs were calculated from the actual doses prescribed in the trial. A standard dose consisted of 300mg/m^2 daily UFT and 90mg daily calcium folinate, both for 28 days followed by a 7-day rest period. Dose reductions and escalations were accounted for by assuming an average dose of 250mg/m^2 for dose reductions and 350mg/m^2 for dose escalations. The mean body surface area of patients in this trial was 1.83 m^2, and all doses are based on this. The expected cost per patient for UFT/LV treatment was £2,315 in the Carmichael trial. The calcium folinate cost was discounted by 87% for both UFT and 5-FU/CV treatments, based on market research conducted by BMS. The 5-FU/LV dose was 425mg/m^2 5-FU with 20mg calcium folinate daily for five days every five weeks. The expected cost per patient on 5-FU/LV treatment was £269.

Administration resource use data were not collected in the Carmichael study, but consultation with an oncologist determined that UFT/LV patients would visit an oncologist once a cycle so that tests could be performed and another cycle could be prescribed. 5-FU/LV patients visited a chemotherapy unit each time their medication was delivered. It was assumed that 5-FU/LV patients would require more expensive day case visits whereas UFT/LV patients would only require the cost of a medical oncology outpatient follow-up appointment. The costs of both appointments were taken from NHS reference costs. The authors took a conservative approach and assumed that UFT/LV patients would visit a specialist once a week for the first treatment cycle, and once each cycle thereafter. The expected cost of chemotherapy administration was £4,160 for patients treated with 5-FU/LV and £592 for patients treated with UFT/LV.

Adverse event costs were given in terms of number and cost of hospital admissions. NHS reference costs were used to estimate the average cost of an admission of patients suffering from various conditions. The admission cost was multiplied by the number of admissions recorded for each condition in the trials. Because many admissions did not fall into any of the categories, however, the number of admissions in the "Other" category was more than all the specific categories combined. Because the "Other" category was so broad, it is possible that there is a large margin for error in these cost estimates. All hospitalisations over the treatment period were included in these calculations, not only those directly resulting from treatment.

The costs of concomitant medications and clinical procedures were also included in the submission, but contributed little to either the incremental cost or the total cost. These medications and tests are generally incurred with all treatments, leading to a similar cost for capecitabine and Mayo as well as UFT/LV.

Table 18 Average Costs Per Patient in the Carmichael Trial,[47] from the BMS submission[48]

Resource component	UFT/LV	5-FU/LV	Incremental cost
Chemotherapy medications	£2,315	£269	£2,046
Chemotherapy administration	£592	£4,160	-£3,568
Hospitalisations	£272	£387	-£115
Concomitant medications	£17	£14	£4
Other medical resources	£50	£69	-£18
Total direct costs	£3,246	£4,897	-£1,651

Table 19: Average costs per patient in the Douillard study,[46] from the BMS submission[48]

Resource component	UFT/LV	5-FU/LV	Incremental cost
Chemotherapy medications	£2,471	£293	£2,178
Chemotherapy administration	£606	£5,279	-£4,673
Hospitalisations	£314	£346	-£32
Healthcare visits	£60	£59	£1
Diagnostic procedures	£166	£158	£8
Concomitant medications	£3	£4	-£1
Total direct costs	£3,620	£6,138	-£2,518

Indirect costs were also estimated in the sponsor submission, in terms of the number of work days lost by patients in the Carmichael trial. The value of lost work time using the UK average weekly wage and the friction-cost method, was approximately £799 per UFT/LV patient and £1,030 per 5-FU/LV patient.

Outcomes

The outcome used in this analysis is improvement in toxicity endpoints. UFT/LV was not inferior to 5-FU/LV in any toxicity endpoint in the trial, which led the authors to perform a cost-effectiveness analysis. Because the authors had decided to do a cost-effectiveness analysis, only the endpoints that favoured UFT/LV were appropriate for the evaluation. The incremental cost-effectiveness ratios derived from these clinical endpoints represent the additional cost of UFT/LV for an additional patient to be free of the specified adverse event. Only toxicity endpoints that significantly favoured UFT/LV were considered in the economic evaluation. These outcomes included both grades 1-4 and grades 3-4 stomatitis/mucositis, leucopenia, and neutropenia, as well as thrombocytopenia of any grade, febrile neutropenia and infection/fever.

Cost-effectiveness analysis

Because the total cost of UFT/LV treatment was lower than 5-FU/LV treatment and the only endpoints used favoured UFT/LV, UFT/LV was found to be dominant in every case, and hence an incremental analysis was not performed.

Sensitivity analysis

A sensitivity analysis showed that the incremental cost of UFT/LV is relatively robust, most sensitive to chemotherapy administration costs and least sensitive to adverse event hospital costs and other medical resource costs. The only scenarios in which UFT/LV cost more than 5-FU/LV was if the cost of chemotherapy administration was £86 for both groups or if calcium folinate was acquired at BNF list prices.[55] The incremental cost of UFT/LV over 5-FU/LV varied from -£2,365 to +£866.

Because cost is most sensitive to administration costs, a threshold analysis was performed to test the number and cost of specialist consultations and outpatient visits for the administration of UFT/LV. In the base case, UFT/LV patients received an average of

1.775 specialist consultations per cycle and each consultation costs £86. To be equal in cost to 5-FU/LV patients, the number of consultations each cycle would be 6.730. If the cost per consultation is £218, cost equivalence would be achieved at 2.657 consultations per cycle.

Discussion of Bristol-Myers Squibb economic evaluation

Bristol-Myers Squibb have presented a comprehensive economic evaluation of UFT/LV as a first-line treatment of advanced colorectal cancer. Their cost calculations are detailed and relatively unbiased, as are the calculations of administration costs. Although only adverse events severe enough to require hospitalisation were costed, the superior adverse effect profile of UFT/LV would likely be reflected by lower costs of adverse event related consultations and drug treatment, and hence costing every element of adverse event management would be unlikely to change the results.

The authors of this study chose not to perform a cost-minimisation analysis as Roche did, but rather a cost-effectiveness analysis. Since the only trials comparing UFT/LV to a recognised regimen (Mayo) were designed to show non-inferiority, the only situation in which UFT/LV has a proven superiority to 5-FU/LV is in selected adverse events. By nature of this selectivity, some of the drawbacks associated with UFT/LV are overlooked, namely significantly reduced time to progression (although only amounting to 0.3 months), and a statistically non-significant but possibly clinically important reduced overall survival (1.0 months in the Douillard study[46]), as well as adverse events that are statistically equivalent between treatment arms. Since the authors had chosen to perform a cost-effectiveness analysis, it would have been useful to have an analysis of the incremental cost-effectiveness (using different outcomes) of 5-FU/LV over UFT/LV as well as UFT/LV over 5-FU/LV. Since UFT/LV has both a slight advantage in terms of adverse events and a slight disadvantage in terms of progression-free and overall survival, the slight advantage is reflected in the economic analysis, but not the slight disadvantage.

The economic evaluation of UFT/LV made no mention of quality of life, although data had been collected and were presented earlier in the report. This could have an impact on the cost-effectiveness analysis, since the QoL data shows that the improved adverse effect profile has no effect on quality of life, and therefore a cost-effectiveness analysis performed exclusively on the basis of the improved adverse effect profile might not reflect the true benefit (or lack thereof) to the patient.

As in the capecitabine analysis, the evaluation showed that the main cost differences between oral therapies and infusional regimens arise from drug cost and administration.

Since neither evaluation performed any kind of sensitivity analysis in which outcomes were tested, it is not known whether cost would be sensitive to variation in outcome.

4.2.2 Summary of Existing Economic Evidence

In summary, the existing economic evidence shows that oral drugs may have an economic advantage over the Mayo intravenous regimen, primarily due to their savings in administration, and possibly due to improved adverse event profiles as well. While the quality of evidence is good in the resource use studies[53,54] these studies do not report costs. Although the South American economic evaluations[52,51] claim to show cost savings associated with UFT usage, the quality of evidence is poor, as the resource use data do not come from trials or broadly based surveys, rate of resource use was not given, and it is doubtful whether the aggregated cost data are applicable to current UK practice. Thus there are no evaluations that can be directly translated to the UK context.

The analyses show that the increased drug acquisition cost associated with oral therapies is offset by the reduced cost of administration, and as a result the cost differences between the oral regimens and the Mayo regimen are small.

The major limitation of both submissions is that there is no economic analysis presented comparing oral drugs to any 5-FU regimen other than the Mayo regimen. Many different 5-FU intravenous regimens are currently used in the UK, and therefore the submissions are only partially relevant to current UK practice.

4.2.3 Quality of Life Evidence

Capecitabine

Although quality of life data were collected in the capecitabine trials, the results have not yet been published. Both trials used the EORTC QLQ-C30 questionnaire, assessed at baseline and at the start of each treatment cycle.

Results reported in the Roche sponsor submission[45] showed that there was no significant difference in global quality of life between capecitabine and Mayo treatments, as measured by the EORTC QLQ-C30 and that quality of life was maintained for patients in both arms of the studies.

The Roche sponsor submission [46] also included a social preferences study (Appendix 5 in the submission), conducted by post on randomly chosen members of the public. These were not people who had necessarily had any personal experience of colorectal cancer. A detailed questionnaire was used to determine social preference weights associated with the different treatment scenarios. The questionnaire was extremely long and complex and may well have been confusing to the respondents.

UFT/LV

Quality of life data for UFT/LV were collected and have been published.[46,47] In the Douillard study,[46] QoL was assessed with the Functional Living Index-Cancer (FLIC) 22-item questionnaire. In the Carmichael trial,[47] the EORTC QLQ-C30 was used. Like the capecitabine results, the UFT/LV trials showed no significant difference in favour of oral therapies. When adjusted for baseline characteristics, the Douillard study[46] revealed

no statistically significant differences between treatment arms. When the Carmichael study was adjusted for baseline characteristics, the subscale for diarrhoea remained statistically different (p=0.022) in favour of the 5-FU/LV arm. This seems at odds with the safety analysis, which showed no statistically significant higher incidence of diarrhoea in the UFT/LV arm, leading the investigators to hypothesise that the timing of the questionnaire may have influenced the results.

Although both oral drugs showed an improved adverse event profile, due to lower frequency of grade 3 and 4 adverse events, this was not reflected in improved quality of life for the patients. This may be because Mayo patients experience severe adverse events during the middle of their cycle, but they have mostly recovered by the time they are receiving their next course of treatment. If quality of life questionnaires are administered at the beginning of each treatment cycle, and (as in the case of the EORTC) only refer to the preceding week, then they are less likely to capture the adverse effects on quality of life of Mayo treatment. It is also possible that quality of life is improved through IV treatment, due to increased contact with nurses and peer support of other patients. It would be useful to investigate these possibilities further in future trials.

4.3 METHODS FOR ECONOMIC EVALUATION

An economic evaluation was undertaken to compare the cost-effectiveness of UFT/LV and capecitabine to intravenous 5-FU/LV. Intravenous 5-FU/LV is an appropriate comparator because it is the most common first-line treatment for metastatic colorectal cancer currently in use around the UK.

A number of intravenous 5-FU regimens are in common use in the UK: the Mayo regimen, the de Gramont (inpatient and outpatient regimens), the modified de Gramont (MdG) regimen and continuous infusion regimens. These are detailed in Appendix 2. The decision of which regimen to use depends on the preferences of the physician and the patient, the resources available at the local treatment centre, and the distances the patient may have to travel in order to receive treatment.

4.3.1 Estimation of net benefits

4.3.1.1 UFT/LV

Two phase III RCTs[46,47] of UFT/LV were identified (011 and 012). Only recently (September 2002) have the full reports of these studies been published.[46,47,43]. These are reviewed in full in section 3.2.2.

4.3.1.1.1 Douillard et al., 2002,[46]

In the Douillard study[46](study 011) comparing UFT/LV to the Mayo regimen, UFT/LV demonstrated statistical equivalence in terms of response rate (12% versus 15%), and

median overall survival (12.4 months versus 13.4 months). UFT/LV had a significantly inferior median progression-free survival rate (3.5 months versus 3.8 months, p=0.011).

Mean survival was calculated from the survival curve published in the sponsor submission using area under the curve analysis. The area under a survival curve gives the mean overall survival experienced in the trial. Therefore, the area between the UFT/LV survival curve and the 5-FU/LV survival curve gives the mean survival benefit of UFT/LV over 5-FU/LV. Calculated in this way, the mean survival of UFT/LV was 15.3 months and the mean survival of 5-FU/LV was 15.7 months.

4.3.1.1.2 Carmichael et al., 2002 [47]

In the Carmichael study[47](study 012), comparing UFT/LV to a modified Mayo regimen, UFT/LV demonstrated equivalence to infusional 5-FU/LV in terms of response rate (11% versus 9%), time to progression (3.4 months versus 3.3 months) and overall survival (12.2 months versus 10.3 months). The values for 5-FU/LV are however lower than would be expected compared to other 5-FU/LV trials [17].

Mean survival was calculated from the survival curve published in the sponsor submission using area under the curve analysis. Mean time to progression was 4.3 months for UFT/LV and 4.6 months for 5-FU/LV, and mean survival was 14.0 months for UFT/LV and 12.7 months for 5-FU/LV.

Discussion of Results

In the Carmichael study,[47] the 5-FU/LV dose was reduced by 25% since it was administered over 5-week intervals instead of 4-week intervals to avoid a monitoring bias. However, median doses were lower than the protocol dosage level in both trials (median of 452 mg/m^2/week versus protocol 531 mg/m^2/week 5-FU in the Douillard study [46]and a median of 418 mg/m^2/week versus protocol 425 mg/m^2/week 5-FU in the Carmichael trial), a difference of only 8%.

