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Abstract

The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation

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Objectives: To evaluate three technologies for the management of advanced colorectal cancer: (1) first-line irinotecan combination [with 5-fluorouracil (5-FU)] or second-line monotherapy; (2) first- or second-line oxaliplatin combination (again, with 5-FU); and (3) raltitrexed, where 5-FU is inappropriate. To examine the role of irinotecan and oxaliplatin in reducing the extent of incurable disease before curative surgery (downstaging).

Sources: Ten electronic bibliographic databases covering the period up to August 2004.

Methods: Searches identified existing studies of the effectiveness and economics of the technologies and any studies that evaluated any of the indications outlined above were included. Data were extracted and assessed generic components of methodological quality. Survival outcomes were meta-analysed.

Results: Seventeen trials were found, of varying methodological quality. Compared with 5-FU, first-line irinotecan improved overall survival (OS) by 2–4 months ($p = 0.0007$), progression-free survival (PFS) by 2–3 months ($p < 0.00001$) and response rates ($p < 0.001$). It offered a different toxicity profile and no quality of life (QoL) advantage. However, second-line irinotecan compared with 5-FU improved OS by 2 months ($p = 0.035$) and PFS by 1 month ($p = 0.03$), and provided a better partial response rate, but with more toxicities and no QoL advantage. Compared with second-line best supportive care, irinotecan improved OS by 2 months ($p = 0.0001$), had a different toxicity profile and maintained baseline QoL longer, but with no overall difference. The addition of oxaliplatin to second-line 5-FU is associated with a borderline significant improvement in overall survival ($p < 0.07$); a significantly higher response rate (<0.0001); and more serious toxicities. There is no evidence for a significant difference in QoL. Schedules with treatment breaks may not reduce clinical effectiveness but reduce toxicity. The addition of oxaliplatin to second-line 5-FU also saw no improvement in OS ($p < 0.07$), better PFS (by 2.1 months, $p = 0.0001$), an 8.9% higher response rate ($p < 0.0001$), more toxicities and no QoL advantage. There was no significant difference in OS or PFS between first-line irinotecan and oxaliplatin combinations except when 5-FU was delivered by bolus injection, when oxaliplatin provided better OS ($p = 0.032$) and response rates ($p = 0.032$), but not PFS ($p = 0.169$). The regimens had different toxicity profiles and neither conferred a QoL advantage. When compared to 5-FU, raltitrexed is associated with no significant difference in overall or progression-free survival; no significant difference in response rates; more vomiting and nausea, but less diarrhoea and mucositis; no significant difference in, or worse QoL. Raltitrexed treatment was cut short in two out of four included trials due to excess toxic deaths. 5-FU followed by irinotecan was inferior to any other sequence. First-line irinotecan/5-FU combination improved OS and PFS, although further unplanned therapy exaggerated the OS effect size. Staged combination therapy (combination oxaliplatin followed by combination irinotecan or vice versa) provided the best OS and PFS, although there was no head-to-head comparison against other treatment plans. In the only trial to use three active chemotherapies in any staged combination, median OS was over 20 months. In another study, the longest median OS from a treatment plan using two active agents was 16.2 months. Where irinotecan or oxaliplatin were used with 5-FU to downstage people with unresectable liver metastases, studies consistently showed response rates of around 50%. Resection rates ranged from 9 to 35% with irinotecan and from 7 to 51% with oxaliplatin. In the one study that compared the regimens, oxaliplatin enabled more resections ($p = 0.02$). Five-year OS rates of 5–26% and disease-free survival rates of 3–11% were reported in studies using oxaliplatin. Alone or in combination, 5-FU was more effective and less toxic when delivered by continuous infusion. Existing economic models were weak because of the use of unplanned second-line therapies in their trial data: the survival benefits in patients on such trials cannot be uniquely attributed to the allocated therapy. Consequently, the economic analyses are either limited to the use of PES (at best, a surrogate outcome) or are subject to confounding. Weaknesses in cost components, the absence of direct in-trial utility estimates and the limited use of sensitivity analysis were identified. Improvements to the methodologies used in existing economic studies are presented. Using data from two trials that planned treatment sequences, an independent economic evaluation of six plans compared with first-line 5-FU followed on progression by second-line irinotecan monotherapy (NHS standard treatment) is presented. 5-FU followed on progression by irinotecan combination cost £13,174 per life-year gained (LYG) and £10,338 per quality-adjusted life-year (QALY) gained. Irinotecan combination followed on progression by additional second-line therapies was estimated to cost £12,418 per LYG and £13,630 per QALY gained. 5-FU followed on progression by oxaliplatin combination was estimated to cost £23,786 per LYG and £31,556 per QALY gained. Oxaliplatin combination followed on progression by additional second-line therapies was estimated to cost £43,531 per LYG and £67,662 per QALY gained. Evaluations presented in this paragraph should be interpreted with caution owing to missing information on the costs of salvage therapies in the trial from which data were drawn. Irinotecan combination followed on progression by oxaliplatin combination cost £12,761 per LYG and £16,663 per QALY gained. Oxaliplatin combination followed on progression by irinotecan combination cost £16,776 per LYG and £21,845 per QALY gained. The evaluation suggests that these two sequences have a cost-effectiveness profile that is favourable in comparison to other therapies currently funded by the NHS. However, the differences in OS observed between the two trials from which data were taken may be a result of heterogeneous patient populations, unbalanced protocol-driven intensity biases or other differences between underlying health service delivery systems.

Conclusions: Treatment with three active therapies appears most clinically effective and cost-effective. NHS routine data could be used to validate downstaging findings and a meta-analysis using individual patient-level data is suggested to validate the optimal treatment sequence.

Contents

Glossary and list of abbreviations

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

Glossary

Adenocarcinoma Form of cancer that involves cells from the lining of the walls of many different organs of the body.

Adenomatous polyp Benign neoplasm derived from glandular epithelium.

Adjuvant chemotherapy Chemotherapy treatment that is given as an add-on to primary cancer treatment, as in surgery or radiation therapy.

Adverse effect Abnormal or harmful effect to an organism caused by exposure to a chemical.

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

Anaemia Too few red blood cells in the bloodstream, resulting in insufficient oxygen to tissues and organs.

Asthenia Lack or loss of strength and energy, weakness.

Best supportive care Use of drugs (other than cytotoxic chemotherapy) and other treatments (radiotherapy, palliative surgery, pain relief, antibiotics, corticosteroids, blood transfusion and social/psychological support) to improve the quality of life of patients.

Bolus administration Injection of a drug (or drugs) in a high quantity (called a bolus) at once, the opposite of gradual administration (as in intravenous infusion).

Chronic bowel inflammation Chronic intestinal disease characterised by inflammation of the bowel, the large or small intestine.

Chronomodulated Delivered over 24-hour period in varied quantities to correspond with biological rhythm, to reduce toxicity and increase response rate.

Disease progression Worsening of a disease over time.

Fatigue State, following a period of mental or bodily activity, characterised by a lessened capacity for work and reduced efficiency of accomplishment, usually accompanied by a feeling of weariness, sleepiness or irritability.

Febrile neutropenia Neutrophil count <500 or $1000\ mm^{-3}$ with predicted decline to $500\ mm^{-3}$.

First-line chemotherapy Treatment of patients who have not previously received chemotherapy for advanced disease.

Hand-foot syndrome 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 Passive introduction of a substance (a fluid or drug or electrolyte) into a vein or between tissues (as by gravitational force).

Leucopenia Reduction in the number of leucocytes in the blood, the count being $\leq 5000\ mm^{-3}$.

continued

Glossary *continued*

Metastasis Spread of cancer from one part of the body to another.

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

Neutropenia Leucopenia in which the decrease in white blood cells is chiefly in neutrophils.

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

Platelets Blood cells that help clots to form and thus control bleeding. Also called thrombocytes.

Progression-free survival Length of time from randomisation to either the first evidence of disease progression or death.

Response rate Percentage of patients showing partial or complete response to the given treatment.

Second-line chemotherapy Treatment of patients who have previously received chemotherapy for advanced disease.

Time to progression Measure of time after a disease is diagnosed (or treated) until the disease starts to get worse.

Toxicity The quality of being poisonous, especially the degree of virulence of a toxic microbe or a poison.

List of abbreviations

ACRC	advanced colorectal cancer
AIC	academic in confidence
AIO	Arbeitsgemeinenschaft Internistische Onkologie
AUC	area under the curve
BNF	British National Formulary
BSC	best supportive care
c.i.	continuous infusion
CCTR	Cochrane Central Register of Controlled Trials
CDSR	Cochrane Database of Systemic Reviews
CEA	carcinoembryonic antigen
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CIC	commercial in confidence
CR	complete response
CRC	colorectal cancer
CT	computed tomography
CTU	Clinical Trials Unit
DARE	Database of Abstract of Reviews of Effectiveness
DP	disease progression
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol 5 Dimensions
FA	folinic acid
FOCUS	Fluorouracil, Oxaliplatin, CPT-11 Use and Sequencing
FOLFIRI	irinotecan plus fluorouracil

continued

List of abbreviations *continued*

FOLFOX	oxaliplatin plus fluorouracil
5-FU	5-fluorouracil
GERCOR	Groupe d'Étude et de Recherche en Oncologie–Radiothérapie
HEED	Health Economics Database
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IPD	individual patient data
Ir	irinotecan
ITT	intention-to-treat
LV	leucovorin
LYG	life-year gained
MdG	modified de Gramont
MIMS	Monthly Index of Medical Specialities
MRC	Medical Research Council
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NR	not reported
ns	not significant
OR	odds ratio
OS	overall survival
Ox	oxaliplatin
PFS	progression-free survival
PICC	peripherally inserted central catheter
PR	partial response
PS	performance status
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QLQ	Quality of Life Questionnaire
QoL	quality of life
QUOROM	Quality of Reporting of Meta-analyses
Ral	raltitrexed
RCT	randomised controlled trial
RECIST	Research Evaluation Criteria in Solid Tumours
Rx	regimen
SCI	Science Citation Index
SD	stable disease
TNM	tumour, node, metastases
UFT	uracil–Tegafur
UR	unconfirmed response
WBC	white blood cell

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

Executive summary

Objectives

The objectives of this study were to evaluate three technologies for the management of advanced colorectal cancer: (1) first-line irinotecan combination [with 5-fluorouracil (5-FU)] or second-line monotherapy; (2) first or second-line oxaliplatin combination (again, with 5-FU); and (3) raltitrexed, where 5-FU is inappropriate. The study also examined the role of irinotecan and oxaliplatin in reducing the extent of incurable disease before curative surgery (downstaging).

Methods

Searches in ten electronic bibliographic databases identified existing studies of the effectiveness and economics of the technologies. Studies that evaluated any of the indications outlined above were included. Two reviewers independently extracted data and assessed generic components of methodological quality. Survival outcomes were meta-analysed.

Results

Seventeen trials were found, of varying methodological quality.

Caveat: over half of first-line trial participants across all studies, except for two, were treated with unplanned second-line therapies (a confounding factor); estimates of overall survival (OS) should be read with caution. Trial data are based on atypically young populations, but available evidence suggests no difference in the efficacy or toxicity of combination therapy in older people.

Compared with 5-FU, first-line irinotecan improved OS by 2–4 months ($p = 0.0007$), progression-free survival (PFS) by 2–3 months ($p < 0.00001$) and response rates ($p < 0.001$). It offered a different toxicity profile and no quality of life (QoL) advantage.

Compared with 5-FU, second-line irinotecan improved OS by 2 months ($p = 0.035$) and PFS by 1 month ($p = 0.03$), and provided a better partial response rate, but with more toxicities and no QoL advantage.

Compared with second-line best supportive care, irinotecan improved OS by 2 months ($p = 0.0001$), had a different toxicity profile and maintained baseline quality of life longer, but with no overall difference.

The addition of oxaliplatin to first-line 5-FU was associated with no difference in OS (see caveat), improved PFS ($p < 0.00001$), higher response rates ($p < 0.0001$), more gastrointestinal and haematological toxicities, and no QoL advantage. Schedules with treatment breaks may not reduce clinical effectiveness but reduce toxicity.

The addition of oxaliplatin to second-line 5-FU is associated with a borderline significant improvement in overall survival ($p < 0.07$); a significantly higher response rate (<0.0001); and more serious toxicities. There is no evidence for a significant difference in QoL.

There was no significant difference in OS or PFS between first-line irinotecan and oxaliplatin combinations except when 5-FU was delivered by bolus injection, when oxaliplatin provided better OS ($p = 0.032$) and response rates ($p = 0.032$), but not PFS ($p = 0.169$). The regimens had different toxicity profiles and neither conferred a QoL advantage.

When compared to 5-FU, raltitrexed is associated with no significant difference in overall or progression-free survival; no significant difference in response rates; more vomiting and nausea, but less diarrhoea and mucositis; no significant difference in, or worse QoL. Raltitrexed treatment was cut short in two out of four included trials due to excess toxic deaths.

5-FU followed by irinotecan was inferior to any other sequence. First-line irinotecan/5-FU combination improved OS and PFS, although further unplanned therapy exaggerated the OS effect size. Staged combination therapy (combination oxaliplatin followed by combination

irinotecan or vice versa) provided the best OS and PFS, although there was no head-to-head comparison against other treatment plans. In the only trial to use three active chemotherapies in any staged combination, median OS was over 20 months. In another study, the longest median OS from a treatment plan using two active agents was 16.2 months.

Where irinotecan or oxaliplatin were used with 5-FU to downstage people with unresectable liver metastases, studies consistently showed response rates of around 50%. Resection rates ranged from 9 to 35% with irinotecan and from 7 to 51% with oxaliplatin. In the one study that compared the regimens, oxaliplatin enabled more resections ($p = 0.02$). Five-year OS rates of 5–26% and disease-free survival rates of 3–11% were reported in studies using oxaliplatin.

Alone or in combination, 5-FU was more effective and less toxic when delivered by continuous infusion.

Existing economic models were weak because of the use of unplanned second-line therapies in their trial data: the survival benefits in patients on such trials cannot be uniquely attributed to the allocated therapy. Consequently, the economic analyses are either limited to the use of PES (at best, a surrogate outcome) or are subject to confounding. Weaknesses in cost components, the absence of direct in-trial utility estimates and the limited use of sensitivity analysis were identified.

Improvements to the methodologies used in existing economic studies are presented. Using data from two trials that planned treatment sequences, an independent economic evaluation of six plans compared with first-line 5-FU followed on progression by second-line irinotecan monotherapy (NHS standard treatment) is presented.

5-FU followed on progression by irinotecan combination cost £13,174 per life-year gained (LYG) and £10,338 per quality-adjusted life-year (QALY) gained. Irinotecan combination followed on progression by additional second-line therapies was estimated to cost £12,418 per LYG and £13,630 per QALY gained. 5-FU followed on progression by oxaliplatin combination was estimated to cost £23,786 per LYG and £31,556 per QALY gained. Oxaliplatin combination followed on progression by additional second-line therapies was estimated to cost £43,531 per LYG and £67,662 per QALY gained. Evaluations presented in this paragraph should be interpreted with caution owing to missing information on the costs of salvage therapies in the trial from which data were drawn.

Irinotecan combination followed on progression by oxaliplatin combination cost £12,761 per LYG and £16,663 per QALY gained. Oxaliplatin combination followed on progression by irinotecan combination cost £16,776 per LYG and £21,845 per QALY gained. The evaluation suggests that these two sequences have a cost-effectiveness profile that is favourable in comparison to other therapies currently funded by the NHS. However, the differences in OS observed between the two trials from which data were taken may be a result of heterogeneous patient populations, unbalanced protocol-driven intensity biases or other differences between underlying health service delivery systems.

Conclusion

Treatment with three active therapies appears most clinically effective and cost-effective.

Recommendations for research

The collection of routine data from within the NHS would help to validate the downstaging of people with liver metastasis. A meta-analysis using individual patient-level data is also suggested to validate the optimal treatment sequence and to provide a baseline against which future treatment sequences could be compared.

Chapter 1

Aim of the review

This review addresses the following question: "are irinotecan, oxaliplatin and raltitrexed clinically and cost-effective in the management of advanced colorectal cancer (ACRC)?"

It updates a previous systematic review and economic evaluation,[1] on which current National Institute for Health and Clinical Excellence (NICE) guidance to the NHS is based.[2]

At the time of writing, NICE recommends 5-fluorouracil (5-FU) as first-line treatment for ACRC. When disease progresses, NICE currently recommends second-line irinotecan monotherapy. Oxaliplatin in combination with 5-Fu is recommended as first-line therapy in patients with metastases confined solely to the liver.

This report reassesses the evidence for existing recommendations and for the following indications not currently recommended by NICE:

- irinotecan as first-line therapy in combination with 5-FU either for the management of ACRC, or for the downstaging of those with unresectable liver metastases to enable a subsequent curative approach to treatment
- oxaliplatin as first-line therapy in combination with 5-FU for all patients
- oxaliplatin as second-line therapy in combination with 5-FU
- raltitrexed where 5-FU is not tolerated or inappropriate.

Irinotecan as second-line therapy in combination with 5-FU is not part of the review as it is not a licensed indication, although it is considered as an element of planned treatment strategies.

Chapter 2

Background

Description of the underlying health problem

Epidemiology

Colorectal cancer is the third most common cancer in the UK, with almost 30,000 new cases registered in England and Wales in 2001, representing over 12% of all new cancer cases (*Table 1*). In 2000, the age-standardised rates for England and Wales were 44.3 and 48.3 per 100,000, respectively.[3]

The incidence of colorectal cancer is gradually increasing; as with most forms of cancer, the probability of developing colorectal cancer rises sharply with age and the UK population is ageing. In young people the risk is very low, but between the ages of 45 and 55 years, the incidence is about 25 per 100,000. Among those aged over 75 the rate is over 300 per 100,000 per year. The median age of patients at diagnosis is over 70 years.[6] A gradual increase in age-specific incidence, particularly among men between 65 and 84, which varies from region to region suggests that lifestyle or environmental factors also contribute to the increasing incidence.

Aetiology

Genetics,[7] experimental[8] and epidemiological[9] studies suggest that colorectal cancer results from complex interactions between inherited susceptibility and environmental factors. A diet that is high in red meat and fat and low in vegetables, folate and fibre may increase the risk of colorectal cancer.[10] Other risk factors associated with colon cancer are lack of physical activity and family history of the disease. There is some evidence that colon cancer in women may be related to sex hormones or reproductive history.[6] The risk of developing colorectal cancer is also raised for patients with a personal history of chronic bowel inflammation or one or more adenomatous polyps, as occurs in familial adenomatous polyposis and other hereditary conditions.[11]

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 liver and the lung are common metastatic sites of colorectal cancer.

A pathology report, made on the basis of tissue taken from a biopsy or surgery, will describe the cell type and grade. The most common colon cancer cell type is adenocarcinoma, which accounts for 95% of cases. Staging information is discussed in the next section.

