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The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation

A Pandor, S Eggington, S Paisley, P Tappenden and P Sutcliffe

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Abstract

The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation

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Objectives: To assess the clinical and cost-effectiveness of oxaliplatin in combination with 5-fluorouracil/leucovorin (5-FU/LV), and capecitabine monotherapy (within their licensed indications), as adjuvant therapies in the treatment of patients with Stage III (Dukes' C) colon cancer after complete surgical resection of the primary tumour, as compared with adjuvant chemotherapy with an established fluorouracil-containing regimen.

Data sources: Ten electronic bibliographic databases were searched from inception to January 2005. Searches were supplemented by hand searching relevant articles, sponsor and other submissions of evidence to the National Institute of Health and Clinical Excellence and conference proceedings.

Review methods: A systematic review and meta-analysis (where appropriate) of clinical efficacy evidence and a cost-effectiveness review and economic modelling were carried out. Marginal costs, life years gained and cost-effectiveness acceptability curves were estimated. Probabilistic sensitivity analysis was used to generate information on the likelihood that each of the interventions was optimal.

Results: Three randomised active-controlled trials, of varying methodological quality, were included in the review. The MOSAIC trial and NSABP C-07 study considered the addition of oxaliplatin to adjuvant treatment (albeit administered in different 5-FU/LV regimens) and the X-ACT study compared oral capecitabine with bolus 5-FU/LV alone. A review of the available evidence indicated that in patients with Stage III colon cancer, oxaliplatin in combination with an infusional de Gramont schedule of 5-FU/LV (FOLFOX4) was more effective in preventing and delaying disease recurrence than infusional 5-FU/LV alone (de Gramont regimen). Serious adverse events and treatment discontinuations due to toxicity were more evident with oxaliplatin-based regimens (FOLFOX4 and FLOX regimen) than infusional or bolus 5-FU/LV alone (de Gramont and Roswell Park regimen). Oral capecitabine was at least equivalent in disease-free survival to the bolus Mayo Clinic 5-FU/LV regimen for patients with resected Stage III colon cancer. Although, the safety and tolerability profile of capecitabine was superior to that of the Mayo Clinic 5-FU/LV regimen, it has not been evaluated in comparison with other less toxic 5-FU/LV regimens currently in common use in the UK. Based on the assumptions and survival analysis methods used, the cost-effectiveness analysis using economic modelling estimated that capecitabine was a dominating strategy and resulted in a cost-saving of approximately £3320 per patient in comparison with the Mayo Clinic 5-FU/LV regimen, while also providing an additional 0.98 quality-adjusted life-years (QALYs) over a 50-year model time horizon. Oxaliplatin in combination with 5-FU/LV (FOLFOX4 regimen) is estimated to cost an additional £2970 per QALY gained when compared with the de Gramont 5-FU/LV regimen and demonstrated superior survival outcomes with marginal costs. The uncertainty analysis suggests that both interventions have a high probability of being cost-effective at a threshold of both £20,000 and £30,000. An indirect comparison of the FOLFOX4 and Mayo Clinic 5-FU/LV regimens suggests that the use of FOLFOX4 in place of the Mayo Clinic 5-FU/LV regimen would cost an additional £5777 per QALY gained. An incremental cost-effectiveness ratio (ICER) is estimated to be approximately £13,000 per QALY gained from treatment with FOLFOX4 compared with capecitabine. However, if the Mayo Clinic and the de Gramont 5-FU/LV regimens are assumed to be equivalent in terms of effectiveness, the ICER of FOLFOX4 in comparison with capecitabine may be greater than £30,000 per QALY.

Conclusions: The evidence suggests that both capecitabine and FOLFOX4 are clinically effective and

cost-effective in comparison with 5-FU/LV regimens (Mayo Clinic and de Gramont schedules). Further research is suggested into the effectiveness, tolerability, patient acceptability and costs of different oxaliplatin/fluoropyrimidine schedules in the adjuvant setting; the effects of treatment duration on efficacy; adverse events; resource data collection strategies and reporting of summary statistics; subgroups benefiting most from adjuvant chemotherapy; and methods for estimating mean survival.

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Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Adjuvant chemotherapy Chemotherapy given to patients in higher risk categories after all detectable tumour has been removed by surgery (or radiotherapy) in order to destroy any remaining cancer cells.

Adverse effects An abnormal or harmful effect to an organism caused by exposure to a chemical or other intervention.

Alopecia Hair loss as a result of chemotherapy or of radiation therapy administered to the head.

Bolus administration The rapid injection of a drug (or drugs) all at once, the opposite of gradual administration (as an infusion).

Disease-free survival The time from trial entry or randomisation to (first time of) relapse/new occurrence of colorectal cancer or death.

Febrile neutropenia Neutrophil count $<500/mm^3$ or $<1000/mm^3$ with predicted decline to $500/mm^3$, accompanied by fever.

Hand–foot syndrome The redness, tenderness, and possibly peeling of the palms and soles. The areas affected can become dry and peel, with numbness or tingling developing.

Infusional administration The passive introduction of a substance (a fluid or drug or electrolyte) into a vein or between tissues (as by gravitational force).

Metastases The spread of cancer from one part of the body to a distant part.

Neuropathy (peripheral) Injury to the nerves that supply sensation to the arms, legs, fingers and toes. Often caused by chemotherapy and other drugs.

Neutropenia An abnormal decrease in the number of neutrophils, a type of white blood cell.

Overall survival Time from trial entry to death or until lost to follow-up.

Relapse-free survival Defined in the same way as disease-free survival but excluding deaths unrelated to disease progression or treatment.

Toxicity The quality of being poisonous or causing adverse events.

List of abbreviations

AUC	area under the curve
BNF	British National Formulary
CCTR	Cochrane Controlled Trials Register
CDSR	Cochrane Database of Systematic Reviews
CEA	carcinoembryonic antigen
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CT	computed tomography
CTC NCI	Common Toxicity Criteria of the National Cancer Institute
DARE	Database of Abstracts of Reviews of Effectiveness
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
ESMO	European Society for Medical Oncology
FA	folinic acid (leucovorin)
FAP	familial adenomatous polyposis
FLOX	Oxaliplatin + Bolus FU
FOCUS	Fluorouracil, Oxaliplatin and Irinotecan: Use and Sequencing
FOLFIRI	Irinotecan + Infusional FU
FOLFOX	Oxaliplatin + Infusional FU
5-FU	5-fluorouracil
GERCOR	Groupe Coopérateur Multidisciplinaire en Oncologie
HCHS	Hospital and Community Health Services
HEED	Health Economics Database
HNPCC	hereditary non-polyposis colorectal cancer
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
LV	leucovorin (folinic acid)
LV5FU2	leucovorin–5-fluorouracil (fortnightly de Gramont regimen)
LYG	life-year gained
MOSAIC	Multicenter International Study of Oxaliplatin/5-fluorouracil and leucovorin in the Adjuvant Treatment of Colon Cancer
MRC	Medical Research Council
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NNTB	number needed to treat in order to benefit
NNTH	number needed to treat in order to harm
NSABP	National Surgical Adjuvant Breast and Bowel Project
OR	odds ratio

continued

List of abbreviations *continued*

OxMdG	oxaliplatin modified de Gramont
PSS	Personal Social Services
PVI	protracted venous infusion
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RNA	ribonucleic acid
SIGN	Scottish Intercollegiate Guidelines Network
TNM	tumour, node, metastasis
VAT	value added tax
WoS	Web of Science
WWW	World Wide Web
X-ACT	Xeloda – Adjuvant Chemotherapy Trial

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Note

Information from academic submissions was submitted in confidence to the National Institute for Health and Clinical Excellence; this information was made available to the NICE Appraisals Committee but has been removed from this version of the report. A note in the relevant portion of the text shows where this has occurred.

Executive summary

Background

In the UK, about 26% of patients diagnosed with colorectal cancer are classified as Stage III (Dukes' C) at presentation. These patients have an overall 5-year survival rate of between 25 and 60%. After a complete surgical resection (undertaken with curative intent), stage III patients with colon cancer have a 50–60% chance of developing recurrent disease. Adjuvant chemotherapy is given after surgery to eliminate any occult micro-metastases that might be present and decrease the incidence of disease recurrence, offering colon cancer patients increased potential for cure.

The management of colorectal cancer is constantly evolving. The administration of 6–7 months of 5-fluorouracil/leucovorin (5-FU/LV) has until recently been considered standard treatment for patients with Stage III (Dukes' C) colon cancer, after curative surgical resection. The most widely used adjuvant treatment schedule in England and Wales is the weekly bolus QUASAR 5-FU/LV regimen given for 30 weeks; however, there remains significant geographical variation in the 5-FU-based regimens currently in use in the UK.

Objectives

The objectives were to assess the clinical and cost-effectiveness of oxaliplatin in combination with 5-FU/LV, and capecitabine monotherapy (within their licensed indications), as adjuvant therapies in the treatment of patients with Stage III (Dukes' C) colon cancer after complete surgical resection of the primary tumour, as compared with adjuvant chemotherapy with an established fluorouracil-containing regimen.

Methods

In all, 10 electronic databases were searched up to January 2005 and over 30 health technology assessment and cancer-related organisations were consulted via the World Wide Web. The sponsor and other submissions of evidence to the National Institute for Health and Clinical Excellence (NICE) and the reference lists of key papers were hand-searched. The extracted data and quality assessment variables were presented for each study. In addition, results of eligible studies were statistically synthesised (meta-analysed) where appropriate.

A new model was developed to assess the costs of the alternative treatments, the differential mean survival duration and the impact on health-related quality of life. Probabilistic sensitivity analysis was used to generate information on the likelihood that each of the interventions was optimal.

Results

Number and quality of studies

Of the 1499 titles and abstracts screened, 88 full papers were retrieved and assessed in detail. Three Phase III randomised controlled trials of varying methodological quality were included in the review.

Summary of benefits and risk

Oxaliplatin used in combination with 5-FU/LV

The evidence to support the addition of oxaliplatin to adjuvant treatment is at present limited to two large trials – the MOSAIC trial and NSABP C-07 study. The MOSAIC trial, a large (n = 2246), international, multi-centre, Phase III, randomised, open-label, active-controlled trial, compared the efficacy and safety of oxaliplatin in combination with an infusional de Gramont schedule of 5-FU/LV (FOLFOX4 regimen) or infusional 5-FU/LV alone (the de Gramont or LV5FU2 regimen) for 6 months in patients with Stage II (40%) or III (60%) colon cancer. The primary trial end-point was disease-free survival. Secondary trial end-points included toxicity and overall survival. The NSABP C-07 study, a large (n = 2492), international, multi-institution, Phase III, randomised, active-controlled trial, compared the efficacy and safety of oxaliplatin in combination with a bolus Roswell Park schedule of 5-FU/LV (FLOX regimen) or bolus 5-FU/LV alone (Roswell Park regimen) for 24 weeks in patients with Stage II (29%) or III (71%) colon cancer. The primary and secondary trial end-points were

similar to those in the MOSAIC trial. No data were reported on quality of life in either trial.

Subgroup analyses by disease stage in the MOSAIC trial (data not reported for the NSABP C-07 study) showed that in patients with Stage III (any T, N1 or N2, M0) colon cancer the probability of remaining disease-free at 3 years was 72.2% and 65.3% for oxaliplatin (in combination with 5-FU/LV) and 5-FU/LV alone, respectively. For the intention-to-treat (ITT) population, the hazard ratio for recurrence was 0.76 (95% CI: 0.62 to 0.92; p = significant), corresponding to a 24% reduction in the risk of relapse or death and an absolute disease-free survival difference of 6.9% and a number needed to treat of 14.2 (95% CI: 8.7 to 44.2) to produce one additional patient who remains alive and disease-free at just over 3 years by using FOLFOX4 instead of infusional 5-FU/LV alone (de Gramont regimen) as adjuvant chemotherapy. These results are similar to those for the overall population of the MOSAIC trial (hazard ratio using ITT analysis, 0.77; 95% CI: 0.65 to 0.91; $p = 0.002$) and the NSABP C-07 study (hazard ratio using per protocol analysis, 0.79; 95% CI: 0.67 to 0.93; $p < 0.004$).

Updated subgroup analyses (not specified in the trial protocol) showed that the benefit observed at 3 years in patients with Stage III colon cancer was maintained and improved with longer follow-up. The probability of disease-free survival at 4 years was 69.7% and 61.0% for oxaliplatin (in combination with 5-FU/LV) and 5-FU/LV alone, respectively. The hazard ratio for recurrence for the ITT population was 0.75 (95% CI: 0.62 to 0.90; $p = 0.002$) with an absolute disease-free survival difference of 8.7% and a number-needed-to-treat of 12.5 (95% CI: 7.9 to 32.4).

The overall results of the MOSAIC trial (patients with Stage II and III colon cancer) showed that the frequency of severe (grade 3 or 4) paraesthesia, neutropenia, diarrhoea, nausea, vomiting and thrombocytopenia were significantly ($p < 0.001$) more pronounced with oxaliplatin plus infusional 5-FU/LV than with infusional 5-FU/LV alone. Similarly, in the NSABP C-07 study, diarrhoea and paraesthesia were more common with oxaliplatin plus bolus 5-FU/LV than with bolus 5-FU/LV alone (p-values not reported). The main safety concern regarding the use of oxaliplatin is neurotoxicity (irrespective of regimen), which, although significant and frequent (all-grade neurotoxicity, >85%; grade 3 neurotoxicity, >8%), does appear to improve within 1 year's time for the majority of patients (grade 3 neurotoxicity, <1.1%). However, approximately 25% of patients in the MOSAIC trial had some form of neurological impairment even 18 months after treatment.

Capecitabine

The evidence to support the use of oral capecitabine as adjuvant treatment is at present limited to the X-ACT study, a large (n = 1987), international, multi-centre, Phase III, randomised, open-label, active-controlled trial. This trial compared oral capecitabine (eight cycles) with a bolus Mayo Clinic regimen of 5-FU/LV (six cycles) for a total of 24 weeks in patients with Stage III (Dukes' C) colon cancer. The primary trial end-point was at least equivalence in disease-free survival. Secondary trial end-points included relapse-free survival, overall survival, safety and quality of life. It should be noted that the Mayo Clinic regimen, although internationally accepted as a reference regimen, is not commonly used in the UK, where it is widely regarded as producing an unacceptably high rate of toxicity.

Capecitabine therapy was shown to be at least equivalent to 5-FU/LV, in that the primary end-point was met [upper limit of the 95% CI of the hazard ratio was significantly ($p < 0.001$) below both predefined margins of 1.25 and 1.20 for at least equivalence]. At 3 years (pre-specified analysis), the probability of remaining disease-free was 64.2% and 60.6% for capecitabine and 5-FU/LV, respectively. For the ITT population, the hazard ratio for recurrence was 0.87 (95% CI: 0.75 to 1.00; $p = 0.05$ for superiority) corresponding to a 13% reduction in the risk of relapse/death and an absolute disease-free survival difference of 3.6%. Updated results (analysis not pre-specified) with a median follow-up of 4.4 years (with minimum follow-up of 3 years for all patients) confirm the earlier results and demonstrate that capecitabine is equivalent to 5-FU/LV (hazard ratio of 0.87; 95% CI: 0.76 to 1.00; $p = 0.055$ for superiority).

Capecitabine therapy improved relapse-free survival. At 3 years (pre-specified analysis), the probability of remaining relapse-free was 65.5% and 61.9% for capecitabine and 5-FU/LV, respectively. For the ITT population, the hazard ratio for recurrence was 0.86 (95% CI: 0.74 to 0.99; $p = 0.04$ for superiority), corresponding to a 14% reduction in the risk of relapse/death and an absolute relapse-free survival difference of 3.6%. Updated results (analysis not pre-specified in the protocol) with a median follow-up of 4.4 years

showed a trend in favour of capecitabine (hazard ratio of 0.87; 95% CI: 0.75 to 1.00; $p = 0.057$ for superiority).

There were no major (statistically significant) differences in quality of life between oral capecitabine and 5-FU/LV from baseline to 25 weeks of trial treatment (no statistical data reported); however, other studies suggest that patients prefer oral chemotherapy to intravenous treatment.

As a result of toxicity, both groups required dose modifications, interruptions and delays (capecitabine 57% versus 5-FU/LV 52%). Adverse events most commonly leading to dose modifications (including treatment interruption and dose reduction) were hand–foot syndrome (31%) and diarrhoea (15%) in the capecitabine group and stomatitis (23%) and diarrhoea (19%) in the 5-FU/LV group. The frequency of severe (grade 3 or 4) stomatitis (2 versus 14%; $p < 0.001$) and alopecia (0 versus <1%; $p < 0.02$) was significantly less common in capecitabine-treated patients than in those receiving 5-FU/LV. The incidence of neutropenia as a grade 3 or 4 laboratory abnormality was significantly ($p < 0.001$) lower in the capecitabine group (2%) than in the 5-FU/LV group (26%). Grade 3 hand–foot syndrome was the only severe adverse event occurring more often with capecitabine than 5-FU/LV (17 versus <1%; $p < 0.0001$, respectively).

Other evidence

Infusional 5-FU/LV adjuvant-based therapy is equivalent to, but with relatively less toxicity than, bolus 5-FU/LV in extending survival and a better quality of life. The major drawbacks of continuous infusion with 5-FU are catheter-associated complications and its adverse effects.

Summary of cost-effectiveness

The independent economic analysis used a state transition (Markov) approach to simulate the disease outcomes of patients up to a time horizon of 50 years post-surgery. This included the use of economic modelling from a recent NICE assessment of chemotherapies for advanced colorectal cancer. The primary outcome of interest in this assessment was the cost per quality-adjusted life-year (QALY) gained, associated with capecitabine and oxaliplatin (in combination with 5-FU/LV). The economic model uses survival analysis techniques to predict long-term survival, therefore assuming that the short-term survival differences observed within the trials are translated into long-term benefits.

With this important proviso, the results of the cost-effectiveness results estimate that capecitabine is a dominating strategy over a 50-year time horizon when compared with the Mayo Clinic 5-FU/LV regimen, saving an average of approximately £3320 per patient. Capecitabine is estimated to improve survival outcomes over the entire 50-year period, through extrapolation of the survival estimates observed in the trial to date. Over the same 50-year period, oxaliplatin in combination with 5-FU/LV (FOLFOX4 regimen) is estimated to cost an additional £2970 per QALY gained when compared with the de Gramont 5-FU/LV regimen, a figure well below the cost-effectiveness ratio of many health interventions currently available on the NHS.

The one-way sensitivity analyses demonstrated that the costs and QALY gains associated with both therapies are driven by the long-term survival of patients who do not relapse. The results of the probabilistic sensitivity analyses demonstrate the robustness of the central estimates of cost-effectiveness. Capecitabine was consistently found to be a dominating intervention when compared with 5-FU/LV. Oxaliplatin (in combination with 5-FU/LV) demonstrated superior survival outcomes, with marginal costs, when compared with the de Gramont 5-FU/LV regimen. Based upon the assumptions made in the economic model, the cost-effectiveness acceptability curves demonstrate that the two interventions have a high probability of being cost-effective at thresholds of both £20,000 and £30,000, when compared with the 5-FU/LV comparator arms in the two trials.

An indirect comparison of the FOLFOX4 and Mayo Clinic 5-FU/LV regimens (using data from both the MOSAIC and X-ACT studies) suggests that the use of FOLFOX4 in place of the standard Mayo Clinic 5-FU/LV regimen would cost an additional £5777 per QALY gained.

Furthermore, an additional indirect comparison demonstrated that there is considerable uncertainty regarding the incremental cost-effectiveness of FOLFOX4 when compared with capecitabine. Using the extrapolated effectiveness data from the trials and the estimated costs of each intervention to inform this comparison suggests an incremental cost-effectiveness ratio of approximately £13,000 per QALY gained from treatment with FOLFOX4, compared with capecitabine. However, if it is assumed that the Mayo Clinic and the de Gramont 5-FU/LV regimens are equivalent in terms of effectiveness

(and therefore using the marginal QALY gains of the two interventions against their 5-FU/LV comparators), the analysis estimates that the ICER of FOLFOX4 in comparison with capecitabine may be greater than £30,000 per QALY. There is therefore considerable uncertainty in this comparison, owing to the differences in long-term survival predicted in the 5-FU/LV regimens in the two trials.

Conclusions

Clinical effectiveness

Evidence from the MOSAIC trial demonstrated that oxaliplatin (in combination with 5-FU/LV) therapy was more effective in preventing or delaying disease recurrence than 5-FU/LV alone in the adjuvant treatment of patients who had undergone complete surgical resection for Stage III colon cancer (data not reported separately for Stage III patients in the NSABP C-07 study). On the whole, serious adverse events and treatment discontinuations due to toxicity were more evident with oxaliplatin in combination with an infusional 5-FU/LV de Gramont schedule (FOLFOX4 regimen) than infusional 5-FU/LV alone (de Gramont regimen) and oxaliplatin in combination with a bolus 5-FU/LV Roswell Park schedule (FLOX regimen) than bolus 5-FU/LV alone (Roswell Park regimen).

Evidence from the X-ACT study demonstrated that capecitabine therapy was at least equivalent in disease-free survival to the bolus Mayo Clinic 5-FU/LV regimen for patients with resected Stage III colon cancer. In terms of relapse-free survival, capecitabine monotherapy was significantly better than bolus 5-FU/LV. The safety and tolerability profile of capecitabine was superior to that of the Mayo Clinic 5-FU/LV regimen, but has not been evaluated in comparison with the less toxic 5-FU/LV regimens currently in common use in the UK.

Cost-effectiveness

Based on the assumptions regarding long-term survival, the results of the independent health economic assessment suggest that both capecitabine and FOLFOX4 appear to have favourable cost-effectiveness profiles in comparison with 5-FU/LV regimens (Mayo and de Gramont schedules), based on levels of cost-effectiveness which are currently considered by NHS policymakers to represent acceptable value for money. Indirect comparisons suggest that FOLFOX4 is cost-effective compared with the Mayo Clinic 5-FU/LV regimen, although it may not be deemed cost-effective by policymakers in comparison with capecitabine. These economic comparisons could only be assessed fully following a trial that directly compared these two regimens.

The mean age of patients in both the MOSAIC and X-ACT studies is considerably lower than that observed in clinical practice and, as a result, the cost-effectiveness analyses may overestimate long-term overall survival for patients in all treatment arms, owing to the shorter life expectancy of these more elderly patients. The marginal benefits of capecitabine and FOLFOX4 versus their respective 5-FU/LV comparators may therefore be overestimates and, as a result, the estimated marginal costs-effectiveness ratios may have been underestimated.

Recommendations for further research

The following areas are suggested for further research.

- A comparison of the effectiveness, tolerability, patient acceptability and costs of different oxaliplatin/fluoropyrimidine schedules in the adjuvant setting.
- Large trials to determine the effects of treatment duration on efficacy.
- Consideration of the best approach to ensure compliance and monitoring of adverse events.
- Future cancer trial protocols incorporating more detailed resource data collection strategies and reporting of summary statistics that are of use within economic evaluations.
- Identification of those subgroups of patients who benefit the most from chemotherapy.
- Methods for estimating mean survival, both in non-curative interventions (in which the survival time is prohibitively long and thus prevents estimation of mean survival) and in curative treatments.

Chapter 1

Aim of the review

This review examined the clinical and cost-effectiveness of oxaliplatin (Eloxatin®, Sanofi-Aventis) in combination with 5-fluorouracil/leucovorin (5-FU/LV), and capecitabine (Xeloda®, Roche) monotherapy within their licensed indications as adjuvant therapies in the treatment of patients with completely resected Stage III (Dukes' C) colon cancer, as compared with adjuvant chemotherapy with an established fluorouracil-containing regimen.

This review does not include an assessment of irinotecan, as the anticipated licensing timescale is not compatible with the scheduling of this appraisal.

Chapter 2
Background

Description of underlying health problem

Introduction

The colon and rectum are parts of the body's digestive system and together form a long, muscular tube called the large intestine. The colon is the first 6 ft of the large intestine and the rectum is the last 8–10 in. Colonic and rectal cancers arise from similar tissues and exhibit a broadly similar natural history and responsiveness to treatment. Owing to the similarities, they are often referred to using the all-encompassing term colorectal cancer. However, largely owing to restrictions imposed by their anatomical location, there are both differences and similarities in the treatment of rectal and colonic tumours. In practice it is very rare to have both. Most patients will have one or the other.

Epidemiology

Cancer of the large bowel – which comprises cancers of the colon and rectum – is the third most common cancer in the UK after breast and lung cancer. In 2002, there were about 30,000 new cases registered in England and Wales, representing over 12% of all new cancer cases (*Table 1*). About two-thirds of tumours develop in the colon and the remainder in the rectal. Although rectal cancers are more common in men than women, colon cancers are equally common between both genders.[1,2] In 2001, the age-standardised incidence rates for England and Wales were 42.8 and 46.6 per 100,000, respectively.[3]

The incidence of colorectal cancer is gradually increasing. One reason for this is the ageing of the population: as with most forms of cancer, the probability of developing colorectal cancer rises sharply with age. In people below the age of 40 years, the risk is very low (less than 5.2 per 100,000 in men and women); however, between the ages of 45 and 49 years, the incidence is about 20 per 100,000 for both males and females. Among those aged 75 years and above, the rate is over 300 per 100,000 per year for males and for women it is over 200 per 100,000 per year.[4] The median age of diagnosis is over 70 years for both colon and rectal cancer patients.[1,2,4] The gradual increase in age-specific incidence, particularly among men between 65 and 84 years of age, which varies by region, suggests that lifestyle or environmental factors also contribute to the increasing incidence.[5,6]

Aetiology

The development of colorectal cancer is poorly understood; however, genetics,[7] experimental[5] and

TABLE 1 *Colorectal cancer incidence, 2002*

Number of new cases	Age bands (years)				All cases
	0–44	45–64	65–74	75+	
England					
Colon cancer	410	3,625	4,937	8,392	17,364
Rectal cancer	256	2,848	3,060	4,105	10,269
Colorectal cancer	666	6,473	7,997	12,497	27,633
Wales					
Colon cancer	27	252	333	567	1,179
Rectal cancer	24	210	219	282	735
Colorectal cancer	51	462	552	849	1,914
England and Wales					
Colon cancer	437	3,877	5,270	8,959	18,543
Rectal cancer	280	3,058	3,279	4,387	11,004
Colorectal cancer	717	6,935	8,549	13,346	29,547

Source: Office for National Statistics[1] and Welsh Cancer Intelligence and Surveillance Unit.[2]

epidemiological studies[6] suggest that colorectal cancer results from complex interactions between inherited susceptibility and environmental factors.[8]

A family history of colorectal cancer (particularly with relatives diagnosed under the age of 45 years)[9] is associated with a higher risk of developing colorectal cancer compared with the general population.[10] There are two specific genetic syndromes which predispose to colorectal cancer, familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC), but clusters of cases also occur in families without either of these.[10] FAP accounts for approximately 1% of all colorectal cancers and is caused by a mutation in the adenomatous polyposis coli gene.[11] People with FAP develop hundreds of polyps in the colon and by the age of 40 years, most will have cancer unless they have surgery to remove the colon.[10] HNPCC accounts for 5% of cases, and is caused by a dominantly inherited alteration in the DNA mismatch repair genes.[12] People with HNPCC develop colorectal cancer at an early age, but it is less often preceded by the growth of multiple polyps. Genetic testing can identify gene carriers in members of affected families.[10]

Environmental factors that may contribute to the development of colorectal cancer include the following: diet of high calorific value, high consumption of red meat (especially if overcooked), high consumption of saturated fat or alcohol, obesity, cigarette smoking and a sedentary lifestyle.[10] It is estimated that up to 80% of colorectal cancer cases are caused by diet alone.[13] Colitis due to inflammatory bowel disease is also associated with increased risk of colorectal cancer and the risk increases with the duration of the condition.[14] Protective factors may include high consumption of fruit and vegetables,[10,15] calcium and antioxidant vitamins,[10] regular use of non-steroidal anti-inflammatory drugs[10,16,17] and the use of hormone replacement therapy (although the benefit is balanced by an increased risk of breast cancer and coronary heart disease).[10]

Pathology

Colorectal cancer includes cancerous growths in the colon, rectum and appendix. Cancer cells eventually spread to nearby lymph nodes (local metastases) and subsequently to more remote lymph nodes and other organs in the body. The pathology of the tumour is usually reported from the analysis of tissue taken from a biopsy or surgery. A pathology report will usually contain a description of cell type and grade. The most common colon cancer cell type is adenocarcinoma, which accounts for 95% of cases. Other, rarer, types include lymphoma and squamous cell carcinoma.[8]

Prognosis

The prognosis, type and effectiveness of treatment depend largely on the degree to which the cancer has spread at diagnosis. Historically, spread has been described in terms of the modified Dukes' staging system, but this is being superseded by the more precise Tumour, Node, Metastases (TNM) classification system. As shown in *Table 2*, long-term survival, particularly of patients with Stage III disease (which covers patients with a broad spectrum of disease, and is reflected in a wide range of 5-year survival within this patient group) is considerably worse than that of those whose tumours are restricted to the bowel wall.[8,18] Similar rates of survival have also been reported by O'Connell and colleagues.[19] Reduced survival is

TABLE 2 *Staging of colorectal cancer, with 5-year survival*[8,18]

TNM Status	Stage	Extension to	Modified Dukes'	5-year overall survival (%)
T *in situ* N0 M0	0	Carcinoma *in situ*	–	Likely to be normal
T1 N0 M0	I	Mucosa or submucosa	A	>90
T2 N0 M0	I	Muscularis propria	B1	85
T3 N0 M0	IIa	Subserosa/pericolic tissue	B2	70–80
T4 N0 M0	IIb	Perforation into visceral peritoneum or invasion of other organs	B3	
T1-2 N1 M0/T2 N2 M0	III	T2, N1: 1–3/N2: ≥4 lymph nodes	C1	25–60
T3 N1 M0/T3 N2 M0	III	T3, N1: 1–3/N2: ≥4 lymph nodes	C2	
T4 N1 M0	III	T4, N1: 1–3/N2: ≥4 lymph nodes	C3	
Any T any N M1	IV	Distant metastases	D	5–30

M, number of metastatic sites; N, number of affected lymph nodes; T, Tumour 1–4.

TABLE 3 *Colorectal cancer mortality, 2002*[24,25]

	Number of deaths		Age-standardised mortality rates[a]	
	Male	**Female**	**Male**	**Female**
England				
Colon cancer	4438	4464	Not reported	Not reported
Rectal cancer	2619	1866	Not reported	Not reported
Colorectal cancer	7057	6330	24.0	14.7
Wales				
Colon cancer	299	297	Not reported	Not reported
Rectal cancer	171	105	Not reported	Not reported
Colorectal cancer	470	402	25.5	14.6
England and Wales				
Colon cancer	4737	4761	Not reported	Not reported
Rectal cancer	2790	1971	Not reported	Not reported
Colorectal cancer	7527	6732	Not reported	Not reported

[a] Directly age-standardised (European) rates per 100,000 population at risk.

a consequence of disease recurrence, which almost always occurs at sites remote from the bowel itself and is assumed to be the result of growth from microscopic tumour deposits seeded from the primary tumour, before its removal.[20]

In the UK, about 26% of patients diagnosed with colorectal cancer are classified as Stage III (modified Dukes' C1 and C2 – patients whose tumour has spread to lymph nodes) at presentation and 32% as Stage II (modified Dukes' B2, and B3), with 11 and 30% of patients having Stage I and IV disease, respectively.[21] Although there are large variations in survival according to the stage of disease, the overall 5-year survival rate for colorectal cancer in England is 35%.[22]

Surgery is undertaken with curative intent in over 80% of those patients with Stage I to III disease (Dukes' A to C), but about half experience cancer recurrence.[8] The status of the resection margin after surgery is one of the most important prognostic factors as it depends both on surgical competence and on tumour biology. Adjuvant chemotherapy is given after surgery [usually to patients whose tumour has spread to lymph nodes (Stage III disease), for whom the benefit of chemotherapy has been most clearly demonstrated][10] to eliminate any occult micro-metastases that might be present and decrease the incidence of disease recurrence, offering colon cancer patients increased potential for cure. An episode of recurrence is inevitably associated with a substantially worse prognosis in terms of overall survival. Patients who experience a recurrence following potentially curative surgery will eventually succumb to their disease, although successful metastasectomy is becoming a more common outcome. After a complete surgical resection, Stage III patients with colon cancer have a 50–60% chance of developing recurrent disease.[23]

Significance in terms of ill-health (burden of disease)

Colorectal cancer is a significant cause of premature death (*Table 3*), with almost half of all related deaths occurring in people under 75 years of age.[8,22] In most cases, death from colorectal cancer ensues only after spread beyond the bowel and regional lymph nodes (Stage IV disease). Mortality rates are higher in men than women and in patients with colon cancer than rectal cancer. In 2002, the age standardised mortality rate for colorectal cancer was 18.8 per 100,000 population in England and 19.5 per 100,000 population in Wales.[24] Colorectal cancer is also a significant cause of morbidity.

When treating patients with Stage III colon cancer, the main aims of treatment are to reduce incidence of disease recurrence, increase survival and improve quality of life (QoL). Individual patient preferences for treatment are also important to consider. Although adjuvant chemotherapy can improve long-term survival for patients with operable colon cancer, current regimens are burdensome and can cause severe adverse effects. For this reason, information regarding health-related QoL, particularly those associated with treatment-related toxicity, will be given careful consideration in this report.

Current service provision

Management of disease and national guidelines

The management of colorectal cancer is constantly evolving. The administration of 6–7 months of 5-FU combined with LV for medically fit patients with node-positive (Stage III, Duke's C) colon cancer after curative surgical resection has until recently been considered standard treatment for the reduction of disease recurrence and improvement in survival. An overview of existing 5-FU/LV regimens is given in Appendix 1. The most widely used adjuvant treatment schedule in England and Wales is the weekly intravenous bolus 5-FU/LV for 30 weeks [QUASAR (QUick And Simple And Reliable) regimen]; however, there remains significant geographical variation in the 5-FU-based regimens currently in use in the UK.[26,27]

In 2004, the National Institute for Health and Clinical Excellence (NICE) issued guidance on improving outcomes in colorectal cancer to clinicians within the NHS in England and Wales.[10] The guidance on adjuvant therapy recommends that "systemic chemotherapy should be offered to all patients who, after surgery for Dukes' stage C colon or rectal cancer, are fit enough to tolerate it … Judgments about a patient's fitness to receive chemotherapy should be made on the basis of his or her performance status and co-morbidity, rather than age … The standard treatment has been a course of 5-FU and LV given over 6 months." The guidance also adds that adjuvant chemotherapy for patients with Dukes' B cancers should be a matter of discussion between patients and their oncologists.[10]

The guidance given by NICE is broadly similar to the guidelines issued in 2003 by the Scottish Intercollegiate Guidelines Network (SIGN) for the NHS in Scotland.[28] SIGN recommends the routine use of adjuvant chemotherapy for patients with Stage III (Dukes' C) colon or rectal cancers. However, adjuvant chemotherapy is not routinely recommended for patients with Stage II (Dukes' B) tumours of the colon or rectum. Although NICE do not specify a regimen of choice, the SIGN guidelines recommend bolus 5-FU and low-dose LV, ideally administered over 5 days every 4 weeks, with 30 weekly treatments being an acceptable alternative.[28] In addition, SIGN state that a retrospective analysis of data from the QUASAR trial[29] suggests that the weekly bolus 5-FU/LV (5-FU, 370 mg/m^2 plus LV, 25 mg) is as active as and less toxic than a regimen in which the same agents are given in the same doses as a 5-day course every 4 weeks. They conclude that although there is less evidence available to support this regimen, it may be a preferable option for certain patients.

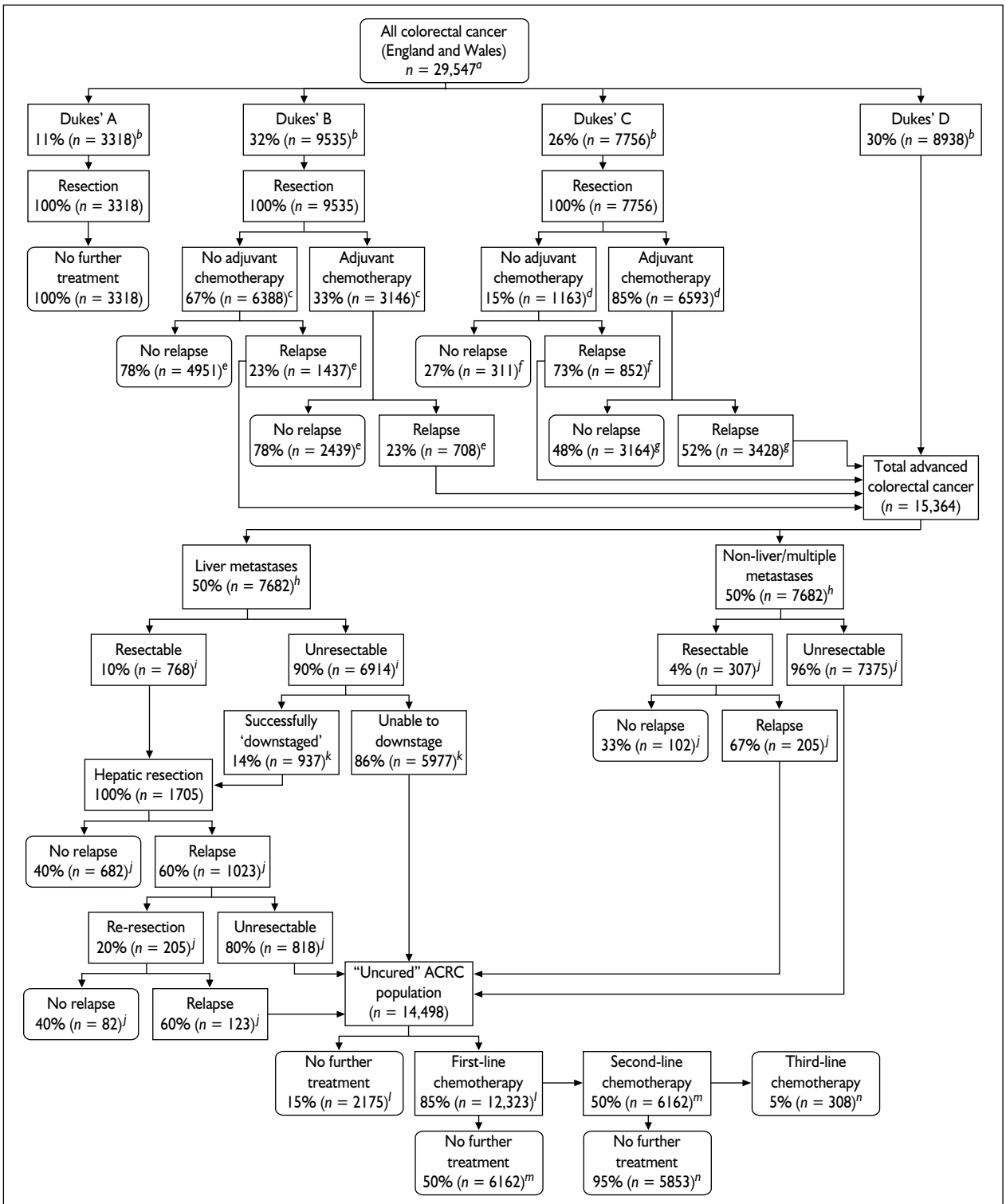
Guidelines for the management of colorectal cancer, published in 2001 by the Association of Coloproctology of Great Britain and Ireland,[30] recommend adjuvant chemotherapy for patients with Stage III (Dukes' C) colon cancer. These guidelines do not recommend the routine use of adjuvant chemotherapy in patients with Stage II (Dukes' B) colon cancer; however it may be considered for high-risk patients.

Current service cost

A treatment algorithm (developed by researchers at the School of Health and Related Research, University of Sheffield), as shown in *Figure 1*, demonstrates the various treatment pathways for patients with all stages of colorectal cancer (should be considered as illustrative of the scale of the service). The algorithm suggests that there are 7756 incident cases of Stage III (Dukes' C) colorectal cancer per year in England and Wales. Of these patients, approximately 63% have colon cancer[1,2] and undergo curative surgery; 85% of the patients undergoing surgery will then undergo a 6-month course of adjuvant chemotherapy in the form of intravenous 5-FU/LV, delivered primarily using the Mayo Clinic regimen. Hence approximately 4150 patients per year will receive adjuvant chemotherapy for Stage III colon cancer. It has been estimated that the total cost to the NHS for surgical, adjuvant and palliative treatment is in excess of £300 million per year for all colorectal cancer.[8,31] The specific cost to the NHS of chemotherapies for the adjuvant treatment of Stage III colon cancer is unknown and any attempt to model it is dependent on many variables for which no routine data are available: (1) it is uncertain how many people have Stage III colon cancer and (2) it is uncertain how much it costs to treat.

Variation in services

Although there has been no systematic survey of modes of delivery for 5-FU/LV, anecdotal evidence suggests considerable variation across the UK and is based on the facilities available at individual trusts[8] and lack of consensus over the optimum regimen of 5-FU/LV. Although it is not within the scope of this report to assess the clinical effectiveness of these different regimens, evidence reviewed in the section 'Bolus or infusional 5-FU for the adjuvant treatment of colon cancer?' (p. 34)



[a] Office for National Statistics;[32] Welsh Cancer Intelligence and Surveillance Unit.[33] [b] South West Cancer Intelligence Service.[21] [c] Personal communication, Professor Matt Seymour, Leeds Teaching Hospitals NHS Trust: between 33 and 60% of people with Dukes' B cancer receive adjuvant chemotherapy (we have assumed the lower estimate). [d] Personal communication, Professor Seymour: more than 85% receive adjuvant chemotherapy. [e] Personal communication, Professor Seymour: 20–25% of patients with Duke's B will relapse. [f] Relative risk increase applied to 5-year disease-free survival estimates from X-ACT study.[34] [g] 5-year disease-free survival estimates from X-ACT study.[34] [h] Personal communication, Professor Tim Maughan, Velindre Hospital, Cardiff. [i] Data from case series[35] suggest that up to 20% may be resectable, although this is an aggressive stance; a maximum of 15% of patients are suitable (personal communication, Professor Maughan). [j] Personal communication, Mr Graeme Poston, Royal Liverpool University Hospital. [k] Data from case series.[35] [l] Personal communication, Professor Seymour: 85–90% of advanced patients receive chemotherapy. [m] Assumption.[36] [n] Personal communication, Dr Rob Glynne Jones, Watford and Barnet General Hospitals, London: only 3–5% patients would receive third-line therapy.

FIGURE 1 *Treatment algorithm for people with colorectal cancer in England and Wales*

suggests that infusional 5-FU/LV adjuvant-based therapy is equivalent to, but with relatively less toxicity than, bolus 5-FU/LV in extending survival and a better QoL. However, the bolus QUASAR weekly regimen is most commonly used within the NHS in England and Wales. It is noteworthy that in some areas, Strategic Health Authorities have already provided funding for adjuvant capecitabine, a focus of this review.[26]

Colon and rectal tumours are very similar in many ways and, when metastatic, show similar responsiveness to cytotoxic chemotherapy. However, radiotherapy has a much greater role to play in the perioperative management of rectal tumours, making any assessment of the impact of adjuvant chemotherapy more difficult. Consequently, patients with rectal cancer are often excluded from drug studies because of the confounding influence of surgery and radiotherapy upon their disease outcome. However, such evidence as there is indicates that patients with Stage III (Dukes' C) cancers of the rectum gain a survival advantage from adjuvant chemotherapy[37] and SIGN guidance suggests that this should be part of routine clinical practice.[28]

Description of technology under assessment

Two cytotoxic drugs, oxaliplatin (in combination with 5-FU/LV) and capecitabine, have been proposed for the adjuvant treatment of patients with completely resected Stage III (Dukes' C) colon cancer. The following section of the report summarises the product characteristics[38,39] of the two interventions separately (available from the electronic Medicine Compendium at www.medicines.org.uk). General guidance from the BNF[40] on the use of cytotoxic drugs can be found in Appendix 2.

Summary of interventions

Oxaliplatin (Eloxatin®, Sanofi-Aventis)

Description

Oxaliplatin is an intravenously administered, diaminocyclohexane platinum compound, which acts in a similar way to other platinum drugs by forming cross-linkages between and within strands of DNA, thereby preventing DNA replication. The recommended dose for oxaliplatin (in the adjuvant setting) is 85 mg/m^2 administered intravenously over 2–6 hours, prior to the administration of 5-FU/LV, and repeated every 2 weeks for 12 cycles (6 months).

Licensed indications

Oxaliplatin in combination with 5-FU/LV is indicated for the following.

- Adjuvant treatment of Stage III (Dukes' C) colon cancer after complete resection of the primary tumour.
- Treatment of metastatic colorectal cancer.

Contraindications

Oxaliplatin is contraindicated in the following patients.

- Have a known history of hypersensitivity to oxaliplatin.
- Are breast feeding.
- Have myelosuppression prior to starting first course, as evidenced by baseline neutrophils $<2 \times 10^9$/l and/or platelet count of $<100 \times 10^9$/l.
- Have a peripheral sensitive neuropathy with functional impairment prior to first course.
- Have a severely impaired renal function (creatinine clearance less than 30 ml/min).

Special warnings and special precautions for use

Oxaliplatin should only be used in specialised departments of oncology and should be administered under the supervision of an experienced oncologist. Precautions and warnings for the use of capecitabine are as follows.

- **Neurological toxicity**. Neurological toxicities of oxaliplatin (paraesthesia, dysaesthesia) are dose limiting and should be carefully monitored, especially if co-administered with other medications with specific neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter.
- **Gastrointestinal toxicity**. Gastrointestinal toxicity which manifests as nausea and vomiting warrants prophylactic and/or therapeutic antiemetic therapy. Dehydration, paralytic ileus, intestinal obstruction, hypokalaemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis, particularly when combining oxaliplatin with 5-FU.
- **Haematological toxicity**. If haematological toxicity occurs (neutrophils $<1.5 \times 10^9$/l or platelets $<50 \times 10^9$/l), administration of the next course of therapy should be postponed until haematological values return to acceptable levels. A full blood count with white cell differential should be performed prior to start of therapy and before each subsequent course.
- **Mucositis/stomatitis**. If mucositis/stomatitis occurs with or without neutropenia, the next

treatment should be delayed until recovery from mucositis/stomatitis to grade 1 or less and/or until the neutrophil count is $\geq 1.5 \times 10^9$/l.
- **Impaired renal function**. Administration (with close monitoring of renal function and dose adjustments according to toxicity) in patients with moderately impaired renal function should only be considered after suitable appraisal of the benefit and risks to the patient.
- **History of allergy**. Patients with a history of allergic reaction to platinum compounds should be monitored for allergic symptoms. In the case of an anaphylactic-like reaction to oxaliplatin, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. In the case of oxaliplatin extravasation, the infusion must be stopped immediately and usual local symptomatic treatment initiated.
- **Dose modifications**. For oxaliplatin combined with 5-FU (with or without LV), the usual dose adjustments for 5-FU associated toxicities should apply. In addition, if grade 4 diarrhoea, grade 3 or 4 neutropenia (neutrophils $<1.0 \times 10^9$/l), grade 3 or 4 thrombocytopenia (platelets $<50 \times 10^9$/l) occur, the dose of oxaliplatin should be reduced from 85 to 75 mg/m^2 in the adjuvant setting.
- **Other**. Patients must be adequately informed of the risk of diarrhoea/emesis, mucositis/stomatitis and neutropenia after oxaliplatin and 5-FU administration so that they can urgently contact their treating physician for appropriate management.

Capecitabine (Xeloda®, Roche)

Description

Capecitabine {*N*-[1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1,2-dihydro-2-oxo-4-pyrimidinyl]-*m*-pentyl carbamate; Ro 09–1978; Xeloda®} is a cytotoxic fluoropyrimidine carbamate. Capecitabine, in itself, is a non-cytotoxic fluoropyrimidine carbamate, which functions as a precursor of 5-FU. Capecitabine is activated via several enzymatic steps. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase, is found in tumour tissues at higher levels than in normal tissue. The metabolism of 5-FU is thought to interfere with the synthesis of DNA. The incorporation of 5-FU also leads to inhibition of RNA and protein synthesis. This effect of 5-FU is thought to provoke unbalanced growth and promote cell death.

The recommended dose for capecitabine (in the adjuvant setting) 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 7-day rest period. Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Treatment should be discontinued if progressive disease or intolerable toxicity is observed.

Licensed indications

Capecitabine is indicated for the following.

- The adjuvant treatment of patients following surgery of Stage III (Dukes' stage C) colon cancer.
- First-line monotherapy of metastatic colorectal cancer.
- A combination therapy with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Capecitabine is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

Contraindications

Capecitabine is contraindicated in the following patients.

- Have a history of severe and unexpected reactions to fluoropyrimidine therapy.
- Have known hypersensitivity to capecitabine, fluorouracil or any of the excipients.
- Have known dihydropyrimidine dehydrogenase deficiency.
- Are pregnant and lactating.
- Have severe leucopenia, neutropenia, or thrombocytopenia.
- Have severe hepatic impairment.
- Have severe renal impairment (creatinine clearance below 30 ml/min).
- Have treatment with sorivudine or its chemically related analogues, such as brivudine.
- Have contra-indications for docetaxel, which also applies to the capecitabine plus docetaxel combination.

Special warnings and special precautions for use

Capecitabine should only be prescribed by a qualified physician experienced in the utilisation of antineoplastic agents. Precautions and warnings for the use of capecitabine are as follows.

- **Dose-limiting toxicities**. These include diarrhoea, abdominal pain, nausea, stomatitis and hand–foot syndrome. Most adverse events are reversible and do not require permanent

discontinuation of therapy, although doses may need to be withheld or reduced.

- **Diarrhoea**. Capecitabine can induce the occurrence of diarrhoea, which has been observed in 50% of patients. Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Standard antidiarrhoeal treatments (e.g. loperamide) may be used. If grade 2, 3 or 4 diarrhoea occurs, administration of capecitabine should be immediately interrupted until the diarrhoea resolves or decreases in intensity to grade 1. Following grade 3 or 4 diarrhoea, subsequent doses of capecitabine should be decreased or treatment discontinued permanently (grade 4).
- **Hand–foot syndrome**. This is also known as hand–foot skin reaction or palmar–plantar erythrodysaesthesia or chemotherapy induced acral erythema. If grade 2 or 3 hand–foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand–foot syndrome, subsequent doses of capecitabine should be decreased.
- **Cardiotoxicity**. Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiographic changes. These adverse events may be more common in patients with a prior history of coronary artery disease. Cardiac arrhythmias, angina pectoris, myocardial infarction, heart failure and cardiomyopathy have been reported in patients receiving capecitabine. Caution must be exercised in patients with a history of significant cardiac disease.
- **Hypo- or hypercalcaemia**. Hypo- or hypercalcaemia has been reported during capecitabine treatment. Caution must be exercised in patients with pre-existing hypo- or hypercalcaemia.
- **Central or nervous system disease**. Caution must be exercised in patients with central or peripheral nervous system disease, e.g. brain metastasis or neuropathy.
- **Diabetes mellitus or electrolyte disturbances**. Caution must be exercised in patients with diabetes mellitus or electrolyte disturbances, as these may be aggravated during capecitabine treatment.
- **Coumarin-derivative anticoagulation**. Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulation therapy should have their anticoagulant response (international normalisation ratio or prothrombin time) monitored closely and the anticoagulant dose adjusted accordingly.
- **Hepatic impairment**. Capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence of liver metastasis.
- **Renal impairment**. The incidence of grade 3 or 4 adverse events in patients with moderate renal impairment (creatinine clearance 30–50 ml/min) is increased compared with the overall population.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

Identification of studies

The following searches were carried out to:

- identify studies for inclusion in the review of clinical effectiveness
- identify studies for inclusion in the review of cost-effectiveness
- inform the development of the independent economic assessment.

The search strategy used to identify studies for the review of clinical effectiveness is reported in this section. All other searches are reported in the section 'Identification of studies' (p. 41).

Identification of studies for the review of clinical effectiveness

The aim of the search was to provide as comprehensive a retrieval as possible of randomised controlled trials (RCTs) of oxaliplatin or capecitabine as adjuvant therapies in the treatment of colon cancer.

Sources searched

Nine electronic databases were searched, providing coverage of the biomedical and grey literature and current research. The publications lists and current research registers of over 30 health services research-related organisations were consulted via the World Wide Web (WWW). Keyword searching of the WWW was undertaken using the Google search engine. The submissions of evidence to NICE by sponsors were hand-searched in addition to references in retrieved papers. A list of the sources searched is provided in Appendix 3.

Keyword strategies

Sensitive keyword strategies using free text and, where available, thesaurus terms were developed to search the electronic databases. Synonyms relating to the intervention (oxaliplatin, capecitabine) were combined with synonyms relating to the condition (colon cancer). Keyword strategies for all electronic databases are provided in Appendix 3.

Search restrictions

A methodological filter aimed at restricting search results to RCTs was used in the searches of MEDLINE, EMBASE and Web of Science (WoS). The search of PUBMED was restricted to the last 180 days to capture recent and unindexed MEDLINE references. Date limits were not used on any other database. Language restrictions were not used on any database. All searches were undertaken in January 2005.

Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts. Full papers of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. The relevance of each study was assessed according to the criteria set out below. Studies that did not meet all the criteria were excluded and their bibliographic details listed with reasons for exclusion in Appendix 4. Any disagreements were resolved by discussion.

Population

Patients (either gender at any age) with Stage III (Dukes' stage C) colon cancer after complete surgical resection of the primary tumour were included.

Interventions

This review covered the effectiveness of the following two alternative chemotherapeutic agents, used within their respective licensed indications:

- oxaliplatin (Eloxatin®, Sanofi-Aventis) used in combination with 5-FU/LV
- capecitabine (Xeloda®, Roche).

Comparators

The comparator treatment included chemotherapy as adjuvant therapy with an established fluorouracil-containing regimen.

Outcomes

Data on the following outcomes were included:

- overall survival
- disease-free or relapse-free survival
- time to treatment failure
- adverse effects of treatment/toxicity
- health-related QoL.

Overall survival was defined as the interval from randomisation to death from any cause. Disease-free survival was defined as the time from trial entry or randomisation until recurrence of colorectal cancer or death from any cause. Relapse-free survival was defined in the same way as disease-free survival but excluding deaths unrelated to disease progression or treatment. Time to treatment failure was defined as the interval from randomisation to discontinuation of treatment for any reason (including treatment toxicity and death). Adverse effects of treatment, toxicities and health-related QoL were abstracted as reported, however defined.

Study design

RCTs that compared oxaliplatin in combination with 5-FU/LV or oral capecitabine with an adjuvant chemotherapy with an established fluorouracil-containing regimen were included in the assessment of clinical effectiveness.

Data abstraction strategy

Data relating to both study design and quality were extracted by one reviewer into a standardised data extraction form and independently checked for accuracy by a second. Any discrepancies were resolved by consensus. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Critical appraisal strategy

The quality of the individual studies was assessed by one reviewer and independently checked for agreement by a second. Disagreements were resolved by consensus. The quality of the clinical effectiveness studies was assessed according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination.[41] Full details of the critical appraisal strategy are reported in Appendix 5.

Methods of data synthesis

The extracted data and quality assessment variables were presented for each study, both in structured tables and as a narrative description. Where sufficient data were available, treatment effects were presented in the form of hazard ratios. Where sufficient data were available, the absolute risk reduction and number needed to treat were calculated using the method described by Altman and Andersen.[42]

In addition, results of eligible studies were statistically synthesised (meta-analysed) where (a) there was more than one trial with similar populations, interventions and outcomes and (b) there were adequate data. All analyses were by intention-to-treat (ITT). For time-to-event analyses (disease, relapse or overall survival), combined hazard ratios and 95% confidence intervals (CIs) were calculated using the Cochrane Collaboration Review Manager 4.2.3 software. This uses the log(hazard ratio) and its variance from the relevant outcome of each trial. These, in turn, were calculated using a Microsoft Excel spreadsheet authored by Matt Sydes of the Medical Research Council Clinical Trials Unit, which incorporates Parmar's methods for extracting summary statistics to perform meta-analyses of the published literature for survival end-points.[43]

The log(hazard ratio) and its variance were estimated indirectly from the hazard ratio and its 95% CIs using method three of Parmar's hierarchy of methods (depending on the availability of summary statistics). Note that the Forest plots generated by the meta-view software present hazard ratios, although they are labelled 'OR' (odds ratio).

A fixed-effects model was used for the analyses. Heterogeneity between trial results was tested where appropriate using the χ^2 test and I^2 measure. The χ^2 test measures the amount of variation in a set of trials. Small p-values suggest that there is more heterogeneity present than would be expected by chance. The χ^2 text is not a particularly sensitive test: a cut-off of $p < 0.10$ is often used to indicate significance, but lack of statistical significance does not mean there is no heterogeneity. The I^2 measure is the proportion of variation that is due to heterogeneity rather than chance. Large values of I^2 suggest heterogeneity. I^2 values of 25, 50 and 75% could be interpreted as representing low, moderate and high heterogeneity, respectively.[44]

Handling of the company submission

Company submissions were screened for data additional to that identified in published studies retrieved from the literature search.