The survival rate of the 5-FU/LV arm was lower in the Carmichael study[47] than in the Douillard study,[46] while the survival rate of the UFT/LV arm remained the same. The regimen used in the Carmichael study is, however, not considered to be a good comparator, given that the protocol 5-FU doses used in the modified Mayo arm were 20% lower than standard Mayo regimens and the survival rates from that trial are considerably lower than expected for an efficient 5-FU regimen. The survival rates in the Douillard study[46] were similar to those observed in other 5-FU trials.[17]

For the purposes of economic analysis the results of the Douillard study[46]were used, since this study involved a larger number of participants and used the widely recognised 4-week Mayo regimen as its comparator treatment. The UFT/LV results were consistent between the two trials, so the choice of the Douillard study[46] does not bias the analysis.

4.3.1.2 Capecitabine

Two international RCTs[40,41] with identical protocols compared capecitabine to the Mayo Clinic regimen. The data from these two trials were also pooled in a report by Twelves (2002).[36] These are reviewed in full in section 2.2.1

4.3.1.2.1 Hoff et al, 2001[40]

In a published trial by Hoff et al.,[40] capecitabine demonstrated equivalence with the Mayo regimen in median time to progression (4.3 months versus 4.7 months) and median survival (12.5 months versus 13.3 months). Capecitabine had a superior response rate (24.8% versus 15.5%).

The survival and progression-free survival curves were also published in the article, and were used to calculate mean time to progression (5.4 months for capecitabine and 5.5 months for Mayo) and mean survival (14.8 months for capecitabine and 15.1 months for Mayo).

4.3.1.2.2 Van Cutsem et al, 2001[41]

In a published trial by Van Cutsem et al,[41] comparing capecitabine with Mayo regimen 5-FU/LV, capecitabine demonstrated an improved response rate (26.6% vs. 17.9%), and equivalent survival (13.2 months vs. 12.1 months) and progression-free survival (5.2 months vs. 4.7 months). The median survival and progression-free survival rates were similar to those seen in other studies of 5-FU/LV in the treatment of metastatic colorectal cancer patients [20,19].

The mean survival of capecitabine, calculated through AUC analysis of the survival curves, was 15.1 months, and the mean survival of Mayo was 14.1 months. The mean time to progression was 5.4 months for capecitabine and 5.8 months for Mayo.

4.3.1.2.3 Twelves, 2002[36]

In a report[36] using pooled data from Hoff et al[40] and Van Cutsem et al,[41] capecitabine demonstrated a significantly superior response rate (25.7% versus 16.7%, $p<0.0002$) and equivalent median progression-free survival (4.6 months versus 4.7 months) and overall survival (12.9 months versus 12.8 months). The mean survival, estimated using AUC analysis, of capecitabine was 15.7 months and the mean survival of Mayo was 15.1 months.

We have chosen to use the results published in the Twelves 2002 paper[36] in our analysis. The trials were performed using identical protocols for the purpose of pooling the data at a later date. The pooled study includes a very large number of patients at a wide range of centres and provides high-quality data for comparison.

4.3.2 Choice of comparator regimen

The Mayo regimen was used as a comparator in the trials because it is internationally the most widely used regimen. There is however no gold standard therapy in the UK for the treatment of advanced colorectal cancer. It is not known with certainty to what extent different regimens are used. However a recent survey, based on responses from 43 members of the British Oncology Pharmacy Association, reported that 37% of hospitals covered by the survey used low dose FA and 5-FU bolus (weekly or monthly) more often than any other regimen for first-line chemotherapy options for advanced colorectal cancer. The proportion of hospital using Modified de Gramont, de Gramont and PVI 5-FU more often than any other regimen were 26 %, 12 % and 7% respectively.[56]

We have therefore chosen to compare the oral drugs against the Mayo regimen and two infusional regimens: the modified de Gramont (MdG) regimen, given on an outpatient basis and the inpatient de Gramont regimen.

There is however no direct trial evidence comparing oral drugs with infusional 5-FU regimens. Therefore to compare the oral drugs against the MdG and inpatient de Gramont regimens it is necessary to consider an indirect comparison of the Mayo regimen against infusional regimens.

4.3.2.1 Efficacy of bolus v infusional 5-FU regimens

A range of published survival estimates for the de Gramont regimen are outlined in Appendix 5. These range from 42 to 64 weeks. Case-mix selection is an important determinant of survival and may account for the variability in these estimates.

Little published evidence was identified on the MdG regimen, although it is now widely used in the UK. The MdG regimen preserves the main elements of the de Gramont regimen: dose intensive exposure to FU with LV for 48 hours every 2 weeks, with minimal haematological gastrointestinal toxicity.[21] The UK Medical Research Council (MRC) have made the decision to move over to the MdG regimen without a large randomised equivalence trial because the modified de Gramont regimen is more 5FU-dose intensive and it has better non-randomised phase II response rates than the old de Gramont regimen. (Seymour M, Cookridge Hospital, Leeds: personal communication, 2002). In addition it is more convenient for patients and hospitals.

Evidence on the efficacy of bolus regimens (such as the Mayo) against infusional regimens (such as the de Gramont and the modified de Gramont) is limited.
A small number of studies have been identified and these are considered below.

Meta-analysis Group in Cancer, 1998 [15] **(Appendix 3)**
In a meta-analysis of trials comparing continuous infusion (CI) 5-FU regimens to bolus 5-FU regimens, CI regimens were found to be slightly more effective than bolus regimens. However only two of the trials involved regimens in which bolus or continuous

infusions were given alongside calcium folinate. In these two trials no significant survival benefit was demonstrated for continuous infusional regimens. In addition the meta-analysis used the results of six trials, none of which involved the de Gramont regimen and only one of which involved the Mayo regimen. All of the continuous infusion arms of these trials used prolonged infusions that continued for a number of days without interruption, and hence differ from the modified de Gramont regimen used in the UK. This meta-analysis is therefore not considered to provide high quality evidence on the relative effectiveness of the Mayo and de Gramont regimens.

De Gramont et al, 1997 [17] **(Appendix 4)**

A study by de Gramont et al[17] compared the Mayo regimen to the de Gramont regimen. The de Gramont regimen had higher response rates (32.6% vs 14.4%, p=0.0004), increased median time to progression (27.6 weeks v 22 weeks, p=0.004) and insignificantly increased overall survival (62 weeks v 56.8 weeks, p=0.067). Overall grade 3-4 toxicity was also lower on the de Gramont regimen (11.1% vs 23.9%, p=0.0004).

Although overall survival rates were higher for the de Gramont regimen, the difference was not statistically significant. In addition the survival rates in the Mayo arm of the de Gramont trial (56.8 weeks) are higher than those observed in the capecitabine and UFT/LV trials. They are also at the upper end of the published survival rates for de Gramont regimen (Appendix 5). This suggests that other factors are impacting on survival in the de Gramont trial. These may include issues relating to patient selection as well as possible early diagnosis of metastatic disease.

Cheeseman et al 2002 [21]

A recently published phase II trial by Cheeseman et al [21] to establish dose intensities for the modified de Gramont regimen reports that the optimum doses were 350 mg calcium folinate , 400 mg/m^2 bolus 5-FU followed by 2800 mg/m^2 5-FU infusion given over 46 hours. This regimen was given on an outpatient basis, with the bolus infusion being given during an outpatient attendance and a district nurse visiting the patient at home to disconnect the patient's line and flush it weekly. 46 patients participated in the trial. At the optimum infusion dose level, eight out of twenty-two (36%) patients experienced a partial response, with disease stability achieved in a further seven (32%). Median failure-free survival was 9.3 months. 15 of the 22 patients went on to receive second-line chemotherapy, and median overall survival from starting treatment was 16.8 months. This survival is similar to that seen in de Gramont et al 1997 [17]. The toxicity profile is similar to de Gramont regimen. The most common toxicities observed were nausea or vomiting and lethargy, with no adverse events worse than grade 3. No hospitalisation data were reported.

In conclusion, the limited evidence available demonstrates that the de Gramont regimen is superior to the Mayo regimen in terms of progression-free survival and in relation to toxicity, but that there is no statistically significant survival benefit.

For purposes of the economic analysis we have assumed that the survival benefits for the MdG and de Gramont regimens are identical. In addition it is assumed that the de Gramont regimens offer the same survival benefit as the Mayo regimen. This assumption has been tested in sensitivity analysis.

4.3.3 Estimation of net costs

No published UK costs for the use of oral drugs in advanced colorectal cancer were identified.

Costs estimates were divided into three categories: drug acquisition costs; chemotherapy administration costs; and adverse event management costs (including hospital admissions, physician consultations and drug treatment).

All costs are inflated to the year 2002 using the Hospital and Community Health Service (HCHS)[57] cost index until 2001 and GDP from 2001 to 2002. Unit costs are reported in Appendix 9.

No discounting has been applied given that the median survival times of patients with advanced metastatic colorectal cancer are around 12 months.

4.3.3.1 Drug costs

Drug acquisition costs were based on an individual with a body surface area of 1.75 m^2, undergoing therapy at standard treatment doses as listed in the Summaries of Product

Characteristics.[45,48] It was assumed that doses remained at the prescribed level for the duration of treatment. This may result in a slight overestimate because in the trials the average doses administered were lower than the prescribed dose. The impact of this assumption is tested in the sensitivity analysis.

The prescribed capecitabine dose was 4300 mg daily: 4 x 500 mg tablets and 1 x 150 mg tablet administered each morning and evening. The prescribed UFT dose was 5 UFT capsules each day, or 1680 mg/m^2/week. The prescribed Mayo dose was 425 mg/m^2/day 5-FU with 20 mg/m^2/day LV. The De Gramont dose was assumed to be 1000 mg/m^2/day 5-FU with 200 mg/m^2/day LV. The Modified de Gramont dose was assumed to be 350 mg LV, 400 mg/m^2 5-FU bolus then 2800 mg/m^2 5-FU infusion over 46 hours.

Drug costs for 5-fluorouracil, calcium folinate (LV) and capecitabine were taken from the British National Formulary website (BNF No. 43).[55] Drug costs for UFT were taken from the letter announcing price changes included in the sponsor submission from Bristol-Myers Squibb.[48] VAT was calculated on all drug costs.

A sensitivity analysis was tested in which calcium folinate was acquired at a discounted price, based on estimated discounts (87% for both tablets and vials) established by market research in the unpublished BMS submission [48]. We were able to verify from discussions with a number of pharmacists, that substantial discounts are often offered to hospitals for this drug. As discounts are kept confidential to hospitals, we were not able to verify the estimated discount. The impact of the discount of LV on the cost of the Mayo and de Gramont regimens is substantial, given that LV accounts for over 50% of the total drug cost for these regimens.

Costs were calculated per cycle and then adjusted to generate a cost per 28 day period to allow comparison. The drug cost per 28 day period was £464 for capecitabine, £892 for UFT/LV, £189 for the Mayo regimen, £563 for the de Gramont and £394 for MdG regimens. These costs include VAT, but not discounts.

4.3.3.2 Administration costs

Administration costs were divided into two groups: costs that were incurred each cycle (cyclical costs) and costs that were incurred only once over the period of treatment (one-off costs). One-off costs included education for patients on oral therapies, and line insertion and overnight admissions associated with the outpatient de Gramont regimens. Cyclical costs included inpatient and outpatient hospital visits, a creatinine test for capecitabine patients, preparatory drugs, community nurse infusion administration and home visits, infusion pumps, pharmacy preparation and materials.

The costs of outpatient appointments were taken from the Chrisitie Hospital (Hawkins R, Chrisitie Hospital, Manchester: personal communication, 2002). The cost of an outpatient appointment with chemotherapy is assumed to be £ 150, whilst the cost of an outpatient clinic appointment without chemotherapy is assumed to be £ 80. The costs of inpatient

stays and other administration costs were taken from the PSSRU.[58] The cost of OP appointments were the key driver to the cost of administration for capecitabine, UFT/LV, the Mayo and the MdG regimen. These costs were tested in sensitivity analysis.

Diagnostic tests have not been included in the analysis. They are assumed to be similar across all treatment arms. Costs of primary care and transportation (in hospital ambulances) were reported in the sponsor submissions but have not been included as they make only a small contribution to total incremental costs.

One-off costs

The costs of time and materials for patient education were estimated following discussion with a number of clinicians. Patients receiving oral drugs are assumed to receive a fifteen-minute nurse appointment at the beginning of their treatment to discuss their role and responsibilities. They were also given materials to take home with them. The estimated cost of £ 7, based on 15 minutes of nurse time, was assumed to be the same for both capecitabine and UFT/LV treatment. The MdG regimen was assumed to have a one-off cost of £ 265 for line insertion.[59] The Mayo regimen and the inpatient de Gramont regimen were assumed to have no one-off costs.

Cyclical Costs

Patients undergoing oral therapies were assumed to attend one outpatient appointment each cycle (Orr B, Weston Park Hospital, Sheffield: personal communication, 2002). Patients on the Mayo regimen incurred the costs of five outpatient attendances to a cancer ward each cycle, as well as the cost of the infusions themselves.[60] Patients on the MdG regimen incurred one outpatient attendance to the cancer ward each cycle and two community nurse home visits each cycle to disconnect and maintain their infusion lines.[21] They also incurred the costs of infusion pumps and materials associated with pump and line maintenance.

The 28-day cyclical administration costs were £113 for capecitabine, £64 for UFT/LV, £839 for Mayo patients, £650 for MdG and £ 1500 for inpatient de Gramont.

4.3.3.3 Management of adverse events

Both oral drugs have been reported to have improved toxicity profiles compared to the Mayo regimen. In addition the adverse event rates reported in the trials suggest that the toxicity profile of capecitabine may be slightly better than the toxicity profile of UFT/LV with lower adverse event rates in every category except hand-foot syndrome, but little major overall difference.

The costs of management of adverse events was divided into three groups: hospitalisations, physician consultations and drug treatment costs.

Capecitabine

For capecitabine, resources used relating to hospitalisations and physician consultations were taken from the study by Twelves et al[53] and combined with UK unit costs taken from the PSSRU.[58] Only hospitalisations directly related to adverse events associated with treatment were considered. Costs of drug treatment for adverse events were taken from the Roche sponsor submission[45] and checked against common treatments and costs according to clinicians and the BNF.