Prognosis

Prognosis for patients depends on the spread of the cancer at diagnosis. Historically, spread has been given in terms of modified Dukes' stage, but this is being superseded by the more precise tumour, node, metastases (TNM) classification system (*Table 2*).[12]

Large differences in survival exist according to the stage of disease.[14] The overall 5-year survival rate in England is 35%; however, within Britain there is evidence of wide variations in treatment and

TABLE 1 *Colorectal cancer: incidence (2001)*

	Age (years)				
	0–44	**45–64**	**65–74**	**75+**	**All cases**
England	662	6,447	8,128	12,292	27,529
Wales	45	451	603	844	1943
England and Wales	707	6,898	8,731	13,136	29,472

Sources: Office for National Statistics;[4] Welsh Cancer Intelligence and Surveillance Unit.[5]

TABLE 2 Staging of colorectal cancer, with 5-year survival[13]

TNM status	Stage	Modified Dukes'	5-year overall survival
T *in situ* N0 M0	0	–	Likely to be normal
T1 N0 M0	I	A	75%
T2 N0 M0	I	B1	57%
T3 N0 M0	II	B2	
T4 N0 M0	II	B3	
T2 N1 M0/T2 N2 M0	III	C1	35%
T3 N1 M0/T3 N2 M0	III	C2	
T4 N1 M0	III	C3	
Any T any N M1	IV	D	12%

TABLE 3 Colorectal cancer: mortality

Mortality (2002)[3]		England	Wales
Numbers	Males	7,057	470
	Females	6,330	402
	Total	13,387	872
Age-standardised rates	Males	24	25.5
	Females	14.7	14.6
	Total	18.8	19.5

Directly age-standardised (European) rate per 100,000 population at risk.

outcomes.[15] *Table 2* shows the modified Dukes' staging of colorectal cancer with 5-year survival. On average patients survive for 3 years after diagnosis.[16] Median survival after diagnosis of metastatic disease is approximately 6–9 months. The 5-year survival rate for ACRC is lower than 5%.

Patients may develop a variety of symptoms during this time, both physical and psychological, which may detract from their quality of life and often require hospital admission.[17] ACRC is either metastatic or so locally advanced that surgical resection is unlikely to be carried out with curative intent. Of these, around 50% will have liver metastases.[18] Approximately 55% of patients in England and Wales present with ACRC (stage III or IV; Dukes' C or D),[15] so even where surgical removal of the primary tumour is an option, accurate staging is essential for appropriate choice of treatment.

About 80% of patients diagnosed with colorectal cancer undergo surgery.[15] Many have potentially good survival outcomes following surgery (with adjuvant chemotherapy in some cases), but over 50% of those who have undergone surgery with apparently complete excision will eventually develop advanced disease and distant metastases (typically presenting within 2 years of initial diagnosis).

The most frequent site of metastatic disease is the liver. In as many as 50% of patients with advanced disease, the liver may be the only site of spread, and for these patients surgery provides the only chance of a cure. Reported 5-year survival rates for resection of liver metastases range from 16 to 48%, considerably better than those for systemic chemotherapy; however, reported operative mortality rates range from 0 to 14%, and postoperative complications are common and often serious.[16]

Significance in terms of ill-health

Colorectal cancer is a significant cause of premature death (*Table 3*), with almost half of related deaths occurring in the under-75 age group.[19] It is also a significant cause of morbidity. When treating patients with metastatic colorectal cancer, the main aims of treatment are to relieve symptoms, increase survival and improve quality of life (QoL). Individual patient preferences for treatment are also important to consider.

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

TABLE 4 *Comparison of key 5-FU regimens*

Regimens	Description
Bolus schedules	
Mayo Clinic[22]	Monthly for 5 days with low-dose FA (5-FU 425 mg m^{-2}; FA 20 mg m^{-2})
Machover[23]	Monthly for 5 days with high-dose FA (5-FU 400 mg m^{-2}; FA 200 mg m^{-2} over 2 h by infusion)
Roswell Park[24]	Weekly (5-FU 500 mg m^{-2}; FA 500 mg m^{-2} over 2 h by infusion)
Infusional schedules	
Lokich[25]	Protracted infusion (5-FU 300 mg m^{-2})
de Gramont[26]	48-h both bolus and continuous infusion bimonthly (5-FU 400 mg m^{-2} bolus, 600 mg m^{-2} c.i. over 22 h, FA 200 mg m^{-2} over a 2-h infusion day 1 and 2 before 5-FU)
Modified de Gramont[27] (MdG)	48-h both bolus and continuous infusion bimonthly (5-FU 400 mg m^{-2} bolus, 2800 mg m^{-2} c.i. over 46 h; FA 175 mg m^{-2} over a 2-h infusion day 1 before 5-FU)
Grupo Espanol para el Tratamiento de Tumores Digestivos (TTD)[28]	48-h infusion weekly (5-FU 3000 mg m^{-2})
Arbeitsgemeinschaft Internistische Onkologie (AIO)[29]	24-h infusion weekly (5-FU 2600 mg m^{-2}; FA 500 mg m^{-2})
Chronomodulated delivery[30]	5-FU 700 mg m^{-2}; FA 300 mg m^{-2} per day, peak delivery rate at 04.00 h for 5 days

c.i., continuous infusion.

Current service provision

In 2000, the NHS Executive document '*Improving outcomes in colorectal cancer*' summarised contemporary service provision for diagnosis, treatment and follow-up of patients with ACRC.[16] The only potential for long-term survival from metastatic disease came from resection of liver metastases in cases where there was no evidence of extrahepatic disease and the position and size of the metastases was favourable. Some patients have also survived after resection of lung metastases, but such cases are rare.

In 2002[2] and 2003,[20] NICE issued guidance on therapies for the management of advanced colorectal cancer. Technologies from four pharmaceutical classes are currently licensed for the management of ACRC in the UK: fluoropyrimidines (5-Fu), topoisomerase I inhibitors (irinotecan), platinum compounds (oxaliplatin) and thymidylate synthase inhibitors (raltitrexed). These technologies are introduced in this section.

Fluoropyrimidines (5-FU)

5-FU was synthesised in the late 1950s and for many years delivered in various bolus schedules. In the 1980s many studies demonstrated superior response rates for 5-FU with folinic acid (FA) compared to 5-FU alone, although most of these trials were not designed and powered to identify a difference in overall survival.[21] By the early 1990s, portable pump technology became universally accessible, allowing the administration of 5-FU as an intravenous (i.v.) infusion over prolonged periods. The most commonly-used bolus and infusional 5-FU regimens are detailed in *Table 4*. Two oral fluoropyrimidines, capecitabine (Xeloda®, Roche) and tegafur-uracil-Ftorafur (UFT)-LV (also known as Tegafur-Uracil, Uftoral®, Bristol-Myers Squibb), have recently become available. The clinical effectiveness of different delivery modalities is examined in the section 'Fluorouracil-containing treatment: differential effects' (p. 57).

5-FU is licensed for use in monotherapy or combination therapy in the first- or second-line management of ACRC. The existing NICE guidance recommends that patients with metastatic disease who are sufficiently fit are treated with either intravenous[2] or oral[20] 5-FU alone in first-line therapy (note: at the time of writing, capecitabine and UFT-LV are not licensed for combination therapy). Those with a performance status greater than 2 would usually be deemed unsuitable for chemotherapy, instead of which they would receive best supportive care (BSC).[31]

5-FU does not have a cumulative dose limit, and in some countries it is standard practice to continue treatment until disease progression.[17] About 60% of patients with advanced colorectal cancer have either a response or a period of stable disease with first-line 5-FU-based therapy, but in all cases this is temporary as they develop resistance to the drug. The remaining 40% have disease which is refractory to 5-FU. Both groups have a very poor prognosis. Second-line therapy is considered both for those patients who do not respond to first-line 5-FU-based therapy (primary non-responders) and for those who initially responded to such therapy when the disease eventually but inevitably progresses. In some cases, those who are disease resistant to bolus 5-FU will respond to infusional 5-FU, and this has led to the use of infusional 5-FU regimens as second-line therapy, but response rates are usually low.[32] In most studies, median overall survival for people with ACRC treated with 5-FU is consistently between 10 and 12 months.[33]

Irinotecan (Pfizer Ltd)

Irinotecan hydrochloride (CPT-11, Campto®) inhibits topoisomerase I, an enzyme that is essential for cell division, and thus kills cancer cells. The UK licence for irinotecan is held by Pfizer Ltd. It is marketed as Campto, in 20 mg/2 ml and 100 mg/5 ml concentrate for solution for intravenous infusion. It is currently indicated for "the treatment of patients with advanced colorectal cancer: in combination with 5-fluorouracil and folinic acid in patients without prior chemotherapy for advanced disease; as a single agent in patients who have failed an established 5-fluorouracil containing treatment regimen."[34]

The previous guidance issued by NICE in March 2002 recommended irinotecan monotherapy for patients who had failed to respond to an established fluorouracil-containing treatment. A combination of fluorouracil and folinic acid with either irinotecan or oxaliplatin was not recommended for routine first-line treatment of ACRC.[2]

British National Formulary (BNF)[35] general guidance on use of cytotoxic drugs can be found in Appendix 1. Clinicians are cautioned that irinotecan hydrochloride may result in a raised plasma bilirubin concentration. Those receiving irinotecan should be monitored closely for neutropenia if their plasma bilirubin concentration is up to 1.5 times the upper limit of the normal range. Irinotecan is contraindicated in those with chronic inflammatory bowel disease, bowel obstruction, or a plasma bilirubin concentration more than 1.5 times the upper limit of reference range. It is also contraindicated in pregnant women. Women should avoid conception for at least 3 months after cessation of treatment and breast-feeding should be discontinued. In addition to dose-limiting myelosuppression, side-effects of irinotecan include acute cholinergic syndrome (with early diarrhoea), gastrointestinal effects (delayed diarrhoea requiring prompt treatment may follow irinotecan treatment), asthenia, alopecia and anorexia.[35]

The recommended dose in first-line combination therapy is 180 mg m^{-2} administered as an intravenous infusion every 2 weeks over 30–90 minutes, followed by 5-FU infusion, and in second-line monotherapy is 350 mg m^{-2} as an intravenous infusion over 30–90 minutes every 3 weeks.[36]

Oxaliplatin (Sanofi-Aventis Ltd)

Oxaliplatin (L-OHP, Eloxatin®) is a stable, water-soluble platinum cytotoxic compound. It is licensed in the UK, "in combination with 5-fluorouracil (5-FU) and folinic acid (FA) and is indicated for: adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumor; treatment of metastatic colorectal cancer."[37]

The previous guidance issued by NICE in March 2002 recommended that oxaliplatin, in combination with fluorouracil and folinic acid, should be considered first-line treatment for ACRC only in patients with metastases that are confined to the liver and that could be resected following a response to treatment. A combination of fluorouracil and folinic acid with oxaliplatin was not recommended for routine first-line treatment of ACRC.[2]

BNF general guidance on use of cytotoxic drugs can be found in Appendix 1. Clinicians are cautioned that oxaliplatin can lead to renal failure: the manufacturer recommends avoiding its use if cretanine clearance is less than 30 ml per minute. It is contraindicated in peripheral neuropathy with functional impairment. The manufacturer recommends that oxaliplatin is not used in pregnant women and that breast-feeding be discontinued.

Neurotoxic side-effects (including sensory peripheral neuropathy) are dose limiting. Other side-effects include gastrointestinal disturbances, ototoxicity and myelosuppression. Manufacturers advise renal function monitoring in moderate impairment.

TABLE 5 *Licensed indications*

	First-line monotherapy	First-line combination therapy	Second-line monotherapy	Second-line combination therapy
5-FU i.v.	✓	✓	✓	✓
Oral fluoropyrimidines	✓	✕	✓	✓[b]
Irinotecan	✕	✓	✓	✕
Oxaliplatin	✕	✓	✕	✓[c]
Raltitrexed	✓[a]	✕	✓	✕

[a] When fluorouracil and folinic acid cannot be used.
[b] Capecitabine only.
[c] Indication licensed subsequent to issue of original guidance.

The approved dose is 85 mg m^{-2} every 2 weeks by intravenous infusion over 2–6 hours before the administration of 5-FU.

Raltitrexed (AstraZeneca)

Raltitrexed (ZD 1694, Tomudex) is a thymidylate synthase inhibitor. It is marketed in 2-mg vials. It is licensed in the UK for the palliation of adults with ACRC when fluorouracil and folinic acid cannot be used.[35] It is delivered intravenously.

The previous guidance issued by NICE in March 2002 did not recommend raltitrexed for the treatment of ACRC, but that its use should be confined to clinical studies.[2]

BNF general guidance on use of cytotoxic drugs can be found in Appendix 1. It is contraindicated in pregnant women, women who may become pregnant during treatment and women who are breast-feeding, and patients with severe renal impairment.[36] It is generally well tolerated, but can cause marked myelosuppression and gastrointestinal side-effects.

The approved dose is 3 mg m^{-2} by 15-minute intravenous infusion, repeated every 3 weeks.[36]

Current licensed indications and NICE guidance

In summary, licensed indications are shown in *Table 5*.

The three technologies that are the subject of this report were previously assessed in 2000.[1] In 2002, NICE issued guidance which informs current provision:

> "1.1 On the balance of clinical and cost-effectiveness, neither irinotecan nor oxaliplatin in combination with 5-fluorouracil and folinic acid (5-FU) are recommended for routine first-line therapy for advanced colorectal cancer.
>
> "1.2 Oxaliplatin should be considered for use as first-line therapy, in combination with 5-FU, in advanced colorectal cancer in patients with metastases that are confined solely to the liver and may become resectable ('down staged') following treatment.
>
> "1.3 Irinotecan monotherapy is recommended in patients who have failed an established 5-fluorouracil containing treatment regimen.
>
> "1.4 On the balance of evidence relating to its clinical and cost-effectiveness, raltitrexed is not recommended for the treatment of advanced colorectal cancer. Its use for this patient group should be confined to appropriately designed clinical studies.
>
> "1.5 It is likely that patients currently receiving irinotecan or oxaliplatin in combination with 5-FU or raltitrexed could suffer loss of well being if their treatment is discontinued at a time they did not anticipate. Because of this, patients and their consultants may wish to continue therapy until they consider it is appropriate to stop."[2]

The NICE guidance also made the following recommendations for further research:

> "1.1 It is anticipated that the MRC CR08 (FOCUS) trial, due to report in 2004, will provide further clinical evidence on the clinical and cost-effectiveness of first-line irinotecan and oxaliplatin combination therapies. Clinicians are encouraged to discuss enrolment in this study with their patients.
>
> "1.2 The collection and analysis of clinical and economic data for patients receiving oxaliplatin for the purposes of 'down staging' will help to clarify the cost effectiveness of this approach for future appraisals, and it is strongly urged that these data are collected.

"1.3 Further prospective or retrospective clinical studies are needed that compare raltitrexed with best supportive care or other treatments that do not contain 5-FU/FA.

"1.4 Older patients, who represent the majority of individuals with advanced colorectal cancer, are consistently under-represented in clinical trials, which affect the generalisability of the results. Organisers of these trials are particularly encouraged, therefore, not to exclude these patients from studies on the basis of age alone."

Another technology assessment report evaluated the use of two oral fluoropyrimidines, capecitabine and tegafur with uracil, in ACRC.[19] In 2002, NICE issued guidance which informs current provision:

1.1 Oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) is recommended as an option for the first-line treatment of metastatic colorectal cancer.

1.2 The choice of regimen (intravenous fluorouracil/folinic acid [5-FU] or one of the oral therapies) should be made jointly by the individual and the clinician(s) responsible for treatment. The decision should be made after an informed discussion between the clinician(s) and the patient; this discussion should take into account contraindications and the side-effect profile of the agents as well as the clinical condition and preferences of the individual.

1.3 The use of capecitabine or tegafur with uracil to treat metastatic colorectal cancer should be supervised by oncologists who specialise in colorectal cancer.[20]

Although oral fluoropyrimidines are not currently licensed for use in combination with the technologies reviewed in this report, they have not been excluded a priori from the review.

Current service cost

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.[38] The specific cost to the NHS of chemotherapies for ACRC is unknown and any attempt to model it is dependent on many variables for which no routine data are available: it is uncertain how many people have advanced colorectal cancer, and it is uncertain how much it costs to treat. The algorithm shown in *Figure 1* should be considered illustrative of scale of the service.

Variation in services

Although there has been no systematic survey of modes of delivery for 5-FU, anecdotal evidence suggests considerable variation across the UK based on the facilities available at individual trusts. Although it is not within the scope of this report to assess the clinical effectiveness of these different regimens, evidence reviewed in the section 'Fluorouracil-containing treatment: differential effects' (p. 57) suggests that the mode of delivery has a significant impact on outcomes.

Description of proposed indications

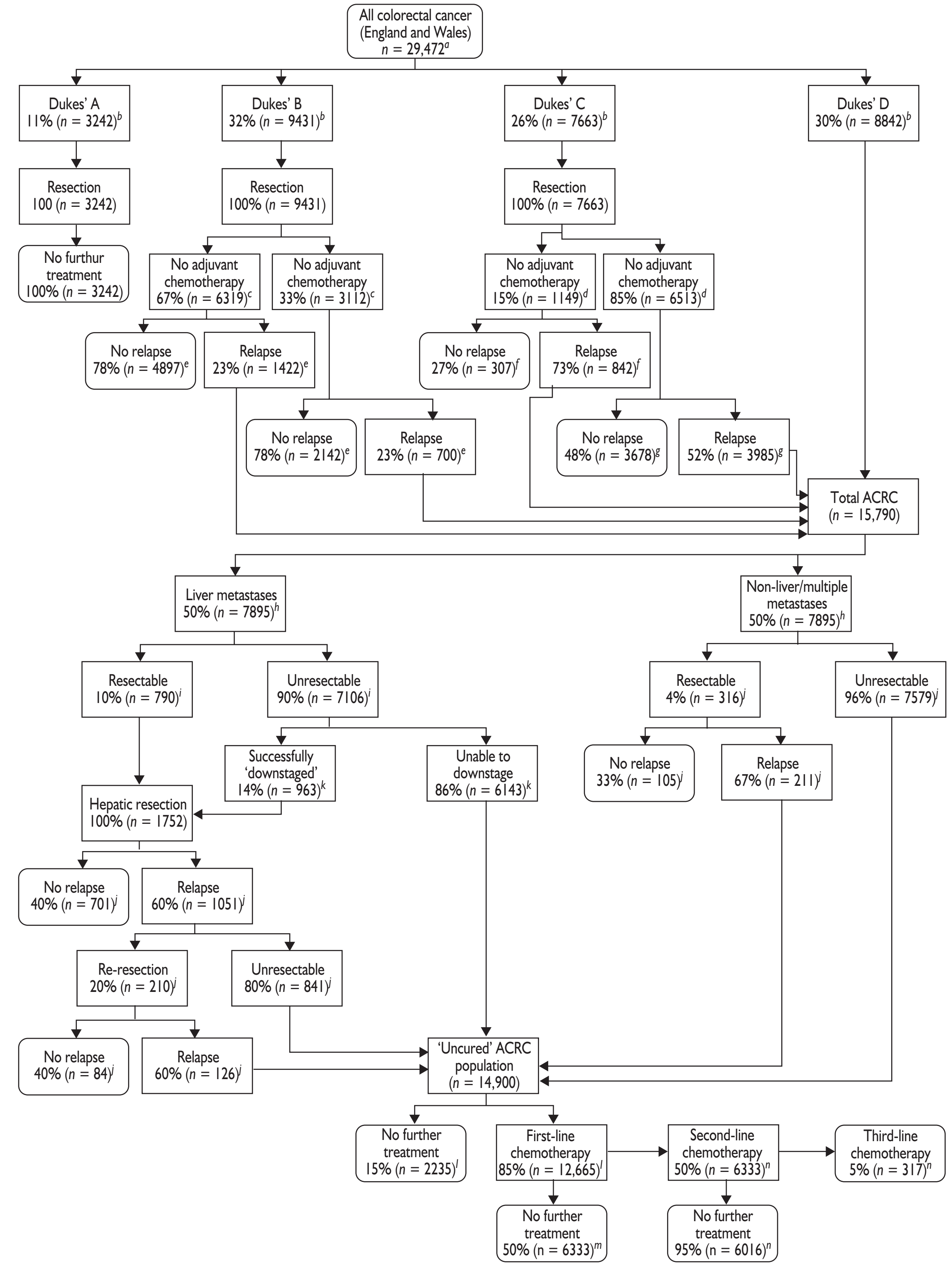
New published evidence for the clinical and cost-effectiveness of the following indications, already recommended by NICE in the 2002 guidance, will be reviewed in Chapter 3:

- irinotecan as second-line monotherapy
- oxaliplatin as first-line therapy in combination with 5-FU in ACRC in patients with metastases confined solely to the liver.