Results: oxaliplatin

Quantity and quality of research available

Number and type of studies identified

A total of 1499 titles and abstracts were screened for inclusion in the review of clinical effectiveness. Of the titles and abstracts screened, 88 full papers were retrieved and assessed in detail. A flow chart describing the process of identifying relevant literature can be found in Appendix 6.

Number and type of studies included

Two RCTs were identified: The Multicenter International Study of Oxaliplatin/5-fluorouracil and leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial[45] and the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial.[46] Both studies included patients with Stage III (Dukes' C) colon cancer and investigated the efficacy and safety of oxaliplatin (in combination with 5-FU/LV) as an adjuvant therapy after complete resection of the primary tumour. In addition to the main publication of the MOSAIC study,[45] we identified 13 papers/abstracts reporting on (additional) aspects of the trial.[47–59] Other than the main publication of the NSABP C-07 study,[46] we identified five papers/abstracts reporting on (additional) aspects of the trial.[60–64]

Number and type of studies excluded

A total of 52 studies were excluded. The majority of the excluded articles were non-systematic reviews, commentaries and letters to the editor. A full list of the excluded studies with reasons for exclusion is presented in Appendix 4.

Ongoing studies

One ongoing, Phase III, adjuvant RCT comparing oxaliplatin (in combination with 5-FU/LV) with 5-FU/LV alone in patients with Stage III colon cancer was identified. This study provided safety data, which have been reported in the review, but no efficacy data. The COLON-OXALAD multi-centre study[65] was designed to investigate if the addition of oxaliplatin to 5-FU/LV prolonged disease-free and overall survival in very high-risk patients with Stage III (Dukes' C) colon cancer.

Assessment of effectiveness

Description of included studies (design and patient characteristics)

The MOSAIC study[45] and the NSABP C-07 study[46] were large, multi-centre, Phase III, randomised, active-controlled trials. A summary of the design and study characteristics are presented in *Table 4* and patient characteristics are presented in *Table 5*. Full data extraction tables are presented in Appendix 7.

The MOSAIC trial[45] recruited 2246 patients between October 1998 and January 2001 at 146 medical centres in 20 countries (the majority in France, the UK, Spain and Italy) and included patients aged between 18 and 75 years. The NSABP C-07 study recruited 2492 patients between February 2000 and November 2002[60] at 158 NSABP institutions[64] across the USA, Canada and Australia[61] and included patients of any age. Both studies included adult patients with confirmed Stage II and III colon cancer (see *Table 2*), who had undergone complete surgical resection of the primary tumour and were treated within 7 weeks following surgery. In the MOSAIC trial,[45] patients were randomly assigned to receive either oxaliplatin in combination with an infusional de Gramont schedule of 5-FU/LV (FOLFOX4 regimen) or infusional 5-FU/LV alone (de Gramont or LV5FU2 regimen) for 6 months (i.e. 12 cycles), whereas in the NSABP C-07 trial,[46] patients were randomly assigned to receive either oxaliplatin in combination with a bolus Roswell Park schedule of 5-FU/LV (FLOX regimen), or bolus 5-FU/LV alone (Roswell Park regimen)[62] for 24 weeks. The primary efficacy end-point of the MOSAIC trial and the NSABP C-07 study were disease-free survival. Secondary end-points included safety and overall survival. In terms of overall survival, the data in both trials were not mature at the time of analysis. Of note, trial definition of disease-free survival in the NSABP C-07 study included censoring of patients at the time of developing a second malignancy; however, this is subtly different from the definition of disease-free survival in the MOSAIC trial, in which patients were censored only at time of relapse of colorectal cancer or death.

Quality characteristics

The main publication of the MOSAIC trial, with 3 years of follow-up, was reported in a peer-reviewed journal;[45] however, updated efficacy results with a median follow-up of approximately 4 years were available only in abstract,[47] conference presentation[48] or prescribing information[57] form. The NSABP C-07 study was reported only in abstract[46] or conference presentation[60] form and provided limited information. It is unclear if the study was well designed and conducted and of good quality. The evaluation of both trials in relation to study quality is shown in *Table 6*.

Adequate methods of randomisation and allocation concealment were used in the MOSAIC trial. In this study, randomisation was performed centrally (by a computer via a central randomisation system) with stratification (minimisation method) according to centre, tumour stage (T2 or T3 versus T4 and N0, N1 or N2) and presence or absence of bowel obstruction or tumour perforation. Stratification ensured that the treatment groups were as alike as possible for strong prognostic factors. Although patients were randomised in the NSABP C-07 trial, it is not

TABLE 4 *Summary of design and study characteristics – MOSAIC trial and NSABP C-07 trial*

Study	Design	Power calculations	Numbers randomised	Interventions	Treatment duration	Duration of follow-up	Outcome measures	Funding	Comments
MOSAIC[45,47,48]	Phase 3, open-label, multi-centre RCT	Assuming 3-year disease-free survival rates of 79% in T1 and 73% in T2, with ratio of Stage II to Stage III disease of 0.4:0.6, recruitment and follow-up period of 3 years, decrease in risk of relapse after 3 years, statistical power of 90%, and an α value of 0.05 and two-sided *p* values derived with the use of the log-rank test, the authors estimated a sample size of 2200 patients	T1: 1123 T2: 1123	T1: oxaliplatin in combination with 5-FU/LV (FOLFOX4 regimen)[a] T2: 5-FU/LV alone (de Gramont regimen)[b]	6 months (12 cycles)	T1: median 37.9 months (range 27–54) T2: median 37.8 months (range 27–54)	Primary outcomes • Disease-free survival (after 3 years of follow-up) Secondary outcomes • Safety • Overall survival	Sanofi-Synthelabo	Additional analyses, not specified in the protocol, were requested by drug regulatory agencies. These ad hoc analyses were undertaken once all patients had been followed up for a minimum of 3 years, by which time the median follow-up was 48.6 months in T1 and 48.4 months in T2. Follow-up is ongoing for a minimum of 5 years for final survival analysis
NSABP C-07[60–64]	Phase 3, multi-institution RCT	Trial designed with 89% power to detect a 5.4% increase in disease-free survival (no other information provided)	T1: 1247 T2: 1245	T1: oxaliplatin in combination with bolus 5-FU/LV (FLOX regimen)[c] T2: 5-FU/LV alone (Roswell Park bolus regimen)[d]	24 weeks (8-week cycle repeated 3 times)	T1: median 34 months (range not reported) T2: median 34 months (range not reported)	Primary outcomes • Disease-free survival (after 3 years of follow-up) Secondary outcomes • Overall survival • Safety (adverse events)	National Cancer Institute, National Institutes of Health, Department of Health and Human Services, USA	Caution: study reported only in abstract form

T1, treatment 1; T2, treatment 2; 5-FU/LV, 5-fluorouracil plus leucovorin.

[a] FOLFOX4 regimen: 2-h infusion of 200 mg/m^2 intravenous LV followed by intravenous bolus 400 mg/m^2 5-FU and then a 22-h infusion of 600 mg/m^2 5-FU on 2 consecutive days plus oxaliplatin 85 mg/m^2 over 2 h on day 1 (given simultaneously with LV).

[b] De Gramont regimen: 2-h infusion of 200 mg/m^2 intravenous LV followed by intravenous bolus 400 mg/m^2 5-FU and then a 22-h infusion of 600 mg/m^2 5-FU on 2 consecutive days.

[c] FLOX regimen: 5-FU 500 mg/m^2 plus LV 500 mg/m^2 intravenous bolus weekly for 6 weeks plus oxaliplatin 85 mg/m^2 intravenous on weeks 1, 3 and 5 of each 8-week cycle in the absence of disease progression or unacceptable toxicity.

[d] Roswell Park bolus regimen: 5-FU 500 mg/m^2 plus LV 500 mg/m^2 intravenous bolus weekly for 6 weeks.

TABLE 5 *Summary of patient characteristics – MOSAIC trial and NSABP C-07 trial*

Study	Inclusion criteria	Exclusion criteria	Age (years)	Disease stage	Sex (male/female)	Performance status score	Tumour stage (T2/T3/T4/unknown)
MOSAIC[45,47,48]	Complete resection of histologically confirmed Stage II (T3 or T4, N0, M0) or Stage III (any T, N1 or N2, M0) colon cancer Treatment commencing within 7 weeks after surgery Aged between 18 and 75 years Karnofsky performance status score of at least 60 Carcinoembryonic antigen level of less than 10 ng/ml	Patients who had previously received chemotherapy, immunotherapy, or radiotherapy Inadequate blood counts, liver and kidney function (not defined)	T1: median 61 (range 19–75) T2: median 60 (range 20–75)	Stage II colon cancer: T1: 451 (40%) T2: 448 (40%) Stage III colon cancer: T1: 672 (60%) T2: 675 (60%)	T1: 630 (56%)/493 (44%) T2: 588 (52%)/535 (48%)	Karnofsky performance status score (<60/60 to 70/80 to 100) T1: 5 (<1%)/150 (13%)/968 (86%) T2: 5 (<1%)/134 (12%)/984 (88%)	T1: 51 (5%)/853 (76%)/213 (19%)/6 (<1%) T2: 54 (5%)/852 (76%)/208 (19%)/9 (<1%)
NSABP C-07[46,60,62,63]	Previously resected potentially curable Stage II (T3 or T4, N0, M0) or Stage III (any T, N1 or N2, M0) colon cancer Treatment commencing within 6 weeks after surgery Any age ECOG performance status 0 to 2 Life expectancy ≥ 10 years	Patients who had previously received chemotherapy, immunotherapy, or radiotherapy Inadequate blood counts, liver and kidney function Clinically significant cardiovascular disease Pregnant or lactating women and sexually active patients who were unwilling to use contraception	T1: not reported T2: not reported	Stage II colon cancer:[a] T1: 348 (29%) T2: 350 (29%) Stage III colon cancer:[a] T1: 852 (71%) T2: 857 (71%)	T1: not reported T2: not reported	ECOG performance status score (0/1/2) T1: not reported T2: not reported	T1: not reported T2: not reported

ECOG, Eastern Cooperative Oncology Group.
[a] Numbers and percentages based on per protocol analysis, i.e. all Stage II, $n = 698$ (29%); all Stage III, $n = 1709$ (71%).

TABLE 6 *Trial quality assessment: oxaliplatin*

	MOSAIC trial	**NSABP C-07**
Was the method used to assign participants to the treatment groups really random?	Y	?
What method of assignment was used?	Computer-generated numbers	?
Was the allocation of treatment concealed?	Y	?
What method was used to conceal treatment allocation?	Central remote randomisation	?
Was the number of participants who were randomised stated?	Y	Y
Were details of baseline comparability presented?	Y	Y
Was baseline comparability achieved?	Y	Y
Were the eligibility criteria for study entry specified?	Y	Y
Were any co-interventions identified that may influence the outcomes for each group?	?	?
Were the outcome assessors blinded to the treatment allocations?	N	?
Were the individuals who administered the intervention blinded to the treatment allocation?	N	?
Were the participants who received the intervention blinded to the treatment allocation?	N	?
Was the success of the blinding procedure assessed?	NA	?
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y	Y
Were the reasons for withdrawal stated?	Y	Y
Was an ITT analysis included?	Y	N

N, no; NA, not applicable; ?, not enough information or not clear; Y, item addressed.

clear if adequate methods of randomisation and allocation concealment were used.

The baseline demographic characteristics between treatment groups were well balanced with respect to age, sex, disease stage, Karnofsky or Eastern Cooperative Oncology Group (ECOG) performance status or tumour histology (see Appendix 7 for further information) and the eligibility criteria were clearly reported in both trials. Additional co-interventions or contaminations that may influence the outcomes in each treatment group were not reported in both trials.

In the MOSAIC study, patients, investigators and outcome assessors were all unblinded (unmasked). With many cytotoxic cancer drugs, the nature of the interventions precludes blinding (i.e. drug toxicities or manner of administration) for the practical and ethical reason that informed dose monitoring and adjustment are required. However, to overcome this partly, an independent data and safety monitoring board reviewed safety data every 6 months during the treatment period.[45] The NSABP C-07 trial did not report if patients, investigators and outcome assessors were blinded or unblinded.

At the end of the planned 3 years of follow-up in the MOSAIC trial (and *ad hoc* analysis of data at approximately 4 years), less than 20% of participants in each group were reported to have been lost to follow-up and all withdrawals were accounted for. Efficacy analysis was conducted using the ITT approach. Similarly, at the end of the planned 3 years of follow-up in the NSABP C-07 trial, less than 20% of participants in each group were reported to have been lost to follow-up and all withdrawals were accounted for. The efficacy analyses were not conducted using the ITT approach, but were based on a per-protocol analysis [i.e. randomised subjects who were non-eligible (including loss to follow-up) were excluded].

Efficacy (disease-free and overall survival)

In the MOSAIC trial, efficacy data were provided for disease-free survival and overall survival with a median follow-up of approximately 37.9 months (pre-specified in study protocol) and 48.6 months (analysis not specified in study protocol). Pre-specified subgroup analyses were also undertaken by disease stage (Stage II or III colon cancer) and other baseline prognostic factors (see Appendix 7). In the NSABP C-07 study, efficacy data were only

provided for disease-free survival with a median follow-up of 34 months (pre-specified in study protocol). The results for Stage II and III patients were not reported separately. Although the remit of this review is for Stage III patients only, the overall results for both Stage II and III patients are reported in brief.

Primary outcome analysis – disease-free survival
The results of MOSAIC trial and NSABP C-07 study are summarised in *Table* 7. Detailed results are presented in Appendix 7.

Patients with Stage II and Stage III colon cancer.
The primary outcome analyses of the MOSAIC trial and the NSABP C-07 study were focused on disease-free survival at 3 years in patients with Stage II or III colon cancer. In the MOSAIC trial, the combination of oxaliplatin with infusional 5-FU/LV (FOLFOX4 regimen) was significantly more effective than infusional 5-FU/LV alone ($p = 0.002$). Similarly, in the NSABP C-07 trial, the combination of oxaliplatin with bolus 5-FU/LV (FLOX regimen) was significantly more effective than bolus 5-FU/LV alone ($p < 0.004$). Although the populations and outcomes were similar in both trials, the interventions were different with respect to the route of administration (including dosage) of 5-FU/LV and oxaliplatin regimens. With this in mind, a *post hoc* meta-analysis was conducted by the review team (Appendix 8), which showed that the overall disease-free survival effect at approximately 3 years was significantly better for individuals treated with oxaliplatin in combination with 5-FU/LV than for those treated with 5-FU/LV alone (hazard ratio for recurrence was 0.78, 95% CI: 0.69 to 0.88; $p < 0.0001$). There was no significant heterogeneity ($\chi^2 = 0.05$, df = 1, $p = 0.83$, $I^2 = 0\%$). Updated results of the MOSAIC trial,[47,48,57] analysis not specified in the study protocol, showed that the benefit attained at 3 years was increased with longer follow-up ($p = 0.0008$).

Patients with Stage III colon cancer only. A pre-specified subgroup analysis reported by the MOSAIC authors (data not reported for the NSABP C-07 trial) showed that for patients with Stage III colon cancer the probability of remaining disease free at 3 years was 72.2% (95% CI: not reported) in the oxaliplatin plus 5-FU/LV group and 65.3% (95% CI: not reported) in the 5-FU/LV group.[45] For the ITT population, the hazard ratio for recurrence was 0.76 (95% CI: 0.62 to 0.92; p = significant), corresponding to a 24% reduction in the risk of relapse/death and an absolute disease-free survival difference of 6.9% and a number-needed-to-treat to benefit (NNTB) of 14.2 (95% CI: 8.7 to 44.2). Updated subgroup analyses (not specified in the study protocol) showed that the benefit observed at 3 years in patients with Stage III colon cancer was maintained and improved with longer follow-up. The probability of remaining disease free at 4 years was 69.7% (95% CI: 66.2 to 73.3) in the oxaliplatin plus 5-FU/LV group and 61.0% (95% CI: 57.1 to 64.8) in the 5-FU/LV group ($p = 0.002$).[47,48,57] The hazard ratio for recurrence was 0.75 (95% CI: 0.62 to 0.90) in favour of oxaliplatin plus 5-FU/LV, with an absolute disease-free survival difference of 8.7% and an NNTB of 12.5 (95% CI: 7.9 to 32.4).

Secondary outcome analysis – overall survival
The overall survival results are summarised in *Table* 7. Detailed results are presented in Appendix 7.

Patients with Stage II and Stage III colon cancer.
The secondary outcome analyses of the MOSAIC trial and the NSABP C-07 study were overall survival at 5 years for patients with Stage II and III colon cancer. Overall survival data in the MOSAIC trial (data not reported for the NSABP C-07 trial) were not mature at the time of the primary (specified) and secondary (*ad hoc*) analysis. In the ITT population of the MOSAIC trial, no statistically significant differences were observed between the two treatment groups after a median follow-up of approximately 37.9 months or after a median follow-up of approximately 48.6 months ($p = 0.236$).[45,47,48,57]

Patients with Stage III colon cancer only. Analysis by subgroup in the MOSAIC trial found that the majority of the patients who died (after a median follow-up of approximately 37.9 months) had Stage III colon cancer. In this subpopulation, no statistically significant differences in overall survival were observed between the two treatment groups [hazard ratio for death, 0.86 (95% CI: 0.66 to 1.11)]. These results were confirmed with longer follow-up [hazard ratio for death after a median follow-up 47 months, 0.86 (95% CI: 0.68 to 1.08); $p = 0.196$].[57]

Adverse events (toxicities)
The safety results of the MOSAIC trial have been comprehensively reported in a peer-reviewed publication.[45] However, the safety results from the NSABP C-07 trial are limited and have been reported only in abstract[46] or conference presentation form.[60] Although the remit of this review is for Stage III patients only, the overall results for both Stage II and III patients have been

TABLE 7 *Disease-free and overall survival for the MOSAIC[a] and NSABP C-07[b] trial*

Study/Outcome	Median follow-up (months)	Event rate		Hazard ratio[d] (95% CI)	*p*-Value
		Oxaliplatin (plus 5-FU/LV)[c]	5-FU/LV[c]		
Disease-free survival					
All patients (Stage II and III colon cancer)					
MOSAIC[45]	37.9	237/1123 (21.1%)	293/1123 (26.1%)	0.77 (0.65 to 0.91)	$p = 0.002$
NSABP C-07[60]	34.0	272/1200 (22.7%)	332/1207 (27.5%)	0.79 (0.67 to 0.93)	$p < 0.004$
MOSAIC (*ad hoc* analysis)[47,48,57]	48.6	267/1123 (23.8%)	332/1123 (29.6%)	0.76 (0.65 to 0.90)	$p = 0.0008$
Patients with Stage III colon cancer only					
MOSAIC[45]	37.9	181/672 (26.9%)	226/675 (33.5%)	0.76 (0.62 to 0.92)	Not reported
NSABP C-07[60]	34.0	Not reported	Not reported	Not reported	Not reported
MOSAIC (*ad hoc* analysis)[47,48,57]	48.6	200/672 (29.8%)	252/675 (37.3%)	0.75 (0.62 to 0.90)	$p = 0.002$
Overall survival					
All patients (Stage II and III colon cancer)					
MOSAIC[45]	37.9	133/1123 (11.8%)	146/1123 (13.0%)	0.90 (0.71 to 1.13)	Not significant
NSABP C-07[60]	34.0	Not reported	Not reported	Not reported	Not reported
MOSAIC (*ad hoc* analysis)[47,48,57]	48.6	176/1123 (15.7%)	194/1123 (17.3%)	0.89 (0.72 to 1.09)	$p = 0.236$
Patients with Stage III colon cancer only					
MOSAIC[45]	37.9	104/672 (15.5%)	119/675 (17.6%)	0.86 (0.66 to 1.11)	Not significant
NSABP C-07[60]	34.0	Not reported	Not reported	Not reported	Not reported
MOSAIC (*ad hoc* analysis)[57]	48.6	Not reported	Not reported	0.86 (0.68 to 1.08)	$p = 0.196$

[a] ITT analysis.
[b] Per protocol analysis.
[c] MOSAIC trial, infusional 5-FU/LV (de Gramont regimen); NSABP C-07 trial, bolus 5-FU/LV (Roswell Park regimen).
[d] Hazard ratio <1.0 favours oxaliplatin (plus 5-FU/LV).

summarised and reported because the safety data for Stage III patients are very limited.

In the MOSAIC trial,[45] 828 (74.7%) patients in the oxaliplatin plus 5-FU/LV group and 961 (86.5%) patients in the 5-FU/LV group received the planned 12 cycles. Dose modifications, based on worst adverse effects during the previous cycle, were required during the treatment period. Discontinuation of treatment due to adverse events occurred in 160 (14.4%) patients receiving oxaliplatin plus 5-FU/LV in comparison with 61 (5.6%) patients receiving 5-FU/LV alone (p not reported).[54] The NSABP C-07 trial did not provide any details of dose modifications or discontinuation of treatment due to adverse events; however, 876 (73%) of patients in the oxaliplatin plus 5-FU/LV group received the protocol-stipulated cumulative dose[60] (data not reported for the 5-FU/LV group). The amount of oxaliplatin planned (nine treatments) in the FLOX regimen (765 mg/m^2) of the NSABP C-07 study was approximately 25% less than the amount of oxaliplatin planned in 12 treatments of the FOLFOX4 regimen (1020 mg/m^2) of the MOSAIC trial.

Frequent adverse events and severe toxicity

Patients with Stage II and Stage III colon cancer. Gastrointestinal, haematological, neurological and other toxicities in the MOSAIC study and NSABP C-07 trial are reported in *Table 8*. Detailed results are provided in Appendix 7.

In the overall population (patients with Stage II and III colon cancer) of the MOSAIC trial,[45] increased toxicities were more pronounced with oxaliplatin (in combination with 5-FU/LV) than with 5-FU/LV alone. The main toxicities (grade 3 and 4) associated with oxaliplatin plus infusional 5-FU/LV were neutropenia and paraesthesia ($p < 0.001$ for both).[45] Other more frequent grade 3 and 4 adverse events in the oxaliplatin plus infusional 5-FU/LV group were diarrhoea, nausea and vomiting ($p < 0.001$ for all). All-grade neutropenia occurred in 78.9% of patients receiving oxaliplatin plus 5-FU/LV compared with 39.9% of patients receiving 5-FU/LV alone ($p < 0.001$), with grade 3 and 4 events reported in 41.1 and 4.7% ($p < 0.001$), respectively.[45] Only 0.7% of patients treated with oxaliplatin plus 5-FU/LV and 0.1% of patients treated with 5-FU/LV alone developed grade 3 and 4 febrile neutropenia.[48] Although the data were limited, the MOSAIC authors[54] reported that patients with Stage II colon cancer had a better adverse (toxicity) safety profile with oxaliplatin plus 5-FU/LV than in patients with Stage III colon cancer (see Appendix 7). In the NSABP C-07 study,[60] gastrointestinal toxicity was the most common dose-limiting toxicity, with a few cases of grade 3 and 4 granulocytopenia (approximately 3% in each group). The incidence of grade 3 and 4 diarrhoea in the oxaliplatin (in combination with bolus 5-FU/LV) group was approximately 40%,[60] which is much higher than the 11% rate observed in the MOSAIC trial.[45] Hospitalisation for diarrhoea or dehydration associated with bowel wall thickening in the NSABP C-07 trial occurred in 56 (4.5%) patients in the oxaliplatin plus bolus 5-FU/LV group compared with 34 (2.7%) patients in the bolus 5-FU/LV alone (p not reported).[60]

During the treatment period of the MOSAIC trial,[45] 92% (all grades) of patients treated with oxaliplatin plus infusional 5-FU/LV had peripheral neuropathy (paraesthesia). Of these 48.2% were of grade 1. Grade 3 paraesthesias were observed in 12.4% of patients exposed to oxaliplatin plus 5-FU/LV; however, with follow-up, the neurotoxic effects improved. After 1 year of follow-up, the incidence of grade 3 neuropathy remained only in 1.1% of patients and declined further to 0.5% after 18 months of follow-up. Moreover, 23.7% of patients had some form of neurological impairment even 18 months after treatment.[45] Similarly in the NSABP C-07 study,[60] all-grade neurotoxicity was observed in 85.4% of patients treated with oxaliplatin plus bolus 5-FU/LV. No data were reported for patients receiving bolus 5-FU/LV alone. Grade 3 neurotoxicity was observed in 8% of patients exposed to oxaliplatin plus 5-FU/LV compared with 1% of patients receiving 5-FU/LV. After 1 year of follow-up, grade 3 neuropathy in the oxaliplatin plus bolus 5-FU/LV group remained in only 0.5% of patients.

All-cause mortality under treatment in the MOSAIC trial[45] was the same in both groups ($n = 6$). In the oxaliplatin plus infusional 5-FU/LV group, four patients died of infection or sepsis (two with neutropenia) and two with intracranial haemorrhage. In the 5-FU/LV group, two patients died from cardiac causes, one from sepsis, one from anoxic cerebral infarction and one from Stevens–Johnson syndrome and one person committed suicide. In the NSABP C-07 study,[46,60] mortality under treatment was similar in both arms, with 15 (1.2%) patients dying in the oxaliplatin plus bolus 5-FU/LV group compared with 14 (1.1%) patients in the bolus 5-FU/LV alone group.

Although the data are based on an atypically young and fit population, the incidence of severe

TABLE 8 *Adverse events (toxicities)[a] during treatment*

	MOSAIC trial[45] (%)		NSABP C-07 trial[60] (%)	
	Oxaliplatin plus 5-FU/LV[b] (*n* = 1108)	**5-FU/LV[b] (*n* = 1111)**	**Oxaliplatin plus 5-FU/LV[c] (*n* = 1200)**	**5-FU/LV[c] (*n* = 1207)**
Gastrointestinal toxicity (grade 3 or 4)				
Nausea	5.1*	1.8	Not reported	Not reported
Diarrhoea	10.8*	6.6	40***	Not reported
Vomiting	5.8*	1.4	Not reported	Not reported
Stomatitis	2.7**	2.2	Not reported	Not reported
Granulocytopenia	Not reported	Not reported	3***	3
Haematological toxicity (grade 3 or 4)				
Neutropenia	41.1*	4.7	Not reported	Not reported
Thrombocytopenia	1.7*	0.4	Not reported	Not reported
Anaemia	0.8**	0.3	Not reported	Not reported
Neutropenia with fever or infection	1.8*	0.2	Not reported	Not reported
Neurological and other toxicity (grade 3 or 4)				
Paraesthesia (grade 3 only)	12.4*	0.2	8***	1
Skin[d]	2.0	2.4**	Not reported	Not reported
Alopecia	Not reported[e]	Not reported[e]	Not reported	Not reported
Allergic reaction	2.9*	0.2	Not reported	Not reported
Thrombosis or phlebitis	1.2	1.8**	Not reported	Not reported

[a] For the MOSAIC trial, adverse effects were graded according to the Common Toxicity Criteria of the National Cancer Institute (i.e. grade 3, severe adverse effects; grade 4, life-threatening adverse effects). For the NSABP C-07 trial, the grading system for overall toxicity was not specified; however, grade 3 paraesthesia was graded according to the National Cancer Institute–Sanofi neurosensory toxicity criteria (i.e. paraesthesia/dysaesthesia with pain or function impairment that interfered with activities of daily living).
[b] Infusional 5-FU/LV (de Gramont regimen).
[c] Bolus 5-FU/LV (Roswell Park regimen).
[d] Includes hand–foot syndrome.
[e] Incidence of grade 2 alopecia: 5.0% in each group.
* $p < 0.001$; ** $p > 0.05$; *** p not reported.

toxicities with oxaliplatin plus 5-FU/LV in the MOSAIC trial was similar in patients between 70 and 75 years of age ($n = 152$) and below 70 years of age ($n = 952$); however, some toxicities increased with age (neutropenia thrombocytopenia and anaemia).[58] Further details are provided in Appendix 7.

Patients with stage III colon cancer only.
Analysis by subgroup in the MOSAIC trial (data limited) found that serious (not defined) adverse events, [168 (25.4%) versus 102 (15.3%)] and treatment discontinuations due to toxicity [106 (16.0%) versus 35 (5.3%)] were more evident with oxaliplatin in combination with 5-FU/LV than 5-FU/LV alone, respectively; however, all-cause mortality under treatment was similar in both groups [5 (0.8%) patients in the oxaliplatin plus 5-FU/LV group versus 3 (0.5%) patients in the 5-FU/LV group].[54] These findings are similar to those for the overall MOSAIC population.[54]

Additional safety data (reported in abstract form) based on the first 81 patients from an ongoing Phase III randomised trial – the Argentinean COLON-OXALAD trial[65] – showed that in very high-risk patients with colon cancer (i.e. complete resection of proven Stage III colon cancer, with ≥4 positive nodes, or ≥1 positive node with perforated or total inclusion in the primary tumour) neutropenia [2 (5%) patients in the oxaliplatin plus bolus 5-FU/LV group versus 2 (4%) in the bolus 5-FU/LV group] and diarrhoea [4 (11%) patients in the oxaliplatin plus bolus 5-FU/LV group versus 5 (11%) in the bolus 5-FU/LV group] were similar between treatment groups with no toxic-related deaths. Although peripheral neurotoxicity data were not available for the 5-FU/LV group, 2 (5%) patients in the oxaliplatin plus bolus 5-FU/LV group had peripheral neurotoxicity.[65]

Quality of life

No data were reported on QoL in the MOSAIC trial or the NSABP C-07 study.

Discussion of results

The strength of the evidence (internal validity)

Results of many types of scientific research are presented at professional meetings and summarised in abstracts. The reliability of results presented in abstract form is questionable. Abstracts may present preliminary results of an ongoing trial and may differ from those eventually published in full.[66] In order to minimise this type of bias and to verify (and obtain unpublished) information presented in the abstract or conference presentation, authors of abstracts in the MOSAIC trial and NSABP C-07 study were contacted.

Although adequate methods of randomisation and allocation concealment were used in the MOSAIC trial, patients, investigators and outcome assessors were all unblinded (unmasked) to the assigned treatment. Blinding protects against performance bias and measurement bias[67] and its absence (i.e. double blinding) in RCTs tends to result in larger treatment effects.[68] As noted earlier in the section 'Quality characteristics' (p. 13), it is almost universally absent from oncology trials. In the NSABP C-07 trial, patients were randomly assigned to treatment or active control; however, it was not clear if adequate methods of randomisation and allocation concealment were used.

The inclusion criteria of the MOSAIC trial prescribed an upper age limit of 75 years; as a result there is uncertainty as to what extent the results of the MOSAIC trial apply to patients over 75 years of age. Although no age limit was specified in the NSABP C-07 trial, the majority of patients (>80%) were aged under 70 years of age. The median age of the oxaliplatin (in combination with 5-FU/LV) and 5-FU/LV alone group in the MOSAIC trial was 61 and 60, respectively. The MOSAIC trial and the NSABP C-07 study represent a substantially younger population of colorectal cancer patients than the NHS population in England and Wales, where the median age is over 70 years[1,2] [see the section 'Epidemiology' (p. 3)].

Disease-free survival, rather than overall survival, was the primary objective in both trials. Andre and colleagues[45] argued that disease-free survival rates after 3 years' follow-up (most relapses from colon cancer occur within the first 3 years after curative surgery)[69] accurately predict overall survival rates after 5 years and cite the results of Sargent and colleagues[70] to support their contention. On the basis of individual data from a total of almost 13,000 patients from 15 large randomised Phase III colon adjuvant clinical trials, Sargent and colleagues[70] found that there was a very high statistical correlation in outcome between 3-year disease-free survival and 5-year overall survival. Although this statistical initiative may turn out to be valid (a correlation is not enough to demonstrate the value of a surrogate end-point), the primary goal should be to obtain direct evidence about the intervention's effect on safety measures and true clinical outcomes.[71,72] In a trial of adjuvant therapy, overall survival remains as the most reliable and meaningful cancer end-point.[73]

The MOSAIC trial used an ITT approach for analysing statistical data. Analysis by ITT aims to include all participants randomised into a trial according to the assigned treatment group, regardless of the treatment they actually received, protocol deviations, compliance or adherence to treatment or loss to follow-up. ITT analyses are generally preferred as they are unbiased, and also because they address a more pragmatic and clinically relevant question.[74] A limitation of the ITT approach is that the estimate of treatment effect is generally conservative because of dilution due to non-compliance.[75] The NSABP C-07 study used a 'per protocol' approach for analysing statistical data. The main issue arising from this approach is that it might introduce bias related to excluding participants from analysis and may enhance any difference between the treatments rather than diminish it.[76]

Survival can be estimated in several ways. Median survival, although the accepted currency for survival outcomes in cancer trials, is an inadequate measure of overall survival, as it ignores the distribution of survival times. In many cases, using the median is likely to overestimate survival by picking up the maximum difference (where curves have diverged at the median event and later converge and/or cross) and may not reflect the actual survival difference between treatments. Survival curves are typically incomplete (right censored) because trials are not able to follow all patients to death. Mean survival would be more appropriate, calculated as the area under the curve (AUC).[8,77]

The applicability of the results (external validity)

The incidence of colorectal cancer rises with increasing age and peaks between 80 and 90 years of age.[78] Patients with newly diagnosed colorectal cancer have a median age of 70 years, while the median age of cohorts in clinical trials is usually

ten years less.[79] Elderly patients who enter clinical trials are a select group, with good performance status and cognition, access to transportation and limited numbers of coexisting conditions.[80] The extent to which the results of the MOSAIC trial and NSABP C-07 study provide an accurate basis for generalisation to the NHS is unclear. There is concern that elderly people with colorectal cancer are excluded and under-represented in clinical trials,[78] the evidence base is limited for adjuvant colorectal cancer therapy in very elderly patients (more than 80 years of age),[81] elderly patients with Stage III colon cancer are both offered and receive adjuvant chemotherapy less frequently than younger patients,[82] there are inequalities in the delivery of adjuvant chemotherapy in ethnic minority and lower socioeconomic groups[83,84] and although adjuvant chemotherapy is extensively used for Stage III colon cancer, trial results may not reflect outcomes in everyday practice where treatment rates decline dramatically with chronological age.[83,85] In the UK, people aged over 75 years are not routinely considered for adjuvant chemotherapy because of its potential toxicity, although there is no evidence to support or refute this policy.[86] NICE guidance for the appropriate selection of patients for adjuvant therapy is based on physiological age (including performance status and co-morbidities) rather than biological age.[10]

In the adjuvant setting, 6 months of 5-FU in combination with LV has become the standard chemotherapy for patients with resected Stage III colon cancer.[87,88] The current options for the delivery of adjuvant 5-FU monotherapy are as a bolus, as a protracted infusion (or combination of bolus and protracted infusion, the de Gramont regimen) or oral administration [further details on the relative clinical effectiveness of bolus and infusional 5-FU in the adjuvant setting are provided in the section 'Bolus or infusional 5-FU for the adjuvant treatment of colon cancer?' (p. 34)]. In the control group of the MOSAIC trial,[45] patients were treated with a bimonthly, combined bolus and infusional 5-FU/LV de Gramont regimen. This has been shown to have similar efficacy (not equivalence) and less toxicity than the monthly bolus modified Mayo Clinic 5-FU/LV regimen.[88] However, there are concerns about catheter-associated complications, patient inconvenience and expense of infusional treatment.[27,89–91] In the control group of the NSABP C-07 trial, 5-FU/LV was given on the weekly bolus Roswell Park schedule. As the semi-monthly infused 5-FU/LV de Gramont regimen and the weekly bolus 5-FU/LV Roswell Park regimen are not widely used in the UK,[92] it is unclear how transferable these data would be to the NHS.

The FOLFOX4 regimen (oxaliplatin in combination with an infusional schedule of 5-FU/LV), as used in the MOSAIC trial,[45] was designed in 1995[93] and has been shown to be effective for metastatic and adjuvant colorectal cancer.[45] However, limiting toxicities are neutropenia, mainly due to 5-FU bolus, and cumulative sensory neurotoxicity, which is dose limiting for oxaliplatin.[94] In addition, the infusional schedule used in FOLFOX4 is cumbersome and requires frequent hospital or clinic visits.[95] Simplified infusion schedules of FU/LV have been developed with similar efficacy (FOLFOX6[96] and FOLFOX7),[94,97,98] but have only been evaluated in the metastatic setting. In the absence of supportive data for simplified infusion schedules in the adjuvant setting, it is unclear how transferable these data would be to the NHS.

In the MOSAIC trial,[45] the rate of death was similarly low during treatment between both groups and, at 0.5%, is among the lowest figures reported in trials of adjuvant therapy.[45] Although the rate of death in the NSABP C-07 trial[60] was similar between both treatment groups (approximately 1%), it was slightly higher than in the MOSAIC trial. In general, gastrointestinal, haematological and neurological toxicities (and also discontinuation of treatment due to adverse events) were significantly more pronounced with oxaliplatin-based regimens than with 5-FU/LV-alone schedules. The FLOX regimen (oxaliplatin plus Roswell Park 5-FU/LV weekly bolus schedule) was associated with high rates of grade 3 and 4 diarrhoea,[60] whereas the FOLFOX4 regimen (oxaliplatin in combination with an infusional schedule of 5-FU/LV) was associated with high rates of grade 3 and 4 neutropenia.[45] The main safety concern regarding the use of oxaliplatin is neurotoxicity (irrespective of regimen), which, although significant and frequent, does appear to improve within 1 year for the majority of patients. However, approximately 25% of patients in the MOSAIC trial had some form of neurological impairment even 18 months after treatment[45] (data not reported for the NSABP C-07 trial), suggesting that oxaliplatin-based therapy may not be suitable for all patients, that is, people with neuropathy. These data are broadly similar to those reported in reviews of oxaliplatin-related adverse effects.[99–101] Cassidy and Misset[100] state that oxaliplatin-induced neurotoxicity consists of a rapid-onset acute sensory neuropathy and late-

onset cumulative sensory neuropathy that occurs after several cycles of therapy. The condition is reported to be reversible in about 75% of patients, with a median time to recovery of 13 weeks after treatment discontinuation. Cassidy and Misset[100] and Grothey[101] conclude that oxaliplatin-related adverse events are predictable and easily managed (active management) with appropriate awareness from patients and care providers.

The role of adjuvant chemotherapy in patients with Stage III colon cancer was the focus of this review. Meaningful information from subgroup analyses within a randomised trial is restricted by multiplicity of testing and low statistical power. In general, subgroup analyses should be pre-defined on the basis of known biological mechanisms, patient prognosis or in response to findings in previous studies.[102,103] The MOSAIC study was adequately powered to demonstrate improved survival outcomes in patients with Stage II (40% of total population) or Stage III (60% of total population) colon cancer. However, the study was not powered to detect a therapeutic effect by subgroup. Nevertheless, subgroup analyses were pre-specified by stage (Stage II versus Stage III) of disease (an important prognostic indicator of survival in early colon cancer) and were presented separately. The NSABP C-07 trial was also adequately powered to demonstrate improved survival outcomes in patients with Stage II (approximately 30% of total population) or Stage III (approximately 70% of total population) colon cancer; however, the data were not presented by disease stage. The applicability of the results from the NSABP C-07 trial to patients with Stage III colon cancer only is unclear.

A detailed discussion on the value of adjuvant chemotherapy for Stage II colon cancer is not the remit of this review. However, the appropriateness of adjuvant therapy in patients with Stage II colon cancer remains controversial.[87,104–106] Recently, the American Society of Clinical Oncology published guidelines on adjuvant chemotherapy for colon cancer to facilitate decision making in clinical practice.[23] These guidelines, based on a systematic review and meta-analysis by Figueredo *et al.*,[107] were against the routine use of adjuvant chemotherapy for medically fit patients with Stage II colon cancer (absolute improvement in 5-year survival less than 5%). However, high-risk Stage II patients were considered an appropriate group for adjuvant therapy, if well informed (i.e. discussion with the patients about the nature of evidence supporting the treatment, anticipated morbidity of treatment, presence of high-risk prognostic features on individual prognosis and patient preferences).[23] In their recently published manual on improving outcomes for colorectal cancer, NICE concluded that the place of adjuvant chemotherapy in the treatment of patients with Dukes' stage B (Stage II) cancer must be a matter for discussion between patients and their oncologists.[10] It is noteworthy that the impact of newer combinations such as those studied in the MOSAIC trial[45] (the NSABP C-07 study did not present data by disease stage) were not considered in either of the above guidelines. Although the MOSAIC trial was not powered to detect a difference in disease-free survival between oxaliplatin (in combination with 5-FU/LV) and 5-FU/LV alone in various subgroups, the data do not support a statistically significant disease-free survival advantage for Stage II patients; however, in patients with high-risk Stage II colon cancer the difference in disease-free survival, in favour of oxaliplatin (in combination with 5-FU/LV), was more promising with an absolute difference greater than 5% (not significant).

Summary of effectiveness data for oxaliplatin

The evidence to support the addition of oxaliplatin to adjuvant treatment is at present limited to two large trials – the MOSAIC trial and NSABP C-07 study. The MOSAIC trial, a large (n = 2246), international, multi-centre, Phase III, randomised, open-label, active-controlled trial, compared the efficacy and safety of oxaliplatin in combination with an infusional de Gramont schedule of 5-FU/LV (FOLFOX4 regimen) or infusional 5-FU/LV alone (de Gramont or LV5FU2 regimen) for 6 months in patients with Stage II or III colon cancer. The primary trial end-point was disease-free survival. Secondary trial end-points included toxicity and overall survival. The NSABP C-07 study, a large (n = 2492), international, multi-institution, Phase III, randomised, active-controlled trial, compared the efficacy and safety of oxaliplatin in combination with a bolus Roswell Park schedule of 5-FU/LV (FLOX regimen) or bolus 5-FU/LV alone (Roswell Park regimen) for 24 weeks in patients with Stage II or III colon cancer. The primary and secondary trial end-points were similar to those in the MOSAIC trial.

Primary outcome – disease-free survival

Oxaliplatin in combination with 5-FU/LV was more effective than 5-FU/LV alone [irrespective of the route of administration (including dosage) of 5-FU/LV and oxaliplatin regimens] in the adjuvant treatment of patients who had undergone complete surgical resection for Stage II and III colon cancer.

- At 3 years (pre-specified analysis), the combination of oxaliplatin with infusional de Gramont 5-FU/LV (FOLFOX4 regimen) was significantly more effective than infusional de Gramont 5-FU/LV alone (hazard ratio using ITT analysis, 0.77; 95% CI: 0.65 to 0.91; $p = 0.002$). Similarly, in the NSABP C-07 trial, the combination of oxaliplatin with bolus Roswell Park 5-FU/LV (FLOX regimen) was significantly more effective than bolus Roswell Park 5-FU/LV alone (hazard ratio using per protocol analysis, 0.79; 95% CI: 0.67 to 0.93; $p < 0.004$).
- Updated *ad hoc* results of the MOSAIC trial, with a median follow-up of approximately 48.6 months (with a minimum follow-up of 3 years for all patients) confirm the earlier results and demonstrate that oxaliplatin (in combination with 5-FU/LV) is more effective than 5-FU/LV alone (hazard ratio of 0.76; 95% CI: 0.65 to 0.90; $p = 0.0008$).
- Subgroup analyses by disease stage in the MOSAIC trial (data not reported for the NSABP C-07 trial) showed that in patients with Stage III (any T, N1 or N2, M0) colon cancer the probability of remaining disease free at 3 years was 72.2 and 65.3% for oxaliplatin (in combination with 5-FU/LV) and 5-FU/LV alone, respectively. For the ITT population, the hazard ratio for recurrence was 0.76 (95% CI: 0.62 to 0.92), corresponding to a 24% reduction in the risk of relapse or death and an absolute disease-free survival difference of 6.9% and an NNTB of 14.2 (95% CI: 8.7 to 44.2).
- Updated subgroup analyses (*ad hoc*) showed that the benefit observed at 3 years in patients with Stage III colon cancer was maintained and improved with longer follow-up. The probability of disease-free survival at 4 years was 69.7 and 61.0% for oxaliplatin (in combination with 5-FU/LV) and 5-FU/LV alone, respectively. The hazard ratio for recurrence for the ITT population was 0.75 (95% CI: 0.62 to 0.90; $p = 0.002$) with an absolute disease-free survival difference of 8.7% and an NNTB of 12.5 (95% CI: 7.9 to 32.4).

Secondary outcomes – overall survival

Overall survival data in the MOSAIC trial (data not reported for the NSABP C-07 trial) were not mature at the time of analysis.

- In the ITT population (patients with Stage II and III colon cancer) of the MOSAIC trial, no statistically significant differences were observed between the two treatment groups after a median follow-up of approximately 37.9 months or after a median follow-up of approximately 48.6 months ($p = 0.236$).
- Analysis by subgroup in the MOSAIC trial found that the majority of the patients who died (after a median follow-up of approximately 37.9 months) had Stage III colon cancer. In this subpopulation, no statistically significant differences in overall survival were observed between the two treatment groups [hazard ratio for death, 0.86 (95% CI: 0.66 to 1.11)]. These results were confirmed with longer follow-up [hazard ratio for death after a median follow-up 47 months, 0.86 (95% CI: 0.68 to 1.08); $p = 0.196$)].

Quality of life

No data were reported on QoL in the MOSAIC trial or the NSABP C-07 study.

Adverse events (toxicities)

Although the data were limited for patients with Stage III colon cancer only, the overall results of the MOSAIC trial (patients with Stage II and III colon cancer) showed that the frequencies of severe (grade 3 or 4) paraesthesia, neutropenia, diarrhoea, nausea, vomiting and thrombocytopenia were significantly ($p < 0.001$) more pronounced with oxaliplatin plus infusional 5-FU/LV than with infusional 5-FU/LV alone. Similarly, in the NSABP C-07 study, diarrhoea and paraesthesia were more common with oxaliplatin plus bolus 5-FU/LV than with bolus 5-FU/LV alone (p-values not reported). The main safety concern regarding the use of oxaliplatin is neurotoxicity (irrespective of regimen), which, although significant and frequent (all-grade neurotoxicity, >85%; grade 3 neurotoxicity, >8%), does appear to improve within 1 year's time for the majority of patients with Stage II or III colon cancer (grade 3 neurotoxicity, <1.1%). However, approximately 25% of patients in the MOSAIC trial had some form of neurological impairment even 18 months after treatment.

Results: capecitabine

Quantity and quality of research available

Number and type of studies identified

A total of 1499 titles and abstracts were screened for inclusion in the review of clinical effectiveness. Of the titles and abstracts screened, 88 full papers were retrieved and assessed in detail. A flow chart describing the process of identifying relevant literature can be found in Appendix 6.

Number and type of studies included

One RCT was identified which investigated the efficacy and safety of treatment with capecitabine in the postoperative adjuvant setting, in patients with Stage III (Dukes' C) colon cancer. In addition to the main publication of the trial,[108] we identified 15 papers/abstracts reporting on (additional) aspects of the Xeloda – Adjuvant Chemotherapy Trial (X-ACT).[34,109–122]

Number and type of studies excluded

A total of 52 studies were excluded. The majority of the excluded articles were non-systematic reviews, commentaries and letters to the editor. A full list of the excluded studies with reasons for exclusion is presented in Appendix 4.

Assessment of effectiveness

Description of included studies (design and patient characteristics)

The X-ACT study[108] was a large, international, multi-centre, phase III, randomised, open-label, active-controlled trial. A summary of the design and study characteristics are presented in *Table 9* and patient characteristics are presented in *Table 10*. Full data extraction tables are presented in Appendix 7.

The X-ACT study[108] recruited 1987 patients between November 1998 and November 2001 at 164 centres (clinics) in 25 countries. The trial included adult patients aged between 18 and 75 years (although some ≥ 75 years of age were given waivers to participate in the study) with histologically confirmed Stage III (Dukes' C) colon cancer that had been surgically resected leaving no macroscopic or microscopic evidence of residual disease and were treated within 8 weeks following surgery.[34] Patients with evidence of metastatic disease, including tumour cells in ascites at study entry, were ineligible, as were patients who had received cytotoxic chemotherapy or organ allografts.[108] Patients were randomly assigned to receive either oral capecitabine or bolus 5-FU/LV alone (Mayo Clinic regimen) for a total of 24 weeks. The X-ACT study was designed to demonstrate that capecitabine was at least equivalent to 5-FU/LV in achieving the primary efficacy end-point of disease-free survival when administered as adjuvant treatment following surgery for Stage III (Dukes' C) colon cancer. Secondary end-points included relapse-free survival, overall survival, safety (including treatment toxicity), pharmaeconomics and QoL.[34,108,109] In terms of overall survival, the data were not mature at the time of analysis.

Quality characteristics

The main publication of the X-ACT study, with approximately 4 years of median follow-up, was reported in a peer-reviewed journal.[108] Planned safety analysis (conducted 19 months after the enrolment of the last patient) was also reported in a peer-reviewed journal.[109] Although updated efficacy results at a median follow-up of 4.3 years were reported in abstract form,[122] the latest efficacy results, with a median follow-up of 4.4 years, were reported in the Roche company submission to NICE.[20] The evaluation of the trial in relation to study quality is shown in *Table 11*.

Adequate methods of randomisation and allocation concealment were used in the X-ACT study. Randomisation schedules (stratified by centre with a block size of four) within the trial were produced by computer-generated random numbers and allocation concealment using scratch-off labels. The baseline demographic characteristics between treatment groups were well balanced with respect to median age, ECOG performance status score, sex, nodal status, tumour differentiation and preoperative carcinoembryonic antigen (CEA) values (see Appendix 7 for further information) and the eligibility criteria were clearly reported. Additional co-interventions or contaminations that may influence the outcomes in each treatment group were not reported.

Patients, investigators and outcome assessors were all unblinded (unmasked). Blinding would be virtually impossible when comparing an oral drug with a bolus 5-FU/LV regimen, as the mode of delivery is different for the two treatments. In addition, for practical and ethical reasons informed dose monitoring and adjustment are required with many cytotoxic cancer drugs.

During the follow-up period (and reanalysis of data at a median follow-up of 4.4 years), more than 20% of participants in each group were reported to have been lost to follow-up (ranging from 20 to 27%); however, it was similar for the two groups and all withdrawals were accounted for. Efficacy analysis was conducted using the ITT approach.

Efficacy (disease-free, relapse-free and overall survival)

In the X-ACT study, efficacy data were provided for disease-free, relapse-free and overall survival with a median follow-up of approximately 3.8 years (pre-specified in study protocol) and 4.4 years (analysis not specified in study protocol).

TABLE 9 *Summary of design and study characteristics – X-ACT study*

Study	Design	Power calculations	Numbers randomised	Interventions	Treatment duration	Duration of follow-up	Outcome measures	Funding	Comments
X-ACT[20,34,108,109]	Phase 3, open-label, multi-centre RCT	Study powered to establish at least equivalence (80% power) of capecitabine to bolus 5-FU/LV if upper limit of the 95% CI for the hazard ratio was below 1.25 (or 1.20) with a Type I error of 2.5%. The statistical assumptions for a sample size of 1956 patients were based on a 3-year disease-free survival rate of 70%, including exclusion of approximately 15% of patients from the per protocol population	T1: 1004 T2: 983	T1: capecitabine (oral)[a] T2: 5-FU/LV alone (Mayo Clinic bolus regimen)[b]	24 weeks (8 cycles in T1 and 6 cycles in T2)	T1: median 3.8 years (range not reported) T2: median 3.8 years (range not reported)	Primary outcomes • Equivalence in disease-free survival Secondary outcomes • Relapse-free survival • Overall survival • Safety • QoL • Pharmaeconomics	Hoffmann-La Roche	Additional analyses, not specified in the protocol, were requested by the US Food and Drug Administration. These *ad hoc* analyses were undertaken once all patients had been followed up for a minimum of 3 years, by which time the median follow-up was 4.4 years in T1 and T2 Main analysis for disease-free survival driven by the number of events and performed after 632 events had occurred in the per protocol population. If equivalence analyses proved to be positive, tests for superiority were conducted

[a] Oral capecitabine: 1250 mg/m^2 taken twice daily on days 1–14 every 21 days.
[b] Mayo Clinic bolus regimen: LV 20 mg/m^2 intravenous by rapid infusion followed immediately by 5-FU 425 mg/m^2 intravenous bolus on days 1–5 every 28 days.

TABLE 10 *Summary of patient characteristics – X-ACT study*

Study	Inclusion criteria	Exclusion criteria		Age (years)	Disease stage status score	Sex (male/female) (T1-2/T3/T4)	Performance	Tumour stage
X-ACT[20,34,108,109]	Complete resection of histologically confirmed stage III colon cancer Treatment commencing within 8 weeks after surgery Aged between 18 and 75 years (although some ≥ 75 years were given waivers to participate in study) ECOG performance status 0 or 1 Life expectancy ≥ 5 years	Metastatic disease Prior cytotoxic chemotherapy or organ allografts Clinically significant cardiac disease Sever renal impairment Central nervous system disorders Pregnant or lactating women and sexually active patients who were unwilling to use contraception	T1: median 62 (range 25–80) T2: median 63 (range 22–82)	All Stage III (Dukes' C) colon cancer		T1: 542 (54%)/462 (46%) T2: 532 (54%)/451 (46%)	ECOG performance status score (0/1) T1: 853 (85%)/151 (15%) T2: 836 (85%)/147 (15%)	T1: 100 (10%)/763 (76%)/141 (14%) T2: 98 (10%)/747 (76%)/138 (14%)

TABLE 11 *Trial quality assessment: capecitabine*

	X-ACT study
Was the method used to assign participants to the treatment groups really random?	Y
What method of assignment was used?	Stratified block randomisation
Was the allocation of treatment concealed?	Y
What method was used to conceal treatment allocation?	Treatment allocation codes (scratch-off labels)
Was the number of participants who were randomised stated?	Y
Were details of baseline comparability presented?	Y
Was baseline comparability achieved?	Y
Were the eligibility criteria for study entry specified?	Y
Were any co-interventions identified that may influence the outcomes for each group?	?
Were the outcome assessors blinded to the treatment allocations?	N
Were the individuals who administered the intervention blinded to the treatment allocation?	N
Were the participants who received the intervention blinded to the treatment allocation?	N
Was the success of the blinding procedure assessed?	NA
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	N
Were the reasons for withdrawal stated?	Y
Was an ITT analysis included?	Y

N, no; NA, not applicable; ?, not enough information or not clear; Y, item addressed.

Pre-specified subgroup analyses for disease-free survival were also undertaken according to baseline prognostic factors (see Appendix 7).

Primary outcome analysis – disease-free survival
The results of the X-ACT study are summarised in *Table 12*. Detailed results are presented in Appendix 7. After a median follow-up of 3.8 years, 656 (65%) patients in the capecitabine group did not have an event (relapse or new occurrence of colon cancer or death due to any cause), compared with 603 (61%) in the 5-FU/LV group, corresponding to a 13% reduction in the risk of relapse or death (hazard ratio of 0.87; 95% CI: 0.75 to 1.00) with an absolute disease-free survival difference of 3.6%. Capecitabine was shown to be at least equivalent to 5-FU/LV, in that the primary end-point was met [upper limit of the 95% CI of the hazard ratio (1.0) was significantly ($p < 0.001$) below both predefined margins of 1.25 and 1.20 for at least equivalence]. A pre-specified superiority analysis showed that capecitabine was not statistically superior to 5-FU/LV ($p = 0.05$). The difference between the 3-year rates of disease-free survival (a pre-specified end-point) in the capecitabine group (64.2%) and in the 5-FU/LV group (60.6%) was not significant ($p = 0.12$).[108] Updated analyses,[20] not specified in the study protocol, showed that with longer follow-up (4.4 years with minimum follow-up of 3 years for all patients) capecitabine therapy remained at least as effective as 5-FU/LV (hazard ratio of 0.87; 95% CI: 0.76 to 1.00; $p = 0.055$ for superiority).

Secondary outcome analyses – relapse-free and overall survival
The results of X-ACT study are summarised in *Table 12*. Detailed results are presented in Appendix 7.