UFT/LV

The adverse event rates given in the UFT/LV trials are not considered to be reliable. Although the number of hospitalisations was consistent between the two UFT/LV trials, the hospitalisation rates appear to include all non-administration-related hospitalisations. This includes adverse events associated with disease symptoms and other illnesses as well as treatment-related adverse events. This is likely to overestimate the cost of managing treatment-related adverse events. In addition the BMS sponsor submission[48] recorded very few expensive drugs treatment: this may be because drugs administered in the hospital were not recorded. Given that expensive antibiotics tend to be administered during hospital treatment drug costs may be therefore be underestimated. A more reliable estimate of treatment-related adverse events is therefore required.

Since the adverse event profile is equivalent or superior to Mayo in nearly all categories, however, it could be assumed that the resource use rates for treatment-related adverse events would be similar but slightly lower than those incurred in Mayo treatment. Therefore a reasonable maximum cost would be the treatment-related adverse event costs of Mayo treatment calculated from the Twelves analysis;[53] that is, £851. Although this may still be an overestimate, it is more reasonable than counting all non-administration-related costs.

Mayo

Adverse event costs for the Mayo regimen were calculated using the same methodology as for the costs of adverse events for capecitabine. The cost estimate obtained for Mayo treatment was very close to the figure previously reported in a recent NICE analysis of colorectal cancer drugs.[24]

De Gramont and MdG

The de Gramont and MdG regimens are assumed to have the same toxicity profile . They are assumed to be less toxic than the Mayo regimen (de Gramont et al[17]). The number of hospital days and drug treatment costs were taken from a previous NICE analysis of colorectal therapies[24] and multiplied by the PSSRU cost of a medical oncology inpatient day. However, since different trials and hence different patient groups are being considered these costs must be viewed with caution.

The cost of line complications needs to be taken into account for patients on outpatient regimens, such as the MdG regimen. Complications range from minor to major, and may even require re-siting of the line. Estimates of the frequency of occurrence and cost of treating complications has been provided by Professor James. (James R, Mid Kent Oncology Centre, Maidstone. Personal communication 2002). Based on 100 patients receiving treatment it is assumed that 20 patients experience a minor complication at a cost of £50, 10 patients experience a major complication at a cost of £250 and 5 patients require re-siting of the line at a cost of £ 250. A total cost of £4,750 for 100 patients.

The 28-day cost of treating adverse events is £131 for capecitabine, £170 for Mayo (and UFT), and £29 for the MdG regimen and £22 for the inpatient de Gramont regimen. Given the uncertainty relating to estimation of adverse event costs, a sensitivity analysis

was examined in which adverse events were excluded and only drug acquisition and administration costs were considered.

4.3.3.4 Total Treatment Costs

Total treatment costs were derived by multiplying the cost per 28 day period by the treatment duration, and adding on the one-off administration costs.

No consistent policy exists amongst UK clinicians regarding duration of treatment for patients receiving chemotherapy for advanced colorectal cancer.[61] Treatment for patients who are responding or who have stable disease can be continued until disease progression or stopped after a fixed period of time, usually between 3 and 6 months.

A recent study by Maughan et al [61] which compared continuous or intermittent chemotherapy for advanced colorectal cancer suggested that there was no clear evidence of a benefit in continuing therapy indefinitely. Patients who were responding or had stable disease after receiving 12 weeks of de Gramont, Lockich or Raltitrexed were randomised to either "continue" therapy until progression or "stop", re-starting on the same therapy on progression. Of the 178 patients allocated to stop therapy, 39% re-started treatment for a median time of 83 days. There was no clear evidence of a difference in progression-free survival or overall survival. In addition there appears to be a gain in quality of life for patients on intermittent therapy, supporting a stopping policy for chemotherapy after 12 weeks.

For the purposes of economic evaluation it was assumed that all patients would be treated for 12 weeks. The survival results reported in the RCTs of the oral drugs are based on patients treated until disease progression. It was assumed that there was no detrimental impact on survival resulting from stopping treatment at 12 weeks. The assumption that patients are treated for only 12 weeks may underestimate total treatment costs given that, based on the Maughan et al study [61] a proportion of patients who stop treatment at 12 weeks may continue treatment on first line therapy at a later stage. A sensitivity analysis was considered in which patients were treated until disease progression. In reality treatment duration may well lie between these two scenarios for many patients.

Treatment costs are likely to be overestimated given that treatment may be stopped earlier for some patients due to toxic effects or progression.

The estimated total treatment costs are given in table 20.

Table 20. Total Treatment Costs

	Capecitabine	UFT/LV	Mayo	MdG (outpatient)	de Gramont (inpatient)
Drug Cost	£ 464	£ 892	£ 189	£ 394	£ 563
Administration	£ 113	£ 64	£ 839	£ 650	£ 1,500
Adverse events	£ 131	£ 170	£ 170	£ 29	£ 22
Total 28 day costs	**£ 708**	**£ 1,126**	**£ 1,198**	**£ 1,073**	**£ 2,085**
One-time costs	£ 7	£ 7	£ -	£ 265	
Treatment period (in weeks)	12	12	12	12	12
Total treatment costs	**£ 2,132**	**£ 3,385**	**£ 3,593**	**£ 3,485**	**£ 6,255**

Discussion of results

The costs of both capecitabine and UFT/LV were estimated to be lower than the treatment costs for the three intravenous regimens based on a treatment duration of 12 weeks. The cost estimates for UFT/LV, the Mayo regimen and the MdG regimen were similar. The cost estimate for inpatient de Gramont is substantially higher than for the MdG regimen delivered on an outpatient basis, both in terms of drug costs and administration costs.

It should be noted however that the cost of UFT/LV and the infusional regimens do not take into account the substantial discount offered on BNF prices on calcium folinate.

For capecitabine and UFT/LV the relatively high drug costs of the oral drugs were offset by lower administration costs.

A comparison of the costs estimates derived by ScHARR and those provided in the sponsor submissions is given in table 21. The sponsor submission costs have been converted into 28 day costs for ease of comparison.

Table 21: Comparison of 28 day Treatment Costs

	Capecitabine		UFT/LV		Mayo		
	ScHARR	Roche	ScHARR	BMS	ScHARR	BMS	Roche
Drug cost	£464	£395	£892	£422	£189	£77	£145
Administration	£113	£0	£64	£121	£839	£1,100	£541
Adverse event management	£131	£122	£170	£75	£170	£84	£243
Other	N/A	£0	N/A	£34	N/A	£34	£67
Total 28 day costs	**£708**	**£517**	**£1,126**	**£652**	**£1,198**	**£1,295**	**£996**

Comparison of treatment costs is not straight forward. For instance ScHARR's estimates for drug costs include VAT, whereas the sponsor submissions do not. In addition the BMS estimates for drug costs include a discount of 87% on the BNF price of LV. When these were taken in to account there is little difference in the costs of drugs between the ScHARR estimates and the sponsor submissions.

The Roche submission presented the incremental cost of administration over the Mayo regimen and therefore did not include a cost for administration of capecitabine. The BMS submission took a conservative approach to estimating the cost of administering UFT/LV by assuming that patients visited a specialist weekly during the first cycle of chemotherapy, as opposed to once per cycle.

The "other" category in the Roche cost estimates includes transportation for hospital administration. The "other" category In the estimation of BMS cost includes concomitant medications and clinical procedures. These medical resources had little impact on the cost of medical resources.

4.3.4 Second line treatment

The Carmichael study[47] records the number of participants who go on to receive second line treatment after treatment with UFT/LV and Mayo regimens. In this study, 41% of UFT/LV patients and 39% of modified Mayo patients went on to receive second line treatment. 49% of the UFT/LV patients and 47% of the Mayo patients received 5-FU treatment, 28% of each arm received irinotecan only, and 13% of UFT/LV patients and 16% of Mayo patients received either oxaliplatin or irinotecan with oxaliplatin. The effect of second line treatment on survival was similar across both arms.

In the recent NICE rapid review of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer[24] it was estimated that 30-35% of patients who die of colorectal cancer have received chemotherapy, and of these patients, approximately 65%

go on to have second-line chemotherapy. The proportion of patients who are likely to receive second line treatment in normal clinical practice is unknown.

If it is assumed that a similar proportion of patients receiving oral therapies and intravenous therapies will go onto receive second line treatment and that the duration of treatment is similar for both, then the cost of second line therapy will not change between the different therapies and will not influence the incremental cost between therapies.

The cost of second-line treatment is not included in the base-case scenario. It is included in a sensitivity analysis to demonstrate the possible costs incurred.

4.4 COST ANALYSIS

4.4.1 Methods

A cost-minimisation analysis was performed for comparisons of capecitabine and UFT/LV with the Mayo regimen, since the survival benefits have been shown to be were statistically equivalent.

A cost-minimisation analysis was also performed for comparisons of capecitabine and UFT/LV with the infusional regimens. This was based on no proven evidence of survival difference between the Mayo and the infusional regimens and hence no assumed survival difference between the oral drugs and the infusional regimens (refer to section 4.3.2.1)

4.4.2 RESULTS

The results of the cost minimisation analyses are presented in table 22.

Table 22: Cost Savings from Oral Drugs

	Capecitabine	Mayo	MdG (outpatient)	de Gramont (inpatient)
Total treatment costs	**£ 2,132**	**£ 3,593**	**£ 3,485**	**£ 6,255**
Cost saving from capecitabine		-£ 1,461	-£ 1,353	-£ 4,123
	UFT/LV			
Total treatment costs	**£ 3,385**	**£ 3,593**	**£ 3,485**	**£ 6,255**
Cost saving from UFT/LV		-£ 209	-£ 101	-£ 2,870

4.4.3 Discussion of Results

In comparison to the intravenous regimens, both capecitabine and UFT/LV were shown to have lower costs. Although the drug costs are higher, oral drugs offer the advantage of a lower volume of hospital visits and avoid the need for line insertions and their potential complications or inpatient administration of chemotherapy.

Fewer hospital visits may however be seen as a disadvantage, as it provides less opportunity for symptom monitoring and consultation with medical staff. Clearly, this has dangerous implications for patient safety, and some patients may need varying degrees of monitoring in order to ensure their safety. Roche currently offer a Hospital at Home service to patients on capecitabine. This involves a trained nurse contacting new patients by phone twice within the first two weeks to check patient are coping adequately and also provides a support line for patients with concerns or questions. If this service is withdrawn by the manufacturer it may be necessary for hospitals or the community to provide support to patients on oral chemotherapy. Provision of this service has not be included in the cost analysis.

The costs used in the economic evaluation were not based on published studies and are subject to uncertainty. Key uncertainties related to the price of LV, which is known to be discounted substantially below BNF prices, the treatment duration for different therapies which impacts on their total treatment cost, the costs of managing adverse events and the cost of outpatient appointments. These issues are tested in sensitivity analysis.

The greatest uncertainty is based around the comparison of oral drugs with the de

Gramont regimens. This is based on an indirect comparison. The evidence comparing bolus and infusional regimens is limited and subject to debate. The study by de Gramont et al [19] comparing the Mayo regimen with the de Gramont regimen reported that overall survival rates were higher for the de Gramont regimen, but that the difference was not statistically significant (62 weeks v 56.8 weeks, p=0.067). This difference of 5.2 weeks may however be considered clinically significant. A cost-effectiveness analysis was therefore performed to demonstrate the impact assuming a survival difference between the de Gramont regimens over oral drugs.

In addition the use of a cost minimisation approach for comparing the de Gramont regimens with the oral drugs ignores the advantages offered by the de Gramont regimen over the Mayo regimen in terms of response rates, progression-free survival, toxicity and quality of life. In the de Gramont study [19] the de Gramont regimen had increased median time to progression (27.6 weeks v 22 weeks, p=0.004) and lower grade 3-4 toxicity than the Mayo regimen (11.1% vs 23.9%, p=0.0004). An additional cost-effectiveness analysis was therefore performed to explore the impact of these factors on the economic evaluation.

4.4 Sensitivity analysis

A number of assumptions were made in the base case methodology that could have an impact on the final results. To study the potential impact of these assumptions, they were tested in a sensitivity analysis.

Scenario A: Base case

Scenario B: Discounts on drug costs

In the base case the drugs were all costed according to the list prices on the BNF website [55]. In practice, many hospitals obtain discounts on drugs, some of which can be very substantial. There was no indication that discounts were offered on capecitabine, Uftoral or 5-fluorouracil; however calcium folinate (LV), which accompanies UFT and both intravenous regimens, is often discounted heavily. A sensitivity analysis was tested in which LV was costed, based on estimated discounts of 87% for tablets, as established by market research in the unpublished BMS submission.[48] For consistency the same discount was applied to LV vials. The exact cost of LV is likely to vary between institutions.

Scenario C: Dose intensity

In the base case, doses were costed according to the indications in the Summaries of Product Characteristics [45] [48]. In practice, however, doses are often adjusted due to adverse effects. Median doses prescribed in the trials were lower than the indicated doses set out in the trial protocol. A scenario was tested in which the average doses were costed instead of the protocol doses.

For UFT/LV the median dose intensity in the Douillard study[46] was 1555 mg/m^2/week (93%), and 1542 mg/m^2/week (98%) in the Carmichael study.[47] The average trial dose of 93% from the Douillard study[46] was used in the sensitivity analysis .For capecitabine an average of 81% was used in the sensitivity analysis, based on the average capecitabine dose intensity in the trials: 80% in the Hoff trial[40] and 82% in the Van Cutsem trial.[41] For the Mayo regimen the delivered dose was 85% in the Douillard study,[46,42] 86% in the Hoff trial[40] and 95% in the Van Cutsem trial.[41] An average of 90% was used in the sensitivity analysis. For studies using the de Gramont and modified de Gramont regimens, only the prescribed dosage was reported so no dose adjustment was used in the sensitivity analysis.