The evidence for the clinical and cost-effectiveness of the following indications, not recommended by NICE in the 2002 guidance, will also be reviewed:

- irinotecan as first-line therapy in combination with 5-FU and in the context of unresectable liver metastases

***FIGURE 1** Treatment algorithm for people with ACRC in England and Wales. (opposite)*
[a] Office for National Statistics,[4] Welsh Cancer Intelligence and Surveillance Unit[5]; [b] South West Cancer Intelligence Service[13]; [c] Seymour M, Leeds Teaching Hospitals NHS Trust: personal communication: between 33 and 60% of people with Dukes' B cancer receive adjuvant chemotherapy (this study assumed the lower estimate); [d] Seymour M: personal communication: more than 85% receive adjuvant chemotherapy; [e] Seymour M: personal communication: 20–25% of patients with Dukes' B will relapse; [f] estimated 40% relative risk increase of relapse for surgery alone versus chemotherapy, from pooled multicentre trial.[39] Relative risk increase applied to 5-year disease-free survival estimates from X-ACT trial[40]; [g] 5-year disease-free survival estimates from X-ACT trial[40]; [h] Maughan T, Velindre Hospital, Cardiff: personal communication; [i] data from case series[41] suggest up to 20% may be resectable, although this is an aggressive stance; a maximum of 15% of patients are suitable; Maughan T: personal communication; [j] Poston G, Royal Liverpool University Hospital: personal communication; [k] data from case series[41]; [l] Seymour M: personal communication: 85–90% of advanced patients receive chemotherapy.[42]; [m] preliminary data from FOCUS trial[42]; [n] Glynne Jones R, Watford and Barnet General Hospitals, London: personal communication: only 3–5% patients would receive third-line therapy.


All colorectal cancer (England and Wales) n = 29,472[a]
Dukes' A 11% (n = 3242)[b]
Dukes' B 32% (n = 9431)[b]
Dukes' C 26% (n = 7663)[b]
Dukes' D 30% (n = 8842)[b]
Resection 100 (n = 3242)
Resection 100% (n = 9431)
Resection 100% (n = 7663)
No furthur treatment 100% (n = 3242)
No adjuvant chemotherapy 67% (n = 6319)[c]
No adjuvant chemotherapy 33% (n = 3112)[c]
No adjuvant chemotherapy 15% (n = 1149)[d]
No adjuvant chemotherapy 85% (n = 6513)[d]
No relapse 78% (n = 4897)[e]
Relapse 23% (n = 1422)[e]
No relapse 27% (n = 307)[f]
Relapse 73% (n = 842)[f]
No relapse 78% (n = 2142)[e]
Relapse 23% (n = 700)[e]
No relapse 48% (n = 3678)[g]
Relapse 52% (n = 3985)[g]
Total ACRC (n = 15,790)
Liver metastases 50% (n = 7895)[h]
Non-liver/multiple metastases 50% (n = 7895)[h]
Resectable 10% (n = 790)[i]
Unresectable 90% (n = 7106)[i]
Resectable 4% (n = 316)[j]
Unresectable 96% (n = 7579)[j]
Successfully 'downstaged' 14% (n = 963)[k]
Unable to downstage 86% (n = 6143)[k]
No relapse 33% (n = 105)[j]
Relapse 67% (n = 211)[j]
Hepatic resection 100% (n = 1752)
No relapse 40% (n = 701)[j]
Relapse 60% (n = 1051)[j]
Re-resection 20% (n = 210)[j]
Unresectable 80% (n = 841)[j]
No relapse 40% (n = 84)[j]
Relapse 60% (n = 126)[j]
'Uncured' ACRC population (n = 14,900)
No further treatment 15% (n = 2235)[l]
First-line chemotherapy 85% (n = 12,665)[l]
Second-line chemotherapy 50% (n = 6333)[n]
Third-line chemotherapy 5% (n = 317)[n]
No further treatment 50% (n = 6333)[m]
No further treatment 95% (n = 6016)[n]

- oxaliplatin as first-line therapy in combination with 5-FU for all patients
- oxaliplatin as second-line therapy in combination with 5-FU
- raltitrexed where 5-FU is not tolerated or inappropriate.

As ACRC will usually be managed with more than two or more successive combination therapies, two recent trials designed to evaluate the relative clinical effectiveness of entire treatment sequences will also be discussed.

While the technologies under review are predominantly for use in disease stabilisation, their use in downstaging individuals with otherwise unresectable liver metastases is also discussed.

Finally, as two of the technologies under review are licensed for use in combination with 5-FU, the relative effectiveness of different 5-FU regimens will also be evaluated.

Chapter 3
Effectiveness

Methods for reviewing effectiveness

This systematic review was carried out according to the recommendations of the Quality of Reporting of Meta-analyses (QUOROM) statement.[43] A checklist can be found in Appendix 2.

Search strategy

The search aimed to identify all literature relating to the clinical and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed (Appendix 3). The main searches were conducted in June, July and August 2004. No language, study/publication or date restrictions were applied to the main searches. Searches were performed in MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CCTR), Database of Abstracts of Reviews of Effectiveness (DARE), Science Citation Index (SCI), Office of Health Economics Health Economics Database (OHE HEED), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment Database (NHS HTA) and CINAHL.

Inclusion and exclusion criteria

Phase III randomised controlled trials (RCTs) were included if they compared any of the proposed indications with existing recommended indications (see the section 'Description of proposed indications', p. 8). Primary outcomes were identified as overall survival (OS) and progression-free survival (PFS). Secondary outcomes were identified as health-related quality of life, response rate and adverse events. Studies were excluded if they did not report either of the primary outcomes. Use of data from Phase II studies and from non-randomised studies was only considered where there was insufficient evidence from good-quality Phase III trials, the former being studies appropriately powered to assess efficacy outcomes, rather than those directly associated with clinical effectiveness, and both being subject to selection bias. Reports of any studies not available in English were excluded as the timescale of the review precluded time for translation.

Trials were included if they recruited participants with ACRC, as defined in the section 'Prognosis' (p. 3).[18]

Only trials that compared 5-FU (with or without folinic acid), irinotecan, oxaliplatin or raltitrexed in licensed combinations were included in this study. Where the extent of the treatment effect was confounded by the presence of active agents from other pharmaceutical classes, the trial was excluded.

Only trials that reported at least one of the primary outcomes, OS and PFS, were included. OS was defined as the interval from randomisation to death from any cause. PFS was defined as the interval from randomisation to first evidence of disease progression or death from any cause. Secondary outcomes, response rates, toxicities and quality of life were recorded where reported. Response rates were defined as the number of patients in each regimen achieving a partial or complete response, however defined. Toxicities and quality of life were abstracted as reported, however defined.

This review also includes all included studies in the original assessment report that meet the current inclusion criteria. A flowchart describing the process of identifying relevant literature can be found in Appendix 4, and a table summarising the reasons for excluding those trials included in the previous review and the industrial submissions can be found in Appendix 5.

Validity assessment

Published papers were assessed according to the accepted hierarchy of evidence, whereby meta-analyses of RCTs are taken to be the most authoritative forms of evidence, with uncontrolled observational studies the least authoritative. Two researchers (DH and IT) assessed papers, unblinded, for four generic dimensions of methodological quality associated with estimates of treatment effects in controlled trials.[44] The purpose of this assessment was to give a narrative assessment of the potential for bias in the studies and, in the event that statistical synthesis (meta-analysis) was appropriate, to inform sensitivity analysis. A table summarising data on validity assessment can be found in Appendix 6.

Data abstraction

All abstracts were read and studies meeting inclusion criteria were identified. Data from identified studies, reviews and other evidence were extracted by two reviewers using a standardised data extraction form.

Analysis

The most complete data set feasible was assembled. Results of eligible studies were statistically synthesised (meta-analysed) if appropriate (there was more than one trial with like populations, interventions and outcomes) and possible (there were adequate data). All analyses were by intention to treat (ITT). For time to event analyses (OS and PFS), combined hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cochrane Collaboration Review Manager 4.2.3 software. This uses the log hazard ratio and its variance from the relevant outcome of each trial. These, in turn, were calculated using an MS Excel spreadsheet authored by Matt Sydes of the Medical Research Council's (MRC's) Clinical Trials Unit, which incorporates Parmar's methods for extracting summary statistics to perform meta-analyses of the published literature for survival end-points.[45]

The log hazard ratio and its variance were estimated by two of Parmar's hierarchy of methods, depending on the availability of summary statistics: method 3, which estimates the variance of the log hazard ratio indirectly from the hazard ratio and its 95% confidence intervals, and method 10, which estimates the log hazard ratio and its variance from survival curves. Where event numbers were not published, the 'effective number of deaths' for each arm, as calculated in the MRC spreadsheet, are reported in the Review Manager forest plots. These figures in no way affect the calculation of the hazard ratio and its variance and should be considered illustrative. *Table 75* in Appendix 7 records the summary statistics used for this purpose.

A fixed effects model was used for the primary analyses. Heterogeneity between trial results was tested where appropriate using two tests: χ^2 and I^2 tests. The χ^2 test measures the amount of variation in a set of trials. Small p-values suggest that there is more heterogeneity present than would be expected by chance. χ^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 that there is no heterogeneity. I^2 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.[46]

It was stated prospectively that subgroup analyses would be performed on the basis of whether 5-FU was delivered by bolus injection or continuous infusion. This is because it is widely believed that there is a systematic difference in treatment effect based on the mode of delivery which is likely to interact in different ways with the new interventions under evaluation.

Results: irinotecan – first-line combination

Quantity and quality of research available

Number of studies identified

The search retrieved 2207 citations.

Number and type of studies included

Seven studies were identified as meeting the inclusion criteria to address two comparisons: (1) irinotecan (Ir) + 5-FU versus 5-FU alone; and (2) Ir + 5-FU versus oxaliplatin (Ox) + 5-FU. One trial addressed both comparisons.[42] Data additional to those in the public domain were submitted to the review team as 'academic in confidence' (AIC) for this trial. All other trial data were derived from sources in the public domain. Study information is reported in *Table 6*.

Four multicentre Phase III RCTs were retrieved that compared first-line Ir + 5-FU with 5-FU alone.[42,47–49] In one case, the 5-FU was delivered by bolus injection.[49] In the remaining three cases, 5-FU was delivered by continuous infusion.[42,47–49]

Four multicentre Phase III RCTs were retrieved that compared first-line Ir + 5-FU with Ox + 5-FU. In one case, the 5-FU was delivered by bolus injection.[50] In two studies, 5-FU was delivered by continuous infusion.[42,51] In the fourth trial, the 5-FU in the Ir arm was delivered by bolus injection and the 5-FU in the Ox arm was delivered by continuous infusion.

Number and type of studies excluded, with reasons for specific exclusions

A flow chart is provided in Appendix 4, as recommended by the QUOROM statement,[43] and reasons for all trial exclusions are given in Appendix 5. Seven clinical trials, included in the original review[1] and industry submissions,[52] were excluded from this review. Six were excluded on

TABLE 6 *First-line Ir: study characteristics*

Study	Participants	Interventions	Outcomes	Comments
Douillard *et al.*, 2000 (France)[47]	Age 18–75 years; histologically proven adenocarcinoma of colon or rectum; WHO PS ⩽2; life expectancy >3 months; no previous chemotherapy (except adjuvant); prior adjuvant chemotherapy completed for ⩾6 months	*Arm 1* (Ir + 5-FU): Ir 80 mg m^{-2} + 5-FU 2300 mg m^{-2} + FA 500 mg m^{-2} weekly (*n* = 54); or Ir 180 mg m^{-2} fortnightly + 5-FU 400 IV/600 C.I. mg m^{-2} days 1 and 2 every 2 weeks (de Gramont) (*n* = 145) *Arm 2* (5-FU): 5-FU 2300 mg m^{-2} weekly, every 7 weeks 500 mg m^{-2} (AIO) (*n* = 43); or 5-FU 400 i.v./600 C.I. mg m^{-2} days 1 and 2 every 2 weeks, 200 mg m^{-2} , days 1 and 2 every 2 weeks (de Gramont) (*n* = 143)	Time to progression; duration of response; time to treatment failure; OS, QoL	39% of the Ir group and 58% of the non-Ir group received further chemotherapy; 31% of the non-Ir group subsequently received Ir. 16% in the Ir group and 13% in the non-Ir group received further treatment with Ox. Analysis by ITT
Köhne *et al.*, 2003 (Germany)[48,56]	Histologically confirmed CRC, chemonaive metastatic, measurable or evaluable, previous adjuvant treatment if completed 6 months before randomisation, no severe concomitant disease, age>18 years (no upper age limit), informed consent	*Arm 1* (Ir + 5-FU): Ir 80 mg m^{-2} i.v. 30 minutes, LV 500 mg m^{-2} i.v. 2 h, 5-FU 2300 mg m^{-2} i.v. 24 h reduced to 2000 mg m^{-2} i.v. 24 h. Day 1, 8, 15, 22, 29, 36 (weekly ×6), repeat day 50 (AIO) (*n* = 214) *Arm 2* (5-FU): FA 500 mg m^{-2} i.v. 2 h, 5-FU 2600 g m^{-2} i.v. 24 h. Days 1, 8, 15, 22, 29, 36 (weekly ×6), repeat day 50 (*n* = 216)	OS; PFS; Toxicity; tumour response rate	Randomisation stratification by institution, prior adjuvant treatment, WHO PS, alkaline phosphatase. Analysis: adjusted a = 0.04 (one interim analysis), power 80%, two sided log-rank test
Saltz *et al.*, 2000 (USA)[49]	Histologically documented CRC; measurable metastatic disease; ECOG PS = 0–2; adequate organ function; no prior pelvic irradiation; no prior therapy for metastatic disease; previous adjuvant 5-FU only where patient remained disease free for >1 year	*Arm 1* (Ir + 5-FU): Ir 125 mg m^{-2} 90-minute infusion + 5-FU 500 mg m^{-2} bolus + FA 20 mg m^{-2} bolus weekly 4/6 weeks (*n* = 231) (Saltz) *Arm 2* (5-FU): Ir 125 mg m^{-2} 90-minute infusion weekly 4/6 weeks (*n* = 226) *Arm 3* (5-FU): 5-FU 425 mg m^{-2}, 5 days every 4 weeks/ FA 20 mg m^{-2}, 5 days every 4 weeks (Mayo) (*n* = 226)	Primary: PFS; secondary: OS; response rate; QoL	Randomisation stratified according to age (<65/>65), ECOG PS (0/1–2), interval from diagnosis to enrolment (<6/=6 months) and prior adjuvant 5-FU. Of those followed up; 52% Ir + 5-FU, 70% 5-FU and 79% Ir received poststudy chemotherapy, including Ir for 56% 5-FU patients. Analysis by ITT

continued

TABLE 6 *First-line Ir: study characteristics (cont'd)*

Study	Participants	Interventions	Outcomes	Comments
Seymour, 2004 (UK)[42]	Histologically confirmed adenocarcinoma of colon or rectum; inoperable metastatic or locoregional disease (synchronous or recurrence); no previous chemotherapy for established metastatic disease, Measurable disease and adequate bone marrow, hepatobiliary and renal function; WHO PS ≤2 and considered fit and able to undergo all possible treatments; for women of childbearing potential, negative pregnancy test and adequate contraceptive precautions	*Arm A* (MdG followed by Ir at progression; $n = 710$) *Arm B* (MdG followed by Ir MdG at progression; $n = 356$) *Arm C* (Ir MdG; $n = 356$) *Arm D* (MdG followed by Ox MdG at progression; $n = 356$) *Arm E* (Ox MdG; $n = 357$)	Primary: OS (all causes of death); secondary: PFS; objective response rates; QoL (palliation, toxicity, functional impairment); economic evaluation	Analysis by ITT
Comella *et al.*, 2004 (Italy)[50]	Histologically diagnosed adenocarcinoma of colon or rectum; age ≥18 years; life expectancy >3 months; ECOG PS ≤2	*Arm 1* (Ir + 5-FU): Ir 200 mg m^{-2}, bolus 5-FU 850 mg m^{-2}, FA 250 mg m^{-2} ($n = 136$) *Arm 2* (Ox + 5-FU): Ox (100 mg m^{-2}), bolus 5-FU 1050 mg m^{-2}, FA 250 mg m^{-2} ($n = 140$)	Primary: response rate; secondary: failure-free survival; PFS	Study calculated 80% power to detect a 15% difference in response rate between the experimental and control regimens
Goldberg *et al.*, 2004 (USA)[55]	Histologically proven unresectable colorectal adenocarcinoma, biopsy required if Dukes' A or B primary or ≥5 years since surgery; age ≥18 years; life expectancy >12 weeks; ECOG PS ≤2; effective contraception if of childbearing potential; neutrophils ≥1.5 × 109 L^{-1}, Platelets ≥100 × 109 L^{-1}, haemoglobin ≥9.0 g dL^{-1}, creatinine, total bilirubin ≤1.5 × institutional upper normal limit, aspartate aminotransferase, alkaline phosphatase ≤5 × institutional upper normal limit; signed informed consent; institutional review board approval	*Arm 1* (Ir + 5-FU): Ir 125 mg m^{-2} and bolus FU 500 mg m^{-2} plus FA 20 on days 1, 8, 15 and 22 every 6 weeks (Saltz) ($n = 264$) *Arm 2* (Ox + 5-FU): Ox 85 mg m^{-2} on day 1 and bolus FU 400 mg m^{-2} plus FA 200 mg m^{-2} followed by FU 600 mg m^{-2} in 22-h infusions on days 1 and 2 every 2 weeks (de Gramont) ($n = 267$)	PFS; OS; response rate	Randomisation through dynamic allocation designed to balance random assignment for the following factors: PS score, prior adjuvant chemotherapy (yes/no), prior immunotherapy (yes/no), age (<65/≥65 years) and randomising location. Analysis by ITT

continued

TABLE 6 *First-line Ir: study characteristics (cont'd)*

Study	Participants	Interventions	Outcomes	Comments
Tournigand *et al.*, 2004 (France)[51]	Adenocarcinoma of colon or rectum; unresectable metastases; at least one bidimensionally measurable lesion of ⩾2 cm or a residual non-measurable lesion; adequate bone marrow, liver, total bilirubin and renal function; WHO PS ⩽2; age 18–75 years; previous adjuvant chemotherapy, if given, must have been completed at least 6 months before inclusion; written informed consent	*Arm A* (Ir + 5-FU): l-LV 200 mg m^{-2} or dl-LV 400 mg m^{-2} as a 2-h infusion, and Ir 180 mg m^{-2} given as a 90-minute infusion in 500 ml dextrose 5% via a Y-connector, followed by bolus FU 400 mg m^{-2} and a 46-h infusion of FU 2400 mg m^{-2} for two cycles, increased to 3000 mg m^{-2} from cycle 3 in case of no toxicity > grade 1 during the two first cycles, repeated every 2 weeks (de Gramont) ($n = 109$) *Arm B* (Ox + 5-FU): same LV + FU regimen, with the substitution of Ox 100 mg m^{-2} on day 1, given as a 2-h infusion in 500 ml dextrose 5%, concurrent with LV. Antiemetic prophylaxis with a 5-HT_3-receptor antagonist was administered. The use of implantable ports and disposable or electronic pumps allowed chemotherapy to be administered on an outpatient basis (de Gramont) ($n = 111$)	PFS; OS; objective tumour response; toxicity	Randomisation was performed using a minimisation technique, stratifying patients by centre and by presence or absence of measurable disease. Analysis by ITT

CRC, colorectal cancer; LV, leucovorin; ECOG, Eastern Cooperative Oncology Group; 5-HT, 5-hydroxytryptamine.

the ground that they were not Phase III studies.[53] One study, which compared Ir + 5-FU with Ir + 5-FU + bevacizumab, was also excluded.[54]

Quality and characteristics of studies

All seven studies were large multicentre centre studies. In four cases, mature results were written up in peer-reviewed journal articles.[47] In one case, 3-year follow-up data were mature, but available only in abstract and conference presentation form; although an AIC manuscript was also provided, only data from the conference presentation have been presented here.[48] In two cases, 2-year follow–up data were mature, but had only recently been analysed and presented at a conference.[50]

The inclusion criteria of two included studies prescribed an upper age limit of 75 years (*Table 6*).[47] Five trials stated no upper age limit and recruited participants aged 80,[48] 85[49] and 88[55] (*Table 7*). Where reported, the median age of the treatment arms across the studies was between 61 and 63, except for one where the median was 65 years. This means that the trials present a substantially younger population than the NHS population of colorectal cancer patients, where the median age is over 70 and the incidence increases with age until around after the 75–79 years bracket (see the section 'Epidemiology', p. 3).