Relapse-free survival. Capecitabine therapy significantly improved relapse-free survival in comparison with 5-FU/LV ($p = 0.04$ for superiority). The hazard ratio for recurrence was 0.86 (95% CI: 0.74 to 0.99), corresponding to a 14% reduction in the risk of relapse or death, with an absolute relapse-free survival difference of 3.6% and an NNTB of 23.3 (95% CI: 12.2 to 336.0). The 3-year rates of relapse-free survival (not a pre-specified end-point) were 65.5% in the capecitabine group and 61.9% in the 5-FU/LV group ($p = 0.12$).[108] Secondary *ad hoc* analyses[20] showed that after a median follow-up of 4.4 years, 654 (65%) patients in the capecitabine group did not have an event (relapse or new occurrence of colon cancer or death unrelated to disease progression or treatment) compared with 602 (61%) patients in the 5-FU/LV group,

TABLE 12 *Disease-free, relapse-free and overall survival for the X-ACT study (ITT analysis)*

Study/outcome	Median follow-up (years)	Event rate		Hazard ratio[a] (95% CI)	*p*-Value for	
		Capecitabine	5-FU/LV (Mayo Clinic bolus regimen)		Equivalence	Superiority
Disease-free survival						
Patients with Stage III colon cancer only						
X-ACT[108]	3.8	348/1004 (35%)	380/983 (39%)	0.87 (0.75 to 1.00)[b]	$p < 0.001$[e]	$p = 0.05$
X-ACT (*ad hoc* analysis)[20]	4.4	372/1004 (37%)	404/983 (41%)	0.87 (0.76 to 1.00)	Not reported	$p = 0.055$
Relapse-free survival						
Patients with Stage III colon cancer only						
X-ACT[108]	3.8	327/1004 (33%)	362/983 (37%)	0.86 (0.74 to 0.99)[c]	Not reported	$p = 0.04$
X-ACT (*ad hoc* analysis)[20]	4.4	350/1004 (35%)	381/983 (39%)	0.87 (0.75 to 1.00)	Not reported	$p = 0.057$
Overall survival						
Patients with Stage III colon cancer only						
X-ACT[108]	3.8	200/1004 (20%)	227/983 (23%)	0.84 (0.69 to 1.01)[d]	$p < 0.001$[f]	$p = 0.07$
X-ACT (*ad hoc* analysis)[20]	4.4	241/1004 (24%)	265/983 (27%)	0.88 (0.74 to 1.05)	Not reported	$p = 0.169$

[a] Hazard ratio < 1.0 favours capecitabine.
[b] Per protocol analysis: hazard ratio, 0.89 (95% CI: 0.76 to 1.04; $p = 0.157$ for superiority).
[c] Per protocol analysis: hazard ratio, 0.87 (95% CI: 0.74 to 1.02; $p = 0.078$ for superiority).
[d] Per protocol analysis: hazard ratio, 0.90 (95% CI: 0.73 to 1.10; $p = 0.298$ for superiority).
[e] The upper limit of the hazard ratio was compared with the non-inferiority margin of 1.20, as specified in the study protocol.
[f] The upper limit of the hazard ratio was compared with the non-inferiority margin of 1.25, as specified in the study protocol.

corresponding to a 13% non-significant reduction in the risk of relapse or death (hazard ratio of 0.87; 95% CI: 0.75 to 1.00; $p = 0.057$ for superiority).

Overall survival. Overall survival data were not mature at the time of the primary (specified) and secondary (*ad hoc*) analysis. In the ITT population, no statistically significant differences were observed in overall survival between the two groups ($p = 0.07$ for superiority); however, 804 (80%) patients in the capecitabine group were alive at 3.8 years (median-follow-up) in comparison with 756 (77%) in the 5-FU/LV group.[108] Secondary *ad hoc* analyses[20] showed that after a median follow-up of 4.4 years (with minimum follow-up of 3 years for all patients), 763 (76%) patients in the capecitabine group were alive in comparison with 718 (73%) patients in the 5-FU/LV group, corresponding to a 12% reduction in the risk of death (hazard ratio of 0.88; 95% CI: 0.74 to 1.05). Although an improved trend in overall survival was observed with capecitabine, no statistically significant differences were observed between the two groups ($p = 0.169$ for superiority).

Adverse events (toxicities)

In the X-ACT study, premature withdrawal due to adverse events was infrequent in both groups and occurred in 119 (12%) patients receiving capecitabine and in 78 (8%) patients receiving 5-FU/LV. In total, 833 (84%) patients receiving capecitabine completed all eight cycles of treatment (24 weeks) whereas 862 (89%) patients receiving 5-FU/LV completed all six cycles (24 weeks).[109]

As a result of toxicity, both groups required adjustments (for delay, dose reduction or interruption of treatment) in the dose of the study drug (capecitabine 57% versus bolus 5-FU/LV 52%) as well as dose reductions (capecitabine 42% versus bolus 5-FU/LV 44%). More interruptions (15 versus 5%) and delays (46 versus 29%) were required with capecitabine. However, most patients in the capecitabine group completed at least four of the eight chemotherapy cycles without a reduction in the dose of the medication (76 versus 68% in the 5-FU/LV group after three of the six chemotherapy cycles).[108] Adverse events most commonly leading to dose modifications (including treatment interruption and dose reduction) were hand–foot syndrome (31%) and diarrhoea (15%) in the capecitabine group and stomatitis (23%) and diarrhoea (19%) in the 5-FU/LV group. The median time to the first dose reduction was longer for patients receiving capecitabine (78 days) than 5-FU/LV (41 days). Second-level dose reductions (to less than 60% of the capecitabine starting dose and less than 75% of the 5-FU/LV starting dose) were less frequent (13 versus 26%) and later (median 113 versus 57 days) in the capecitabine group.[109]

Frequent adverse events and severe toxicity

Gastrointestinal, haematological, neurological and other toxicities in the X-ACT study are reported in *Table 13*. Detailed results, including early severe toxicities, laboratory abnormalities and impact of age, are provided in Appendix 7.

In the X-ACT study,[108] severe (grade 3 or 4) stomatitis (2 versus 14%; $p < 0.001$) and alopecia (0 versus <1%; $p < 0.02$) were significantly less common in capecitabine-treated patients than in those receiving 5-FU/LV, respectively. The incidence of grade 3 hand–foot syndrome was, however, significantly ($p < 0.001$) higher with capecitabine (17%) than 5-FU/LV (<1%). The overall incidence of hand–foot syndrome (grade 1 to 3) was also significantly higher in the capecitabine group versus the 5-FU/LV group (60 versus 9%; $p < 0.001$). The incidence of neutropenia as a grade 3 or 4 laboratory abnormality was significantly lower in the capecitabine group than in the 5-FU/LV group ($p < 0.001$). All-grade neutropenia (32 versus 63%; $p < 0.001$)[108] and neutropenia, as a clinical adverse event requiring medical intervention, were significantly less common in patients treated with capecitabine (2 versus 8%; $p < 0.001$).[109] A higher proportion of patients receiving capecitabine experienced hyperbilirubinaemia as a grade 3 or 4 laboratory abnormality compared with 5-FU/LV ($p < 0.001$).[108,109] Similarly, with the exception of hand–foot syndrome, the grade 3 or 4 adverse event profile in patients over 65 years[109] and in the elderly over 70 years of age[114] appeared to be better in capecitabine-treated patients than 5-FU/LV recipients (data based on an atypically young and fit population). In addition, capecitabine demonstrated a similar favourable safety profile in patients <65 ($n = 596$) or ≥65 years of age ($n = 397$); however, some toxicities increased with age (hand–foot syndrome, diarrhoea, stomatitis and neutropenia).[109] Further details are provided in Appendix 7.

All-cause mortality under treatment was similar in both groups, with three deaths occurring in the capecitabine group (one patient each died due to multi-organ failure, septic shock and pneumonia) and four deaths occurring in the 5-FU/LV group (one patient each died due to severe diarrhoea and vomiting, respiratory arrest, gastrointestinal haemorrhage and bronchopneumonia).[109]

TABLE 13 *Most common treatment-related adverse events[a] in the X-ACT study[108]*

	Capecitabine (%) (n = 995)	5-FU/LV[b] (%) (n = 974)	p-Value
Gastrointestinal toxicity (grade 3 or 4)[c]			
Diarrhoea	11	13	Not significant
Nausea or vomiting	3	3	Not significant
Stomatitis	2	14	$p < 0.001$
Haematological toxicity (grade 3 or 4)[c]			
Neutropenia[d]	2	26	$p < 0.001$
Neurological and other toxicity (grade 3 or 4)[c]			
Hand–foot syndrome[e]	17	<1	$p < 0.001$
Fatigue or asthenia	1	2	Not significant
Abdominal pain	2	1	Not significant
Alopecia	0	<1	$p < 0.02$
Lethargy	<1	<1	Not significant
Anorexia	<1	<1	Not significant
Hyperbilirubinaemia[d]	20	6	$p < 0.001$

[a] Data are an update of Scheithauer and colleagues, 2003.[109]
[b] Mayo Clinic bolus regimen.
[c] Graded according to National Cancer Institute of Canada common toxicity criteria, 1991.[109]
[d] Diagnosis based on laboratory values.
[e] Grade 3 only (defined as severe discomfort, unable to work or perform activities of daily living).[123]

Quality of life

QoL was assessed in the X-ACT study as a secondary outcome measure at baseline and before the start of treatment cycles, namely weeks 7, 16 and 25 in the capecitabine group and weeks 9, 17 and 25 in 5-FU/LV group. QoL parameters were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) with global health status being the primary parameter for the QoL evaluation. In both treatment groups, scores for global health status were constant over time (from baseline to 25 weeks of trial treatment) and there were no major (statistically significant) differences between the two groups[34,108] (no statistical data reported).

Discussion of results

The strength of the evidence (internal validity)

Some of the issues (blinding in oncology trials, disease-free survival as the primary end-point, median survival as a survival outcome and publication and related biases) which are relevant in assessing the internal validity of the X-ACT study have been discussed in detail in the section 'Discussion of results' (p. 21).

Although adequate methods of randomisation and allocation concealment were used in the X-ACT study, patients, investigators and outcome assessors were all unblinded (unmasked) to the assigned treatment. Blinding would be virtually impossible when comparing an oral drug with a bolus 5-FU/LV regimen, as the mode of delivery is different for the two treatments.

At baseline, approximately 9% of patients in both groups had abnormal carcinoembryonic antigens, suggesting that patients may not have been completely resected. However, the study groups were comparable at baseline, so the likelihood of confounding bias is low. In addition, the median age of the capecitabine group and 5-FU/LV group was 62 and 63 years, respectively. The X-ACT study represents a substantially younger population of colorectal cancer patients than the NHS population in England and Wales, where the median age is over 70 years.[1,2]

In the X-ACT study, more than 20% of participants in each group were reported to have been lost to follow-up (ranging from 20 to 27%). The greater the number of subjects who are lost, the more the trial may be subject to bias because patients who are lost often have different prognoses from those who are retained. Patients may discontinue their participation in studies because they are not prepared to accept the treatment, they recover, they move address or they have died.[124] In the X-ACT study, attrition bias should be low as the loss to follow-up was similar for the two treatment groups, all patients were accounted for and an ITT analysis was performed.

Estimating the sample size is important in the design of clinical trials. The minimum information needed to calculate sample size includes the power, the level of significance, the underlying event rate in the population under investigation and the size of the treatment effect sought. The calculated sample size should then be adjusted for other factors such as expected compliance rates and unequal allocation ratio.[125] The X-ACT study was adequately powered (80% power) to show equivalence in the primary end-point (disease-free survival), with the main analysis driven by the number of events (i.e. 632 events). The likelihood that the results were due to chance is low.

The applicability of the results (external validity)

The main issues (median age, elderly versus younger patients, bolus 5-FU/LV) governing the external validity of the X-ACT study has been discussed in detail in the section 'Discussion of results' (p. 21). Briefly, in England and Wales, patients with newly diagnosed colorectal cancer have a median age over 70 years,[1,2] whereas the median age of cohorts in clinical trials is usually 10 years less.[79,109] The extent to which the results of the X-ACT study provide an accurate basis for generalisation to the UK NHS is unclear. The monthly 5-day bolus Mayo Clinic 5-FU/LV regimen given for 6 months, as used in the control group of the X-ACT study, is often used as a reference treatment in Phase III trials;[27,88] however, it is not frequently used in the UK [see the sections 'Management of disease and national guidelines' (p. 6) and 'Discussion of results' (p. 38)], and is widely regarded as producing an unacceptably high rate of toxicity. This regimen has not been evaluated in comparison with the less toxic 5-FU/LV regimens currently in common use in the UK.

In the X-ACT study, the rate of death was similarly low during treatment between both groups (less than 0.5%), and is among the lowest figures reported in trials of adjuvant therapy. Capecitabine and 5-FU/LV are similar with respect to the overall range of adverse events (all grade) commonly encountered by patients: diarrhoea, vomiting, nausea, stomatitis and hand–foot syndrome. However, the frequencies of severe (grade 3 or 4) stomatitis, neutropenia and alopecia are significantly lower with oral capecitabine than 5-FU/LV. The only adverse event occurring more often with capecitabine is hand–foot syndrome. These data are broadly similar to those reported in reviews of capecitabine-related adverse events,[123,126–128] which also suggest that these symptoms can be managed effectively by dose interruption or dose modification.

Almost 60% of patients in the capecitabine group, all of whom received full doses of capecitabine at the beginning, did not require dose reduction, suggesting that it is important to maintain the dose of capecitabine in the adjuvant setting.[108,129] On the other hand, dose modifications, interruptions or delays in capecitabine therapy were required in 57% of patients, indicating that active management of toxicities is required.[34,108] In the UK, the effective delivery of such oral home-based chemotherapy represents a significant challenge to all individuals involved in cancer care. Oral chemotherapy requires just as much care as intravenous chemotherapy; however, education of the patient for compliance with medication (self-medication), adverse event recognition and reporting (nature/severity) and prompt management (intervention by interruption/modifications of the oral dosing schedule) are some of the key challenges facing patients, community health workers and healthcare practitioners in cancer care.[130]

Both anecdotally and in clinical trials, dose reductions below the starting dose in the X-ACT study (2500 mg/m^2/day) are common, and many American oncologists routinely use a lower starting dose in the metastatic setting.[131,132] Allegra and Sargent[131] and Saltz[132] suggest that the use of a lower starting dose would not be recommended in the adjuvant setting in the absence of supportive data, and the full 2500 mg/m^2/day should be used, with dose adjustments applied as needed for toxicity.

Oral capecitabine is administered at home and patients require fewer hospital visits compared with patients receiving intravenous treatment. Administration of 5-FU/LV (Mayo Clinic regimen) requires patients to attend the clinic/hospital for five consecutive days during every 28-day treatment cycle.[109] When given a choice, most patients with cancer prefer oral chemotherapy to intravenous treatment, provided that efficacy is not compromised.[133,134] The main reasons for this preference are increased convenience, less distress over repeated intravenous access and more control over their own treatment. In addition, Payne[135] demonstrated that the patients' QoL was significantly improved with home-based treatment compared with hospital-based therapy. In the X-ACT study, capecitabine therapy showed an improved adverse event profile compared with bolus Mayo Clinic regimen of 5-FU/LV; however,

this was not reflected in improved QoL for the patients. The EORTC QLQ-C30, which was used in the X-ACT study, is a psychometrically robust health-related QoL measure for a generic cancer population; however, it is not aimed at detecting specific health-related QoL aspects related to colorectal cancer sufferers (e.g. oral formulation versus intravenous regimen) and may not provide a comprehensive overview of the impact of new therapies on patients health-related QoL.[136] In addition, Ward and colleagues[22] suggest that the lack in improvement in QoL may be because patients receiving the bolus Mayo Clinic regimen of 5-FU/LV 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, and if QoL questionnaires are administered at the beginning of each treatment cycle and (as in the case of the EORTC QLQ-C30) refer only to the preceding week, then they are less likely to capture the adverse effects on QoL of the Mayo Clinic regimen. It is also possible that QoL is improved through intravenous treatment, owing to increased contact with nurses and peer support of other patients.

Summary of effectiveness data for capecitabine

The evidence to support the use of oral capecitabine to adjuvant treatment is at present limited to the X-ACT study, a large (n = 1987), international, multi-centre, Phase III, randomised, open-label, active-controlled trial. This trial compared oral capecitabine (eight cycles) with a bolus Mayo Clinic regimen of 5-FU/LV (six cycles) for a total of 24 weeks in patients with Stage III (Dukes' C) colon cancer. The primary trial end-point was at least equivalence in disease-free survival. Secondary trial end-points included relapse-free survival, overall survival, safety and QoL.

Primary outcome – disease-free survival

Capecitabine therapy was shown to be at least equivalent to 5-FU/LV, in that the primary end-point was met [upper limit of the 95% CI of the hazard ratio was significantly ($p < 0.001$) below both predefined margins of 1.25 and 1.20 for at least equivalence]. A pre-specified superiority analysis showed that capecitabine was not statistically superior to 5-FU/LV ($p = 0.05$).

- At 3-years (pre-specified analysis), the probability of remaining disease free (relapse/new occurrence of colon cancer or death due to any cause) was 64.2 and 60.6% for capecitabine and 5-FU/LV, respectively. For the ITT population, the hazard ratio for recurrence was 0.87 (95% CI: 0.75 to 1.00), corresponding to a 13% reduction in the risk of relapse or death and an absolute disease-free survival difference of 3.6%.
- Updated results (analysis not pre-specified) with a median follow-up of 4.4 years (with a minimum follow-up of 3 years for all patients) confirm the earlier results and demonstrate that capecitabine is equivalent to 5-FU/LV (hazard ratio of 0.87; 95% CI: 0.76 to 1.00; $p = 0.055$ for superiority).

Secondary outcomes – relapse-free survival and overall survival

Relapse-free survival

Capecitabine therapy improves relapse-free survival.

- At 3 years (pre-specified analysis), the probability of remaining relapse free were 65.5 and 61.9% for capecitabine and 5-FU/LV, respectively. For the ITT population, the hazard ratio for recurrence was 0.86 (95% CI: 0.74 to 0.99; $p = 0.04$ for superiority), corresponding to a 14% reduction in the risk of relapse/death and an absolute relapse-free survival difference of 3.6%.
- Updated results (analysis not pre-specified in the protocol) with a median follow-up of 4.4 years showed a trend in favour of capecitabine (hazard ratio of 0.87; 95% CI: 0.75 to 1.00; $p = 0.057$ for superiority).

Overall survival

Overall survival data were not mature at the time of analysis.

- In the ITT population, no statistically significant differences were observed between the two groups after a median follow-up of 3.8 years ($p = 0.07$ for superiority) or after a median follow-up of 4.4 years ($p = 0.169$ for superiority).

Quality of life

There were no major (statistically significant) differences in QoL between oral capecitabine and 5-FU/LV from baseline to 25 weeks of trial treatment (no statistical data reported); however, other studies suggest that patients prefer oral chemotherapy to intravenous treatment.

Adverse events (toxicities)

As a result of toxicity, both groups required dose modifications, interruptions and delays

(capecitabine 57% versus 5-FU/LV 52%). Adverse events most commonly leading to dose modifications (including treatment interruption and dose reduction) were hand–foot syndrome (31%) and diarrhoea (15%) in the capecitabine group and stomatitis (23%) and diarrhoea (19%) in the 5-FU/LV group.

The frequency of severe (grade 3 or 4) stomatitis (2 versus 14%; $p < 0.001$) and alopecia (0 versus <1%; $p < 0.02$) were significantly less common in capecitabine-treated patients than in those receiving 5-FU/LV. The incidence of neutropenia as a grade 3 or 4 laboratory abnormality was significantly ($p < 0.001$) lower in the capecitabine group (2%) than in the 5-FU/LV group (26%). Grade 3 hand–foot syndrome was the only severe adverse event occurring more often with capecitabine than 5-FU/LV (17 versus <1%; $p < 0.0001$).

Bolus or infusional 5-FU for the adjuvant treatment of colon cancer?

NICE requested that the review team summarise trial evidence for the relative clinical effectiveness of bolus versus infusional 5-FU.

Caution is urged in the use of the results presented in this section, as the included studies have not been through the same rigorous process of critical appraisal as the studies reviewed in the sections 'Results: oxaliplatin' (p. 12) and 'Results: capecitabine' (p. 24).

Introduction

In the adjuvant setting, 6 months of FU in combination with LV has become the standard chemotherapy for patients with resected Stage III colon cancer.[87,88] Evidence emerging from adjuvant studies conducted in the 1990s showed that 5-FU and low-dose LV (20 mg/m^2) is equivalent to 5-FU and high-dose LV (200–500 mg/m^2); 5-FU/LV given for 6 months is as effective as when given for 12 months and there is no significant difference between the two most commonly used bolus 5-FU/LV dose schedules, the Mayo Clinic (5-FU 425 mg/m^2, LV 20 mg/m^2 on days 1–5 every 4 weeks) and Roswell Park (5-FU 500 mg/m^2 and LV 500 mg/m^2 weekly times six every 8 weeks for three cycles) regimens.[137] The current options for the delivery of adjuvant 5-FU monotherapy are as a bolus, as a protracted infusion (or combination of bolus and protracted infusion, the de Gramont regimen) or oral administration. The following section evaluates the evidence for the clinical effectiveness of bolus versus infusional 5-FU in the adjuvant treatment of colon cancer.

Quantity and quality of research available

Number of studies identified

Within the database of 1499 references, 827 articles were identified as potentially relevant to this section using the search term 'fluorouracil' or '5-FU'. The majority were rejected as they focused on advanced or metastatic colon cancer.

Number and type of studies included

Three published RCTs were identified.[88,138,139] These studies included patients with Stage III (Dukes' C) colon cancer and investigated the efficacy and safety of bolus versus infusional 5-FU as an adjuvant therapy after complete resection of the primary tumour. In addition to the main publication by Chau and colleagues[138] we identified one paper reporting on additional aspects of the study.[140]

Assessment of effectiveness

Description and quality of included studies

A description of the included studies is summarised below and the quality assessment of the randomised studies is presented in *Table 14*.

Andre and colleagues[88]

This study was an open-label randomised trial comparing two adjuvant chemotherapy regimens [fortnightly de Gramont regimen (LVFU2) versus a monthly (5-FU/LV) regimen of 5-FU and LV] and two treatment durations (24 versus 36 weeks of each regimen) using a two by two factorial design in patients with resected Stage II or III colon cancer. A dynamic minimisation procedure was used to stratify patients according to institution, disease stage (Stage II versus Stage III), number of affected nodes for Stage III cancer, adjacent organ invasion and time since surgery.[88]

A total of 905 patients, recruited by 93 centres in France between July 1996 and November 1999, were randomly assigned to each treatment group. Patients randomly assigned to the LVFU2 group received dl-LV 200 mg/m^2 (or l-LV 100 mg/m^2) as a 2-hour infusion, followed by bolus 5-FU 400 mg/m^2 and a 22-hour infusion of 5-FU 600 mg/m^2 for two consecutive days every 14 days ($n = 452$). Patients in this group received either 12 or 18 cycles of treatment depending on whether they were assigned to the 24- or the 36-week treatment group. In the 5-FU/LV group, patients received an infusion of dl-LV 200 mg/m^2 (or l-LV

TABLE 14 *Trial quality assessment: bolus versus infusional 5-FU*

	Andre *et al.*, 2003[88]	**Chau *et al.*, 2005[138]**	**Poplin *et al.*, 2005[139]**
Was the method used to assign participants to the treatment groups really random?	Y	Y	Y
What method of assignment was used?	Dynamic minimisation	Permuted blocks	Dynamic minimisation
Was the allocation of treatment concealed?	?	Y	?
What method was used to conceal treatment allocation?	?	Central randomisation	?
Was the number of participants who were randomised stated?	Y	Y	Y
Were details of baseline comparability presented?	Y	Y	Y
Was baseline comparability achieved?	Y	Y	Y
Were the eligibility criteria for study entry specified?	Y	Y	Y
Were any co-interventions identified that may influence the outcomes for each group?	?	?	?
Were the outcome assessors blinded to the treatment allocations?	N	?	?
Were the individuals who administered the intervention blinded to the treatment allocation?	N	?	?
Were the participants who received the intervention blinded to the treatment allocation?	N	?	?
Was the success of the blinding procedure assessed?	NA	?	?
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y	N	N
Were the reasons for withdrawal stated?	Y	Y	Y
Was an ITT analysis included?	Y	Y	Y

N, no; NA, not applicable; ?, not enough information or not clear; Y, item addressed.

100 mg/m^2) for 15 minutes, followed by a 15-minute bolus of 5-FU 400 mg/m^2 for five consecutive days, every 28 days (n = 453). Six or nine cycles of treatment were received for 24 or 36 weeks of treatment, respectively.[88]

The primary end-point was disease-free survival (defined as colorectal cancer relapse, second colorectal cancer or death) at 3 years. Secondary end-points include overall survival and safety (toxicities). The study was designed with 70–80% power to detect an 8% difference in disease-free survival between the LVFU2 and 5-FU/LV or 24 and 36 weeks of treatment. Characteristics at baseline were similar between treatment groups. The duration of follow-up was approximately 3 years with a median follow-up of 40 months in the LVFU2 group and 41 months in the 5-FU/LV group. At the end of the planned 3 years of follow-up, less than 20% of participants in each group were reported to have been lost to follow-up (approximately 15%) and all withdrawals were accounted for. All analyses were by ITT.[88]

Chau and colleagues[138]

This Phase III study was a multi-centre randomised trial comparing the efficacy and toxicity of 12 weeks of 5-FU alone by protracted venous infusion (PVI 5-FU) against the standard bolus monthly (Mayo Clinic) regimen of 5-FU/LV given for 6 months as adjuvant treatment in colorectal cancer.[138] Patients were randomly allocated by an independent randomisation office to either PVI 5-FU or bolus 5-FU/LV on a 1:1 basis using random permuted blocks and stratified by treatment centre.[140] It is unclear if patients, investigators and outcome assessors were blinded or unblinded to the assigned treatments.

A total of 801 eligible patients, recruited from nine oncology centres in the UK between 1993 and 2003, were randomised to each treatment group.[138] In the PVI 5-FU group (administered via a 'Hickman line'), 5-FU was given as a continuous intravenous infusion at a dose of 300 mg/m^2/day using a portable pump for 12 weeks (n = 397). Patients assigned to the bolus 5-FU/LV group

received leucovorin at a dose of 20 mg/m^2/day as a bolus intravenous injection followed by a bolus injection of 5-FU at a dose of 425 mg/m^2/day for five consecutive days, repeated every 28 days for a total of six cycles (n = 404).[140]

The primary end-point was overall survival (defined as death from any cause) at 5 years. Secondary end-points were relapse-free survival (event defined as cancer recurrence or second primary tumour), toxicity and QoL. The original sample size was designed to detect a minimum improvement in overall survival from 60 to 70% after 5 years of follow-up, thus giving 80% power. Characteristics at baseline were similar between treatment groups. The duration of follow-up was approximately 5 years with a median follow-up of 66 months in the PVI 5-FU group and 62 months in the 5-FU/LV group. During the follow-up period, more than 20% of participants in each group were reported to have been lost to follow-up (approximately 30%); however, it was similar for the two groups and all withdrawals were accounted for. All analyses were by ITT.[138]

Poplin and colleagues[139]

This Phase III study was a randomised trial comparing the efficacy of continuous infusional 5-FU plus levamisole with 5-FU/LV (Mayo Clinic regimen) plus levamisole in the adjuvant treatment of high-risk patients with Dukes' B2 or Dukes' C colon cancer. Patients were randomly allocated to treatment using a dynamic balancing algorithm that stratified by tumour or node stage and time from surgery. It is unclear if patients, investigators and outcome assessors were blinded or unblinded to the assigned treatments.

Between December 1994 and December 1999, 1135 patients were accrued from the Southwest Oncology Group, the ECOG, the Cancer and Leukaemia Group B and the North Central Cancer Treatment Group. Of these, 940 patients were eligible. In the continuous infusional 5-FU plus levamisole group, 5-FU was given at 250 mg/m^2/day for 56 days every 9 weeks for three cycles (n = 477). Patients assigned to the bolus 5-FU/LV group received LV at a dose of 20 mg/m^2/day as an intravenous injection followed by a bolus injection of 5-FU at a dose of 425 mg/m^2/day for five consecutive days, repeated every 28–35 days for a total of six cycles (n = 463). All patients received 50 mg of levamisole every 8 hours for three consecutive days every 14 days for a total of 6 months.

The primary end-point was overall survival at 5 years. Secondary end-points were disease-free survival and safety (toxicity). The study had an accrual goal of 1800 eligible patients (reduced to 1500) allowing for a 90% power to detect a 35% improvement in survival in favour of the continuous infusional 5-FU plus levamisole group. Characteristics at baseline were similar between treatment groups and the median duration follow-up was 6.52 years. During the follow-up period, more than 20% of participants in each group were reported to have been lost to follow-up (approximately 30%); however, it was similar for the two groups and all withdrawals were accounted for. All analyses were by ITT.

Efficacy (disease-free, relapse-free and overall survival) and safety (toxicity)

Three randomised comparisons of bolus versus infusional 5-FU have been published so far. Only two studies followed up individuals for 5 years, a suitable proxy time-point for long-term survival. A summary of the efficacy and safety results are presented in *Table 15*.

In the French study,[88] with a median follow-up of 41 months, disease-free survival was similar between the LVFU2 and 5-FU/LV groups [127 vs 124 events; hazard ratio = 1.04 (95% CI: 0.81 to 1.34); p = 0.74] and between 24 and 36 weeks of therapy [128 vs 123 events; hazard ratio = 0.94 (95% CI: 0.74 to 1.21); p = 0.63]. Analysis of overall survival showed a slight excess in the number of deaths in the LVFU2 group compared with 5-FU/LV (73 vs 59); however, this difference was not statistically different [hazard ratio = 1.26 (95% CI: 0.90 to 1.78); p = 0.18]. Although the trial was not powered to detect differences in patients with Stage II or III colon cancer, a descriptive treatment comparison showed that 52 events were observed among patients with Stage II disease, evenly distributed between the LVFU2 and 5-FU/LV groups: 27 and 25 events (with 12 and 10 deaths), respectively. In Stage III patients, 199 events were observed, also evenly distributed between the LVFU2 and 5-FU/LV group: 100 and 99 events (with 60 and 49 deaths), respectively. Compliance was good and premature withdrawal rates were 23 and 19% for LVFU2 and 5-FU/LV group, respectively. The most commonly observed grade 3–4 toxicities were neutropenia, diarrhoea and mucositis. Toxicities were significantly lower in the LVFU2 group (all toxicities, $p < 0.001$). Four patients died within 60 days of initiation of treatment, three in the LVFU2 and one in the 5-FU/LV group (p = 0.37). All-cause mortality (0.7% of total population) under treatment was similar in both arms, four patients in the LVFU2 group (two sudden deaths, one case of sepsis

TABLE 15 *Randomised trials comparing monthly bolus 5-FU/LV versus continuous infusional 5-FU with or without LV and/or levamisole*

	Andre *et al.*, 2003[88] LVFU2 (6 or 9 months) vs monthly 5-FU/LV (6 or 9 months)	**Chau *et al.*, 2005[138] 5-FU protracted infusion (3 months) vs bolus 5-FU/LV (6 months)**	**Poplin *et al.*, 2005[139] 5-FU infusion plus levamisole (6 months) vs bolus 5-FU/LV plus levamisole (6 months)**
Total number of patients (per treatment group)	905 (452/453)	801 (397/404)	940 (477/463)
Median follow-up	41 months	64 months	6.52 years
Cancer of colon/rectum	100/0%	60/40%	100/0%
Stage II/III	43/57%	44/56%	Not reported
Efficacy data			
Overall survival (OS)	Event rate: 73 vs 59 3 year OS: 86.0 vs 88.0% Hazard ratio: 1.26 (95% CI: 0.90 to 1.78; $p = 0.18$)	Event rate: 99 vs 121 5 year OS: 75.7 vs 71.5% Hazard ratio: 0.79 (95% CI: 0.61 to 1.03; $p = 0.083$)	Event rate: 151 vs 135 5 year OS: 69 vs 70% Hazard ratio: 1.16 (95% CI: 0.93 to 1.44; $p = 0.18$)
Disease-free survival (DFS)	Event rate: 127 vs 124 3 year DFS: 73.0 vs 72.0% Hazard ratio: 1.04 (95% CI: 0.81 to 1.34; $p = 0.74$)	–	Event rate: 175 vs 174 5 year-DFS: 63 vs 61% Hazard ratio: 1.05 (95% CI: 0.86 to 1.3; $p = 0.65$)
Relapse-free survival (RFS)	–	Event rate: 104 vs 127 5-year RFS: 73.3 vs 66.7% Hazard ratio: 0.8 (95% CI: 0.62 to 1.04; $p = 0.1$)	–
Toxicity data[a]			
Grade 3/4 neutropenia	7 vs 16% ($p < 0.001$)	1.1 vs 55.4% ($p < 0.0001$)	0.4 vs 31.6[b,c]
Grade 3/4 diarrhoea	4 vs 9% ($p < 0.001$)	5.4 vs 15.9% ($p < 0.0001$)	1.3 vs 4.6%[b]
Grade 3/4 mucositis	2 vs 7% ($p < 0.001$)	3.6 vs 18.2% ($p < 0.0001$)	Not reported
Grade 3/4 nausea/vomiting	1 vs 3% ($p = 0.093$)	1.5 vs 2.3% ($p < 0.0001$)	0.0 vs 1.7%[b,d]
Grade 3/4 HFS	0 vs 0%	7.1 vs 3% ($p < 0.0001$)	Not reported
All Grade 3/4 toxicities	11 vs 26% ($p < 0.001$)	Not reported	5.2 vs 39.7%[b]

HFS, hand–foot syndrome.
[a] According to National Cancer Institute Common Toxicity criteria.
[b] Grade 4/5 toxicity (grading criteria method not specified).
[c] Neutropenia or granulocytopenia.
[d] Vomiting only.

without aplasia and one death unrelated to treatment) and two in the 5-FU group (one case each of febrile aplasia and sepsis without aplasia). Four of those six deaths were within 60 days of initiation of treatment, three in the LVFU2 and one in the 5-FU/LV group ($p = 0.37$).

In the UK study,[138] with a median follow-up of 5.3 years, 220 deaths were observed, 99 in the PVI 5-FU group and 121 in the bolus 5-FU/LV group. PVI 5-FU was associated with a trend for better survival [hazard ratio = 0.79 (95% CI: 0.61 to 1.03); $p = 0.083$]. The 5-year survival was 75.7% (95% CI: 70.8 to 79.9%) for PVI 5-FU and 71.5% (95% CI: 66.4 to 75.9%) for bolus 5-FU/LV. Based on these results, the authors reported that the probability of 12 weeks of PVI 5-FU being inferior to 6 months of bolus 5-FU/LV was very low ($p < 0.005$). Although not significant, in most subgroups, including patients with Stage II or III colorectal disease, the survival trend was in favour of PVI 5-FU, consistent with the whole population. A total of 231 patients had developed disease relapses, 104 in the PVI 5-FU group and 127 in the bolus 5-FU/LV group. The 5-year relapse-free survival was 73.3% (95% CI: 68.4 to 77.6%) for PVI 5-FU and 66.7% (95% CI: 61.6 to 71.3%) for bolus 5-FU/LV with a hazard ratio of 0.8 (95% CI: 0.62 to 1.04; $p = 0.1$). Significantly less diarrhoea, stomatitis, nausea and vomiting, alopecia, lethargy and neutropenia events (all with $p < 0.0001$) were observed with PVI 5-FU. Hand–foot syndrome was, nonetheless, more frequent ($p < 0.0001$) compared with bolus 5-FU/LV. No details of compliance, (premature) discontinuation of therapy and mortality due to treatment were reported.[138] However, planned interim results (published previously)[140] based on a sample of 716 patients showed that the global QoL scores were significantly better ($p < 0.001$) for patients with PVI 5-FU than bolus 5-FU.[140]

In the American study,[139] with a median follow-up of 6.52 years, overall survival and disease-free survival was similar between the treatment groups; however, the 5-FU infusion plus levamisole group was found to have less severe toxicity than the bolus 5-FU/LV plus levamisole group. However, a greater number of patients discontinued treatment early because of adverse effects in the continuous infusion group ($n = 106$) than in the bolus group ($n = 64$). Most patients receiving continuous infusion 5-FU complained, not necessarily about high-grade toxicities, but about the logistics of pump therapy, pump malfunctions, clotting episodes, neck pain associated with the catheter and chronic hand–foot syndrome. Moreover, this study was prematurely closed when a planned interim analysis showed that the chances of finding significant differences between the treatment arms were too low.[139]

Discussion of results

The strength of the evidence (internal validity)

Although adequate methods of randomisation were reported, it is not clear if adequate methods of allocation concealment were used in two studies.[88,139] No trials reported blinding; one reported open-label status. Blinding is almost universally absent from oncology trials.

The study groups in the included trials were comparable at baseline, so the likelihood of confounding bias is low; however, additional co-interventions or contaminations that may influence the outcomes in each treatment group were not reported. The absence (non-collection) of these data should not generate concern; however, it may have affected the internal validity of the study to an unknown extent.

In both the UK[138] and American[139] studies, more than 20% of participants in each treatment group were reported to have been lost to follow-up (approximately 30%). The greater the number of subjects who are lost, the more the trial may be subject to bias because patients who are lost often have different prognoses from those who are retained. In both of these studies, attrition bias should be low as the loss to follow-up was similar for the two treatment groups, all patients were accounted for and an ITT analysis was performed.

The authors of the French study[88] reported that their trial was clearly undersized to confirm or refute small benefits in terms of disease-free survival or overall survival rate; however, with longer follow-up and a larger number of events, the uncertainty will be substantially reduced. Sobrero[141] suggested that there were a number of factors limiting the validity of the UK study. These reasons were as follows: limited number of patients planned; the inclusion of both colon and rectal cancer patients and Stage II and III patients; the inclusion of patients with clearly suboptimal surgery (tumour-free margins of just >1 mm); reserving radiotherapy to T4 rectal cancers, but at the same time leaving the decision about preoperative radiotherapy to the treating physician; giving more than 4 months of PVI 5-FU (instead of 3 months) in rectal cancer patients receiving radiotherapy; and, above all, the treatments are radically different in duration and schedule (3 months of PVI 5-FU versus 6 months

of bolus 5-FU/LV). The American study[139] reduced the number of patients planned, included both Stage II and III patients and suffered from a high ineligibility rate (17.2%).

The applicability of the results (external validity)

At present, the evidence suggests that infusional intravenous fluoropyrimidine-based adjuvant therapy is equivalent to, but with relatively less toxicity than, bolus 5-FU/LV in extending survival and a better QoL.[88,138–140] One study even suggested that 3 months of PVI 5-FU may be comparable to 6 months of bolus 5-FU/LV.[138] However, there are concerns about catheter-associated complications, patient inconvenience and the expense of infusional treatment.[27,88–91] In the treatment of advanced colorectal cancer, a meta-analysis of three Phase III RCTs (n = 938) involving unconfounded, direct comparisons of bolus and infusional regimes found that 5-FU was significantly more effective and less toxic when delivered by continuous infusion rather than bolus injection, whether or not it was used in combination with other technologies.[8]

In the adjuvant setting, the most widely used chemotherapy regimen in England and Wales is bolus 5-FU/LV. The large UK-based trial, QUASAR, has been important in identifying simple but better tolerated regimens of bolus 5-FU and LV. The QUASAR trial has firmly established its 5-day monthly schedule with low-dose LV to be as effective as and less toxic than high-dose LV;[142] however, the status of QUASAR's weekly schedule as a standard option is more contentious, depending as it does on a very large but non-randomised comparison.[29] Patel and colleagues[27] reported that some oncologists now use the 5-day monthly treatment at 370 mg/m^2 5-FU with low-dose LV, on the basis that the QUASAR trial randomly validated this schedule against a standard regimen. Others, reassured by the large size and well-balanced patient characteristics in QUASAR's non-randomised comparison of schedules, have adopted the weekly regimen, which gives the same doses weekly for 30 weeks, so giving the same total planned dose (11.1 g/m^2) but with lower planned dose intensities (370 versus 462 mg/m^2/week).[27] Within the Greater Manchester and Cheshire Cancer Network (the largest in the UK), the current standard adjuvant treatment is weekly intravenous bolus 5-FU/LV for 30 weeks (QUASAR regimen); however, it is recognised that there are significant geographical variations in the use of 5-FU-based regimens in the UK.[26]

Summary of effectiveness data for bolus or infusional 5-FU

Infusional 5-FU/LV adjuvant-based therapy is equivalent to, but with relatively less toxicity than, bolus 5-FU/LV in extending survival and a better QoL. The major drawbacks of continuous infusion with 5-FU are catheter-associated complications and its adverse effects. Nevertheless, the most widely used adjuvant treatment in England and Wales is the weekly intravenous bolus 5-FU/LV for 30 weeks (QUASAR regimen); however, there remain significant geographical variations in the 5-FU-based regimens currently in use in the UK.

Chapter 4

Assessment of cost-effectiveness

This section of the assessment focuses on the health economics of capecitabine monotherapy and oxaliplatin in combination with 5-FU/LV (FOLFOX4) in comparison with standard therapies. It includes a review of existing economic evaluations of the relevant therapies, a critique of each of the industry submission economic evaluations and a detailed explanation of the methodologies and results of the independent assessment group economic model.

The key outcome of the analysis is the marginal cost per quality-adjusted life-year (QALY) gained of the two interventions when compared with standard treatment, using data from the MOSAIC and X-ACT studies to model disease-free survival, overall survival, costs incurred and QoL benefits achieved.

The next section presents the results of the systematic review of economic literature and a subsequent review of relevant economic evaluations, along with the reviews of the two industry submissions. The independent assessment group's approach is discussed in the subsequent section, followed by the results of the analysis.

Systematic review of existing economic literature

This review examined the cost-effectiveness of oxaliplatin (Eloxatin®, Sanofi-Aventis) in combination with 5-FU/LV and capecitabine (Xeloda®, Roche) monotherapy within their licensed indications as adjuvant therapies in the treatment of patients with completely resected Stage III (Dukes' C) colon cancer, as compared with adjuvant chemotherapy with an established 5-FU-containing regimen.

Identification of studies

The aim of the search was to provide as comprehensive a retrieval as possible of economic evaluations of oxaliplatin or capecitabine as adjuvant therapies in the treatment of colon cancer.

Sources searched

Seven electronic databases providing coverage of the biomedical and health technology assessment literature were searched. The publications lists and current research registers of over 30 health services research-related organisations were consulted via the Internet. Keyword searching of the World Wide Web was undertaken using the Google search engine. The economic assessments submitted by sponsors were identified as studies for inclusion in the review.[20,143] In addition, the sponsor submissions were hand-searched for further references to studies. A list of the sources searched is provided in Appendix 9.

Keyword strategies

The keyword strategies developed in the review of clinical effectiveness were used, with the RCT methodological filter being replaced by a filter aimed at restricting search results to economic and cost-related studies. Keyword strategies for all electronic databases are provided in Appendix 9.

Search restrictions

The same limits and restrictions used in the review of clinical effectiveness were applied with the exception of the methodological filter as described above. All searches were undertaken in January 2005.

Inclusion and exclusion criteria

Studies were selected for inclusion according to predetermined inclusion and exclusion criteria. Studies were included if they reported the cost-effectiveness of oxaliplatin or capecitabine in the adjuvant treatment of colorectal cancer. Studies that were considered to be methodologically unsound, that were not reported in sufficient detail or that did not report an estimate of cost-effectiveness (e.g. costing studies) were excluded. Two reviewers independently screened all titles and abstracts. Disagreement was settled through discussion. Full papers were obtained for any titles/abstracts that were considered relevant or where the title/abstract information was not sufficient to make a decision.

Quality assessment

The Drummond checklist[144] was used to assess the quality of each economic evaluation considered, enabling a thorough, detailed and structured evaluation of the strengths and weaknesses of each study and industry submission to be made (see Appendix 10). The use of the checklist ensures a

consistent approach to assessing the quality of each economic evaluation.

Results of cost-effectiveness review

The systematic searches resulted in a total of 178 studies for potential inclusion in the review. Three studies were identified as meeting the review criteria.[115,145,146] Together with the two sponsor submissions,[20,143] a total of five studies were identified for inclusion in the review (see Appendix 11). Three studies considered the cost-effectiveness of oxaliplatin and two studies considered the cost-effectiveness of capecitabine. Details of the studies excluded from the review, and the reasons for exclusion, are given in Appendix 12.

In the following section an overview of the methods and results of the studies identified through the searches is presented.[115,145,146] The subsequent section provides a detailed critique of the sponsor submissions.[20,143]

Cost-effectiveness review

Douillard and colleagues (2004).[115] Pharmacoeconomic analysis of capecitabine in the adjuvant setting. Results from the X-ACT trial comparing capecitabine with 5-FU/LV in patients with Dukes' C colon cancer

Overview

Douillard and colleagues[115] report an economic evaluation of capecitabine versus 5-FU/LV in patients with Stage III (Dukes' C) colon cancer. This analysis was presented as a poster at the 2004 European Society for Medical Oncology (ESMO),[147] coupled with an abstract outlining the main findings.[115] The economic analysis was undertaken from the perspective of the NHS.

Summary of effectiveness data

Evidence on the effectiveness of capecitabine and 5-FU/LV was obtained from the X-ACT study.[109] Health outcomes were assessed through the use of overall and relapse-free survival curves for the duration of follow-up, after which the curves were extrapolated using Weibull functions to estimate death and relapse thereafter (up to 10 years post-surgery).

A state transition model similar to that used by Monz and colleagues[148] was developed, with costs and utilities and costs attached to the following three states:

- stable (relapse-free)
- post-relapse
- dead.

The study reports that the time spent in each health state was estimated using partitioned survival of the trial data, with projections beyond the study period (up to 10 years) estimated using the extrapolated Weibull curves. The extrapolation of relapse-free survival may not be appropriate as empirical trial evidence suggests that the incidence of relapse, 5 years beyond resection of the primary tumour, is unlikely.[149] It is not possible to determine from the published literature what assumption was made with regard to the cycle length used within the Markov model. Utility estimates for relapse-free and relapse health states were obtained from Ramsey and colleagues;[150] these were held constant over time. Utilities were combined with the estimated survival in order to calculate the number of QALYs gained within each treatment arm.

Cost analysis

Safety and resource use data collected within the clinical trial were used to determine the costs associated with each treatment arm. The cost analysis included drug acquisition and administration costs, costs of hospitalisation for adverse events, medication costs associated with the treatment of adverse events and the number of physician consultations (e.g. GP visits, hospital outpatient visits and accident and emergency attendances). Costs of treating patients whose disease had relapsed are not included, although had this been included, the expected difference between the total costs of the two treatment arms would be greater (since patients on capecitabine are less likely to relapse than those on 5-FU/LV).

Sensitivity analysis

Probabilistic sensitivity analyses were not undertaken; however, a number of one-way sensitivity analyses were performed, by varying the drug acquisition and administration costs by 25% and through the use of alternative time horizons.

Summary

Owing to the reduced drug administration costs associated with capecitabine, the study concludes that capecitabine is a dominating strategy compared with 5-FU/LV, costing on average £1864 less per patient than the 5-FU/LV arm, coupled with a survival gain of 8.7 quality-adjusted life-months. Both costs and health benefits were discounted at 3.5%. Chemotherapy drug acquisition and administration costs were varied simultaneously in a sensitivity analysis, which confirmed that capecitabine would be cost saving to the NHS.

Because the study is presented in abstract and poster form, some of the detailed methodologies employed within the economic model are unclear. It is therefore not possible to comment upon the use of the Markov model, since the time horizon used is unknown. Probabilistic sensitivity analyses were not undertaken, therefore the robustness of the cost-effectiveness results generated from the model is unclear. The extrapolation of the overall survival curves is likely to overestimate long-term survival, since it does not take into account the likely reduction in the hazard of death beyond 5 years post-surgery; the hazard of death after 5 years is likely to be lower, because of the reduction in the number of patients relapsing towards the end of that period.

Koperna and Semmler (2003).[145] Innovative chemotherapies of Stage III colon cancer: a cost-effectiveness study

Overview

Koperna and Semmler report the methods and results of a health economic model (the exact form of which is unclear) to assess the cost-effectiveness of oxaliplatin in combination with 5-FU/LV versus 5-FU/LV monotherapy in patients with resected Stage III colon cancer. Data from a number of studies were used to calculate survival estimates. The analysis was undertaken from the perspective of the Austrian provider institution. Both costs and health benefits were discounted at 6%. Estimates of overall and disease-free survival associated with oxaliplatin and irinotecan were derived from trials of these therapies in metastatic cancer, and their applicability to the adjuvant setting is assumed to be appropriate by the author.

Summary of effectiveness data

Efficacy data on 5-FU/LV were extracted from six studies in which disease-free survival and overall survival were the primary end-points. Equivalent efficacy data for oxaliplatin in combination with 5-FU/LV were estimated using trials of this regimen in trials of patients with advanced (Stage IV) colorectal cancer, and is therefore unlikely to be representative of survival outcomes for patients receiving adjuvant chemotherapy. The structure of the model and the methods for synthesising trial evidence identified by the authors are unclear.

Cost analysis

Cost data were collected prospectively within a study of 47 patients with colon cancer, 13 of whom had metastatic disease. Patients in this study were randomised to receive either 5-FU/LV or oxaliplatin in combination with 5-FU/LV for six treatment cycles (with 5-FU/LV administered using the Mayo Clinic regimen). The costs included those of follow-up (up to 5 years post-treatment), detection of recurrent disease, chemotherapy drug costs, laboratory resource, nursing time, physician consultations, hospitalisations for adverse events, CEA level tests, abdominal sonography, chest X-ray, colonoscopy and overheads. Costs of subsequent palliative treatment (including costs of liver resection, palliative chemotherapy and drug costs associated with side-effects) were also incorporated, and were estimated using a mean of the patients treated within the hospital over a 12-month period.

Summary

The cost-effectiveness results are presented as an incremental analysis, although all results are actually compared against best supportive care. Further analysis by the Assessment Group of the marginal cost and survival results given in the paper enabled an incremental analysis to be performed, which suggested that the incremental cost per life-year gained (LYG) of the addition of oxaliplatin to 5-FU/LV is £24,952. One-way sensitivity analyses were performed by varying parameters relating to drug acquisition, follow-up, palliative care, discount rates, survival benefits of combination therapy and the associated reduction in mortality rate. The results of the sensitivity analysis are, however, not fully reported.

This study is subject to a number of methodological flaws, the most important of which is the assumption that disease-free and overall survival have been estimated from trials relating to patients with advanced colorectal cancer, whose prognosis does not mirror that of patients with Stage III disease. This means that survival is likely to have been underestimated, leading to a high estimate of cost-effectiveness. The collection of the cost data is also flawed, with the inclusion of patients with metastatic disease likely to misrepresent the true costs associated with the treatment of patients with Stage III colon cancer. The structure of the economic model is not well described, and it is therefore difficult to comment upon other assumptions made within the economic analysis.

Aballea and colleagues (2005).[146] Cost-effectiveness analysis of oxaliplatin/5-FU/LV in adjuvant treatment of colon cancer in the US

Overview

This conference abstract outlines a cost-effectiveness analysis of oxaliplatin in combination with 5-FU/LV, using data from the MOSAIC trial. Although not a complete economic paper, this

study has nevertheless been included in the review because it is one of the few which presents an estimate of the cost-effectiveness of oxaliplatin in combination with 5-FU/LV in the adjuvant setting. The authors used patient-level data from the MOSAIC trial to estimate the cost per LYG over a lifetime. The perspective of the analysis was that of the US Medicare system.

Summary of effectiveness data
At the time of the analysis, 4-year data on disease-free and overall survival were available, hence a Weibull function was fitted to the disease-free survival curve and extrapolated to 5 years post-randomisation, with no further relapses assumed to occur beyond this time. The overall survival curve was extrapolated beyond 4 years using the extrapolated disease-free survival estimates and data on observed survival in relapsing patients.

Cost analysis
Costs up to 4 years post-randomisation (excluding patients who relapse) were calculated using data from the trial, with costs of relapse and follow-up beyond 4 years estimated from the literature. The cost analysis was performed from a US Medicare perspective, with a discount rate of 3% applied to both costs and health benefits.

Summary
The cost per LYG associated with FOLFOX4 was estimated to be US$27,300. Sensitivity analyses were performed using bootstrap methods, with repeated random samples being taken from the patient-level data. These analyses found that the lifetime disease-related costs were $52,500 and $34,000 for FOLFOX4 and 5-FU/LV respectively, although no breakdown of these costs is given. The analysis is presented only in abstract form, hence it is difficult to comment upon the specific methodologies and the appropriateness of their use.

Evidence from industry submissions

Economic evidence relating to the cost-effectiveness of oxaliplatin and capecitabine was contained within the two sponsor submissions to NICE.[20,143]

Roche submission to NICE: Xeloda® (capecitabine)[20]

Overview
The Roche submission uses data from the X-ACT trial to estimate the cost-effectiveness of capecitabine compared with 5-FU/LV (Mayo Clinic regimen). The study assessed the efficacy of the two drugs over a 24-week treatment cycle, following resection of the primary tumour in patients with Stage III (Dukes' C) colon cancer. The economic analysis attempts to demonstrate a reduction in treatment-related costs together with an increase in overall survival and quality-adjusted survival. The primary outcome for the economic analysis is cost per QALY gained. The analysis was undertaken from the perspective of the NHS, with a secondary analysis undertaken from the societal perspective. Costs and health outcomes were discounted at 6 and 1.5%, respectively. The model extrapolates relapse-free and overall survival benefits observed within the trial period using log-normal functions to estimate long-term health benefits to a time horizon of 40 years post-surgery. AUC analysis was then applied to each curve in turn to estimate the mean survival associated with each treatment. Costs of drug acquisition, drug administration, side-effect management, hospital visits and relapse are applied. Utilities associated with the treatment, post-treatment and relapse periods are included within the economic model.

Summary of effectiveness data
The model uses empirical relapse-free and overall survival curves up to 5 years post-surgery (disease-free survival was not considered within the economic analysis). Log-normal functions were fitted to these curves using a least-squares approach in order to extrapolate expected health outcomes for up to 40 years post-surgery. Although the fits of the log-normal curves appear to provide a reasonably good fit when compared with the early empirical data, both curves seem to overestimate both relapse-free survival and overall survival. In the capecitabine arm, the fitted curves estimate probabilities of 15 and 21% for overall and relapse-free survival at 40 years post-surgery respectively; both estimates seem excessive given that the mean baseline age of patients in the capecitabine arm of the X-ACT study was 60.4 years. Further examination of a plot of the fitted log-normal functions (*Figure 2*) demonstrates an important logical inconsistency: after approximately 18 years post-surgery, the probability of relapse-free survival is greater than the probability of overall survival. This gives a strong indication that the methodology is inappropriate. This inconsistency occurs owing to independent modelling of relapse and survival.

Utilities were applied to patients using six health states, using figures from a study of long-term survival of colorectal cancer patients reported by Ramsey and colleagues:[150]

- the (chemotherapy) treatment period
- stable/remission state

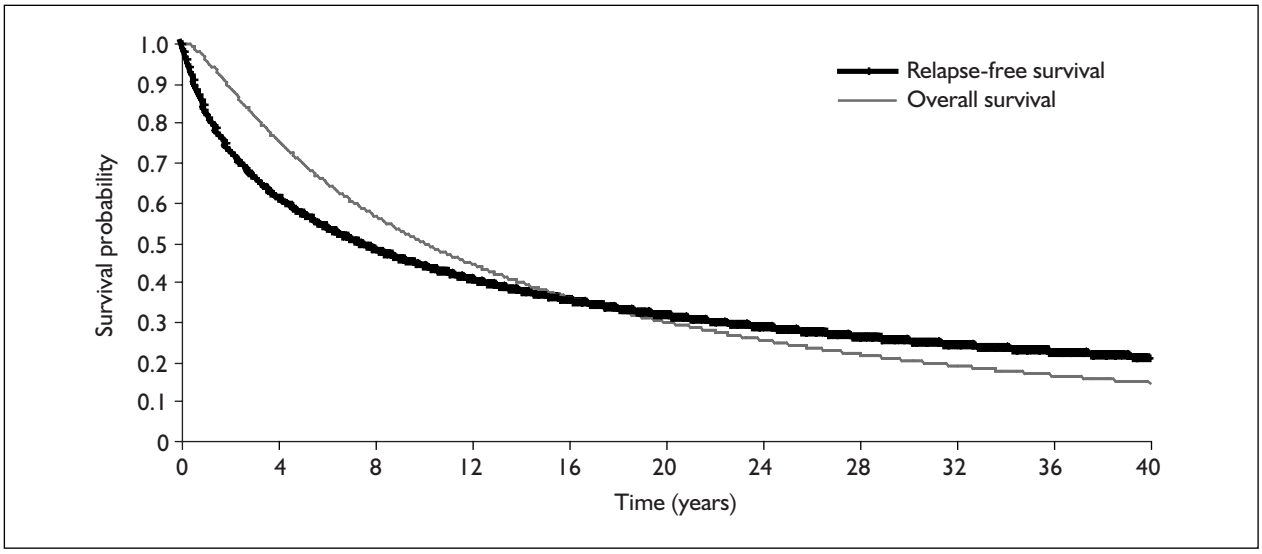


FIGURE 2 *Fitted relapse-free and overall survival from Roche submission*

- the relapse period
- the post-relapse period
- the 12-month period before death
- death.

The Ramsey study[150] did not differentiate between patients who relapsed and those who did not. Two separate utility estimates were therefore derived to represent patients in remission and those undergoing treatment following relapse by adjusting the published utilities for the proportion of patients free of relapse.

Patients in remission were assigned a utility of 0.86 and those in states 3–5 a utility of 0.59, thus reflecting their lower health-related QoL. A utility of 0.80 was assumed for patients during the chemotherapy period, although it is unclear from the submission exactly how this utility estimate was derived. The utilities were assumed to be the same for both treatment groups, and are assumed to include disutilities associated with drug side-effects and adverse events. The assumption of equivalent utilities in both arms is favourable to the 5-FU/LV treatment arm, in which a higher number of adverse events were reported than in the capecitabine arm.