Scenario D: Cost of OP appointments

In the base case it was assumed that a cost difference existed between OP appointments with chemotherapy and outpatient appointments without chemotherapy. The OP costs were assumed to be £150 and £80 respectively and were supplied by Christie Hospital. (Hawkins R, Christie Hospital, Manchester: personal communication, 2002). It is known that these OP costs will vary between institutions. A scenario was tested in which OP appointments for infusional chemotherapy and OP appointments for oral drugs were assumed to incur the same costs, based on the cost of medical oncology outpatient attendance of £ 109 from Netten et al.[58] In addition the cost of an medical oncology OP follow-up appointment, £ 86 and the cost of a day case appointment, £212 from NHS reference costs were also tested in the sensitivity analysis.

Scenario E: Exclusion of costs of managing adverse events

Due to lack of resource-use information, particularly regarding UFT/LV and MdG treatments, many assumptions were made in calculation of the costs of treating adverse events. Because of the resultant uncertainty, a scenario was tested in which adverse event costs were not included, and costs could be compared only on the basis of drug costs and administration costs, the two main cost drivers.

Scenario F: Treatment until disease progression.

The total cost of treatment was sensitive to the length of treatment time. This may vary between regimens. A scenario in which patients were treated until disease progression was considered to reflect possible variations in treatment period. Time to progression for capecitabine, UFT/LV and Mayo were 4.6 months, 3.5 months and 4.7 months respectively. It was assumed that the time to progression for the MdG and De Gramont regimens was the same as that for the Mayo. However there is evidence available that the de Gramont regimen offer advantages over the Mayo regimen in terms of time to progression. This is explored further in section 4.5.2.

Scenario G: Cost of second line therapy included

There is little information regarding how treatment would differ after disease progression for patients on different treatment arms, therefore no costs after progression (tests, primary care, palliative treatment, second-line treatment) were estimated in the base case.

A sensitivity analysis was undertaken in which second line treatment costs were included. It was assumed that 40% of patients received second line chemotherapy and that all these patients received irinotecan. Patients undergoing second-line therapy were assumed to be treated for 3 months after disease progression. The monthly cost of second-line chemotherapy with irinotecan was taken from the NICE rapid review of irinotecan, oxaliplatin and raltitrexed.[24] The cost of second line treatment per patient, based on these figures, is £ 2125.

Table 23. Treatment costs in scenarios B to G

	Capecitabine	UFT/LV	Mayo	MdG (outpatient)	de Gramont (inpatient)
A: Basecase	**£ 2,132**	**£ 3,385**	**£ 3,593**	**£ 3,485**	**£ 6,255**
B: Discounted LV price	£ 2,132	£ 2,504	£ 3,296	£ 2,615	£ 4,852
C: Average dose intensities from trials	£ 1,867	£ 3,197	£ 3,536	£ 3,485	£ 6,255
D1: OP appointments have equal cost	£ 2,258	£ 3,460	£ 3,015	£ 3,254	£ 6,255
D2 : OP appointments based on NHS reference cos	£ 2,164	£ 3,404	£ 4,687	£ 3,923	£ 6,255
E: Adverse events costs excluded	£ 1,738	£ 2,875	£ 3,084	£ 3,400	£ 6,188
F: Treatment until Progression	£ 3,546	£ 4,288	£ 6,115	£ 5,745	£ 10,645
G: Cost of second line therapy included	£ 4,257	£ 5,510	£ 5,718	£ 5,610	£ 8,380

Table 24. Incremental costs in sensitivity scenarios

	Capecitabine Mayo (outpatient)	Capecitabine MdG (inpatient)	Capecitabine de Gramont	UFT/LV Mayo (outpatient)	UFT/LV MdG (inpatient)	UFT/LV de Gramont
A: Basecase	-£ 1,461	-£ 1,353	-£ 4,123	-£ 209	-£ 101	-£ 2,870
B: Discounted LV price	-£ 1,164	-£ 483	-£ 2,721	-£ 792	-£ 111	-£ 2,349
C: Average dose intensities from trials	-£ 1,669	-£ 1,618	-£ 4,388	-£ 339	-£ 288	-£ 3,058
D1: OP appointments have equal cost	-£ 757	-£ 996	-£ 3,997	£ 445	£ 206	-£ 2,795
D2 : OP appointments based on NHS reference cos	-£ 2,523	-£ 1,759	-£ 4,091	-£ 1,283	-£ 519	-£ 2,851
E: Adverse events costs excluded	-£ 1,346	-£ 1,662	-£ 4,450	-£ 209	-£ 524	-£ 3,312
F: Treatment until Progression	-£ 2,569	-£ 2,199	-£ 7,099	-£ 1,827	-£ 1,457	-£ 6,357
G: Cost of second line therapy included	-£ 1,461	-£ 1,353	-£ 4,123	-£ 209	-£ 101	-£ 2,870

Discussion of results of scenarios B to G

The sensitivity analysis showed that the cost estimates for capecitabine were robust to changes in the cost parameters. Capecitabine offered cost savings relative to all three intravenous therapies under all scenarios. UFT/LV costs were lower than all intravenous regimens except in scenario D1 where OP appointments with and without chemotherapy are assumed to be have the same cost. However the majority of institutions do appear to differentiate in cost terms between OP appointments for oral drugs and OP appointments at which intravenous chemotherapy is administered (often classified as day case visits rather than OP appointments) and therefore this scenario is unlikely to reflect the costing policy of most NHS Trusts.

The cost savings offered by capecitabine were minimised in Scenario C in which a substantial discount is assumed for LV. This discount reduced the cost of all the intravenous regimens. In this scenario the cost difference between capecitabine and the MdG regimen is less than £500. This scenario may well reflect currently costs to many NHS institutions, although the exact size of the discount received by individual institutions is not known. This discount also reduces the cost of UFT/LV and therefore the impact of this scenario on the cost savings offered by UFT/LV were lower.

Treatment costs are sensitive to treatment duration. In the base case all treatments were assumed to be given for 12 weeks. Given that the time to progression is assumed to be higher for the de Gramont regimens than for oral therapies using the assumption that patients were treated until progression substantially increased the cost saving offered by oral therapies. Due to lack of evidence no difference to the survival benefits offered by the regimens was assumed whether treatments were given for 12 weeks or until progression.

4.5 COST PER LIFE YEAR AND COST PER LIFE YEAR GAINED

4.5.1 Survival difference between the de Gramont regimens and the oral drugs

The base case assumed that the survival outcomes for the de Gramont regimens were equivalent to the outcomes from the oral drugs.[40,41] A sensitivity analysis was carried out to demonstrate the impact of assuming that the de Gramont regimens offered a survival advantage over the oral drugs.

The survival difference between the de Gramont regimen and the Mayo comparator from the de Gramont trial[17] was 5.2 weeks. The impact of this survival difference was assessed in terms of the cost per life year gained.

Capecitabine

The results of the cost-effectiveness analysis showed that capecitabine offered a cost saving of £1,461 over the MdG regimen and £4,123 over the inpatient de Gramont

regimen, but resulted in a reduction in survival benefit of 5.2 weeks. Expressed in terms of a cost per life year gained, the cost per life-year gained of MdG treatment over capecitabine treatment was £13,571 and the cost per life-year gained of inpatient de Gramont treatment over capecitabine treatment was £ 41,344. The additional survival benefit of MdG over capecitabine is therefore achieved at a reasonable cost and therefore the cost saving from oral drugs is not sufficient to make it a more cost effective option.

UFT/LV

The results of the cost-effectiveness analysis showed that UFT/LV offered a cost saving of £209 over the MdG regimen and £2,870 over the inpatient de Gramont, but resulted in a reduction in survival benefit of 1.2 months. Expressed in terms of a cost per life year gained, the cost per life-year gained of MdG treatment over UFT/LV treatment was £758 and the cost per life-year gained of inpatient de Gramont treatment over UFT/LV treatment was £21,631. The additional survival benefit of MdG and inpatient de Gramont over UFT/LV is achieved at a reasonable cost and therefore the cost saving from UFT/LV is not sufficient to make it a more cost effective option.

These numbers are illustrative only. However they do show that the cost savings offered by the oral drugs, particularly in relation to MdG are not large and therefore if the oral drugs do reduce the survival of patients by an order of 5.2 weeks, oral drugs cannot be considered a cost effective option relative to the MdG regimen. It is difficult to draw any firm conclusions from this cost-effectiveness analysis, given that it is based on an indirect comparison of patients from two different studies.

4.5.2 Difference in progression-free survival between de Gramont regimens and oral drug regimens

Progression-free survival is considered important because disease progression may impair both physical and emotional health. In addition progression-free survival is an important outcome measure, given that the relationship between progression-free survival and overall survival may be confounded by the use of second line treatment following progression.

Capecitabine
The progression-free survival difference between the de Gramont regimen and the Mayo comparator from the de Gramont trial [17] was 5.6 weeks. The progression-free survival gain of MdG over capecitabine was therefore assumed to be 5.6 weeks. The cost per progression-free life-year gained was £12,567. The progression-free survival gain of inpatient de Gramont over capecitabine was also assumed to be 5.6 weeks. The cost per progression-free life-year gained was £32,286.

UFT/LV
The progression-free survival gain of modified de Gramont over UFT/LV was assumed to be 6.9 weeks. The cost per progression-free life-year gained was £ 758. The progression-free survival gain of inpatient de Gramont over UFT/LV was also assumed to be 6.9 weeks. The cost per progression-free life-year gained was £21,631.

These numbers are illustrative only. The results of the cost-effectiveness analyses should be viewed with caution, since the outcomes are based on an indirect comparison of regimens from different trials. However they do show that the cost savings offered by the oral drugs, particularly in relation to MdG are not large and therefore on the assumption that oral drugs do reduce the progression-free survival of patients by an order of 5.6 weeks, oral drugs cannot be considered a cost effective option relative to the MdG regimen in terms of the cost per progression-free life years gained.

4.5.3 Difference in quality-adjusted progression-free survival between de Gramont regimens and oral drug regimens

The purpose of chemotherapy for advanced metastatic disease is as much for palliation of symptoms as for relatively small survival benefits. It is essential to ensure therefore that the burden of treatment does not negate the palliative and survival benefits**.**

None of the clinical trials measured utility values. However Petrou et al 1997[62] has previously assessed utility values for patients with advanced 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, given as 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.

In order to estimate the effect of adjusting progression-free survival for quality of life the following assumptions were made. All days in hospital, whether for chemotherapy (including outpatient administration) or toxic effects, count as zero. The value of zero is arbitrary and is tested in a sensitivity analysis using the value 0.5. The remaining days are multiplied by the QALY value shown by Petrou for stable disease of 0.95. The method outlined above has been used in a previous NICE report [41] and has similarities to

the Q-TWIST method described by Gelber[63].

The progression-free survival gain of MdG over capecitabine was previously assumed to be 1.3 months (5.6 weeks). Taking account of the potential impact of quality of life the progression-free survival gain fell to 1.2 months. The MdG regimen involved higher hospitalisation for administration but lower hospitalisation for adverse events. In addition the benefit of the remaining time prior to progression was reduced by the assumed utility value of 0.95. The overall effect was however small.

The progression-free survival gain of MdG over UFT/LV was previously assumed to be 1.6 months (6.9 weeks). Taking account of the potential impact of quality of life the progression-free survival gain rose to 1.7 months. The UFT/LV involved higher hospitalisation for adverse events, which offset the reduction in benefit of the remaining time prior to progression by the assumed utility value of 0.95. The overall effect was however small.

4.6 IMPACT ON THE NHS

4.6.1 Patient volumes

In 2003, it is estimated, based on current colorectal cancer incidence rates, that the number of new patients presenting with colorectal cancer will be 29,643 [5]. Of these patients, it is estimated that 29% (8,596) will present with metastatic colorectal cancer [1] and 50% (10,524) of those remaining will go on to develop metastatic disease [58]. This results in a pool of 19,120 patients annually with metastatic colorectal cancer.

Approximately 30% of those who die of metastatic colorectal cancer have received chemotherapy treatment [58]. It has been suggested that not all patients who could benefit from chemotherapy currently receive treatment , with a further 15% having the capacity to benefit from such treatment [58]. Based on these figures , 5,736 patients with colorectal cancer would therefore be treated with first line chemotherapy at current rates, with the potential to treat up to 8,604 patients. Since some patients who currently refuse intravenous therapy would accept oral therapy, it is likely that widespread use of oral therapies will increase the proportion of patients who are treated.

4.6.2 Market Share of Oral drugs

The proportion of patients currently receiving oral drugs is not known.

Factors influencing the proportion of patients, who are fit for treatment, likely to receive oral agents as first line therapy in the future include:

a) proportion of patients not eligible for or who refuse the FOCUS trial
b) proportion of patients not eligible for oxaliplatin downstaging of liver metastases
c) proportion of patients experiencing line complications with 5-FU

Use of oral therapies will also be dependent on patient preference and is therefore likely to vary between providers.

It is assumed that 45% (8,604) of patients with metastatic colorectal cancer receive chemotherapy. Of these it is assumed that 10% enter the FOCUS trial and that 10% receive oxaliplatin. The remaining patients could then receive either oral drugs or intravenous 5-FU.

The maximum number of patients who receiving oral drugs would be 6883 (36% of all patients with metastatic cancer) assuming no patients receive intravenous 5-FU.

4.6.3 Impact on the drugs budget

An increase in the proportion of patients on oral drugs, will result in an increase in expenditure on drugs.

It is assumed that 6883 patients receive intravenous 5-FU. The additional drug cost to the NHS of these patients switching to capecitabine treatment would be £ 0.6 m. The additional drug cost of these patients switching to UFT/LV treatment would be £ 3.5 m. This cost saving will be an over-estimate, given that some patients are already receiving oral drugs.

4.6.4 Impact on total costs

The cost of drug prescriptions is the only resource that will directly impact on the NHS budget. However other resource use will change, including costs relating to chemotherapy infusions and hospitalisations. In particular oral drugs required one outpatient visit per cycle rather than day case or inpatient visits for intravenous regimens.

Assuming that 6883 patients currently receive intravenous 5-FU, divided evenly between Mayo and MdG and inpatient regimens, the total cost saving to the NHS of these patients switching to capecitabine treatment would be £ 12.6 m. The cost savings of these patients switching to UFT/LV treatment would be £ 4.0 m. This cost saving will be an over-estimate, given that some patients are currently receiving treatment with oral drugs.

