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The use of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer

Produced by	The School of Health and Related Research (ScHARR)	
Authors	Abdullah Pandor	Research Fellow, ScHARR
	Simon Eggington	Operational Research Analyst, ScHARR
	Suzy Paisley	Research Scientist, ScHARR
	Paul Tappenden	Senior Cost-effectiveness Modeller, ScHARR
	Paul Sutcliffe	Research Associate, ScHARR

Correspondence to Abdullah Pandor, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA.

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Publication information

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The School of Health and Related Research (ScHARR) is one of the four Schools that comprise the Faculty of Medicine at the University of Sheffield. ScHARR brings together a wide range of medical- and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research and information science. It includes the Sheffield unit of the Trent Institute for Health Services Research, which is funded by NHS R&D to facilitate high-quality health services research and capacity development.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the effectiveness and cost-effectiveness of healthcare interventions for the NHS R&D Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Health and Clinical Excellence. ScHARR-TAG is part of a wider collaboration of six units from other regions. The other units are: Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen Health Technology Assessment Group (Aberdeen HTA Group), University of Aberdeen; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsular Technology Assessment Group (PenTAG), University of Exeter; NHS Centre for Reviews and Dissemination, University of York; and West Midlands Health Technology Assessment Collaboration (WMHTAC), University of Birmingham.

Contributions 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. Simon Eggington and Paul Tappenden wrote the section on cost-effectiveness.

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The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme. Any errors are the responsibility of the authors.

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Definition of Terms and List of Abbreviations

List of abbreviations

5-FU	5-Fluorouracil
AUC	Area under the curve
BNF	British National Formulary
CEA	Carcinoembryonic Antigen
CDSR	Cochrane Database of Systemic Reviews
CCTR	Cochrane Controlled Trials Register
CI	Confidence interval
CT	Computed tomography
CTC NCI	Common Toxicity Criteria of the National Cancer Institute
DARE	Database of Abstract of Reviews of Effectiveness
DFS	Disease-free survival
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 (also known as leucovorin)
FAP	Familial adenomatous polyposis
FOCUS	Fluorouracil, oxaliplatin and irinotecan: use and sequencing
FOLFIRI	Irinotecan + infusional FU
FOLFOX	Oxaliplatin + infusional FU
FLOX	Oxaliplatin + bolus FU
GERCOR	Groupe Coopérateur Multidisciplinaire en Oncologie
GP	General Practitioner
HEED	Health Economics Database
HCHS	Hospital and Community Health Services
HNPCC	Hereditary non-polyposis colorectal cancer
ITT	Intention-to-treat
IV	Intravenous
LV	Leucovorin (also known as folinic acid)

LV5FU2	Leucovorin 5-fluorouracil (fortnightly de Gramont regimen)
LYG	Life years gained
MOSAIC	Multicenter International Study of Oxaliplatin/5-fluorouracil and leucovorin in the Adjuvant Treatment of Colon Cancer
MRC	Medical Research Council
NHS	National Health Service
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
OS	Overall survival
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
RFS	Relapse-free survival
RNA	Ribonucleic acid
SCI	Science Citation Index
SIGN	Scottish Intercollegiate Guidelines Network
TNM	Tumor, Node, Metastases
UK	United Kingdom
VAT	Value Added Tax
WoS	Web of Science
WWW	World Wide Web
X-ACT	Xeloda – Adjuvant Chemotherapy Trial

Definitions of terms

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 $< 1{,}000/mm^3$ 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.

Executive Summary

Background

The colon and rectum are parts of the body's digestive system and together form a long, muscular tube called the large intestine. Colorectal cancer is a malignant neoplasm arising from the lining (mucosa) of the colon and rectum and 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.

About two thirds of tumours develop in the colon and the remainder in the rectum. Colon cancer affects almost equal proportions of men and women whereas rectal cancer is more common in men. The median age of diagnosis is over 70 years of age for both colon and rectal cancer. The aetiology of colorectal cancer involves genetic and environmental factors. The most important environmental factor is probably diet. The prognosis, type and effectiveness of treatment depend largely on the degree to which the cancer has spread at diagnosis.

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 five year survival rate between 25 to 60%. After a complete surgical resection (undertaken with curative intent), stage III patients with colon cancer have a 50 to 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.

Colorectal cancer is a significant cause of premature death, with almost half of all related deaths occurring in people under 75 years of age. 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.

The management of colorectal cancer is constantly evolving. The administration of six to seven 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

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

Identification of studies: Searches were carried out to inform three aspects of the assessment; the reviews of clinical and cost-effectiveness and the development of the independent economic assessment. In all, ten electronic databases were searched and over thirty 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.

Inclusion/exclusion criteria: Two reviewers independently screened all titles and/or abstracts including economic evaluations. The full manuscript of any study judged to be relevant by either reviewer was obtained and assessed for inclusion or exclusion. Any disagreements were resolved through discussion. Randomised controlled trials that compared oxaliplatin in combination with 5-FU/LV or oral capecitabine, with adjuvant chemotherapy with an established fluorouracil-containing regimen were included in the assessment of clinical effectiveness. For the assessment of cost-effectiveness, a broader range of studies was considered, which initially included all economic and cost-related studies relevant to the assessment. Studies were excluded if they did not assess the cost-effectiveness of oxaliplatin (in combination with 5-FU/LV) or capecitabine, were not reported in sufficient detail or were considered methodologically unsound.

Data extraction and quality assessment: Data from included studies were extracted by one reviewer and independently checked for accuracy by a second reviewer. Where multiple publications of the same study were identified, data were extracted and reported as a single study. Individual studies were assessed for quality by one reviewer and independently checked for accuracy by a second. Any discrepancies were resolved through consensus.

Methods of analysis/synthesis:

The extracted data and quality assessment variables were presented for each study, both in structured tables and as a narrative description. 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. For the cost-effectiveness section of the assessment, details of each identified published economic evaluation, together with a critical appraisal of its quality, were presented.

Handling the company submissions: In terms of clinical effectiveness, the company submissions were screened for data additional to that identified in published studies retrieved from the literature search. All economic evaluations (including accompanying models) included in the company submissions were assessed and a detailed assessment of the assumptions underlying the submitted analyses were undertaken. 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 methods were used to generate information regarding the uncertainty in the cost-effectiveness results.

Results

Number and quality of studies

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. 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 six months in patients with stage II (40%) or III (60%) colon cancer. The primary trial endpoint was disease-free survival. Secondary trial endpoints 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 endpoints were similar to 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 three 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 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 that remains alive and disease-free at just over three years by using FOLFOX4 instead of infusional 5-FU/LV alone (de Gramont regimen) as adjuvant chemotherapy. These results are similar to the overall population of the MOSAIC trial (hazard ratio using intention-to-treat 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 three years in patients with stage III colon cancer was maintained and improved with longer follow-up. The probability of disease-free survival at four 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 intention-to-treat 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) paresthesia, neutropenia, diarrhoea, nausea, vomiting, 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 bolus 5-FU/LV alone (p-values not reported). The main safety concern regarding the use of oxaliplatin is neurotoxicity (irrespective of regimen) while significant and frequent (all grade neurotoxicity,

>85%; grade 3 neurotoxicity, >8%), does appear to improve within one 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 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 endpoint was at least equivalence in disease-free survival. Secondary trial endpoints included relapse-free survival, overall survival, safety and QoL. 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 endpoint 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 three years (pre-specified analysis), the probability of remaining disease-free were 64.2% and 60.6% for capecitabine and 5-FU/LV, respectively. For the intention-to-treat 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 three 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 three 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 intention-to-treat 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 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.

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%; $p<0.0001$, 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 drawback 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 £3,320 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 £2,970 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. These figures were broadly similar to those reported in the sponsor submissions from Roche and sanofi-aventis.

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 to the 5-FU/LV comparator arms in the two trials.

An indirect comparison of the FOLFOX4 and Mayo 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 5-FU/LV regimen would cost an additional £5,777 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 and 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 incremental cost-effectiveness ratio 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.

Discussion

The key assumption in the economic analysis is that the short-term benefits of FOLFOX4 and capecitabine in terms of disease-free and overall survival can be translated into longer-term survival benefits. The absence of consistent long-term follow-up data for patients who do not relapse mean that is it difficult to validate the assumptions made, and the validity of this assumption will only become clear following long-term follow-up of patients in the MOSAIC and X-ACT studies.

Another fundamental assumption made within the economic analysis is that the survival benefits observed in the X-ACT and MOSAIC studies are generalisable to patients with stage III (Dukes' C) colon cancer in England and Wales. The mean age of the patients in these studies is lower than that of the incident colon cancer population, and therefore the cost-effectiveness results may overestimate the benefits of capecitabine and FOLFOX4.

Suggested research priorities

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

- 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 C07 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 determine what safety mechanisms are needed in order to ensure compliance and the monitoring of adverse effects.

- 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 valuations. 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 in 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.

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 economic assessment suggest that, over a 50-year time horizon, both capecitabine and FOLFOX4 are estimated to demonstrate a favourable cost-effectiveness profile in comparison with the Mayo and de Gramont 5-FU/LV regimens respectively. Capecitabine is estimated to be cost-saving over this period in comparison with the Mayo 5-FU/LV regimen (by a total of £3,320 per patient), whilst oxaliplatin (in combination with 5-FU/LV) in comparison with the de Gramont 5-FU/LV regimen is estimated to cost an additional £2,970 per QALY gained.

Indirect comparisons suggest that FOLFOX4 is cost-effective compared with the Mayo 5-FU/LV regimen, although may not be deemed cost-effective in comparison with capecitabine. These economic comparisons could only be made fully assessed following a trial which directly compare 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, due 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.

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.

2. Background

2.1. Description of underlying health problem

2.1.1. 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 six feet of the large intestine and the rectum is the last eight to ten inches. Colonic and rectal cancers arise from similar tissues and exhibit a broadly similar natural history and responsiveness to treatment. Due to the similarities, they are often referred to using the all encompassing term, colorectal cancer. However, largely due to restrictions imposed by their anatomical location there are differences as well as 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.

2.1.2. 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 rectum. Although rectum 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]

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	3625	4937	8392	17364
Rectal cancer	256	2848	3060	4105	10269
Colorectal cancer	666	6473	7997	12497	27633
Wales					
Colon cancer	27	252	333	567	1179
Rectal cancer	24	210	219	282	735
Colorectal cancer	51	462	552	849	1914
England and Wales					
Colon cancer	437	3877	5270	8959	18543
Rectal cancer	280	3058	3279	4387	11004
Colorectal cancer	717	6935	8549	13346	29547

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

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 while for women it is over 200 per 100,000 per year.[4] The median age of diagnosis is over 70 years of age 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]

2.1.3. Aetiology

The development of colorectal cancer is poorly understood, however, genetics,[7] experimental,[5] and 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, most will have cancer unless they have surgery to remove the colon.[10] Hereditary non-polyposis colorectal cancer accounts for 5% of cases, and is caused by a dominantly inherited alteration in the deoxyribonucleic acid (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]

2.1.4. 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]

2.1.5. 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 (covers patients with a broad spectrum of disease, and is reflected in a wide range of five 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 *et al.*[19] Reduced survival is 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]

Table 2: Staging of colorectal cancer, with five year survival[18,8]

Tumour/Node/Metastasis (TNM) Status	Stage	Extension to	Modified Dukes'	Five 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	
T3 N1 M0 / T3 N2 M0	III	T3, N1: 1-3/N2: ≥ 4 lymph nodes	C2	25 – 60%
T4 N1 M0	III	T4, N1: 1-3/N2: ≥ 4 lymph nodes	C3	
Any T any N M1	IV	Distant metastases	D	5 – 30%

Tumour 1-4; N, number of affected lymph nodes; M, number of metastatic sites

In the UK, about 26% of patients diagnosed with colorectal cancer are classified as stage III (modified Dukes' C1, C2, and C3) at presentation and 35% as stage II (modified Dukes' B2, and B3), with 11% and 29% of patients having stage I and IV disease, respectively.[10,21] Although

there are large variations in survival according to the stage of disease, the overall five year survival rate for colorectal cancer in England is 35%.[21]

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 on surgical competence as well as 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; though successful metastasectomy is becoming a more common outcome. After a complete surgical resection, stage III patients with colon cancer have a 50 to 60% chance of developing recurrent disease.[22]

2.1.6. 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.[8,21] 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.[23] Colorectal cancer is also a significant cause of morbidity.

Table 3: Colorectal cancer mortality, 2002[23,24]

	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

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.

2.2. Current service provision

2.2.1. Management of disease and national guidelines

The management of colorectal cancer is constantly evolving. The administration of six to seven 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 regimen), however, there remains significant geographical variation in the 5-FU based regimens currently in use in the UK.[25,26]

In 2004, the National Institute for Health and Clinical Excellence (NICE) issued guidance on improving outcomes in colorectal cancer to clinicians within the National Health Service (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 patients 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.[27] 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 leucovorin, ideally administered over five days every four weeks, with 30 weekly treatments being an acceptable alternative.[27] In addition, SIGN state that a retrospective analysis of data from the QUASAR (QUick And Simple And Reliable) trial[28] suggests that the weekly bolus 5-FU/LV (5-FU, 370mg/m^2 plus LV, 25mg) is as active as and less toxic than a regimen in which the same agents are given in the same doses as a five day course every four weeks. They conclude that although there is less evidence available to support this regimen, it may be a preferable option for certain patients.

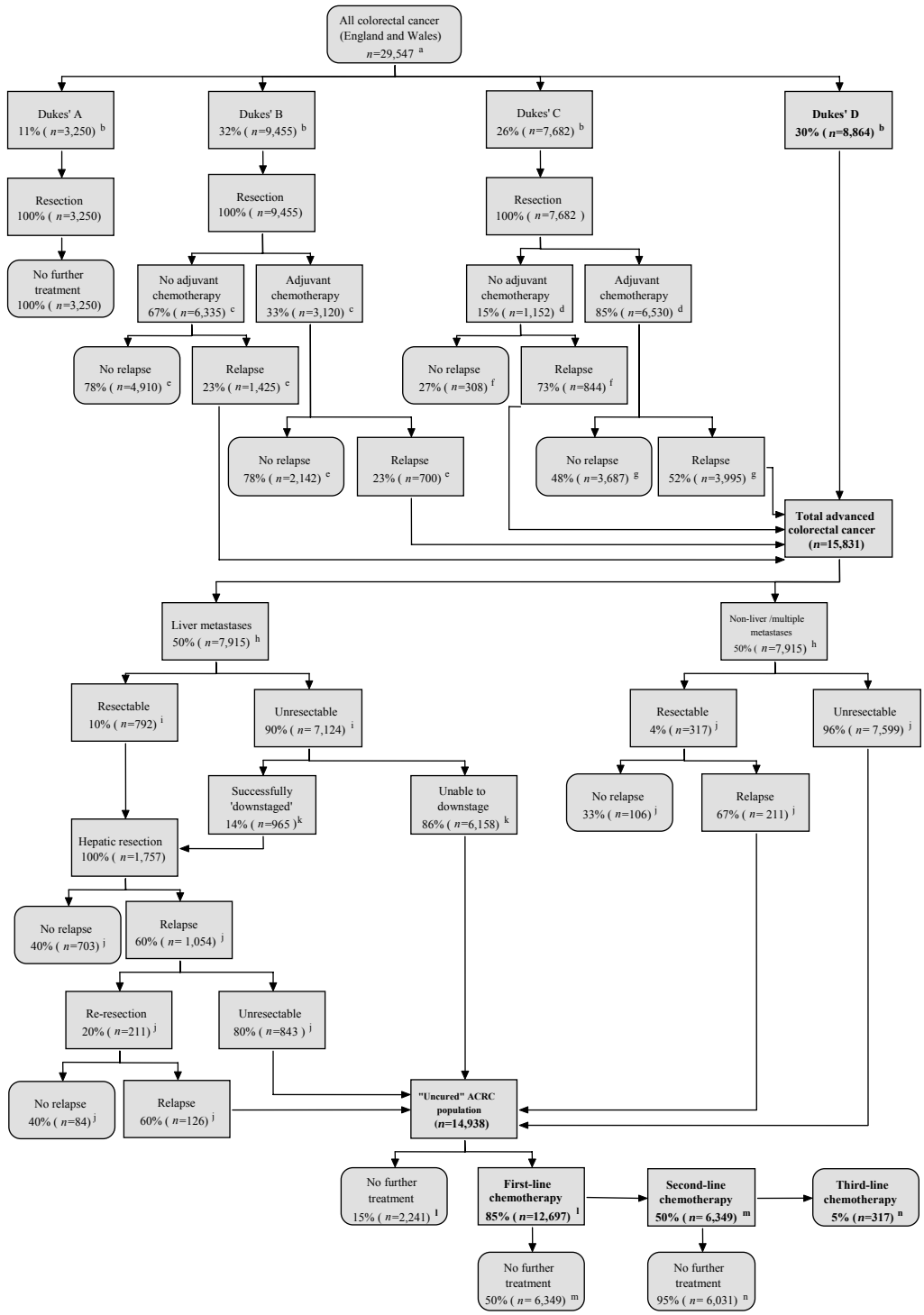
Guidelines for the management of colorectal cancer, published in 2001, by the Association of Coloproctology of Great Britain and Ireland,[29] recommend adjuvant chemotherapy for patients with stage III (Dukes' C) colon cancer. These guidelines do not recommend the routine use of adjuvant chemotherapy in patients with stage II (Dukes' B) colon cancer, however it may be considered for high risk patients.

2.2.2. 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 scale of the

service). The algorithm suggests that there are a total of 7,682 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 six-month course of adjuvant chemotherapy in the form of intravenous 5-FU/LV, delivered primarily using the Mayo Clinic regimen. Hence, approximately 4,100 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.[30,8] 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.

Figure 1: Treatment algorithm for people with colorectal cancer in England and Wales



[a] Office for National Statistics, [31] Welsh Cancer Intelligence and Surveillance Unit;[32] [b] South West Cancer Intelligence Service; [33] [c] personal communication, Dr 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, Dr Seymour: more than 85% receive adjuvant chemotherapy; [e] personal communication, Dr Seymour: 20-25% of patients with Duke's B will relapse; [f] Relative risk increase applied to five-year disease-free survival estimates from X-ACT study;[34] [g] five-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 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, Dr Seymour: 85-90% of advanced patients receive chemotherapy; [m] preliminary data from FOCUS trial;[36] [n] personal communication, Dr Rob Glynne Jones, Watford and Barnet General Hospitals, London: only 3-5% patients would receive third-line therapy.

2.2.3. 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. While it is not within the scope of this report to assess the clinical effectiveness of these different regimens, evidence reviewed in Section 3.4 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.[25]

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.[27]

2.3. 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 British National Formulary (BNF)[40] on the use of cytotoxic drugs can be found in Appendix 2.