QALYs were calculated by multiplying the empirical and fitted parametric survival estimates by the corresponding utilities; these were then discounted at 1.5% per annum in the base-case analysis, in line with current NICE guidelines.

Cost analysis

Cost analysis was undertaken to determine the cost differences between the two treatments over the lifetime of the patient. The cost groups included drug acquisition and administration costs, treatment and management of adverse events, hospital transport and costs associated with long-term disease management (costs of follow-up and relapse). Resource use data from the X-ACT study were multiplied by unit costs to obtain overall cost estimates; where trial data were not available, assumptions regarding resource use and costs were applied. Long-term costs were discounted at 6% per annum.

The key driver of the cost analysis was the difference in the drug administration cost between the capecitabine and 5-FU/LV arms. The resource use estimates for drug administration were based on the mean number of cycles of treatment received by patients in each treatment arm, multiplied by the per-protocol number of administration visits per cycle: one per patient per cycle for capecitabine and five per cycle for patients receiving 5-FU/LV. In the capecitabine arm, these visits are assumed to be for 'administration consultation' only, costing £57 per visit: each patient is assumed to require 7.35 such visits over the course of treatment (based on the mean number of treatment cycles completed per patient). Patients in the 5-FU/LV arm are also assumed to require 7.35 visits over the course of treatment; this is more than one visit per cycle for the 5-FU/LV arm and therefore may slightly overestimate the administration costs. The remaining visits for patients receiving 5-FU/LV are for drug administration only (i.e. no consultation), at a cost of £169 per visit. This figure of £169 is estimated using the mean of four costs from the Department of Health National Tariffs (based on oncology outpatient attendances).[151]

The model assumes that each patient who relapses incurs a cost of £25,000, plus an additional £10,000 upon death. The submission does not give a breakdown of these costs, hence it is unclear what assumptions have been made regarding palliative chemotherapy. Pharmacy costs were not included, although this approach does not favour capecitabine, since the preparation of a course of 5-FU/LV is more costly than for capecitabine.

Sensitivity analyses
A series of one-way sensitivity analyses were performed to determine the robustness of the cost-effectiveness results to changes in the model parameters thought to be subject to some variance in clinical practice. These parameters included the mean chemotherapy cost per patient, cost per drug administration visit, the proportion of patients requiring hospital transport, the total costs of adverse events, the survival increment of capecitabine over 5-FU/LV and the discount rates used for costs and QALYs. The impact upon cost-effectiveness of the use of alternative 5-FU/LV regimens was also explored, in which it is assumed that the survival benefits of the different regimens are equal to those observed in the Mayo arm of the X-ACT study. Where available, published data were used to specify the plausible ranges of these parameter values, though others were determined by applying an arbitrary range of ±50% to the deterministic parameter estimate (the range used for utility parameters was ±20%). In each of these analyses, capecitabine was demonstrated to remain cost-saving in comparison with 5-FU/LV.

Probabilistic sensitivity analyses were not performed. An 'extreme' analysis, derived by setting all of the above parameters to their 'worst-case' values (i.e. unfavourable to capecitabine), concluded that capecitabine remained cost-saving, and therefore probabilistic sensitivity analyses were not deemed necessary. Threshold analyses concluded that the most uncertainty lay in the cost per intravenous drug administration visit; the analysis found that this cost would need to fall to £40 per visit (compared with the figure of £169 used in the model) in order for capecitabine to cost more than 5-FU/LV. The sensitivity analyses did not consider the impact on the cost-effectiveness results of other 5-FU/LV regimens.

Summary
The submission reports that capecitabine is cost-saving over the 40-year time horizon considered, costing an average of £3608 less per patient than 5-FU/LV, while also leading to additional QALYs. Most of this difference is due to the differences in drug administration costs between the two treatment arms, with long-term costs assumed to be approximately equal. Although the X-ACT study was powered to show equivalence in terms of efficacy, the results of the survival analyses presented suggest that the use of capecitabine leads to an additional 0.749 QALY per patient over the 40-year time horizon, when compared with 5-FU/LV. A cost per QALY is not presented, as capecitabine dominates the 5-FU/LV (i.e. additional QALYs and cost savings). The analysis is comprehensive in its inclusion of a range of costs, and many of the assumptions made within the model are unfavourable to capecitabine, suggesting that the costs saved through the use of capecitabine may be greater than those presented in the submission. However, the reader should be aware of the potential problems resulting from the independent modelling of relapse-free survival and overall survival.

Sanofi-Aventis submission to NICE: Eloxatin® (oxaliplatin)[143]

Overview
The Sanofi-Aventis submission uses data from the MOSAIC trial to compare the clinical and cost-effectiveness of FOLFOX4 (oxaliplatin in combination with 5-FU/LV) compared with 5-FU/LV monotherapy (de Gramont regimen). The MOSAIC trial assessed the efficacy of the two treatment regimens over a 24-week treatment cycle, following resection of the primary tumour in patients with Stage II and III colon cancer. The economic analysis attempted to demonstrate a favourable incremental cost per QALY associated with FOLFOX4 when compared with 5-FU/LV. The MOSAIC trial included both patients with Stage II and III colon cancer; however, the economic analysis assesses only the cost-effectiveness of the two therapies in patients with Stage III cancer, in accordance with the scope of this assessment. The primary outcome reported within the economic analysis is the cost per QALY gained. The analysis was undertaken from the perspective of the NHS. Costs and health outcomes were discounted at 3.5%; although the impact of alternative discount rates was explored within the sensitivity analyses, this did not include the use of discount rates of 6 and 1.5% for costs and QALYs, respectively.

The economic model uses patient-level data from the MOSAIC trial and uses observed mortality and disease-free survival data and the relationship between disease-free survival and overall survival to estimate the difference in overall survival between the two treatments. Weibull functions

were used to estimate long-term health benefits to a time horizon of 50 years post-randomisation. The economic analysis incorporated the costs of drug acquisition and administration, costs of hospital consultations, post-treatment surgeries, treatment of adverse events and of patients with relapsing disease.

Summary of effectiveness data

The model uses overall survival and disease-free survival curves from the MOSAIC trial.[45] These Kaplan–Meier curves were extrapolated to estimate survival and disease-free survival up to 50 years post-randomisation. The disease-free survival curve is extrapolated up to 60 months using a generalised gamma function approach suggested by Gelber and colleagues[152] in which a function was fitted to the data between 36 and 48 months and then extrapolated up to 60 months. The authors justify the use of 48-month estimates rather than 60-month estimates owing to the small number of patients.[143] Disease-free survival was then estimated for months 48–60 by multiplying the predicted conditional probabilities from the Gelber method by the Kaplan–Meier estimate of the probability of being alive and disease-free at 36 months.

However, in selecting only those patients who were both alive and free of disease at 36 months to fit this function, the resulting extrapolation is likely to overestimate disease-free survival, as most patients who will relapse will already have done so. The authors assume that no relapses occur beyond 60 months, at which point those patients who are alive and free of disease are assumed to have a life expectancy equivalent to that of those patients in the general population, after adjusting for age and sex. The model is then extrapolated using these assumptions up to 50 years post-surgery.

Overall survival was estimated using two methods. Survival up to 4 years post-resection was measured using the Kaplan–Meier survival data, whereas long-term overall survival was calculated based on a combination of the extrapolated disease-free survival curve and a Weibull model fitted to predict the survival of patients with relapse.

Survival, conditional upon relapse, was estimated using a parametric approach, which was performed in the same manner as the fitting of the disease-free survival curve. Models were fitted to each treatment arm, in which time of relapse was the only covariate. Survival after relapse was then calculated as the product of the survival conditional on relapse and the probability that the disease-free survival end-point was a relapse. Clearly, a key assumption of this analysis is that the survival outcomes observed within the multi-centre MOSAIC trial are representative of potential survival outcomes in patients with Stage III colon cancer in England and Wales.

Utilities were applied using data from the study reported by Ramsey and colleagues.[150] A utility of 0.85 was assumed for patients in remission for the 5-year period following randomisation, after which patients' utilities were assumed to be equivalent to those of people in the general population through the use of average EQ-5D tariffs for different age bands, after adjustment for sex (the EQ-5D is a standardised instrument for use as a measure of health outcome). The utility of 0.85 was also applied to patients during their adjuvant chemotherapy treatment period, and this figure was adjusted for utility decrements associated with adverse events. Utility decrements were applied to patients with neutropenia, neuropathy, nausea, vomiting, diarrhoea and any other toxicities which require hospitalisation. Patients with relapse were assumed to experience a utility of loss of 0.2 for the duration of the period between relapse and death. These utilities were then applied to the extrapolated survival curves to give estimates of total QALYs accumulated over the 50-year time horizon.

Cost analysis

The cost analysis, which was carried out from the perspective of the NHS and Personal Social Services (PSS), encompassed the following main cost groups:

- drug acquisition costs
- drug administration costs
- costs of second adjuvant chemotherapy (for patients discontinuing initial therapy)
- medical oncology consultations (including blood tests and chest X-rays)
- post-treatment surgical procedures relating to cancers in other sites
- treatment of serious adverse events
- costs of relapse (including treatment of local recurrences, liver metastases, lung metastases and other forms of disseminated disease).

Each drug administration visit was assumed to constitute a day-case appointment costing £246.51,[153] with two such visits per cycle. Patients who relapsed were assumed to receive first-line 5-FU/LV, consistent with current NICE guidance for advanced colorectal cancer, whereas those

patients with liver metastases deemed to be eligible for down-staging were assumed to receive FOLFOX4. Upon disease progression, it was then assumed that patients would receive irinotecan in combination with 5-FU/LV as second-line treatment, although this is not a licensed indication and does not reflect NICE guidance. This assumption was based on consultations with UK clinicians. The probabilities of resection following relapse were derived from estimates in the literature and from expert opinion, and were assumed to be independent of the time of relapse.

Sensitivity analyses
A number of one-way sensitivity analyses were carried out, to assess the impact of specific parameters on the cost-effectiveness results. This included varying the costs of relapse, the discount rates used, disease monitoring costs and disutility associated with adverse events. An additional analysis assessed the use of alternative drugs (e.g. capecitabine) as adjuvant therapy.

A paired bootstrap approach was used to randomly sample 1000 patients with replacement from the trial; the cost-effectiveness results were then re-run for each patient in turn. These data were used to generate a cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC).

Summary
The submission reports an incremental cost-effectiveness ratio of £4805 per QALY for FOLFOX4 versus 5-FU/LV, calculated over the 50-year time horizon. The uncertainty analysis reported that, at a cost-effectiveness threshold of £30,000 per QALY, the probability of FOLFOX4 having a cost-effectiveness that is better than that of 5-FU/LV is 96.7%. At a threshold of £20,000 per QALY, the equivalent probability is estimated to be 94.7%. In general, the methodology appears sound; the only potential flaw in the methods used is in the extrapolation of the disease-free survival curve between 48 and 60 months, which does not use all of the previous disease-free survival data.

In June 2005, Sanofi-Aventis submitted to NICE an addendum to the economic analysis,[154] which referenced data from the NSABP C-07 trial. A revised cost-effectiveness analysis was performed, using data from the X-ACT study relating to the probability of patients starting each cycle. The long-term survival estimates for patients in both treatment arms were assumed to be equivalent to those observed within the MOSAIC trial. The incremental cost-effectiveness ratio (ICER) of oxaliplatin in combination with bolus 5-FU/LV compared with bolus 5-FU/LV was estimated to be £6244 per QALY. This indirect comparison is subject to bias, as it draws on data from more than one trial.

Independent economic assessment

Overview of economic analysis
This section details the methods and results of the health economic model constructed by the Assessment Group for the assessment of oxaliplatin in combination with 5-FU/LV and capecitabine for the adjuvant treatment of Stage III (Dukes' C) colon cancer. This was undertaken owing to the methodological flaws in the published cost-effectiveness evidence. The key aim of the analysis was to determine the cost-effectiveness of these two treatment strategies in comparison with the current standard adjuvant treatment of 5-FU/LV. This was carried out using a Markov model which estimates the costs and health effects of adjuvant treatment with 5-FU/LV, oxaliplatin plus 5-FU/LV and capecitabine. The estimated annual cost to the NHS associated with each chemotherapy sequence is also presented.

Sources of evidence
A number of sources were used to develop and populate the model, as listed in *Table 16*. Individual sources are referenced, as appropriate, in the report. An overview of the methods used to identify these sources is presented in Appendix 13.

Health economic outcomes included in analysis
The model estimates two key health economic outcomes: cost per LYG and cost per QALY gained.

TABLE 16 *Sources used to develop and populate the model*

Review of clinical effectiveness (see Chapter 3)
Previous economic analyses of chemotherapy[8,155]
Sponsor submissions to NICE[20,143]
Studies identified through the review of cost-effectiveness
Studies identified through searches undertaken to inform the model
Reference sources (e.g. BNF,[40] NHS Reference Costs[153])
Expert opinion

TABLE 17 *Chemotherapy regimens included in economic assessment*

Regimen	Cycle length (weeks)	Number of cycles (per protocol)	Total protocol dose per cycle
Oxaliplatin in combination with 5-FU/LV	2	12	800 mg/m^2 bolus 5-FU 1200 mg/m^2 infusional 5-FU 400 mg/m^2 leucovorin 85 mg/m^2 oxaliplatin
Capecitabine	3	8	35,000 mg/m^2 capecitabine
5-FU/LV (de Gramont regimen)	2	12	800 mg/m^2 bolus 5-FU 1200 mg/m^2 infusional 5-FU 400 mg/m^2 leucovorin
5-FU/LV (Mayo clinic regimen)	4	6	2,125 mg/m^2 bolus 5-FU 100 mg/m^2 leucovorin

Interventions included in economic assessment

Four adjuvant chemotherapy regimens were considered within the economic evaluation:

1. oxaliplatin in combination with an infusional 5-FU/LV regimen (FOLFOX4)
2. capecitabine monotherapy
3. 5-FU/LV monotherapy (the de Gramont or LV5FU2 infusional regimen)
4. 5-FU/LV monotherapy (Mayo Clinic bolus regimen).

Two 5-FU/LV regimens are included in the model, as the MOSAIC trial used a de Gramont regimen whereas the X-ACT study used the Mayo Clinic regimen. *Table 17* summarises the dosing regimens for each of these treatment strategies.

The incremental cost-effectiveness of oxaliplatin in combination with 5-FU/LV was compared against that of the de Gramont 5-FU/LV regimen, and that of capecitabine was compared against the Mayo Clinic 5-FU/LV regimen. Indirect comparisons were also made between FOLFOX4 and the Mayo 5-FU/LV regimen and between FOLFOX4 and capecitabine. No trials have yet made the latter comparison, hence the result should be interpreted with caution.

Economic methodology

Model structure

The economic model uses a time-dependent state transition approach to estimate disease outcomes for a cohort of patients on each treatment regimen. The state transition methodology is particularly useful for modelling diseases or conditions, whereby risk is ongoing over time, where events may occur more than once and where the timing of events is important. The Markov model used has three states:

- alive without relapse (including patients on adjuvant treatment and those in remission following completion of treatment)
- alive with relapse (receiving palliative chemotherapy)
- dead.

Time-dependent transitions are assumed to occur at 4-week intervals in order to capture the relapses and deaths seen within the 24-week trial period, with transition probabilities estimated from the fitted disease-free and overall survival curves. The first state described above comprises patients on adjuvant treatment in the first 24 weeks of the model, after which they transit either to the relapse or the death state. It is assumed that patients with relapsing disease cannot transit back into the 'alive without relapse' state, and their survival probability thereafter is modelled using the survivor functions fitted to data from the advanced colorectal cancer trials (a very small proportion of patients with relapsing disease may return to the 'alive without relapse' state following further treatment, and any effect of this is taken into account through the modelling of survival for patients with advanced disease using data from advanced cancer trials). Given the assumption that patients do not relapse beyond 5 years post-surgery, the probability of transiting between the 'alive without relapse' and 'alive with relapse' states is set to zero beyond 5 years.

Methods for estimating overall survival and disease-free survival benefits

Kaplan–Meier survival curves from the MOSAIC and X-ACT studies were obtained, giving information on empirical overall survival and disease-free survival. Data from the NSABP C-07 trial[46,60] were not incorporated within the economic analysis as separate analyses for patients with Stage II and III disease were not reported.

All curves were digitally scanned using TECHDIG™ software, which is designed to replicate published survival curves. Data from these scanned curves were then imported into Microsoft Excel. Owing to the large proportion of patients in both studies who were still alive at the end of the studies, parametric survival curves were fitted to the empirical Kaplan–Meier data using Weibull regression techniques to estimate the expected survival duration in all patients enrolled within the clinical trials.

Transition probabilities were estimated from the disease-free survival curve and the partitioned overall survival estimates for patients with and without relapse. The probabilities of transiting between the 'alive without relapse' and 'alive with relapse' states (i.e. the probability of relapsing) were then estimated as follows:

$$p(\text{relapse}) = 1 - [p(\text{death due to causes other than colon cancer}) + p(\text{remaining alive without relapse})]$$

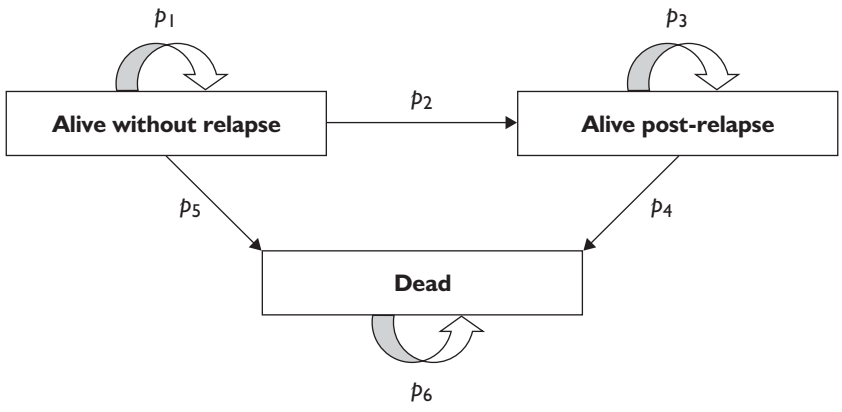
The time-dependent transition probabilities were used to predict the number of patients in each of the three states described above at each 4-week interval, for a period of 50 years following randomisation to adjuvant chemotherapy and for each of the four treatment options. This joint modelling of disease-free and overall survival differs from the approach adopted in the Roche submission model,[20] in which the independent modelling of these two outcomes resulted in counterintuitive survival curves [see the section 'Evidence from industry submissions', (p. 44)]. A schematic of the Assessment Group model is given in *Figure 3*.

Disease-free survival estimation

The model assumes that all relapses occur during the 5 years following resection of the primary tumour; this assumption is supported by empirical evidence.[45,149] In order to represent the uncertainty in disease-free survival, a number of survival functions were fitted to data from the comparator arms in the two trials, including Weibull and Gompertz models. The analysis indicated that Weibull functions fitted the empirical data more closely than the Gompertz models, hence the Weibull functions were used within the economic model. The process of fitting Weibull functions involves the use of linear regression methods, which are described below.

The Weibull survivor function, $S(t)$, is given by

$$S(t) = \exp(-\lambda t^{\gamma})$$



p_1 and p_5 are estimated from the fitted Gompertz function [estimated from life-table data[156] – see section 'Overall survival estimation' (p. 51)]
p_2 is estimated from the fitted DFS curves for the MOSAIC[45] and X-ACT[109] trials (see the section 'Disease-free survival estimation' (above)]
p_3 and p_4 are estimated from fitted Weibull function of survival following relapse, using data from the Fluorouracil, Oxaliplatin and Irinotecan: Use and Sequencing (FOCUS)[157] and Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR)[158] studies
$p_6 = 1$

FIGURE 3 *Schematic of patient pathways in economic model*

where λ = scale parameter, t = time and γ = shape parameter. Transforming the survivor function $S(t)$ gives the linear relationship

$$\ln[-\ln S(t)] = \ln\lambda + \gamma \ln t$$

where $\ln t$ is the independent variable and $\ln[-\ln(S(t)]$ is the dependent variable.

This transformation applied to the Kaplan–Meier survival estimates results in an approximately straight line whereby $\ln[-\ln S(t)] = y$, $\ln\lambda$ = intercept, γ = gradient and $\ln t = x$. A summary of the results of the Weibull regression analyses is given in Appendix 14.

The fitted Weibull survival functions for the control arms within the X-ACT and MOSAIC trials were then extrapolated up to 5 years post-randomisation to allow comparison with the empirical survival. These Weibull functions were fitted using the entire disease-free survival curve, as opposed to the approach adopted in the Sanofi-Aventis submission, in which the empirical survival data were up to 48 months, beyond which an extrapolated curve was estimated from the empirical data between 36 and 48 months. Disease-free survival over the 5-year period in the capecitabine and FOLFOX4 treatment arms was estimated by applying published hazard ratios (see Chapter 3) to represent the differences in disease-free survival between the treatment and comparator arms. Plots of the fitted disease-free survival curves are presented in Appendix 14. Uncertainty in the disease-free survival estimates was introduced in two ways. First, the CIs around each hazard ratio were used to derive normal distributions, from which samples could be drawn to reflect the uncertainty in the hazard ratio. Normal distributions were considered appropriate because of the symmetrical nature of the CIs around the mean hazard ratio in each case. Further uncertainty was introduced through sampling the parameters of the fitted Weibull functions using a multivariate normal distribution, which samples the two parameters (the shape parameter, γ, and the scale parameter, λ) from a joint distribution, to take into account their correlation. This distribution uses random numbers and the variance–covariance matrix of the two parameters, which can be estimated directly from the regression output.

The disease-free survival curves do not directly represent the probability of being relapse free at a given point in time, but the probability of **being alive and not having relapsed**. Therefore, the hazard of relapsing or dying for patients without relapse could be estimated directly from the disease-free survival curves, the inverse of which is simply the probability of remaining alive and disease-free at each point in time.

Overall survival estimation

The likely long-term survival of patients alive at 5 years post-randomisation is not clear. Searches were undertaken to try to identify studies of the longer term survival of patients receiving chemotherapy or undergoing resection (see Appendix 13). The searches confirmed a dearth of evidence relating to the long-term survival of patients with Stage III colon cancer, with studies reporting a wide range of estimates of overall survival at 10 years, with values of 24,[159] 39,[160] 59,[161] 45[162] and 55%.[149] It is not possible to determine whether these differences are due to patient characteristics (e.g. age), surgical expertise or the effect of adjuvant chemotherapy. It is also important to bear in mind that a proportion of the patients alive after 5 years will have relapsed, therefore the survival of the entire cohort of patients at this point in time is subject to greater uncertainty.

Overall survival estimates reported within the trials (up to 5 years) include those patients who have relapsed and died within the 5-year period. Given the assumption that no patients will relapse beyond this time, it is unlikely that patients who are alive will continue to die at the rate observed within the first 5 years. This trend, however, may continue for a short time since some patients with relapsing disease will still be alive at 5 years post-randomisation. For this reason, the overall survivals of patients who relapse and those who do not relapse were treated as separate cohorts within the analysis.

Overall survival of patients who relapse

Patients who relapse are assumed to do so within 5 years of randomisation to adjuvant therapy; such patients are assumed to relapse with advanced colorectal cancer. It is assumed that these patients have a similar life expectancy to those patients who are initially diagnosed with advanced colorectal cancer (i.e. people who have not previously been treated for Dukes' C colon cancer). A number of options exist for treatment of advanced colorectal cancer, including the sequences of therapies used in the Fluorouracil, Oxaliplatin and Irinotecan: Use and Sequencing (FOCUS)[157] (G Griffiths, MRC Clinical Trials Unit, London: personal communication, 2005 and Professor A de Gramont, Hôpital Saint Antoine, Paris: personal

TABLE 18 *Treatment plans for patients with relapsing disease*

Treatment plan	First-line treatment	Second-line treatment
FOCUS Plan A	5-FU/LV (modified de Gramont)	Single-agent irinotecan
FOCUS Plan B	5-FU/LV (modified de Gramont)	Irinotecan in combination with 5-FU/LV (modified de Gramont)
FOCUS Plan C	Irinotecan in combination with 5-FU/LV (modified de Gramont)	–
FOCUS Plan D	5-FU/LV (modified de Gramont)	Oxaliplatin in combination with 5-FU/LV (modified de Gramont)
FOCUS Plan E	Oxaliplatin in combination with 5-FU/LV (modified de Gramont)	–
GERCOR (1)	Oxaliplatin in combination with 5-FU/LV (FOLFOX6)	Irinotecan in combination with 5-FU/LV (FOLFIRI)
GERCOR (2)	Irinotecan in combination with 5-FU/LV (FOLFIRI)	Oxaliplatin in combination with 5-FU/LV (FOLFOX6)

communication, 2005) and Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR)[158] studies. Owing to confounding of effectiveness estimates within the majority of advanced cancer chemotherapy trials due to unplanned (and unrecorded) second-line therapies, together with the paucity of comprehensive resource use estimates, the FOCUS and GERCOR trials were used to describe the costs and health outcomes associated with patients who relapse. *Table 18* summarises these treatment options.

The choice of chemotherapy treatment for these patients depends on a number of factors. Patients who have received FOLFOX4 as adjuvant chemotherapy would be unlikely to receive oxaliplatin again if they relapsed within 1 year; however, beyond that, it may be considered as a viable treatment option (Dr M Saunders, Christie Hospital, Manchester: personal communication, 2005). The age of a patient at the time of relapse affects subsequent treatment administration, since the more elderly patients are the subgroup of patients least able to tolerate the toxicities associated with combination therapies and therefore are more likely to receive 5-FU/LV as first-line therapy. Patient preference also plays a role in the treatment of relapsing colorectal cancer; for example, female patients are more likely to demonstrate a preference for oxaliplatin-based therapies, since irinotecan is associated with alopecia (Dr M Saunders, Christie Hospital, Manchester: personal communication, 2005). Both the FOCUS and GERCOR studies specifically excluded any patients previously exposed to oxaliplatin or irinotecan, but despite this, these data represent the most suitable data for modelling post-relapse survival.

At the time of writing, NICE had not updated its official guidance relating to the use of oxaliplatin, irinotecan and raltitrexed in the treatment of advanced colorectal cancer. The base-case analysis assumes that patients will receive first-line 5-FU/LV, followed upon disease progression by single-agent irinotecan; this is in line with guidance issued by NICE in 2002.[10]

Weibull survival functions were fitted to the empirical survival data collected within the FOCUS and GERCOR trials, and were extrapolated beyond the duration of the clinical trials. The results of the Weibull regression analysis are presented in Appendix 15.

Overall survival of patients who do not relapse

Throughout the entire 50-year time horizon, the overall survival of patients without relapse is assumed to be equivalent to a broadly age-matched population of people without previous colorectal cancer.[163,164] The probability of death from any cause other than colon cancer (i.e. the probability of death for patients who do not relapse) was estimated using life-tables.[156] The mean age of patients in each treatment arm at the start of the two trials was used to fit a Gompertz survival function for the patients in each treatment group using regression methods. For example, the mean age at baseline of patients in the capecitabine arm of the X-ACT study was 60 years. A Gompertz survival function was fitted to the life expectancy of people of this age in the general population, using the death hazard rates given in the life-tables. The Gompertz survivor function takes the form

$$S(t) = b_1 e^{-e^{-b_2*(t-b_3)}}$$

where b_1, b_2 and b_3 are the parameters of the Gompertz and t = time.

This process was repeated for the three other treatment arms in turn, using the mean age at baseline of the patients in each arm. The mean ages of patients in the X-ACT study were 60.4 and 61.0 years in the capecitabine and 5-FU/LV arms, respectively,[20] whereas in the MOSAIC trial, the mean age in both treatment groups was 58.8 years.[143] The fitted survival functions were then extrapolated to a time horizon of 50 years.

The probability of mean overall survival was then calculated by summing the probabilities of being alive (without relapse) and alive (with relapse) at each point in time, which was used to generate an overall survival curve. The fitted overall survival curves are given in Appendix 16.

Calculation of disease-free and overall survival
Mean disease-free and overall survival were estimated using the AUC method, based on the extrapolated Weibull functions.

Model assumptions

The model employs a number of simplifying assumptions, which are detailed below.

- The survival of patients who relapse is assumed to be independent of the time of relapse. This is unlikely to be true as patients who relapse shortly after surgery have a worse prognosis than those who relapse later. However, without patient-level data, this assumption is inevitable. Given that a large proportion of patients relapse within 2 years of surgery, survival for patients may be slightly overestimated.
- The survival of patients with relapse is equivalent to that of patients who are initially diagnosed with Stage IV disease (i.e. patients who have not previously received adjuvant chemotherapy for Stage III disease).
- All relapses occur within 5 years following resection of the primary tumour. Clinical evidence[149] from long-term follow-up of patients undergoing adjuvant chemotherapy supports this assumption.
- Patients with relapsing disease are assumed to receive first-line 5-FU/LV followed upon progression by single-agent irinotecan. This assumption is based upon existing NICE guidance for patients with advanced colorectal cancer.[10]
- Patients receiving 5-FU/LV via the de Gramont regimen are assumed to receive their treatment on an outpatient basis, as this was the administration schedule used in the MOSAIC trial.

Cost analysis

The cost analysis was conducted from the perspective of the NHS, and incorporated costs incurred during the trial period, during post-treatment follow-up and following relapse. Costs incurred during the 6-month trial period included costs of drug acquisition and administration, treatment of adverse events and toxicities (including hospitalisations), routine hospital tests and primary care costs. Beyond the end of the trial period, patients were assumed to follow a standard follow-up protocol, with 5 years of hospital visits, scans and colonoscopies. Patients who relapse with advanced colorectal cancer are assumed to receive first-line palliative chemotherapy, followed upon progression by second-line chemotherapy. Cost estimates have been taken from a variety of published and unpublished sources (see Appendix 13), and have been uplifted to current prices using Hospital and Community Health Services (HCHS) Inflation Indices.[165]

Drug acquisition costs were obtained from the BNF,[40] with total costs over the adjuvant treatment period estimated by multiplying these costs by the recommended dose, the mean number of cycles and using a mean body size of 1.75 m^2. *Table 19* shows the acquisition costs in terms of cost per milligram.

TABLE 19 *Drug acquisition costs*[40]

Drug	Description of product	mg per vial/pack	Cost per vial/pack (£)	Cost per mg (£)
Fluorouracil	As sodium salt	5,000	64	0.0128
Leucovorin (folinic acid)	As calcium salt – powder for reconstitution	30	8.36	0.279
Oxaliplatin	Powder for reconstitution	100	330	3.30
Capecitabine	Tablets	60,000	295.06	0.00492
Irinotecan (relapsing patients only)	Concentrate for intravenous infusion	100	130	1.30

TABLE 20 *Drug administration costs*

Appointment type	Cost per appointment (£)	Reference
Line insertion (one-off cost for i.v. 5-FU/LV and FOLFOX4)	451	Boland *et al.*, 2003[166]
Outpatient attendance for check-up (all treatment regimens)	59	NHS Reference Costs TOPWA 370[153]
Outpatient attendance for drug administration (bolus 5-FU/LV)	118	NHS Reference Costs TDCWA 370[153]
Day-case attendance for drug administration (i.v. 5-FU/LV, FOLFOX4)	170	NHS Reference Costs TRDNA F98[153]
Medical oncology inpatient	373	Netten *et al.*, 1999[167]

TABLE 21 *Per-cycle costs of pumps and sundries*[a]

Treatment	Pump costs per cycle	Sundry costs per cycle
Adjuvant treatment		
Bolus 5-FU/LV	–	£32.40
FOLFOX4 (7 pumps per cycle)	£105	£12
i.v. 5-FU/LV (6 pumps per cycle)	£90	£12
Treatment of relapsing disease		
5-FU/LV (modified de Gramont regimen) (3 pumps per cycle)	£65	£12
Irinotecan + MdG (outpatient) (3 pumps per cycle)	£65	£12
Oxaliplatin + MdG (outpatient) (3 pumps per cycle)	£65	£12

[a] Michelle Rowe, Christie Hospital, Manchester: personal communication, 2005.

Drug administration is more complex, and there is considerable variation in UK practice regarding drug administration protocols, given the number of possible treatment regimens available. Regardless of the treatment being prescribed, it is assumed within the model that all patients require one routine outpatient appointment per treatment cycle, to enable clinicians to monitor their progress. Patients receiving bolus 5-FU/LV are assumed to require five further outpatient appointments per cycle at which they receive their chemotherapy. Those patients being treated with either FOLFOX4 or intravenous 5-FU/LV (de Gramont regimen) require an appointment for the insertion of an intravenous line at the start of their treatment, in addition to two day-case appointments per cycle for treatment administration. Patients receiving palliative chemotherapy on an inpatient basis [see the section 'Application of costs to survival estimates (p. 56)] are assigned the cost of an inpatient stay. The costs used for these appointments are given in *Table 20*.

In addition to these direct drug administration charges there are the pump costs for infusional regimens, and the costs of sundries associated with certain treatment regimens; these are given in *Table 21*.

Evidence suggests that pharmacy costs vary between treatment arms, given the differences in drug preparation time.[92] Per-cycle pharmacy costs for each treatment regimen have therefore been included in the economic analysis, as shown in *Table 22*.

All patients are assumed to receive regular diagnostic tests throughout the duration of the adjuvant treatment period for disease monitoring purposes. It is assumed within the economic analysis that each patient requires one blood test and one CEA test per treatment cycle, in addition to two computed tomography (CT) scans (one at the start of the adjuvant treatment phase and one upon completion of treatment; Dr D Radstone, Weston Park Hospital, Sheffield: personal communication, 2005) and one ultrasound scan. The costs of these tests are given in *Table 23*.

The costs associated with adverse events and treatment-related toxicities were addressed in two ways. Resource use data regarding the number of

TABLE 22 *Pharmacy costs per cycle*

Treatment	Pharmacy cost per cycle (£)	Reference
Adjuvant treatment		
Capecitabine	12	Michelle Rowe, Christie Hospital, Manchester: personal communication, 2005
Bolus 5-FU/LV	46	
FOLFOX4	266	
i.v. 5-FU/LV	228	
Treatment of relapsing disease		
5-FU/LV (modified de Gramont regimen)	114	Michelle Rowe, Christie Hospital, Manchester: personal communication, 2005
Irinotecan	23	
Irinotecan + MdG (outpatient)	152	
Oxaliplatin + MdG (outpatient)	152	
Irinotecan + MdG (inpatient)	138	
Oxaliplatin + MdG (inpatient)	138	

TABLE 23 *Costs of routine tests during adjuvant treatment period*

Test/diagnostic procedure	Cost (£)	Reference
CEA test	9.30	Renehan *et al*., 2004[168]
Full blood test	9.30	Renehan *et al*., 2004[168]
CT scan	185	Follow-up after colorectal surgery (FACS) trial protocol[169]
Ultrasound scan	35	Follow-up after colorectal surgery (FACS) trial protocol[169]

TABLE 24 *Costs of adverse events requiring treatment*

Adverse event	Treatment	Cost per cycle (£)	Reference
Nausea grade 3+	Cyclizine, 50 mg per day for 5 days. Domperidone suppositories, 1 per day for 5 days	1.64	Sanofi-Aventis submission[143]
Neutropenia grade 3+	1 hospital consultation (medical oncology)	118.23	Sanofi-Aventis submission[143]
Neuropathy grade 3+	1 hospital consultation (medical oncology)	118.23[a]	Sanofi-Aventis submission[143]
Diarrhoea grade 3+	Loperamide hydrochloride, 2 mg per day for 12 days	0.49	Sanofi-Aventis submission[143]

[a] One-off cost during entire treatment period, rather than cost per cycle.

hospitalisations and mean length of stay in the X-ACT study[39] were used to estimate the total costs of hospitalisation. Equivalent data were not available in the submission by Sanofi-Aventis,[143] which presented the number of serious adverse events observed during the trial period. However, some of these events would not require hospitalisation and, since no data were presented regarding mean length of stay following hospitalisation, the mean number of hospitalisations and the mean length of stay observed in the 5-FU/LV (Mayo Clinic regimen) and capecitabine arms of the X-ACT study were assumed to apply to both treatment arms of the MOSAIC trial. The duration of each hospitalisation was multiplied by the cost per day of a medical oncology inpatient attendance (assumed to be £373 per day).[167]

A wide range of adverse events were reported in both the X-ACT and MOSAIC studies. A small number of these adverse events were assumed to require treatment (though not hospitalisation), which are shown in *Table 24*, along with the treatment assumed to be administered for each event and the cost.

TABLE 25 *Follow-up plan and costs*

Year	No. of outpatient appointments (£59.10 per appointment)[169]	No. of ultrasound scans (£35 per scan)[169]	No. of CT scans (£185 per scan)[169]	No. of colonoscopies (£175 per colonoscopy)[169]
1	4	1	1	0
2	4	1	1	0
3	1	0	0	0
4	1	0	0	0
5	1	0	0	1

TABLE 26 *Breakdown of costs of relapse*

Cost component	FOCUS Plan A	FOCUS Plan B	FOCUS Plan C	FOCUS Plan D	FOCUS Plan E	GERCOR (1)	GERCOR (2)
Drug acquisition	[**Confidential information removed**]						
Drug administration	[**Confidential information removed**]						
Pharmacy costs	[**Confidential information removed**]						
Tests (blood and CEA)	[**Confidential information removed**]						
Line insertion	[**Confidential information removed**]						
Total	[**Confidential information removed**]						

FOCUS Plan A: first-line 5-FU/LV, second-line irinotecan.
FOCUS Plan B: first-line 5-FU/LV, second-line irinotecan in combination with 5-FU/LV.
FOCUS Plan C: first-line irinotecan in combination with 5-FU/LV.
FOCUS Plan D: first-line 5-FU/LV, second-line oxaliplatin in combination with 5-FU/LV.
FOCUS Plan E: first-line oxaliplatin in combination with 5-FU/LV.
GERCOR (1): first-line FOLFOX6, second-line FOLFIRI.
GERCOR (2): first-line FOLFIRI, second-line FOLFOX6.

Adverse event data from the two trials[45,109] were multiplied by the above costs to generate total costs of hospitalisation and treatment of adverse events.

Costs of long-term follow-up may be expected to be unrelated to the adjuvant treatment received; however, the differences in disease-free and overall survival demonstrated within the X-ACT and MOSAIC trials mean that assuming equivalence between treatment arms would be biased. Follow-up is assumed to last for 5 years post-treatment (in the absence of relapse), and constitutes regular outpatient attendances, CT and ultrasound scans and colonoscopies. *Table 25* summarises the follow-up plan applied in the economic analysis, along with the associated costs of each component.

Patients who relapse are assigned a one-off cost within the model, which is assumed to be incurred at the time of relapse. In the base-case analysis (whereby patients with relapse receive first-line 5-FU/LV followed upon disease progression by single-agent irinotecan), the total cost of relapse (regardless of the chemotherapy received in the adjuvant setting) is estimated to be [**Confidential information removed**]. *Table 26* presents a breakdown of this cost, along with the total costs of relapse when alternative palliative treatment options are considered. This ensures the use of the best available economic evidence regarding chemotherapies for advanced colorectal cancer.

Application of costs to survival estimates

The total costs associated with each treatment arm over the 50-year time horizon were derived using the state populations estimated from the fitted survival functions, trial data relating to the number of cycles of treatment received and the relative dose intensities administered in each treatment arm (*Table 27*). This approach ensures that the costs are weighted by the probabilities of survival and relapse at each point in time. For example, patients who die 2 years post-treatment do not incur the follow-up costs for years three, four and five.

The total costs of relapse are assumed to apply in the period in which relapse occurs: in the base-case analysis, it is assumed that all patients who

TABLE 27 *Mean number of treatment cycles received and relative dose intensities observed in the MOSAIC and X-ACT studies*

Treatment	Component	Mean relative dose intensity (%)	Mean number of treatment cycles (standard error)
5-FU/LV (Mayo regimen)	5-FU LV	87.3 91.0	5.6 (0.04)
Capecitabine	Capecitabine	86.2	7.35 (0.06)
5-FU/LV (de Gramont regimen)	5-FU LV	95.0 88.0	11.26 (0.07)
FOLFOX4	5-FU LV Oxaliplatin	83.4 80.2 77.2	10.68 (0.08)

TABLE 28 *Proportion of patients with advanced disease treated as inpatients/outpatients*

Treatment	Proportion of patients treated as inpatients (%)	Proportion of patients treated as outpatients (%)	Reference
5-FU/LV (modified de Gramont)	21	79	Aventis submission to NICE[171]
FOLFOX6	25	75	
FOLFIRI	7	93	
Irinotecan	17	83	

relapse receive first-line 5-FU/LV, followed upon progression by single-agent irinotecan. Given the likely variation in administration protocols for the various treatment options for advanced colorectal cancer, data from the Aventis submission to NICE for the appraisal of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer[8] were used to formulate assumptions regarding the proportion of patients who are treated as inpatients and as outpatients. These estimates were checked against Hospital Episode Statistics data, which give similar proportions for patients receiving chemotherapy on an inpatient/outpatient basis.[170] The Aventis data are given, by treatment plan, in *Table 28*.

These proportions were applied to the palliative treatment options in the model, to reflect the differences in treatment administration both between individual treatments and between adjuvant and palliative chemotherapy.

Methods for estimating quality-adjusted survival benefits

In order to derive estimates of QALYs for each treatment plan, the survival benefits seen within the trials need to be weighted by patients' QoL over that period. The most common method of deriving QALY estimates is by assigning health utilities to the various health states in which patients could be. *Table 29* gives a summary of utility estimates associated with different states of health in patients with colorectal cancer available within the literature.

Utilities for four states are used in the economic model:

- utility whilst on adjuvant chemotherapy (with no serious side-effects)
- utility whilst on adjuvant chemotherapy (with serious side-effects)
- utility whilst in remission (post-adjuvant treatment)
- utility whilst on palliative chemotherapy.

QoL data were not routinely collected within the MOSAIC trial, whereas in the X-ACT study, the EORTC QLQ C-30 (a cancer-specific QoL instrument) was used to monitor patients' QoL for the duration of the adjuvant treatment period. The results show very little difference between the 5-FU/LV and capecitabine arms, with QoL relatively constant over the 25 weeks. However, since the results of the EORTC QLQ C-30 cannot easily be translated into index utilities, a search of literature relating to QoL in patients with colon cancer was carried out, to determine appropriate utilities for the states given above (see Appendix 13).

Utility estimates for patients on adjuvant treatment were taken from a study by Ness and colleagues.[174]

TABLE 29 *Utility estimates for patients with Dukes' Stage III colon cancer*

Study	Time period	Reported utility	Standard error	Sample size
Ramsey *et al.*, 2000[150]	13–24 months post-diagnosis	0.82	0.15	–
	25–36 months post-diagnosis	0.95	–	1
	37–60 months post-diagnosis	0.79	0.25	–
	>60 months post-diagnosis	0.92	0.05	–
Smith *et al.*, 1993[172]	Chemotherapy with no recurrence	0.88	–	–
	Chemotherapy with recurrence	0.88	–	–
Norum *et al.*, 1997[173]	No relapse	0.83	–	–
Ness *et al.*, 1999[174]	Chemotherapy without significant side-effects	0.7	0.036	40
	Chemotherapy with significant side-effects	0.63	0.036	41
Ramsey *et al.*, 2002[175]	Stage at diagnosis	0.87	0.08	29

TABLE 30 *Utility parameters used in the economic model*

Health state	Utility	Standard error	Reference
On adjuvant chemotherapy (without significant side-effects)	0.70	0.036	Ness *et al.*, 1999[174]
On adjuvant chemotherapy (with significant side-effects)	0.63	0.036	Ness *et al.*, 1999[174]
In remission	0.92	0.05	Ramsey *et al.*, 2000[150]
On palliative chemotherapy	0.24	0.041	Ness *et al.*, 1999[174]

This study used a standard gamble approach to elicit utilities from 81 patients with colorectal cancer [Stage I–IV (Dukes' A–D)] who had previously undergone resection for colorectal cancer. The results report utilities for all stages, including those of patients with Stage III disease undergoing resection and chemotherapy, which is broken down into two separate utilities for patients who experienced significant side-effects and those who did not. These two utilities were 0.63 and 0.70 for patients with and without significant side-effects, respectively, reflecting a degree of utility loss associated with treatment-related adverse events.

Ramsey and colleagues[150] conducted a study of 173 patients with colorectal cancer, 40 of whom had Stage III disease. Generic and cancer-specific QoL tools were administered at regular intervals following diagnosis, starting at 13 months post-diagnosis. The study is therefore not useful in assessing utilities whilst on adjuvant treatment; however, beyond 60 months, after which patients are assumed to no longer be at risk of relapse, the mean utility reported is 0.92. This has been used as a proxy utility for patients in remission following adjuvant chemotherapy.

A single utility score is applied to patients who relapse for their entire survival period following relapse, using data from the study by Ness and colleagues,[174] which gave a mean utility of 0.24. The utility estimates used within the economic model are summarised in *Table 30*.

The state populations at each point in time (derived from the Markov modelling) were then multiplied by the above utilities to give estimates of QALYs for each treatment regimen over the 50-year period. The standard errors associated with each utility estimate were used to derive normal distributions, from which sampled utilities were drawn within the probabilistic sensitivity analysis.

Discounting

The economic analysis assumes that costs and QALYs are discounted at 6 and 1.5% per annum, respectively. Although current recommendations from the UK Treasury suggest the use of 3.5% for both costs and QALYs (as does the NICE Reference Case), these will not be fully implemented until the 11th Wave of NICE technology appraisals. The base-case analysis therefore uses 6% for costs and 1.5% for QALYs, with 3.5% used within the sensitivity analyses.

One-way sensitivity analysis

In order to explore the impact upon the cost-effectiveness results of changes to individual

parameters and assumptions, a number of scenario analyses were performed.

Although the current NICE Guidelines for patients with advanced colorectal cancer recommend the use of first-line 5-FU/LV, followed upon disease progression by single-agent irinotecan,[10] this is subject to change in the light of the updated appraisal of the clinical and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for advanced colorectal cancer.[8] A number of scenario analyses were therefore undertaken to explore the impact of alternative treatment options for patients with relapsing disease upon the cost-effectiveness results. In addition, a sensitivity analysis was performed in which both costs and QALYs were discounted at 3.5% per annum.

One of the key assumptions within the economic model is that no patient relapses beyond 5 years post-randomisation. In order to test the validity of this assumption, sensitivity analyses were conducted whereby the fitted disease-free survival curves were extrapolated up to 7.5 and 10 years, generating revised cost-effectiveness results.

Probabilistic sensitivity analysis

Deterministic economic modelling assumes that all parameter values are known with certainty; however, many of the parameters described above are subject to some degree of uncertainty. Although this can be explored to a limited extent with one-way sensitivity analysis, this approach does not capture the impact of the joint uncertainty in all model parameters on the cost-effectiveness results. As uncertainty within health economic models is ubiquitous, all model parameters should ideally be described by uncertain distributions. Probabilistic sensitivity analysis was undertaken in order to generate information on the likelihood that each of the interventions is optimal.

The baseline overall survival and disease-free survival curves within the model were described by multivariate normal distributions of the form $X \sim N(m, V)$, where m is the vector of means (the scale and shape parameters of the baseline Weibull survivor function) and V is the covariance matrix of these means. As the standard errors for the hazard ratios between treatments (for both disease-free and overall survival) were symmetrical, these were sampled from normal distributions.

Standard errors surrounding the mean number of adjuvant treatment cycles were used to derive normal distributions, along with distributions for the mean number of cycles of palliative treatment observed within the FOCUS[157] (G Griffiths, MRC Clinical Trials Unit, London: personal communication, 2005 and with Professor A de Gramont, Hôpital Saint Antoine, Paris: personal communication, 2005) and GERCOR[158] trials. As chemotherapy acquisition costs and other administration costs are estimated on a cyclical basis, sample variation in the mean number of cycles received results in 'knock-on' variation in the total costs of both drug acquisition and administration. The proportion of patients who receive palliative chemotherapy as inpatients was described by a beta distribution of the form $X \sim Be(a, b)$, where a is the number of events and b is the sample size, using all data from the four treatment groups described in *Table 28*.

Normal distributions were also used to represent the uncertainty in the four utility estimates applied within the model, based on the standard errors reported in the two QoL studies used.[150,174]

Given the variability in published estimates for all cost parameters used within the economic model, uncertainty in these parameters was introduced through the use of triangular distributions, which represents both the uncertainty in the true values and the appropriate functional form of these costs. This was introduced into the model by assuming that each cost parameter could range between 50 and 150% of its deterministic estimate, with each parameter being sampled using random numbers.

The probabilistic analysis was carried out by allowing all of the above parameters to vary according to the uncertainty specified in their probability distributions, with 10,000 sets of random numbers used to generate 10,000 sets of cost-effectiveness results. These results were then used to derive cost-effectiveness planes and CEACs for each direct treatment comparison.

Indirect comparisons

In the absence of an RCT which directly compares capecitabine with FOLFOX4 in the adjuvant setting, an economic comparison of the two interventions is problematic and subject to bias. Nevertheless, this comparison was made indirectly using data from the MOSAIC and X-ACT studies and the associated cost analysis, in an attempt to generate a broad estimate of cost-effectiveness for this comparison. Given that the de Gramont 5-FU/LV regimen is not a standard treatment schedule in the adjuvant setting, an additional indirect economic comparison was made, to estimate the incremental cost-effectiveness of FOLFOX4 versus the Mayo 5-FU/LV regimen.

This comparison, although subject to bias, is considered worthwhile on the basis that it assesses the cost-effectiveness of FOLFOX4 against a more relevant comparator.

Budget impact

The total annual cost to the NHS was estimated using the treatment cost estimates from the adjuvant phase for each intervention. This included drug acquisition and administration costs, pharmacy costs, adverse event management and hospitalisation costs and the costs of diagnostic tests during the adjuvant treatment phase (e.g. CT scans). Value added tax (VAT) was added to the drug acquisition costs for the purposes of the budget impact analysis.

Results of economic assessment

This section details the results of the health economic model. The cost-effectiveness results for capecitabine and FOLFOX4 are presented as marginal estimates when compared against the two 5-FU/LV regimens (Mayo Clinic and de Gramont, respectively). All results are presented in terms of marginal cost per life-year gained (LYG) and cost per QALY gained. The results presented relate only to overall survival; no cost-effectiveness analysis has been undertaken for disease-free survival. The results are reported in four sections. The next section presents the overall survival analysis results as estimated using AUC analysis of the fitted survival functions. The following section reports the central estimates of cost-effectiveness under the base-case assumptions. The subsequent section reports the results of a number of one-way sensitivity analyses, with the results of the probabilistic sensitivity analysis presented in the final section.

Estimated overall survival benefits

Table 31 shows the results of the AUC analysis of discounted and undiscounted mean LYGs and QALYs, as calculated from the long-term fitted survival functions for each of the two comparisons. In the base case, palliative treatment was assumed to be first-line 5-FU/LV, followed upon progression by single-agent irinotecan.

The results suggest that both capecitabine and FOLFOX4 are beneficial compared with their respective 5-FU/LV arms, both in terms of LYGs and QALYs gained. These improvements are primarily due to the lower relapse rates observed in the two trials, ensuring that, on average, patients on capecitabine or FOLFOX4 live for longer than those treated with 5-FU/LV. The QALY gain of capecitabine compared with the Mayo 5-FU/LV regimen is higher than that reported in the Roche submission.[20] This discrepancy is attributable to the different survival methodologies used in the Roche submission and the Assessment Group model.

The results demonstrate that the application of utilities to the LYG data has little impact, since the life expectancy of patients who relapse is less than 2 years, so the difference in QALYs between these patients and those who do not relapse over that period is relatively small.

Central estimates of cost-effectiveness for overall survival period

This section reports central estimates of cost-effectiveness under the base-case model assumptions. *Table 32* reports the deterministic results for the overall survival period, in terms of cost per LYG.

The total cost savings made through the use of capecitabine in comparison with the Mayo 5-FU/LV regimen (£3320) are slightly less than those reported in the Roche submission.[20] This is primarily due to the differences between the two models in the costs associated with relapse. The Roche submission assumes a higher cost of relapse than the Assessment Group model, and because

TABLE 31 *Discounted LYGs and QALYs estimated from fitted survival functions (overall survival)*

Adjuvant treatment	Mean undiscounted LYGs	Mean discounted LYGs	Mean undiscounted QALYs	Mean discounted QALYs
5-FU/LV (Mayo Clinic regimen)	11.46	9.87	9.91	8.47
Capecitabine	12.75	10.88	11.15	9.45
Marginal benefit (capecitabine versus Mayo)	1.30	1.02	1.24	0.98
5-FU/LV (de Gramont)	12.60	10.80	11.02	9.39
FOLFOX4	14.27	12.15	12.64	10.71
Marginal benefit (FOLFOX4 versus de Gramont)	1.66	1.36	1.61	1.33

TABLE 32 *Central estimates of cost per LYG*

Adjuvant treatment	Mean survival (discounted LYG)	Mean total costs (discounted)
5-FU/LV (Mayo Clinic)	9.87	£13,239
Capecitabine	10.88	£9,919
Cost per LYG (capecitabine versus Mayo Clinic)	Dominating (cost-saving by £3,320)	
5-FU/LV (de Gramont)	10.80	£22,261
FOLFOX4	12.15	£26,202
Cost per LYG (FOLFOX4 versus de Gramont)	£2,908	

TABLE 33 *Central estimates of cost per QALY gained*

Adjuvant treatment	Mean discounted QALYs	Mean total costs (discounted)
5-FU/LV (Mayo Clinic)	8.47	£13,239
Capecitabine	9.45	£9,919
Cost per QALY (capecitabine versus Mayo Clinic)	Dominating (cost-saving by £3,320)	
5-FU/LV (de Gramont)	9.39	£22,261
FOLFOX4	10.71	£26,202
Cost per QALY (FOLFOX4 versus de Gramont)	£2,970	

the relapse rate is lower in the capecitabine arm, greater cost savings are observed within the Roche analysis.

By contrast, the cost difference between FOLFOX4 and the de Gramont 5-FU/LV regimen deduced from *Table 32* (£3941) is greater than that reported within the Sanofi-Aventis submission.[143] This is attributable to the differences in the assumptions made regarding the costs of relapse. The Sanofi-Aventis submission assumes a higher cost of relapse for patients initially treated with 5-FU/LV than for those treated with FOLFOX4.[143] As a result, this reduces the marginal cost of FOLFOX4 compared with 5-FU/LV in the Sanofi-Aventis submission. The Assessment Group model assumes that all patients incur the same cost upon relapse, regardless of previous treatment, and hence the cost difference between the two treatment arms is greater.

Table 33 presents the equivalent results in terms of cost per QALY gained.

Both sets of estimates demonstrate that in the base-case analysis, capecitabine is dominant when compared with the Mayo Clinic 5-FU/LV regimen, as it has improved survival and quality-adjusted survival and lower costs. Over the 50-year period, capecitabine is estimated to cost an average of £3320 less than 5-FU/LV. The results also suggest that the additional health gains seen in patients receiving FOLFOX4 outweigh the marginal costs, when compared with the de Gramont 5-FU/LV regimen, assuming a cost-effectiveness threshold of more than £3000.

Sensitivity analysis results

A number of sensitivity analyses were conducted to determine the impact of altering assumptions and individual model parameters on the cost-effectiveness results (see the section 'One-way sensitivity analysis', p. 58).

Impact on cost-effectiveness results of alternative discount rates

The base-case analysis discounted costs and QALYs at 6 and 1.5% per annum, respectively. This scenario analysis reports the impact on the cost-effectiveness results of employing two different discount rates combinations. First, both costs and QALYs were discounted at 3.5% per annum, followed by an equivalent analysis using a discount rate of 0% per annum. The results of these are shown in *Tables 34* and *35*.

The use of these alternative discount rates has little impact on the cost-saving nature of capecitabine seen within the base-case analysis, although the QALY gain when compared with the Mayo Clinic 5-FU/LV regimen is reduced by 0.24 QALYs. The marginal cost per QALY of FOLFOX4 compared with the de Gramont 5-FU/LV regimen is increased by around £800 per

TABLE 34 *Scenario analysis of cost-effectiveness results with discount rates of 3.5% on costs and QALYs*

Treatment comparison	Marginal costs (£)	Marginal QALYs	Marginal cost per QALY (£)
Capecitabine vs 5-FU/LV (Mayo Clinic)	–3379	0.74	Dominating
FOLFOX4 vs 5-FU/LV (de Gramont)	3894	1.05	3723

TABLE 35 *Scenario analysis of cost-effectiveness results with discount rates of 0% on costs and QALYs*

Treatment comparison	Marginal costs (£)	Marginal QALYs	Marginal cost per QALY (£)
Capecitabine vs 5-FU/LV (Mayo Clinic)	–3472	1.24	Dominating
FOLFOX4 vs 5-FU/LV (de Gramont)	3816	1.61	2364

TABLE 36 *Scenario analysis of cost-effectiveness results with relapse utility of 0.575*

Treatment comparison	Marginal costs (£)	Marginal QALYs	Marginal cost per QALY (£)
Capecitabine vs 5-FU/LV (Mayo Clinic)	–3320	0.96	Dominating
FOLFOX4 vs 5-FU/LV (de Gramont)	3940	1.28	3069

TABLE 37 *Scenario analysis of cost-effectiveness results with remission utility of 0.5*

Treatment comparison	Marginal costs (£)	Marginal QALYs	Marginal cost per QALY (£)
Capecitabine vs 5-FU/LV (Mayo Clinic)	–3320	0.53	Dominating
FOLFOX4 vs 5-FU/LV (de Gramont)	3940	0.71	5584

QALY. Discount rates of 0% for both costs and QALYs were also used as model inputs to examine the impact on the cost-effectiveness results; the results are shown in *Table 35*.