5. IMPLICATIONS FOR OTHER PARTIES

Work Days Lost

The study by Ollendorf [54] includes number of work days missed by patients employed at baseline (25%), and concludes that patients undergoing UFT/LV therapy miss fewer days of work than patients undergoing Mayo regimen treatment. In the BMS sponsor submission, [48] the value of these lost days is calculated using the friction-cost method. The cost of work days lost was £799 per patient employed for the UFT/LV arm and £1,030 for the modified Mayo arm, resulting in a cost saving of £231 per employed patient.

Support of Families and Friends

Costs are also incurred by the patient's family and friends. They may also miss work through caring for patients or taking them to hospital. Regimens with many hospital visits are likely to require more support from friends and families, as are regimens with serious adverse events. Also, some patients may not be competent enough on their own to take oral medications reliably, but may be prescribed them if they have someone to help them comply with their therapy.

Transportation

In the Roche sponsor submission,[45] the cost per patient of transportation to and from hospital, only including transportation by hospital ambulances, for infusion administration was estimated (£333, for Mayo regimen patients only). It could be assumed to be much higher if it were to include private costs as well. While the Roche estimate can only be illustrative as they have not counted any administration costs incurred by capecitabine patients, it demonstrates the possible costs of transportation, which will of course be greater for patients who have to visit the hospital more frequently, i.e. patients on the Mayo regimen in particular, but also modified de Gramont patients, who visit once every two weeks instead of once every three weeks.

6. FACTORS RELEVANT TO THE NHS

Outreach clinics

Oral chemotherapeutic agents offer the advantage of delivery outside a specialist cancer centre. Outreach clinics, for example may be a particularly useful place for delivery of oral chemotherapeutic agents for patients who are either geographically isolated or prefer not to travel to a cancer centre. This raises many issues with regard to patient education and the monitoring of adverse events which normally take place within the specialist cancer centre. Therefore the needs of patients with regard to education and support must be considered if patients are to receive oral chemotherapeutic agents in an outreach clinic. The provision of staff, such as chemotherapy nurses to provide for these needs must be taken into account when planning such a service.

Cost incentives within the NHS

A shift towards the greater use of oral drugs within the NHS may exert cost pressures on NHS Trusts, as a result of existing contracting arrangements. An oral prescription is classed as an outpatient visit, whilst OP intravenous chemotherapy is classed as a day case expense. A shift towards using oral drugs is therefore likely to provide less income to the Trust and may also result in the Trust failing to meet activity targets under existing contracts. Further cost pressures may be exerted on Cancer Centres in terms of reduced activity, if oral drugs are made available to patients via local outreach units rather than patients travelling into Cancer Centres to receive intravenous therapy. Consideration will therefore need to be given to methods of activity measurement in future NHS Trust contracts.

Pharmacy and Nursing Time

Oral therapies can be prescribed and monitored during an outpatient appointment with an oncologist and dispensed without procedure at the hospital pharmacy. In contrast, infusional regimens are costly not only in terms of nurses and doctors administering the infusions, but also in terms of pharmacy time and resources. Infusional drugs need to be prepared in a special isolated area, while other costs of bags, pumps and tubing are also incurred. While pharmacist time and disposables have been costed in this analysis, the costs imposed by the necessity of dedicated isolator cabinets situated in pharmaceutical clean rooms has not been counted, nor has the cost of training specialist pharmacists to deal with cytotoxic drugs. More specialist staff are needed in all areas of administration for infusional regimens, as radiologists and radiographers may also be needed for line insertion, while specialist pharmacists and nurses are needed for the preparation and administration of drugs.

Training for Doctors and Nurses

The introduction of oral therapies may necessitate additional training for doctors and nurses in patient identification and education. Since it is very important for the safety of the patients that they are well-enough informed to assume responsibility for their treatment and physically and mentally competent to take it reliably, it is therefore vital that physicians offer oral treatment only to patients who are able to take it, and that they

have a suitable relationship with patients to encourage them to report any problems. The same is also true of the nurses charged with educating patients on the risks of non- and over-compliance.

Concordance

Concordance is a key factor when using oral chemotherapeutic agents. Concerns have been raised by the FDA concerning the use of an oral formulation of a cytotoxic anticancer drug over a parenteral formulation because of the uncertainty of the amount actually taken by the patient and the narrow safety margin. This uncertainty is less important with drugs for other conditions where the safety margin is much greater.[49] The majority of dangers with these drugs lies in over-compliance rather than under-compliance, as patients may be motivated to take medication even when they are experiencing adverse effects.

There is a need for patient support in the community to ensure patient safety, for example an oncology nurse who is available for telephone contact or who initiates contact with the patient at regular intervals. GPs would also be closely involved with the treatment of patients and monitoring of adverse events. People with colorectal cancer are often elderly and therefore may have problems with confusion and home support.

Place of oral chemotherapy in combination therapy

It has been suggested that in future, chemotherapy for metastatic colorectal cancer may consist of a combination of therapies including potentially irinotecan or oxaliplatin.[64] If this is the case, it is important to consider that these drugs may still need to be administered in a parenteral manner and the place of oral chemotherapies in combination with these treatments must be carefully considered as much of the saving on administration cost would no longer apply.

7. DISCUSSION

7.1 MAIN RESULTS

7.1.1 Capecitabine

Two trials were identified [40,41] that compared capecitabine with 5-FU/LV administered via the Mayo regimen. An additional study was identified[36] that pooled the data from these two trials. No studies were identified that compared capecitabine treatment with the de Gramont or modified de Gramont 5-FU/LV regimens.

One study[41] reported only investigator-assessed overall response rates to be significantly greater in the capecitabine group compared with the 5-FU/LV group. The other trial[40] and the pooled data both found that investigator-assessed and IRC-assessed overall response rates were significantly greater in the capecitabine group compared with the 5-FU/LV group.

Duration of response, time to disease progression or death, time to treatment failure and overall survival were not found to be significantly different between the capecitabine groups and the 5-FU/LV groups in the two trials and in the pooled data.

With regard to toxicity, patients in the capecitabine groups reported less diarrhoea, stomatitis, nausea and alopecia of all grades than those in the 5-FU/LV groups. Those in the capecitabine group also had significantly less grade 3/4 neutropenia and less frequent hospitalisation for adverse events. Hand-foot syndrome and grade 3 hyperbilirubinemia was significantly greater in the capecitabine group.

7.1.2 UFT/LV

Two trials comparing treatment with UFT/LV with 5-FU/LV[46,47] were identified in the literature searches. These two trials are not comparable for two main reasons. First the comparator in the Douillard study[46] is the standard Mayo 5-FU/LV regimen while the comparator in the Carmichael study[47] is a modification of the Mayo 5-FU/LV regimen that has not been tested for efficacy. Secondly, the Douillard study[46] uses two different doses of leucovorin, depending on the study site while the Carmichael study[47] uses only one dosage.

There were no significant differences with regard to overall response rates, duration of response or survival between UFT/LV and 5-FU/LV in either trial. Time to disease progression was inferior for the UFT/LV group compared to the 5-FU/LV group in the Douillard study.[46] There was no difference in time to disease progression between the two groups in the Carmichael study[47] although this is possibly due to the use of a non-standard Mayo regimen. The use of this less dose intensive regimen would make it less effective thereby obscuring any deficit in the effectiveness of UFT/LV.

UFT/LV was associated with significantly fewer adverse effects apart from significantly increased bilirubin in the Douillard study.[46]

7.1.3 Patient Preference

Studies[50,65] have shown that patients prefer oral therapies over IV if efficacy is not compromised. However, other factors apart from patient preference must be taken into account. Although oral chemotherapeutic agents offer greater convenience and avoidance of problems related to venous access among others, oral administration may be associated with over- or under-compliance and control of side effects may be difficult.[66]

Liu[65] administered a structured questionnaire to 103 patients with advanced cancer who would be undergoing palliative treatment. The purpose of the questionnaire was to determine preferences regarding route of administration of treatment. Of those responding, 89% preferred oral therapy but 70% were unwilling to accept a lower response rate and 74% were unwilling to accept a shorter duration of response.

One study[50] measuring patient preference for UFT/LV treatment was identified. The results of this small study found that patients preferred the UFT/LV regimen to the 5-FU/LV regimen. No studies of patient preference involving capecitabine were identified.

7.1.4 Quality of Life

Both capecitabine trials and both UFT/LV trials included health related quality of life data although the capecitabine QoL data has not been published and was available in the sponsor submissions only.[45,48] Neither UFT/LV or capecitabine therapy was associated with an improvement in health related quality of life.

7.1.5 Economic results

Two economic studies [55,54] and two resource use studies [56,57] were identified. The economic studies were not relevant to the UK context.

The two unpublished sponsor submissions compared the oral drugs to the Mayo regimen, a bolus 5-FU/LV regimen. In both sponsor submissions the economic analysis presented showed that the oral drugs may have an economic advantage over the Mayo regimen, primarily due to savings in administration costs.

However a number of different intravenous 5-FU/LV regimens are currently in use in the UK. No cost analysis was presented in the sponsor submissions comparing oral drugs to any 5-FU/LV regimen other than the Mayo regimen. An economic evaluation was therefore undertaken to compare the cost-effectiveness of UFT/LV and capecitabine with three intravenous 5-FU/LV regimens widely used in the UK: the Mayo regimen, the MdG regimen (outpatient) and the inpatient de Gramont regimen.

A cost-minimisation analysis was performed for comparisons of capecitabine and

UFT/LV with the Mayo regimen, since the survival benefits have been shown to be statistically equivalent The costs of capecitabine and UFT/LV were estimated to be £2,132 and £3,385 respectively, based on 12 weeks treatment period. The cost of the Mayo regimen was estimated to be £3,593. The estimated cost savings of the oral therapies relative to the Mayo regimen were £1,461 and £209 for capecitabine and UFT/LV respectively. Drug acquisition costs were higher for the oral therapies than for the Mayo regimen, but were offset by lower administration costs. Adverse event treatment costs were similar across the three regimens.

A cost minimisation analysis of the oral therapies against the MdG and the inpatient de Gramont the oral therapies was performed on the basis of no proven survival benefit of the de Gramont regimen over the Mayo regimen. The oral therapies were once again shown to be cost saving. The cost of the MdG regimen and the de Gramont regimen were estimated to be £3,485 and £6,255 respectively.

However the only randomised trial identified which compares the de Gramont regimen with the Mayo bolus regimen found the de Gramont regimen had an increased overall survival (62 weeks v 56.8 weeks, p=0.067) [19]. This survival difference of 5.2 weeks was not statistically significant but is considered clinically significant. In addition the infusional regimens, such as the de Gramont regimens, have been shown to be more effective in terms of progression-free survival and toxicity [19]. The impact of these differences in outcome were explored in terms of cost per LYG and cost per PFLY of the oral drugs relative to the de Gramont regimens.

Based on a survival difference of 5.2 weeks between the oral therapies and the MdG and the de Gramont regimens the cost per life year gained of MdG treatment over capecitabine treatment was £13,571 and the cost per life-year gained of inpatient de Gramont treatment over capecitabine treatment was £41,344. On this basis the cost saving from oral drugs is not sufficient to make it a more cost effective option. The cost per life-year gained of MdG treatment over UFT/LV treatment was £758 and the cost per life-year gained of inpatient de Gramont treatment over UFT/LV treatment was £21,631. These numbers are illustrative only. However they do show that the cost savings offered by the oral drugs, particularly in relation to MdG are not large and therefore if the oral drugs do reduce the survival of patients by an order of 5.2 weeks, oral drugs cannot be considered a cost effective option relative to the MdG regimen. It is difficult to draw any firm conclusions from this cost-effectiveness analysis, given that it is based on an indirect comparison of patients from two different studies.

Likewise provisional estimates of the cost per progression-free life year gained of MdG and inpatient de Gramont over capecitabine and UFT/LV showed that the cost savings offered by the oral drugs, particularly in relation to MdG are not large. On the assumption that oral drugs do reduce the progression-free survival of patients by an order of 5.6 weeks, oral drugs cannot necessarily be considered a cost effective option relative to the MdG regimen in terms of the cost per progression-free life years gained. Further work is

needed is this area.

7.2 ASSUMPTIONS, LIMITATIONS AND UNCERTAINTIES

The RCT evidence for oral drugs compares capecitabine and UFT/LV against the Mayo regimen. However a number of different intravenous 5-FU/LV regimens are currently in use in the UK. No direct comparisons of the oral drugs and infusional regimens were identified. For purposes of economic evaluation an indirect comparison was therefore required.

The costs used in the economic evaluation were not based on published studies and are subject to uncertainty. Key uncertainties related to the price of LV, which is known to be discounted substantially below BNF prices, the treatment duration for different therapies which impacts on their total treatment cost, the costs of managing adverse events and the cost of outpatient appointments. These issues are tested in sensitivity analysis.

In addition there is no trial evidence on utility data**.**

7.3 COST AND BENEFIT ASSUMPTIONS

There is considerable uncertainty in the economic analysis, particularly in relation to the indirect comparison of the oral drugs with the infusional regimens.

Costs

The drug costs were based on an assumed individual with a body surface area of 1.75 m^2 undergoing treatment with no dose reductions, and assuming that all drugs were supplied at BNF list prices. Drug discounts were not included in the base case. Substantial discounts are however currently available on calcium folinate (LV), although the precise scale of the discount is confidential and will vary between hospitals.

The cost of a hospital outpatient appointment was assumed to differ for patients on oral therapy and patients receiving intravenous therapy. Cost data from a local provider was used but is likely to vary between institutions.

No published data was available relating to the cost of managing adverse events. Resource use data was taken from the unpublished sponsor submissions. However a number of assumptions had to be made and therefore this cost data is open to uncertainty.

Benefits

A cost-minimisation analysis was performed for comparisons of capecitabine and UFT/LV with the Mayo regimen, since the survival benefits have been shown to be statistically equivalent.