Where reported, baseline performance status (PS) was generally well balanced, apart from in one trial of Ir + 5-FU versus Ox + 5-FU, where the percentage of patients with World Health Organisation (WHO) PS score 2 significantly favoured the Ox + 5-FU arm (*Table 7*).[51] In four trials, the site of primary tumour was the colon for the majority of participants in both arms.[47] In one trial the rectum was the site of primary tumour for the majority of participants in the 5-FU alone arm.[48] One trial did not report the site of primary tumour in the baseline characteristics.[55]

In those studies that provided the relevant information, participants who had previously received adjuvant 5-FU were evenly distributed. Only two studies planned second-line treatments and analysed on the basis of treatment sequences.[42]

Only two trials reported an adequate method of allocation concealment (central randomisation by telephone after confirmation of eligibility);[47] in the other cases the method of allocation concealment was unclear (*Table 8*). The same two trials reported an adequate method of randomisation (computer-generated numbers).

None of the trials reported large numbers of withdrawals, and all withdrawals were accounted for.

No trials reported blinding; in fact, three reported open-label status.[29] While there is empirical evidence that the absence of blinding tends to result in exaggerated reports of treatment effects,[44] it is almost universally absent from oncology trials, for the pragmatic and ethical reason that informed dose monitoring and adjustment is required.

In summary, as far as can be ascertained from the published literature, all of the trials are relatively well designed and conducted, and include relatively balanced populations. The main issue of concern is that their populations are relatively young and, by implication, fit, which may exaggerate the extent of the likely treatment effect in the UK population as a whole, although not necessarily the 'treatable population' (typically those with a performance status of 2 or less[31]).

Outcomes: OS and PFS

Survival outcomes for studies assessing first-line Ir are summarised in *Table 9*. Three studies did not report progression-free survival.[47,49,55]

In trials comparing Ir + 5-FU with 5-FU alone, the addition of Ir improved median OS by between 2.2 and 3.3 months, and median PFS by between 2.3 and 2.5 months.

There was no significant difference between Ir and Ox when both were used in conjunction with infusional 5-FU. When Ir + bolus 5-FU was compared with Ox + bolus 5-FU, Ox + 5-FU improved median OS by 3.2 months ($p = 0.032$) and PFS by 0.7 months ($p = 0.169$).

Trials that compared Ir + 5-FU with 5-FU alone were meta-analysed using hazard ratios derived from the literature, published survival curves and one AIC dataset.[47]

OS was significantly better for individuals treated with Ir + 5-FU than for those treated with 5-FU alone (four trials; 2340 participants; HR = 0.84, 95% CI 0.76 to 0.93, $p = 0.0007$). There was no significant heterogeneity ($\chi^2 = 0.56$, df = 3, $p = 0.91$, $I^2 = 0\%$). In the analysis of prospectively identified intervention subsets, OS was significantly better when delivered via infusional (HR = 0.84, 95% CI 0.75 to 0.94, $p = 0.003$)[61] but not bolus regimens (HR = 0.84, 95% CI 0.68 to 1.05, $p = 0.12$).[49]

TABLE 7 *First-line Ir: population characteristics*

Study	Median age	Male (%)	WHO PS	Site of primary tumour	Site of metastases	Previous 5-FU
Douillard *et al.*, 2000[47]	*Arm 1* (Ir + 5-FU): 62 (27–75) *Arm 2* (5-FU): 59 (24–75)	*Arm 1* (Ir + 5-FU): 67 *Arm 2* (5-FU): 53	*Arm 1* (Ir + 5-FU): 0 = 51%, 1 = 42%, 2 = 7% *Arm 2* (5-FU): 0 = 51%, 1 = 41%, 2 = 8%	*Arm 1* (Ir + 5-FU): colon 55%, rectum 45% *Arm 2* (5-FU): colon 65%, rectum 35%	Number of involved organ sites: *Arm 1* (Ir + 5-FU):1 = 62%, 2 = 23%, >2 = 15% *Arm 2* (5-FU): 1 = 63%, 2 = 28%, >2 = 9%	*Arm 1* (Ir + 5-FU): 26% *Arm 2* (5-FU): 24%
Köhne *et al.*, 2003[48,56]	*Arm 1* (Ir + 5-FU): 61(32–78) *Arm 2* (5-FU): 61(24–80)	*Arm 1* (Ir + 5-FU): 64 *Arm 2* (5-FU): 61	Risk group (WHO, WBC, no lesions, alkaline phosphatase): *Arm 1* (Ir + 5-FU): poor = 19%; intermediate = 39%, good = 42%, missing <1% *Arm 2* (5-FU): poor 18%, intermediate 42%, good 39%, missing <1%	Primary colon: *Arm 1* (Ir + 5-FU): 55%, *Arm 2* (5-FU): 47%	NR	NR
Saltz *et al.*, 2000[49]	*Arm 1* (Ir + 5-FU): 62 (25–85) *Arm 2* (5-FU): 61 (30–87) *Arm 3* (Ir): 61 (19–85)	*Arm 1* (Ir + 5-FU): 65 *Arm 2* (5-FU): 54 *Arm 3* (Ir): 64	*Arm 1* (Ir + 5-FU): 0 = 39%, 1 = 46%, 2 = 15% *Arm 2* (5-FU): 0 = 46%, 1 = 46%, 2 = 8% *Arm 3* (Ir): 0 = 41%, 1 = 45%, 2 = 13%	*Arm 1* (Ir + 5-FU): colon 81, rectum 17 *Arm 2* (5-FU): colon 85, rectum 14 *Arm 3* (Ir): colon 84, rectum 15	Number of involved organs: *Arm 1* (Ir + 5-FU): 1 = 64%, 2 = 26%, >2 = 10% *Arm 2* (5-FU): 1 = 66%, 2 = 23%, >2 = 10% *Arm 3* (Ir): 1 = 62%, 2 = 28%, >2 = 9% Liver involvement *Arm 1* (Ir + 5-FU): yes 11%, no 89% *Arm 2* (5-FU): yes 8%, no 92%	*Arm 1* (Ir + 5-FU): 11% *Arm 2* (5-FU): 8% *Arm 3* (Ir): 10%
Seymour, 2004[42]	No data	No data	No data	No data	No data	No data

continued

TABLE 7 *First-line Ir: population characteristics (cont'd)*

Study	Median age	Male (%)	WHO PS	Site of primary tumour	Site of metastases	Previous 5-FU
Comella *et al.*, 2004[50]	*Arm 1* (Ir + 5-FU): 62 (38–80) *Arm 2* (Ox + 5-FU): 63 (37–76)	*Arm 1* (Ir + 5-FU): 53 *Arm 2* (Ox + 5-FU): 51	*Arm 1* (Ir + 5-FU): 0 = 60%, 1–2 = 40% *Arm 2* (Ox + 5-FU): 0 = 61%, 1–2 = 39%	*Arm 1* (Ir + 5-FU): colon 71%, rectum 29% *Arm 2* (Ox + 5-FU): colon 72%, rectum 28%	Number of metastatic organs: *Arm 1* (Ir + 5-FU): 1 = 54%, 2 = 36%, >3 = 10%; liver positive 73%, synchronous metastasis 60% *Arm 2* (Ox + 5-FU): 1–55%, 2–33%, >3–12%: liver positive 75%, synchronous metastasis 67%	*Arm 1* (Ir + 5-FU): 25% *Arm 2* (Ox + 5-FU): 22%
Goldberg *et al.*, 2004[55]	*Arm 1* (Ir + 5-FU): 61 (28–88) *Arm 2* (Ox + 5-FU): 61 (27–88)	*Arm 1* (Ir + 5-FU): 65 *Arm 2* (Ox + 5-FU): 59	ECOG PS *Arm 1* (Ir + 5-FU): 0–1 = 93%, 2 = 5%, unknown = 2% *Arm 2* (Ox + 5-FU): 0–1 = 93%, 2 = 5%, unknown = 2%	NR	NR	*Arm 1* (Ir + 5-FU): yes 15%, no 83%, unknown 2% *Arm 2* (Ox + 5-FU): yes 16%, no 82%, unknown 2%
Tournigand *et al.*, 2004[51]	*Arm A* (Ir + 5-FU): 61(29–75) *Arm B* (Ox + 5-FU): 65 (40–75)	*Arm A* (Ir + 5-FU): 57 *Arm B* (Ox + 5-FU): 72	*Arm A* (Ir + 5-FU): 0 = 45%, 1 = 39%, 2 = 17% *Arm B* (Ox + 5-FU): 0 = 47%, 1 = 47%, 2 = 6%	*Arm A* (Ir + 5-FU): colon 67%, rectum 33%, multiple 0% *Arm B* (Ir + 5-FU): colon 72%, rectum 26%, multiple 2%	*Arm A* (Ir + 5-FU): 1 = 59%, ⩾2 = 41% *Arm B* (Ox + 5-FU): 1 = 59%, ⩾2 = 41%	*Arm A* (Ox+5-FU): yes 17%, no = 83% *Arm B* (Ox + 5-FU): yes = 21%, no = 79%

NR, not reported.

TABLE 8 *First-line Ir: quality assessment*

Study	Allocation concealment	Randomisation	Blinding	Withdrawals	Comments
Ir + 5-FU vs 5-FU					
Douillard *et al.*, 2000[47]	Adequate	Adequate	Unclear	Adequate	Allocation concealment: central randomisation. Randomisation: computer-generated. Withdrawals: 2 participants (0.5%). 97 (25%) received weekly treatment; 288 (75%) received fortnightly treatment
Köhne *et al.*, 2003[48,56]	Unclear	Unclear	Inadequate	Adequate	Abstract only. Sample size was specified as 215 participants per arm (total 430). Participants were randomised to 5-FU (n = 216) or Ir + 5-FU (n = 214). Some analyses report 213 participants in each arm and the dropouts are not explained
Saltz *et al.*, 2000[49]	Unclear	Unclear	Inadequate	Adequate	16 patients never received therapy; 4 received the wrong treatment. Power calculation required 220 patients in each arm to detect a 40% improvement in median PFS (from 5 to 7 months) with a power of 0.85. One arm (5-FU/LV alone) treated only 219 patients
Seymour, 2004[42]	Adequate	Adequate	Inadequate	No data	Abstract only
Ir + 5-FU vs. Ox + 5-FU					
Comella *et al.*, 2004[50]	Unclear	Unclear	Unclear	Unclear	A more recent abstract has been found;[57] however, this has been excluded from the review as it includes a new third treatment arm on which no information is available in the protocol[58] or the interim analysis.[59] This abstract supplies only response rates and toxicities, whereas the earlier interim analysis also provides survival data
Goldberg *et al.*, 2004[55]	Unclear	Unclear	Unclear	Adequate	Power calculation: with 795 participants randomised, 80% chance to detect an HR of 0.75. Treatment violations, ineligible participants and cancelled treatment accounted for 21 participants (2.6%). Effectiveness outcomes (OS and PFS) by ITT; others reported per protocol
Tournigand *et al.*, 2004[51]	Unclear	Unclear	Unclear	Adequate	There was an imbalance in baseline characteristics: more males and participants aged > 65 years in the Ox + 5-FU arm than in the Ir + 5-FU arm. Six (3%) of randomised participants were ineligible and not treated. Analysis was by ITT
Seymour, 2004[42]	Adequate	Adequate	Inadequate	No data	Abstract only

TABLE 9 *First-line Ir: OS and PFS*

Study	Follow-up (months)			OS (months)	
Ir +5-FU vs 5-FU		**Ir + 5-FU**	**5-FU**	**HR (95% CI)**	***p***
Douillard *et al.*, 2000[47a]	23	17.4	14.1	0.77 (0.60 to 0.98)	0.036
Köhne *et al.*, 2003[48a]	36	20.1	16.8	0.86	0.278
Saltz *et al.*, 2000[49b]	42	14.8	12.6	0.78 (0.63 to 0.97)	0.037
Seymour *et al.*, 2004[60a]	36	16.2	13.7	0.86 (0.74 to 1.00)	0.058
Ir +5-FU vs Ox + 5-FU		**Ir + 5-FU**	**Ox + 5-FU**	**HR (95% CI)**	***p***
Comella *et al.*, 2004[50b]	19	15.7	18.9	0.70	0.032
Goldberg *et al.*, 2004[55c]	20.4	15.0	19.5	0.66 (0.54 to 0.82)	0.0001
Seymour *et al.*, 2004[60a]	30	16.2	15	0.92	NR
Tournigand *et al.*, 2004[51a]	43.9	21.5	20.6	NR	0.99
Study	**Follow-up (months)**			**PFS (months)**	
Ir +5-FU vs 5-FU		**Ir +5-FU**	**5-FU**	**HR (95% CI)**	***p***
Köhne *et al.*, 2003[48a]	36	8.8	6.3	0.78	0.0001
Seymour *et al.*, 2004[60a]	36	8.6	6.3	0.77 (0.67 to 0.88)	<0.001
Ir +5-FU vs. Ox + 5-FU		**Ir +5-FU**	**Ox + 5-FU**	**HR (95% CI)**	***p***
Comella *et al.*, 2004[50b]	19	7.5	8.2	0.82	0.169
Seymour *et al.*, 2004[60b]	30	8.6	8.8	1.00	NR
Tournigand *et al.*, 2004[51a]	43.9	8.5	8.0	NR	0.26

[a] Infusional 5-FU; [b] bolus 5-FU; [c] bolus 5-FU (Ir arm) and infusional 5-FU (Ox arm).

PFS was significantly better for individuals treated with Ir + infusional 5-FU than for those treated with infusional 5-FU alone (HR = 0.73, 95% CI 0.65 to 0.82, $p < 0.00001$). There was moderate heterogeneity ($\chi^2 = 1.89$, df = 1, $p = 0.17$, $I^2 = 47.0\%$). Two trials, including the only study delivering 5-FU by bolus injection, could not be included in the meta-analysis as they reported time-to-progression rather than PFS.

Trials that compared Ir + 5-FU with Ox + 5-FU were also meta-analysed. The analysis of OS and PFS (*Figures 4* and *5*) used hazard ratios derived from the literature and published survival curves and one AIC dataset.[50,51,55,60] Survival outcomes are summarised in *Table 9*.

In the analysis of OS, the direction of effect favoured Ox + 5-FU (four trials; 1740 participants; HR = 1.12, 95% CI 1.00 to 1.25, $p = 0.05$), but there was significant heterogeneity ($\chi^2 = 17.01$, df = 3, $p = 0.0007$, $I^2 = 82.4\%$) (see the section 'Discussion of results', p. 24). In the analysis of prospectively identified intervention subsets (including one AIC data set), there was no significant difference between Ir + 5-FU and Ox + 5-FU when 5-FU was delivered by continuous infusion (HR = 0.92, 95% CI 0.80 to 1.07, $p = 0.28$).[51,60] There was no significant heterogeneity ($\chi^2 = 0.04$, df = 1, $p = 0.28$, $I^2 = 0\%$). In the trial where both Ir and Ox were delivered in conjunction with bolus 5-FU, median OS was significantly longer in the oxaliplatin group (published summary statistics: HR = 0.70, $p = 0.032$[50]). In the trial that compared Ir + bolus 5-FU with Ox + infusional 5-FU, median OS was significantly better for patients receiving Ox (published summary statistics: HR = 0.66, 95% CI 0.54 to 0.82; $p = 0.0001$[55]).

In the analysis of PFS, no significant difference was found between Ir + 5-FU and Ox + 5-FU (three trials; 1209 participants; HR = 1.04, 95% CI 0.94 to 1.14, $p = 0.46$). There was no statistical heterogeneity ($\chi^2 = 1.92$, df = 2, $p = 0.38$, $I^2 = 0\%$). In the analysis of prospectively identified intervention subsets (including one AIC dataset), there was no significant difference between arms when 5-FU was delivered with infusional regimes (HR = 1.02, 95% CI 0.92 to 1.12, $p = 0.77$).[51] There was no significant heterogeneity between trials ($\chi^2 = 0.49$, df = 1, $p = 0.48$, $I^2 = 0\%$). In the one trial where both Ir and Ox were delivered in conjunction with bolus 5-FU, PFS was not significantly better in the