Again, these changes to the model input parameters have little effect on the results, with improved QALY gains seen in both comparisons and lower costs in both cases, owing to longer term health benefits and costs being given more weight in the analysis through the absence of discounting.

A number of alternative utility estimates for patients with relapse were used as model inputs, since several studies have reported higher utilities for these patients than the value used in the base-case analysis.[150,176] *Table 36* shows the cost-effectiveness results when a utility of 0.575 is used for patients with relapse, based on the 'progressive disease' state reported in the study by Petrou and Campbell.[176]

This also has little impact on the cost-effectiveness results, primarily because the relapse period is generally short and so the weight carried by this utility within the model is relatively small.

An alternative scenario was also considered for patients in remission following adjuvant chemotherapy. The base-case analysis assumed that patients in remission were assigned a utility of 0.92 for the remainder of their lives (assuming no subsequent relapse), and therefore a lower estimate of 0.5 was used within the scenario analyses to address the possibility of QoL being overestimated in the base-case analysis. The cost-effectiveness results of this scenario analysis are given in *Table 37*.

This utility has a greater impact than that of the utility for patients with relapse, since the model predicts survival of patients without relapse up to 50 years post-surgery. The QALY gain in each comparison is seen to be lower than in the base-

TABLE 38 *Impact on cost-effectiveness results of using first-line 5-FU/LV, followed by second-line irinotecan in combination with 5-FU/LV, for patients with relapse*

Treatment comparison	Marginal costs (£)	Marginal QALYs	Marginal cost per QALY (£)
Capecitabine vs 5-FU/LV (Mayo Clinic)	–3413	0.98	Dominating
FOLFOX4 vs 5-FU/LV (de Gramont)	3789	1.32	2860

TABLE 39 *Impact on cost-effectiveness results of using first-line 5-FU/LV, followed by second-line oxaliplatin in combination with 5-FU/LV, for patients with relapse*

Treatment comparison	Marginal costs (£)	Marginal QALYs	Marginal cost per QALY (£)
Capecitabine vs 5-FU/LV (Mayo Clinic)	–3505	0.98	Dominating
FOLFOX4 vs 5-FU/LV (de Gramont)	3638	1.32	2746

TABLE 40 *Impact on cost-effectiveness results of using first-line FOLFOX6, followed by second-line FOLFIRI, for patients with relapse*

Treatment comparison	Marginal costs (£)	Marginal QALYs	Marginal cost per QALY (£)
Capecitabine vs 5-FU/LV (Mayo Clinic)	–4388	0.97	Dominating
FOLFOX4 vs 5-FU/LV (de Gramont)	2196	1.31	1679

TABLE 41 *Impact on cost-effectiveness results of using first-line FOLFIRI, followed by second-line FOLFOX6, for patients with relapse*

Treatment comparison	Marginal costs (£)	Marginal QALYs	Marginal cost per QALY (£)
Capecitabine vs 5-FU/LV (Mayo Clinic)	–4476	0.97	Dominating
FOLFOX4 vs 5-FU/LV (de Gramont)	2051	1.31	1565

case results, although capecitabine remains dominating because the cost savings are maintained in this scenario analysis. The cost per QALY of FOLFOX4 in comparison with the de Gramont regimen increases by approximately £2600 (compared with the base-case result).

It is expected that NICE will shortly provide new guidance on the use of oxaliplatin, irinotecan and raltitrexed in the treatment of advanced colorectal cancer. The base-case analysis assumed that patients with relapse would receive first-line 5-FU/LV followed by irinotecan (upon disease progression), as per current NICE guidance. However, a number of sensitivity analyses have been undertaken to determine whether the routine use of combination therapies in the advanced setting affect the base-case cost-effectiveness results.

Tables 38–41 present these results for four different chemotherapy sequences:

- first-line 5-FU/LV, followed by second-line irinotecan in combination with 5-FU/LV
- first-line 5-FU/LV, followed by second-line oxaliplatin in combination with 5-FU/LV
- first line FOLFOX6, followed by second-line FOLFIRI
- first line FOLFIRI, followed by second-line FOLFOX6.

The results demonstrate that capecitabine remains cost-saving in comparison with the Mayo Clinic 5-FU/LV regimen, and the deterministic estimate of the marginal cost per QALY of FOLFOX4 in comparison to the de Gramont regimen is never greater than £6000. As the costs of treating metastatic disease increase (e.g. through the use of bevacizumab), the ICERs of the two most effective adjuvant treatments (compared with the respective 5-FU/LV regimens used in the trials) become more favourable. Although the four alternative chemotherapy sequences are all more expensive

than that assumed in the base-case analysis, the lower relapse rates observed in the capecitabine and FOLFOX4 arms mean that, over the 50-year time horizon, the total costs of relapse in patients originally treated with these drugs are lower than in the 5-FU/LV comparator arms. Therefore, as the costs of palliative chemotherapy increase, so the cost-effectiveness profile of FOLFOX4 and capecitabine is improved.

The Assessment Group economic model assumed a cost of £0.279 per milligram of leucovorin, which differed from the corresponding cost assumed in the two industry submissions.[20,143] Two additional sensitivity analyses were therefore performed, using a cost per milligram of leucovorin of £0.3694 (from the Roche submission)[20] and £0.2599 (from the Sanofi-Aventis submission).[143] Using the higher cost from the Roche submission, capecitabine was found to be cost saving in comparison with the Mayo 5-FU/LV regimen by £3424 (compared with –£3320 in the base-case analysis), and the cost per QALY of FOLFOX4 compared with the de Gramont 5-FU/LV regimen was estimated to be £2855 (compared with £2970 in the base-case analysis). Analysis using lower costs reported in the Sanofi-Aventis submission estimated that capecitabine would be cost-saving by –£3299 per patient, with a cost per QALY gained of £2988 for the comparison between FOLFOX4 and the de Gramont 5-FU/LV regimen.

Separate analyses were carried out in which the assumption of no relapses beyond 5 years was relaxed, first with patients eligible for relapse up to 7.5 years post-randomisation. Given the increase in the relapse rate associated with this change, the resulting change in the cost-effectiveness estimates is favourable to both capecitabine and FOLFOX4. Capecitabine was estimated to be cost-saving by £3633, whilst the cost per QALY of FOLFOX4 versus the de Gramont 5-FU/LV regimen was estimated to be £2319. An equivalent analysis was performed, with the relapse assumption relaxed further to allow relapses up to 10 years post-randomisation. Under this scenario, capecitabine was estimated to be cost-saving by £3885, whereas the comparison of FOLFOX4 against the de Gramont 5-FU/LV regimen yielded a cost per QALY of £1963.

The one-way sensitivity analyses only estimate the impact of changing one model parameter at a time. Using the set of scenario analyses, a further 'worst-case' scenario has been considered for each intervention, using the least favourable assumptions regarding discount rates, utilities and palliative treatment. For the 'worst-case' comparison of capecitabine versus the Mayo Clinic 5-FU/LV regimen, costs and QALYs were discounted at 0% and a utility of 0.1 was applied to patients with relapse, resulting in cost savings of £2782 per patient on capecitabine compared with £3391 in the base-case analysis. By setting the model parameters to the 'worst-case' scenario for the comparison of FOLFOX4 versus the Mayo Clinic 5-FU/LV regimen (using a discount rate of 3.5% for both costs and QALYs, a utility of 0.575 for patients with relapse and a utility of 0.5 for patients in remission), the cost per QALY gained is estimated to be £7587, compared with £2970 in the base-case analysis.

A final sensitivity analysis attempted to address the discrepancies in the age of patients in the MOSAIC and X-ACT studies compared with that of clinical practice, by assuming that the mean age of patients in the two studies was in fact 70 years (and therefore more in line with the average age of newly diagnosed patients). Ideally, this would have involved using patient-level data from the trials, but as these were not available, it was necessary to perform this analysis by re-fitting the Gompertz survivor function (for patients without relapse) from a starting age of 70 years, and assuming that the disease-free survival benefits observed in the trials are directly applicable to this more elderly group of patients. The extent to which this assumption is valid is worthy of further research through trials in more elderly patient groups. This analysis estimated that capecitabine remains cost-saving in comparison with bolus 5-FU/LV (Mayo regimen), costing on average £6446 less per patient and providing 0.53 additional QALYs. FOLFOX4 is estimated to cost an additional £4157 per QALY in comparison with infusional 5-FU/LV (de Gramont regimen), costing an additional £3940 and providing an additional 0.95 QALYs.

Probabilistic sensitivity analysis results

This section reports the results of the probabilistic sensitivity analysis. The results are presented as cost-effectiveness planes for each of the treatment comparisons, and subsequently presented as CEACs. *Figure 4* presents the marginal costs and QALYs of capecitabine in comparison with the Mayo Clinic 5-FU/LV regimen, based on 10,000 probabilistic model runs.

This plot demonstrates that in all 10,000 model runs, capecitabine is cost saving in comparison with 5-FU/LV, with the level of cost saving ranging from £502 to £6255 per patient. The results also

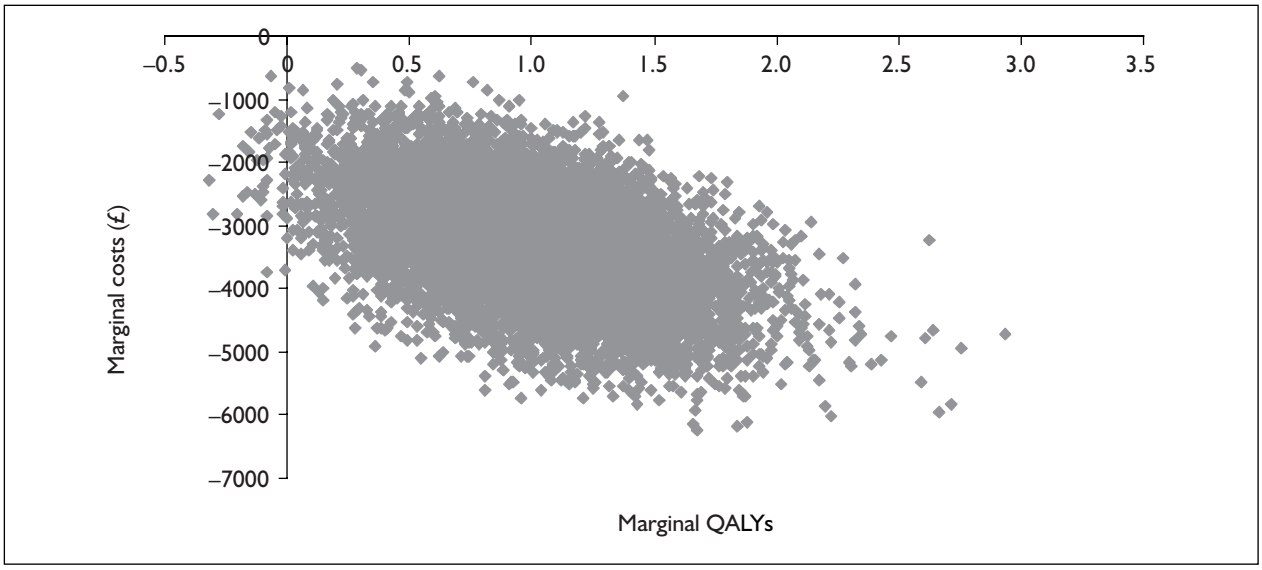


FIGURE 4 *Cost-effectiveness plane: capecitabine versus 5-FU/LV (Mayo Clinic regimen)*

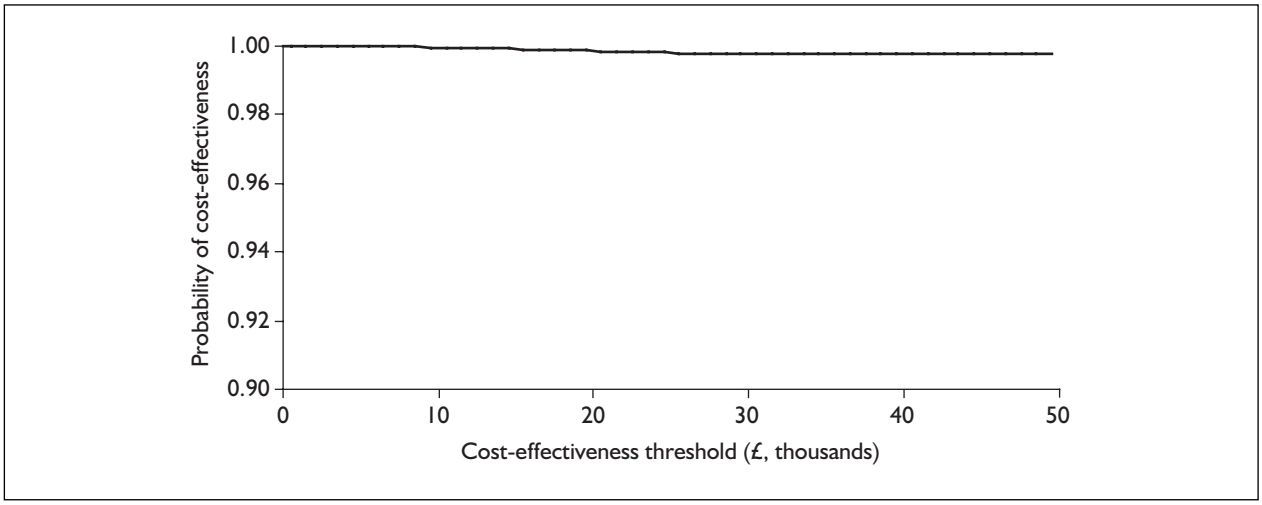


FIGURE 5 *Cost-effectiveness acceptability curve (capecitabine)*

suggest that, in all but a small number of cases (0.25% of all model runs), capecitabine is more effective than 5-FU/LV in terms of QALYs gained per patient.

Figure 5 shows the CEAC for the capecitabine arm, demonstrating the probability of cost-effectiveness at a variety of cost-effectiveness thresholds.

This plot shows that by employing cost-effectiveness thresholds of between £1000 and £50,000, capecitabine has a very high probability of being cost-effective compared with the Mayo Clinic regimen. At a threshold of £30,000, the probability of capecitabine being cost-effective is 99.78%, compared with 99.86% at a threshold of £20,000. These results demonstrate the robustness of the cost-effectiveness results to changes in the threshold employed.

Figure 6 presents the marginal costs and QALYs of FOLFOX4 in comparison with the de Gramont 5-FU/LV regimen, also based on 10,000 probabilistic model runs.

The cost-effectiveness plane shows that in all cases, FOLFOX4 is a predominantly more expensive regimen than de Gramont 5-FU/LV, incurring additional costs in 98.9% of model runs, compared with 5-FU/LV. The observed additional costs range from –£2571 to £10,946. FOLFOX4 is also seen to be more effective in terms of QALY gains, with the combination therapy being superior in all but one of the 10,000 stochastic model runs. *Figure 7*

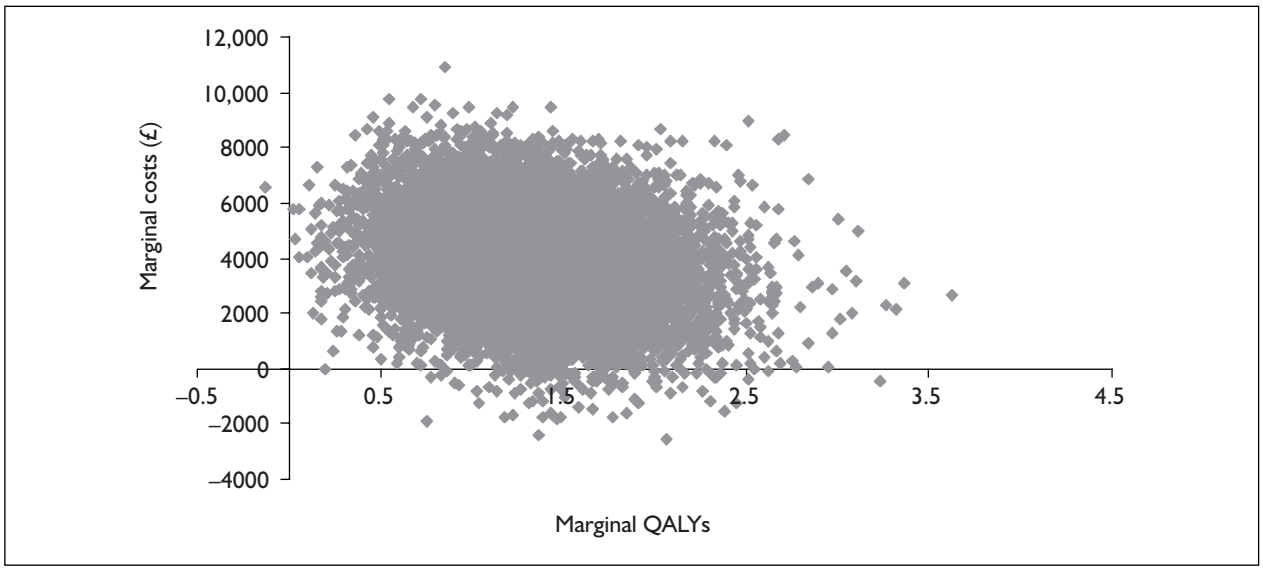


FIGURE 6 *Cost-effectiveness plane: FOLFOX4 versus 5-FU/LV (de Gramont regimen)*

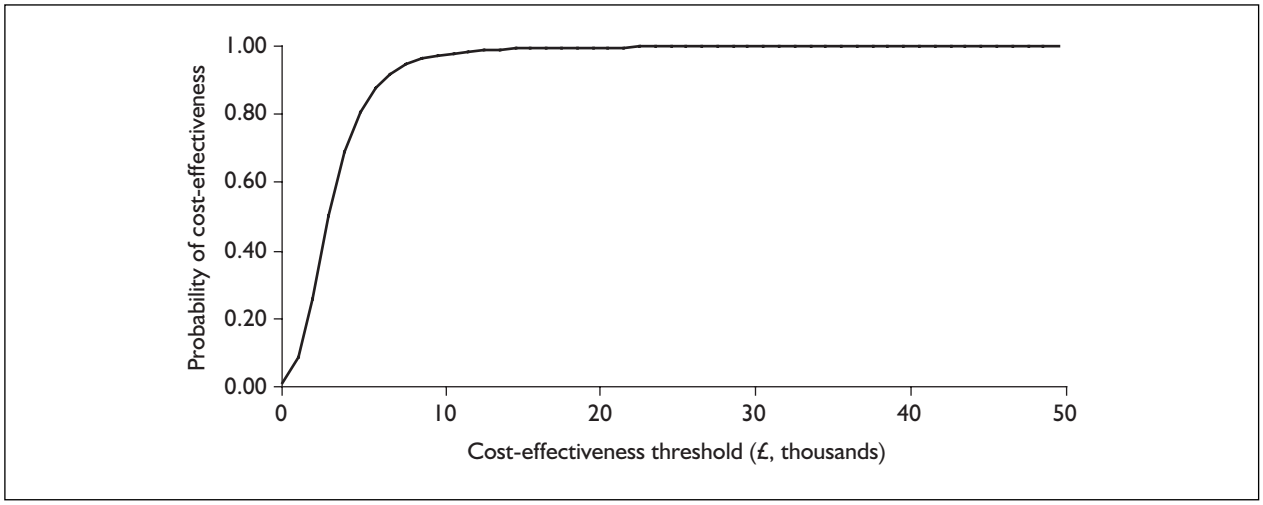


FIGURE 7 *Cost-effectiveness acceptability curve (FOLFOX4)*

shows the CEAC for the FOLFOX4 arm, demonstrating the probability of cost-effectiveness at a variety of cost-effectiveness thresholds, when compared with the de Gramont 5-FU/LV regimen.

If a cost per QALY threshold of around £20,000 were employed, the CEAC suggests a probability of 99.62% of FOLFOX4 being cost-effective compared with 5-FU/LV, rising to 99.86% at a threshold of £30,000 per QALY. The probability of cost-effectiveness falls below 90% only at thresholds of less than £6,000.

Cost-effectiveness analysis using indirect comparisons

Using the extrapolated survival data and the estimates of costs over the 50-year time horizon, an assessment was made of the incremental cost-effectiveness of FOLFOX4 versus capecitabine. The analysis was undertaken in two ways, first using the absolute predicted long-term survival and cost data from the Assessment Group model, and second by comparing the marginal cost-effectiveness of FOLFOX4 and capecitabine against the comparator 5-FU/LV arms in the MOSAIC and X-ACT trials respectively (i.e. making the assumption that the efficacies of the Mayo and de Gramont 5-FU/LV regimens are equivalent).

The additional discounted costs associated with adjuvant treatment with FOLFOX4 when compared with capecitabine (over a 50-year time horizon) are estimated to be £16,283, associated

TABLE 42 *Budget impact*

Treatment	Total cost (£)	Incremental cost (£)
Capecitabine	14,883,523	–
5-FU/LV (Mayo Clinic regimen)	23,367,191	8,483,668
5-FU/LV (de Gramont)	62,334,442	38,967,251
Oxaliplatin plus 5-FU/LV	84,056,181	21,721,739

with a gain of 1.26 QALYs, giving an incremental cost per QALY of £12,874 (by comparing the data shown in *Table 33* for the two regimens). By considering the QALY gains of FOLFOX4 and capecitabine against their respective 5-FU/LV comparators [i.e. FOLFOX4 compared with 5-FU/LV (de Gramont regimen)], and assuming equivalent effectiveness of the Mayo and de Gramont 5-FU/LV regimens, the FOLFOX4 regimen is estimated to generate an additional 0.35 QALYs compared with capecitabine, at an additional cost of £16,283. This generates an estimated cost per QALY of FOLFOX4 versus capecitabine of £46,814. There is therefore considerable uncertainty in the incremental cost-effectiveness of FOLFOX4 in comparison with capecitabine, and these results suggest that the incremental cost per QALY may be greater than £30,000.

A second indirect comparison to estimate the incremental cost-effectiveness of FOLFOX4 versus the Mayo 5-FU/LV regimen (using data from the MOSAIC and X-ACT trials) was undertaken owing to the prevalent use of bolus 5-FU/LV regimens in the adjuvant setting [see the section 'Discussion of results' (p. 38)]. The additional discounted costs associated with adjuvant treatment with FOLFOX4 compared with the Mayo 5-FU/LV regimen (over a 50-year time horizon) are estimated to be £12,963, associated with a gain of 2.24 QALYs, giving an incremental cost per QALY of £5777, suggesting that FOLFOX4 is cost-effective in comparison with the UK standard Mayo regimen. As with the previous indirect comparison, this result should be interpreted with caution, owing to the absence of this treatment comparison in any RCT.

Budget impact analysis results

Table 42 summarises the estimated total cost to the NHS of treating patients with Stage III (Dukes' C) colon cancer with each of the four treatment interventions from the MOSAIC and X-ACT studies.

Chapter 5

Assessment of factors relevant to the NHS and other parties

Implications for other parties

Patient education

The vital role of education and information for patients receiving capecitabine has been comprehensively reviewed by Chau and colleagues.[177] For home-based oral therapy to be successful, it is vital that patients take an active part in their care.[130,177] To ensure that patients are properly informed about their treatment, various tools need to be developed, including prescription guides, diary cards and support kits. For patients in the UK, a range of materials have been produced and include a guide to capecitabine therapy, a credit card-sized patient card with useful telephone numbers, a side-effect recognition sheet and a patient education video.[130,177] However, this should not remove the decision-making and sense of responsibility from doctors, nurses and pharmacists.

In addition, patient education, for both oral and intravenous administration, must emphasise recognition of early signs and symptoms and ways to report changes, and also information to assist patients in preventing exacerbations.[178] This process might be facilitated through patient care groups which can provide patients with advice on symptoms, and could eventually lead to home delivery of intravenous chemotherapy.

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 (e.g. weekly 5-FU/LV) 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.[22] If patients are not sufficiently competent to self-administer oral tablets, it may be considered appropriate that they should be prescribed intravenous chemotherapy as a means of increasing compliance and preventing overdose.

Transportation

The costs of transportation will be greater for patients who have to visit the hospital more frequently, i.e. patients receiving a Mayo Clinic regimen in particular, but also patients receiving a de Gramont treatment regimen, who visit once every 2 weeks instead of once every 3 weeks.[22]

Factors relevant to NHS

Outreach clinics

One of the primary advantages of the use of oral chemotherapy is the reduction in the time patients spend within the hospital setting. This reduction in the number of hospital attendances over the course of the treatment period is particularly beneficial to patients who are either geographically isolated or prefer not to travel to their nearest cancer centre. Oral chemotherapy does not require the facilities found in cancer centres, and the provision of outreach clinics for delivery of oral drugs offers a more convenient option for these patients. This raises issues with regards to patient education and the monitoring of adverse effects/toxicities, which would normally be dealt with in the cancer centres.

The needs of patients in terms of education and support must be considered if patients are to receive oral treatment via such outreach clinics. The provision of staff, such as chemotherapy nurses, to provide for these needs must be taken into account when planning such a service. Since the adverse effects/toxicities associated with oral chemotherapy can be just as severe as those of intravenous chemotherapy, we believe it is important that both patients and medical staff are educated about this, to prevent the assumption being made that patients receiving oral chemotherapy are easier to deal with.

The use of outreach clinics for patients receiving oral chemotherapy would be beneficial from the patients' perspective, as they would reduce the patient travel time required over the course of treatment.

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, whereas 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: this has, to date, prevented some hospitals administering capecitabine.[22] The impact of differing adverse event/toxicity profiles between treatments needs to be considered alongside this, as this will impact upon the number of hospital visits and admissions. 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.[22]

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. Given the bias towards bolus 5-FU/LV administration as opposed to infusional in the adjuvant setting, this may become less of an issue. More specialist staff are needed in all areas of administration for infusional regimens, as radiologists and radiographers may also be needed for line insertion, and specialist pharmacists and nurses are needed for the preparation and administration of drugs.[22]

Capecitabine dispensing is undertaken in the main dispensary area in many hospitals, although it would not be viewed as a simple prescription to dispense, given the different tablet strengths and the need for careful labelling and tablet counting checks owing to the potential consequences of over-prescribing the drug. It is estimated that dispensing a capecitabine prescription would currently take around 15 minutes per patient, although this process could be streamlined if capecitabine became routine therapy.[22]

The routine use of oxaliplatin in combination with 5-FU/LV is also expected to have significant implications for pharmacy services, owing to its toxicity, its short expiry following reconstitution and the preparation time required per infusion. Some hospitals use rounded doses, so that there is more usage of chemotherapy by other patients if it cannot be used by its intended patient (Dr M Saunders, Christie Hospital, Manchester: personal communication, 2005). Given the short expiry of oxaliplatin, and the associated risk of drug wastage, pharmacy units would require confirmation of the patient's attendance before preparing the drug for administration. This may have implications for the patient, in terms of necessitating two clinic visits per administration or excessive waiting times while the drug is being prepared.

Drug administration

In addition to the impact of new guidance on pharmacy services mentioned above are issues relating to drug administration with the novel therapies. If capecitabine were to be used routinely, it is expected that this may reduce the number of hospital attendances per drug cycle. This would have implications in terms of saving clinicians' time and lowering the costs associated with administration of intravenous chemotherapies.

The administration of oxaliplatin and 5-FU/LV typically requires a day-case attendance for each day of therapy, which is more costly from the hospital's perspective than a simple outpatient attendance. The exact number of administration appointments is governed to some extent by the administration regimen employed and by facilities available at cancer centres.

Training for doctors and nurses

Since not all patients with colon cancer would be considered eligible for adjuvant treatment with oral chemotherapy, the introduction of such therapies as routine treatment may necessitate additional training for doctors and nurses in patient identification and education. It is important to emphasise to patients that it is essential to stop taking their chemotherapy if they become unwell and to make medical staff aware of their treatment if they are admitted to hospital. Physicians need to be able to make decisions regarding which patients could tolerate oral chemotherapy, as well as establishing suitable relationships with patients to encourage them to report any treatment-related problems. This is also true of nurses charged with educating patients on the risks of non- and under-compliance.

The use of capecitabine defines a more prominent role for the oncology nurse in patient care and management. The oncology nurse will be required

to be involved in the initial contact and education of the patient, and also follow-up (clinic visits, home visits and telephone contact), including urgent telephone contact and liaison with the clinician if necessary.[179] In addition, the potential difficulties that may arise as a function of expanding the role of oncology nurses include overburdening staff with additional responsibilities.[179,180]

Compliance

The issue of patient compliance with oral chemotherapies is a key factor in their use. Most patients (typically more than 90%) with cancer comply well with their chemotherapy,[181] but over-compliance can sometimes be a problem as patients may be motivated to take medication even when they are experiencing adverse effects.[22] Patients with cancer may also be at risk of overdose due to depression (Dr M Saunders, Christie Hospital, Manchester: personal communication, 2005). It is therefore important to ensure that patients are fully educated on the dangers of over-compliance, ensure that patients understand the consequences of not adhering to their medication schedule and provide details of the treatment regimen (i.e. number of tablets, timing of doses during the day and relative to meals and how to manage missed doses).

Patient support in the community may be needed to ensure patient safety and to act as an outlet for patients with concerns regarding compliance. This may involve an oncology nurse being available for telephone or face-to-face contact with the patient and a greater involvement of GPs in the monitoring of adverse effects. Services for elderly patients would also be required to deal with problems with confusion and home support.

Availability of alternative therapies

Within the NICE programme are a suite of appraisals relating to chemotherapies for colorectal cancer, including oxaliplatin, capecitabine, irinotecan, bevacizumab and cetuximab in a variety of indications. The use of the therapies within this appraisal needs to be considered alongside possible future NICE recommendations, although the initial results of irinotecan-based trials suggest that it is not an effective treatment in the adjuvant setting.[182–184] Any new recommendations regarding therapies for metastatic colorectal cancer should also be borne in mind, as these may impact upon the assumptions made within this appraisal regarding standard treatment for advanced disease.

It has been suggested that in the future, capecitabine may be used as combination therapy for metastatic colorectal cancer (in combination with oxaliplatin or irinotecan). This would have implications for drug administration, as resource use and cost savings made through the administration of single-agent capecitabine would be lost if the drug was used in combination with intravenously administered therapies. It is considered likely that if capecitabine and oxaliplatin were to be used routinely in the adjuvant setting, this may lead to a tendency for the two drugs to be given in combination, as off-licence therapy. This would reduce the drug administration cost savings associated with single-agent capecitabine.

Age

It is important to consider the impact of age upon the choice of therapy. Younger patients are more likely to be fitter and therefore more able to tolerate the adverse effects/toxicities of combination oxaliplatin chemotherapy than more elderly patients. Older patients may therefore be more likely to receive single-agent 5-FU/LV, hence the higher relapse rates seen in elderly patients. The routine use of capecitabine may offer such patients a reduced risk of relapse and therefore an improved life expectancy.

Off-licence use

Patients with rectal cancer

It is expected that any recommendations made by NICE regarding oxaliplatin and capecitabine for colon cancer will have implications for patients with rectal cancer, with these drugs being more readily used as off-licence therapy. Patients with rectal cancer are not included in the trials because of the confounding influence of surgery and radiotherapy upon their disease outcome; however, we are not aware of any evidence to suggest that either drug is ineffective in rectal cancer. Initially, this may be restricted to those patients with rectal disease who have either received no radiotherapy or only short-course pre-operative radiotherapy, owing to the lack of evidence for patients treated with long-course radiotherapy. Evidence from the ongoing CHRONICLE trial[185] should indicate the suitability of adjuvant chemotherapy for these patients.

Patients with Stage II cancer

The MOSAIC trial included patients with both Stage II and III colon cancer, reflecting the potential efficacy of chemotherapy for patients with high-risk Stage II cancer. Although the scope of this appraisal considers only patients with Stage III colon cancer, it is expected that any new recommendations arising from this appraisal are likely to lead to more off-licence use of these therapies in patients with high-risk Stage II cancer.

Chapter 6
Discussion

Principal findings

The clinical effectiveness review and cost-effectiveness analysis have indicated that both capecitabine and FOLFOX4 are effective and cost-effective (given the assumptions made regarding long-term survival) in comparison with standard 5-FU/LV therapy in the adjuvant treatment of Stage III (Dukes' C) colon cancer. The deterministic estimates of cost-effectiveness suggest that the use of capecitabine as opposed to the Mayo Clinic 5-FU/LV regimen is estimated to save around £3320 per patient over a 50-year time horizon, while in turn providing an additional 0.98 QALYs per patient. The comparison of FOLFOX4 with the de Gramont 5-FU/LV regimen has estimated that over the same 50-year time horizon, FOLFOX4 costs an additional £3940 per patient, resulting in a net gain of 1.33 QALYs, giving a marginal cost-effectiveness ratio of £2970 per QALY. Both of these results are favourable in comparison with many other interventions currently available on the NHS.

Scenario and extreme analyses have demonstrated that capecitabine remains cost saving and provides additional health gains when compared with the Mayo Clinic 5-FU/LV regimen, regardless of the assumptions made concerning discount rates, utilities and the choice of palliative therapy for patients with relapse. The marginal cost-effectiveness of FOLFOX4 versus the de Gramont 5-FU/LV regimen also remains favourable when conservative values of these model parameters are used (from the perspective of FOLFOX4), with the marginal cost per QALY never being above £7600.

The probabilistic sensitivity analyses indicated that there are similar degrees of uncertainty in the QALY gains of the two treatments as in the costs differences. However, the costs and QALYs of each comparison are correlated, as a higher gain in QALYs implies fewer relapses and therefore lower costs (because the cost of relapse is higher than the cost of remaining relapse free). The CEACs show that both capecitabine and FOLFOX4 have a high probability of cost-effectiveness at thresholds of both £20,000 and £30,000 per QALY, in comparison with their respective 5-FU/LV comparators. The cost-effectiveness planes of both comparisons show that both FOLFOX4 and capecitabine consistently provide additional QALYs.

The indirect comparison to assess the cost-effectiveness of FOLFOX4 compared with the Mayo 5-FU/LV regimen suggests that the ICER would not be significantly higher than that estimated using the de Gramont 5-FU/LV regimen. A second indirect comparison assessed the incremental cost-effectiveness of FOLFOX4 versus capecitabine, and demonstrated that there is considerable uncertainty in this comparison. If the Mayo and de Gramont 5-FU/LV regimens are assumed to be equally effective, then the incremental cost per QALY of FOLFOX4 compared with capecitabine may not be considered cost-effective. These indirect comparisons should be interpreted with caution; direct comparisons could only be performed with the availability of trial data in which these interventions were directly compared.

A comparison of oxaliplatin in combination with bolus 5-FU/LV has not been made in the economic analysis. If bolus and infusional regimens are assumed to have equivalent efficacy, then the marginal cost-effectiveness of oxaliplatin in combination with bolus 5-FU/LV versus bolus 5-FU/LV will be the same as for the comparison between FOLFOX4 and infusional 5-FU/LV (de Gramont regimen).

Limitations of the assessment

The key assumption made within the economic analysis is in the long-term survival of patients without relapse. The absence of consistent long-term data for this group of patients means that is it difficult to validate this assumption. As a result, the most appropriate survival analysis methods have been applied to estimate long-term survival. The true validity of these methods can only be determined when long-term follow-up data from the MOSAIC and X-ACT studies become available.

It is important to note also the discrepancies in the ages of patients in the MOSAIC and X-ACT studies and those of patients in clinical practice

are not equivalent, and hence the long-term survival benefits associated with each intervention may have been overestimated, which is likely to have a negative impact on the cost-effectiveness profile of both FOLFOX4 and capecitabine. Although evidence from a meta-analysis of trials in the adjuvant setting,[186] which conducted separate analyses for patients aged 70 years or under and those aged above 70 years, suggests that there is no significant difference in either overall or disease-free survival at 8 years post-randomisation, the distribution of patient ages within each group is not reported and it is unclear whether the survival curves presented in the paper include all-cause mortality within the disease-free survival curves.

No account was taken of the impact of the adjuvant treatment received upon treatment decisions for patients with relapse. The existing NICE guidance was used to form the base-case analysis and the impact on the cost-effectiveness results of alternative therapies for advanced colorectal cancer were explored in the scenario analyses, to reflect the expected changes to the guidance regarding treatment of these patients. However, in practice, the most likely scenario is that a variety of sequencing therapies will be used in the future, depending on patient and clinician preference, previous chemotherapy, time between cessation of adjuvant chemotherapy and relapse, and patient age.

Evidence from the submission to NICE by the Royal College of Physicians suggests that the Assessment Group model may have underestimated the costs of hospitalisation and side-effects associated with capecitabine. However, since drug administration costs are the key driver of the total costs in all treatment arms, it is unlikely that any underestimate of the side-effect treatment costs for the capecitabine arm would have a significant impact upon the cost-effectiveness analysis.

Uncertainties

One of the fundamental assumptions made within the economic analysis is that the survival benefits observed in the X-ACT and MOSAIC trials are generalisable to patients with Stage III (Dukes' C) colon cancer in England and Wales. Patients in the MOSAIC trial demonstrated superior disease-free and overall survival compared with patients in the X-ACT study, and although the inclusion criteria for the two studies appear similar, there may be subtle differences between the two populations (e.g. age distribution) which account for this.

Other relevant factors

A further issue of relevance to the interpretation of the cost-effectiveness results presented in this assessment is that the patent for oxaliplatin is due to expire in 2006–7. Inevitably, a reduction in the price of this drug would improve the cost-effectiveness and reduce the annual cost to the NHS of oxaliplatin-containing chemotherapy sequences as reported within this analysis. The degree to which the introduction of a generic product into the cancer treatment market would impact on price structures for proprietary drugs is unclear.

Further research

The following points have been identified as areas requiring further research, although several of these questions are being addressed in ongoing trials.

Ongoing trials

A list of ongoing adjuvant therapy trials comparing different combination therapies, such as oral capecitabine plus oxaliplatin (XELOX),[187] including oral fluoropyrimidines and the new targeted therapies, can be found in Appendix 17.

Suggested research priorities

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

- The identification of novel, effective and cost-effective treatments in the adjuvant setting.
- Adjuvant chemotherapy trials should include QoL data. Research should be conducted by independent researchers, using well-validated instruments. It some cases it may be necessary to use more than one instrument in order to identify differences in QoL or components of QoL that vary with different treatments.
- Despite the benefits observed with FOLFOX4 in the adjuvant setting, the infusion schedule used in FOLFOX4 is cumbersome. Simplified infusion schedules of 5-FU/LV have been developed (OxMdG, FOLFOX6 and FOLFOX7) but have only been evaluated in the metastatic setting. The bolus FLOX schedule used in the NSABP C-07 trial also avoids some of the inconveniences of infusional therapy, and an ongoing trial is evaluating the combination

of oxaliplatin plus capecitabine. Research is needed to compare the effectiveness, tolerability, patient acceptability and costs of these different oxaliplatin/fluoropyrimidine schedules in the adjuvant setting.

- The optimum duration of adjuvant therapy is not known. Shorter duration might potentially reduce the costs, inconvenience, toxicity and risks of adjuvant therapy, but large trials are required to determine whether there is any reduction in efficacy.
- The issue of patient compliance with oral chemotherapies is a key factor in their use. Research is needed to demonstrate what the best approach is in order to ensure compliance and monitoring of adverse events.
- The issue of patient preference must be given careful consideration in future trials and all trials should incorporate a measurement of patient preference.
- The findings of the review on the clinical and cost-effectiveness of oxaliplatin (in combination with 5-FU/LV) and capecitabine monotherapy are restricted by limitations in the external validity of the included trials. All of the included clinical trials recruited patients who were, on average, younger than the typical colon cancer population who are treated on the NHS. This is a common observation within many oncology trials. Further research concerning the effectiveness of oxaliplatin in combination with 5-FU/LV and capecitabine monotherapy in the treatment of older patients is merited.
- There is a need for future cancer trial protocols to incorporate more detailed resource data collection strategies and to report summary statistics that are of use within economic evaluations. In order to restrict the medical resources to those patients who benefit most, research is needed to identify those subgroups of patients who benefit the most from chemotherapy.
- All of the trials included within this review have used median disease-free and relapse-free survival as the primary measure of clinical benefit. The median is an estimate of benefit at a single time point and does not relate to the overall, disease-free or relapse-free survival benefit observed across the entire patient group. The mean provides a more appropriate measure of overall clinical benefit, from a health economic (and potentially a clinical) perspective. However, there are methodological difficulties in estimating mean survival. Further research is therefore required on methodologies for estimating mean survival, both in non-curative interventions (in which the survival time is prohibitively long and thus prevents estimation of mean survival) and in curative treatments.
- A comparison of the incremental cost-effectiveness of FOLFOX4 versus capecitabine has been carried out. However, this indirect comparison is subject to considerable potential bias, which could only be eliminated through an RCT which directly compares these two interventions.

Chapter 7
Conclusions

Clinical effectiveness

Evidence from the MOSAIC trial demonstrated that oxaliplatin (in combination with 5-FU/LV) therapy was more effective in preventing or delaying disease recurrence than 5-FU/LV alone in the adjuvant treatment of patients who had undergone complete surgical resection for Stage III colon cancer (data not reported separately for Stage III patients in the NSABP C-07 study). On the whole, serious adverse events and treatment discontinuations due to toxicity were more evident with oxaliplatin in combination with an infusional 5-FU/LV de Gramont schedule (FOLFOX4 regimen) than infusional 5-FU/LV alone (de Gramont regimen) and oxaliplatin in combination with a bolus 5-FU/LV Roswell Park schedule (FLOX regimen) than bolus 5-FU/LV alone (Roswell Park regimen).

Evidence from the X-ACT study demonstrated that capecitabine therapy was at least equivalent in disease-free survival to the bolus Mayo Clinic 5-FU/LV regimen for patients with resected Stage III colon cancer. In terms of relapse-free survival, capecitabine monotherapy was significantly better than bolus 5-FU/LV. The safety and tolerability profile of capecitabine was superior to that of the Mayo Clinic 5-FU/LV regimen, but has not been evaluated in comparison with the less toxic 5-FU/LV regimens currently in common use in the UK.

Cost-effectiveness

The results of the independent health economic assessment suggest that both capecitabine and FOLFOX4 appear to have favourable cost-effectiveness profiles in comparison with 5-FU/LV regimens (Mayo and de Gramont schedules), based on levels of cost-effectiveness which are currently considered by NHS policymakers to represent acceptable value for money.[188] Capecitabine is estimated to be cost-saving over this period in comparison with the Mayo 5-FU/LV regimen (by a total of £3320 per patient), whereas oxaliplatin (in combination with 5-FU/LV) in comparison with the de Gramont 5-FU/LV regimen is estimated to cost an additional £2970 per QALY gained.

Indirect comparisons suggest that FOLFOX4 is cost-effective compared with the Mayo Clinic 5-FU/LV regimen, although it may not be deemed cost-effective by policymakers in comparison with capecitabine. These economic comparisons could only be assessed fully following a trial which directly compared these two regimens.

It is important to note that the mean age of patients in both the MOSAIC and X-ACT studies is considerably lower than that observed in clinical practice and, as a result, the cost-effectiveness analyses may overestimate long-term overall survival for patients in all treatment arms owing to the shorter life-expectancy of these more elderly patients. The marginal benefits of capecitabine and FOLFOX4 versus their respective 5-FU/LV comparators may therefore be overestimates and, as a result, the estimated marginal cost-effectiveness ratios may have been underestimated.

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Contribution of authors

Abdullah Pandor (Research Fellow) coordinated the review. Suzy Paisley (Research Scientist) developed the search strategy and undertook searches; Abdullah Pandor, Paul Sutcliffe (Research Associate), Simon Eggington (Operational Research Analyst) and Paul Tappenden (Senior Cost-effectiveness Modeller) screened the search results. Abdullah Pandor, Paul Sutcliffe, Simon Eggington and Paul Tappenden screened retrieved papers against inclusion criteria, appraised the quality of papers and abstracted data from papers. Abdullah Pandor and Simon Eggington wrote to authors of papers for additional information. Abdullah Pandor, Simon Eggington, Paul Tappenden and Paul Sutcliffe analysed the data. Abdullah Pandor wrote the background section, Abdullah Pandor and Paul Sutcliffe wrote the section on clinical effectiveness and Simon Eggington and Paul Tappenden wrote the section on cost-effectiveness.

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Appendix 1

Summary of 5-FU/LV regimens

Regimen	Description
Bolus schedules	
QUASAR (weekly regimen)	Weekly dose of 370 mg/m^2 5-FU and 175 or 25 mg LV for 30 weeks
QUASAR (monthly regimen)	Daily dose of 370 mg/m^2 5-FU and 175 or 25 mg LV for 5 days, repeated every 4 weeks for 6 months
Modified weekly regimen	Weekly dose of 425 mg/m^2 5-FU and 45 mg LV for 24 weeks
Mayo Clinic	Monthly for 5 days with low-dose LV (5-FU 425 mg/m^2; LV 20 mg/m^2)
Roswell Park	Weekly (5-FU 500 mg/m^2; LV 500 mg/m^2 over 2 h by infusion)
Machover	Monthly for 5 days with high-dose LV (5-FU 400 mg/m^2; LV 200 mg/m^2 over 2 h by infusion)
Infusional schedules	
Lokich	Protracted infusion (5-FU 300 mg/m^2)
De Gramont	48-h both bolus and continuous infusion bimonthly (5-FU 400 mg/m^2 bolus, 600 mg/m^2 continuous infusion over 22 h, LV 200 mg/m^2 over a 2-h infusion days 1 and 2 before 5-FU)
Modified de Gramont (MdG)	48-h both bolus and continuous infusion bimonthly (5-FU 400 mg/m^2 bolus, 2800 mg/m^2 continuous infusion over 46 h, LV 175 mg/m^2 over a 2-h infusion day 1 before 5-FU)
Grupo Español para el Tratamiento de Tumores Digestivos (TTD)	48-h infusion weekly (5-FU 3000 mg/m^2)
Arbeitsgemeinschaft Internistische Onkologie (AIO)	24-h infusion weekly (5-FU 2600 mg/m^2; LV 500 mg/m^2)
Chronomodulated delivery	5-FU 700 mg/m^2; LV 300 mg/m^2/day, peak delivery rate at 04.00 a.m. for 5 days

Appendix 2

BNF general guidance on use of cytotoxic drugs[40]

The chemotherapy of cancer is complex and should be confined to specialists in oncology. Cytotoxic drugs have both anti-cancer activity and the potential for damage to normal tissue. Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms. In an increasing number of cases chemotherapy may be combined with radiotherapy or surgery or both as either neoadjuvant treatment (initial chemotherapy aimed at shrinking the primary tumour, thereby rendering local therapy less destructive or more effective) or as adjuvant treatment (which follows definitive treatment of the primary disease, when the risk of subclinical metastatic disease is known to be high). All chemotherapy drugs cause side-effects and a balance has to be struck between likely benefit and acceptable toxicity.

Committee on the Review of Medicines (CRM) guidelines on handling cytotoxic drugs:

1. Trained personnel should reconstitute cytotoxics.
2. Reconstitution should be carried out in designated areas.
3. Protective clothing (including gloves) should be worn.
4. The eyes should be protected and means of first aid should be specified.
5. Pregnant staff should not handle cytotoxics.
6. Adequate care should be taken in the disposal of waste material, including syringes, containers and absorbent material.

Intrathecal chemotherapy
A Health Service Circular (HSC 2003/010) provides guidance on the introduction of safe practice in NHS Trusts where intrathecal chemotherapy is administered. Support for training programmes is also available.

Copies and further information may be obtained from:

Department of Health
PO Box 777
London SE1 6XH
Fax: 01623 724524

Combinations of cytotoxic drugs are frequently more toxic than single drugs but have the advantage in certain tumours of enhanced response, reduced development of drug resistance and increased survival. However, for some tumours, single-agent chemotherapy remains the treatment of choice.

Most cytotoxic drugs are teratogenic, and all may cause life-threatening toxicity; administration should, where possible, be confined to those experienced in their use.

Because of the complexity of dosage regimens in the treatment of malignant disease, dose statements have been omitted from some of the drug entries. In all cases detailed specialist literature should be consulted.

Prescriptions should not be repeated except on the instructions of a specialist.

Cytotoxic drugs fall naturally into a number of classes, each with characteristic antitumour activity, sites of action and toxicity. Knowledge of sites of metabolism and excretion is important because impaired drug handling as a result of disease is not uncommon and may result in enhanced toxicity.

Appendix 3

Identification of studies for the review of clinical effectiveness

This appendix contains information on the sources searched and keyword strategies for the systematic review of clinical-effectiveness.