However no direct comparisons of the oral drugs and the de Gramont regimens (MdG and inpatient de Gramont) were identified and therefore an indirect comparison was undertaken for the purposes of economic evaluation. Evidence on the survival benefits of the Mayo regimen versus the de Gramont regimen was reviewed. On the basis that there is no proven survival difference between the Mayo and the de Gramont regimens, it was inferred that there was no survival difference between the oral drugs and the de Gramont regimens. Therefore a cost-minimisation analysis was also performed for comparisons of capecitabine and UFT/LV with the de Gramont regimens.

Evidence on the efficacy of the MdG regimen is limited. There are no randomised trials of MdG versus the traditional de Gramont regimen. The UK Medical Research Council (MRC) have made the decision to move over to MdG without a large randomised equivalence trial because the MdG regimens are more 5FU-dose intensive and they have better non-randomised phase II response rates than the old de Gramont regimen.(Seymour M, Cookridge Hospital, Leeds: personal communication, 2002). In addition they are more convenient for patients and hospitals. The economic analysis assumes that de Gramont and MdG regimens are equally effective and that they have similar adverse event profiles.

Although there is no proven survival benefit of infusional regimens, such as the de Gramont regimen, over bolus regimens, such as the Mayo regimen, in advanced colorectal cancer, infusional regimens have been shown to be more effective in terms of progression-free survival, tumour response and toxicity [19]. The impact of a potential difference in progression-free survival between the oral drugs and the infusional regimens was explored in terms of the impact on the cost per progression-free year gained.

No significant differences in quality of life were found between the oral drugs and the Mayo regimen. Values from a previous study in colorectal cancer using nurses as a proxy subjects have been used to explore the potential impact of utility on estimated benefits in terms of quality-adjusted progression-free life years. These are shown for illustrative purposes only

7.4 NEED FOR FURTHER RESEARCH

The following points have been identified as areas requiring further research:

- Quality of life data should be included in trials of colorectal cancer treatments. Well validated instruments should be used and this research should be conducted by independent researchers. It may be necessary to use more than one instrument

in order to identify differences in QoL. It may also be necessary to identify the components of QoL that vary with different treatments.

- More research is needed to determine the place of effective oral treatments in the treatment of colorectal cancer. This should focus on when such treatments should be given alone and when they should be given in combination with other chemotherapeutic agents. Research is needed on the combination of oral agents with other chemotherapy agents (notably irinotecan and oxaliplatin) and novel agents.
- Some types of patients may benefit more from oral treatment than others. Research is needed to determine what safety mechanisms are needed in order to ensure compliance and the monitoring of adverse effects.
- The optimum duration of treatment needs to be determined for example, to disease progression, to response, to unacceptable toxicity or death. Intermittent treatment with a pause after 12 weeks for those with stable or responding disease also needs to be considered.
- The issue of patient preference must be given careful consideration in future trials and all trials should incorporate the measurement of patient preference.
- In order to make a precise estimate of the cost-effectiveness of capecitabine and UFT/LV versus modified de Gramont treatment, a phase III comparative trial would be necessary to determine whether there was any survival advantage. This would also give clinicians clear information on survival to present to patients who can then make an informed choice with regard to treatment.

8. CONCLUSIONS

There is good evidence to suggest that capecitabine is effective in improving overall response rates compared with Mayo regimen 5-FU/LV therapy in the treatment of metastatic colorectal cancer. Duration of response, time to disease progression or death, time to treatment failure and overall survival were found to be equivalent. Capecitabine use was associated with fewer adverse events apart from hand-foot syndrome and hyperbilirubinemia.

There is no evidence to suggest that UFT/LV is more effective than Mayo regimen 5-FU/LV and some evidence to suggest that UFT/LV treatment is associated with inferior time to disease progression. UFT/LV was associated with fewer adverse events than the 5-FU/LV regimen.

There was no evidence that either capecitabine or UFT/LV affects health related quality of life. No studies were identified regarding patient preference for capecitabine. One small cross-over trial found that patients preferred UFT/LV treatment over treatment with 5-FU/LV.

Given that the survival benefits of therapy have been shown to be similar for the oral and the Mayo regimen, a cost-minimisation analysis was undertaken. The results of the economic analysis showed that both capecitabine and UFT/LV offer cost advantages against the Mayo regimen. The cost savings offered by capecitabine and UFT/LV in relation to the Mayo regimen were estimated to be £1461 and £209 respectively. Savings in the cost of administration more than offset the higher drug costs of the oral therapy regimens.

There is no direct evidence to compare the survival benefits of MdG or inpatient de Gramont regimen with the oral regimens. No evidence was identified that showed a significant survival advantage de Gramont regimens over the Mayo regimen and therefore a cost minimisation analysis was undertaken. The results of the economic analysis showed that both capecitabine and UFT/LV offer cost advantages against the MdG regimen and the inpatient de Gramont regimen. However infusional regimens have been shown to be more effective in terms of progression-free survival, tumour response and toxicity.[17] Preliminary analysis undertaken to explore the impact of these factors on cost effectiveness suggest that oral drugs cannot necessarily be considered a cost effective option relative to the MdG regimen in terms of the cost per progression-free life years gained. Further evidence in terms of both benefits and costs is needed is this area.

Costs and cost-effectiveness are sensitive to discounts on the drug acquisition cost of calcium folinate, the cost of outpatient appointments and the treatment time.

In order to make a precise estimate of the cost-effectiveness of capecitabine and UFT/LV versus MdG treatment, a phase III comparative trial would be necessary to determine whether there was any survival advantage. This would also give clinicians clear

information on survival to present to patients who can then make an informed choice with regard to treatment.

9. APPENDICES

APPENDIX 1. World Health Organisation Criteria for Evaluation of Response[67]

Bidimensionally or unidimensionally measurable disease.

Complete response

Disappearance of all known disease, determined by two observations not less than four weeks apart.

Partial response

In case of bidimensionally measurable disease, decrease by at least 50% of the sum of the products of the largest perpendicular diameters of all measurable lesions as determined by two observations not less than four 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 four 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% of the sum of the products of the largest perpendicular diameters of all measurable lesions as determined by two observations not less than four 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 four 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 <25% decrease and <25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions. For unidimensionally measurable disease, <25% decrease and <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: 5-FU Based Treatment Regimens

Regimen	**Schedule**
Bolus 5FU	
Mayo	5FU 425mg/m^2/d + FA 20mg/m^2/d for 5 days every 4 weeks
Infusional 5FU	
AIO	2- hour infusion of FA (500mg/m^2) followed by a 24-hour infusion of 5FU (2,600mg/m^2), weekly for 6 weeks; cycle time 8 weeks
de Gramont	2-hour infusion of FA (200mg/m^2) + bolus 5FU (400mg/m^2) followed by a 22-hour infusion of 5FU (600mg/m^2) on days 1 and 2 of each fortnight[11]
Modified de Gramont	FA (350mg) + bolus 5FU (400mg/m^2) followed by a 46-hour infusion of 5FU (2800 mg/m^2) fortnightly[44]
Lokich	5FU 250-300mg/m^2 as prolonged continuous iv infusion until progression/toxicity

APPENDIX 3: Continuous versus bolus 5-FU regimens-Meta-analysis

Study	Research question	Number of trials	Searches	Study selection
Meta-analysis Group in Cancer, 1998[15]	To compare the administration of 5-FU by continuous intravenous infusion with bolus administration in patients with advanced colorectal cancer.	Six randomised clinical trials	MEDLINE from 1984-1994, proceedings of major congresses, personal contacts with investigators	Seven trials were identified, one was excluded because original patient data could not be retrieved and the randomisation procedure was based on hospital record numbers.

Study details

Study	Included trials	Treatment schedules and number of patients			
Meta-analysis Group in Cancer, 1998	Eastern Cooperative Oncology Group Study (ECOG), 1996 National Cancer Institute of Canada (NCIC), 1992 Southwest Oncology Group (SWOG 1), 1995 Mid-Atlantic Oncology Program (MAOP), 1989 France, 1992 Southwest Oncology Group (SWOG 2), 1995 Jerusalem, 1989	*Study*	*5-FU ci*	*5-FU Bolus*	*No. of patients*
		ECOG	5-FU 300 mg/m^2/d without interruption then 5-FU 600mg/m^{2}d, q7d	5-FU mg/m^2 dl-d5,	324
		NCIC	5-FU 350 mg/m^2 dl-d15, q28d	5-FU 400-450 mg/m^2/dl-d5, q28d	185
		SWOG 1	5-FU 300 mg/m^2 dl-d28, q35d	5-FU 500 mg/m^2/dl-d5, q35d	181
		MAOP	5-FU 300 mg/m^2/d without interruption	5-FU 500 mg/m^2/dl-d5, q35d	173
		France	5-FU 750 mg/m^2 dl-d7, q21d	5-FU 500 mg/m^2/dl-d5, q28 d	155
		SWOG 2	5-FU 200 mg/m^2 dl-d28, q35d + folinic acid 20 mg/m^2 iv, q7d	5-FU 425 mg/m^2 + folinic acid 20 mg/m^2 iv d1-d5, q28dx2, then q35d	175
		Jerusalem	5-FU 600 mg/m^2 + folinic acid 15mg/6h orally d1-d5, q21d	5-FU 600 mg/m^2 + folinic acid 15 mg/6h orally d1-d5, q21d	26

d=days; q=every; iv=intravenous; h=hours, ci = continuous infusion

Study details continued

Study	Trial characteristics	Predicted cumulative doses of 5-Fu in 5-FU bolus arm and in 5-FU CI arm (doses express in mg/m^2)					
		Trial	**Treatment Arm**	**After week 1**	**4**	**8**	**12**
Meta-analysis Group in Cancer, 1998	ECOG was a three-arm trial with one arm receiving 5-FU ci plus cisplatin. This arm was not included in the meta-analysis. The SWOG trial had seven arms, three of which were not included in the meta-analysis. In the ECOG and MAOP trials ci 5-FU was administered without a rest period. In the SWOG trial, 5-FU infusion was maintained over 80% of the time. In the NCIC and the French trial, duration of 5-FU infusion was between 33% and 50% of the time.	ECOG	5-FU ci	2100	8400	16800	25200
			5-FU bolus	2500	3700	6100	8500
		NCIC	5-FU ci	2450	4900	9800	14700
			5-FU bolus	2250	2250	4500	6750
		SWOG 1	5-FU ci	2100	8400	14700	21000
			5-FU bolus	2500	2500	5000	7500
		MAOP	5-FU ci	2100	8400	16800	25200
			5-FU bolus	2500	2500	5000	7500
		France	5-FU ci	5250	10500	15750	21000
			5-FU bolus	2500	2500	5000	7500
		SWOG 2	5-FU ci	1400	5600	9800	14000
			5-FU bolus	2125	2125	4250	6375
		Jerusalem	5-FU ci	3000	6000	9000	12000
			5-FU bolus	3000	6000	9000	12000

Patient characteristics

Study	Patient characteristics							
Meta-analysis Group in Cancer, 1998	*Trial*	*Accrual Period*	*Treatment arm*	*No. patients*	*Primary colon (%)*	*PS<2 (%)*	*Metastases (%)*	
							Liver only	Lung only
	ECOG	1987-90	5-FU ci	162	81	94	23	8
			5-FU bolus	162	80	89	23	7
	NCIC	1986-89	5-FU ci	95	68	85	49	5
			5-FU bolus	90	78	89	49	4
	SWOG1	1989-92	5-FU ci	88	85	88	NA	NA
			5-FU bolus	93	72	89	NA	NA
	MAOP	1984-86	5-FU ci	88	76	90	34	5
			5-FU bolus	85	74	91	34	8
	France	1987-90	5-FU ci	77	66	92	44	12
			5-FU bolus	78	64	90	51	12
	SWOG2	1989-92	5-FU ci	86	70	92	NA	NA
			5-FU bolus	89	72	88	NA	NA
	Jerusalem	1984-86	5-FU ci	11	38	82	45	18
			5-FU bolus	15	80	93	33	13
	TOTAL	1984-92	5-FU ci	607	75	91	35	7
			5-FU bolus	612	75	90	36	7
	PS=performance status, NA=not available; SWOG 1 and SWOG 2 refer to two different arms of 1 SWOG trial. A total of 1,219 patients were considered in the meta-analysis. The median patient age was 63 years and 61% of patients were male. At the time of analysis, 91% of patients had died.							