2.3.1. Summary of interventions

2.3.1.1. Oxaliplatin (Eloxatin®, sanofi-aventis)

a) 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/m² administered intravenously over two to six hours, prior to the administration of 5-FU/LV, and repeated every two weeks for 12 cycles (six months).

b) Licensed indications

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

- adjuvant treatment of stage III (Dukes' C) colon cancer after complete resection of the primary tumour
- treatment of metastatic colorectal cancer

c) Contra-indications

Oxaliplatin is contra-indicated in patients who:

- 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)

d) 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 anti-emetic therapy. Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, 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 case of an anaphylactic-like reaction to oxaliplatin, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. In 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/m² 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

2.3.1.2. Capecitabine (Xeloda®, Roche)

a) 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 ribonucleic acid (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 seven 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.

b) Licensed indications

Capecitabine is indicated:

- for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer
- for first line monotherapy of metastatic colorectal cancer
- as 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

c) Contra-indications

Capecitabine is contra-indicated in patients who:

- 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

d) Special warnings and special precautions for use

Capecitabine should only be prescribed by a qualified physician experienced in the utilisation of anti-neoplastic 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
- **Diarhoea.** 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 anti-diarrhoeal 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** (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, caridogenic 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 anti-coagulation.** Patients receiving concomitant capecitabine and oral coumarin-derivative anti-coagulation 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 to 50 ml/min) is increased compared with the overall population

3. Assessment of Clinical Effectiveness

3.1. Methods for reviewing effectiveness

3.1.1. Identification of studies

Searches were carried out to:

- to identify studies for inclusion in the review of clinical effectiveness
- to identify studies for inclusion in the review of cost-effectiveness
- to 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 Section 4.1.1. (Assessment of cost-effectiveness).

3.1.1.1. 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.

a) 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 thirty plus 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 as well as references of retrieved papers. A list of the sources searched is provided in Appendix 3.

b) 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**.**

c) 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.

3.1.2. Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts. Full paper manuscripts 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.

a) 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.

b) 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)

c) Comparators

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

d) 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.

e) Study design

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

3.1.3. 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.

3.1.4. 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.

3.1.5. 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. For time-to-event analyses (disease-, relapse-, or overall- survival), combined hazard ratios and 95% confidence intervals (CI) 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 endpoints.[43]

The log hazard ratio and its variance were estimated indirectly from the hazard ratio and its 95% confidence intervals 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 chi^2 test and I^2 measure. The chi^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. Chi^2 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.[44]

3.1.6. Handling of the company submission

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

3.2. Results: Oxaliplatin

3.2.1. Quantity and Quality of research available

3.2.1.1. 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.

3.2.1.2 Number and type of studies included

Two randomised controlled trials 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.[47,48,49,50,51,52,53,54,55,56,57,58,59] Other than the main publication of the NSABP C-07 study,[46] we identified five papers/abstracts reporting on (additional) aspects of the trial.[60,61,62,63,64]

3.2.1.3. 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 exclusions is presented in Appendix 4.

a) Ongoing studies

One ongoing, phase III, adjuvant randomised controlled trial 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 has 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.

3.2.2. Assessment of effectiveness

3.2.2.1. 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 United Kingdom, Spain and Italy)

and included patients aged between 18 and 75 years of age. The NSABP C-07 study recruited 2492 patients between February 2000 and November 2002[60] at 158 NSABP institutions[64] across the United States, Canada and Australia[61] and included patients of any age. Both studies included adult patients with confirmed stage II and stage III colon cancer (see Table 2), who had undergone complete surgical resection of the primary tumour and were treated within seven 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 endpoint of the MOSAIC trial and the NSABP C-07 study were disease-free survival. Secondary endpoints 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.

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, randomised controlled trial	Assuming three year disease-free survival rate 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 three years, decrease in risk of relapse after three years, 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, 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 to 54) T2: median 37.8 months (range 27 to 54)	Primary outcomes ▪ Disease-free survival (after 3 years 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[60,61,62,63,64]	Phase 3, multi-institution, randomised controlled trial	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	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 follow-up) Secondary outcomes ▪ Overall survival	National Cancer Institute, National Institutes of Health, Department	Caution, study only reported in abstract form

				alone (Roswell Park bolus regimen) [d]			▪ Safety (adverse events)	of Health and Human Services, USA	

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

[a] FOLFOX4 regimen: 2 hour infusion of 200 mg/m^2 intravenous leucovorin followed by intravenous bolus 400 mg/m^2 fluorouracil, and then a 22-hour infusion of 600 mg/m^2 fluorouracil on 2 consecutive days plus oxaliplatin 85 mg/m^2 over 2 hours on day 1, (given simultaneously with leucovorin)

[b] De Gramont regimen: 2 hour infusion of 200 mg/m^2 intravenous leucovorin followed by intravenous bolus 400 mg/m^2 fluorouracil, and then a 22-hour infusion of 600 mg/m^2 fluorouracil on 2 consecutive days

[c] FLOX regimen: 5-fluorouracil 500 mg/m^2 plus leucovorin 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-fluorouracil 500 mg/m^2 plus leucovorin 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 10ng/ml	▪ Patients who had previously received chemotherapy, immunotherapy, or radiotherapy ▪ Inadequate blood counts, liver and kidney function (not defined)	T1: median 61 (range 19 to 75) T2: median 60 (range 20 to 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[46,60,63,62]	▪ 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	▪ Patients who had previously received chemotherapy, immunotherapy, or radiotherapy ▪ Inadequate blood counts, liver and kidney function	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%)	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

	weeks after surgery ▪ Any age ▪ ECOG Performance Status 0 to 2 ▪ Life expectancy ≥ 10 years	▪ Clinically significant cardiovascular disease ▪ Pregnant or lactating women and sexually active patients who were unwilling to use contraception		T2: 857 (71%)			

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

3.2.2.2. Quality characteristics

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

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?	N/A	?
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 intention-to-treat analysis included?	Y	N

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

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 vs. 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 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 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 is required. However, to partly overcome this, an independent data and safety monitoring board reviewed safety data every six 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 three years of follow-up in the MOSAIC trial (and *ad hoc* analysis of data at approximately four years), less than 20% of participants in each group were reported to have been loss to follow-up and all withdrawals were accounted for. Efficacy analysis was conducted using the intention-to-treat approach. Similarly, at the end of the planned three years of follow-up in the NSABP C-07 trial, less than 20% of participants in each group were reported to have been loss to follow-up and all withdrawals were accounted for. The efficacy analyses were not conducted using the intention-to-treat approach, but were based on a per-protocol analysis (i.e. randomised subjects who were non-eligible [including loss to follow-up] were excluded).

3.2.2.3. 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 stage 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 stage 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.

a) 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 focussed on disease-free survival at three years in patients with stage II or stage 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 three years was significantly better for individuals treated with oxaliplatin in combination with 5-FU/LV than 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 three years was increased with longer follow-up (p=0.0008).

- Patients with stage III colon cancer only

A pre-specified subgroup analyses reported by the MOSAIC authors (data not reported for NSABP C-07 trial) showed that for patients with stage III colon cancer the probability of

remaining disease-free at three 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 intention-to-treat 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 (benefit) 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 three years in patients with stage III colon cancer was maintained and improved with longer follow-up. The probability of remaining disease-free at four 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 a number needed to treat (benefit) of 12.5 (95% CI: 7.9 to 32.4).

b) 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 five years for patients with stage II and III colon cancer. Overall survival data in the MOSAIC trial (data not reported for NSABP C-07 trial) were not mature at the time of the primary (specified) and secondary (*ad hoc*) analysis. In the intention-to-treat 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]

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 stage 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 stage 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

5-FU, 5-fluorouracil; LV, leucovorin; CI, confidence interval

[a] Intention-to-treat 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 less than 1.0 favours oxaliplatin (plus 5-FU/LV)

3.2.2.4. 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 only been reported 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 summarised and reported because the safety data for stage III patients is 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 to 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.

a) 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 stage 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 was 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 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 one 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 one year of follow-up, grade 3 neuropathy in the oxaliplatin plus bolus 5-FU/LV group remained only in 0.5% of patients.

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†	2.0%	2.4%**	Not reported	Not reported
Alopecia	Not reported ‡	Not reported ‡	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 and 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)

* $p<0.001$; ** $p>0.05$; *** p-value not reported

† Includes hand-foot syndrome; ‡Incidence of Grade 2 alopecia: 5.0% in each group

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, 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.

Although the data is based on an atypically young and fit population, the incidence of severe toxicities with oxaliplatin plus 5-FU/LV in the MOSAIC trial was similar in patients between 70 and 75 (n=152) years of age 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 (five [0.8%] patients in the oxaliplatin plus 5-FU/LV versus three [0.5%] patients in the 5-FU/LV group).[54] These findings are similar to those found 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]

3.2.2.5. Quality of life

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

3.2.2.6. Discussion of results

The strength of the evidence (internal validity)

Results of many types of scientific research are presented at professional meetings and summarized 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, abstract authors of the MOSAIC and NSABP C-07 trial 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 randomised controlled trials tends to result in larger treatment effects.[68] As noted earlier in section 3.2.2.2., 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 Section 2.1.2.).

Disease-free survival, rather than overall survival, was the primary objective in both trials. Andre *et al.*[45] argued that disease-free survival rates after three years follow-up (most relapses from colon cancer occur within the first three years after curative surgery)[69] accurately predict overall survival rates after five years and cite the results of Sargent *et al.*[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 *et al.*[70] found that there was a very high statistical correlation in outcome between three year disease-free survival and five 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 endpoint), 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 endpoint.[73]

The MOSAIC trial used an intention-to-treat approach for analysing statistical data. Analysis by intention-to-treat 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. Intention-to-treat 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 intention-to-treat 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 UK 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 while 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 chronologic age.[83,85]

Although elderly patients are more likely to have significant co-morbidities, poorer functional status and/or social conditions that may affect tolerance and benefits of therapy, randomised trials of adjuvant therapy have found that the elderly benefit the same as their younger counterparts (without a significant increase in toxic effects)-[81,84,86,80] an effect also seen in the general population receiving treatment outside clinical trials.[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.[87] NICE guidance for the appropriate selection of patients for adjuvant therapy is based on physiologic age (including performance status and co-morbidities) rather than biologic age.[10]

In the adjuvant setting, six months of 5-FU in combination with LV has become the standard chemotherapy for patients with resected stage III colon cancer.[86,88] 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 section 3.4). 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.[89,90,26,91] 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 this 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),[97,98,94] 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 this 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 the MOSAIC trial. In general, gastrointestinal, haematological and neurological toxicities (as well as 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) while significant and frequent, does appear to improve within one 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 NSABP C-07 trial) suggesting that oxaliplatin based therapy may not be suitable for all patients i.e. people with neuropathy. These data are broadly similar with those reported in reviews of oxaliplatin-related adverse effects.[99,100,101] 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 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.[86,104,105,106] Recently, the American Society of Clinical Oncology published guidelines on adjuvant chemotherapy for colon cancer to facilitate decision making in clinical practice.[22] These guidelines, based on a systematic review and meta-analysis by Figuerdo *et al*.[107] were against the routine use of adjuvant chemotherapy for medically fit patients with stage II colon cancer (absolute improvement in five 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).[22] 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 both these 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).

3.2.3. 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 six months in patients with stage II or III colon cancer. The primary trial endpoint was disease-free survival. Secondary trial endpoints 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 endpoints were similar to 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 three 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 intention-to-treat 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 minimum follow-up of three 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 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 three 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 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 a number needed to treat (benefit) of 14.2 (95% CI: 8.7 to 44.2)

- Updated subgroup analyses (*ad hoc*) showed that the benefit observed at three years in patients with stage III colon cancer was maintained and improved with longer follow-up. The probability of disease-free survival at four 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 intention-to-treat 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 (benefit) 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 NSABP C-07 trial) were not mature at the time of analysis.

- In the intention-to-treat 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 frequency of severe (grade 3 or 4) paresthesia, neutropenia, diarrhoea, nausea, vomiting, 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 bolus 5-FU/LV alone (p-values not reported). The main safety concern regarding the use of oxaliplatin is neurotoxicity (irrespective of regimen) while significant and frequent (all grade neurotoxicity, >85%; grade 3 neurotoxicity, >8%), does appear to improve within one year's time for the majority of patients with stage II or stage 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.

3.3. Results: Capecitabine

3.3.1. Quantity and Quality of research available

3.3.1.1. 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.

3.3.1.2. Number and type of studies included

One randomised controlled trial 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).[109,110,111,34,112,113,114,115,116,117,118,119,120,121,122]

3.3.1.3. 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 exclusions is presented in Appendix 4.

3.3.2. Assessment of effectiveness

3.3.2.1. 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) centres 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 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 eight 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 endpoint of disease-free survival when administered as adjuvant treatment following surgery for stage III (Dukes' C) colon cancer. Secondary endpoints included relapse-free survival, overall survival, safety (including treatment toxicity), pharmaeconomics and QoL.[108,109,34] In terms of overall survival, the data were not mature at the time of analysis.

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[108,109,34,20]	Phase 3, open label, multi-centre, randomised controlled trial	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 three 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 ▪ Quality of life ▪ Pharmaeconomics	Hoffmann-La Roche	Additional analyses, not specified in the protocol, were requested by the US Food and Drugs 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.

T1, treatment 1; T2, treatment 2; 5-FU/LV, 5-fluorouracil plus leucovorin; CI, confidence interval; US, United States

[a] Oral capecitabine: 1250 mg/m^2 taken twice daily on days 1 to 14 every 21 days

[b] Mayo Clinic bolus regimen: Leucovorin 20 mg/m^2 intravenous by rapid infusion followed immediately by 5-fluorouracil 425 mg/m^2 intravenous bolus on days 1 to 5 every 28 days

Table 10: Summary of patient characteristics – X-ACT study

Study	Inclusion criteria	Exclusion criteria	Age (years)	Disease stage	Sex (male/female)	Performance status score	Tumour stage (T1-2 / T3 / T4)
X-ACT[108,109,34,20]	▪ 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 to 80) T2: median 63 (range 22 to 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%)

T1, treatment 1; T2, treatment 2; 5-FU/LV, 5-fluorouracil plus leucovorin; ECOG, Eastern Cooperative Oncology Group

3.3.2.2. Quality characteristics

The main publication of the trial the X-ACT study, with approximately four 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 median follow-up of 4.3 years were reported in abstract form,[122] the latest efficacy results, with 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.

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 intention-to-treat analysis included?	Y

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

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, Eastern Cooperative Oncology Group performance status score, sex, nodal status, tumour differentiation, and preoperative carcinoembryonic antigen 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 is required with many cytotoxic cancer drugs.

During the follow-up period (and reanalysis of data at median follow-up of 4.4 years) more than 20% of participants in each group were reported to have been loss 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 intention-to-treat approach.

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

a) Primary outcome analysis – Disease-free survival

The results of 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 endpoint 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 as compared with 5-FU/LV ($p=0.05$). The difference between the three year rates of disease-free survival (a pre-specified endpoint) 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 three 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).

b) 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 to 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 a number needed to treat (benefit) of 23.3 (95% CI: 12.2 to 336.0). The three year rates of relapse-free survival (not a pre-specified endpoint) 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, 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).

Table 12: Disease-free, relapse-free and overall survival for the X-ACT study (intention-to-treat 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 (95% CI: 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 (95% CI: 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 (95% CI: 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 (95% CI: 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 (95% CI: 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 (95% CI: 0.74 to 1.05)	Not reported	p=0.169

5-FU, 5-fluorouracil; LV, leucovorin; CI, confidence interval

[a] Hazard ratio less than 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

- Overall survival

Overall survival data were not mature at the time of the primary (specified) and secondary (*ad hoc*) analysis. In the intention-to-treat 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 to 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 three years for all patients), 763 (76%) patients in the capecitabine group were alive in comparison to 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).

3.3.2.4. 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) compared with 5-FU/LV (41 days). Second level dose reductions (to less than 60% of capecitabine starting dose and less than 75% of 5-FU/LV starting dose) were less frequent (13% versus 26%) and later (median 113 versus 57 days) in the capecitabine group.[109]

a) 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 lower in the capecitabine group versus the 5-FU/LV group (60% versus 9%; p<0.001, respectively). 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 of each patient died due to multi-organ failure, septic shock and pneumonia) and four deaths occurring in the 5-FU/LV group (one of each patient 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 *et al*., 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]

3.3.2.5. Quality of life

Quality of life was assessed in the X-ACT study as a secondary outcome measure at baseline and before the start of treatment cycles i.e. weeks 7, 16, and 25 in the capecitabine group and weeks 9, 17, and 25 in 5-FU/LV group. Quality of life 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[108,34] (no statistical data reported).

3.3.2.6. Discussion of results

The strength of the evidence (internal validity)

Some of the issues (blinding in oncology trials, disease-free survival as the primary endpoint, 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 section 3.2.2.6.

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, 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.[1,2]

In the X-ACT study, more than 20% of participants in each group were reported to have been loss 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 and move address or because 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 intention-to-treat 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 endpoint (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 section 3.2.2.6. Briefly, in England and Wales, patients with newly diagnosed colorectal cancer have a median age over 70 years,[1,2] while the median age of cohorts in clinical trials is usually 10 years less.[109,79] The extent to which the results of the X-ACT study provide an accurate basis for generalisation to the UK NHS is unclear. The relative benefit of adjuvant chemotherapy does not diminish with advancing patient age and randomised trials of adjuvant therapy, including the X-ACT study,[109] have found that the elderly benefit the same as their younger counterparts (without a significant increase in toxic effects). The monthly 5-day bolus Mayo Clinic 5-FU/LV regimen given for six months, as used in the control group of the X-ACT study, is often used as a reference treatment in phase III trials,[88,26] however, it is not widely used in the UK (see Section 2.2.1. and Section 3.4.3.3.), 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 frequency 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 with those reported in reviews of capecitabine-related adverse events,[126,127,123,128] 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.[108,34] 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 health care 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] suggests 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 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 *et al*.[21] 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) only refer 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, due to increased contact with nurses and peer support of other patients.

3.3.3. 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 endpoint was at least equivalence in disease-free survival. Secondary trial endpoints 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 endpoint 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 as compared with 5-FU/LV ($p=0.05$).

- At three years (pre-specified analysis), the probability of remaining disease-free (relapse/new occurrence of colon cancer or death due to any cause) were 64.2% and 60.6% for capecitabine and 5-FU/LV, respectively. For the intention-to-treat 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 minimum follow-up of three 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 three 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 intention-to-treat 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 intention-to-treat 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, respectively).

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

NICE requested that the review team summarize 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 Sections 3.2. and 3.3.

3.4.1. Introduction

In the adjuvant setting, six months of FU in combination with LV has become the standard chemotherapy for patients with resected stage III colon cancer.[86,88] Evidence emerging from adjuvant studies conducted in the 1990's showed that 5-FU and low-dose LV (20 mg/m^2) is equivalent to 5-FU and high-dose LV (200 to 500 mg/m^2); 5-FU/LV given for six 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 through 5 every four weeks) and Roswell Park (5-FU 500 mg/m^2 and LV 500 mg/m^2 weekly times six every eight 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 fluorouracil in the adjuvant treatment of colon cancer.

3.4.2. Quantity and quality of research available

3.4.2.1. 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 focussed on advanced or metastatic colon cancer.