Electronic databases

The following electronic databases were searched:

- BIOSIS
- CDSR Cochrane Database of Systematic Reviews
- CENTRAL Cochrane Central Register of Controlled Trials
- DARE–NHS EED–HTA Database of Abstract of Reviews of Effectiveness, NHS Economic Evaluation Database, Health Technology Assessment Database
- CINAHL Cumulative Index of Nursing and Allied Health Literature
- EMBASE
- MEDLINE
- PUBMED
- WoS Web of Science

The World Wide Web

The following resources were consulted via the Internet:

- ACGBI Association of Coloproctology of Great Britain and Ireland
- AHRQ Agency for Healthcare Research and Quality
- AIHW Australian Institute of Health and Welfare
- AHFMR Alberta Heritage Foundation for Medical Research
- ASCO American Society of Clinical Oncology
- Bandolier
- Blue Shield, Blue Cross Association
- CCOHTA Canadian Co-ordinating Office for Health Technology Assessment
- CCT Controlled Clinical Trials
- CenterWatch
- CHE Centre for Health Economics
- CRD Centre for Reviews and Dissemination
- DTB Drug and Therapeutics Bulletin
- FDA Food and Drug Administration
- Harvard CEA Registry Harvard Cost Effectiveness Analysis Registry
- HEBE Health Boards Executive
- HERC Health Economics Research Centre
- HERG Health Economics Research Group
- HERU Health Economics Research Unit
- HSRU Health Services Research Unit
- INAHTA Clearing House International Network of Associations for Health Technology Assessment
- mRCT Meta Registers of RCTs
- MSAC Medical Services Advisory Committee
- MTRAC Midland Therapeutic Review and Advisory Committee
- NPC National Prescribing Centre
- NCCHTA National Co-ordinating Centre for Health Technology Assessment
- NCRN National Cancer Research Network
- NHS Quality Improvement, Scotland
- NHS R&D Programmes
- NHSC National Horizon Scanning Centre
- NIH National Institutes of Health
- NIH Clinical Trials Database
- North of England Guidelines
- PPA Prescription Pricing Authority
- PSSRU, Kent Personal and Social Services Research Unit
- RAND Corporation

- RCP Royal College of Physicians
- RCS Royal College of Surgeons
- SBU Swedish Health Technology Assessment
- SIGN Scottish Intercollegiate Guidelines
- Therapeutics Initiative (Vancouver)

Database keyword strategies

BIOSIS
1985–2004
SilverPlatter WebSPIRS Version 4.3
Search undertaken January 2005

#18. #16 and #17
#17. trial
#16. #14 and #15
#15. (carcinoma* or neoplasia* or neoplasm* or cancer* or tumo* or malignan*) near3 (colorectal or colon* or rect* or intestin* or bowel*)
#14. #7 or #13
#13. #8 or #9 or #10 or #11 or #12
#12. x act
#11. 5 deoxy 5 fluoro n pentyloxy carbonyl cytidine
#10. 154361-50-9
#9. xeloda
#8. capecitabine
#7. #1 or #2 or #3 or #4 or #5 or #6
#6. mosaic
#5. 1r 2r 1 2 cyclohexanediamine n n oxalato 2 o o platinum
#4. eloxatin
#3. l ohp
#2. 61825-94-3
#1. oxaliplatin

COCHRANE LIBRARY (CDSR and CENTRAL)
Issue 4, 2004
Wiley version
Search undertaken January 2005

oxaliplatin or "l ohp" or l-ohp or eloxatin or mosaic or capecitabine or xeloda or "x act" or x-act in All Fields and colorectal or colon* or rectal or rectum in All Fields

CINAHL
1982–2005
Ovid Online version 9.3
Search undertaken January 2005

1. oxaliplatin.af.
2. "63121 00 6".af.
3. l ohp.af.
4. eloxatin.af.
5. 1r 2r 1 2 cyclohexanediamine n n oxalato 2 o o platinum.af.
6. mosaic.af.
7. or/1-6
8. capecitabine.af
9. xeloda.af.
10. 154361 50 9.af.
11. 5 deoxy 5 fluoro n pentyloxy carbonyl cytidine.af.
12. x act.af.
13. or/8-12
14. 7 or 13
15. exp Colonic Neoplasms/
16. exp Rectal Neoplasms/
17. or/15-16
18. Neoplasms/
19. Carcinoma/
20. Adenocarcinoma/
21. or/18-20
22. exp Colonic Diseases/
23. exp Rectal Diseases/
24. exp Colon/
25. exp Rectum/
26. or/22-25
27. 21 and 26
28. ((carcinoma$ or neoplasia$ or neoplasm$ or cancer$ or tumo$ or malignan$) adj3 (colorectal or colon$ or rect$ or intestin$ or bowel$)).tw.
29. 17 or 27 or 28
30. 14 and 29

DARE-NHS EED-HTA
Date coverage not known (approx. 1994–2005)
CRD website version
Search undertaken January 2005

Oxaliplatin or l ohp or eloxatin or mosaic or capecitabine or xeloda or x act/All fields AND colorectal or colon or rectal or rectum/All fields

EMBASE
1980–2004
SilverPlatter WebSPIRS Version 4.3
Search undertaken January 2005

#33. #31 and #32
#32. explode 'clinical-trial' / all subheadings in DEM,DER,DRM,DRR
#31. #14 and #30
#30. #18 or #28 or #29
#29. (carcinoma* or neoplasia* or neoplasm* or cancer* or tumo* or malignan*) near3 (colorectal or colon* or rect* or intestin* or bowel*)
#28. #22 and #27

#27. #23 or #24 or #25 or #26
#26. explode 'rectum-disease' / all subheadings in DEM,DER,DRM,DRR
#25. explode 'colon-disease' / all subheadings in DEM,DER,DRM,DRR
#24. explode 'rectum-' / all subheadings in DEM,DER,DRM,DRR
#23. explode 'colon-' / all subheadings in DEM,DER,DRM,DRR
#22. #19 or #20 or #21
#21. explode 'adenocarcinoma-' / all subheadings in DEM,DER,DRM,DRR
#20. explode 'carcinoma-' / all subheadings in DEM,DER,DRM,DRR
#19. explode 'neoplasm-' / all subheadings in DEM,DER,DRM,DRR
#18. #15 or #16 or #17
#17. explode 'colorectal-tumor' / all subheadings in DEM,DER,DRM,DRR
#16. explode 'colorectal-carcinoma' / all subheadings in DEM,DER,DRM,DRR
#15. explode 'colorectal-cancer' / all subheadings in DEM,DER,DRM,DRR
#14. #7 or #13
#13. #8 or #9 or #10 or #11 or #12
#12. x act
#11. 5 deoxy 5 fluoro n pentyloxy carbonyl cytidine
#10. 154361-50-9
#9. xeloda
#8. capecitabine
#7. #1 or #2 or #3 or #4 or #5 or #6
#6. mosaic
#5. 1r 2r 1 2 cyclohexanediamine n n oxalato 2 o o platinum (0 records)
#4. eloxatin
#3. l ohp
#2. 61825-94-3
#1. oxaliplatin

MEDLINE
1966–2005
Ovid Online version 9.3
Search undertaken January 2005

1. oxaliplatin.af.
2. "63121 00 6".rn.
3. l ohp.af.
4. eloxatin.af.
5. 1r 2r 1 2 cyclohexanediamine n n oxalato 2 o o platinum.af.
6. mosaic.af.
7. or/1-6
8. capecitabine.af.
9. xeloda.af.
10. 154361 50 9.af.
11. 5 deoxy 5 fluoro n pentyloxy carbonyl cytidine.af.
12. x act.af.
13. or/8-12
14. 7 or 13
15. exp Colorectal Neoplasms/
16. Neoplasms/
17. Carcinoma/
18. Adenocarcinoma/
19. or/16-18
20. Colonic Diseases/
21. Rectal Diseases/
22. exp Colon/
23. exp Rectum/
24. or/20-23
25. 19 and 24
26. (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
27. (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
28. (neoplasm$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
29. (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
30. (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
31. (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
32. (tumour$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
33. (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
34. or/26-33
35. 15 or 25 or 34
36. 14 and 35
37. randomized controlled trial.pt.
38. controlled clinical trial.pt.
39. Randomized controlled trials/
40. Random allocation/
41. Double-blind method/
42. Single-blind method/
43. or/37-42
44. clinical trial.pt.
45. exp Clinical trials/
46. (clin$ adj25 trial$).tw.
47. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw.
48. Placebos/
49. placebo$.tw.
50. random$.tw.
51. Research design/
52. or/44-51
53. "comparative study"/
54. exp evaluation studies/
55. Follow-up studies/
56. Prospective studies/
57. (control$ or prospectiv$ or volunteer$).tw.
58. or/53-57
59. 43 or 52 or 58

60. "animal"/
61. "human"/
62. 60 not 61
63. 59 not 62
64. 36 and 63

PUBMED
July 2004–2005
Version not known
Search undertaken January 2005

#18. Search #15 and #16 Field: All fields, Limits: 180 Days
#17. Search #15 and #16
#16. Search colorectal or colon* or rectal or rectum
#15. Search #8 or #14
#14. Search #9 or #10 or #11 or #12 or #13
#13. Search x act
#12. Search 5 deoxy 5 fluoro n pentyloxy carbonyl cytidine
#11. Search 154361-50-9
#10. Search xeloda
#9. Search capecitabine
#8. #1 or #2 or #3 or #4 or #5 or #6 or #7
#7. Search mosaic
#6. Search 1r 2r 1 2 cyclohexanediamine n n oxalato 2 o o platinum
#5. Search eloxatin
#4. Search l ohp
#3. Search 63121-00-6
#2. Search 63121 00 6
#1. Search oxaliplatin

WoS
1981–2005
Version not known
Search undertaken January 2005

#21. #17 or #20
#20. #13 and #16
#17. #13 and #15
#16. ts=random*
#15. ts=trial*
#13. #9 or #11 or #12
#12. #3 and #8
#11. #3 and #7
#9. #3 and #5
#8. ts=rectal or ts=rectum
#7. ts=colon or ts=colonic
#5. ts=colorectal
#3. #1 or #2
#2. ts=capecitabine or ts=xeloda or ts=x act
#1. ts=oxaliplatin or ts=l ohp or ts=eloxatin or ts=mosaic

Appendix 4

Studies excluded from the review of clinical effectiveness

Author, year	Reason for exclusion
Abushullaih *et al.*, 2002[189]	Advanced/metastatic cancer
Anon, 2004[190]	Letter/comment/editorial
Anon, 2004[191]	Letter/comment/editorial
Anon, 2003[192]	Economics
Arkenau and Porschen, 2004[193]	Review – not systematic
Au *et al.*, 2003[81]	Wrong comparator/intervention/outcome
Berg, 2003[178]	Review – not systematic
Bleiberg, 2000[194]	Review – not systematic
Borner *et al.*, 2001[195]	Review – not systematic
Brezault *et al.*, 1999[196]	Review – not systematic
Cascinu *et al.*, 2001[197]	Review – not systematic
Cascinu *et al.*, 2000[198]	Review – not systematic
Cassidy and Misset, 2002[100]	Review – not systematic
Cersosimo, 2005[99]	Wrong comparator/intervention/outcome
Conroy and Blazeby, 2003[199]	Review – not systematic
Coppola *et al.*, 2002[65]	Ongoing
de Gramont *et al.*, 2004[200]	Letter/comment/editorial
Dogliotti *et al.*, 2000[201]	Review – not systematic
Efficace *et al.*, 2004[136]	Wrong comparator/intervention/outcome
Garufi *et al.*, 2003[202]	Letter/comment/editorial
Gill *et al.*, 2004[87]	Wrong comparator/intervention/outcome
Goldberg *et al.*, 2002[203]	Review – not systematic
Goodman, 2002[204]	Letter/comment/editorial
Kohne *et al.*, 2001[79]	Review – not systematic
Kullmann, 2003[205]	Review – not systematic
Kullmann, 2003[206]	Review – not systematic
Kullmann, 2003[207]	Review – not systematic
Labianca *et al.*, 2004[208]	Wrong comparator/intervention/outcome
Laino, 2003[209]	Letter/comment/editorial
Mamounas *et al.*, 1999[105]	Wrong comparator/intervention/outcome
Mandala *et al.*, 2004[210]	Letter/comment/editorial
Marse *et al.*, 2004[128]	Review – not systematic
Marshall, 2004[129]	Review – not systematic
Maung *et al.*, 2003[211]	Letter/comment/editorial
Maxwell-Armstrong and Scholefield, 2004[86]	Review – not systematic
Mayer, 2004[73]	Letter/comment/editorial
National Horizon Scanning Centre, 2003[212]	Review – not systematic
Patel *et al.*, 2004[27]	Wrong comparator/intervention/outcome
Ragnhammar *et al.*, 2001[213]	Review – not systematic
Reddy and Chu, 2004[214]	Letter/comment/editorial
Rougier *et al.*, 2004[78]	Review – not systematic
Saini *et al.*, 2003[140]	Wrong comparator/intervention/outcome
Sakamoto *et al.*, 2004[106]	Wrong comparator/intervention/outcome
Sargent *et al.*, 2004[70]	Wrong comparator/intervention/outcome
Sargent *et al.*, 2001[80]	Wrong comparator/intervention/outcome
Sorich *et al.*, 2004[215]	Review – not systematic
Thomas *et al.*, 2003[216]	Case report
Tisman *et al.*, 2004[217]	Case report
Walko, 2005[126]	Review – not systematic
Wils *et al.*, 2001[218]	Review – not systematic
Zaniboni, 2000[219]	Review – not systematic
Zeuli *et al.*, 2001[220]	Review – not systematic

Appendix 5

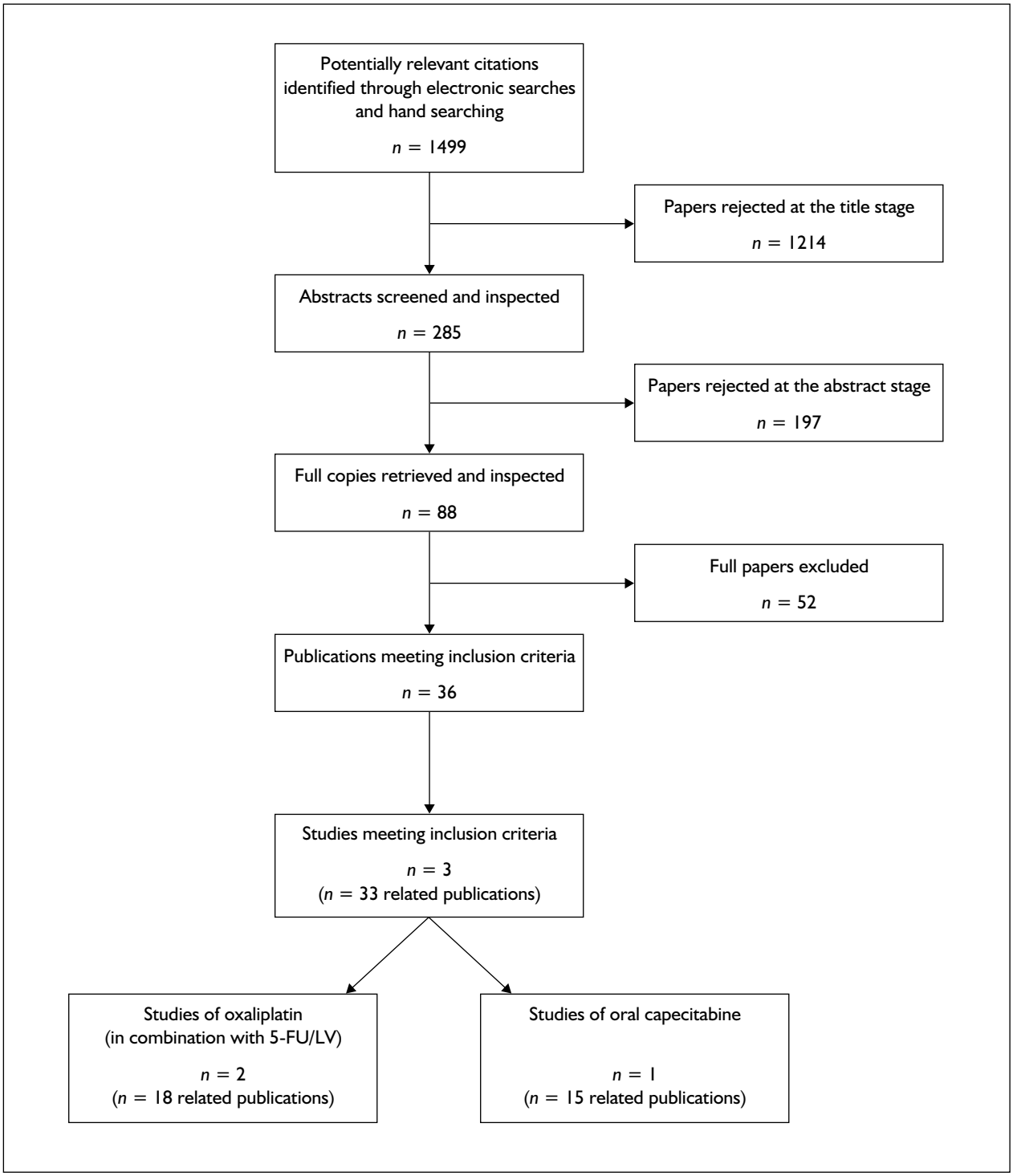
Quality assessment scale for randomised controlled trials (adapted)[41]

1. Was the method used to assign participants to the treatment groups really random?
2. What method of assignment was used?
   (Computer-generated random numbers and random number tables were accepted as adequate, while inadequate approaches will include the use of alternation, case record numbers, birth dates and days of the week.)
3. Was the allocation of treatment concealed?
4. What method was used to conceal treatment allocation?
   (Concealment was deemed adequate where randomisation is centralised or pharmacy controlled, or where the following are used: serially numbered identical containers, on-site computer-based systems where the randomisation sequence is unreadable until after allocation, other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque.)
5. Was the number of participants who were randomised stated?
6. Were details of baseline comparability presented?
7. Was baseline comparability achieved?
8. Were the eligibility criteria for study entry specified?
9. Were any co-interventions identified that may influence the outcomes for each group?
10. Were the outcome assessors blinded to the treatment allocations?
11. Were the individuals who administered the intervention blinded to the treatment allocation?
12. Were the participants who received the intervention blinded to the treatment allocation?
13. Was the success of the blinding procedure assessed?
14. Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?
15. Were the reasons for withdrawal stated?
16. Was an ITT analysis included?

Items were graded in terms of yes (item addressed), no (item not properly addressed); unclear or not enough information (?) or not applicable (NA).

Appendix 6

QUORUM trial flow chart (clinical effectiveness)



Appendix 7

Data extraction tables

Trial: MOSAIC

Study and design	Data extraction	
Trial MOSAIC	***Review details*** **Author, year**	Andre *et al.*, 2004[45] *[**1**]: de Gramont *et al.*, 2003[52] *[**2**]: de Gramont *et al.*, 2005[47] *[**3**]: de Gramont *et al.*, 2005[48] *[**4**]: Hickish *et al.*, 2004[56] *[**5**]: Hickish *et al.*, 2004[54] *[**6**]: Sanofi-Synthelabo, 2004[57] *[**7**]: Tabah-Fisch *et al.*, 2002[58] *[**8**]: de Gramont, 2004[51]
Study design Phase 3, multi-centre RCT	**Objective**	To determine if postoperative adjuvant treatment with oxaliplatin in combination with 5-FU and LV (*[**2**]: LV5FU2) chemotherapy improves survival outcomes in patients with Stage II or III colon cancer
	Publication type (i.e. full report or abstract)	Full report
	Country of corresponding author	France
	Language of publication	English
	Sources of funding	Supported by Sanofi-Synthelabo (who also collected, managed and analysed the data)
	Interventions **Focus of interventions (comparisons)**	Oxaliplatin in combination with LV5FU2 (*[**3**]: FOLFOX4 regimen) versus LV5FU2 alone
	Description T1: Intervention group, dose, timings	Oxaliplatin (85 mg/m^2 over 2 h on day 1, given simultaneously with LV, with use of a Y infusion device) in combination with LV5FU2 (2-h infusion of 200 mg/m^2 LV plus a bolus of 400 mg/m^2 5-FU on day 1, followed by a 22-h infusion of 600 mg/m^2 5-FU on 2 consecutive days every 14 days for 12 cycles)
	T2: Control group, dose, timings	LV5FU2 alone (2-h infusion of 200 mg/m^2 LV plus a bolus of 400 mg/m^2 5-FU on day 1, followed by a 22-h infusion of 600 mg/m^2 5-FU on 2 consecutive days every 14 days for 12 cycles)
	Intervention site (healthcare setting, country)	146 medical centres in 20 countries (France, UK, Spain, Italy Belgium, Greece, Hungary, The Netherlands, Portugal, Germany, Sweden, Austria, Poland, Denmark, Norway, Cyprus and Switzerland, Australia, Israel, Singapore)
	Duration of intervention	12 cycles (6 months)
	Length of follow-up	~3 years T1: median 37.9 months (range 27–54) T2: median 37.8 months (range 27–54)

continued

Study and design	Data extraction	
		COMMENT Final results for the overall population (cut-off date for primary statistical analysis, 22 April 2003) with a median follow-up of ~3 years have been reported in a peer-reviewed journal. *[**2**]: Follow-up is ongoing for a minimum of 5 years for each patient for final survival analysis. Additional updated results (abstract form) have been reported for a median follow-up of 48.6 months (*[**3**]: (as of June 1, 2004) T1: median follow-up 48.6 months; T2: median follow-up 48.4 months)
	Study characteristics	
	Method of randomisation	
	Description Generation of allocation sequences	Patients were randomly assigned to receive either oxaliplatin (in combination with LV5FU2) or LV5FU2 alone Randomisation was performed centrally (by a computer via a central randomisation system) with stratification (minimisation method) according to centre, tumour stage (T2 or T3 vs T4 and N0, N1 or N2) and presence or absence of bowel obstruction or tumour perforation
		COMMENT Adequate method
	Allocation concealment?	Yes, central remote randomisation (de Gramont A, Hôpital Saint Antoine, Paris: personal communication, 2005)
		COMMENT Adequate method
	Blinding level	Unblinded (unmasked) (de Gramont A, Hôpital Saint Antoine, Paris: personal communication, 2005)
		COMMENT Patients, investigators, outcome assessors and statistical analyst were all unblinded (unmasked) (de Gramont A, Hôpital Saint Antoine, Paris: personal communication, 2005)
	Numbers included in the study	2246
	Numbers randomised	T1: 1123 T2: 1123
	Population characteristics	
	Target population (describe)	Adult patients with confirmed Stage II (T3 or T4, N0, M0) or Stage III (any T, N1 or N2, M0) colon cancer, who had undergone complete surgical resection of the primary tumour
	Inclusion/exclusion criteria (*n*)	Inclusion (eligibility) criteria • Complete resection of histologically confirmed Stage II (T3 or T4, N0, M0) or Stage III (any T, N1 or N2, M0) colon cancer • Treatment commencing within 7 weeks after surgery • Aged between 18 and 75 years • Karnofsky performance-status score of at least 60 • CEA level of less than 10 ng/ml • Written informed consent

continued

Study and design	Data extraction

Exclusion criteria
- Patients who had previously received chemotherapy, immunotherapy or radiotherapy
- Inadequate blood counts, liver and kidney function

DEFINITION
Resection of histologically proven Stage II (T3 or T4, N0, M0) or Stage III (any T, N1 or N2, M0) colon cancer
Defined by the presence of the inferior pole of the tumour above the peritoneal reflection – that is, at least 15 cm from the anal margin

COMMENT
- Adequate blood counts; liver and kidney function – not defined
- 41 patients (1.8%) who were included in the trial did not strictly meet all eligibility criteria (see table below):

Reason	T1	T2
Resection of primary tumour incomplete	1	1
History of cancer including colorectal cancer	4	6
Stage IV cancer	4	9
Cancer of middle, lower rectum	2	1
Other eligibility violations	4	9
Total	15	26

Recruitment procedures used (participation rates if available)

Patients (n = 2246) were recruited between October 1998 and January 2001 at medical centres in 20 countries. The overall median duration between surgery and the beginning of chemotherapy was 5.7 weeks (range: 1.1–17.0).

COMMENT
Not clear how many patients were initially screened

Characteristics of participants at baseline

Age (mean, years)

Baseline characteristics

Characteristics	T1 (n = 1123)	T2 (n = 1123)
ALL PATIENTS		
Age (years)		
Median	61	60
Range	19–75	20–75
Age <65 years: No. (%)	723 (64.4)	743 (66.2)
Sex: No. (%)		
Male	630 (56.1)	588 (52.4)
Female	493 (43.9)	535 (47.6)

continued

Study and design	Data extraction

Characteristics	T1 (*n* = 1123)	T2 (*n* = 1123)
Karnofsky performance-status score: No. (%)		
<60	5 (0.4)	5 (0.4)
60–70	150 (13.4)	134 (11.9)
80–100	968 (86.2)	984 (87.6)
Disease stage: No. (%)		
II	451 (40.2)	448 (39.9)
III	672 (59.8)	675 (60.1)
Depth of invasion: No. (%)		
T2	51 (4.5)	54 (4.8)
T3	853 (76.0)	852 (75.9)
T4	213 (19.0)	208 (18.5)
Unknown	6 (0.5)	9 (0.8)
Bowel obstruction: No. (%)	201 (17.9)	217 (19.3)
Perforation: No. (%)	78 (6.9)	78 (6.9)
Histological appearance: No. (%)		
Well differentiated	934 (83.2)	914 (81.4)
Poorly differentiated	142 (12.6)	148 (13.2)
Unknown	47 (4.2)	61 (5.4)
PATIENTS WITH STAGE III DISEASE: No. (%)		
Number of nodes involved		
1–4	499 (44.4)	513 (45.7)
>4	170 (15.1)	160 (14.2)
Unknown	2 (0.2)	2 (0.2)
PATIENTS WITH STAGE II DISEASE: No. (%)		
T4	84 (18.6)	87 (19.4)
Number of lymph nodes examined		
<10	152 (33.7)	149 (33.3)
≥10	295 (65.4)	294 (65.6)
Bowel obstruction	71 (15.7)	87 (19.4)
Perforation	38 (8.4)	43 (9.6)
Histological appearance		
Well differentiated	385 (85.4)	378 (84.4)
Poorly differentiated	47 (10.4)	42 (9.4)
Unknown	19 (4.2)	28 (6.3)

continued

Study and design	Data extraction	
	Gender (male/female)	See table above (baseline characteristics)
	Performance scale/status	See table above (baseline characteristics)
	Tumour stage	See table above (baseline characteristics)
	Other information	Baseline assessments involved a medical history taking, physical examination, biological tests, measurement of the CEA level, chest radiography and abdominal ultrasonography or CT
	Were intervention and control groups comparable?	Yes, baseline patient characteristics were well balanced between treatment groups
	Outcomes	
	Definition of primary outcomes	• Disease-free survival (after 3 years of follow-up) DEFINITIONS Defined as the time from randomisation to relapse of colorectal cancer or death, whichever occurred first. Second colorectal cancers were considered relapses, whereas non-colorectal tumours were disregarded in the analyses COMMENT Disease-free survival was selected as the primary end-point of the study because the authors assumed that the absence of relapse was the best indicator of efficacy, since it relates directly to the effect of the treatment under investigation
	Definition of secondary outcomes	• Safety (including long-term adverse effects) • Overall survival DEFINITIONS • Overall survival was defined as the time of randomisation to death from any cause
	Definition of tertiary outcomes	Not applicable
	Definition of other outcomes	Not applicable
	Analysis	
	Statistical techniques used	*Primary outcome analysis* Comparison of disease-free survival between groups after 3 years of follow-up (ITT principle, with use of two-sided log-rank test stratified according to baseline disease stage). Cox proportional hazards model used to calculate hazard ratios and 95% CIs. Survival curves drawn according to Kaplan–Meier methods *Secondary outcome analysis* • Descriptive analyses of overall survival • Safety analyses included patients who had received at least one cycle of treatment. Adverse events were graded according to the criteria of the National Cancer Institute Common Toxicity, where a score of 1 indicates mild adverse effects, 2 moderate adverse effects, 3 severe adverse effects and 4 life-threatening adverse effects

continued

Study and design	Data extraction	
		COMMENT Additional analyses, not specified in the protocol, were requested by drug regulatory agencies (de Gramont A, Hôpital Saint Antoine, Paris: personal communication, 2005 and *[**6**]). *[**6**]: An *ad hoc* analysis was carried out after all the patients in the MOSAIC trial had been followed up for a minimum of 3 years, *[**2**];*[**3**]: by which time the median follow-up was 48.6 months (as of 1 June 2004). Follow-up is ongoing for a minimum of 5 years for each patient for final survival analysis
	ITT analysis	Yes
	Does technique adjust for confounding?	*Additional analyses* To assess consistency of the effect of treatment on disease-free survival across prognostic subgroups, hazard ratios and 95% CIs were calculated for the following variables: • Sex • Age • Disease stage (II vs III) • Baseline serum CEA level • Number of involved lymph nodes (≥ 4 vs >4) • T classification (T4 vs T1, T2 or T3) • Degree of cellular differentiation (well vs poorly differentiated) • Presence or absence of perforation, obstruction and venous invasion
	Power calculation (*a priori* sample calculation)	Yes, assuming a 3-year disease-free survival rate of 79% in T1 and 73% in T2, with a ratio of Stage II disease to Stage III disease of 0.4:0.6, a recruitment and follow-up period of 3 years, a decrease in the risk of relapse after three years, a statistical power of 90% and an alpha value of 0.05 and two-sided *p*-values derived with the use of the log-rank test, the authors estimated a sample size of 2200 patients (*[**1**]: 1100 per treatment arm) COMMENT • *[**1**]: Based on the above hypotheses, the cut-off date for the final analysis was foreseen as 3 years after the entry date of the last subject enrolled or the date where 27% of the patients would have relapsed or died • Trial not powered to detect differences in disease-free survival beyond 3 years or various subgroups
	Attrition rates (overall rates) i.e. loss to follow-up	**Numbers followed and loss to follow-up**

	T1 (*n* = 1123)	**T2 (*n* = 1123)**
At 3 years		
Known alive	990 (88.2%)	977 (87.0%)
Confirmed death	133 (11.8%)	146 (13.0%)
*[3]: At 4 years		
Known alive	947 (84.3%)	929 (82.7%)
Confirmed death	176 (15.7%)	194 (17.3%)

continued

Study and design	Data extraction	
	Was attrition adequately dealt with?	Yes, ITT
	Number (%) followed up from each condition	See table above (loss to follow-up)
	Compliance with study treatment	See below
	Adherence to study treatment	Chemotherapy *Discontinuations* *[**6**]: Discontinuation of treatment owing to adverse effects occurred in 15% of patients receiving T1 *Cycles* • Of the 1123 patients assigned to T1, 1108 (98.7%) received at least one cycle of oxaliplatin plus LV5FU2. Of the 1123 patients assigned to T2, 1111 (98.9%) received at least one cycle of LV5FU2 • Median number of cycles of chemotherapy received in both groups was 12 (T1: 74.7% and T2: 86.5% received the planned 12 cycles) *Dosing* A summary of the dosing is given below:

	T1 (*n* = 1108)	**T2 (*n* = 1111)**
Median relative dose intensity (%)		
5-FU	84.4	97.7
Oxaliplatin	80.5	Not applicable

COMMENT
Dose reductions based on worst adverse effects during previous cycle. Oxaliplatin reduced to 75 mg/m^2 in event of persistent (at least 14 days) paraesthesias, temporary painful paraesthesias or functional impairment. In cases of persistent painful paraesthesias or functional impairment, oxaliplatin was discontinued. Together with reductions in dose of oxaliplatin, the bolus dose of 5-FU was reduced to 300 mg/m^2 and the infusion to 500 mg/m^2 in event of grade 3 or 4 neutropenia or thrombocytopenia (or both), diarrhoea, stomatitis or other drug-related adverse effects of grade 3. Only dose of 5-FU scheduled to be reduced in event of skin-related adverse effects of grade 3 or 4. Treatment delayed up to 3 weeks until patient recovered from various adverse effects, neutrophil count exceeded 1500/mm^3 and platelet count exceeded 100,000/mm^3. Chemotherapy was stopped in event of cardiac neurocerebellar adverse effects or grade 3 or 4 allergic reactions

continued

Study and design	Data extraction
	Results **Quantitative (e.g. estimates of effect size); qualitative results; effect of the intervention on other mediating variables** (Example outcomes: overall survival, relapse-free survival, disease-free survival, response rates)

Primary outcome analysis

Disease-free survival at 3 years (ITT analysis)

Parameter	T1	T2
All patients (Stage II and III colon cancer)		
Number of patients	1123	1123
Median follow-up (months)	37.9	37.8
Number of events (relapse or death)	237 (21.1%)	293 (26.1%)
Relapse	208 (18.5%)	279 (24.8%)
Death without relapse	29 (2.6%)	14 (1.2%)
Number of patients without event	886 (78.9%)	830 (73.9%)
Disease-free survival at 3 years	78.2% (95% CI: 75.6 to 80.7)	72.9% (95% CI: 70.2 to 75.7)
Hazard ratio (for recurrence)	0.77 (95% CI: 0.65 to 0.91)	
Reduction in risk of relapse	23%	
Stratified log-rank test	$p = 0.002$	
NNTB	18.2 (95% CI: 11.7 to 47.5)	
Absolute difference in survival	5.3%	

COMMENT

Author reports that the global test for interaction between treatment and tumour stage (Stage II and III colon cancer) was not significant ($p = 0.77$)

***[3]: Disease-free survival at 4 years (ITT)[a]**

Parameter	T1	T2
All patients (Stage II and III colon cancer)		
Number of patients	1123	1123
Median follow-up (months)	48.6	48.4
Number of events (relapse or death)	267 (23.8%)	332 (29.6%)
Relapse	Not reported	Not reported
Death without relapse	Not reported	Not reported
Number of patients without event	856 (76.2%)	791 (70.4%)
Disease-free survival at 4 years	75.9% (*[**6**]: 95% CI: 73.4 to 78.5)	69.1% (*[**6**]: 95% CI: 66.3 to 71.9)
Hazard ratio (for recurrence)	0.76 (95% CI: 0.65 to 0.90)	
Reduction in risk of relapse	24%	
Stratified log-rank test	$p = 0.0008$	
NNTB	15.6 (95% CI: 10.5 to 38.4)	
Absolute difference in survival	6.8%	

continued

Study and design	Data extraction

[a] All data from *[**3**]; however, missing data extracted from *[**6**]. *[**3**] reports exactly the same data as *[**6**]; however, data from *[**6**] report median follow-up (with minimum follow-up of 41 months) as T1 47.7 months, T2 47.4 months. This suggests that no relapses or deaths occurred between the analyses conducted by *[**3**] and *[**6**]

Secondary outcome analysis

Overall survival at 3 years (*Caution – survival data not mature at time of analysis*)

Parameter	T1	T2
All patients (Stage II and III colon cancer)		
Number of patients	1123	1123
Median follow-up (months)	37.9	37.8
Death from any cause	133 (11.8%)	146 (13.0%)
Number of patients alive	990 (88.2%)	977 (87.0%)
Overall survival at 3 years	87.7% (95% CI: not reported)	86.6% (95% CI: not reported)
Hazard ratio (for death)	0.90 (95% CI: 0.71 to 1.13)	
Reduction in risk of mortality	10%	
Stratified log-rank test	p = not significant	
NNTB	79.7 (95% CI: NNTB 27.1 to NNTH 62.3)	
Absolute difference	1.1%	

NNTH, number needed to treat in order to harm

***[3]: Overall survival at 4 years**[a] (*Caution – survival data not mature at time of analysis*)

Parameter	T1	T2
All patients (Stage II and III colon cancer)		
Number of patients	1123	1123
Median follow-up (months)	48.6	48.4
Death from any cause	176 (15.7%)	194 (17.3%)
Number of patients alive	947 (84.3%)	929 (82.7%)
Alive without recurrence	856 (76.2%)	791 (70.4%)
Alive with recurrence	91 (8.1%)	138 (12.3%)
Overall survival at 4 years	84.0% (95% CI: not reported)	82.4% (95% CI: not reported)
Hazard ratio (for death)	0.89 (95% CI: 0.72 to 1.09)	
Reduction in risk of mortality	11%	
Stratified log-rank test	*[**6**]: p = 0.236	

continued

Study and design	Data extraction

Parameter	T1	T2
NNTB	56.4 (95% CI: NNTB 21.8 to NNTH 70.3)	
Absolute difference	1.6%	

[a] All data from *[**3**]; however, missing data extracted from *[**6**]. *[**3**] reports exactly the same data as *[**6**]; however, data from *[**6**] report median follow-up (with minimum follow-up of 41 months) as T1 47.7 months, T2 47.4 months. This suggests that no deaths occurred between the analyses conducted by *[**3**] and *[**6**]

Additional analyses

Disease-free survival at 3 years

Parameter	T1	T2
Median follow-up (months)	37.9	37.8
Patients with Stage III (any T, N1 or N2, M0) colon cancer		
Number of patients	672	675
Number of events (relapse or death)	181 (26.9%)	226 (33.5%)
Number of patients without event[a]	491 (73.1%)	449 (66.5%)
Disease-free survival at 3 years	72.2% (95% CI: not reported)	65.3% (95% CI: not reported)
Hazard ratio (for recurrence)	0.76 (95% CI: 0.62 to 0.92)	
Reduction in risk of relapse	24%	
Stratified log-rank test	p = significant	
NNTB	14.2 (95% CI: 8.7 to 44.2)	
Absolute difference in survival	6.9%	
Patients with Stage II (T3 or T4, N0, M0) colon cancer		
Number of patients	451	448
Number of events (relapse or death)	56 (12.4%)	67 (15.0%)
Number of patients without event[a]	395 (87.6%)	381 (85%)
Disease-free survival at 3 years	87.0% (95% CI: not reported)	84.3% (95% CI: not reported)
Hazard ratio (for recurrence)	0.80 (95% CI: 0.56 to 1.15)	
Reduction in risk of relapse	20%	
Stratified log-rank test	p = not significant	
NNTB	34.1 (95% CI: NNTB 15.2 to NNTH 44.9)	
Absolute difference in survival	2.7%	
***[4]: High-risk patients with Stage II colon cancer[b]**		
Number of patients	286	290
Number of events (relapse or death)	Not reported	Not reported

continued

Study and design	Data extraction

Parameter	T1	T2
Number of patients without event[a]	Not reported	Not reported
Disease-free survival at 3 years	*[8]:84.9%	*[8]:79.8%
Hazard ratio (for recurrence)	0.72 (95% CI: 0.48 to 1.08)	
Reduction in risk of relapse	28%	
Stratified log-rank test	p = not significant	
NNTB	19.2 (95% CI: NNTB 10.1 to NNTH 70.1)	
Absolute difference in survival	5.1%	

[a] Data extrapolated

[b] T4 and/or bowel obstruction and/or tumour perforation and/or poorly differentiated tumour and/or venous invasion and/or <10 examined lymph nodes

***[3]: Disease-free survival at 4 years[a]**

Parameter	T1	T2
Median follow-up (months)	48.6	48.4
Patients with Stage III (any T, N1 or N2, M0) colon cancer		
Number of patients	672	675
Number of events (relapse or death)	*[6]: 200 (29.8%)	*[6]: 252 (37.3%)
Disease-free survival at 4 years	69.7% (*[6]: 95% CI: 66.2 to 73.3)	61.0% (*[6]: 95% CI: 57.1 to 64.8)
Hazard ratio (for recurrence)	0.75 (95% CI: 0.62 to 0.90)	
Reduction in risk of relapse	25%	
Stratified log-rank test	p = 0.002	
NNTB	12.5 (95% CI: 7.9 to 32.4)	
Absolute difference in survival	8.7%	
Patients with Stage II (T3 or T4, N0, M0) colon cancer		
Number of patients	451	448
Number of events (relapse or death)	*[6]: 67 (14.9%)	*[6]: 80 (17.9%)
Disease-free survival at 4 years	85.1% (*[6]: 95% CI: 81.7 to 88.6)	81.3 (*[6]: 95% CI: 77.6 to 85.1)
Hazard ratio (for recurrence)	0.80 (95% CI: 0.58 to 1.11)	
Reduction in risk of relapse	20%	
Stratified log-rank test	*[6]: p = 0.179	
NNTB	29.1 (95% CI: NNTB 13.5 to NNTH 54.6)	
Absolute difference in survival	3.8%	

continued

Study and design	Data extraction

Parameter	T1	T2
High-risk patients with stage II colon cancer[b]		
Number of patients	286	290
Number of events (relapse or death)	Not reported	Not reported
Disease-free survival at 4 years	Not reported	Not reported
Hazard ratio (for recurrence)	0.77 (95% CI: not reported)	
Reduction in risk of relapse	23%	
Stratified log-rank test	p = not significant	
NNTB	Not calculable	
Absolute difference in survival	5.4%	

[a] All data from *[**3**]; however, missing data extracted from *[**6**]. *[**3**] reports exactly the same data as *[**6**]; however, data from *[**6**] report median follow-up (with minimum follow-up of 41 months) as T1 47.7 months, T2 47.4 months. This suggests that no relapses or deaths occurred between the analyses conducted by *[**3**] and *[**6**]

[b] T4 and/or bowel obstruction and/or tumour perforation and/or poorly differentiated tumour and/or venous invasion and/or <10 examined lymph nodes

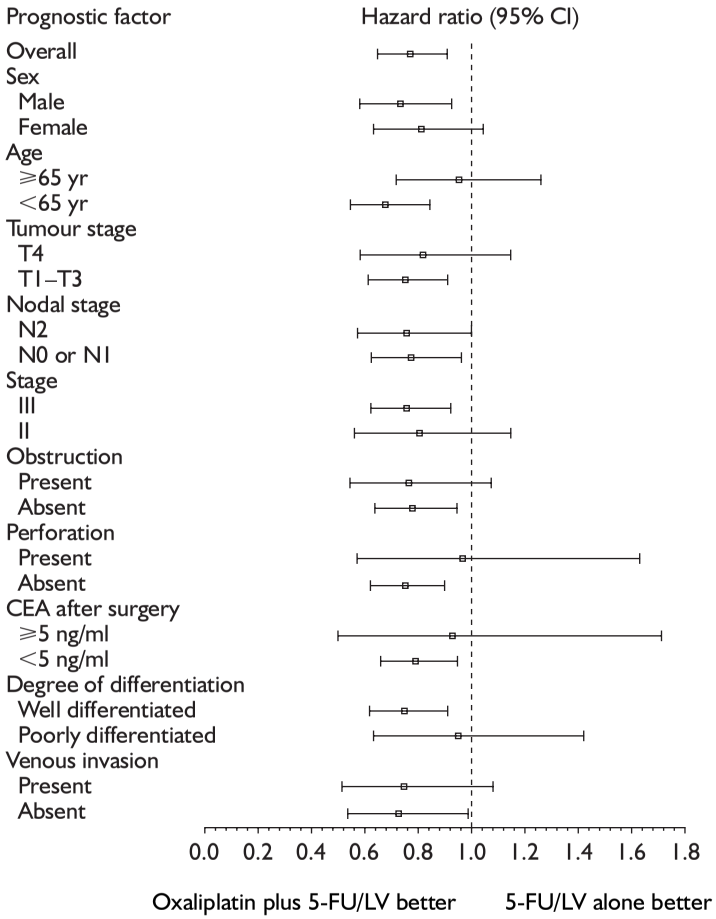
Disease-free survival at 3 years according to baseline prognostic factors and ITT (hazard ratios and 95% CIs)

In a subpopulation, the potential association of disease-free survival with other baseline prognostic factors was evaluated using a Cox model analysis. As shown in the figure below, calculation of hazard ratios and 95% CIs showed that the reduced risk of recurrence was consistent in all subgroups defined on the basis of prognostic factors at baseline.

continued

Study and design	Data extraction

Subgroup analysis: disease-free survival at 3 years



continued

Study and design	Data extraction		
	Overall survival at 3 years (*Caution – survival data not mature at time of analysis*)		
	Parameter	**T1**	**T2**
	Median follow-up (months)	37.9	37.8
	Patients with Stage III (any T, N1 or N2, M0) colon cancer		
	Number of patients	672	675
	Death from any cause	104 (15.5%)	119 (17.6%)
	Number of patients alive	568 (84.5%)	556 (82.4%)
	Overall survival at 3 years	Not reported	Not reported
	Hazard ratio (for death)	0.86 (95% CI: 0.66 to 1.11)	
	Reduction in risk of mortality	14%	
	Stratified log-rank test	p = not significant	
	NNTB	Not calculable	
	Absolute difference in survival	Not reported	
	Patients with Stage II (T3 or T4, N0, M0) colon cancer		
	Number of patients	451	448
	Death from any cause	29 (6.4%)	27 (6.0%)
	Number of patients alive	422 (93.6%)	421 (94.0%)
	Overall survival at 3 years	Not reported	Not reported
	Hazard ratio (for death)	Not reported	
	Reduction in risk of mortality	Not reported	
	Stratified log-rank test	Not reported	
	NNTB	Not calculable	
	Absolute difference in survival	Not reported	
	***[6]: Overall survival at 4 years** (*Caution – survival data not mature at time of analysis*)		
	Parameter	**T1**	**T2**
	Median follow-up (months)	47	47
	Patients with Stage III (any T, N1 or N2, M0) colon cancer		
	Number of patients	672	675
	Death from any cause	Not reported	Not reported
	Number of patients alive	Not reported	Not reported
	Overall survival at 4 years	Not reported	Not reported
	Hazard ratio (for death)	0.86 (95% CI: 0.68 to 1.08)	
	Reduction in risk of mortality	14%	
	Stratified log-rank test	p = 0.196	
	NNTB	Not calculable	
	Absolute difference in survival	Not reported	

continued

Study and design	Data extraction

Parameter	T1	T2
Patients with Stage II (T3 or T4, N0, M0) colon cancer		
Number of patients	451	448
Death from any cause	Not reported	Not reported
Number of patients alive	Not reported	Not reported
Overall survival at 4 years	Not reported	Not reported
Hazard ratio (for death)	0.98 (95% CI: 0.63 to 1.53)	
Reduction in risk of mortality	2%	
Stratified log-rank test	$p = 0.94$	
NNTB	Not calculable	
Absolute difference in survival	Not reported	

Toxicity

Secondary outcome analysis – treatment-related adverse events

Discontinuations

*[**6**]: Discontinuation of treatment due to adverse effects occurred in 15% of patients receiving T1; however, *[**5**] reported discontinuations as T1 14.4% versus T2 5.5% (see table below – adverse event profile by stage of disease)

Mortality after 28 days of treatment

The incidence of death within 28 days of last treatment, regardless of causality, was 0.5% ($n = 6$) in both T1 and T2 (see table below):

Cause of death	T1 ($n = 1108$)	T2 ($n = 1111$)
Infection or sepsis	4[a]	1
Intracranial haemorrhage	2	–
Anoxic cerebral infarction	–	1
Stevens–Johnson syndrome	–	1
Cardiac causes	–	2
Suicide	–	1
Total	6 (0.5%)	6 (0.5%)

[a] Two with neutropenia

Mortality after 60 days of treatment

The incidence of death within 60 days of last treatment, regardless of causality, was 0.3% ($n = 3$) in both T1 and T2

continued

Study and design	Data extraction

Adverse event profile (all data are percentages)[a]

Adverse Event	T1 (n = 1108)			T2 (n = 1111)			p-Value[b]	
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3 and 4
Paraesthesia	92.0	12.4	NA	15.6	0.2	NA	<0.001	0.001
Neutropenia	78.9	28.8	12.3	39.9	3.7	1.0	<0.001	<0.001
Thrombocytopenia	77.4	1.5	0.2	19.0	0.2	0.2	<0.001	0.001
Anaemia	75.6	0.7	0.1	66.9	0.3	0.0	<0.001	0.09
Nausea	73.7	4.8	0.3	61.1	1.5	0.3	<0.001	<0.001
Diarrhoea	56.3	8.3	2.5	48.4	5.1	1.5	<0.001	<0.001
Vomiting	47.2	5.3	0.5	24.0	0.9	0.5	<0.001	<0.001
Stomatitis	41.6	2.7	0.0	39.6	2.0	0.2	0.34	0.41
Skin[c]	31.5	1.4	0.6	35.5	1.7	0.7	0.05	0.67
Alopecia[d]	30.2	NA	NA	28.1	NA	NA	0.28	NA
Allergic reaction	10.3	2.3	0.6	1.9	0.1	0.1	<0.001	<0.001
Thrombosis or phlebitis	5.7	1.0	0.2	6.5	1.7	0.1	0.48	0.29
Neutropenia with fever or infection	1.8	1.4	0.4	0.2	0.1	0.1	<0.001	<0.001

NA, not applicable

[a] Adverse effects graded according to the Common Toxicity Criteria of the National Cancer Institute, version 1 (i.e. grade 1, mild adverse effects; grade 2, moderate adverse effects; grade 3, severe adverse effects; and grade 4, life-threatening adverse effects)

[b] Fisher's exact test used to calculate p-values

[c] Includes hand–foot syndrome

[d] Incidence of grade 2 alopecia was 5.0% in each group

Incidence of neurosensory systems during treatment and follow-up[a]

Grade[b]	During treatment (n =1106)	1 month follow-up (n = 1092)	6 months follow-up (n = 1058)	12 months follow-up (n = 1018)	18 months follow-up (n = 967)
0	87 (7.9%)	424 (38.8%)	624 (59.0%)	718 (70.5%)	738 (76.3%)
1	533 (48.2%)	439 (40.2%)	338 (31.9%)	240 (23.6%)	191 (19.8%)
2	349 (31.6%)	174 (15.9%)	82 (7.8%)	49 (4.8%)	33 (3.4%)
3	137 (12.4%)	55 (5.0%)	14 (1.3%)	11 (1.1%)[c]	5 (0.5%)

[a] Only patients who actually received treatment were included in the analysis

continued

Study and design	Data extraction

[b] Grade 0 indicates no change or no symptoms; grade 1 indicates mild paraesthesia and loss of deep tendon reflexes; grade 2 indicates a mild or moderate objective sensory loss and moderate paraesthesia; grade 3 indicates a severe objective sensory loss or paraesthesias that interfere with function

[c] Of these, two patients found to have underlying disease that could have caused symptoms (diabetes and hemiplegia, respectively)

***[5]: Subgroup analyses – adverse event (toxicity) profile by stage of disease (Stage II or III colon cancer)**

Parameter	Stage II (n = 899)	Stage III (n = 1347)	Stage II and III (n = 2246)
Number of treated patients			
Total	891	1328	2219
T1	446	662	1108
T2	445	666	1111
Median no. of T1 cycles received/planned	12/12	11/12	12
Median oxaliplatin cumulative dose (mg/m^2) in T1	914.7 (89.7%)	865.3 (84.8%)	–
Patients having received at least 10 cycles			
Total	779 (87.4%)	1126 (84.8%)	1905 (85.8%)[a]
T1	377 (84.5%)	525 (79.3%)	902 (81.4%)[a]
T2	402 (90.3%)	601 (90.2%)	1003 (90.3%)[a]
Patients with any serious adverse event[b]			
Total	144 (16.2%)	270 (20.3%)	414 (18.7%)[a]
T1	84 (18.8%)	168 (25.4%)	252 (22.7%)[a]
T2	60 (13.5%)	102 (15.3%)	162 (14.6%)[a]
Treatment discontinuation for toxicity[b]			
Total	80 (9.0%)	141 (10.6%)	221 (10.0%)[a]
T1	54 (12.1%)	106 (16.0%)	160 (14.4%)[a]
T2	26 (5.8%)	35 (5.3%)	61 (5.5%)[a]
Death on treatment[b]			
Total	4 (0.4%)	8 (0.6%)	12 (0.5%)
T1	1 (0.2%)	5 (0.8%)	6 (0.5%)
T2	3 (0.7%)	3 (0.5%)	6 (0.5%)

[a] Calculated, based on data presented for Stage II and III patients

[b] Percentages based on treated patients

COMMENT

*[**6**]: discontinuation of treatment due to adverse effects reported as 15% in patients receiving T1 in comparison with 14.4% as noted above

continued

Study and design	Data extraction	
		***[7]: Subgroup analyses – toxicity profile of T1 (grade 3/4)[a] in patients aged <70 years and between 70 and 75 years**

Parameter	Age <70 years	Age between 70–75 years
Number of patients	952	152
Thrombocytopenia	1	3
Anaemia	0.4	3
Neutropenia	40	44
Transaminases/bilirubin	2/4	1/3
Stomatitis	3	1
Vomiting	6	6
Diarrhoea	11	12
Fever/infection	1/4	1/3
Allergy	2	3
Neurotoxicity	12	12

[a] Adverse effects graded according to the Common Toxicity Criteria of the National Cancer Institute

QoL	Not reported
Other information	Not applicable
Summary	
Authors' overall conclusions	The addition of oxaliplatin to a regimen of 5-FU and LV improved the adjuvant treatment of colon cancer
Reviewers' comments	

Trial: NSABP C-07

Study and design	Data extraction	
Trial NSABP C-07	***Review Details*** **Author, year**	Wolmark *et al.*, 2005[46] *[**1**]: Wolmark, 2005[60] *[**2**]: Smith *et al.*, 2003[64] *[**3**]: National Cancer Institutes PDQ® database, 2005[63] *[**4**]: Maung *et al.*, 2004[62] *[**5**]: de Gramont *et al.*, 2003[61]
Study design Phase 3, multi-institution, RCT	**Objective**	*[**3**]: To compare the efficacy of oxaliplatin in combination with 5-FU and LV calcium (FLOX) with 5-FU and LV calcium alone (5-FU/LV) in prolonging disease-free survival and overall survival in patients with Stage II or III carcinoma of the colon
	Publication type (i.e. full report or abstract)	Abstract
	Country of corresponding author	USA
	Language of publication	English
	Sources of funding	Supported by Public Health Service grants from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services
	Interventions **Focus of interventions (comparisons)**	FLOX versus 5-FU/LV alone (*[**4**]: Roswell Park regimen)
	Description	
	T1: Intervention group, dose, timings	Oxaliplatin (85 mg/m^2 i.v. administered on weeks 1, 3 and 5 of each 8-week cycle) in combination with 5-FU/LV (5-FU; 500 mg/m^2 i.v. bolus of 5-FU (*[**3**]: administered after 1 h of LV calcium) plus 500 mg/m^2 i.v. LV calcium for 6 weeks in three 8-week cycles *[**3**]: in the absence of disease progression or unacceptable toxicity)
	T2: Control group, dose, timings	5-FU/LV (5-FU; 500 mg/m^2 i.v. bolus of 5-FU (*[**3**]: administered after 1 h of LV calcium) plus 500 mg/m^2 i.v. LV calcium for 6 weeks in three 8-week cycles *[**3**]: in the absence of disease progression or unacceptable toxicity)
	Intervention site (healthcare setting, country)	*[**2**]: 158 National Surgical Adjuvant Breast and Bowel Project (NSABP) institutions *[**5**]: across the USA, Canada and Australia
	Duration of intervention	24 weeks T1: 8-week cycle of 6 weekly treatments followed by 2 weeks of rest plus oxaliplatin given on weeks 1, 2 and 5, repeated for three cycles T2: 8-week cycle of 6 weekly treatments followed by 2 weeks of rest, repeated for three cycles

continued

Study and design	Data extraction	
	Length of follow-up	~3 years T1: median 34 months T2: median 34 months COMMENT *[**3**]: Patients are followed at 6, 9 and 12 months, then every 6 months for 4 years, and then annually thereafter
	Study characteristics	
	Method of randomisation	
	Description	Patients were randomly assigned to receive either oxaliplatin (in combination with 5–FU/LV) or 5-FU/LV alone
	Generation of allocation sequences	Not reported
	Allocation concealment?	Not reported
	Blinding level	Not reported
	Numbers included in the study	*[**1**]: 2492
	Numbers randomised	*[**1**]: T1: 1247 *[**1**]: T2: 1245
	Population characteristics	
	Target population (describe)	Adult patients with Stage II (T3 or T4, N0, M0) or Stage III (any T, N1 or N2, M0) colon cancer, who had undergone complete surgical resection of the primary tumour
	Inclusion/exclusion criteria (*n*)	*[**3**]: Inclusion (eligibility) criteria • Previously resected potentially curable Stage II or III carcinoma of the colon (T3, 4; N0, 1, 2; M0) • Any age • ECOG performance status 0–2 • At least 10 years (excluding cancer) of life expectancy • Distal extent of tumour(s) at least 12 cm from anal verge on endoscopy • No tumours demonstrating free perforation as manifested by free air or fluid in the abdomen (walled-off perforations allowed) • Adjacent structures (e.g. bladder, small intestine, ovary) involved with primary tumour must have been curatively resected • No prior or concurrent colon tumours other than carcinoma (sarcoma, lymphoma, carcinoid) • No prior invasive colon or rectal malignancy • No primary tumours involving both colon and rectum • No isolated, distant, or non-contiguous intra-abdominal metastases, even if resected • Intestinal obstruction allowed • No more than 42 days since prior curative resection • No prior non-curative surgical resection for this malignancy, except colostomy • No prior laparoscopically assisted colectomy (unless participating in Intergroup Protocol INT 0146 or the Australasian ALCCaS protocol)

continued

Study and design	Data extraction
	• No other concurrent investigational drugs • No concurrent halogenated antiviral agents (e.g. sorivudine) • Granulocyte count at least 1500/mm^3 • Platelet count at least 100,000/mm^3 • Bilirubin normal • Alkaline phosphatase normal • SGOT/SGPT normal • Creatinine normal • No active ischaemic heart disease (New York Heart Association class III–IV) • No myocardial infarction within the past 6 months • No concurrent symptomatic arrhythmia • No other malignancy within the past 5 years except curatively treated squamous cell or basal cell skin cancer, carcinoma in situ of the cervix treated by resection only or lobular carcinoma in situ of the breast • Not pregnant or nursing • Fertile patients must use effective contraception • No non-malignant systemic disease that would preclude study entry • No grade 2 or greater peripheral neuropathy • No psychiatric or addictive disorder that would preclude informed consent *[**3**]: Exclusion criteria • Patients who had previously received chemotherapy, immunotherapy or radiotherapy
Recruitment procedures used (participation rates if available)	*[**1**]: Patients (n = 2492) were recruited between February 2000 and November 2002 at *[2]: 158 NSABP institutions COMMENT Not clear how many patients were initially screened
Characteristics of participants at baseline	
Age (mean, years)	***[1]: Baseline characteristics[a,b]**

Characteristics	T1 (n = 1200)	T2 (n = 1207)
ALL PATIENTS		
Age (years)		
<60	624 (52%)	604 (50%)
60–69	384 (32%)	398 (33%)
70+	192 (16%)	205 (17%)
Positive nodes – No. (%)		
0	348 (29%)	350 (29%)
1–3	540 (45%)	555 (46%)
≥4	312 (26%)	302 (25%)

continued

Study and design	Data extraction

Characteristics	T1 (*n* = 1200)	T2 (*n* = 1207)
Tumour location – No. (%)		
Left colon	240 (20%)	253 (21%)
Right colon	552 (46%)	507 (42%)
Sigmoid	396 (33%)	447 (37%)

[a] Percentages rounded up to whole numbers
[b] Numbers calculated based on percentages

COMMENT
- *[**1**]: Authors reported that 29% of patients in each group had Stage II (Dukes' B) colon cancer
- There appear to be some discrepancies within the table, i.e. percentages do not add up with regard to positive nodes and tumour location in T1

Gender (male/female)	Not reported
Performance scale/status	Not reported
Tumour stage	See table above (baseline characteristics)
Other information	Not reported
Were intervention and control groups comparable?	*[**1**]: Yes, author reports that baseline patient characteristics were well balanced between treatment groups with respect to age, sex, tumour location and node status
Outcomes	
Definition of primary outcomes	• Disease-free survival (after 3 years of follow-up) DEFINITIONS *[**1**]: Defined as the time from randomisation to first recurrence, second primary cancer or death from any cause
Definition of secondary outcomes	• *[**1**]: Overall survival • *[**2**]: Safety (adverse events) DEFINITIONS • Not defined
Definition of tertiary outcomes	Not applicable
Definition of other outcomes	Not applicable
Analysis	
Statistical techniques used	*[**1**]: Primary outcome analysis Comparison of disease-free survival between groups after 3 years of follow-up

continued

Study and design	Data extraction	
	ITT analysis	No, based on per-protocol analysis [i.e. randomised subjects who were non-eligible (including loss to follow-up) were excluded]
	Does technique adjust for confounding?	Not reported
	Power calculation (*a priori* sample calculation)	*[1]: Yes, trial designed with 89% power to detect a 5.4% increase in disease-free survival COMMENT Not clear how or what assumptions were made for the *a priori* sample calculation
	Attrition rates (overall rates), i.e. loss to follow-up	***[1]: Numbers followed and loss to follow-up**

	T1	T2
Randomised	1247	1245
Ineligible or lost to follow-up	47 (3.8%)	38 (3.1%)
Analysis	1200 (96.2%)	1207 (96.9%)

Was attrition adequately dealt with?	Not clear
Number (%) followed-up from each condition	See table above (loss to follow-up)
Compliance with study treatment	Not reported
Adherence to study treatment	*[1]: *Cycles* Proportion of patients completing full oxaliplatin cycles Cycle1: 86.9% Cycle 2: 68.6% Cycle 3: 62.5% COMMENT 72.6% of patients received their full planned chemotherapy dose
Results **Quantitative (e.g. estimates of effect size); qualitative results; effect of the intervention on other mediating variables** (Example outcomes: overall survival, relapse-free survival, disease-free survival, response rates)	***[1]: Primary outcome analysis** **Disease-free survival at 3 years (per protocol analysis)**

Parameter	**T1**	**T2**
All patients (Stage II and III colon cancer)		
Number of patients (analysed)	1200	1207
Median follow-up (months)	34	34

continued

Study and design	Data extraction

Parameter	T1	T2
Number of events (relapse or death)	272 (22.7%)	332 (27.5%)
Relapse	Not reported	Not reported
Death without relapse	Not reported	Not reported
Number of patients without event	928 (77.3%)	875 (72.5%)
Disease-free survival at 3 years	76.5% (95% CI: not reported)	71.6% (95% CI: not reported)
Hazard ratio (for recurrence)	0.79 (95% CI: 0.67 to 0.93)	
Reduction in risk of relapse	21%	
Stratified log-rank test	$p < 0.004$	
Absolute difference in survival	4.9%	

COMMENT

*[1]: Author reports that the global test for interaction between treatment and tumour stage (Stage II and III colon cancer) was not significant ($p = 0.70$)

Toxicity

Treatment-related adverse events

Mortality during treatment

	T1	T2
Death	15 (1.2%)	14 (1.1%)

Overall toxicity profile

*[1]: Gastrointestinal toxicity most common dose-limiting toxicity

- Few cases of dose-limiting grade 3 and 4 granulocytopenia (approximately 3% in either arm)

*[1]: the incidence of grade 3 to 4 diarrhoea in the oxaliplatin (in combination with bolus 5-FU/LV) group was approximately 40%

*[1]: Hospitalisation for diarrhoea or dehydration associated with bowel wall thickening occurred in 56 (4.5%) patients in T1 and 34 (2.7%) patients in T2.