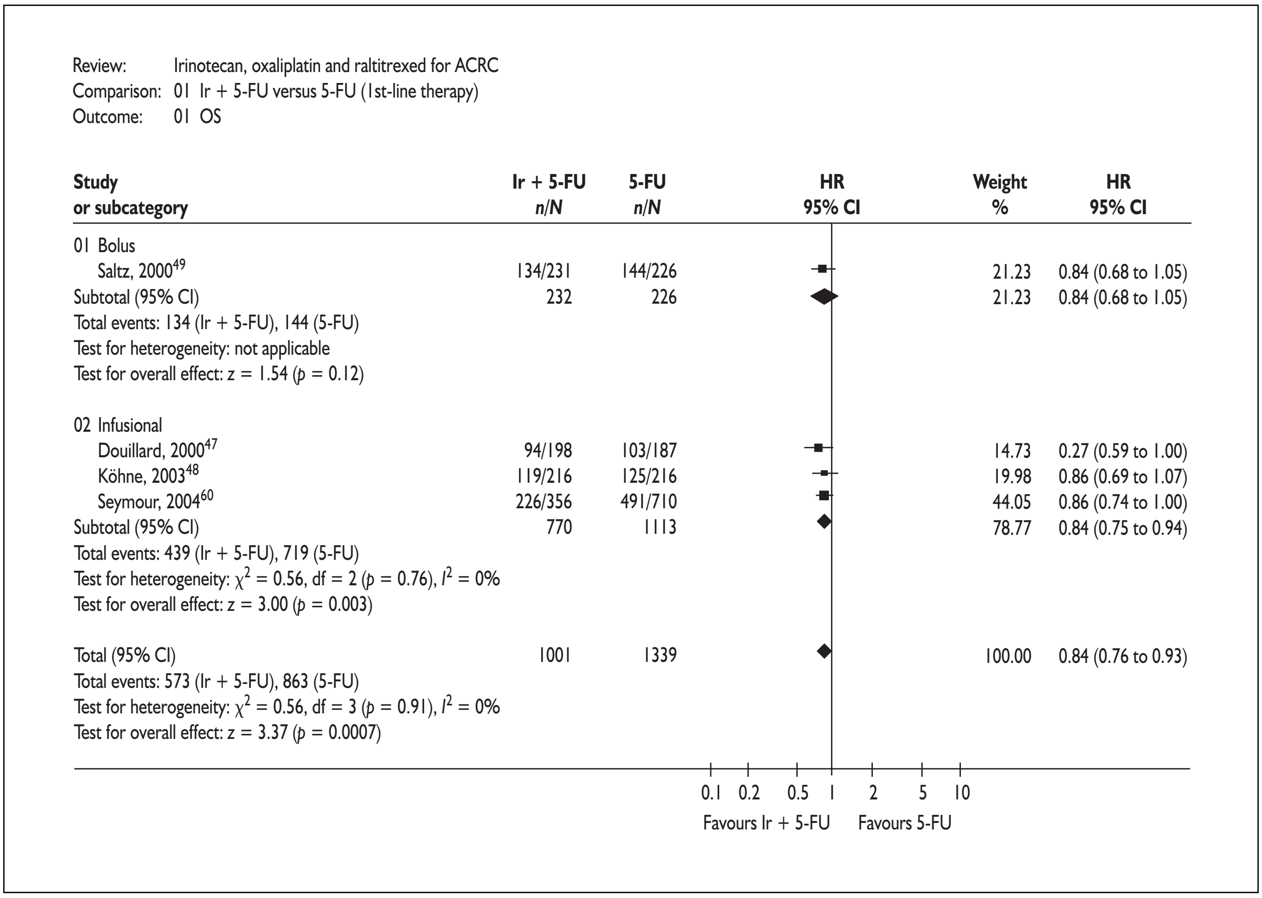


***FIGURE 2** Ir + 5-FU versus 5-FU (first line): OS*

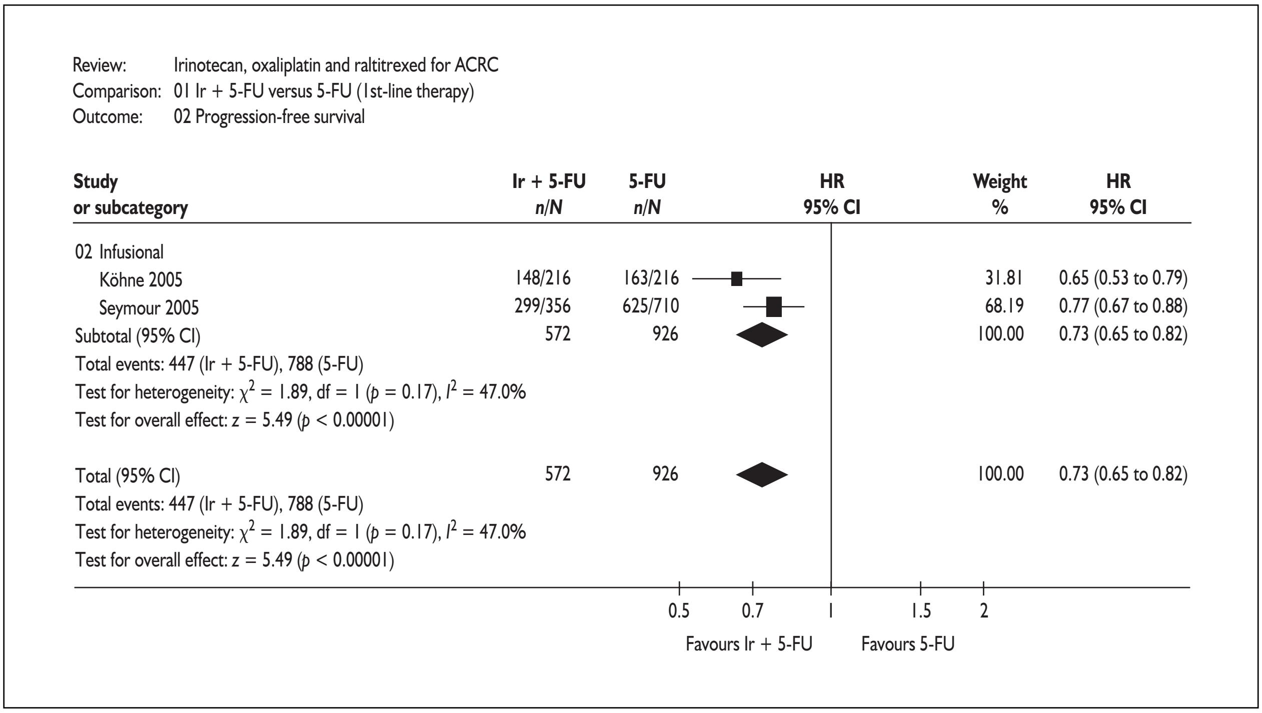


***FIGURE 3** Ir + 5-FU versus 5-FU (first line): PFS*

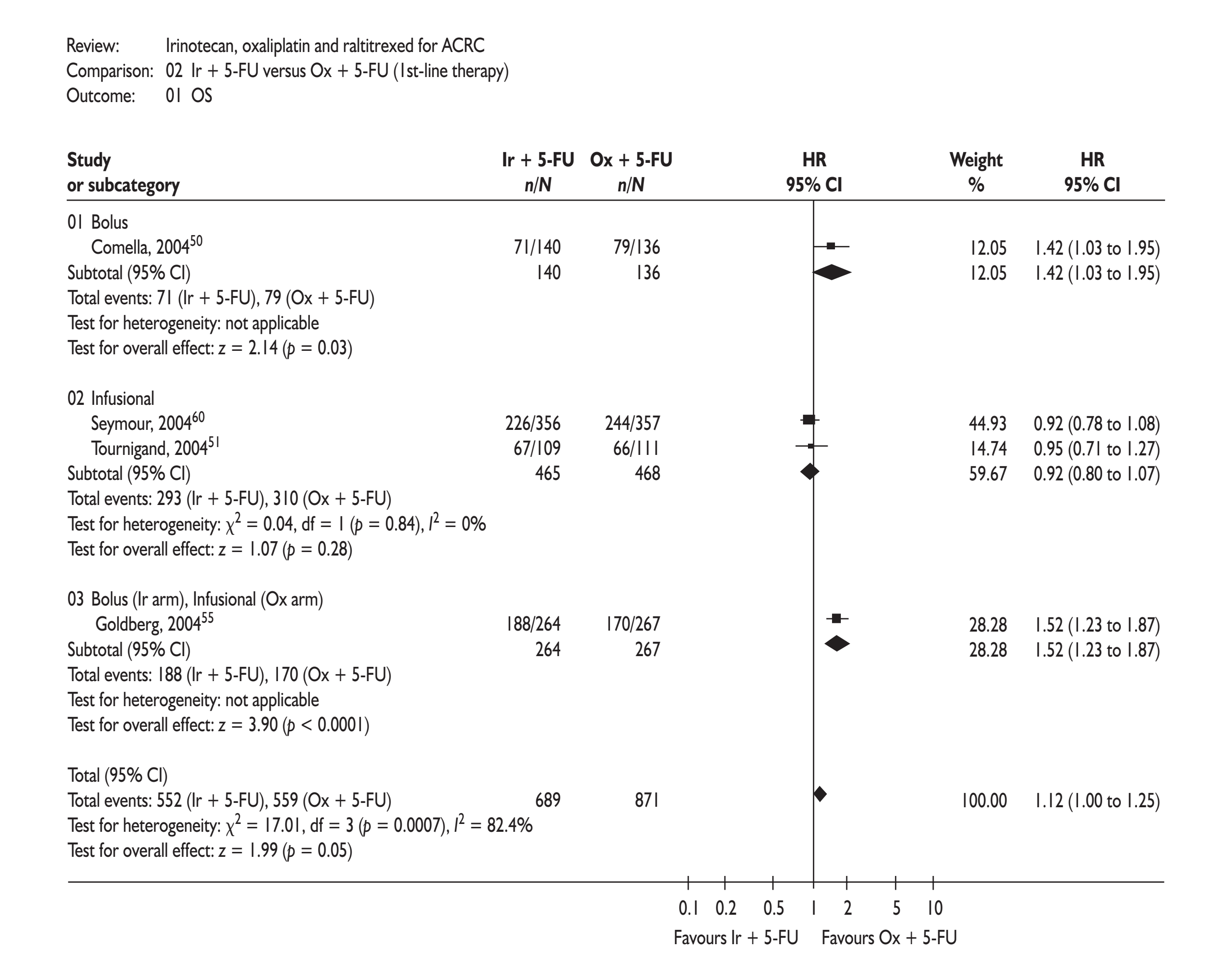


FIGURE 4 *Ir + 5-FU versus Ox + 5-FU (first-line therapy): OS*

oxaliplatin group (published summary statistics: HR = 0.82; p = 0.169[50]). The trial that compared Ir + bolus 5-FU with Ox + infusional 5-FU reported time-to-progression rather than PFS and could not be included in the meta-analysis.[55]

Outcomes: response rates

Response rates are reported in *Table 10*.

In four studies that compared Ir + 5-FU with 5-FU alone, response rates were between 18 and 23% higher in the Ir arm (statistically significant in every case). This difference was present regardless of whether 5-FU was delivered by bolus injection or continuous infusion.

When Ir + bolus 5-FU was compared with Ox + bolus 5-FU, response rates were 16% better in the Ox + 5-FU arm (p = 0.032). When Ir + bolus 5-FU was compared with Ox + infusional 5-FU, response rates were 14% better in the Ox + 5-FU arm (p = 0.002). In studies that compared Ir + infusional 5-FU with Ox + infusional 5-FU, there was no significant difference between arms in response rates.

Outcomes: toxicities

Gastrointestinal, haematological and neurological toxicities are reported in *Tables 11*, *12* and *13*, respectively.

Ir + 5-FU was generally associated with a higher prevalence of grade 3–4 gastrointestinal toxicities (vomiting, nausea, diarrhoea, stomatitis and mucositis) than 5-FU alone or Ox + 5-FU. However, people in an Ir + 5-FU arm were less affected by haematological (except febrile neutropenia) or neurological toxicities than 5-FU and Ox + 5-FU. Only two studies reported the significance of the toxic effects. In one study patients treated with Ir + 5-FU had significantly

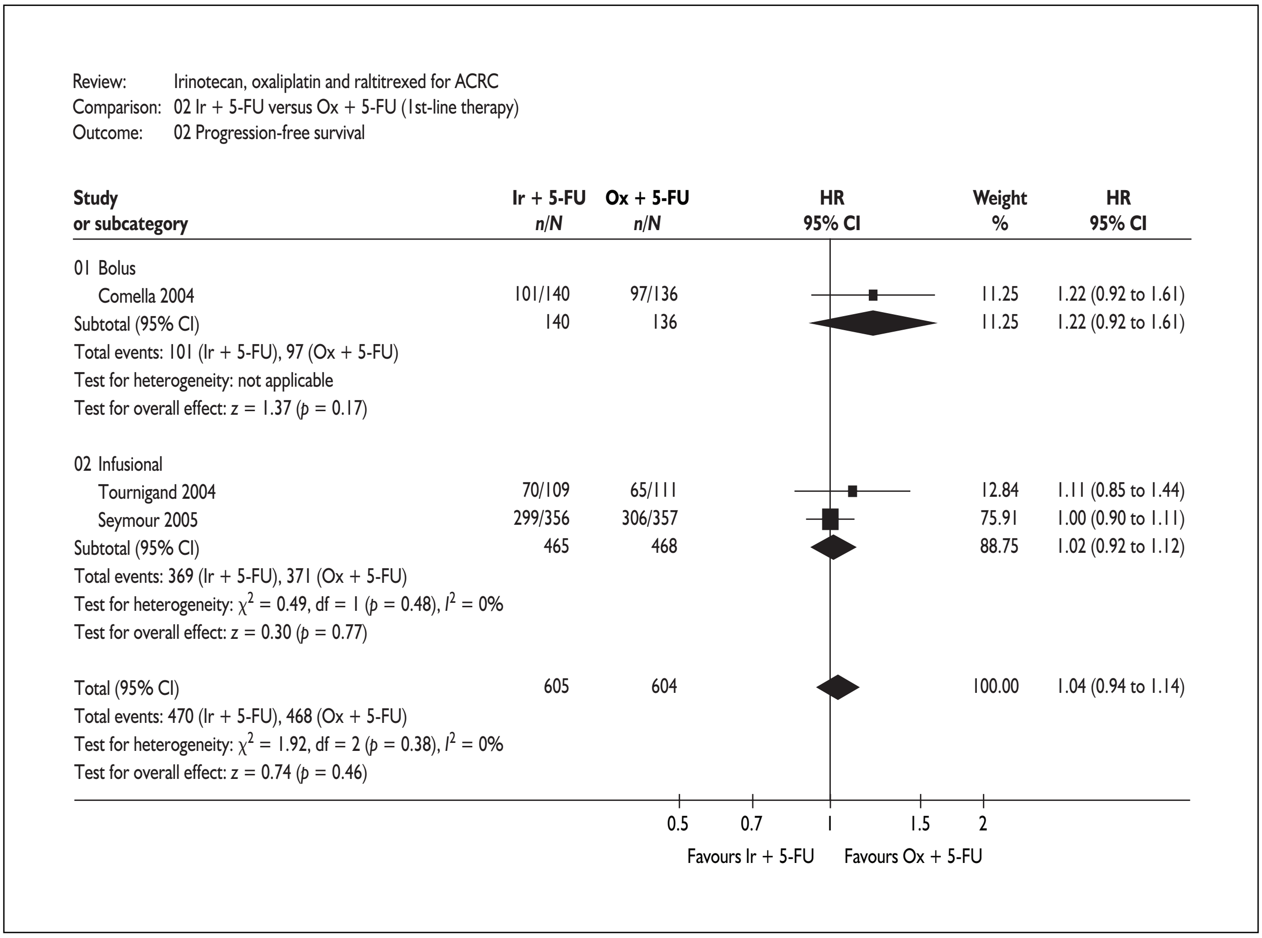


FIGURE 5 *Ir + 5-FU versus Ox + 5-FU (first line): PFS*

TABLE 10 *First-line Ir: response rates*

Treatment/study	Response rate (%)		
5-FU + Ir vs 5-FU	**Ir + 5-FU**	**5-FU**	***p***
Douillard *et al.*, 2000[47a]	49	31	<0.001
Köhne *et al.*, 2003[48a]	54.2	31.5	<0.0001
Saltz *et al.*, 2000[49b]	50	28	<0.0001
Seymour *et al.*, 2004[60a]	No data	No data	No data
5-FU + Ir vs Ox +5-FU	**Ir+ 5-FU**	**Ox + 5-FU**	***p***
Goldberg *et al.*, 2004[55c]	31	45	0.002
Comella *et al.*, 2004[50b]	31	47	0.032
Tournigand *et al.*, 2004[51a]	56	54	ns
Seymour *et al.*, 2004[60a]	No data	No data	No data

[a] Infusional 5-FU; [b] bolus 5-FU; [c] bolus 5-FU (Ir arm) and infusional 5-FU (Ox arm).
ns, not significant.

TABLE 11 *First-line Ir: gastrointestinal toxicity*

Treatment/study	**Toxicity (grade 3–4)**							
	Vomiting (%)		**Nausea (%)**		**Diarrhoea (%)**		**Stomatitis (mucositis) (%)**	
Ir+5-FU vs 5-FU	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**
Douillard *et al.*, 2000[47a]	4	2	NR	NR	14	6	NR (4)	NR (3)
Köhne *et al.*, 2003[48a]	7	5	8 (G3)	7 (G3)	29	21	3	1
Saltz *et al.*, 2000[49b]	10	4	NR	NR	23	13	NR (2)	NR (17)
Seymour *et al.*, 2004[60a]	7.3	5.9	6.7	5.9	11.3	12.6	1.8	2.1
Ir+5-FU vs Ox+5-FU	**Ir + 5-FU**	**Ox + 5-FU**	**Ir + 5-FU**	**Ox + 5-FU**	**Ir + 5-FU**	**Ox + 5-FU**	**Ir + 5-FU**	**Ox + 5-FU**
Goldberg *et al.*, 2004[55c]	14	3	16	6	28	12	NR	NR
Comella *et al.*, 2004[50b]	NR	NR	NR	NR	12	28	4	3
Tournigand *et al.*, 2004[51a]	8 (G3) 2 (G4)	3 (G3) 0 (G4)	13 (G3) 0 (G4)	3 (G3) 0 (G4)	9 (G3) 5 (G4)	9 (G3) 2 (G4)	NR (10 G3) (0 G4)	NR (1 G3) (0 G4)
Seymour *et al.*, 2004[60a]	7.3	7.6	6.7	5.7	11.3	8.8	1.8	1.8

[a] Infusional 5-FU; [b] bolus 5-FU; [c] bolus 5-FU (Ir arm) and infusional 5-FU (Ox arm).
G3, grade 3; G4, grade 4.

higher rates of diarrhoea (p = 0.001), vomiting (p = 0.001), nausea (p = 0.001) and febrile neutropenia (p = 0.001) and a significantly lower rate of neutropenia (p = 0.001) compared with the Ox + 5-FU group.[55]

The other study reported more frequent grade 3–4 neutropenia (p = 0.003) in the Ox + 5-FU arm than in Ir + 5-FU. Grade 3–4 febrile neutropenia (p = 0.007), nausea (p = 0.005), vomiting (p = 0.027), mucositis (p = 0.003) and fatigue (p = 0.028) were significantly more frequent with Ir + 5-FU than with Ox + 5-FU.[51]

Outcomes: quality of life

Quality of life outcomes are reported in *Table 14*.

In the comparison of Ir + 5-FU versus 5-FU alone, two trials reported quality of life outcomes.[47] Neither found any significant difference in overall quality of life between treatment arms, although one identified that deterioration in quality of life and performance status occurred significantly later in the Ir + 5-FU.

Discussion of results

Strength of the evidence (internal validity)

With the exception of blinding, no trial reported clearly inadequate approaches to generic components of clinical trial design that minimise systematic error (bias). As noted above, blinding is rare in oncology trials and its absence in the included trials should not generate concern.

However, the internal validity of the survival outcomes was compromised by another facet of study design, the use of unplanned further therapies in five trials.[55] In the four studies that reported on this variable, between 49 and 75% of participants in any study arm went on to an unplanned second-line therapy.[55] There is no way to gauge the consequences for the estimate of the treatment effect in terms of overall survival. Variations in the baseline comparability of populations may also have affected the internal validity of studies to an unknown extent.

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). Mean survival would be more appropriate, calculated as the area under the curve.

Applicability of the results (external validity)

The issue of unplanned second-line therapies also affects the applicability of the results (external validity). If, in the UK NHS, most of those whose disease progresses are likely to receive a second-line treatment then, to provide a correct basis for generalisation, a trial must also analyse the effect not of a single intervention, but of sequences of interventions. Only two included studies planned

TABLE 12 *First-line Ir: haematological toxicity*

Treatment/study	Toxicity (grade 3–4)									
	Neutropenia (%)		Anaemia (%)		Leucopenia (%)		Febrile neutropenia (%)		Platelets (%)	
Ir 5+FU vs 5-FU	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**
Douillard *et al.*, 2000[47a]	46	14	NR	NR	NR	NR	NR	NR	NR	NR
Köhne *et al.*, 2003[48a]	NR	NR	NR	NR	7	3	3	1	NR	NR
Saltz *et al.*, 2000[49b]	54	67	NR	NR	NR	NR	NR	NR	NR	NR
Seymour *et al.*, 2004[60a]	19	13.7	2.7	3.7	NR	NR	NR	NR	0.6	0.6
Ir +5-FU vs Ox +5-FU	**Ir + 5-FU**	**Ox + 5-FU**	**Ir + 5-FU**	**Ox + 5-FU**	**Ir + 5-FU**	**Ox + 5-FU**	**Ir + 5-FU**	**Ox + 5-FU**	**Ir + 5-FU**	**Ox + 5-FU**
Goldberg *et al.*, 2004[55c]	40	50	NR	NR	NR	NR	15	4	NR	NR
Comella *et al.*, 2004[50b]	31	29	1	1	NR	NR	7	3	1	3
Tournigand *et al.*, 2004[51a]	15 (G3) 9 (G4)	31 (G3) 13 (G4)	31 (G3) 1 (G4)	3 (G3) 0 (G4)	NR	NR	4 (G3) 3 (G4)	0 (G3) 0 (G4)	0 (G3) 0 (G4)	5 (G3) 0 (G4)
Seymour *et al.*, 2004[60a]	19	27.1	2.7	7.0	NR	NR	NR	NR	0.6	2.4

[a] Infusional 5-FU; [b] bolus 5-FU; [c] bolus 5-FU (Ir arm) and infusional 5-FU (Ox arm).