3.4.2.2. Number and type of studies included

Three published randomised clinical trials 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 *et al*.,[138] we identified one paper reporting on additional aspects of the study.[140]

3.4.3. Assessment of effectiveness

3.4.3.1. 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.

a) Andre et al.[88]

This study was an open-label randomised trial comparing two adjuvant chemotherapy regimens (semi-monthly de Gramont regimen (LVFU2) versus a monthly (5-FU/LV) regimen of fluorouracil and leucovorin) 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 stage 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-leucovorin 200 mg/m^2 (or l-leucovorin 100 mg/m^2) as a two hour infusion, followed by bolus FU 400 mg/m^2 and a 22 hour infusion of 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 24 or the 36 week treatment group. In the 5-FU/LV group, patients received an infusion of dl-leucovorin 200 mg/m^2 (or l-leucovorin 100 mg/m^2) for 15 minutes, followed by a 15 minute bolus of 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 endpoint was disease-free survival (defined as colorectal cancer relapse, second colorectal cancer or death) at three years. Secondary endpoints include overall survival and safety (toxicities). The study was designed with 70 to 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 three 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 three years of follow-up, less than 20% of participants in each group were reported to have been loss to follow-up (approximately 15%) and all withdrawals were accounted for. All analyses were by intention-to-treat.[88]

b) Chau et al.[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 six 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 in 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 five 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 minimal improvement in overall survival from 60 to 70% after five 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 loss to follow-up (approximately 30%) however, it was similar for the two groups and all withdrawals were accounted for. All analyses were by intention-to-treat.[138]

c) Poplin et al.[139]

This phase III study was a randomised trial comparing the efficacy of continuous infusional FU plus levamisole to 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 Eastern Cooperative Oncology Group, the Cancer and Leukaemia Group B and the North Central Cancer Treatment Group. Of these, 940 patients were eligible. In the continuous infusional FU plus levamisole group, FU was given at 250 mg/m^2/day for 56 days every nine weeks for three cycles (n=477). Patients assigned to bolus 5-FU/LV group received leucovorin at a dose of 20 mg/m^2/day as a 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 to 35 days for a total of six cycles (n=463). All patients received 50 mg levamisole every eight hours for three consecutive days every 14 days for a total of six months.

The primary end point was overall survival at five 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 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 loss to follow-up (approximately 30%) however, it was similar for the two groups and all withdrawals were accounted for. All analyses were by intention-to-treat.

Table 14: Trial quality assessment: bolus versus infusional fluorouracil

	Andre *et al.*[88]	Chau *et al.*[138]	Poplin *et al.*[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?	N/A	?	?
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 intention-to-treat analysis included?	Y	Y	Y

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

3.4.3.2. 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 five 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 5FU/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 stage 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 group: respectively, 27 and 25 events (with 12 and 10 deaths). In stage III patients, 199 events were observed, also evenly distributed between the LVFU2 and 5-FU/LV group: respectively, 100 and 99 events (with 60 and 49 deaths). 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 to 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 with LVFU2 and one with 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 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 with LVFU2 and one with 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 five 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 PVI 5-FU being inferior to six months bolus 5-FU/LV was very low (p<0.005). Although not significant, in most subgroups, including patients with stage II or stage 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 five 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 (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, 5-FU infusion plus levamisole group was found to have less severe toxicity than 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 with the bolus group (n=64). Most patients receiving continuous infusion 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]

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*.[88] LVFU2 (6 or 9 months) vs. Monthly 5-FU/LV (6 or 9 months)	Chau *et al*.[138] 5-FU protracted infusion (3 months) vs. Bolus 5-FU/LV (6 months)	Poplin *et al*.[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]

5-FU, 5-Fluorouracil; LV, leucovorin; vs., versus; 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

3.4.3.3. 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 this 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] study, more than 20% of participants in each treatment group were reported to have been loss 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 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 intention-to-treat 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 and Sciallero[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 stage III patients; the inclusion of patients with clearly suboptimal surgery (tumour free margins of just >1mm); reserving radiotherapy to T4 rectal cancers, but at the same time leaving the decision about preoperative radiotherapy to the treating physician, giving more than four months of PVI 5-FU (instead of three months) in rectal cancer patients receiving radiotherapy and above all, the treatments are radically different by duration and schedule (three months of PVI 5-FU versus six months of bolus 5-FU/LV). The American study[139] reduced the number of patients planned, included both stage II and stage III patients and suffered from a high ineligibility rate (17.2%).

The applicability of the results (external validity)

At present, the evidence suggest 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.[88,138,140,139] One study even suggested that three months of PVI 5-FU may be comparable to six months of bolus 5-FU/LV.[138] However, there are concerns about catheter associated complications, patient inconvenience and expense of infusional treatment.[89,90,88,26,91] In the treatment of advanced colorectal cancer, a meta-analysis of three phase III randomised controlled trials (*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 five-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.[28] Patel *et al*.[26] reported that some oncologists now use the five-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).[26] 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.[25]

3.4.4. 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 drawback 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 remains significant geographical variation in the 5-FU based regimens currently in use in the UK.

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 to 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 (DFS), overall survival (OS), costs incurred and quality of life benefits achieved.

Section 4.1 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 Section 4.2, with the results of the analysis presented in Section 4.3.

4.1. Systematic Review of existing economic literature

This review examined the 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.

4.1.1. 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.

a) Sources searched

Seven electronic databases were searched providing coverage of the biomedical and health technology assessment literature. The publications lists and current research registers of thirty plus health services research related organisations were consulted via the WWW. Keyword searching of the WWW 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.

b) 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.

c) 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.

4.1.2. Inclusion / exclusion criteria

Studies were selected for inclusion according to pre-determined 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 which were considered to be methodologically unsound, that were not reported in sufficient detail or that did not report an estimate of costs-effectiveness (e.g. costing studies) were excluded. Two reviewers independently screened all titles and abstracts. Disagreement was settled through discussion. Full paper manuscripts were obtained for any titles/abstracts that were considered relevant or where the title/abstract information was not sufficient to make a decision.

4.1.3. 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.

4.1.4. 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 (4.1.5) an overview of the methods and results of the studies identified through the searches is presented.[115,145,146] This is followed by a detailed critique of the sponsor submissions[20,143] (Section 4.1.6).

4.1.5. Cost-effectiveness review

a) Douillard *et al.* (2004) *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*[115]

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 UK 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 ten years post-surgery).

A state transition model similar to that used by Monz *et al.*[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 ten 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, five 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 *et al.*;[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 a number of physician consultations (e.g. General Practitioner [GP] visits, hospital outpatient visits, and accident and emergency attendances). Costs of treating patients whose disease relapses 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

Due 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 £1,864 pounds 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, and 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 five years post-surgery; the hazard of death after five years is likely to be lower, because of the reduction in the number of patients relapsing towards the end of that period.

b) Koperna *et al.* (2003) *Innovative chemotherapies of stage III colon cancer: a cost-effectiveness study.*[145]

Overview

Koperna and colleagues 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 endpoints. Equivalent efficacy data for oxaliplatin in combination with 5-FU/LV was 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 is 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 five 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 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.

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

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 life-year gained 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, four year data on disease-free and overall survival were available, and hence a Weibull function was fitted to the DFS curve and extrapolated to five years post-randomisation, with no further relapses assumed to occur beyond this time. The overall survival curve was extrapolated beyond four years using the extrapolated DFS estimates and data on observed survival in relapsing patients.

Cost analysis

Costs up to four years post-randomisation (excluding patients who relapse) were calculated using data from the trial, with costs of relapse and follow-up beyond four years were 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 $27,300. Sensitivity analyses were performed using boostrap 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, and hence it is difficult to comment upon the specific methodologies and the appropriateness of their use.

4.1.6. 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]

a) Roche submission to the National Institute for Health and Clinical Excellence: Xeloda® (capecitabine)[20]

Overview

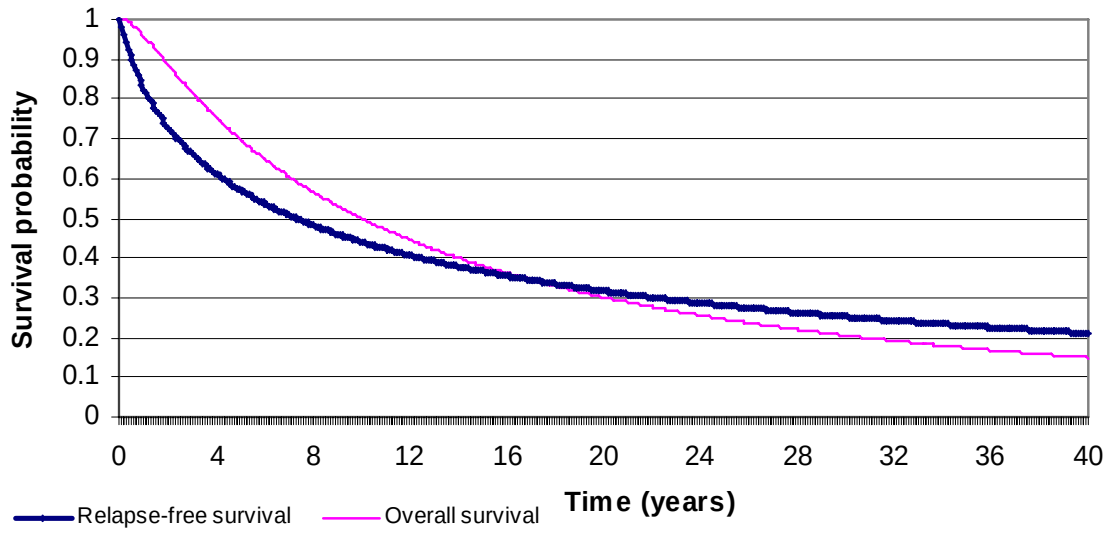
The Roche submission uses data from the X-ACT trial to estimate the cost-effectiveness of capecitabine compared with 5-FU/LV (Mayo Clinic regimen). The study assessed the efficacy of the two drugs over a 24-week treatment cycle, following resection of the primary tumour in patients with stage III (Dukes' 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. Area under the curve 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 five years post-surgery (disease-free survival was not considered within the economic analysis). Lognormal functions were fitted to these curves using a least squares approach in order to extrapolate expected health outcomes for, up to forty years post-surgery. Whilst the fit of the lognormal 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 forty 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 lognormal functions (see 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 due to independent modelling of relapse and survival.

Figure 2: Fitted relapse-free and overall survival from Roche submission



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 *et al*.[150]

- The (chemotherapy) treatment period
- Stable / remission state
- The relapse period
- The post-relapse period
- The twelve 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, whilst those in states 3 to 5 were assigned a utility of 0.59, thus reflecting their lower health-related quality of life. 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: 1 per patient per cycle for capecitabine and 5 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, thus 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 to 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 thus probabilistic sensitivity analyses were not deemed necessary. Threshold analyses concluded that the most uncertainty lay in the cost per intravenous (IV) 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 £3,608 less per patient than 5-FU/LV, whilst also leading to additional QALYs. The vast majority 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 QALYs 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 suggest 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.

b) sanofi-aventis submission to the National Institute for Health and Clinical Excellence: 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 stage 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 stage 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[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 due to the small number of patients.[143] Disease-free survival was then estimated for months 48 to 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 no relapses occur beyond 60 months, at which point those patients who are alive and free of disease are assumed to have an equivalent life expectancy to 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 four years post-resection was measured using the Kaplan-Meier survival data, whilst 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 endpoint 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.[150] A utility of 0.85 was assumed for patients in remission for the five year period following randomisation, after which patients utilities were assumed to be equivalent to 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 costs 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, whilst 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, though 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 1,000 patients with replacement from the trial; the cost-effectiveness results were then re-run for each patient in turn. These data were then used to generate a cost-effectiveness plane and cost-effectiveness acceptability curve.

Summary

The submission reports an incremental cost-effectiveness ratio of £4,805 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 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 Protocol 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 of oxaliplatin in combination with bolus 5-FU/LV compared with bolus 5-FU/LV was estimated to be £6,244 per QALY. This indirect comparison is subject to bias, as it draws on data from more than one trial.

4.2. 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 due 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 to 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.

Table 16: Sources used to develop and populate model

Review of clinical effectiveness (see Section 3)
Previous economic analyses of chemotherapy [155,8]
Sponsor submissions to NICE[143,20]
Studies identified through the review of cost-effectiveness
Studies identified through searches undertaken to inform the model
Reference sources (e.g. BNF,[156] NHS Reference Costs[153])
Expert opinion

Health economic outcomes included in analysis

The model estimates two key health economic outcomes: cost per life year gained and cost per QALY gained.

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 (de Gramont 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, while the X-ACT study used the Mayo Clinic regimen. Table 17 summarises the dosing regimens for each of these treatment strategies:

Table 17: Chemotherapy regimens included in economic assessment

Regimen	Cycle length	Number of cycles (per protocol)	Total protocol dose per cycle
Oxaliplatin in combination with 5-FU/LV	2 weeks	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 weeks	8	35,000 mg/m^2 capecitabine
5-FU/LV (de Gramont regimen)	2 weeks	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 weeks	6	2,125 mg/m^2 bolus 5-FU 100 mg/m^2 leucovorin

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

4.2.1. Economic methodology

4.2.1.1. 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 four 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. Given the assumption that patients do not relapse beyond five years post-surgery, the probability of transiting between the "alive without relapse" and "alive with relapse" states is set to zero beyond five years.

Methods for estimating overall survival and disease-free survival benefits

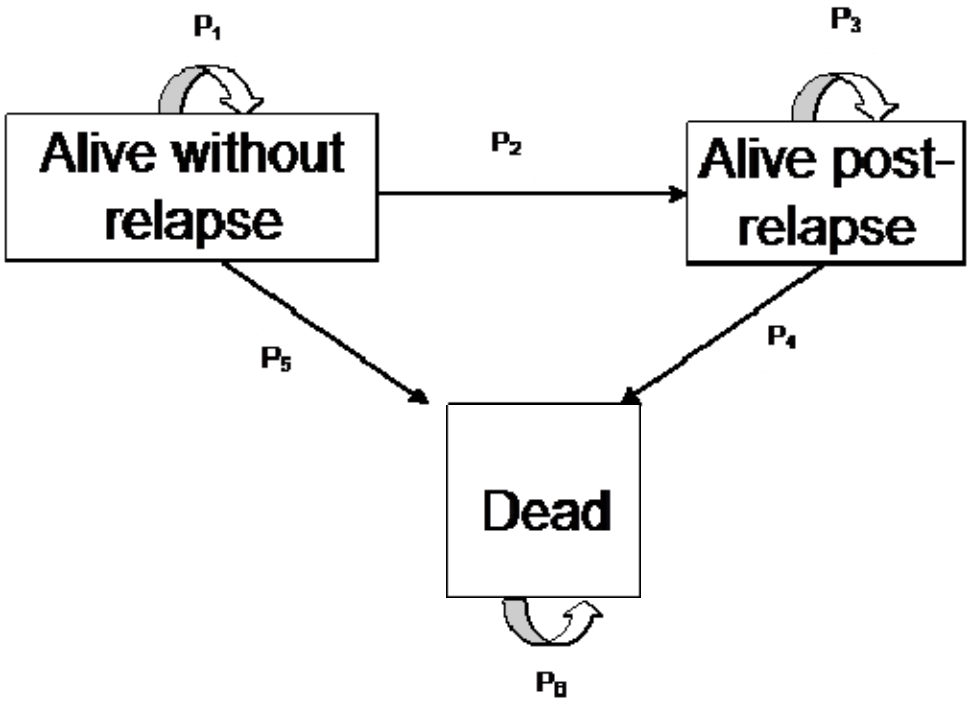
Kaplan-Meier survival curves from the MOSAIC and X-ACT studies were obtained, giving information on empirical overall survival and disease-free survival. Data from the NSABP C-07 trial[46,60] were not incorporated within the economic analysis as separate analyses for patients with stage II and stage 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 EXCEL. Owing to the large proportion of patients in both studies that 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(relapse) = 1 – [P(death due to causes other than colon cancer) + P(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 four-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 counter-intuitive survival curves (see Section 4.1.6). A schematic of the Assessment Group model is given in Figure 3.

Figure 3: Schematic of patient pathways in economic model



where P_1 and P_5 are estimated from the fitted Gompertz function (estimated from life-table data[157] - see section 4.2.1.3)

P_2 is estimated from the fitted DFS curves for the MOSAIC[45] and X-ACT[109] trials (see section 4.2.1.2)

P_3 and P_4 are estimated from fitted Weibull function of survival following relapse, using data from the FOCUS[158] and GERCOR[159] studies.

$P_6 = 1$

4.2.1.2. Disease-free survival estimation

The model assumes that all relapses occur during the five years following resection of the primary tumour; this assumption is supported by empirical evidence.[149,45] 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, and 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:

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

where λ = scale parameter, t = time, and γ = shape parameter.

Transforming the survivor function $S(t)$ gives the linear relationship:

$$\Rightarrow \quad \ln\{-\ln S(t)\} = \ln\lambda + \gamma \ln t$$

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 are detailed in Appendix 14.

The fitted Weibull survival functions for the control arms within the X-ACT and MOSAIC trials were then extrapolated up to five 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 was 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 Section 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. Firstly, the confidence intervals 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 confidence intervals 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.

4.2.1.3. Overall survival estimation

The likely long-term survival of patients alive at five years post-randomisation is not clear-cut. 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%,[160] 39%,[161] 59%,[162] 45%,[163] 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 five 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 five years) includes those patients who have relapsed and died within the five 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 five years. This trend, however, may continue for a short time since some patients with relapsing disease will still be alive at five years post-randomisation. For this reason, the overall survival 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 five 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)[158] (personal communication with G. Griffiths, MRC Clinical Trials Unit, London, and with Professor A. de Gramont, Hopital Saint Antoine, Paris) and Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR)[159] 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.

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)

The choice of chemotherapy treatment for these patients depends upon a number of factors. Patients who have received FOLFOX4 as adjuvant chemotherapy would be unlikely to receive oxaliplatin again if they relapsed within one year, however, beyond that, it may be considered as a viable treatment option (Personal communication with Dr M. Saunders, Christie Hospital, Manchester). The age of a patient at the time of relapse affects subsequent treatment administration, since the more elderly patients are the sub-group 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 (Personal communication with Dr M. Saunders, Christie Hospital, Manchester).

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.[164,165] 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.[157] 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 years and 61.0 years in the capecitabine and 5-FU/LV arms respectively,[20] whilst 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.

4.2.1.4. 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 two 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 five 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

4.2.1.5. Cost analysis

The cost analysis was conducted from the perspective of the UK NHS, and incorporated costs incurred during the trial period, during post-treatment follow-up and following relapse. Costs incurred during the six 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 five 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.[166]

Drug acquisition costs were obtained from the British National Formulary,[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 $1.75m^2$. Table 19 shows the acquisition costs in terms of cost per mg.

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	5000	£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

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 intra-venous 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 Section 4.2.1.6) are assigned the cost of an inpatient stay. The costs used for these appointments are given in Table 20.

Table 20: Drug administration costs

Appointment type	Cost per appointment	Reference
Line insertion (one-off cost for IV 5-FU/LV and FOLFOX4)	£451	Boland *et al.*[167]
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 (IV 5-FU/LV, FOLFOX4)	£170	NHS Reference Costs TRDNA F98[153]
Medical oncology inpatient	£373	Netten & Dennet (1999)[168]

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

Table 21: Per-cycle costs of pumps and sundries (Personal communication with Michelle Rowe, Christie Hospital, Manchester)

Treatment	Pump costs per cycle	Sundry costs per cycle
Adjuvant treatment		
Bolus 5-FU/LV	-	£32.40
FOLFOX4 (7 pumps per cycle)	£105	£12
IV 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

IV = intravenous

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.

Table 22: Pharmacy costs per cycle

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

IV = intravenous

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 patients 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 – Personal communication, Dr D. Radstone, Weston Park Hospital, Sheffield) and one ultrasound scan. The costs of these tests are given in Table 23.