***[1]: Overall toxicity profile**[a]

Grade	T1 ($n = 1200$)	T2 ($n = 1207$)
0–2	456 (38%)	591 (49%)
3	600 (50%)	495 (41%)
4	120 (10%)	109 (9%)
5	12 (1%)	12 (1%)

[a] Numbers calculated based on percentages

continued

Study and design	Data extraction
	COMMENT • The overall toxicity profile was higher in T1 than T2 • Not clear on what grading system was used for assessing overall toxicity • Missing data or data not reported in T1 for 12 patients (1%)

***[1]: Neurotoxicity in oxaliplatin-treated patients[a]**

Grade[b]	During treatment (n = 1200)	12-month follow-up
All patients (grade > 1)	85.4%	29.4
1	Not reported	Not reported
2	Not reported	Not reported
3	8%	0.5%
4	Not reported	Not reported

[a] Only patients who actually received treatment were included in the analysis

[b] Grade 1 indicates paraesthesia/dysaesthesia that do not interfere with function; grade 2 indicates paraesthesia/dysaesthesia interfering with function, but not activities of daily living; grade 3 indicates paraesthesia/dysaesthesias with pain or interference with activities of daily living; grade 4 indicates persistent paraesthesia/dysaesthesias that are disabling or life threatening

	Other *[**2**]: Preliminary safety results, which were previously reported on 1850 patients, revealed that the occurrence of severe enteropathy in the form of (i) hospitalisation for diarrhoea or dehydration with bowel wall injury (5.9% versus 3.3%) and (ii) grade 3/4 diarrhoea with grade 4 neutropenia or enteric sepsis (1.9% versus 0.6%) were higher in the oxaliplatin-based arm, although the duration and severity were similar
Quality of life	Not reported
Other information	Not applicable
Summary **Authors' overall conclusions**	The addition of oxaliplatin to weekly 5-FU/LV significantly improves 3-year disease-free survival in patients with Stage II and III colon cancer
Reviewers' comments	Caution, study only reported in abstract form

Trial: X-ACT

Study and design	Data extraction	
Trial X-ACT	***Review details*** **Author, year**	Twelves *et al.*, 2005[108] *[**1**]: Scheithauer *et al.*, 2003[109] *[**2**]: Cassidy *et al.*, 2004[112] *[**3**]: Cassidy *et al.*, 2004[34] *[**4**]: Diaz-Rubio *et al.*, 2004[114] *[**5**]: Douillard *et al.*, 2004[115] *[**6**]: McKendrick *et al.*, 2004[116] *[**7**]: McKendrick *et al.*, 2004[117] *[**8**]: Roche Products Limited, 2005[20]
Study design Phase 3, multi-centre, randomised, open-label, controlled trial	**Objective**	To demonstrate that disease-free survival with capecitabine is at least equivalent to that achieved with 5-FU plus LV (5-FU/LV, the Mayo Clinic regimen) when administered as adjuvant treatment following surgery for Stage III (Dukes' C) colon cancer
	Publication type (i.e. full report or abstract)	Full report
	Country of corresponding author	UK
	Language of publication	English
	Sources of funding	Supported by Hoffmann-La Roche
	Interventions **Focus of interventions (comparisons)**	Capecitabine versus 5-FU/LV
	Description T1: Intervention group, dose, timings T2: Control group, dose, timings	Oral capecitabine (1250 mg/m^2 of body surface area) taken twice daily on days 1–14, every 21 days Intravenous LV (20 mg/m^2) by rapid infusion followed immediately by an i.v. bolus of 5-FU (425 mg/m^2) on days 1–5, every 28 days (Mayo Clinic regimen)
	Intervention site (healthcare setting, country)	164 centres (clinics) in *[**1**]: 25 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Croatia, Czech Republic, France, Germany, Greece, Israel, Italy, Latvia, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland, Thailand, UK, Uruguay, USA and Yugoslavia)
	Duration of intervention	24 weeks (approximately 6 months) T1: 8 cycles T2: 6 cycles
	Length of follow-up	Median follow-up: 3.8 years

continued

Study and design	Data extraction	
	Study characteristics	
	Method of randomisation	
	Description	Patients were randomly assigned to receive oral capecitabine or 5-FU/LV (the Mayo Clinic regimen) alone
	Generation of allocation sequences	Computer-generated random numbers (Cassidy J, Cancer Research UK Beatson Laboratories, Glasgow: personal communication, 2005) with stratified (by centre) block (size of four) randomisation
		COMMENT Adequate method
	Allocation concealment?	Treatment allocation codes (scratch-off labels)
		COMMENT Adequate method
	Blinding level	Unblinded (unmasked) (Cassidy J, Cancer Research UK Beatson Laboratories, Glasgow: personal communication, 2005)
		COMMENT Patients, investigators, outcome assessors and statistical analyst were all unblinded (unmasked) (Cassidy J, Cancer Research UK Beatson Laboratories, Glasgow: personal communication, 2005)
	Numbers included in the study	1987
	Numbers randomised	T1: 1004 T2: 983
	Population characteristics	
	Target population (describe)	Adult patients with confirmed Stage III (any T, N1 or N2, M0) colon cancer, who had undergone complete surgical resection of the primary tumour
	Inclusion/exclusion criteria (*n*)	Inclusion (eligibility) criteria • Aged 18–75 years (*[**3**]: although some ≥ 75 years were given waivers to participate in study) • Fully recovered after surgery for histologically confirmed Stage III (Dukes' C) colon cancer • Surgery performed within 8 weeks before randomisation • ECOG Performance Status of 0 (indicating normal activity) or 1 (indicating presence of symptoms but nearly full ambulatory capacity) • Life expectancy ≥ 5 years
		Exclusion criteria • Metastatic disease, including tumour cells in ascites or microscopic evidence of residual disease • Prior cytotoxic chemotherapy or organ allografts • Clinically significant cardiac disease • Sever renal impairment • Central nervous system disorders • Pregnant or lactating women and sexually active patients who were unwilling to use contraception

continued

Study and design	Data extraction
Recruitment procedures used (participation rates if available)	Patients (n = 1987) were recruited between November 1998 and November 2001 at participating centres worldwide. The duration between surgery and the beginning of chemotherapy was ≤8 weeks COMMENT Not clear how patients were selected
Characteristics of participants at baseline Age (mean, years)	**Baseline characteristics of patients in the ITT population**

Characteristics	**T1 (n = 1004)**	**T2 (n = 983)**
Age (years)		
*[**8**]:Mean	60.4	61.0
Median	62	63
Range	25 to 80	22 to 82
Age group – number[a] (%)		
<70 years	813 (81)	777 (79)
≥70 years	191 (19)	206 (21)
Gender – number[a] (%)		
Male	542 (54)	532 (54)
Female	462 (46)	451 (46)
Ethnicity – number[a] (%)		
*[**8**]: Caucasian	978 (97)	954 (97)
ECOG performance score – number[a] (%)		
0	853 (85)	836 (85)
1	151 (15)	147 (15)
Nodal status[b] – number[a] (%)		
N1	693 (69)	698 (71)
N2	311 (31)	285 (29)
Tumour stage[b] – number[a] (%)[c]		
T1 or T2	100 (10)	98 (10)
T3	763 (76)	747 (76)
T4	141 (14)	138 (14)
CEA level – number[a] (%)		
≤ ULN	833 (83)	835 (85)
>ULN	90 (9)	69 (7)
Missing data	80 (8)	79 (8)
*[**8**]: Median time from surgery to randomisation (days)	40	40

ULN, upper limit of normal
[a] Numbers calculated based on reported percentages
[b] Staging classification according to *[**8**]: Union Internationale Contre le Cancer
[c] High numbers indicate greater depth of tumour penetration through the bowel wall

continued

Study and design	Data extraction	
	Gender (male/female)	See table above (baseline characteristics)
	Performance scale/status	See table above (baseline characteristics)
	Tumour stage	See table above (baseline characteristics)
	Other information	*[**1**]: Baseline assessments involved medical history taking, physical examination, vital signs, physical measurements, performance status, laboratory tests (haematology, blood chemistry, pregnancy test, urinalysis, CEA level), CT scan or magnetic resonance imaging of abdomen and pelvis, chest X-ray and QoL assessment (QLQ-C30)
	Were intervention and control groups comparable?	Yes, baseline patient characteristics were well balanced between treatment groups. COMMENT There were slightly more patients with CEA levels above the upper limit of normal at baseline in T1 (8.6%) than T2 (7.0%). The proportion of patients with involvement of four or more regional lymph nodes (Stage N2 disease), as opposed to involvement of one to three nodes (Stage N1 disease), was slightly higher in T1 (30.8%) than T2 (29.4%)
	Outcomes	
	Definition of primary outcomes	Primary end-points • Equivalence in disease-free survival DEFINITION Disease-free survival: defined as the time between randomisation and the first relapse, a second primary colon cancer, death from any cause when no evidence of relapse was recorded or the last date at which the patient was known to be free of disease (censoring time)
	Definition of secondary outcomes	Secondary end-points • Relapse-free survival • Overall survival • Safety (*[**3**]: recorded and graded according to National Cancer Institute of Canada Common Toxicity Criteria) • *[**3**]: Pharmaco-economics and medical resource utilisation • *[**3**]: QoL DEFINITIONS Relapse-free survival: defined as the time between randomisation and the first relapse, a second primary colon cancer, death due to treatment-related toxic effects or colon cancer if relapse had not been reported. Data on patients without documented relapse or with death unrelated to colon cancer or the study treatment were censored as of the last date on which the patient was known to be free of disease Overall survival: defined as the time from randomisation to death or the date at which the patient was last confirmed to be alive (censoring time)

continued

Study and design	Data extraction	
	Definition of tertiary outcomes	Not applicable
	Definition of other outcomes	Not applicable
	Analysis	
	Statistical techniques used	Disease-free survival and overall survival were analysed with the use of proportional-hazards regression and presented as Kaplan–Meier estimates and hazard ratios with 95% CIs. Relapse-free survival was analysed with the use of proportional-hazards regression and presented as a cumulative-incidence plot and hazard ratios with 95% CIs. Planned multivariate analyses to evaluate the robustness of the data on disease-free, relapse-free and overall survival were based on proportional-hazards regression. Subgroup analyses of disease-free survival were also prospectively planned The ITT population comprised all patients who underwent randomisation. In accordance with the study protocol, the per-protocol population excluded patients receiving less than 12 weeks of treatment or less than 50% of the planned dose of the study drug during the initial period as well as those with major violations of inclusion or exclusion criteria The predefined end-point for safety was at least equivalence as demonstrated through comparison of Kaplan–Meier estimates of the incidence and onset of all predefined severe (grade 3 or 4) toxic effects of the fluoropyrimidine (i.e. diarrhoea, stomatitis, nausea, vomiting, hand–foot syndrome, alopecia and neutropenia) in the two groups
	ITT analysis	Yes
	Does technique adjust for confounding?	*[**3**]: Additional analyses Disease-free survival analysis (primary end-point) for prognostic factors included • Sex • Age • Lymph nodes • Baseline carcinoembryonic antigen level
	Power calculation (*a priori* sample calculation)	The primary efficacy analysis was planned when 632 events for the end-point of 3-year disease-free survival had occurred in the per-protocol population. The use of a non-inferiority margin of 1.25 for the hazard ratio and a Type I error of 2.5% ensured 80% power to show at least equivalence between the two study treatments Assuming 3-year disease-free survival rates of 70%, and allowing for ~15% of patients to be excluded from the per-protocol population, an enrolment of 1956 patients was planned. A second hierarchical test evaluated equivalence in disease-free survival with an upper limit of the hazard ratio of 1.20. If these analyses proved to be positive, tests for superiority were planned. Analyses for at least equivalence were performed in the per-protocol and ITT populations; superiority analyses were performed only in the ITT population, to maintain the most conservative approach. No interim analyses were performed

continued

Study and design	Data extraction
	Attrition rates (overall rates), i.e. loss to follow-up

***[1]: Numbers followed and lost to follow-up during treatment**
Five patients in T1 (0.5%) and 4 patients in T2 (0.4%) died during follow-up (i.e. 60-day all-cause mortality)

	T1 (*n* = 1004)	**T2 (*n* = 983)**
Treatment-related deaths	3 (0.3%)	4 (0.4%)
60-day all-cause mortality	5 (0.5%)	4 (0.4%)

Numbers followed and lost to follow-up during study period
Overall, 33 patients were lost to follow-up (T1 15 versus T2 18)

	T1 (*n* = 1004)	**T2 (*n* = 983)**
At median 3.8 years		
Known alive[a]	804 (80%)	756 (77%)
Confirmed death	200 (20%)	227 (23%)
*[**8**]: At median 4.4 years		
Known alive[a]	763 (76%)	718 (73%)
Confirmed death	241 (24%)	265 (27%)

[a] Data extrapolated from reported deaths (confirmed)

Was attrition adequately dealt with?
Yes, ITT

Number (%) followed-up from each condition
Not clear; however, see table above (numbers followed and lost to follow-up during study period)

Compliance with study treatment
See below

Adherence to study treatment
Chemotherapy

Premature withdrawal
- *[**1**]: Premature withdrawals due to adverse events were infrequent in both arms (T1 12%, T2 8%)

Cycles
- *[**1**]: Of the 1004 patients assigned to T1, 993 (98.9%) received at least one dose of study drug and were followed up for safety. Of the 983 patients assigned to T2, 974 (99.1%) received at least one dose of study drug
- *[**1**]: The number of cycles of chemotherapy received was T1 8 and T2 6 (see table below). In total, 84% of patients receiving T1 completed all 8 cycles of treatment (24 weeks) and 89% on T2 received all 6 cycles (24 weeks)

COMMENT
Inconsistent reporting – data in *[**1**] suggest that in total, 84% of patients completed all 8 cycles of treatment in T1 and 89% of patients completed all 6 cycles of treatment in T2. Twelves *et al.*[108] reported these values as 83% and 87%, respectively.

continued

Study and design	Data extraction

***[1]: Number of patients starting each cycle**

	T1 (*n* = 993)	T2[a] (*n* = 974)
Cycle 1	993 (100%)	974 (100%)
Cycle 2	965 (97%)	936 (96%)
Cycle 3	935 (94%)	913 (94%)
Cycle 4	920 (93%)	894 (92%)
Cycle 5	901 (91%)	880 (90%)
Cycle 6	886 (89%)	862 (89%)
Cycle 7	868 (87%)	–
Cycle 8	833 (84%)	–

[a] Mayo Clinic regimen included six cycles of treatment

Dosing

- Both treatment groups required dose reductions in addition to dose interruptions and dose reductions
- The median dose intensity delivered was 93% of that planned for capecitabine and 92% of that planned for 5-FU/LV.
- *[1]: Median time to first dose reduction for T1 78 days versus T2 41 days. Second-level dose reductions [to <60% of capecitabine starting dose (T1 13%) and <75% of 5-FU/LV starting (T2 26%) dose] for T1 113 days versus T2 57 days.

Treatment duration and intensity

	T1 (*n* = 995)	T2 (*n* = 974)
Completed full course of treatment (%)	83[a]	87[b]
Needed dose reduction (%)	42	44
Needed dose reduction, interruption or delay (%)	57	52

[a] Reported as 84% by *[1]
[b] Reported as 89% by *[1]

COMMENT
More interruptions (T1 15% versus T2 5%) and delays (T1 46% versus T2 29%) were required with capecitabine. Nevertheless, most patients in T1 completed at least four of the eight chemotherapy cycles without a reduction in the dose of the medication (T1 76% versus T2 68% after three of the six chemotherapy cycles)

*[1]: After inclusion of 1363 patients, an amendment to the protocol reduced the T1 starting dose by 25% in patients with moderate renal impairment based on newly available data

*[1]: In T1, treatment continued at same dose (without interruption or dose reduction) if patients experienced toxicities no greater than 1 or other toxicities unlikely to become severe or life threatening. In case of

continued

Study and design	Data extraction
	moderate or severe toxicity (grade ≥ 2), all patients instructed to contact clinic for further directions. At second occurrence of grade 2 toxicity, or after appearance of grade 3 or 4 toxicity, the T1 dose was reduced by 25%. In event of further toxicity, a second step dose reduction to 50% of starting dose was allowed. In T2, the dose of LV was not modified, but the 5-FU dose was reduced (to 80 or 70% of preceding dose) or escalated (to 110% of preceding dose) depending on occurrence and severity of either clinical adverse events or haematological/laboratory abnormalities or their absence in the preceding treatment cycles. Treatment not resumed until symptoms resolved to grade 0 or 1. Once T1 or T2 dose reduced, it was not allowed to be increased
Results **Quantitative (e.g. estimates of effect size); qualitative results; effect of the intervention on other mediating variables** ***(Example outcomes: overall survival, relapse-free survival, disease-free survival, response rates)***	**Primary outcome analysis** **Disease-free survival at 3 years (ITT analysis)**

Parameter	T1	T2
All patients (Dukes' C colon cancer)		
Number of patients	1004	983
Median follow-up (years)	3.8	
Number of events (relapse or death)	348 (35%)	380 (39%)
Relapse	Not reported	Not reported
Death without relapse	Not reported	Not reported
Number of patients without event	*[**8**]: 656 (65%)	*[**8**]: 603 (61%)
Disease-free survival at 3 years	64.2% (95% CI: not reported)	60.6% (95% CI: not reported)
Hazard ratio (for recurrence)	0.87 (95% CI: 0.75 to 1.00)[a]	
Reduction in risk of relapse or death	13%	
Level of significance for equivalence	$p < 0.001$[b]	
Level of significance for superiority	$p = 0.05$	
NTTB	24.5 (95% CI: NNTB 12.4 to ∞ to NNTH not calculable)	
Absolute difference in survival	3.6%	

[a] Per protocol analysis *[**2**]: hazard ratio, 0.89 (95% CI: 0.76 to 1.04; *[**8**]: $p = 0.157$)
[b] The upper limit of the hazard ratio was compared with the non-inferiority margin of 1.20, as specified in the study protocol

continued

Study and design	Data extraction

Secondary outcome analysis

Relapse-free survival at 3 years (ITT analysis)

Parameter	T1	T2
All patients (Dukes' C colon cancer)		
Number of patients	1004	983
Median follow-up (years)	3.8	
Number of events (relapse or death)	327 (33%)	362 (37%)
Relapse	Not reported	Not reported
Death without relapse	Not reported	Not reported
Number of patients without event	*[**8**]: 677 (67%)	*[**8**]: 621 (63%)
Relapse-free survival at 3 years	65.5% (95% CI: not reported)	61.9% (95% CI: not reported)
Hazard ratio (for recurrence)	0.86 (95% CI: 0.74 to 0.99)[a]	
Reduction in risk of relapse or death	14%	
Level of significance for equivalence	Not reported	
Level of significance for superiority	$p = 0.04$	
NNTB	23.3 (95% CI: 12.2 to 336.0)	
Absolute difference in survival	3.6%	

[a] Per protocol analysis *[**8**]: hazard ratio, 0.87 (95% CI: 0.74 to 1.02; $p = 0.078$)

***[3]: Overall survival at 3 years – ITT analysis** (*Caution – survival data not mature at time of analysis*)

Parameter	T1	T2
All patients (Dukes' C colon cancer)		
Number of patients	1004	983
Median follow-up (years)	3.8	
Death from any cause	200 (20%)	227 (23%)
Number of patients alive	*[**8**]: 804 (80%)	*[**8**]: 756 (77%)
Overall survival at 3 years	81.3% (95% CI: not reported)	77.6% (95% CI: not reported)
Hazard ratio (for death)	0.84 (95% CI: 0.69 to 1.01)[a]	
Reduction in risk of mortality	16%	
Level of significance for equivalence	$p < 0.001$[b]	
Level of significance for superiority	$p = 0.07$	
NNTB	31.1 (95% CI: NNTB 15.8 to ∞ to NNTH 508.8)	
Absolute difference in survival	3.7%	

[a] Per protocol analysis, *[**8**]: hazard ratio, 0.90 (95% CI: 0.73 to 1.10; $p = 0.298$)

[b] The upper limit of the hazard ratio was compared with the non-inferiority margin of 1.25, as specified in the study protocol

continued

Study and design	Data extraction

Additional analyses (not pre-specified in protocol)

***[8] ITT analysis – disease-free/relapse-free and overall survival at median 4.4 years follow-up**

Parameter	T1	T2
Number of patients	1004	983
Median follow-up (years)	4.4	
Disease-free survival		
Number of events (relapse or death)	372 (37%)[a]	404 (41%)[a]
Relapse	Not reported	Not reported
Death without relapse	Not reported	Not reported
Number of patients without event	632 (63%)	579 (59%)
Disease-free survival at 4 years	Not reported	Not reported
Hazard ratio (for recurrence)	0.87 (95% CI: 0.76 to 1.00)	
Reduction in risk of relapse or death	13%	
Level of significance for equivalence	Not reported	
Level of significance for superiority	$p = 0.055$	
NNTB	Not calculable[b]	
Absolute difference in survival	Not reported	
Relapse-free survival		
Number of events (relapse or death)	350 (35%)[a]	381 (39%)[a]
Relapse	Not reported	Not reported
Death without relapse	Not reported	Not reported
Number of patients without event	654 (65%)	602 (61%)
Relapse-free survival at 4 years	Not reported	Not reported
Hazard ratio (for recurrence)	0.87 (95% CI: 0.75 to 1.00)	
Reduction in risk of relapse or death	13%	
Level of significance for equivalence	Not reported	
Level of significance for superiority	$p = 0.057$	
NNTB	Not calculable[b]	
Absolute difference in survival	Not reported	
Overall survival		
Death from any cause	241 (24%)	265 (27%)
Number of patients alive	763 (76%)	718[c] (73%)
Overall survival at 4 years	Not reported	Not reported
Hazard ratio (for death)	0.88 (95% CI: 0.74 to 1.05)	
Reduction in risk of mortality	12%	
Level of significance for equivalence	Not reported	
Level of significance for superiority	$p = 0.169$	

continued

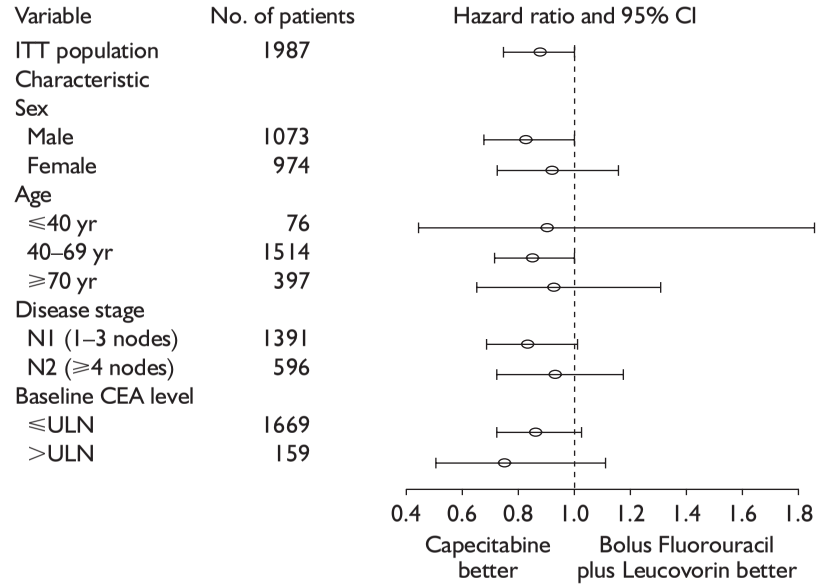
Study and design	Data extraction

Parameter	T1	T2
NNTB	Not calculable[b]	
Absolute difference	Not reported	

[a] Data extrapolated from *[**8**] and is based on number of patients without event
[b] Not calculable because survival probability of control group not reported
[c] Reported as 521 in *[**8**], however recalculated as 718 based on the percentages

Pre-specified subgroup analysis for disease-free survival
Subgroup analyses of disease-free survival showed a consistent trend toward benefit (but not significant) from T1 over T2 among the subgroups categorised according to prognostic factors that were used in the multivariate analysis

Subgroup analysis – disease-free survival analysis for prognostic factors (data on CEA levels were missing for 159 patients who were therefore not included in the analysis for this variable)



continued

Study and design	Data extraction

Multivariate analysis showed that capecitabine treatment, female gender, nodal status and normal CEA were independent prognostic factors for disease-free survival

Multivariate analysis of disease-free survival

Factor	Hazard ratio	95% CI	*p*-Value
Treatment with capecitabine	0.826	0.709 to 0.962	0.0141
*[**3**]: Age	0.999	0.992 to 1.007	0.9010
Female gender	0.764	0.653 to 0.893	*[**3**]: 0.0008
Stage N1 disease	0.583	0.497 to 0.683	*[**3**]: <0.001
*[3]: Time from surgery to randomisation	1.004	0.997 to 1.011	0.3125
Normal CEA	0.389	0.312 to 0.485	*[**3**]: <0.001

When age, gender, lymph nodes, time from surgery to randomisation, baseline CEA and country were considered in multivariate analysis, treatment with capecitabine predicted improved disease-free survival, relapse-free survival and overall survival.

Multivariate analysis – treatment with capecitabine predicted improved disease-free survival, relapse-free survival and overall survival[a]

Multivariate analysis	Hazard ratio	95% CI	*p*-Value
*[**3**]: Disease-free survival	0.826	0.709 to 0.962	0.0141
*[**3**]: Relapse-free survival	0.809	0.691 to 0.946	0.0080
Overall survival	0.788	0.643 to 0.964	0.0208

[a] Factors considered: age, gender, lymph nodes, time from surgery to randomisation, baseline CEA and country

Toxicity

Secondary outcome analysis

***[1]: Treatment-related mortality**

Parameter	T1 (*n* = 1004)	T2 (*n* = 993)
Treatment related deaths	3 (0.3%)[a]	4 (0.4%)[b]
60-day all-cause mortality	5 (0.5%)	4 (0.4%)

[a] Two patients aged <65 years (one on day 23 due to multi-organ failure and one due to septic shock on day 22) and one patient aged ≥65 years (due to pneumonia on day 91)

[b] Three patients aged <65 years (one on day 16 after experiencing severe diarrhoea and vomiting, one due to respiratory arrest on day 69 and one due to gastrointestinal haemorrhage on day 131) and one patient aged ≥65 years (due to bronchopneumonia on day 189)

continued

Study and design	Data extraction

Most common (≥10%) treatment-related adverse events (all grades)[a,b]

Adverse event	All grade of events			Grade 3 or 4 events (severe)		
	T1 (%) (*n* = 995)	T2 (%) (*n* = 974)	*p*-Value	T1 (%) (*n* = 995)	T2 (%) (*n* = 974)	*p*-Value
Diarrhoea	46	64	<0.001	11	13	NS
Nausea or vomiting	36	51	<0.001	3	3	NS
Stomatitis	22	60	<0.001	2	14	<0.001
Hand-foot syndrome	60	9	<0.001	17	<1	<0.001
Fatigue or asthenia	23	23	NS	1	2	NS
Abdominal pain	10	13	NS	2	1	NS
Alopecia	6	22	<0.001	0	<1	<0.02
Lethargy	10	9	NS	<1	<1	NS
Anorexia	9	10	NS	<1	<1	NS
Neutropenia[c]	32	63	<0.001	2	26	<0.001
Hyperbilirubinaemia[c]	50	20	<0.001	20	6	<0.001

NS, not significant

[a] Data are an update of *[**1**]

[b] Treatment-related adverse events were graded according to *[**1**]: National Cancer Institute of Canada common toxicity criteria (NCIC CTC) 1991; hand–foot syndrome graded 1 to 3

[c] Diagnosis based on laboratory values

Additional analyses – early severe toxicities

*[**1**]: Overall, significantly fewer patients in T1 experienced early severe toxicities than T2 (5.4% vs 17%, respectively; $p < 0.001$) (see table below). More patients receiving T2 experienced early grade 3/4 stomatitis (10 vs 1%), diarrhoea (5 vs 3%) and neutropenia (6 vs 1%) than those receiving T2. Older patients (≥65 years) in T2 experienced a higher incidence of early severe toxicities (gastrointestinal toxicities, infections, neutropenia and thrombocytopenia) during the first 21 days of treatment than younger (<65 years) patients (19.7 vs 15.1%, respectively). In contrast, the incidence of early toxicities in T1 were similar in patients <65 and ≥65 years old (4.9 vs 6.3%, respectively)

continued

Study and design	Data extraction

***[1]: Incidence of early severe toxicities (i.e. grade 3 or 4 gastrointestinal toxicities, infections, neutropenia, and thrombocytopenia) occurring within the first 21 days of treatment[a]**

	T1 (%)		T2 (%)	
	<65 years (*n* = 596)	≥65 years (*n* = 397)	<65 years (*n* = 562)	≥65 years (*n* = 412)
Any defined events	4.9	6.3	15.1	19.7
Stomatitis	0.7	1.8	7.7	12.1
Diarrhoea	2.3	3.5	6.0	4.6
Neutropenia[b]	1.7	1.0	4.1	9.2
Thrombocytopenia[b]	1.7	1.8	0.2	0.2
Nausea	1.0	0.8	0.5	0.5
Vomiting	0.7	0.3	1.2	0.5
Abdominal pain	0.7	0.5	0.4	1.5
Intestinal obstruction	0.2	0.3	0.4	0.5
Febrile neutropenia	0.0	0.0	0.4	1.0
Other toxicities[c]	1.0	2.0	1.2	2.2

[a] An individual patient can have more than one specific grade 3 or 4 event
[b] Neutropenia and thrombocytopenia recorded as grade 3 or 4 laboratory abnormalities
[c] Other gastrointestinal toxicities and infections affecting two or less patients in either of the treatment arms

Additional analyses – laboratory abnormalities
The table below shows the most commonly occurring grade 3 or 4 laboratory abnormalities in T1 and T2.
*[**1**]: The overall incidence of neutropenia (all grades) was significantly lower in T1 than T2 (31 vs 61%; $p < 0.001$)

***[1]: Most frequently occurring (≥3%) grade 3 or 4 laboratory abnormalities[a]**

	T1 (%) (*n* = 993)	T2 (%) (*n* = 974)	*p*-Value
Hyperbilirubinaemia[b]	20	6	<0.001
Grade 3[c]	18.6	5.9	<0.001
Grade 4[d]	1.4	0.	<0.001
Lymphocytopenia	13	13	Not significant
Neutropenia	2	26	<0.001
Leucopenia	1	5	<0.001
ASAT	0.7	1.6	Not reported
ALAT	0.3	0.6	Not reported

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase
[a] Figures as reported in original paper

continued

Study and design	Data extraction

[b] Graded according to NCIC CTC 1991 criteria; however, according to the current NCI CTCE (v3.0) system the incidence is negligible (T1 1.4% vs T2 0.3%; $p < 0.001$)
[c] Defined as elevated bilirubin concentrations ≤3 times the upper limit of normal
[d] Defined as elevated bilirubin concentrations >3 times the upper limit of normal

Additional analyses – treatment-related adverse events by age group
An analysis of treatment-related adverse events by age group is shown in the table below. *[1]: Overall, T1 showed a more favourable safety profile than T2 in both younger and older patients with less treatment-related diarrhoea, nausea, vomiting, stomatitis and neutropenia but more hand–foot syndrome (similar findings with grade 3 or 4 adverse events)

***[1]: Most common (≥10%) treatment-related adverse events in patients < or ≥65 years (all grades)**

	T1 (%)		T2 (%)	
	<65 years (*n* = 596)	≥65 years (*n* = 397)	<65 years (*n* = 562)	≥65 years (*n* = 412)
Diarrhoea	42	52	65	63
Stomatitis	19	27	59	62
Nausea	32	34	44	49
Vomiting	13	16	18	21
Hand–foot syndrome	61	63	9	11
Fatigue	13	17	15	15
Abdominal pain	9	12	13	13
Neutropenia	2	3	10	7

***[1]: Most common (>2%) grade 3 or 4 adverse events in patients < or ≥65 years**

	T1 (%)		T2 (%)	
	<65 years (*n* = 596)	≥65 years (*n* = 397)	<65 years (*n* = 562)	≥65 years (*n* = 412)
Diarrhoea	10	13	13	13
Stomatitis	1	3	11	18
Hand–foot syndrome	16	20	<1	<1
Neutropenia[a]	2	3	26	27
Nausea	2	1	2	1
Vomiting	2	1	2	2

[a] Neutropenia as a grade 3 or 4 laboratory abnormality

continued

Study and design	Data extraction

***[4]: Treatment-related adverse events and grade 3/4 abnormalities (>15%) in patients ≥70 years (all grades)[a]**

All grades	T1 (%) ≥70 years (*n* = 186)	T2 (%) ≥70 years (*n* = 205)
Diarrhoea	52	68
Stomatitis	23	67
Hand–foot syndrome	63	8
Nausea	33	47
Fatigue	17	19
Neutropenia (grade 3/4)	4	31
Hyperbilirubinaemia (grade 3/4)[b]	17	5

[a] *p*-Values not calculated owing to the retrospective nature of the analysis
[b] According to National Cancer Institute of Canada Common Toxicity Criteria

Adverse events commonly leading to treatment modification

*[1]: Adverse events most commonly leading to dose modifications (including treatment interruption and dose reduction) in T1: hand–foot syndrome and diarrhoea; T2: stomatitis and diarrhoea (see table below). Premature withdrawal due to adverse events occurred in 12% of patients receiving T1 and 8% in those receiving T2

***[1]: Adverse events commonly leading treatment modification/discontinuation**

	Treatment modification[a]		Treatment discontinuation	
	T1 (%) (*n* = 993)	T2 (%) (*n* = 974)	T1 (%) (*n* = 993)	T2 (%) (*n* = 974)
Diarrhoea	15	19	3	3
Hand–foot syndrome	31	<1	3	<1
Stomatitis	3	23	<1	2
Neutropenia	3	13	0	<1

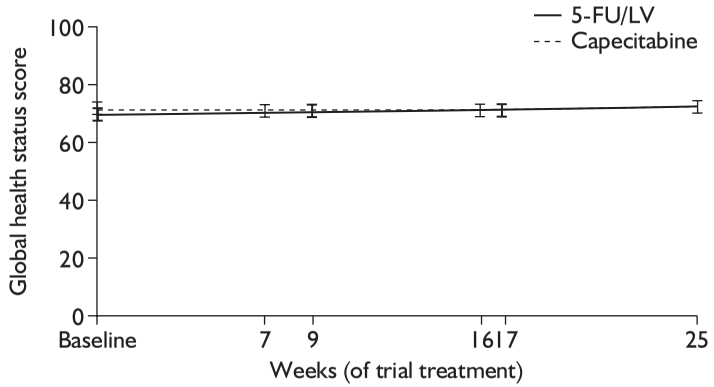
[a] Dose reductions and treatment interruptions included

Quality of life

Health-related QoL data were collected within the trial. The Quality of Life Questionnaire (QLQ-C30, version 2.0) of the European Organization for the Research and Treatment of Cancer (EORTC) was administered at baseline and before the start of treatment cycles in weeks 7, 16 and 25 in T1 and weeks 9, 17 and 25 in T2. As shown in the figure on p. 147 (opposite), no major differences were found between the T1 and T2.

continued

Study and design	Data extraction



*[**3**]: Quality of life over time (EORTC QLQ C-30)

Other information

Resource use: treatments for adverse events

Medications

*[**1**]: Fewer patients receiving T1 required medications for the treatment of adverse events than T2 (703 vs 768 patients, respectively). Most common prescribed treatments for adverse events were loperamide, antibiotics and metoclopramide (see table below). Fewer patients in T1 required loperamide and metoclopramide, reflecting the lower incidence of diarrhoea and nausea/vomiting in this group. The lower incidence of neutropenia in T1 was reflected by less frequent need for granulocyte colony-stimulating factor (G-CSF). *[**7**]: Owing to hand–foot syndrome, patients in T1 used emollients more frequently than T2 (62 vs 10%, respectively)

***[1]: Most frequently (≥10% of patients) administered treatments for adverse events**

Medication	**No. of patients**	
	T1 (*n* = 993)	**T2 (*n* = 974)**
Loperamide	231 (23%)	372 (38%)
Antibiotics	217 (22%)	289 (30%)
Metoclopramide	141 (14%)	243 (25%)
Paracetamol	97 (10%)	107 (11%)
Pyridoxine	152 (15%)	20 (2%)
Benzydamine[a]	25 (3%)	108 (11%)
G-CSF	7 (<1%)	27 (3%)

[a] Benzydamine is a mouthwash/spray used to treat painful inflammatory conditions of oropharynx

continued

Study and design	Data extraction

Days of medication usage

*[**6**]: In terms of medications to treat adverse events, patients in T2 required more days of therapy for higher cost drugs such as antidiarrhoeals, analgesics and antifungals, whereas T1 used more low-cost vitamins and emollients (see table below)

***[7]: Days of medication usage for adverse events**

Medication	Days of use per 100 patients	
	T1 (*n* = 995)	T2 (*n* = 974)
Antibiotics/cephalosporins	185	453
Antiemetics/antidiarrhoeals (e.g. loperamide)	863	1127
Benzodiazapines	159	245
Cytokines/growth factors	5	23
Dermatologicals/emollients	999	230
Non-steroidal anti-inflammatory drugs	474	870
Stomatologicals/triazoles	43	254

***[7]: Ambulatory consultations for treatment of adverse events and drug administration**

Patients receiving chemotherapy visited physician's offices and clinics for both therapy and unscheduled consultations (for the treatment of adverse events). The numbers of unscheduled and routine visits is shown in the table below. During the treatment period, there were similar numbers of unscheduled visits in T1 and T2, with 3% more for patients receiving T1 than T2 (T1 52% vs T2 49%). Per 100 patients, T2 patients had more than 2000 additional ambulatory visits during the treatment period than T1 patients

***[7]: Ambulatory visits to clinics and offices**

	Mean number per 100 patients	
	T1 (*n* = 995)	T2 (*n* = 974)
Adverse treatment	156	147
Drug administration	737	2804
Total	893	2951

Hospitalisations

*[**6**]: According to the protocol, treatment administration included 30 visits for patients receiving T2 (i.e. five daily infusions, days 1–5 every month, for approximately 6 months) and 8 visits for each T1 patient (i.e. one distribution every 3 weeks for approximately 6 months). *[**5**]: Actual visits per patient for drug administration/distribution were 28.0 for those receiving T2 versus 7.4 for those receiving T1

*[**6**]: Treatment-related hospitalisations were lower in T1 than T2 (91 vs 100, respectively), but the total number of associated days hospitalised was similar (961 vs 959, respectively)

continued

Study and design	Data extraction	
		COMMENT Inconsistent reporting – data in *[**7**] suggest that, in total, 18% of patients were hospitalised during the study. Hospitalisations due to adverse events were greater in T2 than T1 (124 vs 106, respectively). The average length of hospital stay was similar in both groups (T1 9.9 vs T2 10.0 days) *[**5**]: A pharmaeconomic analysis has been undertaken by these authors and reported in abstract/poster form (data not abstracted)
	Summary	
	Authors' overall conclusions	Oral capecitabine is an effective alternative to intravenous 5-FU/LV in the adjuvant treatment of colon cancer
	Reviewers' comments	

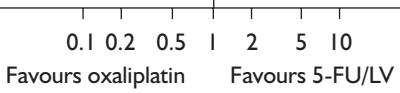
Appendix 8

Meta-analysis of oxaliplatin (in combination with 5-FU/LV) versus 5-FU/LV alone: disease-free survival[a,b]

Review: Oxaliplatin and capecitabine for the adjuvant treatment of colon cancer
Comparison: 01 Oxaliplatin (in combination with 5-FU/LV) versus 5-FU/LV alone
Outcome: 01 Disease free survival (ITT)

Study or subcategory	Oxaliplatin + 5-FU/LV *n/N*	5-FU/LV *n/N*	Peto OR (IPD) 95% CI	Weight %	Peto OR (IPD) 95% CI
MOSAIC	237/1123	293/1123		48.71	0.77 [0.65 to 0.91]
NSABP C-07	272/1247	332/1245		51.29	0.79 [0.67 to 0.93]
Total (95% CI)	2370	2368		100.00	0.78 [0.69 to 0.88]

Total events: 509 (Oxaliplatin + 5-FU/LV), 625 (5-FU/LV)
Test for heterogeneity: $\chi^2 = 0.05$, df = 1 ($p = 0.83$), $I^2 = 0\%$
Test for overall effect: $Z = 4.14$ ($p < 0.0001$)



[a] Forest plots present hazard ratios, although they are labelled 'OR' (odds ratio) by the meta-view software.
[b] Data source for meta-analyses – MOSAIC trial: Follow-up 37.9 months; Parmar method 3; observed events reported in paper; NSABP C-07 trial: Follow-up 34 months; Parmar method 3; observed events reported in paper

Appendix 9

Identification of studies for review of cost-effectiveness

This appendix contains information on the sources searched and keyword strategies for the systematic review of cost-effectiveness.

Electronic databases searched

The following electronic databases were searched:

- CINAHL Cumulative Index of Nursing and Allied Health Literature
- DARE-NHS EED-HTA Database of Abstract of Reviews of Effectiveness, NHS Economic Evaluation Database, Health Technology Assessment Database
- EMBASE
- HEED Office of Health Economic Health Economic Evaluation Database
- MEDLINE
- PUBMED
- WoS Web of Science

Sources consulted via the WWW

See Appendix 3.

Database keyword strategies

CINAHL
1982–2005
Ovid Online version 9.3
Search undertaken January 2005

1. oxaliplatin.af.
2. "63121 00 6".af.
3. l ohp.af.
4. eloxatin.af.
5. 1r 2r 1 2 cyclohexanediamine n n oxalato 2 o o platinum.af.
6. mosaic.af.
7. or/1-6
8. capecitabine.af
9. xeloda.af.
10. 154361 50 9.af.
11. 5 deoxy 5 fluoro n pentyloxy carbonyl cytidine.af.
12. x act.af.
13. or/8-12
14. 7 or 13
15. exp Colonic Neoplasms/
16. exp Rectal Neoplasms/
17. or/15-16
18. Neoplasms/
19. Carcinoma/
20. Adenocarcinoma/
21. or/18-20
22. exp Colonic Diseases/
23. exp Rectal Diseases/
24. exp Colon/
25. exp Rectum/
26. or/22-25
27. 21 and 26
28. ((carcinoma$ or neoplasia$ or neoplasm$ or cancer$ or tumo$ or malignan$) adj3 (colorectal or colon$ or rect$ or intestin$ or bowel$)).tw.
29. 17 or 27 or 28
30. 14 and 29
31. exp Economics
32. ec.fs.
33. (cost$ or economic$ or qaly$ or quality adjusted$).tw.
34. or/31-33
35. 30 and 34

DARE–NHS EED–HTA
Date coverage not known (approx. 1994–2005)
CRD website version
Search undertaken January 2005

Oxaliplatin or l ohp or eloxatin or mosaic or capecitabine or xeloda or x act/All fields AND colorectal or colon or rectal or rectum/All fields

EMBASE
1980–2004
SilverPlatter WebSPIRS Version 4.3
Search undertaken January 2005

#33. #31 and #32
#32. explode 'economic-aspect' / all subheadings in DEM,DER,DRM,DRR
#31. #14 and #30
#30. #18 or #28 or #29
#29. (carcinoma* or neoplasia* or neoplasm* or cancer* or tumo* or malignan*) near3

(colorectal or colon* or rect* or intestin* or bowel*)
#28. #22 and #27
#27. #23 or #24 or #25 or #26
#26. explode 'rectum-disease' / all subheadings in DEM,DER,DRM,DRR
#25. explode 'colon-disease' / all subheadings in DEM,DER,DRM,DRR
#24. explode 'rectum-' / all subheadings in DEM,DER,DRM,DRR
#23. explode 'colon-' / all subheadings in DEM,DER,DRM,DRR
#22. #19 or #20 or #21
#21. explode 'adenocarcinoma-' / all subheadings in DEM,DER,DRM,DRR
#20. explode 'carcinoma-' / all subheadings in DEM,DER,DRM,DRR
#19. explode 'neoplasm-' / all subheadings in DEM,DER,DRM,DRR
#18. #15 or #16 or #17
#17. explode 'colorectal-tumor' / all subheadings in DEM,DER,DRM,DRR
#16. explode 'colorectal-carcinoma' / all subheadings in DEM,DER,DRM,DRR
#15. explode 'colorectal-cancer' / all subheadings in DEM,DER,DRM,DRR
#14. #7 or #13
#13. #8 or #9 or #10 or #11 or #12
#12. x act
#11. 5 deoxy 5 fluoro n pentyloxy carbonyl cytidine
#10. 154361-50-9
#9. xeloda
#8. capecitabine
#7. #1 or #2 or #3 or #4 or #5 or #6
#6. mosaic
#5. 1r 2r 1 2 cyclohexanediamine n n oxalato 2 o o platinum (0 records)
#4. eloxatin
#3. l ohp
#2. 61825-94-3
#1. oxaliplatin

MEDLINE
1966–2005
Ovid Online version 9.3
Search undertaken January 2005

1. oxaliplatin.af.
2. "63121 00 6".rn.
3. l ohp.af.
4. eloxatin.af.
5. 1r 2r 1 2 cyclohexanediamine n n oxalato 2 o o platinum.af.
6. mosaic.af.
7. or/1-6
8. capecitabine.af.
9. xeloda.af.
10. 154361 50 9.af.
11. 5 deoxy 5 fluoro n pentyloxy carbonyl cytidine.af.
12. x act.af.
13. or/8-12
14. 7 or 13
15. exp Colorectal Neoplasms/
16. Neoplasms/
17. Carcinoma/
18. Adenocarcinoma/
19. or/16-18
20. Colonic Diseases/
21. Rectal Diseases/
22. exp Colon/
23. exp Rectum/
24. or/20-23
25. 19 and 24
26. (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
27. (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
28. (neoplasm$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
29. (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
30. (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
31. (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
32. (tumour$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
33. (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
34. or/26-33
35. 15 or 25 or 34
36. 14 and 35
37. Economics/
38. exp "Costs and cost analysis"/
39. Economic value of life/
40. exp Economics, hospital/
41. exp Economics, medical/
42. Economics, nursing/
43. exp models, economic/
44. Economics, pharmaceutical/
45. exp "Fees and charges"/
46. exp Budgets/
47. ec.fs.
48. (cost or costs or costed or costly or costing$).tw.
49. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
50. Quality-adjusted life years/
51. (qaly or qalys).af.
52. (quality adjusted life year or quality adjusted life years).af.
53. or/37-52
54. 36 and 53

PUBMED
July 2004–2005
Version not known
Search undertaken January 2005

#20. Search #18 and #19 Field: All Fields, Limits: 180 Days
#19. Search cost* or economic* or qaly* or quality adjusted Field: All Fields, Limits: 180 Days
#18. Search #15 and #16 Field: All fields, Limits: 180 Days
#17. Search #15 and #16
#16. Search colorectal or colon* or rectal or rectum
#15. Search #8 or #14
#14. Search #9 or #10 or #11 or #12 or #13
#13. Search x act
#12. Search 5 deoxy 5 fluoro n pentyloxy carbonyl cytidine
#11. Search 154361-50-9
#10. Search xeloda
#9. Search capecitabine
#8. #1 or #2 or #3 or #4 or #5 or #6 or #7
#7. Search mosaic
#6. Search 1r 2r 1 2 cyclohexanediamine n n oxalato 2 o o platinum
#5. Search eloxatin
#4. Search l ohp
#3. Search 63121-00-6
#2. Search 63121 00 6
#1. Search oxaliplatin

WoS
1981–2005
Version not known
Search undertaken January 2005

#30. #26 or #27 or #28 or #29
#29. #13 and #25
#28. #13 and #24
#27. #13 and #23
#26. #13 and #22
#25. ts=quality adjusted
#24. ts=qaly*
#23. ts=economic or ts=economics
#22. ts=cost or ts=costs
#13. #9 or #11 or #12
#12. #3 and #8
#11. #3 and #7
#9. #3 and #5
#8. ts=rectal or ts=rectum
#7. ts=colon or ts=colonic
#5. ts=colorectal
#3. #1 or #2
#2. ts=capecitabine or ts=xeloda or ts=x act
#1. ts=oxaliplatin or ts=l ohp or ts=eloxatin or ts=mosiac

Appendix 10

Critical appraisal of economic evidence using the Drummond checklist[144]

Douillard *et al.*, 2004[115]

1.	**Was a well-defined question posed in answerable form?**	
1.1.	Did the study examine both costs and effects of the service(s) or programme(s)?	Yes
1.2.	Did the study involve a comparison of alternatives?	Yes
1.3.	Was a viewpoint for the analysis stated and was the study placed in any particular context?	Yes – NHS perspective
2.	**Was a comprehensive description of the competing alternatives given?**	
2.1.	Were any important alternatives omitted?	No
2.2.	Was (should) a *do-nothing* alternative (be) considered?	No
3.	**Was the effectiveness of the programmes or services established?**	
3.1.	Was this done through an RCT? If so, did the trial protocol reflect what would happen in regular practice?	Yes. Data from the X-ACT trial were used, in which the comparator arm therapy constituted one of the main treatment regimens used in the UK
3.2.	Was effectiveness established through an overview of clinical studies?	No
3.3.	Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	Weibull functions were used to estimate survival up to 10 years. Some patients may be alive at this time, meaning that survival estimates may be underestimated in the analysis. This is offset by the assumption that a Weibull function is appropriate – it does not take into account the fact that very few patients relapse beyond 5 years, and therefore the hazard of death beyond this time may not be equivalent to that seen in the previous 5-year period
4.	**Were all the important and relevant costs and consequences for each alternative identified?**	
4.1.	Was the range wide enough for the research question at hand?	Yes
4.2.	Did it cover all relevant viewpoints?	Yes
4.3.	Were capital costs, as well as operating costs, included?	No
5.	**Were costs and consequences measured accurately in appropriate physical units?**	
5.1.	Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?	No
5.2.	Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	No

6.	**Were costs and consequences valued credibly?**	
6.1.	Were the sources of all values clearly identified?	Yes
6.2.	Were market values employed for changes involving resources gained or depleted?	No
6.3.	Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinical space donated at a reduced rate), were adjustments made to approximate market values?	No
6.4.	Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type of analysis – cost-effectiveness, cost–benefit, cost–utility – been selected)?	Yes
7.	**Were costs and consequences adjusted for differential timing?**	
7.1.	Were costs and consequences which occur in the future discounted to their present value?	Yes. Both costs and QALYs were discounted at 3.5% per annum
7.2.	Was any justification given for the discount rate used?	In line with current NICE guidance
8.	**Was an incremental analysis of costs and consequences of alternatives performed?**	
8.1.	Were the additional (incremental) costs generated by one alternative over another compared with the additional effects, benefits or utilities generated?	Yes
9.	**Was allowance made for uncertainty in the estimates of costs and consequences?**	
9.1.	If data on costs or consequences were stochastic, were appropriate statistical analyses performed?	No stochastic analyses were performed
9.2.	If sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?	Drug acquisition and administration costs were varied by 25% in the conservative direction, although no justification was given for the use of this figure. Alternative time horizons were considered
9.3.	Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the CI around the ratio of costs to consequences)?	No – capecitabine was found to be cost-saving in all cases
10.	**Did the presentation and discussion of study results include all issues of concern to users?**	
10.1.	Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?	The use of an ICER was not appropriate because capecitabine was found to be cost saving
10.2.	Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?	No. The results were compared with other cost-effectiveness benchmarks in oncology
10.3.	Did the study discuss the generalisability of the results to other settings and patient/client groups?	No
10.4.	Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or other ethical issues)?	No
10.5.	Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	No

Koperna and Semmler, 2003[145]

1.	**Was a well-defined question posed in answerable form?**	
1.1.	Did the study examine both costs and effects of the service(s) or programme(s)?	Yes
1.2.	Did the study involve a comparison of alternatives?	Yes
1.3.	Was a viewpoint for the analysis stated and was the study placed in any particular context?	The analysis as carried out from the perspective of the provider institution
2.	**Was a comprehensive description of the competing alternatives given?**	
2.1.	Were any important alternatives omitted?	No
2.2.	Was (should) a *do-nothing* alternative (be) considered?	Yes – best supportive care was used as a baseline comparator
3.	**Was the effectiveness of the programmes or services established?**	
3.1.	Was this done through an RCT? If so, did the trial protocol reflect what would happen in regular practice?	Not trial data as such – data came from two randomised studies
3.2.	Was effectiveness established through an overview of clinical studies?	Efficacy of 5-FU/LV was determined through a review of existing clinical studies. Efficacy of oxaliplatin plus 5-FU/LV was estimated from trials of patients with advanced (Stage IV) colorectal cancer, and is therefore unlikely to be representative of survival outcomes for patients receiving adjuvant chemotherapy, also survival estimates are likely to have been underestimated.
3.3.	Were observational data or assumptions used to establish effectiveness? If so, what are the potential trials in advanced colorectal cancer, biases in results?	
4.	**Were all the important and relevant costs and consequences for each alternative identified?**	
4.1.	Was the range wide enough for the research question at hand?	Yes – various treatments considered
4.2.	Did it cover all relevant viewpoints?	Yes
4.3.	Were capital costs, as well as operating costs, included?	Yes
5.	**Were costs and consequences measured accurately in appropriate physical units?**	
5.1.	Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?	No
5.2.	Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	The trial data used comprised patients with Stage III and IV disease. No account was taken of the impact of this on the results
6.	**Were costs and consequences valued credibly?**	
6.1.	Were the sources of all values clearly identified?	No – it is unclear where many of the cost estimates are derived from, and indeed which currency they relate to
6.2.	Were market values employed for changes involving resources gained or depleted?	No
6.3.	Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinical space donated at a reduced rate), were adjustments made to approximate market values?	No

6.4.	Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type of analysis – cost-effectiveness, cost–benefit, cost–utility – been selected)?	Cost–utility analysis was not performed. Cost-effectiveness results of the different interventions are presented as costs per LYG
7.	**Were costs and consequences adjusted for differential timing?**	
7.1.	Were costs and consequences which occur in the future discounted to their present value?	Yes – costs and effects were discounted at 6% per annum
7.2.	Was any justification given for the discount rate used?	Based upon the suggested discount rate for central Europe given in a previous HTA report[221]
8.	**Was an incremental analysis of costs and consequences of alternatives performed?**	
8.1.	Were the additional (incremental) costs generated by one alternative over another compared with the additional effects, benefits or utilities generated?	No – the study in fact presented marginal cost-effectiveness estimates (compared with best supportive care)
9.	**Was allowance made for uncertainty in the estimates of costs and consequences?**	
9.1.	If data on costs or consequences were stochastic, were appropriate statistical analyses performed?	No stochastic analyses were performed
9.2.	If sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?	Costs were altered by using different assumptions regarding treatment administration. An alternative discount rate of 5% was used although not justified, and sensitivity analysis was also performed by altering the survival benefit associated with 5-FU
9.3.	Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the CI around the ratio of costs to consequences)?	The results were sensitive to changes to the drug administration regimen, although not to changes in discount rate or survival benefit
10.	**Did the presentation and discussion of study results include all issues of concern to users?**	
10.1.	Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?	Yes – some of the limitations of the analysis were discussed
10.2.	Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?	Yes – the differences between studies are attributed to the assumptions made
10.3.	Did the study discuss the generalisability of the results to other settings and patient/client groups?	Yes – the discussion includes reference to patients with advanced colorectal cancer
10.4.	Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or other ethical issues)?	No
10.5.	Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	Yes – different cost-effectiveness thresholds were discussed

Aballea *et al.*, 2005[146]

1.	**Was a well-defined question posed in answerable form?**	
1.1.	Did the study examine both costs and effects of the service(s) or programme(s)?	Yes
1.2.	Did the study involve a comparison of alternatives?	Yes
1.3.	Was a viewpoint for the analysis stated and was the study placed in any particular context?	Yes – a US Medicare perspective was employed
2.	**Was a comprehensive description of the competing alternatives given?**	
2.1.	Were any important alternatives omitted?	No
2.2.	Was (should) a *do-nothing* alternative (be) considered?	No
3.	**Was the effectiveness of the programmes or services established?**	
3.1.	Was this done through an RCT? If so, did the trial protocol reflect what would happen in regular practice?	Yes – patient-level data from the MOSAIC trial were used to estimate costs and health benefits. The comparator arm of the trial did not reflect current UK practice
3.2.	Was effectiveness established through an overview of clinical studies?	No
3.3.	Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	A Weibull model was used to extrapolate disease-free survival and overall survival
4.	**Were all the important and relevant costs and consequences for each alternative identified?**	
4.1.	Was the range wide enough for the research question at hand?	Yes
4.2.	Did it cover all relevant viewpoints?	Yes
4.3.	Were capital costs, as well as operating costs, included?	No
5.	**Were costs and consequences measured accurately in appropriate physical units?**	
5.1.	Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?	No
5.2.	Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	No
6.	**Were costs and consequences valued credibly?**	
6.1.	Were the sources of all values clearly identified?	No – although the analysis is only presented in abstract form
6.2.	Were market values employed for changes involving resources gained or depleted?	No
6.3.	Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinical space donated at a reduced rate), were adjustments made to approximate market values?	No
6.4.	Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type of analysis – cost-effectiveness, cost–benefit, cost–utility – been selected)?	Cost per LYG is the outcome measure used

7.	**Were costs and consequences adjusted for differential timing?**	
7.1.	Were costs and consequences which occur in the future discounted to their present value?	Both costs and health outcomes were discounted at 3% per annum
7.2.	Was any justification given for the discount rate used?	No
8.	**Was an incremental analysis of costs and consequences of alternatives performed?**	
8.1.	Were the additional (incremental) costs generated by one alternative over another compared with the additional effects, benefits or utilities generated?	Yes
9.	**Was allowance made for uncertainty in the estimates of costs and consequences?**	
9.1.	If data on costs or consequences were stochastic, were appropriate statistical analyses performed?	Uncertainty was explored using bootstrapping of the patient-level data
9.2.	If sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?	One-way sensitivity analyses were not performed
9.3.	Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the CI around the ratio of costs to consequences)?	A CI around the cost per life-year gained is not reported
10.	**Did the presentation and discussion of study results include all issues of concern to users?**	
10.1.	Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?	Yes
10.2.	Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?	No
10.3.	Did the study discuss the generalisability of the results to other settings and patient/client groups?	Yes – the results are not compared with those of specific studies, but with "other accepted interventions in oncology"
10.4.	Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or other ethical issues)?	No
10.5.	Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	No

Roche submission to NICE[20]

1.	**Was a well-defined question posed in answerable form?**	
1.1.	Did the study examine both costs and effects of the service(s) or programme(s)?	Yes
1.2.	Did the study involve a comparison of alternatives?	Yes
1.3.	Was a viewpoint for the analysis stated and was the study placed in any particular context?	Yes – UK NHS perspective
2.	**Was a comprehensive description of the competing alternatives given?**	
2.1.	Were any important alternatives omitted?	No
2.2.	Was (should) a *do-nothing* alternative (be) considered?	No