TABLE 13 *First-line Ir: neurological and other toxicity*

Treatment/study	Toxicity (grade 3-4)											
	Neuropathy (%)		Asthenia (%)		Pain (%)		Alopecia (%)		Fatigue (%)		Hand-foot syndrome (%)	
Ir +5-FU vs 5-FU	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**
Douillard *et al.*, 2000[47a]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Köhne *et al.*, 2003[48a]	NR	NR	NR	NR	NR	NR	8	2	NR	NR	1	2
Saltz *et al.*, 2000[49b]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Seymour *et al.*, 2004[60a]	0.9	0.7	NR	NR	20.7	21.2	2.4	4.8	NR	NR	0.6	1.7
Ir+ 5-FU vs Ox +5-FU	**Ir + 5-FU**	**Ox + 5-FU**	**Ir + 5-FU**	**Ox + 5-FU**	**Ir + 5-FU**	**Ox + 5-FU**	**Ir + 5-FU**	**Ox + 5-FU**	**Ir + 5-FU**	**Ox + 5-FU**	**Ir + 5-FU**	**Ox + 5-FU**
Goldberg *et al.*, 2004[55c]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Comella *et al.*, 2004[50b]	3	1	NR	NR	NR	NR	1.5	23	3	2	NR	NR
Tournigand *et al.*, 2004[51a]	0 (G3) NR (G4)	34 (G3) NR (G4)	NR	NR	NR	NR	NR	NR	4 (G3) 0 (G4)	3 (G3) 0 (G4)	2 (G3) 0 (G4)	2 (G3) 0 (G4)
Seymour *et al.*, 2004[60a]	0.9	10.3	NR	NR	20.7	16.6	2.4	1.2	NR	NR	0.6	0.9

[a] Infusional 5-FU; [b] bolus 5-FU; [c] bolus 5-FU (Ir arm) and infusional 5-FU (Ox arm).

TABLE 14 *First-line Ir: quality of life*

Study	QoL: methods of assessment	Findings
Ir + 5-FU vs 5-FU		
Douillard *et al.*, 2000[47a]	EORTC QLQ-C30	385 patients: 62% of Ir group and 59% in no-Ir group. QoL did not differ significantly between groups.[47] Deterioration of QoL and PS occurred later in Ir +5-FU/LV than 5-FU/LV alone.[61]
Köhne *et al.*, 2003[48a]	No data/not assessed	
Saltz *et al.*, 2000[49b]	EORTC QLQ-C30 (version 2)	No significant difference in overall score between Ir + 5-FU/LV and 5-FU/LV alone.[49] Significantly better QoL scores with Ir + 5-FU/LV than with 5-FU/LV alone for subscales of role functioning, fatigue, appetite loss and pain[61]
Seymour *et al.*, 2004[42a]	EQ-5D	Not analysed at time of writing
Ir + 5-FU vs Ox + 5-FU		
Comella *et al.*, 2004[50b]	No data/not assessed	
Goldberg *et al.*, 2004[55c]	No data/not assessed	
Tournigand *et al.*, 2004[51a]	No data/not assessed	

[a] Infusional 5-FU; [b] bolus 5-FU; [c] bolus 5-FU (Ir arm) and infusional 5-FU (Ox arm).
EORTC, European Organisation for Research and Treatment of Cancer; QLQ, Quality of Life Questionnaire; EQ-5D, EuroQoL 5 Dimensions.

treatment subsequent to first-line therapies and analysed accordingly.[42] These trials are the subject of the section 'Sequencing of treatment' (p. 51), where the question of optimal treatment sequences is addressed.

It has been noted that the all study arm populations had median ages of between 10 and 15 years younger than the UK population of people with colorectal cancer. Therefore, the extent to which the results of included trials provide a correct basis for generalisation to the UK NHS is unclear. The incidence of colorectal cancer rises with increasing age[62] and more than half of new cases are in patients aged 70 years or older.[63] There is concern that elderly people with ACRC are excluded or underrepresented in clinical studies,[64] that it is inappropriate to extrapolate from results derived from younger populations[65] and that there is an inadequate evidence base for their treatment with systemic therapy.[66] Declining organ functions and co-morbidities, common in the elderly,[66] are associated with higher rates of treatment-related morbidity and mortality, which has led to the differential use of therapies in elderly patients with ACRC.[67] However, single-arm studies have found no significant difference in response and toxicity between younger and older people treated with Ir + 5-FU.[65] Two included trials confirm that patients over 65 years did not experience increased toxicity with first-line irinotecan compared with younger participants.[51]

The final caveat to the generalisability of the results presented relates to the heterogeneity identified with the meta-analyses comparing Ir + 5-FU with Ox + 5-FU (see the section 'Outcomes: OS and PFS', p. 16). Although the results of the meta-analyses were consistent in direction when Ir + 5-FU was compared to 5-FU alone, regardless of how 5-FU was administered, there was considerable variation between trials in the size and direction of effect when Ir + 5-FU was compared to Ox + 5-FU. On the basis of the published evidence, it is impossible to say whether this heterogeneity is due to the differential effect provided by various modes of 5-FU administration (see the section 'Fluorouracil-containing treatment: differential effects', p. 58), the interaction between these modes of 5-FU administration and the other active chemotherapies, a real difference in effect size between Ir and Ox, or a combination of all three factors. In light of this uncertainty, no attempt should be made to generalise from the weighted average of these four trials as to the relative effectiveness of Ir + 5-FU and Ox + 5-FU. However, it is clear from data presented in this section, as well as in the section 'Results: oxaliplatin – first-line combination' (p. 32), that either Ir + 5-FU or Ox + 5-FU is effective when compared to 5-FU alone.

Assessment of effectiveness

The synthesis of published and unpublished evidence suggests the following.

- The addition of irinotecan to first-line 5-FU significantly improves median OS by between 2 and 4 months ($p = 0.0007$), median PFS by between 2 and 3 months ($p < 0.00001$) and response rates ($p < 0.001$).
- There is no significant difference in OS or PFS between first-line irinotecan with 5-FU and oxaliplatin with 5-FU, except when 5-FU is delivered by bolus injection, when oxaliplatin provides better OS ($p = 0.032$) and response rates ($p = 0.032$), but not PFS ($p = 0.169$).
- Combination therapy with irinotecan and 5-FU is associated with more gastrointestinal toxicities and more febrile neutropenia, but fewer haematological toxicities of other types and fewer neurological toxicities than 5-FU alone and Ox + 5-FU.
- There is no evidence for a significant difference in quality of life between first-line irinotecan combination and either 5-FU alone or oxaliplatin combination therapy.
- It is unknown to what extent outcomes for OS are confounded by over half of the trial participants in five trials receiving unplanned second-line therapy.
- Although the best data are based on an atypically young and fit population, other available evidence suggests that there is no significant difference between the efficacy and toxicity of first-line irinotecan combination therapy in older people.

Results: irinotecan – second-line monotherapy

Quantity and quality of research available

Number of studies identified

The search retrieved 2105 citations.

Number and type of studies included

One Phase III RCT was found that compared Ir alone with 5-FU alone.[68] One Phase III RCT was found that compared Ir + BSC with BSC alone.[69]

Number and type of studies excluded, with reasons for specific exclusions

A flowchart is provided in Appendix 4, as recommended by the QUOROM statement,[43] and reasons for all trial exclusions are given in Appendix 5. Four trials included in the original review[1] and industry submissions[52] were excluded from this review as they were Phase II trials.[70] One Phase II–III trial, which was stopped early and did not contain sufficient data for analysis, was also excluded.[71] One Phase III trial was excluded as it did not report survival data.[72] The results of two studies that randomised participants to treatment sequences including second-line irinotecan[51] were not presented in this section, because they analysed primary survival outcomes from the time of randomisation to first-line therapy (see the section 'Sequencing of treatment', p. 52).

Quality and characteristics of studies

Both included studies were large multicentre Phase III trials with mature results written up in peer-reviewed journal articles.

Both studies had an upper age limit of 75 years (*Table 15*), and the median age of populations in treatment arms ranged from 58 to 62 years, a substantially younger population than in the NHS population (see the sections 'Epidemiology', p. 3, and 'Quality and characteristics of studies', p. 16). Both studies also excluded people with bulky disease, presence or history of CNS metastases, unresolved bowel obstruction or diarrhoea, a past or current history of neoplasm other than colorectal carcinoma, curatively treated non-melanoma skin cancer or *in situ* carcinoma of the cervix.[1] All of which is to say that the populations in both studies were relatively healthy in the context of the range of people with end-stage colorectal cancer.

In one of the studies, treatment arms appeared to be balanced in terms of baseline performance status.[68] In the comparison of Ir versus BSC, there was a significant difference in terms of WHO PS, likely to bias the outcomes in favour of irinotecan. The investigators stratified the results of their multivariate analysis according to PS, but as no adjusted measure of relative or absolute risk was provided, it is impossible to assess the extent of the treatment effect.[73]

Treatment arms were balanced with regard to the site of the primary tumour and previous treatment.

Neither trial reported an adequate method of allocation concealment or randomisation. One trial was reported as open label,[69] while the presence or absence of blinding was unclear in the other.[68] Both trials performed an ITT analysis and, in one, withdrawals were fully accounted for.[68]

In summary, as far as can be ascertained from the published literature, both trials were relatively well designed and conducted. However, the treatment arm populations in one trial appear to be

TABLE 15 *Second-line Ir: study characteristics*

Study	Participants	Interventions	Outcomes	Comments
Cunningham and Glimelius, 1999 (UK)[69]	Age 18–75 years; histologically proven metastatic CRC; WHO PS $\leq$2; disease progression on 5-FU or within 6 months of last 5-FU; 1 previous adjuvant or $\leq$2 palliative 5-FU-based regimens; no previous Ir-based chemotherapy	*Arm 1* (Ir + BSC): Ir 350 mg m^{-2} (300 mg m^{-2} aged >70 or WHO PS = 2) 90-minute i.v. infusion 1 × 3 weeks + BSC (*n* = 189) *Arm 2* (BSC): BSC alone (*n* = 90)	OS; PS; body weight; tumour-related symptoms; QoL	28 (31%) BSC alone received poststudy chemotherapy. Analysis by ITT
Rougier *et al.*, 1998 (Europe)[68]	Age 18–75 years; histologically proven progressive metastatic adenocarcinoma of the colon or rectum; WHO PS $\leq$2; disease progression on or within 3 months of 5-FU; $\leq$1 previous 5-FU regimen	*Arm 1* (Ir + 5-FU): Ir 350 mg m^{-2} (300 mg m^{-2} age >70 or WHO PS = 2) 90-minute i.v. infusion 1 × 3 weeks (*n* = 133) *Arm 2* (5-FU): FU (de Gramont, Lokich or AIO) (*n* = 134)	OS; PFS; tumour response; pain-free survival; PS; symptoms; tolerance; QoL; weight loss	Randomisation stratified by centre and PS. Significant difference at baseline in percentage of patients with hyperleukocytosis (mean WBC counts similar in both arms). Analysis by ITT, but 11 patients were excluded (6 from the Ir and 5 from the non-Ir group) who did not receive the study medication

unbalanced, with unknown consequences for the estimation of treatment effect.[68] The populations were relatively young and fit (*Table 16*) by comparison with the majority of people in the UK who will receive second-line chemotherapy for ACRC, which also means that treatment effects are not necessarily transferable.

An assessment of the quality of the studies is given in *Table 17*.

Outcomes: OS and PFS

Survival outcomes for studies involving second-line Ir are summarised in *Table 18*. In one trial, Ir was significantly more effective than 5-FU, improving median OS by 2.3 months and median PFS by 1.3 months.[68] In the other trial, Ir + BSC was significantly more effective than BSC alone, improving median OS by 2.7 months (PFS was not reported).[69]

Outcomes: response rates

Response rates are reported in *Table 19*. Ir provided a better response than 5-FU.

Outcomes: toxicities

Gastrointestinal, haematological and neurological toxicities are reported in *Tables 20*, *21* and *22*, respectively.

The most frequently occurring adverse effects noted in the irinotecan group were grade 3–4 gastrointestinal adverse effects such as vomiting, diarrhoea and mucositis. Compared with the irinotecan group, patients in BSC group had more grade 3–4 neurological toxicities (asthenia and pain). In the trial that compared Ir with 5-FU more adverse effects were noted in the Ir group. This was most marked with gastrointestinal adverse toxicities, with significantly more grade 3–4 nausea/vomiting ($p = 0.007$) and diarrhoea ($p = 0.03$) in the Ir arm.[68] The other trial reported that patients in the BSC group had significantly more grade 3–4 neurological toxicities such as asthenia ($p = 0.006$) and pain ($p = 0.008$). Diarrhoea was more frequent ($p = 0.02$) in the Ir than in the BSC-group.[69]

Outcomes: quality of life

Quality of life outcomes are reported in *Table 23*. Second-line Ir was significantly better than BSC in the maintenance of quality of life,[69] but there was no significant difference between Ir and 5-FU.[74]

Discussion of results

Strength of the evidence (internal validity)

With the exception of blinding, no trial reported clearly inadequate approaches to generic components of clinical trial design that minimise

TABLE 16 *Second-line Ir: population characteristics*

Study	Median age	Male (%)	WHO PS	Site of primary tumour	Site of metastases	Previous 5-FU
Cunningham and Glimelius, 1999[69]	*Arm 1* (Ir + BSC): 59 *Arm 2* (BSC): 62	NR	*Arm 1* (Ir + BSC): 0 = 47%, 1 = 39%, 2 = 14% *Arm 2* (BSC): 0 = 31%, 1 = 46%, 2 = 23%	*Arm 1* (Ir+BSC): right colon 21%, left colon 32%, rectum 40% *Arm 2* (BSC): colon (right) 20%, colon (left) 30%, rectum 42%	*Arm 1* (Ir + BSC): liver 80%, lung 37%, peritoneum 7% *Arm 2* (BSC): liver 77%, lung 30%, peritoneum 10%	Documented progression on prior 5-FU: *Arm 1* (Ir + BSC): 70% *Arm 2* (BSC): 63%
Rougier *et al.*, 1998[68]	*Arm 1* (Ir): 58 (30–75) *Arm 2* (5-FU): 58 (25–75)	*Arm 1* (Ir): 56.7 *Arm 2* (5-FU): 65.1	*Arm 1* (Ir): 0 = 57.5%, 1 = 34.6%, 2 = 7.9% *Arm 2* (5-FU): 0 = 53.5%, 1 = 43.4%, 2 = 3.1%	*Arm 1* (Ir): right colon 21.3%, left colon 35.4%, rectum 42.5%, rectosigmoid 0.8% *Arm 2* (5-FU): right colon 21.7%, left colon 40.3%, rectum 37.2%, rectosigmoid 0.8%	*Arm 1* (Ir): liver 78.7%, lung 34.6%, peritoneum 15.0% *Arm 2* (5-FU): liver 76.0%, lung 41.1%, peritoneum 10.1%	*Arm 1* (Ir): adjuvant 13.4%, palliative/adjuvant 86.6% *Arm 2* (5-FU): adjuvant 14.7%, palliative/adjuvant 85.3%

TABLE 17 *Second-line Ir: quality assessment*

Study	Allocation concealment	Randomisation	Blinding	Withdrawals	Comments
Cunningham and Glimelius, 1999[69]	Unclear	Unclear	Inadequate	Unclear	Study was powered adequately to have an 80% power to detect a difference in OS of 35%. A greater proportion of patients in the Ir arm had a WHO PS status of 0. It is unclear whether analysis was by ITT
Rougier *et al.*, 1998[68]	Unclear	Unclear	Unclear	Adequate	A significant difference was found at baseline for the percentage of patients with hyperleukocytosis, but the mean WBC counts in the two groups were similar. Reasons were given for the 11 participants (4%) who dropped out (protocol violation, withdrawn consent, etc.)

TABLE 18 *Second-line Ir: survival outcomes*

Treatment/study	**Follow-up (months)**		**OS (months)**		
Ir vs 5-FU		**Ir**	**5-FU**	**HR (95% CI)**	***p***
Rougier *et al.*, 1998[68]	15	10.8	8.5	0.70	0.035
Ir + BSC vs BSC		**Ir + BSC**	**BSC**	**HR (95% CI)**	***p***
Cunningham and Glimelius, 1999[69]	12.9	9.2	6.5	0.54	0.0001
Treatment/study	**Follow-up (months)**		**PFS (months)**		
Ir vs 5-FU		**Ir**	**5-FU**	**HR (95% CI)**	***p***
Rougier *et al.*, 1998[68]	15	4.2	2.9	0.78	0.03
Ir + BSC vs BSC		**Ir + BSC**	**BSC**	**HR (95% CI)**	***p***
Cunningham and Glimelius, 1999[69]	12.9	NR	NR	NR	NR

TABLE 19 *Second-line Ir: response rates*

Treatment/study		**Response rate (%)**	
Ir vs 5-FU	**Ir**	**5-FU**	***p***
Rougier *et al.*, 1998[68]	4.5 (PR) 10.5 (UR)	0.7 (PR) 4.4 (UR)	NR
Ir + BSC vs BSC	**Ir + BSC**	**BSC**	***p***
Cunningham and Glimelius, 1999[69]	NR	NR	NR

PR, partial response; UR, unconfirmed response.

TABLE 20 *Second-line Ir: gastrointestinal toxicity*

Treatment/study	**Toxicity (grade 3–4)**							
	Vomiting (%)		**Nausea (%)**		**Diarrhoea (%)**		**Stomatitis (mucositis) (%)**	
Ir vs 5-FU	**Ir**	**5-FU**	**Ir**	**5-FU**	**Ir**	**5-FU**	**Ir**	**5-FU**
Rougier *et al.*, 1998[68]	14	NR	NR	NR	22	11	NR	NR (5)
Ir + BSC vs BSC	**Ir + BSC**	**BSC**	**Ir + BSC**	**BSC**	**Ir + BSC**	**BSC**	**Ir + BSC**	**BSC**
Cunningham and Glimelius, 1999[69]	14	8	NR	NR	22	6	NR (2)	NR (1)

systematic error (see the section 'Discussion of results', p. 24, for a full discussion). However, the internal validity of the survival outcomes was compromised by the use of unplanned further therapies in at least one trial. In the comparison of Ir and BSC, 7% of participants in the Ir arm and 60% of the BSC arm received further chemotherapy; this would exaggerate the treatment effect of BSC.

Applicability of the results (external validity)
The two study populations had median ages of between 10 and 15 years younger than that of the UK population of people with colorectal cancer. The concern that study populations in clinical trials represent younger, fitter populations than is representative of the NHS has been expressed in the section 'Discussion of results', p. 24. However, the literature suggests that single-agent Ir can be

TABLE 21 *Second-line Ir: haematological toxicity*

Treatment/study	Toxicity (grade 3–4)									
	Neutropenia (%)		Anaemia (%)		Leucopenia (%)		Febrile neutropenia (%)		Platelets (%)	
Ir vs 5-FU	**Ir**	**5-FU**	**Ir**	**5-FU**	**Ir**	**5-FU**	**Ir**	**5-FU**	**Ir**	**5-FU**
Rougier *et al.*, 1998[68a]	14	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ir + BSC vs BSC	**Ir + BSC**	**BSC**	**Ir + BSC**	**BSC**	**Ir + BSC**	**BSC**	**Ir + BSC**	**BSC**	**Ir + BSC**	**BSC**
Cunningham and Glimelius, 1999[69a]	22	NR	NR	NR	NR	NR	NR	NR	NR	NR

[a] Infusional administration.