Table 23: Costs of routine tests during adjuvant treatment period

Test / diagnostic procedure	Cost	Reference
CEA test	£9.30	Renehan *et al.*[169]
Full blood test	£9.30	Renehan *et al.*[169]
CT scan	£185	Follow-up after colorectal surgery (FACS) trial protocol[170]
Ultrasound scan	£35	Follow-up after colorectal surgery (FACS) trial protocol[170]

The costs associated with adverse events and treatment-related toxicities were addressed in two ways. Resource use data regarding the number of hospitalisations and mean length of stay in the X-ACT study[39] were used to estimate the total costs of hospitalisation. Equivalent data was 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).[168]

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

Table 24: Costs of adverse events requiring treatment

Adverse event	Treatment	Cost per cycle	Reference
Nausea grade 3+	Cyclizine 50mg per day for 5 days. Domperidone suppositories 1 supp. 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 *	sanofi-aventis submission[143]
Diarrhoea grade 3+	Loperamide hydrochloride, 2mg per day foir 12 days	£0.49	sanofi-aventis submission[143]
* = One-off cost during entire treatment period, rather than cost per cycle			

Adverse event data from the two trials[109,45] 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 five 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.

Table 25: Follow-up plan and costs

Year	Number of outpatient appointments (£59.10 per appointment)[170]	Number of ultrasound scans (£35 per scan)[170]	Number of CT scans (£185 per scan)[170]	Number of colonoscopies (£175 per colonoscopy)[170]
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

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

(academic in confidence 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.

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	(academic in confidence information removed)						
Drug administration	(academic in confidence information removed)						
Pharmacy costs	(academic in confidence information removed)						
Tests (blood and CEA)	(academic in confidence information removed)						
Line insertion	(academic in confidence information removed)						
Total	(academic in confidence 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

4.2.1.6. 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 (see 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 two years post- treatment do not incur the follow-up costs for years three, four and five.

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	87.3%	5.6 (0.04)
	LV	91.0%	
Capecitabine	Capecitabine	86.2%	7.35 (0.06)
5-FU/LV (de Gramont regimen)	5-FU	95.0%	11.26 (0.07)
	LV	88.0%	
FOLFOX4	5-FU	83.4%	10.68 (0.08)
	LV	80.2%	
	Oxaliplatin	77.2%	

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 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] has been used to formulate assumptions regarding the proportion of patients who are treated as inpatients and as outpatients. These estimates have been checked against Hospital Episode Statistics data which give similar proportions for patients receiving chemotherapy on an inpatient / outpatient basis.[171] The Aventis data is given, by treatment plan, below.

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[172]
FOLFOX6	25%	75%	
FOLFIRI	7%	93%	
Irinotecan	17%	83%	

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.

4.2.1.7. Methods for estimating quality-adjusted survival benefits

In order to derive estimates of quality-adjusted life-years (QALYs) for each treatment plan, the survival benefits seen within the trials need to be weighted by patients quality of life over that period of time. 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 shows a summary of utility estimates associated with different states of health in patients with colorectal cancer available within the literature.

Table 29: Utility estimates for patients with Dukes' Stage III colon cancer

Study	Time period	Reported utility	Standard error	Sample size
Ramsey et al.[150]	13 to 24 months post-diagnosis	0.82	0.15	-
	25 to 36 months post-diagnosis	0.95	-	1
	37 to 60 months post-diagnosis	0.79	0.25	-
	>60 months post-diagnosis	0.92	0.05	-
Smith et al.[173]	Chemotherapy with no recurrence	0.88	-	-
	Chemotherapy with recurrence	0.88	-	-
Norum et al.[174]	No relapse	0.83	-	-
Ness et al.[175]	Chemotherapy without significant side-effects	0.7	0.036	40
	Chemotherapy with significant side-effects	0.63	0.036	41
Ramsey et al.[176]	Stage at diagnosis	0.87	0.08	29

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

Quality of life data were not routinely collected within the MOSAIC trial, whilst in the X-ACT study, the QLQ C-30 (a cancer-specific quality of life instrument) was used to monitor patients quality of life for the duration of the adjuvant treatment period. The results show very little difference between the 5-FU/LV and capecitabine arms, with quality of life relatively constant over the 25 weeks. However, since the results of the QLQ C-30 cannot easily be translated into index utilities, a search of literature relating to quality of life 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 have been taken from a study by Ness *et al*.[175] This study used a standard gamble approach to elicit utilities from 81 patients with colorectal cancer (stage I to IV [Dukes' A to 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 *et al.*[150] conducted a study of 173 patients with colorectal cancer, 40 of whom had stage III disease. Generic and cancer-specific quality of life 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 *et al.*,[175] which gave a mean utility of 0.24. The utility estimates used within the economic model are summarised in Table 30.

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.*[175]
On adjuvant chemotherapy (with significant side-effects)	0.63	0.036	Ness *et al.*[175]
In remission	0.92	0.05	Ramsey *et al.*[150]
On palliative chemotherapy	0.24	0.041	Ness *et al.*[175]

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.

4.2.1.8. 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.

4.2.1.9. 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 patient 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 have therefore been 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 five 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 years and 10 years, generating revised cost-effectiveness results.

4.2.1.10. 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. Whilst 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 (both for 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[158] (personal communication with G.Griffiths, MRC Clinical Trials Unit, London, and with Professor A. de Gramont, Hopital Saint Antoine, Paris) and GERCOR[159] 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 quality of life studies used.[175,150]

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 cost-effectiveness acceptability curves for each direct treatment comparison.

4.2.1.11. Indirect comparisons

In the absence of a randomised controlled trial 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 has been 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 has been 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.

4.2.1.12. 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.

4.3. Results of economic assessment

This section details the results of the health economic model. The cost-effectiveness results of 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 quality-adjusted life-year (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. Section 4.3.1 presents the overall survival analysis results as estimated using AUC analysis of the fitted survival functions. Section 4.3.2 reports the central estimates of cost-effectiveness under the base-case assumptions. Section 4.3.3 reports the results of a number of one-way sensitivity analyses, with the results of the probabilistic sensitivity analysis presented in Section 4.3.4.

4.3.1. Estimated overall survival benefits

Table 31 shows the results of the AUC analysis of discounted and undiscounted mean LYG 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.

Table 31: Discounted life-years gained and QALYs estimated from fitted survival functions (overall survival)

Adjuvant treatment	Mean undiscounted life-years	Mean discounted life-years	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

The results suggest that both capecitabine and FOLFOX4 are beneficial when compared with their respective 5-FU/LV arms, both in terms of LYG 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 two years, and so the difference in QALYs between these patients and those who do not relapse over that period of time is relatively small.

4.3.2. 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.

Table 32: Central estimates of cost per life-year gained

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	

The total cost savings made through the use of capecitabine in comparison with the Mayo 5-FU/LV regimen (£3,320) 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 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 (£3,941) 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.

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	

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 £3,320 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 £3,000.

4.3.3. 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 Section 4.2.1.9).

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. Firstly, 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.

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)	-£3,379	0.74	Dominating
FOLFOX4 versus 5-FU/LV (de Gramont)	£3,894	1.05	£3,723

The use of these alternative discount rates have little impact upon 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 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.

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)	-£3,472	1.24	Dominating
FOLFOX4 versus 5-FU/LV (de Gramont)	£3,816	1.61	£2,364

Again, these changes to the model input parameters have little effect upon the results, with improved QALY gains seen in both comparisons and lower costs in both cases, due 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 a several studies reported higher utilities for these patients than the value used in the base-case analysis.[177,150] 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.[177]

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)	-£3,320	0.96	Dominating
FOLFOX4 versus 5-FU/LV (de Gramont)	£3,940	1.28	£3,069

This too has little impact upon 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 quality of life being over-estimated in the base-case analysis. The cost-effectiveness results of this scenario analysis are given in Table 37.

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)	-£3,320	0.53	Dominating
FOLFOX4 versus 5-FU/LV (de Gramont)	£3,940	0.71	£5,584

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-case results, although capecitabine remains dominating because the cost-savings are maintained in this scenario analysis. The cost per QALY of FOLFOX4 in comparison to the de Gramont regimen increases by approximately £2,600 (compared with the base-case result).

It is anticipated 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 to 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

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)	-£3,413	0.98	Dominating
FOLFOX4 versus 5-FU/LV (de Gramont)	£3,789	1.32	£2,860

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)	-£3,505	0.98	Dominating
FOLFOX4 versus 5-FU/LV (de Gramont)	£3,638	1.32	£2,746

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)	-£4,388	0.97	Dominating
FOLFOX4 versus 5-FU/LV (de Gramont)	£2,196	1.31	£1,679

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)	-£4,476	0.97	Dominating
FOLFOX4 versus 5-FU/LV (de Gramont)	£2,051	1.31	£1,565

The results demonstrate that capecitabine remains cost-saving in comparison to the Mayo Clinic 5-FU/LV regimen, whilst the deterministic estimate of the marginal cost per QALY of FOLFOX4 in comparison to the de Gramont regimen is never greater than £6,000. As the costs of treating metastatic disease increase (e.g. through the use of bevacizumab), the incremental cost-effectiveness ratios 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 mg 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 to the Mayo 5-FU/LV regimen by £3,424 (compared with -£3,320 in the base-case analysis), whilst the cost per QALY of FOLFOX4 compared with the de Gramont 5-FU/LV regimen was estimated to be £2,855 (compared with £2,970 in the base-case). Analysis using lower cost reported in the sanofi-aventis submission erstimated that capecitabine would be cost-saving by -£3,299 per patient, with a cost per QALY gained of £2,988 for the comparison between FOLFOX4 and the de Gramont 5-FU/LV regimen.

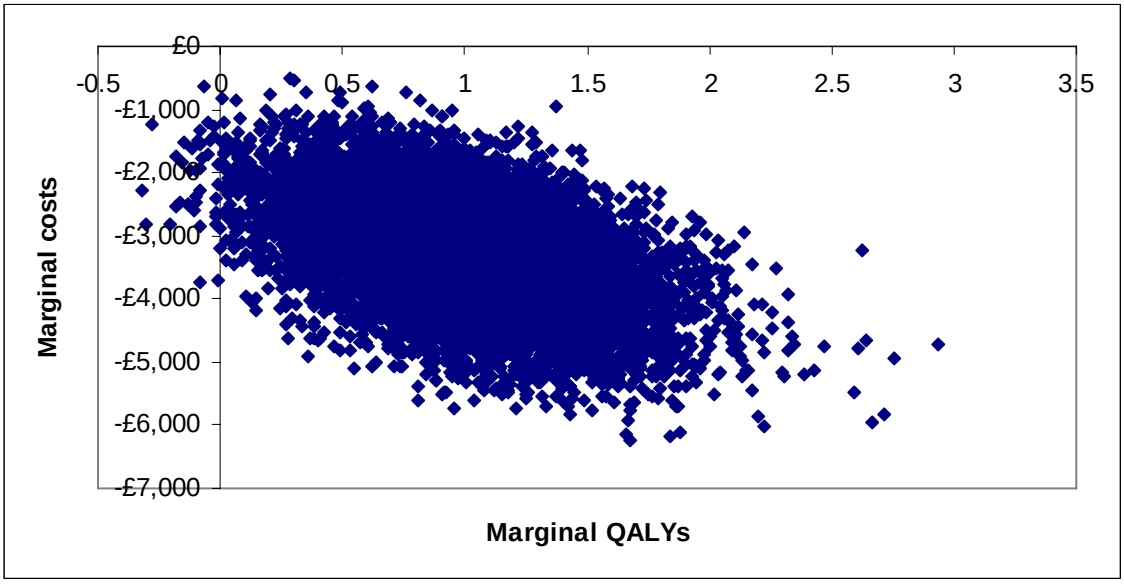
Separate analyses were carried out in which the assumption of no relapses beyond five years was relaxed, firstly with patients eligible for relapse up to 7.5 years post-randomisation. Given the increase in the relapse rate associated with this change, the resulting change in the cost-effectiveness estimates is favourable to both capecitabine and FOLFOX4. Capecitabine was estimated to be cost-saving by £3,633, whilst the cost per QALY of FOLFOX4 versus the de Gramont 5-FU/LV regimen was estimated to be £2,319. 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 £3,885, whilst the comparison of FOLFOX4 against the de Gramont 5-FU/LV regimen yielded a cost per QALY of £1,963.

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 £2,782 per patient on capecitabine, compared with £3,391 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 £7,587, compared with £2,970 in the base-case analysis.

4.3.4. 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 cost-effectiveness acceptability curves (CEACs). Figure 4 presents the marginal costs and QALYs of capecitabine in comparison to the Mayo Clinic 5-FU/LV regimen, based on 10,000 probabilistic model runs.

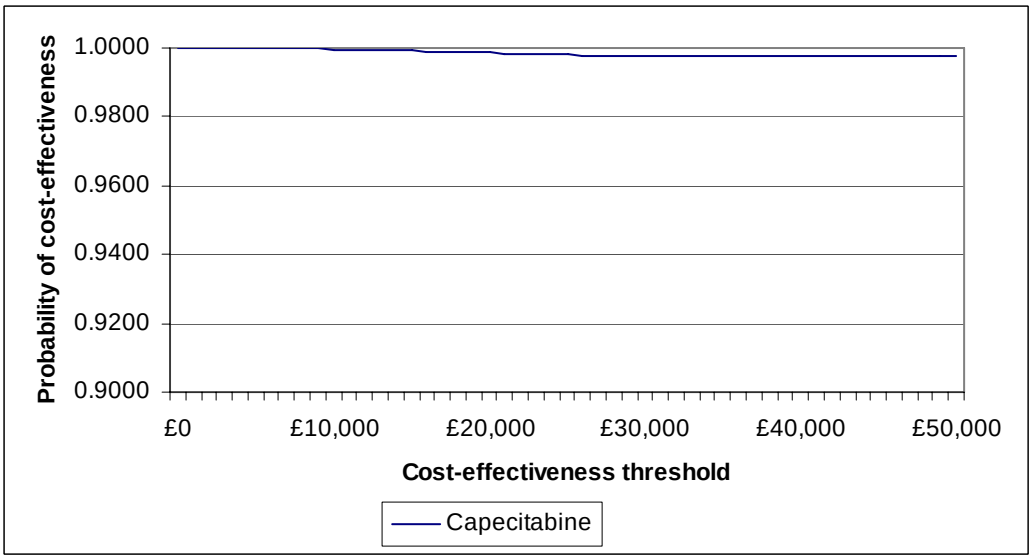
Figure 4: Cost-effectiveness plane: capecitabine versus 5-FU/LV (Mayo Clinic regimen)



This plot demonstrates that in all 10,000 model runs, capecitabine is cost-saving in comparison to 5-FU/LV, with the level of cost saving ranging from £502 to £6,255 per patient. The results also 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.

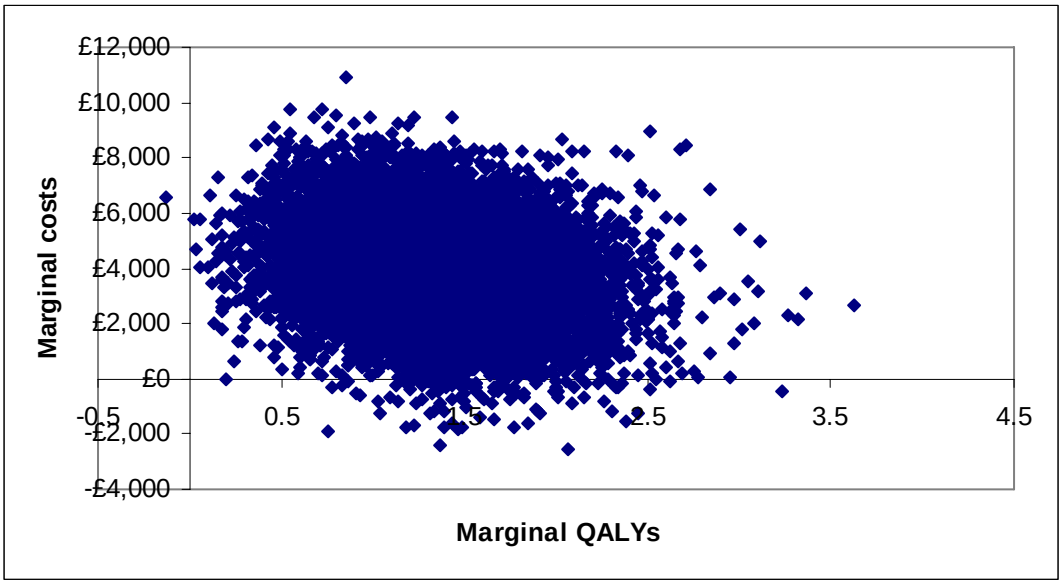
Figure 5: Cost-effectiveness acceptability curve (capecitabine)



This plot shows that by employing cost-effectiveness thresholds of between £1,000 and £50,000, capecitabine has a very high probability of being cost-effective when 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.

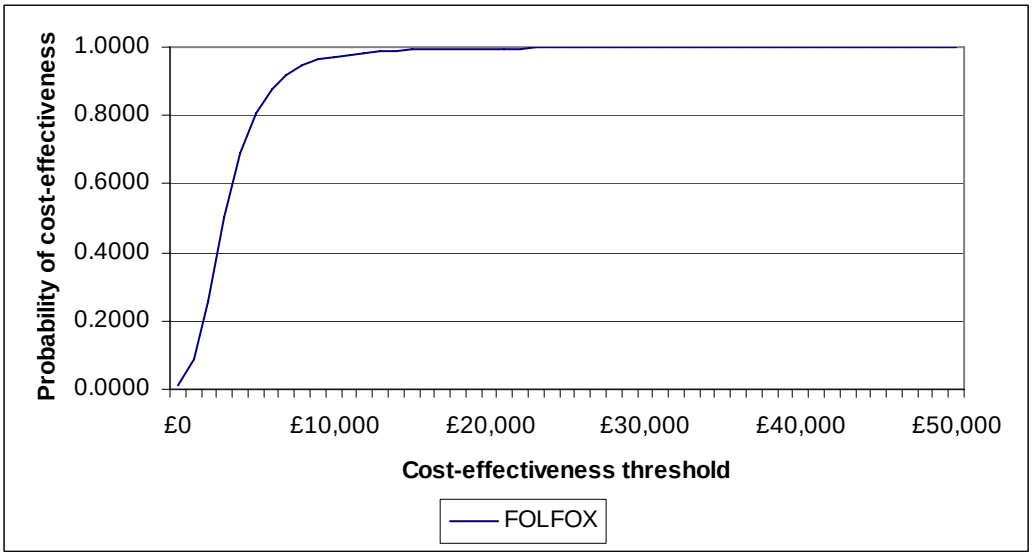
Figure 6 presents the marginal costs and QALYs of FOLFOX4 in comparison to the de Gramont 5-FU/LV regimen, also based on 10,000 probabilistic model runs.

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



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 -£2,571 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 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.

Figure 7: Cost-effectiveness acceptability curve (FOLFOX4)



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 when 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.