3.	**Was the effectiveness of the programmes or services established?**	
3.1.	Was this done through an RCT? If so, did the trial protocol reflect what would happen in regular practice?	Data from the X-ACT trial were used, in which the comparator arm therapy constituted one of the main treatment regimens used in the UK
3.2.	Was effectiveness established through an overview of clinical studies?	No
3.3.	Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	Long-term relapse-free and overall survival were estimated using log-normal functions which are modelled independently, meaning that the results are likely to be biased, with relapse-free survival being greater than overall survival at around 20 years post-surgery
4.	**Were all the important and relevant costs and consequences for each alternative identified?**	
4.1.	Was the range wide enough for the research question at hand?	Yes
4.2.	Did it cover all relevant viewpoints?	Yes – patient travel costs were included in the analysis
4.3.	Were capital costs, as well as operating costs, included?	No
5.	**Were costs and consequences measured accurately in appropriate physical units?**	
5.1.	Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?	No
5.2.	Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	No
6.	**Were costs and consequences valued credibly?**	
6.1.	Were the sources of all values clearly identified?	Yes – clinical judgement used to determine some model parameters
6.2.	Were market values employed for changes involving resources gained or depleted?	No
6.3.	Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinical space donated at a reduced rate), were adjustments made to approximate market values?	No
6.4.	Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type of analysis – cost-effectiveness, cost–benefit, cost–utility – been selected)?	Yes – cost–utility analysis performed
7.	**Were costs and consequences adjusted for differential timing?**	
7.1.	Were costs and consequences which occur in the future discounted to their present value?	Yes – costs and health outcomes were discounted at 6 and 1.5%, respectively
7.2.	Was any justification given for the discount rate used?	Yes – in accordance with NICE guidelines
8.	**Was an incremental analysis of costs and consequences of alternatives performed?**	
8.1.	Were the additional (incremental) costs generated by one alternative over another compared with the additional effects, benefits or utilities generated?	Yes

9.	**Was allowance made for uncertainty in the estimates of costs and consequences?**	
9.1.	If data on costs or consequences were stochastic, were appropriate statistical analyses performed?	Stochastic analyses were not undertaken
9.2.	If sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?	Yes
9.3.	Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the CI around the ratio of costs to consequences)?	No – capecitabine was estimated to be cost saving even in the worst-case scenario
10.	**Did the presentation and discussion of study results include all issues of concern to users?**	
10.1.	Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?	Yes. However, an incremental cost per QALY was not reported, because capecitabine was estimated to be a dominating intervention
10.2.	Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?	No
10.3.	Did the study discuss the generalisability of the results to other settings and patient/client groups?	Yes – the sensitivity analyses included consideration of a comparison of capecitabine with alternative 5-FU/LV regimens
10.4.	Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or other ethical issues)?	Yes – account was taken of the impact upon NHS chemotherapy services
10.5.	Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	Yes – a budget impact analysis was performed

Sanofi-Aventis submission to NICE[143]

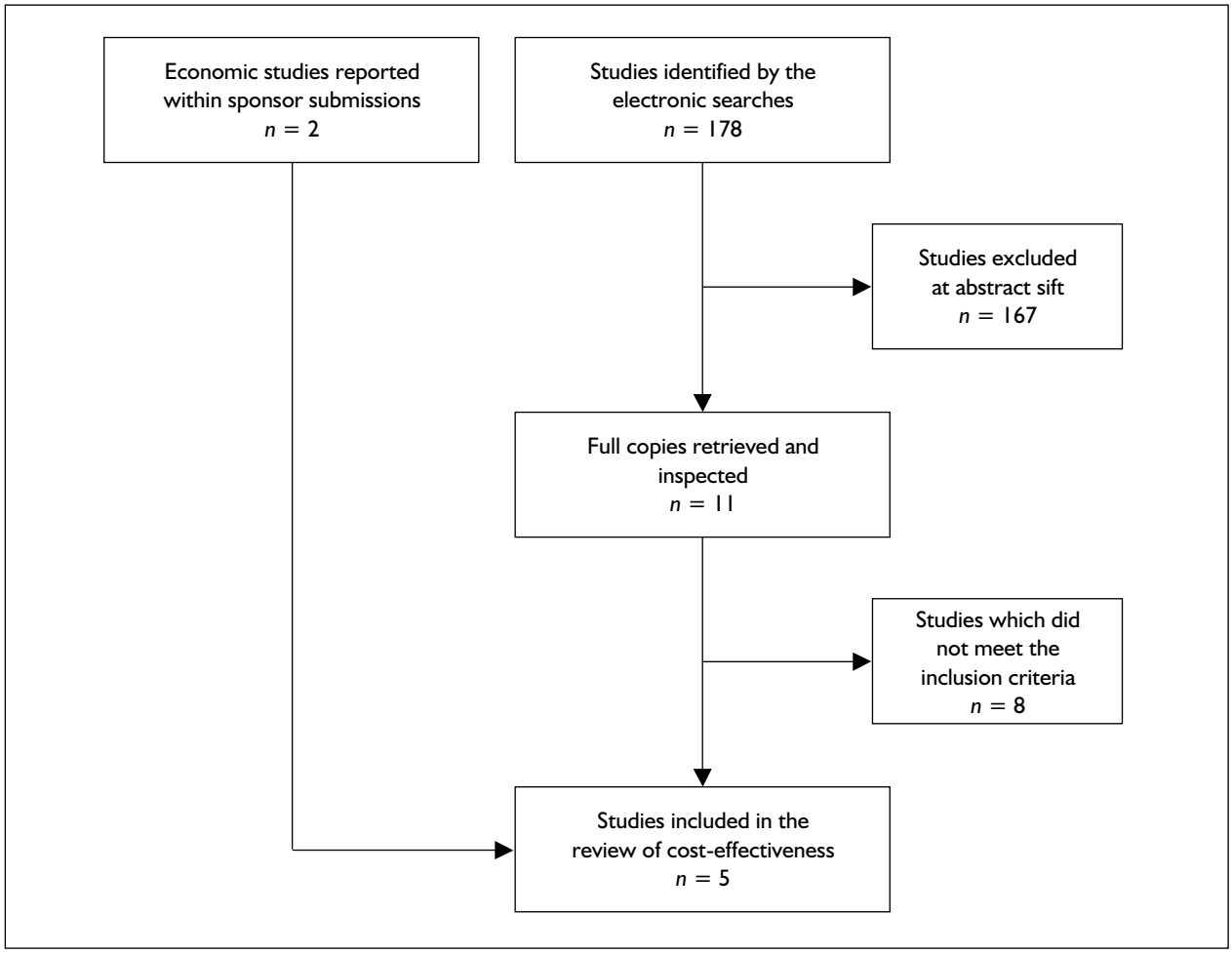
1.	**Was a well-defined question posed in answerable form?**	
1.1.	Did the study examine both costs and effects of the service(s) or programme(s)?	Yes
1.2.	Did the study involve a comparison of alternatives?	Yes
1.3.	Was a viewpoint for the analysis stated and was the study placed in any particular context?	Yes – UK NHS perspective
2.	**Was a comprehensive description of the competing alternatives given?**	
2.1.	Were any important alternatives omitted?	No
2.2.	Was (should) a *do-nothing* alternative (be) considered?	No
3.	**Was the effectiveness of the programmes or services established?**	
3.1.	Was this done through an RCT? If so, did the trial protocol reflect what would happen in regular practice?	Yes – data from the MOSAIC trial were used as the basis for the cost-effectiveness analysis
3.2.	Was effectiveness established through an overview of clinical studies?	No

3.3.	Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	Weibull functions and extrapolations were used to evaluate long-term health outcomes. The extrapolation of disease-free survival may be slightly biased, since it is likely to overestimate long-term disease-free survival
4.	**Were all the important and relevant costs and consequences for each alternative identified?**	
4.1.	Was the range wide enough for the research question at hand?	Yes
4.2.	Did it cover all relevant viewpoints?	Yes
4.3.	Were capital costs, as well as operating costs, included?	No
5.	**Were costs and consequences measured accurately in appropriate physical units?**	
5.1.	Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?	No
5.2.	Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	No
6.	**Were costs and consequences valued credibly?**	
6.1.	Were the sources of all values clearly identified?	Yes
6.2.	Were market values employed for changes involving resources gained or depleted?	No
6.3.	Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinical space donated at a reduced rate), were adjustments made to approximate market values?	No
6.4.	Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type of analysis – cost-effectiveness, cost–benefit, cost–utility – been selected)?	Yes – cost–utility analysis was undertaken
7.	**Were costs and consequences adjusted for differential timing?**	
7.1.	Were costs and consequences which occur in the future discounted to their present value?	Yes – costs and health outcomes were discounted at 3.5% per annum
7.2.	Was any justification given for the discount rate used?	As per NICE guidelines for technology appraisals
8.	**Was an incremental analysis of costs and consequences of alternatives performed?**	
8.1.	Were the additional (incremental) costs generated by one alternative over another compared with the additional effects, benefits or utilities generated?	Yes – an incremental analysis was performed
9.	**Was allowance made for uncertainty in the estimates of costs and consequences?**	
9.1.	If data on costs or consequences were stochastic, were appropriate statistical analyses performed?	Yes – bootstrapping of patient-level data was used to generate stochastic results
9.2.	If sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?	Yes – details of the justification for parameter changes in the sensitivity analyses are given

9.3.	Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the CI around the ratio of costs to consequences)?	The cost per QALY of FOLFOX4 compared with 5-FU/LV increased significantly only when the incremental costs and benefits observed within the trial were considered (i.e. long-term outcomes excluded)
10.	**Did the presentation and discussion of study results include all issues of concern to users?**	
10.1.	Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?	Yes
10.2.	Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?	Yes – the cost-effectiveness results were compared with those from the assessment from the US perspective.[146] Possible explanation for the differences between the two sets of results was postulated
10.3.	Did the study discuss the generalisability of the results to other settings and patient/client groups?	No
10.4.	Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or other ethical issues)?	No
10.5.	Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	No

Appendix 11

QUORUM trial flow chart (cost-effectiveness)



Appendix 12

Studies excluded from the review of cost-effectiveness

Author, year	Reason for exclusion
Monz *et al.*, 2003[148]	Study did not assess capecitabine or oxaliplatin
Bonistalli *et al.*, 1998[222]	Study did not assess capecitabine or oxaliplatin
Brown *et al.*, 1994[223]	Study did not assess capecitabine or oxaliplatin
Jansman *et al.*, 2004[224]	Not a cost-effectiveness analysis. Study population included patients with metastatic disease
Macdonald, 1997[225]	Not an economic evaluation
Messori *et al.*, 1996[226]	Study did not assess capecitabine or oxaliplatin
Michel *et al.*, 1999[227]	Study did not assess capecitabine or oxaliplatin
Norum *et al.*, 1997[173]	Study did not assess capecitabine or oxaliplatin. Did not focus exclusively on patients with colon cancer

Appendix 13

Identification of sources of evidence – economic model

This appendix maps out the evidence base used to inform the development of the independent economic model and provides an overview of the methods used to identify the evidence. A description of the categories of evidence used is presented first. Next, each individual source is listed together with details of how the source was identified and how it was used in the model. Lastly, the keyword strategies of searches undertaken to inform the model and a brief description of the scope of search are provided.

Categories of evidence

The evidence used to inform the development of the model and to populate the parameters within the model can be classified into the seven categories listed in the table below.

Sources used to develop and populate model

Source	Description
Review of clinical effectiveness	Assessment of clinical effectiveness of oxaliplatin and capecitabine presented in earlier section of this report
Previous economic analyses of chemotherapy	Assessment of irinotecan (etc.) undertaken by ScHARR to inform an earlier NICE appraisal[8] (i.e. evidence known to the authors of the current model)
Sponsor submissions to NICE	Economic analyses critiqued in the section 'Evidence from industry submissions' (p. 44)
Studies identified through the review of cost-effectiveness	Inclusion criteria used in the review of cost-effectiveness were expanded and re-applied to the search results to identify studies of possible relevance to the development of the model (i.e. inclusion criteria were not restricted to economic evaluations)
Studies identified through searches undertaken to inform the model	Broad cost searches and searches designed to identify specific evidence requirements of the model. A description of the scope of each search together with search keyword strategies are presented in this appendix
Reference sources (e.g. BNF, NHS Reference Costs)	Standard references sources, manuals, handbooks, etc.
Expert opinion	Clinical experts acting as advisers to the assessment and contacts known to the authors

Individual sources of evidence

The individual sources which make up the categories of evidence are listed below with details of how each source was identified and how each source was used in the model.

Source	Previous analyses of chemotherapy for advanced colorectal cancer[8]
Use(s) in model	Inform the development of the model (e.g. structure, choice of outcomes) Alternative scenarios for sensitivity analysis of treatment of patients with relapsing disease Identification of further sources used to populate the model
Identification process	Analyses already known to the authors
Source	Review of clinical effectiveness
Use(s) in model	Identification of interventions assessed in the model Survival data used to estimate long-term survival Inform the model cycle length Basis of assumption that 5FU/LV patients receive treatment on an outpatient basis Data on incidence of adverse events Support the assumption that all relapses occur during first 5 years Adverse event data
Identification process	Forms part of the same assessment as economic model
Source	Monz *et al.*, 2003[148]
Use(s) in model	As a comparison for the methods and results of the model
Identification process	Cost-effectiveness review search
Source	Moertel *et al.*, 1995[149]
Use(s) in model	Support the assumption that all relapses occur during first 5 years As a comparison for the estimate of long-term survival
Identification process	Searches undertaken to inform model
Source	Staib *et al.*, 2002[159]
Use(s) in model	As a comparison for the estimate of long-term survival
Identification process	Searches undertaken to inform model
Source	McDermott *et al.*, 1981[160]
Use(s) in model	As a comparison for the estimate of long-term survival
Identification process	Searches undertaken to inform model
Source	Pihl *et al.*, 1980[161]
Use(s) in model	As a comparison for the estimate of long-term survival
Identification process	Searches undertaken to inform model
Source	Smith *et al.*, 2004[162]
Use(s) in model	As a comparison for the estimate of long-term survival
Identification process	Existing economic analyses[8]
Source	FOCUS trial[157] and personal communication with the Medical Research Council
Use(s) in model	Identification of treatment plans for patients with relapsing disease Survival data used to estimate long-term survival of patients with relapsing disease Costs of relapse
Identification process	Existing economic analyses[8]

continued

Source	GERCOR trial[158]
Use(s) in model	Identification of treatment plans for patients with relapsing disease Survival data used to estimate long-term survival of patients with relapsing disease Costs of relapse
Identification process	Existing economic analyses[8]
Source	Expert opinion
Use(s) in model	Inform the choice of treatment for patients with relapsing disease Inform the development of model Cost of pumps Pharmacy costs Identification of diagnostic monitoring tests Identification of treatment regimen for sensitivity analysis Identification of further sources and estimates used to populate the model
Identification process	Discussions with clinicians and further contacts
Source	NICE guidance on advanced colorectal cancer[10]
Use(s) in model	Inform the choice of treatment for patients with relapsing disease Support the assumption that overall survival in relapse-free patients is similar to that of health population
Identification process	Reference source
Source	Cancer trends[164]
Use(s) in model	Support the assumption that overall survival in relapse-free patients is similar to that of health population Searches undertaken to inform model
Identification process	Reference source
Source	Life tables[156]
Use(s) in model	Estimate probability of death from causes other than colon cancer
Identification process	Reference source
Source	Hospital and Community Health Services Indices[165]
Use(s) in model	Uplift cost estimates to current prices
Identification process	Reference source
Source	BNF[40]
Use(s) in model	Drug acquisition costs
Identification process	Reference source
Source	Boland *et al.*, 2003[166]
Use(s) in model	Cost of line insertion
Identification process	Existing economic analyses[8]
Source	NHS Reference Costs[153]
Use(s) in model	Drug administration costs
Identification process	Reference source
Source	Netten *et al.*, 1999[167]
Use(s) in model	Cost of inpatient appointment
Identification process	Reference source

continued

Source	Renehan *et al.*, 2004[168]
Use(s) in model	Costs of diagnostic monitoring tests
Identification process	Searches undertaken to inform model
Source	FACS trial protocol[169]
Use(s) in model	Costs of diagnostic monitoring tests Costs of follow-up plan
Identification process	Expert opinion
Source	Roche submission[39]
Use(s) in model	Costs of hospitalisations due to adverse events
Identification process	Sponsor submission to NICE
Source	Sanofi-Aventis submission[143]
Use(s) in model	Costs of treating less serious events
Identification process	Sponsor submission to NICE
Source	Aventis submission for previous NICE appraisal[8]
Use(s) in model	Proportion of inpatient/outpatient treatment of patients with relapsing disease
Identification process	Previous economic analysis[8]
Source	Hospital episode statistics[170]
Use(s) in model	Support the estimate of proportion of inpatient/outpatient treatment of patients with relapsing disease
Identification process	Reference source Searches undertaken to inform model
Source	Ramsey *et al.*, 2000[150]
Use(s) in model	Utility estimate Summary of utility estimates for colorectal cancer
Identification process	Searches undertaken to inform model Sponsor submission
Source	Smith *et al.*, 1993[172]
Use(s) in model	Summary of utility estimates for colorectal cancer
Identification process	Searches undertaken to inform model
Source	Norum *et al.*, 1997[173]
Use(s) in model	Summary of utility estimates for colorectal cancer
Identification process	Searches undertaken to inform model
Source	Ness *et al.*, 1999[174]
Use(s) in model	Utility estimate Summary of utility estimates for colorectal cancer
Identification process	Searches undertaken to inform model
Source	Ramsey *et al.*, 2002[175]
Use(s) in model	Summary of utility estimates for colorectal cancer
Identification process	Searches undertaken to inform model
Source	Petrou and Campbell, 1997[176]
Use(s) in model	Alternative estimate for sensitivity analysis of utilities
Identification process	Existing economic analyses[8]

Search undertaken to inform model

The keyword strategies of searches undertaken to inform the model together with a brief description of the scope of each search is given below.

Extended cost search

Scope	Chemotherapy + colorectal + economics (i.e. not restricted to oxaliplatin/capecitabine)
Purpose	To define relevant cost and resource groups To identify estimates for cost and resource groups
Sources searched	MEDLINE DARE–NHS EED–HTA

MEDLINE
1966–2005
Ovid Online version 9.3
Search undertaken April 2005

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 adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
13. (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
14. (neoplasm$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
15. (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
16. (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
17. (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
18. (tumour$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
19. (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
20. or/12-19
21. 1 or 11 or 20
22. Colorectal Surgery/
23. Surgery/
24. Surgical Procedures, Operative/
25. su.fs.
26. (postoperative or resect$ or operable or surgery or surgical).tw.
27. or/22-26
28. Chemotherapy, Adjuvant/
29. Antineoplastic Combined Chemotherapy Protocols/
30. Combined Modality Therapy/
31. Drug Therapy, Combination/
32. Antineoplastic Agents/
33. fluorouracil.af.
34. leucovorin.af.
35. tegafur.af.
36. uracil.af.
37. (5 fu or lv or fu?lv or uft).af.
38. (58-05-9 or 51-21-8 or 17902-23-7 or 66-22-8).rn.
39. or/28-38
40. Economics/
41. exp "Costs and cost analysis"/
42. Economic value of life/
43. exp Economics, hospital/
44. exp Economics, medical/
45. Economics, nursing/
46. exp models, economic/
47. Economics, pharmaceutical/
48. exp "Fees and charges"/
49. exp Budgets/
50. ec.fs.
51. (cost or costs or costed or costly or costing$).tw.
52. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
53. Quality-adjusted life years/
54. (qaly or qalys).af.
55. (quality adjusted life year or quality adjusted life years).af.
56. or/40-55
57. 21 and 27 and 39 and 56
58. oxaliplatin.af.
59. "63121 00 6".rn.
60. l ohp.af.
61. eloxatin.af.
62. 1r 2r 1 2 cyclohexanediamine n n oxalato 2 o o platinum.af.
63. mosaic.af.
64. or/58-63
65. capecitabine.af.
66. xeloda.af.
67. 154361 50 9.af.
68. 5 deoxy 5 fluoro n pentyloxy carbonyl cytidine.af.
69. x act.af.
70. or/65-69
71. 64 or 70
72. exp Colorectal Neoplasms/
73. Neoplasms/
74. Carcinoma/
75. Adenocarcinoma/
76. or/73-75

77. Colonic Diseases/
78. Rectal Diseases/
79. exp Colon/
80. exp Rectum/
81. or/77-80
82. 76 and 81
83. (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
84. (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
85. (neoplasm$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
86. (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
87. (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
88. (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
89. (tumour$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
90. (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
91. or/83-90
92. 72 or 82 or 91
93. 71 and 92
94. Economics/
95. exp "Costs and cost analysis"/
96. Economic value of life/
97. exp Economics, hospital/
98. exp Economics, medical/
99. Economics, nursing/
100. exp models, economic/
101. Economics, pharmaceutical/
102. exp "Fees and charges"/
103. exp Budgets/
104. ec.fs.
105. (cost or costs or costed or costly or costing$).tw.
106. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
107. Quality-adjusted life years/
108. (qaly or qalys).af.
109. (quality adjusted life year or quality adjusted life years).af.
110. or/94-109
111. 93 and 110
112. 57 not 111
113. 21 and 39 and 56
114. 113 not (111 or 27)

DARE–NHS EED–HTA
Date coverage not known (approx. 1994–2005)
CRD website version
Search undertaken April 2005

Colorectal or colon/All fields AND cost or economic or qaly or quality adjusted/All fields AND Economic evaluations OR Cost,Review,Methodology studies or HTA reports OR HTA Projects

Utility search

Scope	Colorectal cancer and QoL
Purpose	To define utility estimates
Sources searched	MEDLINE MAPI Research Institute EORTC website

MEDLINE
1966–2005
Ovid Online version 9.3
Search undertaken May 2005

Drug administration search

Scope	Chemotherapy and oral or intravenous or home or inpatient or outpatient administration
Purpose	To define cost and resource groups specific to drug administration To identify estimates of costs and resource use To identify proportion of patients receiving inpatient/outpatient chemotherapy To identify possibly relevant issues relating to patient preference/acceptability
Sources searched	MEDLINE Hospital Episodes Statistics Hospital Activity Statistics NHS Cancer Plan Information Strategy

MEDLINE
1966–2005
Ovid Online version 9.3
Search undertaken May 2005

1. Chemotherapy, Adjuvant/
2. Antineoplastic Combined Chemotherapy Protocols/
3. 1 or 2
4. Administration, Oral/
5. Infusions, Intravenous/
6. 4 and 5
7. *Administration, Oral/
8. 6 or 7
9. Ambulatory Care/
10. Outpatient Clinics, Hospital/
11. Ambulatory Care Facilities/
12. Home Care Services/
13. Home Care Services, Hospital-Based/
14. Home Infusion Therapy/
15. or/9-14
16. 3 and 8
17. 3 and 15
18. 16 or 17

Long-term survival search

Scope	(Oxaliplatin/capecitabine or surgery) and colon cancer and long-term survival (i.e. more than 5 years)
Purpose	To identify long-term survival estimates to compare with estimates generated by model
Sources searched	MEDLINE Office of National Statistics Cancer Survival data Cancer registries EUROCARE website

MEDLINE
1966–2005
Ovid Online version 9.3
Search undertaken June 2005

Search 1

1. oxaliplatin.af.
2. "63121 00 6".rn.
3. l ohp.af.
4. eloxatin.af.
5. 1r 2r 1 2 cyclohexanediamine n n oxalato 2 o o platinum.af.
6. mosaic.af.
7. or/1-6
8. capecitabine.af.
9. xeloda.af.
10. 154361 50 9.af.
11. 5 deoxy 5 fluoro n pentyloxy carbonyl cytidine.af.
12. x act.af.
13. or/8-12
14. 7 or 13
15. exp Colorectal Neoplasms/
16. Neoplasms/
17. Carcinoma/
18. Adenocarcinoma/
19. or/16-18
20. Colonic Diseases/
21. Rectal Diseases/
22. exp Colon/
23. exp Rectum/
24. or/20-23
25. 19 and 24
26. (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
27. (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
28. (neoplasm$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
29. (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
30. (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
31. (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
32. (tumour$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
33. (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
34. or/26-33
35. 15 or 25 or 34
36. 14 and 35
37. adjuvant.af.
38. Colorectal Surgery/
39. Surgery/
40. Surgical Procedures, Operative/
41. su.fs.
42. (postoperat$ or post-operat$ or resect$ or operable or surgery or surgical).tw.
43. or/37-42
44. 36 and 43
45. Survival/
46. Survival Rate/
47. survival analysis/
48. Survivors/
49. or/45-48
50. exp Cohort Studies/
51. proportional hazards models/
52. 50 or 51
53. 52 and survival.tw.
54. (year$ adj5 (surviv$ or follow-up)).tw.
55. ((longterm or long-term) adj5 (surviv$ or follow-up)).tw.
56. ((follow$-up or prolong$ or extend$ or increas$ or shorten$ or reduc$ or decreas$) adj5 surviv$).tw.
57. or/49,53-56
58. 44 and 57

Search 2

1. exp Colonic Neoplasms/
2. Neoplasms/
3. Carcinoma/
4. Adenocarcinoma/
5. or/2-4
6. Colonic Diseases/
7. exp Colon/
8. or/6-7
9. 5 and 8
10. ((carcinoma or neoplasia or neoplasm$ or adenocarcinoma or cancer$ or tumor$ or tumour$ or malignan$) adj3 colon$).tw.
11. or/1,9-10
12. Colorectal Surgery/
13. Surgery/
14. Surgical Procedures, Operative/
15. su.fs.
16. (postoperat$ or post-operat$ or resect$ or operable or operat$ or surgery or surgical).tw.
17. or/12-16

18. 11 and 17
19. case series.tw.
20. Survival/
21. Survival Rate/
22. survival analysis/
23. Survivors/
24. exp Cohort Studies/
25. proportional hazards models/
26. 24 or 25
27. 26 and survival.tw.
28. (year$ adj5 (surviv$ or follow-up)).tw.
29. ((longterm or long-term) adj5 (surviv$ or follow-up)).tw.
30. ((follow$-up or prolong$ or extend$ or increas$ or shorten$ or reduc$ or decreas$) adj5 surviv$).tw.
31. or/19-23,27-30
32. 18 and 31

Appendix 14

Disease-free survival analysis and results

This appendix presents the results of the disease-free survival analysis. Disease-free survival is a surrogate outcome, and the generalisability and interpretation of the cost per disease-free LYG is unclear, and has therefore not been included in the primary analysis. *Table 43* shows the regression output for the derivation of the Weibull parameters for the Mayo 5-FU/LV regimen.

TABLE 43 *Results from Weibull regression analysis of Mayo 5-FU/LV regimen*

Multiple *R*	0.976190883
R^2	0.952948639
Adjusted R^2	0.952482784
Standard error	0.129602026
Observations	103
Weibull γ	0.172895174
Weibull λ	0.965517196

The resulting fitted Weibull survival function (for disease-free survival) is shown in *Figure 8*. The published hazard ratio was then applied to this curve to obtain the fitted Weibull survival function for the capecitabine arm (*Figure 9*).

Table 44 shows the regression output for the derivation of the Weibull parameters for the de Gramont 5-FU/LV regimen.

TABLE 44 *Results from Weibull regression analysis of de Gramont 5-FU/LV regimen*

Multiple *R*	0.981260725
R^2	0.96287261
Adjusted R^2	0.962485866
Standard error	0.185219897
Observations	98
Weibull γ	0.014184849
Weibull λ	0.94726062

The resulting fitted Weibull survival function (for disease-free survival) is shown in *Figure 10*. The published hazard ratio was then applied to this to obtain the fitted Weibull survival function for the FOLFOX4 arm (*Figure 11*).

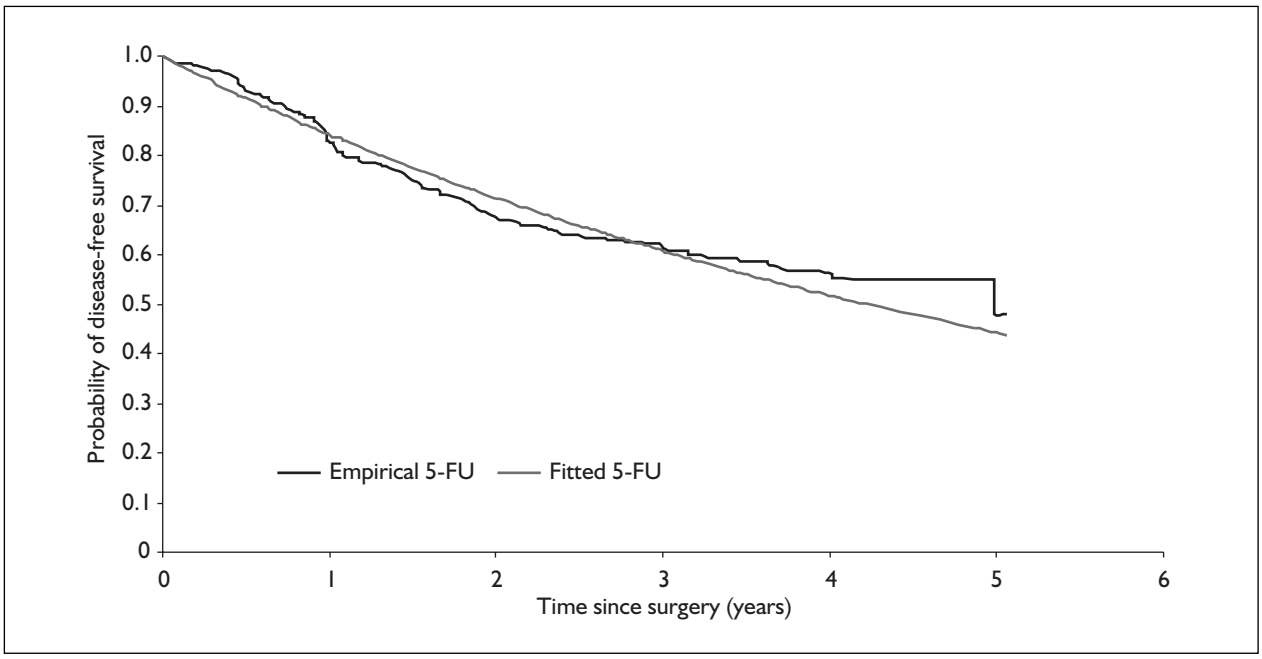


FIGURE 8 *Fitted disease-free survival curves for Mayo 5-FU/LV regimen*

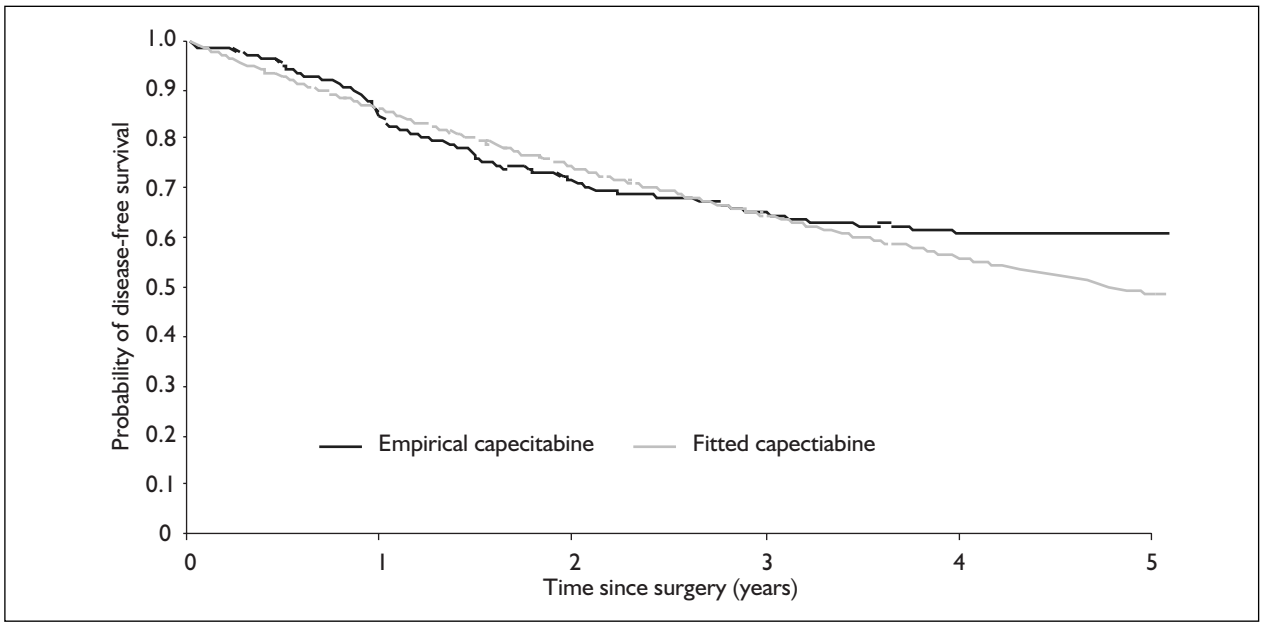


FIGURE 9 *Fitted disease-free survival curves for capecitabine regimen*

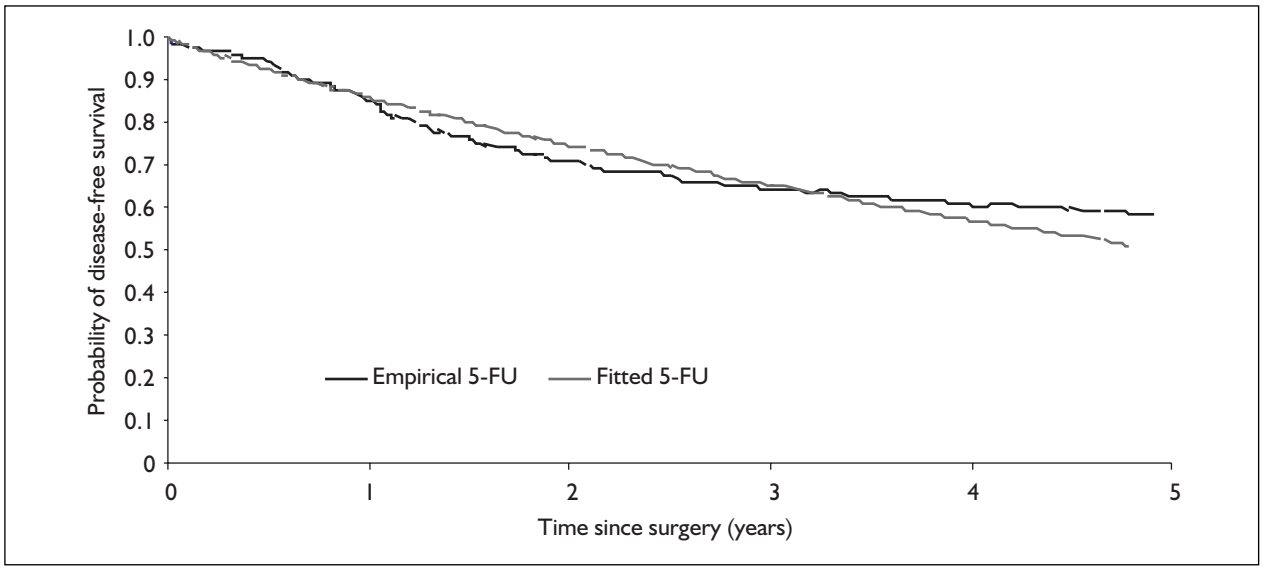


FIGURE 10 *Fitted disease-free survival curves for de Gramont 5-FU/LV regimen*

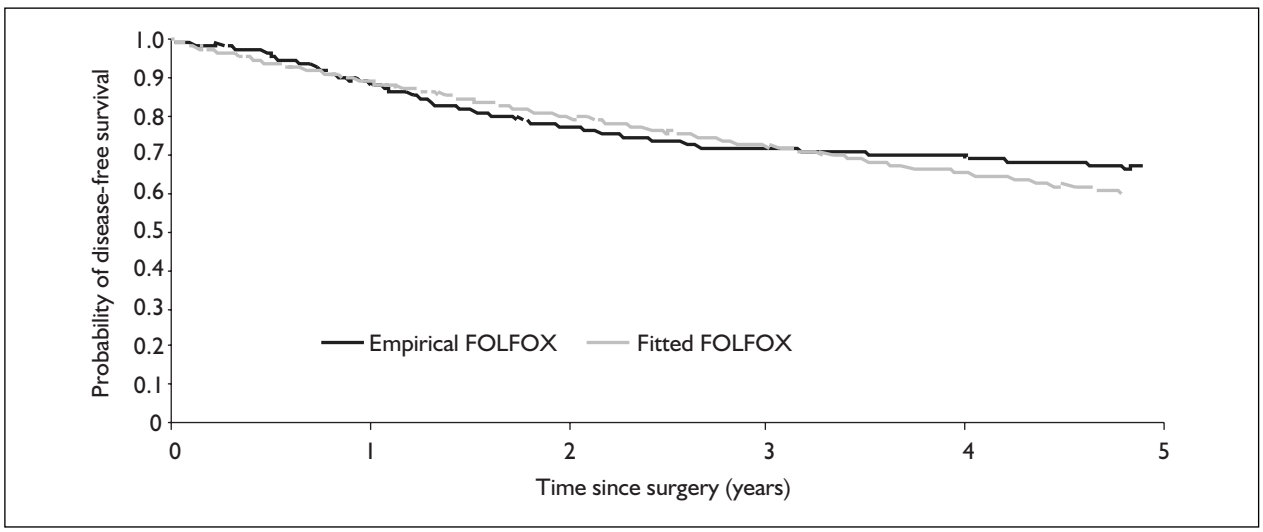


FIGURE 11 *Fitted disease-free survival curves for FOLFOX4 regimen*

Appendix 15

Fitted Weibull functions for patients with relapse

Figures 12–16 show the empirical and fitted overall survival curves for patients following relapse, based on five different palliative chemotherapy regimens.

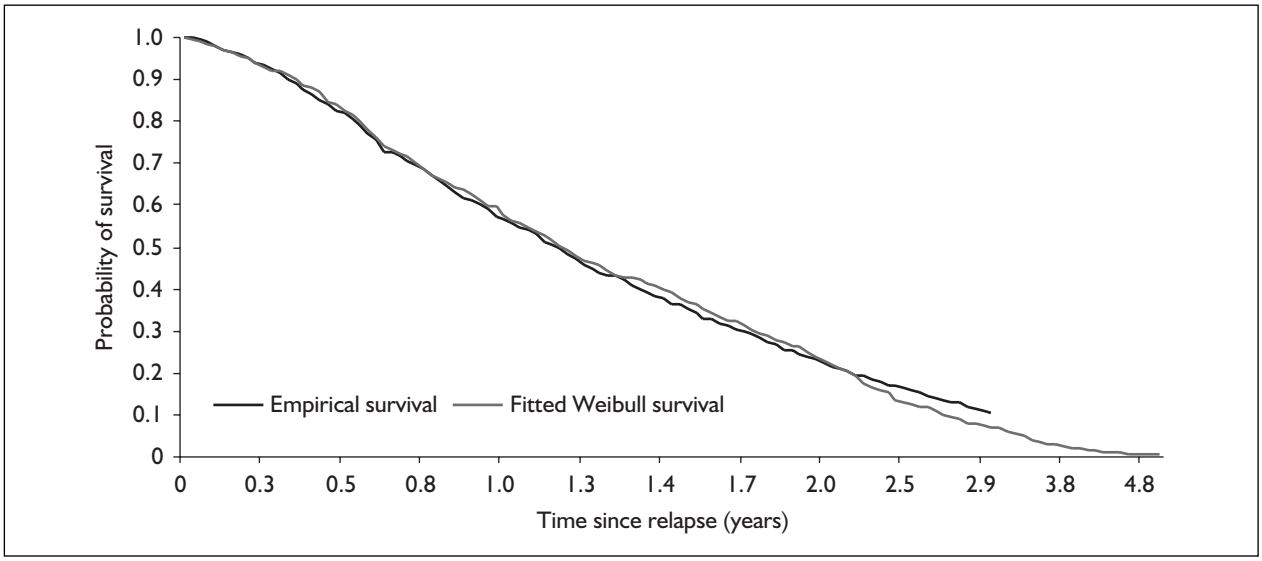


FIGURE 12 *Empirical versus fitted survival for FOCUS Plan A (first-line 5-FU/LV, second-line irinotecan)*

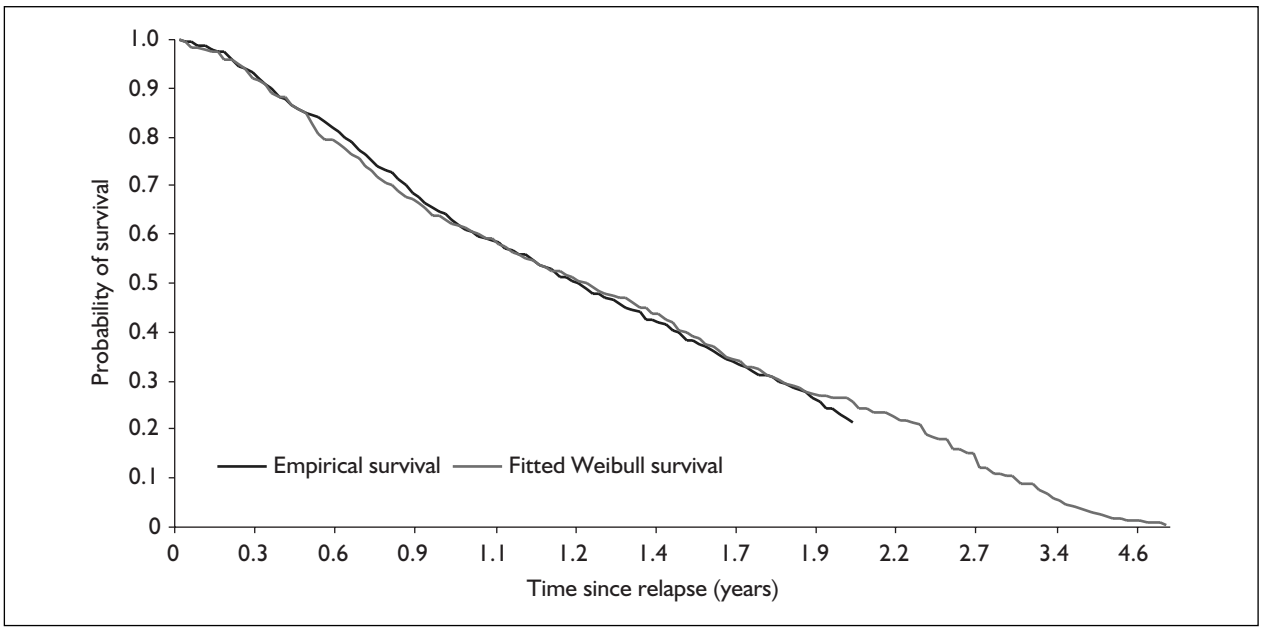


FIGURE 13 *Empirical versus fitted survival for FOCUS Plan B (first-line 5-FU/LV, second-line irinotecan in combination with 5-FU/LV)*

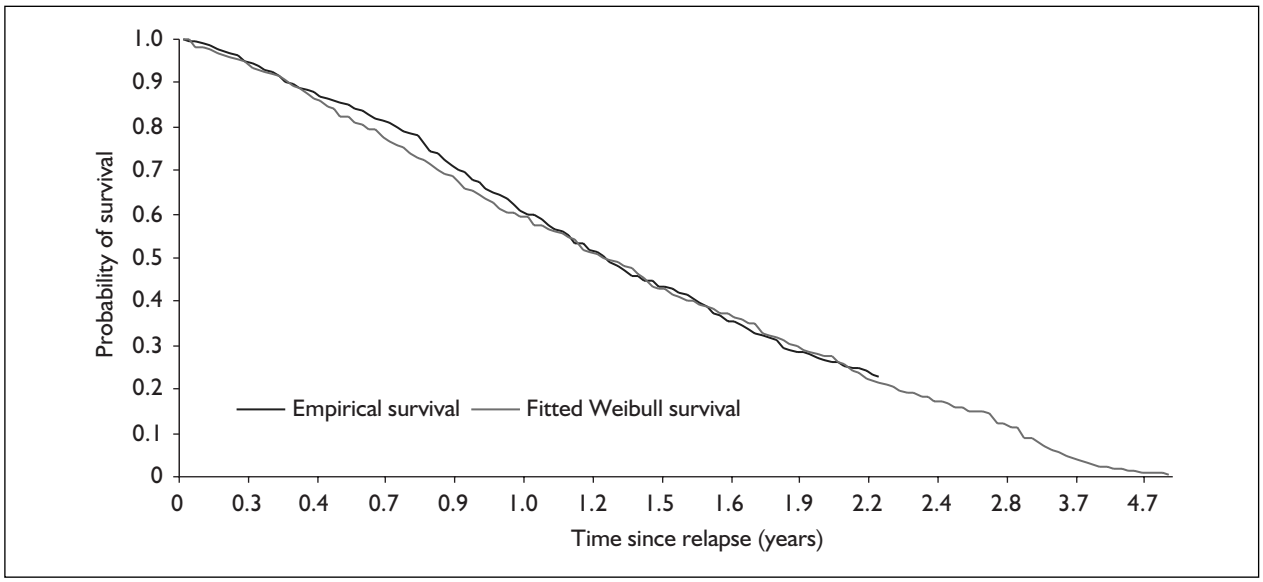


FIGURE 14 *Empirical versus fitted survival for FOCUS Plan D (first-line irinotecan in combination with 5-FU/LV)*

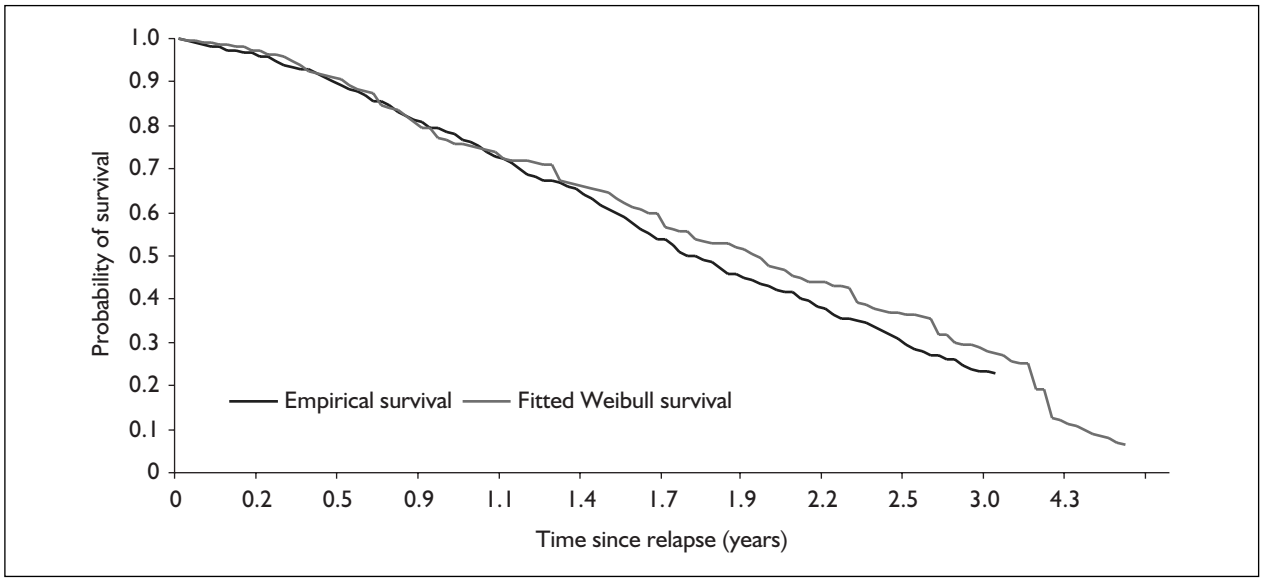


FIGURE 15 *Empirical versus fitted survival for GERCOR arm 1 (first-line FOLFOX, second-line FOLFIRI)*

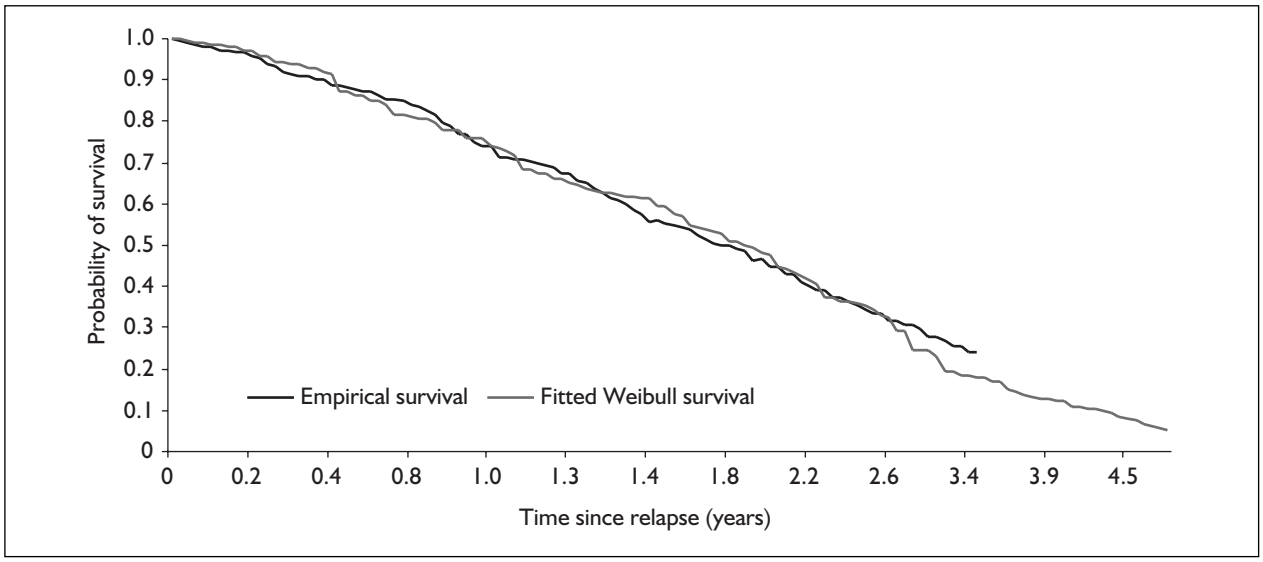


FIGURE 16 *Empirical versus fitted survival for GERCOR arm 2 (first-line FOLFIRI, second-line FOLFOX)*

Appendix 16

Fitted overall survival curves

Figures 17 and *18* show the long-term overall survival extrapolations up to 50-years, along with the available empirical Kaplan-Meier estimates up to 5 years.

In both plots, there is a distinct 'kink' in the extrapolated curves at around 7 years. This is attributable to the assumption of no relapses beyond 5 years. Patients who relapse towards the end of the 5-year period may survive for 1–2 years, therefore the estimates of overall survival continue to decrease at the same rate up to around 7 years. Thereafter, overall survival is represented by patients free of relapse, as defined by the function fitted to the life-table data, and is demonstrated by a reduction in the gradient of the fitted curves.

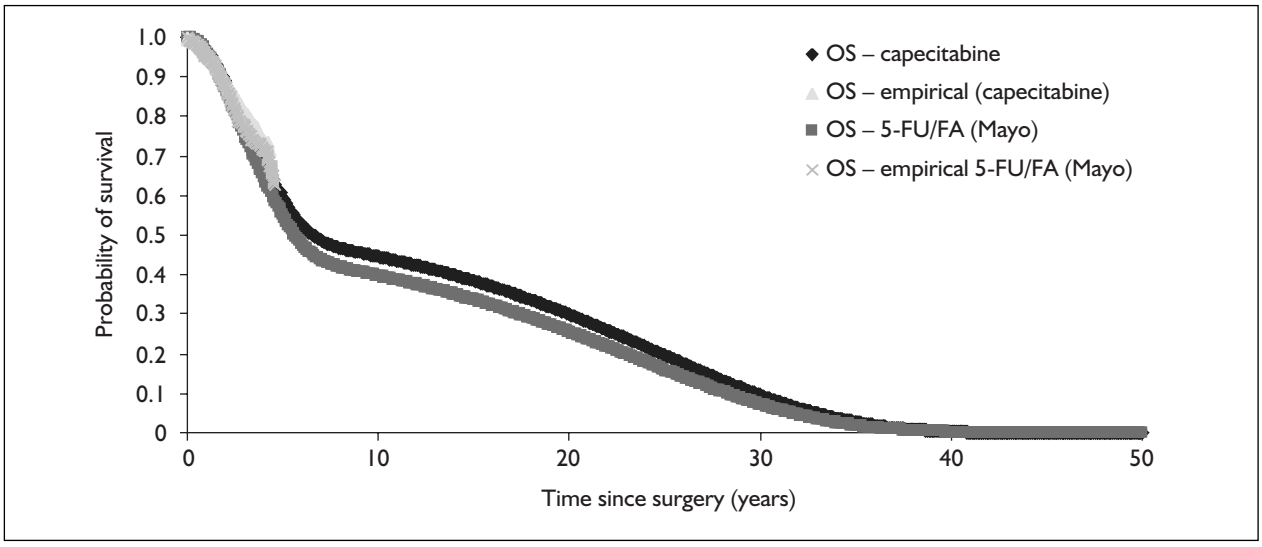


FIGURE 17 *Empirical and fitted overall survival for 5-FU/LV (Mayo) and capecitabine arms*

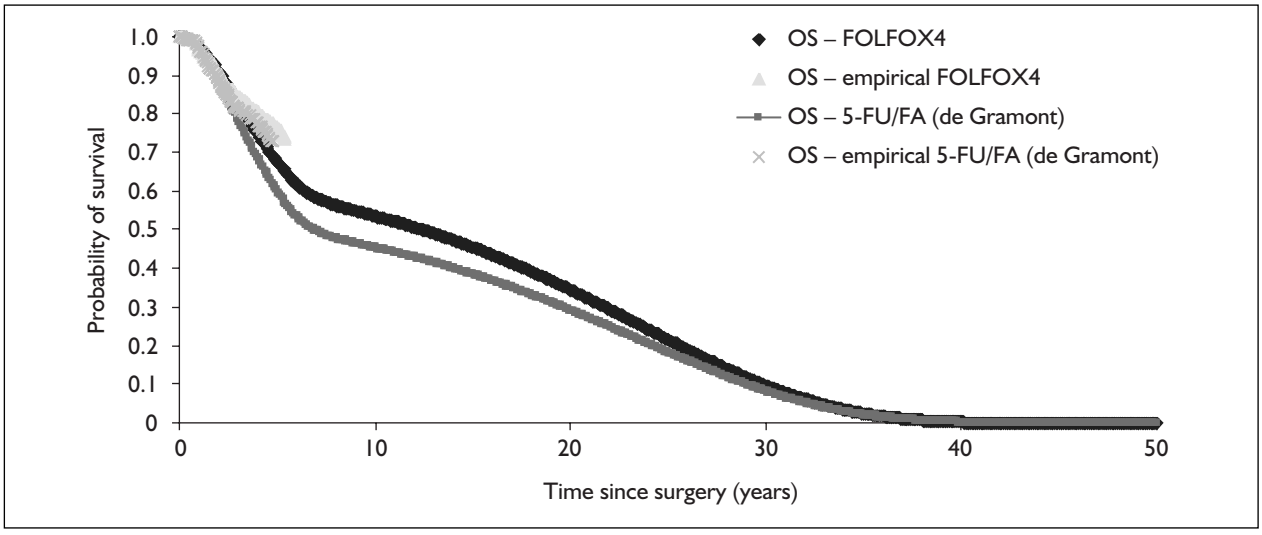


FIGURE 18 *Fitted overall survival for de Gramont 5-FU/LV and FOLFOX4 arms*

Appendix 17

Overview of ongoing adjuvant therapy trials in Stage III colon cancer[20]

Study/trial	Disease stage	Regimens
XELOX	III	Capecitabine plus oxaliplatin versus bolus 5-FU/LV (Mayo Clinic)
PETACC-2	III	AIO infusional 5-FU/LV versus bolus 5-FU/LV (Mayo Clinic)
NSABP C-07	II/III	Oxaliplatin/bolus 5-FU/LV (Roswell Park) versus bolus 5-FU/LV (Roswell Park)
NSABP C-08	II/III	Oxaliplatin/5-FU/LV (FOLFOX6) versus oxaliplatin/5-FU/LV (FOLFOX6) plus bevacizumab
Roche trial (AVANT trial)	II/III	Oxaliplatin/5-FU/LV (FOLFOX4) versus oxaliplatin/5-FU/LV (FOLFOX4) plus bevacizumab versus oxaliplatin/capecitabine (XELOX) plus bevacizumab
N0477	III	Oxaliplatin/5-FU/LV (FOLFOX4) versus irinotecan/5-FU/LV (FOLFIRI) versus FOLFOX plus FOLFIRI All arms ± cetuximab
ACCORD2	III	Irinotecan/5-FU/LV versus 5-FU/LV (de Gramont)
QUASAR II	III (includes high-risk Stage II)	Irinotecan plus capecitabine versus capecitabine Third arm added irinotecan plus capecitabine plus bevacizumab
PETACC-3	II/III	Irinotecan plus 5-FU/LV (de Gramont/AIO) versus 5-FU/LV (de Gramont/AIO)
CALGB C89803	II/III	Irinotecan plus bolus 5-FU/LV versus bolus 5-FU/LV
NCCTG/NCI/ ECOG	III	Irinotecan/bolus 5-FU/LV or oxaliplatin/bolus 5-FU/LV ± cetuximab

AIO, German high-dose infusional regimen.

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Members

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Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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