TABLE 22 *Second-line Ir: neurological and other toxicity*

Ir +5-FU vs. 5-FU Treatment/Study	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**	**Ir + 5-FU**	**5-FU**
	Toxicity (grade 3–4)											
	Neuropathy (%)		Asthenia (%)		Pain (%)		Alopecia (%)		Fatigue (%)		Hand–foot syndrome (%)	
Ir vs 5-FU	**Ir**	**5-FU**	**Ir**	**5-FU**	**Ir**	**5-FU**	**Ir**	**5-FU**	**Ir**	**5-FU**	**Ir**	**5-FU**
Rougier *et al.*, 1998[68]	NR	NR	13	12	17	13	NR	NR	NR	NR	NR	8
Ir + BSC vs BSC	**Ir + BSC**	**BSC**	**Ir + BSC**	**BSC**	**Ir + BSC**	**BSC**	**Ir + BSC**	**BSC**	**Ir + BSC**	**BSC**	**Ir + BSC**	**BSC**
Cunningham and Glimelius, 1999[69]	NR	NR	15	19	19	22	NR	NR	NR	NR	NR	NR

TABLE 23 Second-line Ir: quality of life

Study	Methods of assessment	Findings
Cunningham and Glimelius, 1999[69]	EORTC QLQ-C30	For Ir patients, 71% QoL completed; in BSC plus treatment with topoisomerase-1 inhibitor, 72% QoL completed. Global QoL decreased after start of study in BSC group, but Ir patients maintained scores for long period. Highly significant difference in mean scores between groups. Asthenia, dyspnoea and appetite loss were worse in BSC group. Diarrhoea was worse in Ir patients than controls
Rougier *et al.*, 1998[68]	EORTC QLQ-C30	67% completion in Ir group and 70% completion in 5-FU group. No significant difference on QoL during treatment between Ir and 5-FU. No significant differences on global health status score

safe and effective in second-line treatment of older people with ACRC. A Phase III RCT comparing weekly or 3-weekly schedules of Ir in elderly people with 5-FU-refractory ACRC found both schedules demonstrated similar efficacy and quality of life. The 3-weekly schedule produced a significantly lower incidence of severe diarrhoea.[75] A Phase II trial reported that people over 70 years with 5-FU-refractory ACRC appear to derive the same benefit as those under 70, without experiencing greater toxicity with second-line Ir monotherapy. Additional findings provided no support for recommendations to give a reduced starting dose to the elderly patients.[76] The manufacturer's dose adjustment guideline for Ir monotherapy recommends a reduced starting dose of 300 mg m^{-2} once every 3 weeks for people aged over 70 years with a WHO PS of 2.

Assessment of effectiveness

The synthesis of published and unpublished evidence suggests the following.

- In comparison with second-line 5-FU, irinotecan significantly improves median OS by over 2 months ($p = 0.035$) and median PFS by over 1 month ($p = 0.03$) in people with ACRC. In comparison with BSC, it improves median OS by over 2.5 months ($p = 0.0001$).
- Irinotecan monotherapy in second-line therapy appears to provide a response in more people than 5-FU, but with more toxicities. Irinotecan monotherapy causes more serious gastrointestinal and haematological toxicities than BSC, but fewer neurological toxicities such as asthenia ($p = 0.006$) and pain ($p = 0.008$).
- There is no evidence for a significant difference in quality of life between second-line irinotecan and 5-FU monotherapy but, despite additional toxicity, it maintains baseline quality of life longer than BSC alone.
- It is unknown to what extent outcomes for overall survival are confounded by over half of the trial participants in at least one trial receiving unplanned third-line therapy.
- Although the best data are based on an atypically young and fit population, other available evidence suggests that there is no significant difference between the efficacy and toxicity of second-line irinotecan monotherapy in older people.

Results: oxaliplatin – first-line combination

Quantity and quality of research available

Number of studies identified

The search retrieved 2105 citations.

Number and type of studies included

Four Phase III RCTs were retrieved that compared first-line Ox + 5-FU with 5-FU alone. In three trials, the 5-FU was delivered by continuous infusion in both arms.[42,77,78] In the fourth, 5-FU was delivered by continuous infusion with oxaliplatin, but by bolus infusion when delivered alone.[79] Data additional to those in the public domain were submitted to the review team as AIC for one trial.[42] All other trial data were derived from sources in the public domain. Study information is reported in *Table 24*. Trials comparing first-line Ox + 5-FU with Ir + 5-FU were discussed in the section 'Results: irinotecan – first-line combination' (p. 12).

Number and type of studies excluded, with reasons for specific exclusions

A flow chart is provided in Appendix 4, as recommended by the QUOROM statement,[43] and reasons for all trial exclusions are given in Appendix 5. One Phase II trial[80] and four Phase

TABLE 24 *First-line Ox: study characteristics*

Study	Participants	Interventions	Outcomes	Comments
de Gramont *et al.*, 2000 (Europe)[77]	Adenocarcinoma of the colon or rectum; unresectable metastases; ≥1 bidimensionally measurable lesion of >2 cm; adequate bone marrow, renal and hepatic function; WHO PS ≤2; ability to complete QoL questionnaires; prior adjuvant chemotherapy completed for ≥6 months	*Arm 1* (Ox + 5-FU): Ox 85 mg m^{-2} on day 1 only + 5-FU (de Gramont) + routine antiemetic prophylaxis (n = 210) *Arm 2* (5-FU): 5-FU (de Gramont) (n = 210)	PFS; tumour response; OS; QoL	Randomisation stratified by centre, PS and number of metastatic sites, using a minimisation procedure. Cross-over to the Ox + 5-FU arm when disease progression documented. 58% Ox + 5-FU and 61% 5-FU received poststudy chemotherapy including Ox and/or Ir. Analysis by ITT
Giacchetti *et al.*, 2000 (France)[78]	Aged ≤75; histologically proven CRC; bidimensionally measurable metastatic lesions, one diameter ≥20 mm; WHO PS ≤2; adequate bone marrow, renal and hepatic function; no previous chemotherapy or radiotherapy for metastatic disease; no prior adjuvant chemotherapy within 6 months	*Arm 1* (Ox + 5-FU): Ox (125 mg m^{-2}) 6-h i.v. infusion; 5-FU (chronomodulated, 5 days, 700 mg m^{-2} per day) + FA (300 mg m^{-2} per day) (n = 100) *Arm 2* (5-FU): 5-FU (chronomodulated, 5 days, 700 mg m^{-2} per day) + FA (300 mg m^{-2} per day) (n = 100)	Primary: tumour response; secondary: toxicity; PFS; OS	Randomisation by centre by blocks of four allows the possibility of selection bias. 57% 5-FU received Ox after failure. Analysis by ITT
Grothey *et al.*, 2001 (Germany)[79]	NR (both arms were well balanced for age, gender, PS, primary and metastatic tumour sites)	*Arm 1* (5-FU): 5-FU bolus 425 mg m^{-2}, FA 20 mg m^{-2}, days 1–5 every 5 weeks (Mayo) (n = 129) *Arm 2* (Ox + 5-FU): Ox 50 mg m^{-2}, 2–hour infusion, 5-FU 2000 mg m^{-2}, 24-hour infusion, FA 500 mg m^{-2},days 1, 8, 15 and 22 every 5 weeks (AIO) (n = 123)	OS; PFS; response rate; toxicity	Analysis by ITT. 15.4% of patients in Ox+5-FU had received prior adjuvant chemotherapy vs 24.8 % in 5-FU(Mayo) group
Seymour, 2004 (UK)[42]	Histologically confirmed adenocarcinoma of the colon or rectum; inoperable metastatic or locoregional disease (synchronous or recurrence); no previous chemotherapy for established metastatic disease, measurable disease and adequate bone marrow, hepatobiliary and renal function; WHO PS ≤2 and considered fit and able to undergo all possible treatments; for women of childbearing potential, negative pregnancy test and adequate contraceptive precautions	*Arm A* (MdG followed by Ir) *Arm B* (MdG followed by Ir MdG) *Arm C* (Ir MdG) *Arm D* (MdG followed by Ox MdG) *Arm E* (Ox MdG)	Primary: OS (all causes of death); secondary: PFS; objective response rates; QoL (palliation, toxicity, functional impairment); economic evaluation	Analysis by ITT

TABLE 25 *First line Ox: population characteristics*

Study	Median age	Male (%)	WHO PS	Site of primary tumour	Site of metastases	Previous 5-FU
de Gramont *et al.*, 2000[77]	*Arm 1* (5-FU): 63 (22–76) *Arm 2* (Ox + 5-FU): 63 (20–76)	*Arm 1* (5-FU): 58.1 *Arm 2* (Ox + 5-FU): 60.5	*Arm 1* (5-FU): 0 = 48.6%, 1 = 41.9%, 2 = 9.5% *Arm 2* (Ox + 5-FU): 0 = 43.3%, 1 = 46.2%, 2 = 10.5%	*Arm 1* (5-FU): colon 70%, rectum 29%, multiple or not specified 1% *Arm 2* (Ox + 5-FU): colon 71.9%, rectum 28.1%, multiple or not specified 0%	*Arm 1* (5-FU): liver 82.4%, lung 30%, other 11.4% *Arm 2* (Ox + 5-FU): liver 86.7%, lung 23.4%, other 12.4%	*Arm 1* (5-FU): yes 20.5%, no 79.5% *Arm 2* (Ox + 5-FU): yes 20%, no 80%
Giacchetti *et al.*, 2000[78]	*Arm 1*(5-FU): 61 *Arm 2* (Ox + 5-FU): 61	*Arm 1* (5-FU): 64 *Arm 2* (Ox + 5-FU): 66	*Arm 1* (5-FU): 0 = 66%, 1 = 27%, 2 = 7% *Arm 2* (Ox + 5-FU): 0 = 69%, 1 = 20%, 2 = 11%	*Arm 1* (5-FU): colon 77%, rectum 23% *Arm 2* (Ox + 5-FU): colon 66%, rectum 34%	*Arm 1* (5-FU): liver 86%, lung 37%, other 24% *Arm 2* (Ox + 5-FU): liver 88%, lung 35%, other 24%	*Arm 1* (5-FU): 23% *Arm 2* (Ox + 5-FU): 10%
Grothey *et al.*, 2001[79]	NR	NR	NR	NR	NR	*Arm 1* (Ox + 5-FU): 15.4% *Arm 2* (Mayo): 24.8% received prior adjuvant chemotherapy
Seymour, 2004[42]	NR	NR	NR	NR	NR	

III trials, which compared different oxaliplatin regimens,[30,81–83] included in the original review[1] and industry submissions,[52] were excluded from this review. A further Phase III trial was not included in the review as no mature survival data were available.[84]

Quality and characteristics of studies

All four studies were large multicentre studies. In three cases, mature results were written up in peer-reviewed journal articles.[77] In one case, 2-year follow-up data were mature, but had only recently been analysed and presented at a conference.[42]

One included study had an upper age limit of 75 years.[78] The others stated no upper age limit, one including participants up to the age of 76,[77] there being no data for the other two (*Table 25*). The median age of the treatment arms across all those studies for which it was reported was between 61 and 63 years.[77] This means that the trials present a substantially younger population than the NHS population of colorectal cancer patients (see the sections 'Epidemiology', p. 3 and 'Quality and characteristics of studies', p. 16).

Baseline performance status was relatively well balanced for the two trials for which data were available.[77] In both trials for which data was available, the site of primary tumour was the colon for the majority of participants in both arms.[77]

In one study, participants who had previously received adjuvant 5-FU were evenly distributed between arms. In two, there was some disparity between arms: in both cases, around twice as many participants in the 5-FU alone arm had received previous 5-FU as in the Ox + 5-FU[78,79] and, in

***TABLE 26** First-line Ox: quality assessment*

Study	Allocation concealment	Randomisation	Blinding	Withdrawals	Comments
de Gramont *et al.*, 2000[77a]	Unclear	Unclear	Unclear	Adequate	7 participants (2%) unassessable (ineligible, not treated, withdrawals, early disease-related death)
Giacchetti *et al.*, 2000[78a]	Adequate	Adequate	Unclear	Adequate	Allocation concealment: central randomisation. Randomisation: computer generated. Incidence of primary rectal cancer was greater for Ox + 5-FU; twice as many patients on 5-FU alone had received prior 5-FU (p = 0.013); half as many patients on 5-FU alone had normal CEA levels (p = 0.03). 180 (80%) of the participants were evaluable; analysis was by ITT
Grothey *et al.*, 2001[79b]	Unclear	Unclear	Unclear	Adequate	Fewer patients on Ox + 5-FU had received prior chemotherapy than those on 5-FU alone (p = 0.084). 96% of patients were followed up for survival outcomes; analysis was by ITT
Seymour, 2004[42a]	Adequate	Adequate			

[a] Infusional administration; [b] Ox + infusional 5-FU versus bolus 5-FU.

one, only half as many patients in the 5-FU alone arm had normal carcinoembryonic antigen (CEA) levels as in the Ox + 5-FU arm (raised CEA levels are associated with poor prognosis).[78] These differences were statistically significant and, in each case, may have biased the trial outcomes in favour of Ox + 5-FU.

Only two trials reported an adequate method of allocation concealment (central randomisation by telephone after confirmation of eligibility);[78] in the other cases the method of allocation concealment was unclear. The same two trials reported an adequate method of randomisation (computer-generated numbers). Only one trial reported large numbers of withdrawals (20%).[78] Where reported, all withdrawals were accounted for and all trials analysed by ITT. No trials reported blinding, and one reported open-label status.[42]

In summary, as far as can be ascertained from the published literature, all of the trials were relatively well designed and conducted. There were issues with baseline comparability in two trials. As with other comparisons in this review, trial populations were relatively young and, by implication, fit, which may exaggerate the extent of the likely treatment effect in the UK population.

An assessment of the quality of the studies is given in *Table 26*.

Outcomes: OS and PFS

Survival outcomes for studies involving first line Ox are summarised in *Table 27*. In all four trials, the addition of Ox to 5-FU did not significantly improve median OS (although see caveat on unplanned second-line therapies in the section 'Discussion of results', p. 36), but did significantly improve median PFS (by between 2.5 and 2.8 months).

Trials that compared Ox + 5-FU with 5-FU alone were meta-analysed. The analysis of OS and PFS (*Figures 6* and 7), using hazard ratios derived from the literature, published survival curves and data submitted as AIC, involved four trials (1939 participants).[77]

OS was not significantly better for individuals treated with Ox + 5-FU than for those treated with 5-FU alone (HR = 0.93, 95% CI 0.83 to 1.03, $p = 0.17$), although readers should note the caveat on unplanned second-line therapies in the section 'Discussion of results', in the next column. There was no significant heterogeneity between studies or subgroups ($\chi^2 = 2.68$, df = 3, $p = 0.44$, $I^2 = 0\%$), regardless of how 5-FU was administered.

TABLE 27 *First-line Ox: survival outcomes*

Treatment/study	Follow-up (months)	OS (months)			
Ox + 5-FU vs 5-FU		**Ox + 5-FU**	**5-FU**	**HR (95% CI)**	***p***
de Gramont *et al.*, 2000[77a]	27.7	16.2	14.7	0.86	0.12
Giacchetti *et al.*, 2000[78a]	47	19.4	19.9	1.09	NS
Grothey *et al.*, 2002[85b]	8.1 vs 8.8	20.4	16.1	0.80	0.19
Seymour *et al.*, 2004[60a]	36	15	13.7	0.96 (0.83 to 1.12)	0.608
Treatment/study	**Follow-up (months)**	**PFS (months)**			
Ox + 5-FU vs 5-FU		**Ox + 5-FU**	**5-FU**	**HR (95% CI)**	***p***
de Gramont *et al.*, 2000[77a]	27.7	9.0	6.2	0.73	0.0003
Giacchetti *et al.*, 2000[78a]	47	8.7	6.1	0.83	0.048
Grothey *et al.*, 2002[85b]	27.3	7.9	5.3	0.75	0.0001
Seymour *et al.*, 2004[60a]	36	8.8	6.3	0.75 (0.66 to 0.86)	<0.001

[a] Infusional administration; [b] Ox + infusional 5-FU versus bolus 5-FU.

PFS was significantly better for individuals treated with Ox + 5-FU than for those treated with 5-FU alone (HR = 0.75, 95% CI 0.69 to 0.82, $p < 0.00001$). There was no significant heterogeneity between studies or subgroups ($\chi^2 = 0.80$, df = 3, $p = 0.85$, $I^2 = 0\%$), regardless of how 5-FU was administered.

Outcomes: response rates

Response rates are reported in *Table 28*. Response rates were between 27 and 37% higher in the Ox arm (statistically significant in every case).[77]

Outcomes: toxicities

Gastrointestinal, haematological and neurological toxicities are reported in *Tables 29*, *30* and *31*, respectively. Overall, grade 3–4 gastrointestinal (vomiting, nausea and diarrhoea) and haematological (neutropenia, anaemia and platelets) toxicities were more frequent with Ox than with 5-FU. Grade 3–4 neurological adverse events such as neuropathy and hand–foot syndrome also had more incidences in the Ox group. Pain and alopecia were more frequent in the 5-FU group. In one study, significantly more people in the Ox + 5-FU arm experienced neutropenia ($p < 0.001$), nausea ($p = 0.043$), vomiting ($p = 0.043$), diarrhoea ($p = 0.015$), mucositis ($p = 0.019$) and neurological toxicities ($p < 0.001$).[77] In another, a statistically significant ratio was only observed for diarrhoea ($p = 0.001$) and nausea/vomiting ($p = 0.001$).[78] A third study reported that neutropenia was less frequent and severe in the Ox arm ($p = 0.0003$).[85]

Outcomes: quality of life

Quality of life outcomes are reported in *Table 32*. Data on quality-of-life were only available for one trial. Time to deterioration in global health status was prolonged in the Ox + 5-FU arm, but there was no significant difference between study arms in overall quality of life.[77]

Discussion of results

Strength of the evidence (internal validity)

With the exception of blinding, no trial reported clearly inadequate approaches to generic components of clinical trial design that minimise systematic error (see the section 'Discussion of results', p. 24, for comments on blinding in oncology trials).