4.3.5 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, firstly using the absolute predicted long-term survival and cost data from the Assessment Group model, and secondly 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 to capecitabine (over a 50-year time horizon) are estimated to be £16,283, associated 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 to 5-FU/FA (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-effectiveneness 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 due to the prevalent use of bolus 5-FU/LV regimens in the adjuvant setting (see Section 3.4.3.3). The additional discounted costs associated with adjuvant treatment with FOLFOX4 when compared to 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 £5,777, suggesting that FOLFOX4 is cost-effective in comparison to the UK standard Mayo regimen. As with the previous indirect comparison, this result should be interpreted with caution, due to the absence of this treatment comparison in any randomised controlled trial.

4.3.6 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.

Table 42: Budget impact

Treatment	Total cost	Incremental cost
Capecitabine	£ 14,741,775	-
5-FU/LV (Mayo Clinic regimen)	£ 23,144,646	£ 8,402,871
5-FU/LV (de Gramont)	£ 61,740,781	£ 38,596,134
Oxaliplatin plus 5-FU/LV	£ 83,255,646	£ 21,514,866

5. Assessment of Factors Relevant to the NHS and Other Parties

5.1. Implications for other parties

5.1.1. Patient education

The vital role of education and information for patients receiving capecitabine has been comprehensively reviewed by Chau *et al*.[178] For home based oral therapy to be successful, it is vital that patients take an active part in their care.[178,130] To ensure 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 size patient card with useful telephone numbers, a side effect recognition sheet and a patient education video.[178,130] However, this should not remove the decision-making and sense of responsibility from doctors, nurses and pharmacists *(Personal communication with Prof M. Seymour, Cookridge Hospital, Leeds).*

In addition, patient education, both for oral and intravenous administration, must emphasise recognition of early signs and symptoms and ways to report changes, as well as information to assist patients in preventing exacerbations.[179] This process may be facilitated through patient care groups who can provide patients with advice on symptoms, and could eventually lead to home delivery of intravenous chemotherapy *(Personal communication with Dr M. Saunders, Christie Hospital, Manchester).*

5.1.2. 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.[21] If patients are not sufficiently competent to self-administer oral tablets, they should be prescribed intravenous chemotherapy as a means of increasing compliance and preventing overdose *(Personal communication with Dr M. Saunders, Christie Hospital, Manchester).*

5.1.3. 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 two weeks instead of once every three weeks.[21]

5.2. Factors relevant to NHS

5.2.1. 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, 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 *(Personal communication with Dr M. Saunders, Christie Hospital, Manchester).*

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

5.2.2. Cost incentives within the NHS

A shift towards the greater use of oral drugs within the NHS may exert cost pressures on NHS Trusts, as a result of existing contracting arrangements. An oral prescription is classed as an outpatient visit, whilst outpatient 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.[21] 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 *(Personal communication with Dr M. Saunders, Christie Hospital, Manchester)*. 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.[21]

5.2.3. 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, this may become less of an issue *(Personal communication with Dr M. Saunders, Christie Hospital, Manchester)*. More specialist staff are needed in all areas of administration for infusional regimens, as radiologists and radiographers may also be needed for line insertion, while specialist pharmacists and nurses are needed for the preparation and administration of drugs.[21]

Capecitabine dispensing is undertaken in the main dispensary area in many hospitals, though would not be viewed as a simple prescription to dispense, given the different tablet strengths, the need for careful labelling and tablet counting checks due 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 streamline if capecitabine became routine therapy.[21]

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 *(Personal communication with Dr M. Saunders, Christie Hospital, Manchester)*. 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.

5.2.4. 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 anticipated that this may reduce the number of hospital attendances per drug cycle. This would have implications in terms of saving clinician's 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.

5.2.5. 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 *(Personal communication with Dr M. Saunders, Christie Hospital, Manchester)*. 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, as well as follow-up (clinic visits, home visits, and telephone contact), including urgent phone contact and liaison with the clinician if necessary.[180] In addition, the potential difficulties that may arise as a function of expanding the role of oncology nurses include overburdening staff with additional responsibilities.[180,181]

5.2.6. 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,[182] but over-compliance can sometimes be a problem as patients may be motivated to take medication even when they are experiencing adverse effects.[21] Patients with cancer may also be at risk of overdose due to depression *(Personal communication with Dr M. Saunders, Christie Hospital, Manchester)*. 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 general practitioners in the monitoring of adverse effects. Services for elderly patients would also be required to deal with problems with confusion and home support.

5.2.7. 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 need 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.[183,184,185] 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 would lead to strong tendencies for the two drugs to be given in combination, as off-licence therapy *(Personal communication*

with Prof M. Seymour, Cookridge Hospital, Leeds). This would remove the drug administration cost savings associated with single-agent capecitabine.

5.2.8. 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.

5.2.9. Off-licence use

5.2.9.1. 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, there is currently no evidence to suggest that either drug is not effective in rectal cancer *(Personal communication with Dr M. Saunders, Christie Hospital, Manchester).* Initially, this may be restricted to those patients with rectal disease who have either received no radiotherapy or only short-course pre-operative radiotherapy, due to the lack of evidence for patients treated with long-course radiotherapy. Evidence from the ongoing CHRONICLE trial[186] should indicate the suitability of adjuvant chemotherapy for these patients.

5.2.9.2. Patients with stage II cancer

The MOSAIC trial included patients with both stage II and stage 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.

6. Discussion

6.1. Principle 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 £3,320 per patient over a 50 year time horizon, whilst in turn providing an additional 0.98 QALYs per patient. The comparison of FOLFOX4 versus the de Gramont 5-FU/LV regimen has estimated that over the same 50 year time horizon, FOLFOX4 costs an additional £3,940 per patient, resulting in a net gain of 1.33 QALYs, giving a marginal cost-effectiveness ratio of £2,970 per QALY. Both of these results are favourable in comparison to 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 regarding 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 £7,600.

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 cost-effectiveness acceptability curves 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 to 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 incremental cost-effectiveness ratio 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).

6.2. 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 upon the cost-effectiveness profile of both FOLFOX4 and capecitabine. Although evidence from a meta-analysis of trials in the adjuvant setting,[187] 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. Due to this uncertainty in patient outcomes, sensitivity analyses

have not been performed to assess the impact upon cost-effectiveness of assuming a higher mean age (e.g. 70 years) at baseline.

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 anticipated 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.

6.3. 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 though 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.

6.4. 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.

6.5. Further research

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

6.5.1. Ongoing trials

A list of ongoing adjuvant therapy trials comparing different combination therapies e.g. oral capecitabine plus oxaliplatin (XELOX),[188] including oral fluoropyrimidines and the new targeted therapies can be found in Appendix 17.

6.5.2. 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 quality of life 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 C07 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 determine what safety mechanisms are needed in order to ensure compliance and the monitoring of adverse effects.

- The issue of patient preference must be given careful consideration in future trials and all trials should incorporate a measurement of patient preference.

- 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 in 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 evaluated; however, this indirect comparison is subject to considerable bias, which could only be eliminated though a randomised controlled trial which directly compares these two interventions.

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**

Based on the assumptions regarding long-term survival, the results of the independent economic assessment suggest that, over a 50-year time horizon, both capecitabine and FOLFOX4 are estimated to demonstrate a favourable cost-effectiveness profile in comparison with the Mayo and de Gramont 5-FU/LV regimens respectively. Capecitabine is estimated to be cost-saving over this period in comparison with the Mayo 5-FU/LV regimen (by a total of £3,320 per patient), whilst oxaliplatin (in combination with 5-FU/LV) in comparison with the de Gramont 5-FU/LV regimen is estimated to cost an additional £2,970 per QALY gained.

Indirect comparisons suggest that FOLFOX4 is cost-effective compared with the Mayo 5-FU/LV regimen, although may not be deemed cost-effective in comparison with capecitabine. These economic comparisons could only be made fully assessed following a trial which directly compare 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, due 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.

8. Appendices

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 mg or 25 mg LV, for 30 weeks
QUASAR (monthly regimen)	Daily dose of 370 mg/m^2 5-FU, and 175 mg or 25 mg LV, for 5 days, repeated every 4 weeks for 6 months
Modified weekly regimen	Weekly dose of 425 mg/m2 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 FA (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/m2 c.i. over 22 h, LV 200 mg/m^2 over a 2-h infusion day 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/m2 c.i. over 46 h, LV 175 mg/m^2 over a 2-h infusion day 1 before 5-FU)
Grupo Espanol 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 2600mg/m^2; LV 500mg/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 sub-clinical 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.

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 this chapter. 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 anti-tumour 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.

Table 1: 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

Table 2: 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, Mulder, and Fields, 2003[81]	Wrong comparator/intervention/outcome
Berg, 2003[179]	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, Garufi and Iacobelli, 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[86]	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, Ferretti and Barni, 2004[210]	Letter/comment/editorial
Marse *et al*., 2004[128]	Review - not systematic
Marshall, 2004[129]	Review - not systematic
Maung, Chu, and Jain, 2003[211]	Letter/comment/editorial
Maxwell-Armstrong and Scholefield, 2004[87]	Review - not systematic
Mayer, 2004[73]	Letter/comment/editorial

National Horizon Scanning Centre, 2003[212]	Review - not systematic
Patel *et al*., 2004[26]	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, O'Dwyer and Labianca, 2001[218]	Review - not systematic
Zaniboni, 2000[219]	Review - not systematic
Zeuli, Pino and Cognetti, 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?

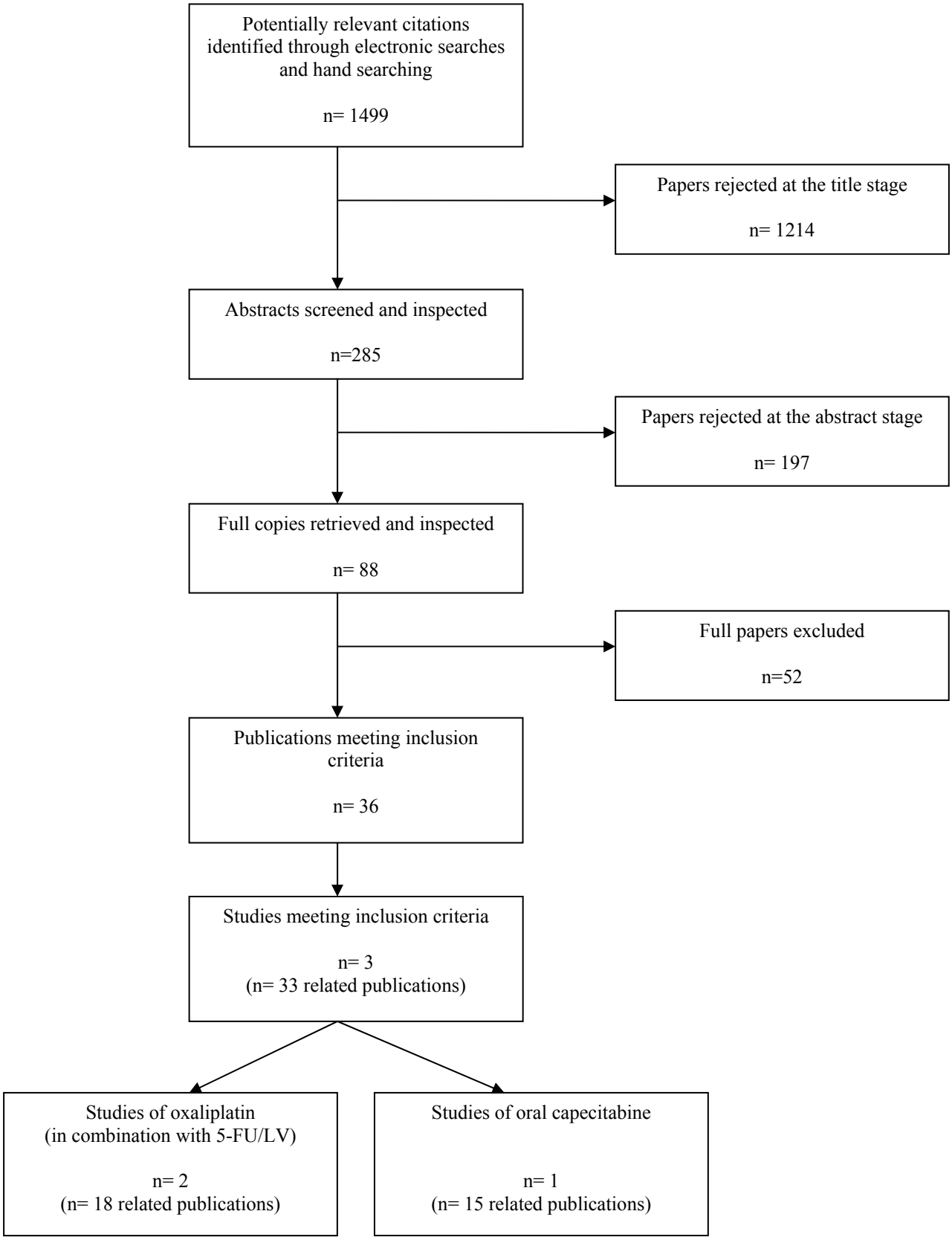
14. Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?

15. Were the reasons for withdrawal stated?

16. Was an intention-to-treat 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

Table 3: Trial: MOSAIC

STUDY & 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 Inc. 2004[57] ***[7]:** Tabah-Fisch *et al*. 2002[58] ***[8]:** De Gramont *et al*. 2004[51]
Study design Phase 3, multi-centre, randomised controlled trial	**Objective**	To determine if postoperative adjuvant treatment with oxaliplatin in combination with fluorouracil and leucovorin (***[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 (85mg/m^2 over 2 hours on day 1, given simultaneously with leucovorin, with use of a Y infusion device) in combination with LV5FU2 (2 hour infusion of 200mg/m^2 leucovorin plus a bolus of 400mg/m^2 fluorouracil on day 1, followed by a 22 hour infusion of 600mg/m^2 fluorouracil on 2 consecutive days every 14 days for 12 cycles)
	T2: Control group, dose, timings	LV5FU2 alone (2 hour infusion of 200mg/m^2 leucovorin plus a bolus of 400mg/m^2 fluorouracil on day 1, followed by a 22 hour infusion of 600mg/m^2 fluorouracil on 2 consecutive days every 14 days for 12 cycles)
	Intervention site (health care setting, country)	146 medical centres in 20 countries (France, United Kingdom, 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	Approximately 3 years T1: median 37.9 months (range 27 to 54) T2: median 37.8 months (range 27 to 54) COMMENT Final results for the overall population (cut-off date for primary statistical analysis, 22 April 2003) with a median follow-up of approximately 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	Patients were randomly assigned to receive either oxaliplatin (in combination with LV5FU2) or LV5FU2 alone
	Generation of allocation sequences	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 (A De Gramont, personal communication) COMMENT Adequate method

	Blinding level	Unblinded (unmasked) (A De Gramont, personal communication) COMMENT Patients, investigators, outcome assessors and statistical analyst were all unblinded (unmasked) (A De Gramont, personal communication)
	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 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 ▪ Carcinoembryonic antigen level of less than 10ng/ml. ▪ Written informed consent 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 percent), that 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 to 17.0).

COMMENT
Not clear how many patients were initially screened

Characteristics of participants at baseline

	Age (mean yr.)	**Baseline characteristics**

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

Baseline characteristics (cont.)

Characteristics	T1 (n = 1123)	T2 (n = 1123)
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)
Histologic appearance		
Well differentiated	385 (85.4)	378 (84.4)
Poorly differentiated	47 (10.4)	42 (9.4)
Unknown	19 (4.2)	28 (6.3)

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, biologic tests, measurement of the carcinoembryonic antigen level, chest radiography and abdominal ultrasonography or computed tomography
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 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	N/A
	Definition of other outcomes	N/A
	ANALYSIS	
	Statistical techniques used	Primary outcome analysis Comparison of disease-free survival between groups after three years of follow-up (intention-to-treat 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% confidence intervals. 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; 4, life-threatening adverse effects COMMENT Additional analyses, not specified in the protocol, were requested by drug regulatory agencies (A De Gramont, personal communication 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.
	Intention-to-treat analysis	Yes

<table>
<tr><td></td><td>Does technique adjust for confounding?</td><td>Additional analyses
To assess consistency of the effect of treatment on disease-free survival across prognostic subgroups, hazard ratios and 95% confidence intervals were calculated for the following variables:
Sex
Age
Disease stage (II vs. III)
Baseline serum carcinoembryonic antigen 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</td></tr>
<tr><td></td><td>Power calculation (priori sample calculation)</td><td>Yes, assuming a three 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 three 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</td></tr>
<tr><td></td><td>Attrition rates (overall rates) i.e. Loss to follow-up</td><td>Numbers followed and loss to follow-up
<table><tr><th></th><th>T1
(n=1123)</th><th>T2
(n=1123)</th></tr><tr><td>At 3 years</td><td></td><td></td></tr><tr><td>Known alive</td><td>990 (88.2%)</td><td>977 (87.0%)</td></tr><tr><td>Confirmed Death</td><td>133 (11.8%)</td><td>146 (13.0%)</td></tr><tr><td>*[3]: At 4 years</td><td></td><td></td></tr><tr><td>Known alive</td><td>947 (84.3%)</td><td>929 (82.7%)</td></tr><tr><td>Confirmed Death</td><td>176 (15.7%)</td><td>194 (17.3%)</td></tr></table></td></tr>
<tr><td></td><td>Was attrition adequately dealt with?</td><td>Yes, intention-to-treat</td></tr>
<tr><td></td><td>Number (%) followed-up from each condition</td><td>See table above (loss to follow-up)</td></tr>
<tr><td></td><td>Compliance with study treatment</td><td>See below</td></tr>
</table>

Adherence to study treatment

Chemotherapy

Discontinuations

***[6]:** discontinuation of treatment due 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 summarised below

	T1 (n=1108)	T2 (n=1111)
Median relative dose intensity		
Fluorouracil	84.4%	97.7%
Oxaliplatin	80.5%	N/A

COMMENT

Dose reductions based on worst adverse effects during previous cycle. Oxaliplatin reduced to 75mg/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 fluorouracil was reduced to 300mg/m^2 and the infusion to 500mg/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 fluorouracil scheduled to be reduced in event of skin related adverse effects of grade 3 or 4. Treatment delayed up to three 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

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 etc)

Primary outcome analysis

Disease-free survival at 3 years (intention-to-treat analysis)

Parameter	T1	T2
All patients (stage II and stage 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	
Number needed to treat (benefit)	18.2 (95% CI: 11.7 to 47.5)	
Absolute difference in survival	5.3%	

CI confidence interval

Primary outcome analysis

***[3]: Disease-free survival at 4 years (intention-to-treat analysis)** [a]

Parameter	T1	T2
All patients (stage II and stage 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	
Number needed to treat (benefit)	15.6 (95% CI: 10.5 to 38.4)	
Absolute difference in survival	6.8%	

CI confidence interval

[a] All data from ***[3]** however, missing data extracted from ***[6]. *[3]** reports exactly the same data as ***[6],** however, data from ***[6]** reports 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 stage 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	
Number needed to treat (benefit)	79.7 (95% CI: NNTB 27.1 to NNTH 62.3)	
Absolute difference	1.1%	

CI confidence interval

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

Parameter	T1	T2
All patients (stage II and stage 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	
Number needed to treat (benefit)	56.4 (95% CI: NNTB 21.8 to NNTH 70.3)	
Absolute difference	1.6%	

CI confidence interval

[a] All data from ***[3]** however, missing data extracted from ***[6]. *[3]** reports exactly the same data as ***[6],** however, data from ***[6]** reports 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	
Number needed to treat (benefit)	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	
Number needed to treat (benefit)	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
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	
Number needed to treat (benefit)	19.2 (95% CI: NNTB 10.1 to NNTH 70.1)	
Absolute difference in survival	5.1%	

CI confidence interval
[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

Additional analyses

***[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	
Number needed to treat (benefit)	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	
Number needed to treat (benefit)	29.1 (95% CI: NNTB 13.5 to NNTH 54.6)	
Absolute difference in survival	3.8%	
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	
Number needed to treat (benefit)	Not calculable	
Absolute difference in survival	5.4%	

CI confidence interval

[a] All data from ***[3]** however, missing data extracted from ***[6]. *[3]** reports exactly the same data as ***[6],** however, data from ***[6]** reports 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].**

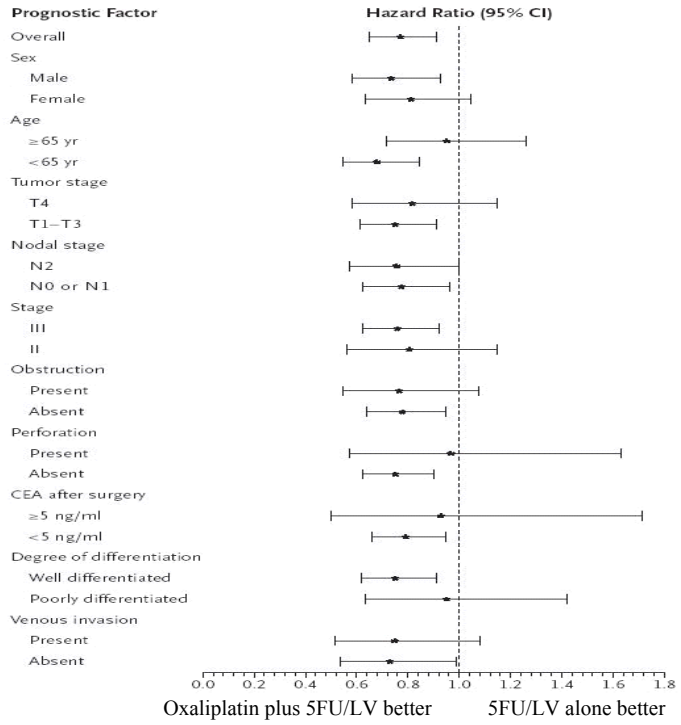
[b] T4 and/or bowel obstruction and/or tumour perforation and/or poorly differentiated tumour and/or venous invasion and/or <10 examined lymph nodes

Additional analyses

Disease-free survival at 3 years according to baseline prognostic factors and intention-to-treat (hazard ratios and 95% confidence intervals)

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% confidence intervals showed that the reduced risk of recurrence was consistent in all subgroups defined on the basis of prognostic factors at baseline.