Study quality

Study	Agreement between reviewers	Similarity of included studies	Tests for homgeneity
Meta-analysis Group in Cancer, 1998	Data were extensively checked and discussed with all collaborators at a plenary meeting of the meta analysis group.	Studies use different regimens of 5-FU both continuous and bolus and two (SWOG 2 and Jerusalem) add LV.	Tests for heterogeneity were calculated for tumour response odds ratios and survival hazards ratios (both NS)

Results

Study	Outcomes measured	Tumour response	Survival	Prognostic factors
Meta-analysis Group in Cancer, 1998	Tumour response and survival	A total of 1,103 patients were included in the tumour response analysis as 116 patients in the SWOG trial had non-measurable disease. 5-FU ci 22% (CR 3%, PR 19%) 5-FU bolus 14% (CR 2%, PR 12%). Overall response odds ratio (OR) was 0.55 (95% CI: 0.41 to 0.75), indicating a highly significant advantage for 5-FU ci (p=0.0002), equivalent to a risk reduction of 45% with a standard error of 12%. However, advantage of 5-FU ci over 5-FU bolus was only statistically significant in three *individual* trials (ECOG, MAOP, French). A logistic regression model showed that treatment and performance status were the only independent prognostic factors with no interaction between the two. *Median duration of tumour response* 5-FU ci 7.1 months (95% CI 5.7 to 8.5 months) 5-FU bolus 6.7 months (95% 5.7 to 8.5 months)	No individual trial showed a benefit of 5-FU ci but their combination showed a small but statistically significant advantage for 5-FU ci over 5-FU bolus (HR: 0.88, 95% CI: 0.78 to 0.99; p=0.04). *Median survival duration* 5-FU CI: 12.1 months (95% CI: 11 to 13.1) 5-FU bolus: 11.3 months (95% CI: 10.5 to 12) *LV modulation* 5-FU/LV (SWOG2 and Jerusalem) overall survival was not significantly better for 5-FU ci compared with 5-FU bolus (HR 1.03; 95% CI: 0.77 to 1.38; p=0.84) but based on too few patients to be informative. Cox regression model stratified for trial showed that treatment, performance status and primary tumour site were independent prognostic factors for survival.	Randomised treatment, age (continuous), sex, performance status (ECOG), primary tumour location (rectum or colon) and site of metastases (liver only or not) were considered in the prognostic factor analyses. Randomised treatment and performance status were independent prognostic factors for haematological toxicity. Patients assigned to 5-FU bolus (p<0.0001) and patients with a poor performance status (p=0.03) had a significantly higher risk of haematological toxicity. Age, sex and performance status were independent prognostic factors for non-haemotological toxicity. Older patients (p=0.01), female patients (p=0.03) and patients with good performance status (p=0.007) had a significantly higher risk of toxicity. Randomised treatment, age and sex were independent prognostic factors for hand-foot syndrome. Survival duration was added to the logistic regression model

Study	Outcomes measured	Tumour response	Survival	Prognostic factors
		5-FU/LV (SWOG2 and Jerusalem) found the difference between 5-FU/LV and bolus 5-FU/LV did not reach statistical significance tumour response OR=0.82, (95% CI: 0.33 to 2.07), but only 145 patients were included in this group. *Duration of treatment* Tumour response OR was 0.55 (95% CI: 0.37 to 0.81) when duration of 5-FU infusion was >80% of the time (ECOG, MAOP, SWOG1) compared with 0.48 (95% CI: 0.26 to 0.89) when 5-FU infusion was between 33% and 50% of the time (χ^2 for interaction 0.14; p=0.70)		and found to be unrelated to haematological toxicity (p=0.99), marginally related to non-hamatological toxicity (p=0.08) and strongly related to hand-foot syndrome (p<0.0001).

Toxicity

Study	Haematological toxicity	Non-haematological toxicity	Hand-foot syndrome
Meta-analysis Group in Cancer, 1998[16]	Overall proportion of grade 3 and 4 haematological toxicity was 4% for patients assigned to 5-FU ci (23 of 607) and 31% for patients assigned to 5-FU bolus (191 of 612). Adjusted haematological toxicity RR was 0.14 (95% CI: 0.09 to 0.21), indicating that patients receiving 5-FU ci were on average seven times less likely to experience a grade 3 to 4 haematological toxicity than patients receiving 5-FU bolus ($p<0.0001$).	Overall grade 3 to 4 non-haematological toxicity occurred in 13% of patients in 5-FU ci (79 of 607) and in 14% of those in 5-FU bolus (84 of 612). Adjusted non-haematological toxicity RR was 0.96 (95% CI: 0.72 to 1.28; $p=0.78$). Risks of severe diarrhoea, nausea/vomiting and mucositis were not different in the 5-FU ci and 5-FU bolus groups: 4% vs. 6%, 3 % vs. 4 % and 9% vs. 7% respectively.	Overall proportion of hand-foot syndrome was 34% for 5-FU ci patients (206 of 607) and 13% for 5-FU bolus patients 977 of 612). The adjusted RR was 1.87 (95% CI: 1.50 to 2.34) which indicates the risk of hand-foot syndrome is almost doubled when 5-FU is given by CI ($p<0.0001$).

APPENDIX 4: Continuous Infusion vs. bolus 5-FU regimens-RCTs

Study	Study site	Comparators, dosage and procedure	Type of study	Numbers randomised	Funding
de Gramont et al, 1997[17]	70 centres in France	Arm A (Mayo): *Monthly* 5-FU bolus, low-dose LV for five consecutive days. LV given by IV bolus at 20 mg/m^2/d and immediately followed by 5-FU bolus at 425 mg/m^2/d, repeated for 5 consecutive days. Cycles every 4 weeks. Arm B (de Gramont): *Bimonthly* high-dose LV with 5-FU bolus and continuous infusion for 2 consecutive days. LV was given at 200 mg/m^2/d as a 2 hour infusion followed by IV bolus 5-FU at 400 mg/m^2/d and 22- hour infusion 5-FU 600 mg/m^2/d all repeated for 2 consecutive days. Cycles at 2 week intervals. The full regimen was administered until disease progression [neutrophils were more than 1500/mm^3, platelet count was more than 100,000/ mm^3, and toxicity remained tolerable (WHO grade 0-2)]. Study regimens were stopped when disease progression occurred and second-line chemotherapy, including 5-FU continuous infusion could be administered in both trial arms.	RCT	448 total patients	Wyeth-Lederle laboratories (Paris, France)

Study design

Study	Length of study	Inclusion criteria	Exclusion criteria	Power calculation	Baseline comparability
de Gramont et al, 1997[17]	Patients assigned to treatment from February 1991 to April 1994; follow-up time for the whole cohort was 43.5 months.	Adenocarcinoma of the colon or rectum, progressive or histologically proven non-resectable metastases at presentation, no central nervous system metastasis, no exclusive bone metastases, no secondary malignancy (except adequately treated in situ carcinoma of the cervix or non-melanomic skin cancer), life expectance over 2 months, age between 19 and 75 years, WHO performance status 0 to 2, no previous therapy for metastatic disease, no previous adjuvant therapy if completed less than 6 months before inclusion or if it included LV, metastases outside the radiation field in patients who had previously had radiation therapy, initial evaluation 2 weeks or less before inclusion, neutrophils greater than $1500/mm^3$, platelets greater than $100,000 /mm^3$, serum creatinine less than 300 μmol/L and partial thrombin time >50%.	As stated in inclusion criteria	Yes, to detect difference in survival	yes

Patient details

Study	Sex (M/F)	Age	Performance score	Primary site	Sites of metastasis
de Gramont et al, 1997[17]	Arm A: 145/71 Arm B: 135/82	Mean ± SD Arm A: 61.7 ± 9.6 Arm B: 60.9 ± 9.5	*WHO Performance Status* **Arm A (%) Arm B (%)** WHO status 0 98 (45.4) 97 (44.7) WHO status 1-2 118 (54.6) 120 (55.3)	**Arm A (%) Arm B (%)** Colon 142 (65.7) 139 (64.1) Rectum 68 (31.5) 73 (33.6) Multiple or non-specified 6 (2.8) 5 (2.3)	**Arm A (%) Arm B (%)** Liver 172 (80.7) 176 (81.5) Lung 34 (16) 34 (15.7) Other 40 (18.8) 40 (18.5) 1 site 182 (85) 182 (84.3) ≥ 2 sites 32 (15) 34 (15.7) number of sites not specified 2 1

Quality Assessment

Study	Randomised/method	Blinding/appropriate method	Description of withdrawals and dropouts	Jadad score
de Gramont et al, 1997[17]	Yes, method not described. Patients were stratified according to performance status, measurable disease, synchronous vs. metachronous metastases and institution.	No blinding described	Withdrawals and dropouts adequately described	2/5

Outcomes

Study	ITT analysis	Primary endpoints	Secondary endpoints	Duration of treatment
de Gramont et al, 1997[17]	No, 348 of 448 original randomised patients were included in the analysis of response rates and 433 of 448 in other analyses.	survival	Tumour response	Patients in Arm A received a median of 5 cycles (range: 1-21) and in Arm B a median of 12 cycles (range: 1-42).

Results

Study	Response rate	Duration of response	Median time to disease progression or death	Survival
de Gramont et al, 1997[17]	*Overall objective tumour responses; number of patients (%)* **Arm A** **Arm B** CR 4 (2.3) 10 (5.7) PR 21 (12.1) 47 (26.9) Stable 68 (39.3) 62 (35.4) Progression 80 (46.2) 56 (32) CR + PR 25(14.45)* 57(32.57)* *p=0.0004	Median duration of response was 48.5 weeks in Arm A and 47 weeks in Arm B (p=0.78)	Not reported	*Progression- free survival* Arm B (bimonthly regimen) had significantly longer median progression free survival than those in Arm A (monthly regimen), 27.6 weeks vs. 22 weeks, (p=0.0010; odds ratio=0.72). *Median survival* Arm B (bimonthly regimen) had slightly longer median survival than Arm A (monthly regimen) (62.0 vs. 56.8 weeks p=0.067). Patients with measurable disease had a median survival of 63 vs. 46 weeks in patients with non-measurable disease (p=0.0186). Interaction test between treatment arms and measurable/non-measurable diseased showed borderline significance (p=0.07). Odds ratio was significant only for patients with measurable disease treated with the bimonthly regimen compared with the monthly regimen (OR=0.75, p=0.015). Median survival in patients with measurable disease was 72 weeks in Arm B and 58.4 weeks in Arm A.

CR=complete response, PR= partial response

Toxicity

Study	Types of side effects					Treatment related deaths
de Gramont et al, 1997[17]	*Toxicity per patient*					One therapy related death in the study in Arm A.
		Arm A (monthly) (n=205)		*Arm B (n=208) (bimonthly)*		*Comparison†*
		Grade 1-2(%)	**Grade 3-4(%)**	**Grade 1-2(%)**	**Grade 3-4(%)**	
	Neutrophils	14 (6.8)	15 (7.3)	20 (9.6)	4 (1.9)	0.0052
	Platelets	1 (0.5)	1 (0.5)	1 (0.48)	2 (1.0)	1.00
	Infection	14 (6.8)	8 (3.9)	11 (5.3)	2 (1.0)	0.095
	Nausea	72 (35.1)	7 (3.4)	80 (38.5)	8 (3.9)	0.95
	Diarrhoea	54 (26.3)	15 (7.3)	59 (28.4)	6 (2.9)	0.039
	Mucositis	38 (18.5)	26 (12.7)	42 (20.2)	4 (1.9)	0.0001
	Angina pectoris	2 (1.0)	0	8 (3.8)	0	(0.14)
	Cutaneous	25 (12.2)	0	31 (14.9)	2 (1.0)	(0.59)
	Alopecia	26 (12.7)	3 (1.5)	25 (12.0)	1 (0.5)	0.37
	Epistaxis	7 (3.4)	0	19 (9.1)	0	(0.019)
	Conjunctivitis	10 (4.9)	0	29 (13.9)	0	(0.003)
	Neurological	3 (1.5)	0	7 (3.4)	1 (0.5)	1.00
	Maximal	90 (43.9)	49 (23.9)	119 (57.2)	23 (11.1)	0.0004
	†Comparisons are for grade 3-4 toxicity Arm A vs. Arm B, those in brackets in the comparison column refer to grade 1-2 toxicities.					

APPENDIX 5: Summary of de Gramont study results

Study	Response rates	Progression free survival	Median overall survival
de Gramont [17]	32.6%	27.6 weeks	62 weeks
de Gramont [19]	28.6%; 22.3%*; 21.9% (ITT)	26.9 weeks; 26.1 weeks*	63.9 weeks
Douillard [20]†	22% (ITT); 31% [de Gramont alone: 21.0% (ITT)]	4.4 months (17.6 weeks) [de Gramont alone: 3.7 months (14.8 weeks)]	14.1 months (56.4 weeks) [de Gramont alone: 13.0 months]
Maughan [18]	23%	25 weeks	294 days (42 weeks)

ITT= intention to treat analysis; *= independent assessor; † In this trial, both de Gramont and AIO regimens included

APPENDIX 6: Performance Status Scales

World Health Organisation Scale for Performance Status

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, 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.

Karnofsky Performance Scale

%	**Description**
100	Normal; no complaints; no evidence of disease
90	Able to carry out normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalisation is indicated although death is not imminent
20	Very sick; hospitalisation necessary, active supportive treatment necessary
10	moribund; fatal processes progressing rapidly
0	Dead

Eastern Cooperative Oncology Group (ECOG) Performance Status

Status	Patient findings
0	No symptoms
1	Patient symptomatic but ambulatory
2	Patient bedridden less than half the day
3	Patient bedridden half the day or longer
4	Patient chronically bedridden and requires assistance with activities of daily living

APPENDIX 7: Search Strategies
Appendix 7.1 Electronic bibliographic databases searched

1. BIOSIS previews (the new online version of Biological Abstracts)
2. CancerLit
3. CCTR (Cochrane Controlled Trials Register)
4. CDSR (Cochrane Database of Systematic Reviews)
5. Cinahl
6. EBM Reviews – ACP Journal Club
7. Embase
8. HEED (Health Economic Evaluations Database)
9. Medline
10. NHS DARE (Database of Assessments of Reviews of Effectiveness)
11. NHS EED (Economic Evaluations Database)
12. NHS HTA (Health Technology Assessment)
13. PreMedline
14. Science Citation Index
15. Social Sciences Citation Index

Appendix 7.2 Other sources searched

1. Adverse Event Reporting System
2. AHRQ (Agency for Healthcare Research and Quality), USA
3. Bandolier
4. Beating Bowel Cancer
5. British Geriatrics Society – Gastro Special Interests Group
6. British Oncological Association
7. British Psychosocial Oncology Society
8. Cancer BACUP
9. Cancer Research UK
10. CCOHTA (Canadian Coordinating Office for Health Technology Assessment)
11. CenterWatch
12. CHE (Centre for Health Economics), York
13. Clinical Evidence
14. CliniWeb
15. CMA (Canadian Medical Association) InfoBase
16. COIN (DoH)
17. Colon Cancer Concern
18. Current Controlled Trials
19. CriB (Current Research in Britain)
20. Drug Safety Research Unit
21. DES Reports (West Midlands Health Technology Assessment Collaboration)
22. DoH
23. eBNF (electronic British National Formulary)
24. eGuidelines
25. EMEA (The European Agency for the Evaluation of Medicinal Products)
26. eMedicines Compendium
27. European Society for Medical Oncology
28. GOOGLE
29. Health Evidence Bulletin, Wales
30. HSRU (Health Services Research Unit), Aberdeen
31. INAHTA (International Network of Agencies for Health Technology Assessment) Clearinghouse
32. Index to Theses (Sheffield University)
33. ISI Proceedings (Web of Science)
34. Long Term Medical Conditions Alliance
35. Macmillan Cancer Relief
36. Marie Curie Cancer Care
37. MEDLINEplus Drug Information
38. MeRec
39. MRC Trials Register
40. National Assembly for Wales
41. National Cancer Alliance
42. National Cancer Research Institute
43. National Guidelines Clearinghouse