Subgroup analysis: Disease-free survival at 3 years



Additional analyses

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	
Number needed to treat (benefit)	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	
Number needed to treat (benefit)	Not calculable	
Absolute difference in survival	Not reported	

CI confidence interval

Additional analyses

***[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	
Number needed to treat (benefit)	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	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	
Number needed to treat (benefit)	Not calculable	
Absolute difference in survival	Not reported	

CI confidence interval

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 treatment

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

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

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†	31.5	1.4	0.6	35.5	1.7	0.7	0.05	0.67
Alopecia‡	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

[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
† Includes hand-foot syndrome
‡ 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 Month follow-up (n = 1058)	12 Month follow-up (n = 1018)	18 Month 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.
[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)

Additional analyses

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

Parameter	Stage II (n=899)	Stage III (n=1347)	Stage II and Stage 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 stage 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 to 14.4% as noted above

Additional analyses

***[7]: Subgroup analyses - Toxicity profile of T1 (Grade 3/4)[a] in patients below 70 years and between 70 to 75 years**

Parameter	Age <70 years	Age between 70 to 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

Quality of life	Not reported
Other information	NA
SUMMARY	
Authors' overall conclusions	The addition of oxaliplatin to a regimen of fluorouracil and leucovorin improved the adjuvant treatment of colon cancer.
Reviewers comments	

Table 4: Trial: NSABP C-07

STUDY & 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, Chu and Jain, 2004[62] ***[5]:** de Gramont et al. 2003[61]
Study design Phase 3, multi-institution, randomised controlled trial	**Objective**	***[3]:** To compare the efficacy of oxaliplatin in combination with fluorouracil and leucovorin calcium (FLOX) with fluorouracil and leucovorin 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 (85mg/m^2, intravenous administered on weeks 1, 3, and 5 of each 8 week cycle) in combination with 5-FU/LV (5-FU; 500 mg/m^2 intravenous bolus of fluorouracil (***[3]:** administered after 1 hour of leucovorin calcium) plus 500mg/m^2 intravenous leucovorin 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 intravenous bolus of fluorouracil (***[3]:** administered after 1 hour of leucovorin calcium) plus 500mg/m^2 intravenous leucovorin calcium for 6 weeks in three 8 week cycles ***[3]:** in the absence of disease progression or unacceptable toxicity)

	Intervention site (health care setting, country)	***[2]:** 158 National Surgical Adjuvant Breast and Bowel Project (NSABP) institutions ***[5]:** across the United States, 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
	Length of follow-up	Approximately 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 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 ▪ Eastern Cooperative Oncology Group 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 noncontiguous intraabdominal metastases, even if resected ▪ Intestinal obstruction allowed ▪ No more than 42 days since prior curative resection ▪ No prior noncurative surgical resection for this malignancy, except colostomy ▪ No prior laparoscopically assisted colectomy (unless participating in Intergroup Protocol INT 0146 or the Australasian ALCCaS protocol) ▪ No other concurrent investigational drugs ▪ No concurrent halogenated antiviral agents (e.g., sorivudine) ▪ Granulocyte count at least 1,500/mm^3 ▪ Platelet count at least 100,000/mm^3 ▪ Bilirubin normal ▪ Alkaline phosphatase normal ▪ SGOT/SGPT normal ▪ Creatinine normal ▪ No active ischemic 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 nonmalignant 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 yr.)	***[1]: Baseline characteristics** [a,b]

Characteristics	T1 (n = 1200)	T2 (n = 1207)
ALL PATIENTS		
Age (years)		
<60	624 (52%)	604 (50%)
60 to 69	384 (32%)	398 (33%)
70+	192 (16%)	205 (17%)
Positive nodes – No. (%)		
0	348 (29%)	350 (29%)
1 to 3	540 (45%)	555 (46%)
≥4	312 (26%)	302 (25%)
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 appears to be some discrepancies within the table i.e. percentages do not add up with regards 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 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	N/A
	Definition of other outcomes	N/A
	ANALYSIS	
	Statistical techniques used	***[1]:** Primary outcome analysis Comparison of disease-free survival between groups after three years of follow-up
	Intention-to-treat 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 (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 priori sample calculation

<table>
<tr><td></td><td>Attrition rates (overall rates) i.e. Loss to follow-up</td><td>*[1]: Numbers followed and loss to follow-up

<table><tr><th></th><th>T1</th><th>T2</th></tr><tr><td>Randomised</td><td>1247</td><td>1245</td></tr><tr><td>Ineligible or loss to follow-up</td><td>47 (3.8%)</td><td>38 (3.1%)</td></tr><tr><td>Analysis</td><td>1200 (96.2%)</td><td>1207 (96.9%)</td></tr></table></td></tr>
<tr><td></td><td>Was attrition adequately dealt with?</td><td>Not clear</td></tr>
<tr><td></td><td>Number (%) followed-up from each condition</td><td>See table above (loss to follow-up)</td></tr>
<tr><td></td><td>Compliance with study treatment</td><td>Not reported</td></tr>
<tr><td></td><td>Adherence to study treatment</td><td>*[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</td></tr>
<tr><td></td><td>RESULTS</td><td></td></tr>
</table>

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 etc)

***[1]: Primary outcome analysis**

Disease-free survival at 3 years (per protocol analysis)

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

CI, confidence interval

COMMENT

***[1]:** Author reports that the global test for interaction between treatment and tumour stage (stage II and stage 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

COMMENT

- The overall toxicity profile was somewhat higher in T1 compared with 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 was similar.
	Quality of life	Not reported
	Other information	NA
	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 stage II colon cancer
	Reviewers comments	Caution, study only reported in abstract form

Table 5: Trial: X-ACT

STUDY & 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 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-fluorouracil plus leucovorin (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	United Kingdom
	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	Oral capecitabine (1250 mg/m^2 of body surface area) taken twice daily on days 1 through 14, every 21 days
	T2: Control group, dose, timings	Intravenous leucovorin (20 mg/m^2) by rapid infusion followed immediately by an intravenous bolus 5-FU (425 mg/m^2) on days 1through 5, every 28 days (Mayo Clinic regimen)

	Intervention site (health care 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
	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 (J Cassidy, personal communication) 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) (J Cassidy, personal communication) COMMENT Patients, investigators, outcome assessors and statistical analyst were all unblinded (unmasked) (J Cassidy, personal communication)
	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 • Eastern Cooperative Oncology Group 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
	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 yr.)

Baseline characteristics of patients in the intention-to-treat 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] (%)†		
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 surgery to randomisation	40 days	40 days

ECOG, Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen; ULN, upper limit of normal
† High numbers indicate greater depth of tumour penetration through the bowel wall
[a] Numbers calculated based on reported percentages
[b] Staging classification according to ***[8]:** Union Internationale Contra le Cancer

	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 a medical history taking, physical examination, vital signs, physical measurements, performance status, laboratory tests (haematology, blood chemistry, pregnancy test, urinalysis, carcinoembryonic antigen level), computed tomography scan or magnetic resonance imaging of abdomen and pelvis, chest X-ray and Quality of life 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 endpoints • Equivalence in disease-free survival DEFINITIONS Disease-free survival was 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 endpoints • Relapse-free survival • Overall survival • Safety (***[3]:** recorded & graded according to National Cancer Institute of Canada Common Toxicity Criteria) • ***[3]:** Pharmaco-economics & medical resource utilisation • ***[3]:** Quality of life 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)

	Definition of tertiary outcomes	N/A
	Definition of other outcomes	N/A
	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% CI. Relapse-free survival was analysed with the use of proportional-hazards regression and presented as a cumulative-incidence plot and hazard ratios with 95 percent confidence intervals. 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 intention-to-treat 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 percent 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.
	Intention-to-treat analysis	Yes
	Does technique adjust for confounding?	***[3]:** Additional analyses Disease-free survival analysis (primary endpoint) for prognostic factors included ▪ Sex ▪ Age ▪ Lymph nodes ▪ Baseline carcinoembryonic antigen level
	Power calculation (priori sample calculation)	The primary efficacy analysis was planned when 632 events for the end point of three-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 three-year disease-free survival rates of 70%, and allowing for approximately 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 intention-to-treat populations; superiority analyses were performed only in the intention-to-treat population, to maintain the most conservative approach. No interim analyses were performed.

<table>
<tr><td></td><td>Attrition rates (overall rates) i.e. Loss to follow-up</td><td>*[1]: Numbers followed and loss 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)
<table><tr><th></th><th>T1
(n=1004)</th><th>T2
(n=983)</th></tr><tr><td>Treatment related deaths</td><td>3 (0.3%)</td><td>4 (0.4%)</td></tr><tr><td>60 day all cause mortality</td><td>5 (0.5%)</td><td>4 (0.4%)</td></tr></table>
Numbers followed and loss to follow-up during study period
Overall, 33 patients were lost to follow-up (T1: 15 versus T2: 18)
<table><tr><th></th><th>T1
(n=1004)</th><th>T2
(n=983)</th></tr><tr><td>At median 3.8 years</td><td></td><td></td></tr><tr><td>Known alive [a]</td><td>804 (80%)</td><td>756 (77%)</td></tr><tr><td>Confirmed Death</td><td>200 (20%)</td><td>227 (23%)</td></tr><tr><td>*[8]: At median 4.4 years</td><td></td><td></td></tr><tr><td>Known alive [a]</td><td>763 (76%)</td><td>718 (73%)</td></tr><tr><td>Confirmed Death</td><td>241 (24%)</td><td>265 (27%)</td></tr></table>[a] Data extrapolated from reported deaths (confirmed)</td></tr>
<tr><td></td><td>Was attrition adequately dealt with?</td><td>Yes, intention-to-treat</td></tr>
<tr><td></td><td>Number (%) followed-up from each condition</td><td>Not clear, however see table above (numbers followed and loss to follow-up during study period)</td></tr>
<tr><td></td><td>Compliance with study treatment</td><td>See below</td></tr>
</table>

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 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 reference***[1]** suggests 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] reports these values as 83% and 87% respectively.

***[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 as well as 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 moderate or severe toxicity (grade ≥2), all patients instructed to contact clinic for further directions. At 2nd 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 leucovorin 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 etc)*	**Primary outcome analysis** **Disease-free survival at 3 years (intention-to-treat 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	
Number needed to treat (benefit)	24.5 (95% CI: NNTB 12.4 to ∞ to NNTH not calculable)	
Absolute difference in survival	3.6%	

CI, confidence interval; NNTB, Number needed to treat in order to benefit; NNTH, number needed to treat in order to harm

[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

Secondary outcome analysis

Relapse-free survival at 3 years (intention-to-treat 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	
Number needed to treat (benefit)	23.3 (95% CI: 12.2 to 336.0)	
Absolute difference in survival	3.6%	

CI, confidence interval

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

Secondary outcome analysis

***[3]: Overall survival at 3 years – intention-to-treat 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	
Number needed to treat (benefit)	31.1 (95% CI: NNTB 15.8 to ∞ to NNTH 508.8)	
Absolute difference in survival	3.7%	

CI, confidence interval; NNTB, Number needed to treat in order to benefit; NNTH, number needed to treat in order to harm

[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

Additional analyses (not pre-specified in protocol)

***[8] Intention-to-treat 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	
Number needed to treat (benefit)	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	
Number needed to treat (benefit)	Not calculable [b]	
Absolute difference in survival	Not reported	

CI, confidence interval

[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 re-calculated as 718 based on the percentages

Additional analyses (not pre-specified in protocol)

***[8] Intention-to-treat analysis – Disease-free / relapse-free and overall survival at median 4.4 years follow-up (cont.)**

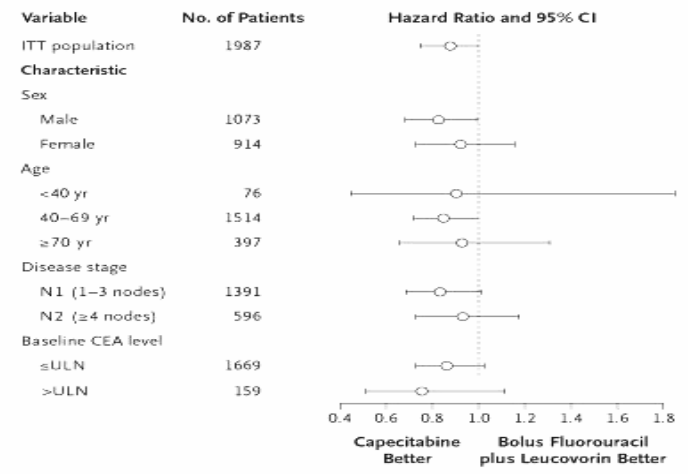
Parameter	T1	T2
Number of patients	1004	983
Median follow-up (years)	4.4	
Overall survival		
Death from any cause	241 (24%)	265 (27%)
Number of patients alive	763 (76%)	718[c] (73%)
Overall survival at 4 years	Not reported	Not reported
Hazard ratio (for death)	0.88 (95% CI: 0.74 to 1.05)	
Reduction in risk of mortality	12%	
Level of significance for equivalence	Not reported	
Level of significance for superiority	p=0.169	
Number needed to treat (benefit)	Not calculable [b]	
Absolute difference	Not reported	

CI, confidence interval

[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 re-calculated 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 categorized according to prognostic factors that were used in the multivariate analysis. **Subgroup analysis – Disease-free survival analysis for prognostic factors** (Data on carcinoembryonic antigen levels were missing for 159 patients who were therefore not included in the analysis for this variable) 

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 carcinoembryonic antigen	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

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

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

Toxicity

Secondary outcome analysis

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

	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 <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)

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

	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%	p<0.001	11%	13%	NS
Nausea or vomiting	36%	51%	p<0.001	3%	3%	NS
Stomatitis	22%	60%	p<0.001	2%	14%	p<0.001
Hand-foot syndrome	60%	9%	p<0.001	17%	<1%	p<0.001
Fatigue or asthenia	23%	23%	NS	1%	2%	NS
Abdominal pain	10%	13%	NS	2%	1%	NS
Alopecia	6%	22%	p<0.001	0%	<1%	p<0.02
Lethargy	10%	9%	NS	<1%	<1%	NS
Anorexia	9%	10%	NS	<1%	<1%	NS
Neutropenia [c]	32%	63%	p<0.001	2%	26%	p<0.001
Hyperbilirubinaemia [c]	50%	20%	p<0.001	20%	6%	p<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%), diarrhea (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 years and ≥65 years (4.9% vs. 6.3%, respectively).

***[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†

	T1 (n = 993)	T2 (n = 974)	p-value
Hyperbilirubinemia [a]	20%	6%	<0.001
Grade 3 [b]	18.6%	5.9%	<0.001
Grade 4 [c]	1.4%	0.3%	<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

† Figures as reported in original paper

[a] Graded according to NCIC CTC 1991 criteria, however according to current NCI CTCE (v3.0) system the incidence is negligible (T1: 1.4% vs. T2: 0.3%; p<0.001)

[b] Defined as elevated bilirubin concentrations ≤3 times the upper limit of normal

[c] Defined as elevated bilirubin concentrations >3 times the upper limit of normal

ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase

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

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

All grades	T1	T2
	≥70 years (n = 186)	≥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) [a]	17%	5%

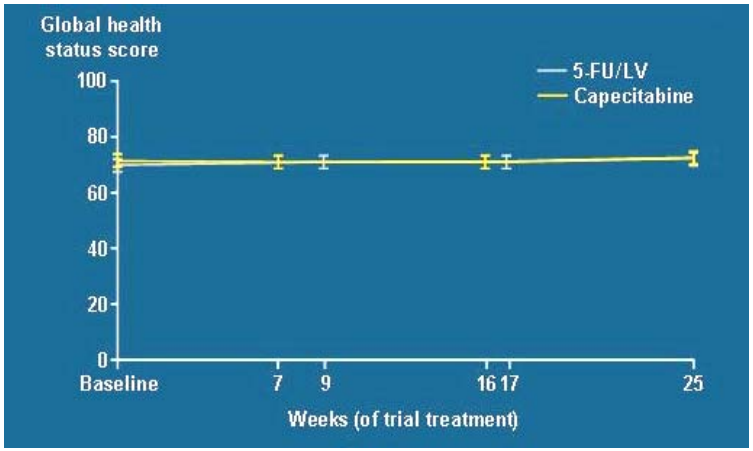
† p –values not calculated due to retrospective nature of analysis
[a] According to National Cancer Institute of Canada Common Toxicity Criteria

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 Quality of Life data was 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 graph below, no major differences were found between the T1 and T2. ***[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]:** Due 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%)
Granulocyte colony-stimulating factor	7 (<1%)	27 (3%)

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

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 anti-diarrhoeals, analgesics and anti-fungals, 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/cephalosporin's	185	453
Antiemetics/anti diarrhoeals (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 a similar number 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.

***[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 compared with T2 (91 vs. 100, respectively) but the total number of associated days hospitalised was similar (961 vs. 959, respectively)

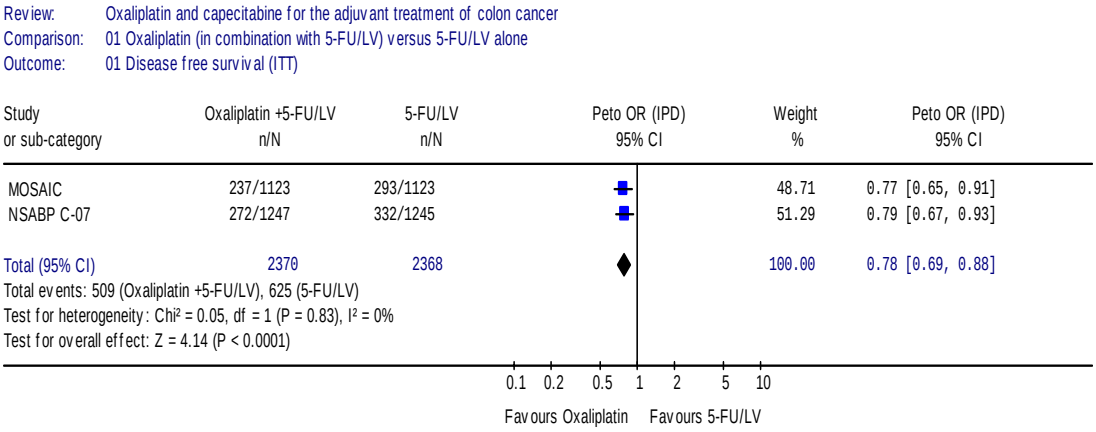
COMMENT

- Inconsistent reporting - Data in reference***[7]** suggests that in total, 18% of patients were hospitalised during the study. Hospitalisations due 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 days 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]



[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.

Table 6: 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 Table 2, Appendix 2

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[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 a randomised controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?	Yes. Data from the X-ACT trial was 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	No

(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? 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? 7.2 Was any justification given for the discount rate used?	Yes. Both costs and QALYs were discounted at 3.5% per annum. 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? 9.2 If sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?	No stochastic analyses were performed. Drug acquisition and administration costs were varied by 25% in the conservative direction, though 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 confidence interval 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 incremental cost-effectiveness ratio 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 generaliseability 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	No

given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	

Koperna et al[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 a randomised controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?	Not trial data as such – data came from 2 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
3.3 Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	Some survival estimates were based on trials in advanced colorectal cancer, meaning that survival estimates are likely to have been underestimated.
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 Stage 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-utility analysis was not performed. Cost-effectiveness results of the different interventions are presented as costs per

cost-effectiveness, cost-benefit, cost-utility been selected)?	life-year gained.
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? 7.2 Was any justification given for the discount rate used?	Yes – costs and effects were discounted at 6% per annum. 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? 9.2 If sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)? 9.3 Were study results sensitive to changes in the values (within the assumed	No stochastic analyses were performed. Costs were altered by using different assumptions regarding treatment administration. An alternative discount rate of 5% was used though not justified, and sensitivity analysis was also performed by altering the survival benefit associated with 5-FU. The results were sensitive to changes to the drug administration regimen, though

range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?	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 generaliseability 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[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 a randomised controlled clinical trial? 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 DFS and OS.
4. Were all the important and relevant costs and consequences for each alternative identified?	
4.1 Was the range wide enough for the	Yes

research question at hand? 4.2 Did it cover all relevant viewpoints? 4.3 Were capital costs, as well as operating costs, included?	 Yes 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? 5.2 Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	 No No
6. Were costs and consequences valued credibly? 6.1 Were the sources of all values clearly identified? 6.2 Were market values employed for changes involving resources gained or depleted? 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? 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)?	 No – though the analysis is only presented in abstract form. No No Cost per life-year gained 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 confidence interval around the ratio of costs to consequences)?	A confidence interval 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	Yes

costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?	
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 generaliseability 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 a randomised controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?	Data from the X-ACT trial was 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 lognormal 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 jusgement 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.	Yes –cost-utility analysis performed

has the appropriate type of analysis – cost-effectiveness, cost-benefit, cost-utility been selected)?	
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? 7.2 Was any justification given for the discount rate used?	 Yes – costs and health outcomes were discounted at 6% and 1.5% respectively. 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? 9.2 If sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)? 9.3 Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?	 Stochastic analyses were not undertaken. Yes 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 generaliseability 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 anlaysis was performed.

Sanofi-Aventis Submission to NICE[143]

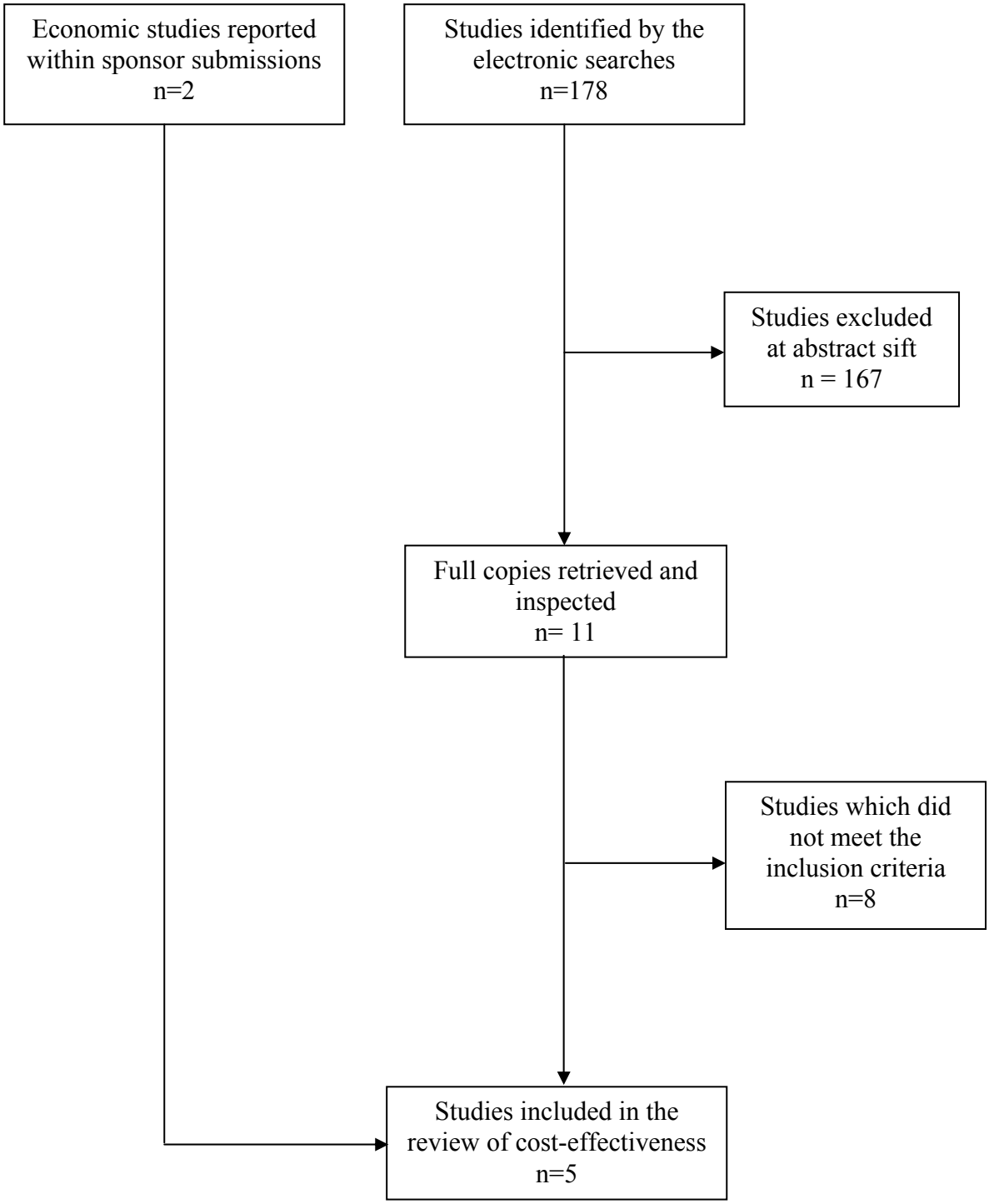
1. Was a well-defined question posed in answerable form?	
1.1 Did the study examine both costs and effects of the service(s) or programme(s)?	Yes
1.2 Did the study involve a comparison of alternatives?	Yes
1.3 Was a viewpoint for the analysis stated and was the study placed in any particular context?	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 a randomised controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?	Yes – data from the MOSAIC trial was 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-	Yes – cost-utility analysis was undertaken.

utility been selected)?	
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? 7.2 Was any justification given for the discount rate used?	Yes – costs and heatlh outcomes were discounted at 3.5% per annum. 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? 9.2 If sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)? 9.3 Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?	Yes – bootstrapping of patient-level data was used to generate stochastic results. Yes – details of the justification for parameter changes in the sensitivity analyses are given. The cost per QALY of FOLFOX4 compared with 5-FU/LV only increased significantly 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 generaliseability 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 clinical 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[174]	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 clinical effectiveness of oxaliplatin and capecitabine presented in earlier section of this report
Previous economic analyses of chemotherapy (ref Paul and Silvia's models)	Assessment of irinotecan (etc.) undertaken by ScHARR to inform an earlier NICE appraisal. (i.e. evidence known to the authors of the current model.)
Sponsor submissions to NICE	Economic analyses critiqued in section 4.1.6
Studies identified through the review of cost-effectiveness	Inclusion criteria used in the review of cost-effectiveness were expanded and re-applied to 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.[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.[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.[160]
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[161]
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.[162]
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[163]
Use(s) in model	As a comparison for the estimate of long term survival
Identification process	Existing economic analyses[8]

Source	FOCUS trial[158] 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]

Source	GERCOR trial[159]
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[165]
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[157]
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[166]
Use(s) in model	Uplift cost estimates to current prices
Identification process	Reference source

Source	British National Formulary[40]
Use(s) in model	Drug acquisition costs
Identification process	Reference source

Source	Boland et al[167]
Use(s) in model	Cost of line insertion
Identification process	Exsting economic analyses[8]

Source	NHS Reference Costs[153]
Use(s) in model	Drug administration costs
Identification process	Reference source

Source	Netten and Dennet(1999)[168]
Use(s) in model	Cost of inpatient appointment
Identification process	Reference source

Source	Renehan[169]
Use(s) in model	Costs of diagnostic monitoring tests
Identification process	Searches undertaken to inform model

Source	FACS trial protocol[170]
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[171]
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[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[173]
Use(s) in model	Summary of utility estimates for colorectal cancer
Identification process	Searches undertaken to inform model

Source	Norum[174]
Use(s) in model	Summary of utility estimates for colorectal cancer
Identification process	Searches undertaken to inform model

Source	Ness[175]
Use(s) in model	Utility estimate Summary of utility estimates for colorectal cancer
Identification process	Searches undertaken to inform model

Source	Ramsey[176]
Use(s) in model	Summary of utility estimates for colorectal cancer
Identification process	Searches undertaken to inform model

Source	Petrou and Campbell[177]
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 quality of life**
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 reource 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 than5 years)
Purpose	To identify longterm 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 life-year gained is unclear, and has therefore not been included in the primary analysis. Table 7 shows the regression output for the derivation of the Weibull parameters for the Mayo 5-FU/LV regimen.

Table 7: Results from Weibull regression analysis of Mayo 5-FU/LV regimen

Multiple R	0.976190883
R Square	0.952948639
Adjusted R Square	0.952482784
Standard Error	0.129602026
Observations	103
Weibull gamma	0.172895174
Weibull lambda	0.965517196

The resulting fitted Weibull survival function (for disease-free survival) is shown in Figure 1 The published hazard ratio was then applied to this curve to obtain the fitted Weibull survival function for the capecitabine arm (see Figure 2)

Figure 1: Fitted disease-free survival curves for Mayo 5-FU/LV regimen

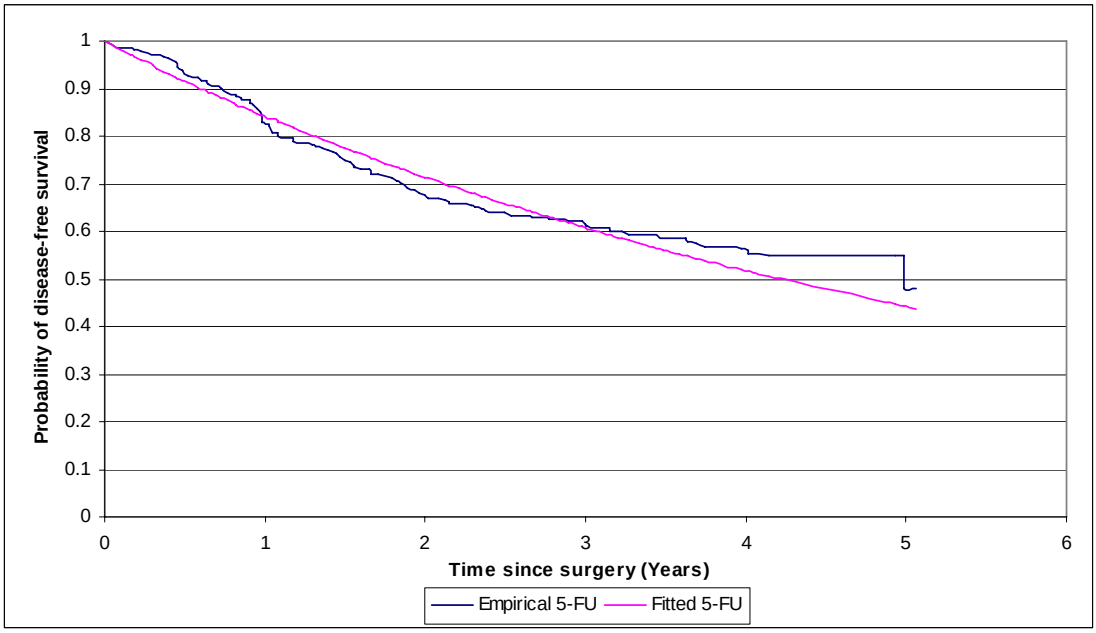


Figure 2: Fitted disease-free survival curves for capecitabine regimen

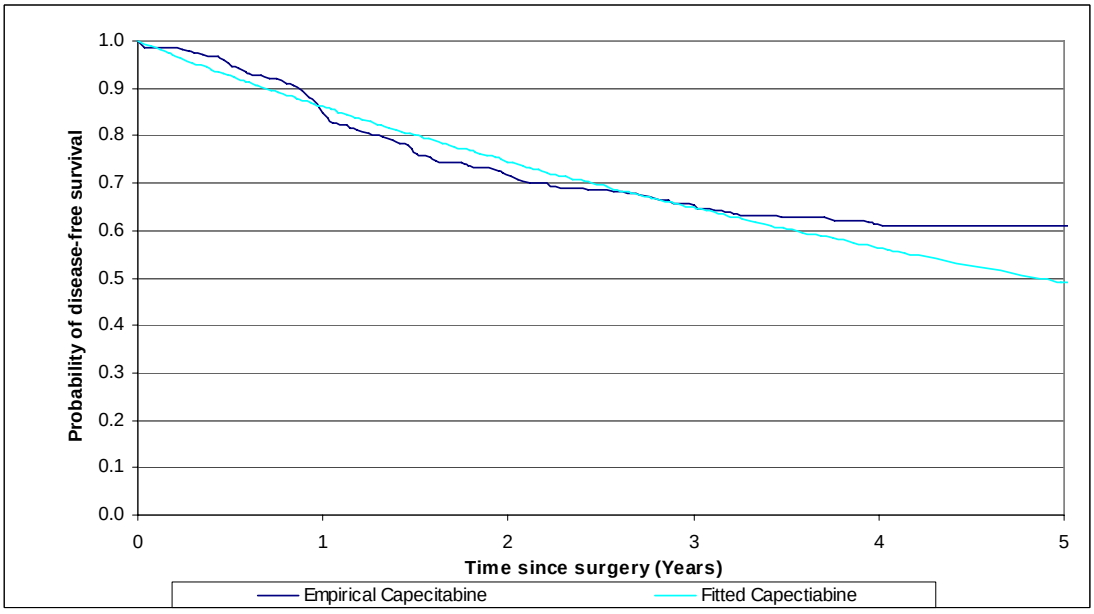


Table 8 shows the regression output for the derivation of the Weibull parameters for the de Gramont 5-FU/LV regimen.

Table 8: Results from Weibull regression analysis of de Gramont 5-FU/LV regimen

Multiple R	0.981260725
R Square	0.96287261
Adjusted R Square	0.962485866
Standard Error	0.185219897
Observations	98
Weibull gamma	0.014184849
Weibull lambda	0.94726062

The resulting fitted Weibull survival function (for disease-free survival) is shown in Figure 3. The published hazard ratio was then applied to this to obtain the fitted Weibull survival function for the FOLFOX4 arm (see Figure 4)

Figure 3: Fitted disease-free survival curves for de Gramont 5-FU/LV regimen

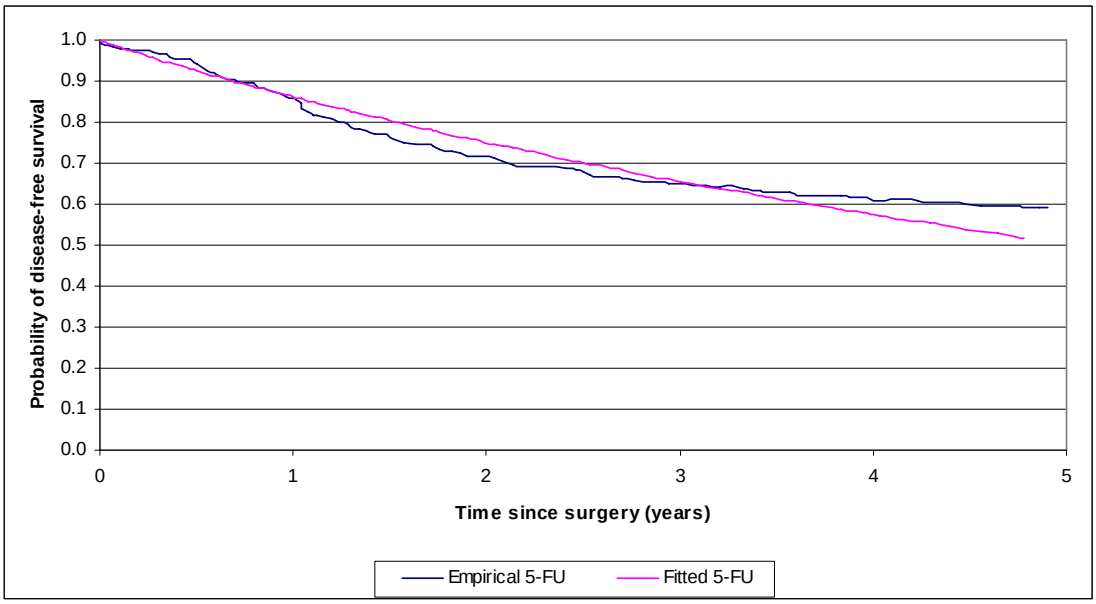
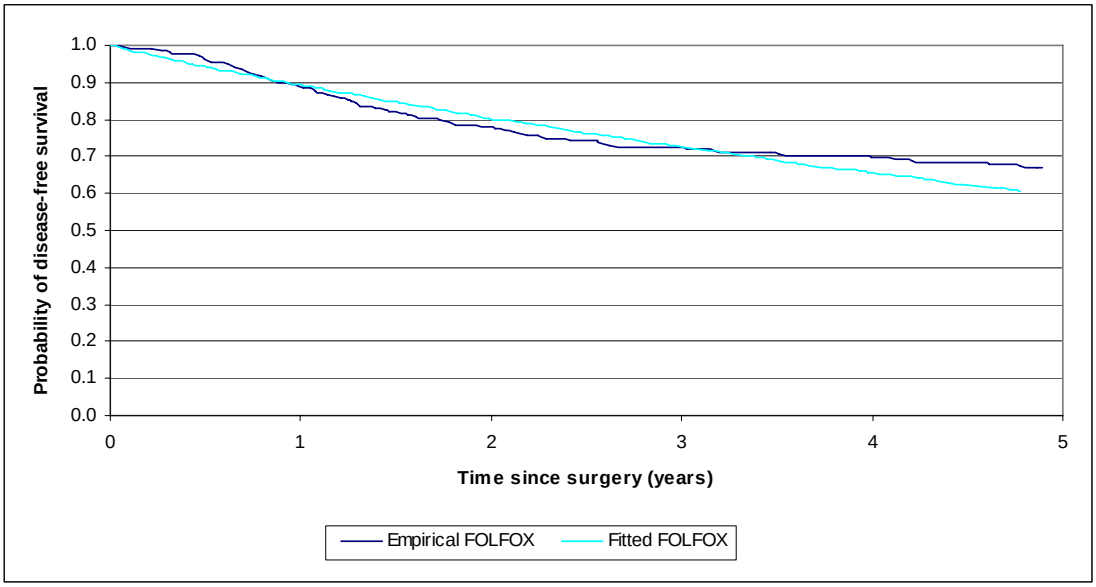


Figure 4: Fitted disease-free survival curves for FOLFOX4 regimen



Appendix 15 Fitted Weibull functions for patients with relapse

Figures 5 to 9 show the empirical and fitted overall survival curves for patients following relapse, based on five different palliative chemotherapy regimens.