44. National Research Register (2002 Issue 2)
45. NCCHTA (National Co-ordinating Centre for Health Technology Assessment)
46. NHS CRD (Centre for Reviews and Dissemination), University of York
47. OMNI
48. POINT (DoH)
49. RAND
50. ReFeR (Research Findings Register)
51. Royal College of General Practitioners
52. Royal College of Nursing
53. Royal College of Physicians
54. Royal College of Radiologists
55. Royal College of Surgeons
56. Royal Pharmaceutical Society
57. ScHARR Library catalogue
58. SIGN (Scottish Intercollegiate Guidelines Network)
59. SEEK (Sheffield Evidence for Effectiveness and Knowledge)
60. Toxline
61. Trent Working Group on Acute Purchasing Reports
62. TRIP (Turning Research into Practice) Database
63. Wessex DEC (Development and Evaluation Committee) Reports
64. WHO

Appendix 7.3 Search strategies used

Biological Abstracts
1985-2002
SilverPlatter WebSPIRS
Search undertaken April 2002

#1	Capecitabine*
#2	Xeloda
#3	154361-50-9
#4	EU?1?00?163?001
#5	EU?1?00?163?002
#6	Ro09?1978
#7	Fluoropyrimidine*
#8	Tegafur*
#9	17902-23-7
#10	Uftoral
#11	PL?11184?0087
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13	Carcinoma* or neoplasia* or neoplasm* or adenocarcinoma* or cancer* or tumor* or tumour* or malignan* or disease*) near3 (colorectal* or colon* or rect* or intestin* or bowel*)
#14	#12 and #13

CDSR and CCTR
2002, Issue 1
The Cochrane Library, Update Software (CD ROM version)
Search undertaken April 2002

#1	COLORECTAL-NEOPLASMS*:ME
#2	NEOPLASMS*:ME
#3	CARCINOMA*:ME
#4	ADENOCARCINOMA*:ME
#5	#2 OR #3 OR #4
#6	COLONIC-DISEASES*:ME
#7	RECTAL-DISEASES*:ME
#8	COLON*:ME
#9	RECTUM*:ME
#10	#6 OR #7 OR #8 OR #9
#11	#5 AND #10
#12	((CARCINOMA* OR NEOPLASIA* OR NEOPLASM* OR ADENOCARCINOMA* OR CANCER* OR TUMOR* OR TUMOUR* OR MALIGNAN*) NEAR (COLORECTAL OR COLON* OR RECT* OR INTESTIN* OR BOWEL*))
#13	#1 OR #11
#14	#12 OR #13
#15	CAPECITABINE*
#16	XELODA*
#17	154361-50-9
#18	EU100163001
#19	EU100163002
#20	RO091978
#21	FLUOROPYRIMIDINE*
#22	TEGAFUR*
#23	17902-23-7
#24	UFTORAL
#25	PL111840087
#26	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
#27	#14 AND #26

Cinahl
1982-2002
Ovid Biomed
Search undertaken April 2002

#1. Exp Colorectal Neoplasms/
#2. Neoplasms/
#3. Carcinoma/
#4. Adenocarcinoma/
#5. or/2-4
#6. Colonic Diseases/
#7. Rectal Diseases/
#8. Exp Colon/
#9. Exp Rectum/
#10. or/6-9
#11. 5 and 10
#12. ((Carcinoma$ or neoplasia or neoplasm$ or adenocarcinoma$ or cancer$ or tumor$ or tumour$ or malignan$) adj3 (colorectal or colon$ or rect$ or intestin$ or bowel$)).tw
#13. 1 or 11 or 12
#14. Capecitabine.af
#15. Xeloda.af
#16. 154361-50-9.af
#17. EU#1#00#163#001.af
#18. EU#1#00#163#002.af
#19. Ro09?1978.af
#20. Fluoropyrimidine$.af
#21. Tegafur.af
#22. 17902-23-7.af
#23. Uftoral.af
#24. PL?11184?0087.af
#25. Or/14-24
#26. 13 and 25

Citation Indexes (Science and Social Sciences)
1981-2002
Web of Science
Search undertaken May 2002

Database limits:
DocType=All document types; All languages; Databases=SCI-EXPANDED, SSCI; Timespan=All years.

((Capecitabine or Xeloda) and (colorectal or colon* or rect* or intestin* or bowel*))
((154361-50-9 or EU?1?00?163?001 or EU?1?00?163?002) and (colorectal or colon* or rect* or intestin* or bowel*))
((Ro09?1978 and (colorectal or colon* or rect* or intestin* or bowel*))
((Fluoropyrimidine* or tegafur or uftoral) and (colorectal or colon* or rect* or intestin* or bowel*))
((17902-23-7) and (colorectal or colon* or rect* or intestin* or bowel*))
((PL?11184?0087) and (colorectal or colon* or rect* or intestin* or bowel*))

CRD Databases (NHS DARE, EED, HTA)
CRD Web site - complete databases
Search undertaken April 2002

Capecitabine/all fields
Xeloda/all fields
Tegafur/all fields
Uftoral/all fields
Fluoropyrimidine/all fields

Embase
1980-2002
SilverPlatter WebSPIRS
Search undertaken April 2002

#1. Explode ‘colorectal-cancer' / all subheadings
#2. Explode ‘colorectal-carcinoma' / all subheadings
#3. Explode ‘colorectal-tumor' / all subheadings
#4. #1 or #2 or #3
#5. Explode ‘neoplasm-‘ / all subheadings
#6. Explode ‘carcinoma-’ / all subheadings
#7. Explode ‘adenocarcinoma-‘ / all subheadings
#8. #5 or #6 or #7
#9. Explode ‘colon-disease' / all subheadings
#10. Explode ‘rectum-disease' / all subheadings
#11. Explode ‘colon-' / all subheadings
#12. Explode ‘rectum-' / all subheadings
#13. #9 or #10 or #11 or #12
#14. #8 and #13
#15. ((Carcinoma* or neoplasia* or neoplasm* or adenocarcinoma* or cancer* or tumo* or malignan*) near3 (colorectal or colon* or rect* or intestin* or bowel*))
#16. #4 or #14 or #15
#17. Capecitabine*
#18. Xeloda*
#19. 154361-50-9
#20. EU?1?00?163?001
#21. EU?1?00?163?002
#22. Ro09?1978
#23. Fluoropyrimidine*
#24. Tegafur*
#25. 17902-23-7
#26. Uftoral
#27. PL?11184?0087
#28. #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27
#29. #16 and #28

HEED (Office of Health Economics Health Economic Evaluation Database)
CD ROM version
Search undertaken May 2002

Search terms:
Capecitabine
Xeloda
Tegafur
Uftoral
Fluoropyrimidine

Fields searched:
Quick search – All data

Medline
1966-2002
Ovid Biomed
Search undertaken April 2002

Exp Colorectal Neoplasms/

#1. Neoplasms/
#2. Carcinoma/
#3. Adenocarcinoma/
#4. or/2-4
#5. Colonic Diseases/
#6. Rectal Diseases/
#7. Exp Colon/
#8. Exp Rectum/
#9. or/6-9
#10. 5 and 10
#11. ((Carcinoma$ or neoplasia or neoplasm$ or adenocarcinoma$ or cancer$ or tumor$ or tumour$ or malignan$) adj3 (colorectal or colon$ or rect$ or intestin$ or bowel$)).tw
#12. 1 or 11 or 12
#13. Capecitabine.af
#14. Xeloda.af
#15. 154361-50-9.af
#16. EU#1#00#163#001.af
#17. EU#1#00#163#002.af
#18. Ro09?1978.af
#19. Fluoropyrimidine$.af
#20. Tegafur.af
#21. 17902-23-7.af
#22. Uftoral.af
#23. PL?11184?0087.af
#24. Or/14-24
#25. 13 and 25

Medline – for the epidemiology of colorectal cancer only
1966-2002
Ovid Biomed
Search undertaken May 2002

Exp Colorectal Neoplasms/

#1. Neoplasms/
#2. Carcinoma/
#3. Adenocarcinoma/
#4. or/2-4
#5. Colonic Diseases/
#6. Rectal Diseases/
#7. Exp Colon/
#8. Exp Rectum/
#9. or/6-9
#10. 5 and 10
#11. ((Carcinoma$ or neoplasia$ or neoplasm$ or adenocarcinoma$ or cancer$ or tumor$ or tumour$ or malignan$) adj3 (colorectal or colon$ or rect$ or intestin$ or bowel$)).tw
#12. 1 or 11 or 12
#13. Colorectal neoplasms/ep
#14. 13 and 14
#15. Limit 15 to yr=1990-2002
#16. (Epidemiolog$ or incidence$ or prevalence$).ti
#17. 16 and 17

Medline – for further references specifically on the two 5-Fluorouracil regimens (de Gramont and Mayo Clinic)
1966-2002
Ovid Biomed
Search undertaken June 2002

#1. Gramont.tw
#2. Mayo.tw
#3. 1 or 2
#4. Exp Fluorouracil/
#5. 3 and 4

Appendix 7.4 Methodological search filters used in Ovid Medline

Systematic reviews/Meta-analyses

#1. Meta-analysis/
#2. Exp review literature/
#3. (Meta-analy$ or meta analy$ or metaanaly$).tw
#4. Meta analysis.pt
#5. Review academic.pt
#6. Review literature.pt
#7. Letter.pt
#8. Review of reported cases.pt
#9. Historical article.pt
#10. Review multicase.pt
#11. or/1-6
#12. or/7-10
#13. 11 not 12

Randomised Controlled Trials

#1. Randomized controlled trial.pt
#2. Controlled clinical trial.pt
#3. Randomized controlled trials/
#4. Random allocation/
#5. Double blind method/
#6. Single blind method/
#7. or/1-6
#8. Clinical trial.pt
#9. Exp clinical trials/
#10. ((Clin$) adj25 (trial$)).ti,ab
#11. ((Singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab
#12. Placebos/
#13. Placebos.ti,ab
#14. Random.ti,ab
#15. Research design/
#16. or/8-15
#17. Comparative study/
#18. Exp evaluation studies/
#19. Follow up studies/
#20. (Control$ or prospective$ or volunteer$).ti,ab
#21. Prospective studies/
#22. or/17-21
#23. 7 or 16 or 22

Economic evaluations

#1. Economics/
#2. Exp “costs and cost analysis”/
#3. Economic value of life/
#4. Exp economics, hospital/
#5. Exp economics, medical/
#6. Economics, nursing/
#7. Economics, pharmaceutical/
#8. Exp models, economic/
#9. Exp “fees and charges”/
#10. Exp budgets/
#11. Ec.fs.
#12. (Cost or costs or costed or costly or costing$).tw
#13. (Economic$ or pharmacoeconomic$ or price$ or pricing).tw
#14. or/1-13

Guidelines

#1. Guideline.pt
#2. Practice guideline.pt
#3. Exp guidelines/
#4. Health planning guidelines/
#5. or/1-4

Quality of life

#1. Exp quality of life/
#2. Quality of life.tw
#3. Life quality.tw
#4. Hql.tw
#5. (Sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36).tw
#6. Qol.tw
#7. (Euroqol or eq5d or eq 5d).tw
#8. Qaly$.tw
#9. Quality adjusted life year$.tw
#10. Hye$.tw
#11. Health$ year$ equivalent$.tw
#12. Health utilit$.tw
#13. Hui.tw
#14. Quality of wellbeing$.tw
#15. Quality of well being.tw
#16. Qwb.tw
#17. (Qald$ or qale$ or Qtime$).tw
#18. Or/1-18

APPENDIX 8: National Cancer Institute Common Toxicity Criteria[67]

Toxicity	0	1	2	3	4
White Blood Count (WBC)	> 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 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 9: Unit costs used in economic evaluation

All costs are adjusted to 2002 prices for use in the economic evaluation.

	Cost	Year	Source
Inpatient day	£359	2001	PSSRU
Outpatient day	£109	2001	PSSRU
OP clinic appointment with chemotherapy	£150	2002	Christie hospital
OP clinic appointment without chemotherapy	£80	2002	Christie hospital
Medical oncology OP follow-up	£86.07	2001	NHS reference costs
Day case	£218	2001	NHS reference costs
District nurse home visit	£20	2001	PSSRU
GP home visit	£59	2001	PSSRU
GP telephone consultation	£22	2001	PSSRU
Day care visit	£125	2001	PSSRU
GP surgery consultation	£19	2001	PSSRU
GP clinic consultation	£26	2001	PSSRU
A and E visit	£61	2001	PSSRU
Other hospital visits	£74	2001	PSSRU
Line insertion	£498	2002	Christie hospital
Line insertion	£537	2001	Revised Christie cost
Line insertion	£250	1996/7	Iveson 1999
Line insertion - PICC	£20	2002	Line insertion by nurse.
Pumps	£65	2002	Christie hospital
Pumps	£62	1996/7	Iveson 1999
Consultant hour	£86	2001	PSSRU
District nurse hour	£43	2001	PSSRU
Gr. D pharmacist hour	£13.25	2000	ASW
MTO 3 pharmacy technician	£9.66	2000	ASW
Staff nurse hour	£27	2001	PSSRU
5-FU 1000 mg vial	£12.80	2002	BNF
5-FU 5000 mg vial	£64.00	2002	BNF
5-FU 500 mg vial	£6.40	2002	BNF
5-FU 250 mg vial	£3.20	2002	BNF
CF 50 mg vial	£19.41	2002	BNF
CF 350 mg vial	£90.98	2002	BNF

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