Figure 5: Empirical versus fitted survival for FOCUS Plan A (first-line 5-FU/LV, second-line irinotecan)

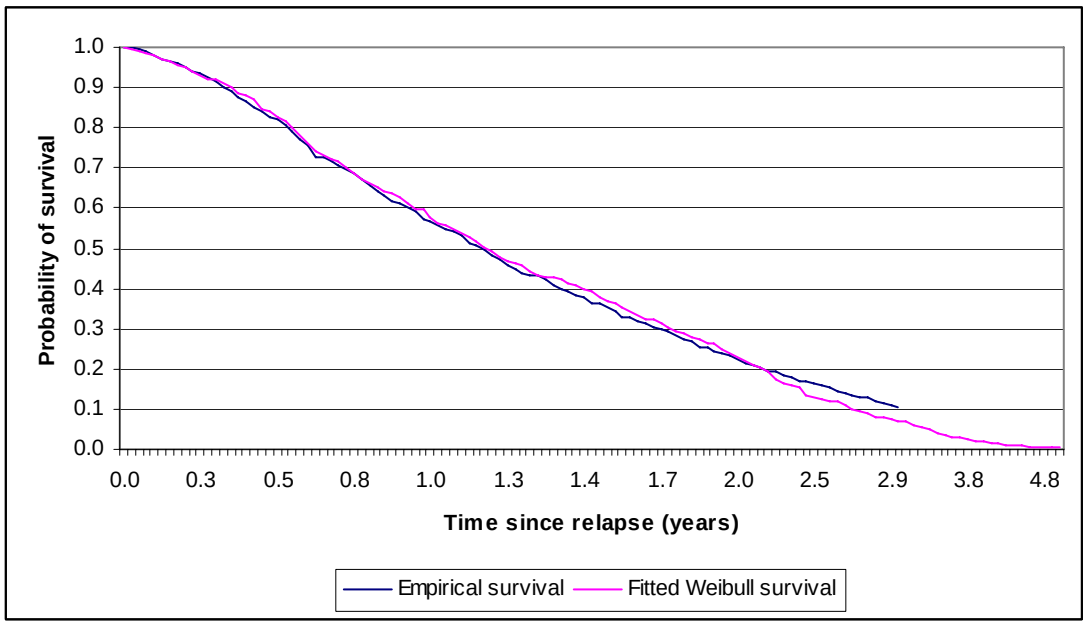


Figure 6: Empirical versus fitted survival for FOCUS Plan B (first-line 5-FU/LV, second-line irinotecan in combination with 5-FU/LV)

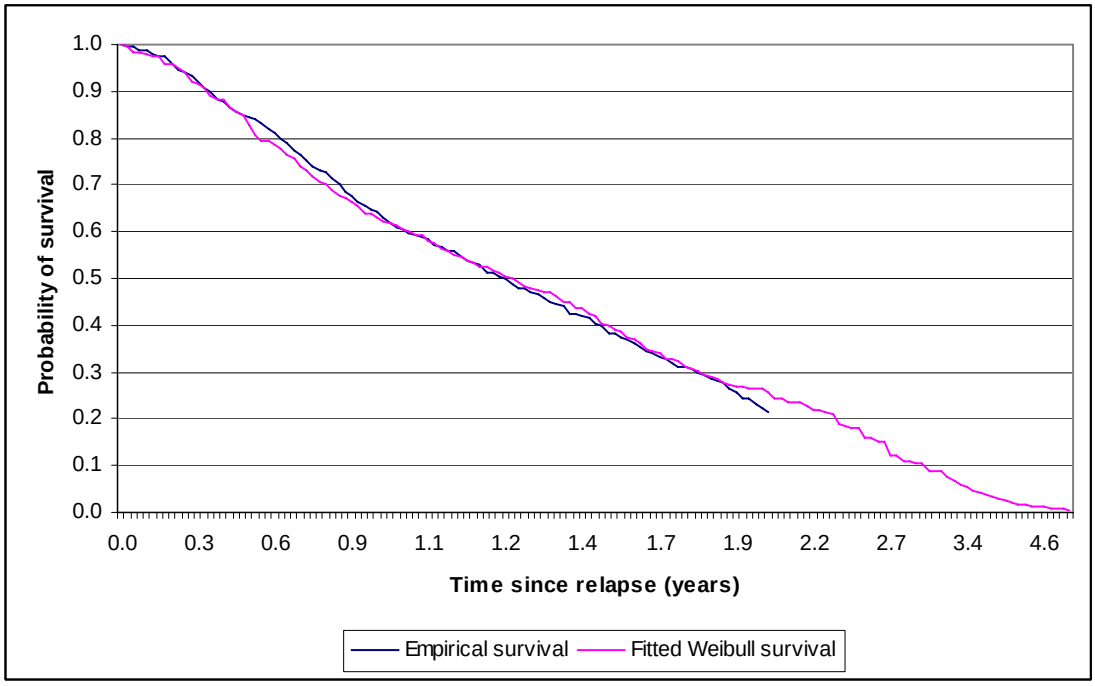


Figure 7: Empirical versus fitted survival for FOCUS Plan D (first-line irinotecan in combination with 5-FU/LV)

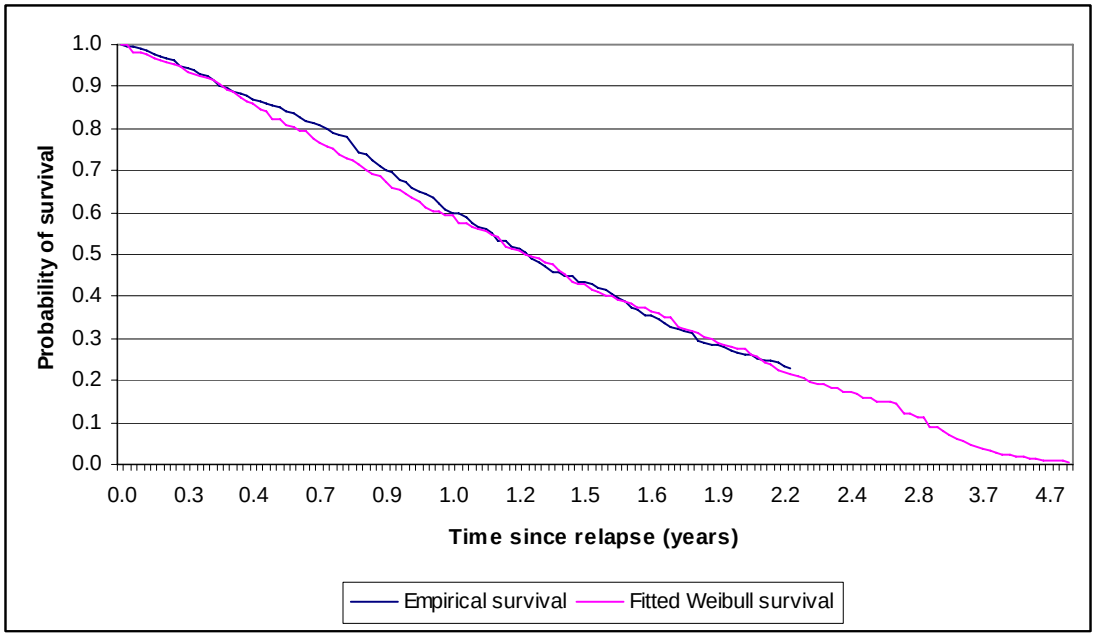


Figure 8: Empirical versus fitted survival for GERCOR arm 1 (first-line FOLFOX, second-line FOLFIRI)

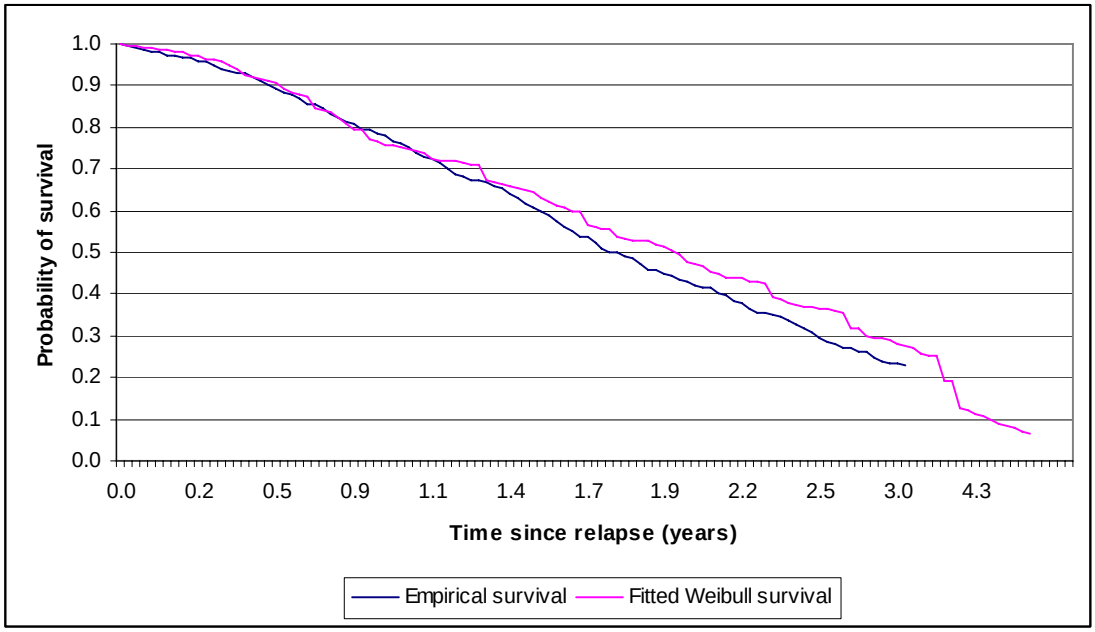
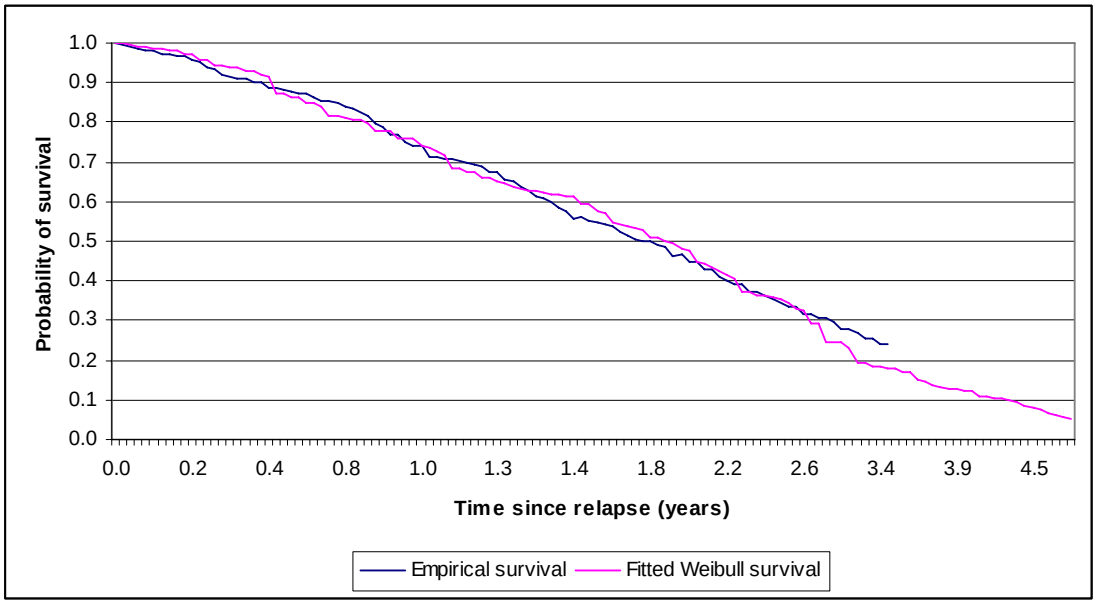


Figure 9: Empirical versus fitted survival for GERCOR arm 2 (first-line FOLFIRI, second-line FOLFOX)



Appendix 16 Fitted overall survival curves

Figures 10 and 11 show the long-term overall survival extrapolations up to 50 years, along with the available empirical Kaplan-Meier estimates up to 5 years.

Figure 10: Empirical and fitted overall survival for 5-FU/LV (Mayo) and capecitabine arms

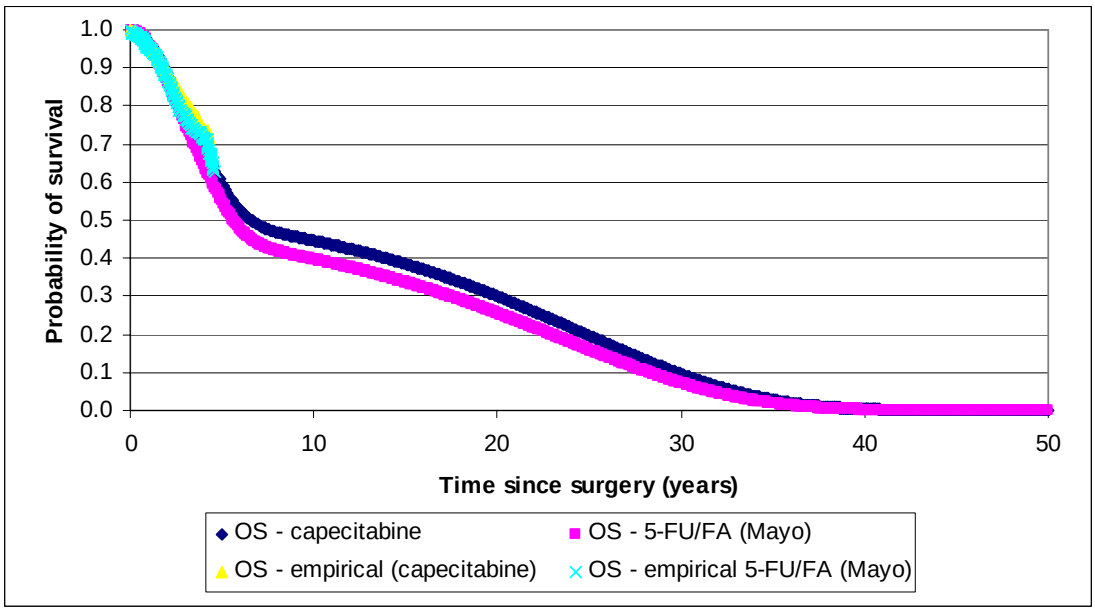
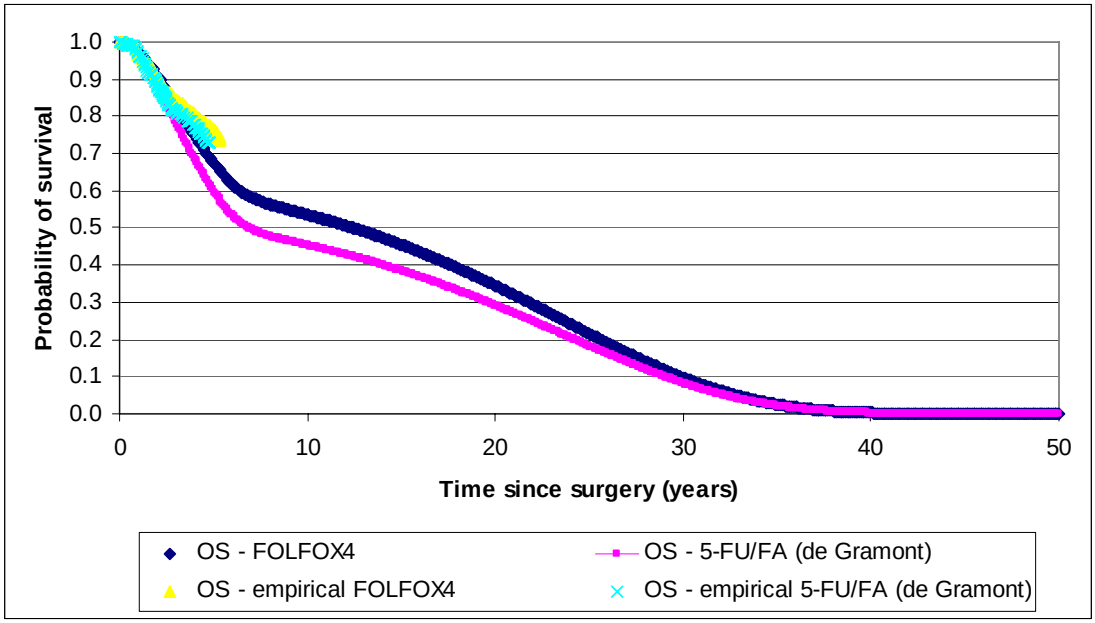


Figure 11: Fitted overall survival for de Gramont 5-FU/LV and FOLFOX4 arms



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 five 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.

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 plus or minus cetuximab
AIO = German high-dose infusional regimen.		

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