However, the internal validity of the primary outcome, OS, was compromised by the use of unplanned second-line therapies in three trials (see the section 'Discussion of results', p. 24).[77] In one trial, 59% of all participants received further chemotherapy and 25% of all participants received irinotecan.[77] In another study, 71% of all participants received second-line irinotecan.[85] The other trial did not quantify the amount of participants who had received further treatment.[78] The confounding effect of this unplanned treatment on the primary outcome, OS, is likely to have exaggerated the results of the 5-FU monotherapy arm, where participants randomised to one active chemotherapy would in fact be receiving two such therapies (see the section 'Discussion of results', p. 55, for a discussion on

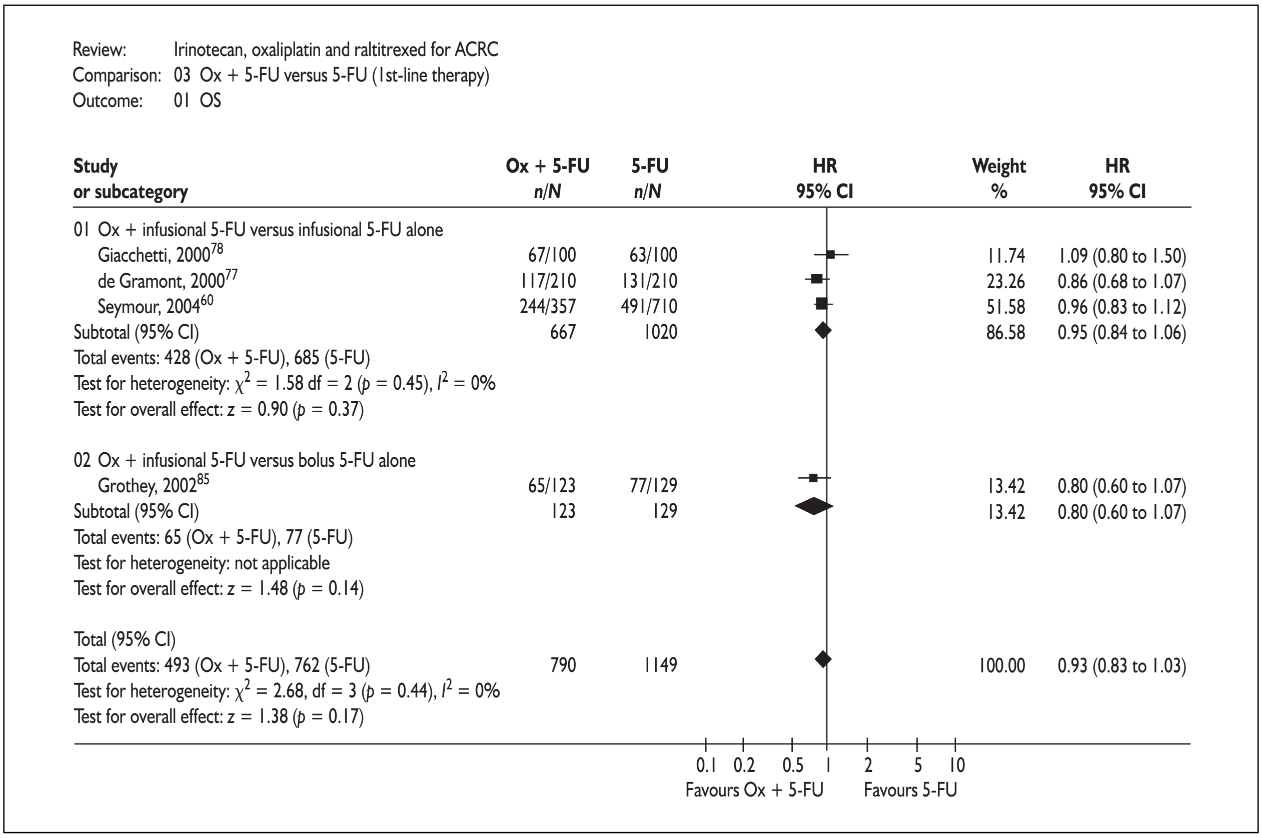


***FIGURE 6** Ox + 5-FU versus 5-FU (first line): OS*

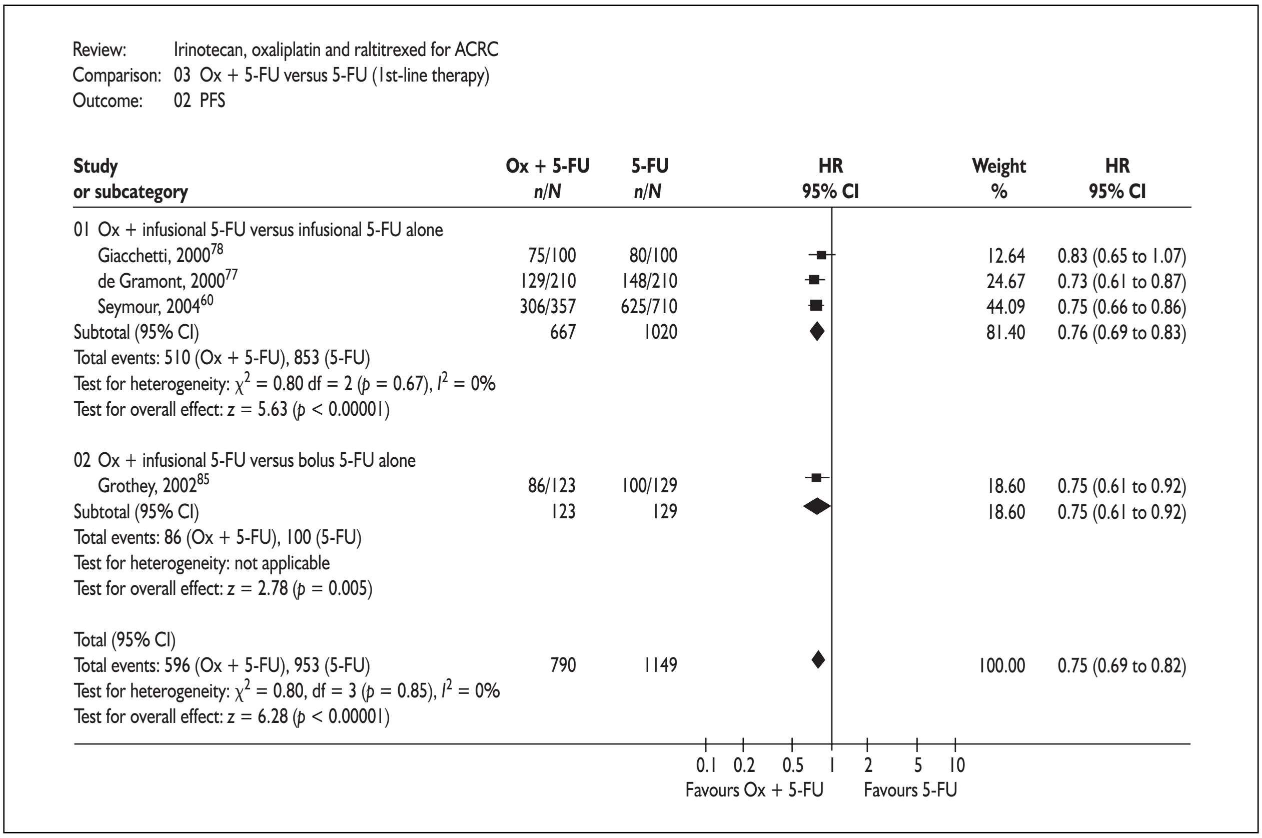


***FIGURE 7** Ox + 5-FU versus 5-FU (first line): PFS*

TABLE 28 *First-line Ox: response rates*

Treatment/study	Response rate (%)		
Ox + 5-FU vs 5-FU	**Ox + 5-FU**	**5-FU**	***p***
de Gramont *et al.*, 2000[77a]	50	21.9	0.0001
Giacchetti *et al.*, 2000[78a]	53	16	<0.0001
Grothey *et al.*, 2002[85b]	49.1	22.6	<0.0001
Seymour *et al.*, 2004[60a]	No data	No data	No data

[a] Infusional administration; [b] Ox + infusional 5-FU versus bolus 5-FU.

TABLE 29 *First-line Ox: gastrointestinal toxicity*

Treatment/study	Toxicity (grade 3–4)							
	Vomiting (%)		Nausea (%)		Diarrhoea (%)		Stomatitis (mucositis) (%)	
Ox + 5-FU vs 5-FU	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**
de Gramont *et al.*, 2000[77a]	NR	NR	NR	NR	11.9	5.3	NR	NR
Giacchetti *et al.*, 2000[78a]	25	2	–	–	43 (G3)	5 (G3)	NR (10)	NR (4)
Grothey *et al.*, 2002[85b]	7.6	3.2	11	3.2	27.1	16.9	NR (5.1)	NR (10.5)
Seymour *et al.*, 2004[60a]	7.6	5.9	5.7	5.9	8.8	12.6	1.8	2.1

[a] Infusional administration; [b] Ox + infusional 5-FU versus bolus 5-FU.

the correlation between the number of active therapies and survival advantage). Weight is added to this proposition when one compares the median OS times of 14–20 months for 5-FU monotherapy in included studies with those from studies where participants did not cross to other active therapies (consistently between 10 and 12 months[33]).

In two trials, variations in the baseline comparability of populations may also have affected the internal validity of studies to an unknown extent.[78,79]

Applicability of the results (external validity)
The issue of unplanned second-line therapies also affects the applicability of the results (see the section 'Discussion of results', p. 24, for further comment).

The prudence of generalising from the included study populations, which are comparatively young, to the NHS setting may also be affected by the atypically young populations. However, an observational study comparing Ox + 5-FU in people above and below 70 years demonstrated comparable benefit without increased toxicity in the older population.[86] These findings are confirmed in another cases series of people aged 70 years and over.[87] Two included trials confirm that patients over 65 years did not experience increased toxicity with first-line oxaliplatin compared with younger participants.[51]

Alternative dosing strategies
It has been proposed that oxaliplatin can be just as effective on a less intensive schedule, with breaks in the treatment: the 'stop and go' procedure.[88] At least one included study allowed treatment breaks for participants receiving oxaliplatin, but results are not available from this study as to the success of the strategem.[42] The use of intensified and repeated brief courses of Ox + 5-FU (FOLFOX) is currently being evaluated in the OPTIMOX study, a Phase III RCT that compares the following regimens as first-line therapy: (1) FOLFOX4 until progression; (2) FOLFOX7 (six cycles) followed by simplified LV5-FU2 (12 cycles) and FOLFOX7 reintroduction. The six cycles with FOLFOX7 followed by simplified LV5-FU2 achieved identical response rates and PFS with reduced toxicity[81] in a multivariate analysis of 37 patients aged 75 years or older in the OPTIMOX study. Age did not appear to be a prognostic factor for tolerance or efficacy, suggesting that these outcomes can be maintained with FOLFOX regimens even among older individuals.[89]

TABLE 30 *First-line Ox: haematological toxicity*

Treatment/study	Toxicity (grade 3–4)									
	Neutropenia (%)		Anaemia (%)		Leucopenia (%)		Febrile neutropenia (%)		Platelets (%)	
Ox + 5-FU vs. 5-FU	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**
de Gramont *et al.*, 2000[77a]	41.7	5.3	NR	NR	NR	NR	NR	NR	2 (G3) 0.5 (G4)	0.5 (G3) 0.0 (G4)
Giacchetti *et al.*, 2000[78a]	2	1	1	3	NR	NR	NR	NR	1	0
Grothey *et al.*, 2002[85b]	6.7	23.4	NR	NR	NR	NR	NR	NR	2.5	0
Seymour *et al.*, 2004[60a]	27.1	13.7	7.0	3.7	NR	NR	NR	NR	2.4	0.6

[a] Infusional administration; [b] Ox + infusional 5-FU versus bolus 5-FU.

TABLE 31 *First-line Ox: neurological and other toxicity*

Treatment/study	Toxicity (grade 3–4)											
	Neuropathy (%)		Asthenia (%)		Pain (%)		Alopecia (%)		Fatigue (%)		Hand–foot syndrome (%)	
Ox + 5-FU vs 5-FU	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**
de Gramont *et al.*, 2000[77a]	18.2	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Giacchetti *et al.*, 2000[78a]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	1
Grothey *et al.*, 2002[85b]	NR	NR	NR	NR	NR	NR	4.2	4.0	NR	NR	5.1	0.8
Seymour *et al.*, 2004[60a]	10.3	0.7	NR	NR	16.6	21.2	1.2	4.8	NR	NR	0.9	1.7

[a] Infusional administration; [b] Ox + infusional 5-FU versus bolus 5-FU.

TABLE 32 First-line Ox: quality of life

Study	Quality of life – methods of assessment	Findings
de Gramont *et al.*, 2000[77a]	EORTC QLQ-C30 (version 2)	351 patients (83.6%) completed QoL assessment. Neither response to treatment nor occurrence of side-effects significantly influenced patients' QoL. Time to deterioration in global health status was prolonged in Ox + 5-FU/LV compared with 5-FU/LV alone group
Giacchetti *et al.*, 2000[78a]	No data/NR	
Grothey *et al.*, 2002[85b]	No data/NR	
Seymour *et al.*, 2004[60a]	No data	

[a] Infusional administration; [b] Ox + infusional 5-FU versus bolus 5-FU.

A study by Maindrault-Gœbel and colleagues[90] found that the reintroduction of oxaliplatin, following a gap in treatment for neurotoxicity or to delay the development of resistance, was safe and clinically beneficial. Reintroduction of oxaliplatin achieved a response or stabilisation in almost three-quarters of patients, which would appear to support the findings of the OPTIMOX study.

Assessment of effectiveness

The synthesis of published and unpublished evidence suggests the following.

- The addition of oxaliplatin to first-line 5-FU has not been shown significantly to improve median OS, but does significantly improve median PFS by between 2.5 and 2.8 months ($p < 0.00001$) in people with ACRC. Although no survival advantage has been demonstrated, it is believed that outcomes for OS are confounded by over half of the trial participants in three trials receiving unplanned second-line therapy, that is, those on 5-FU monotherapy receiving second-line oxaliplatin.
- Combination therapy with oxaliplatin and 5-FU is associated with significantly higher response rates than 5-FU alone ($p < 0.0001$).
- Combination therapy with oxaliplatin and 5-FU is associated with more serious gastrointestinal and haematological toxicities, which were more frequent with oxaliplatin than with 5-FU. Neurological adverse events such as neuropathy and hand–foot syndrome were also more common, but pain and alopecia were more frequent in the 5-FU monotherapy group.
- There is no evidence for a significant difference in quality of life between first-line oxaliplatin combination therapy and 5-FU monotherapy, although the former maintains baseline quality of life for longer.
- Although the best data are based on an atypically young and fit population, other available evidence suggests that there is no significant difference between the efficacy and toxicity of first-line irinotecan combination therapy in older people.
- Schedules that offer treatment breaks do not appear to reduce clinical effectiveness, but may reduce toxicity.

Results: oxaliplatin – second-line combination

Quantity and quality of research available

Number of studies identified

The search retrieved 2105 citations.

Number and type of studies included

One Phase III RCT was retrieved that compared second-line Ox + infusional 5-FU with infusional 5-FU alone.[91]

Number and type of studies excluded, with reasons for specific exclusions

A flowchart is provided in Appendix 4, as recommended by the QUOROM statement,[43] and reasons for all trial exclusions are given in Appendix 5. Two Phase II trials[92] included in the original review[1] and industry submissions,[52] were excluded from this review. The results of two studies that randomised participants to treatment sequences including second-line oxaliplatin[51] are not presented in this section, because they analysed primary survival outcomes from the time of randomisation to first line therapy (see the section 'Sequencing of treatment', p. 52).

TABLE 33 *Second-line Ox: study characteristics*

Study	Participants	Interventions	Outcomes	Comments
Rothenberg *et al.*, 2003 (USA)[93]	Adenocarcinoma of the colon or rectum; progressive disease during or within 6 months of Ir + 5-FU as first-line treatment for metastatic or locally advanced CRC; age ⩾18 years, KPS ⩾50; measurable metastatic disease by RECIST criteria; normal or near-normal baseline organ function, ability to complete tumour-related symptom questionnaire	*Arm 1* (5-FU): FA 200 mg m^{-2} over 2 h, 5-FU 400 mg m^{-2} bolus, 5-FU 600 mg m^{-2} C.I. over 22 h, days 1 and 2 every 2 weeks (de Gramont) (n = 272) *Arm 2* (Ox + 5-FU): Oxaliplatin 85 mg m^{-2} IV day 1 + FA 200 mg m^{-2} over 2 h, 5-FU 400 mg m^{-2} bolus, 5-FU 600 mg m^{-2} C.I. over 2 h, days 1 and 2, every 2 weeks (de Gramont) (n = 270)	Primary: OS. Secondary: objective response rate; time to tumour progression; time to tumour symptom worsening; safety	Analysis by ITT

KPS, Karnofsky Performance Scale, RECIST, Research Evaluation Criteria in Solid Tumours.

TABLE 34 *Second-line Ox: population characteristics*

Study	Median age	Male (%)	WHO PS	Site of primary tumour	Site of metastases	Previous 5-FU
Rothenberg *et al.*, 2003[93]	*Arm 1* (5-FU2): 59 (15–80) *Arm 2* (Ox + 5-FU): 59 (22–88)	*Arm 1* (5-FU2): 56 *Arm 2* (Ox + 5-FU): 57	KPS: *Arm 1* (5-FU2): 70–100 = 96%, 50–60 = 4% *Arm 2* (Ox + 5-FU): 70–100 = 97%, 50–60 = 3%	*Arm 1* (5-FU2): colon 73%, rectum 18%, colorectal 9% *Arm 2* (Ox + 5-FU): colon 69%, rectum 18%, colorectal 13%	Number of metastatic organs: *Arm 1* (5-FU2): 1 = 36%, ⩾2 = 64% *Arm 2* (Ox + 5-FU): 1 = 35%, ⩾2 = 65%	100%

Quality and characteristics of studies

The study was a large multicentre study. Mature results were written up in a peer-reviewed journal article.

No upper age limit was stated (*Table 33*) and participants of up to 88 years of age were included (*Table 34*). However, the median age was 59 years in both arms, a substantially younger population than the NHS population of people with colorectal cancer (see the sections 'Epidemiology', p. 3, and 'Quality and characteristics of studies', p. 16).

Baseline performance status was well balanced, as was the site of primary tumour in both arms. The number of participants who had previously received 5-FU was not reported.

Not enough information on the design and conduct of the trial was available to comment on its quality (*Table 35*), and results should be treated with caution until such time as they are published in a peer-reviewed journal.

Outcomes: OS and PFS

Survival outcomes for the study assessing second-line Ox + 5-FU are summarised in *Table 36*. The addition of Ox to 5-FU improved median OS by 1.1 months, which was not statistically significant. Median PFS was not reported.

Outcomes: response rates

Response rates are reported in *Table 37*. There was a significantly higher response rate in the Ox + 5-FU treatment arm.

TABLE 35 *Second-line Ox: quality assessment*

Study	Allocation concealment	Randomisation	Blinding	Withdrawals	Comments
Rothenberg *et al.*, 2003[93a]	Unclear	Unclear	Unclear	Unclear	Abstract only. Dropouts not reported

[a] Infusional administration.

TABLE 36 *Second-line Ox: survival outcomes*

Treatment/study	Follow-up (months)	OS (months)			
Ox + 5-FU vs. 5-FU		**Ox + 5-FU**	**5-FU**	**HR (95% CI)**	***p***
Rothenberg *et al.*, 2003[91a]	NR	9.8	8.7	0.84 (0.69 to 1.02)	<0.07

[a] Infusional administration.

TABLE 37 *Second-line Ox: response rates*

Treatment/study	Response rate (%)		
Ox + 5-FU vs 5-FU	**Ox + 5-FU**	**5-FU**	**p**
Rothenberg *et al.*, 2003[91a]	9.6	0.7	<0.0001

[a] Infusional administration.

TABLE 38 *Second-line Ox: gastrointestinal toxicity*

Treatment/study	Toxicity (grade 3–4)							
	Vomiting (%)		Nausea (%)		Diarrhoea (%)		Stomatitis (%)	
Ox + 5-FU vs 5-FU	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**
Rothenberg *et al.*, 2003[91a]	9	2	11	3	12	2	3	2

[a] Infusional administration.

Outcomes: toxicities

Data on toxicities are presented in *Tables 38–40*.

Overall, significantly more patients in the Ox arm experienced grade 3–4 gastrointestinal toxicities (vomiting, $p = 0.05$; nausea, $p = 0.05$; and diarrhoea, $p = 0.05$) and haematological toxicities (neutropenia, $p = 0.05$; febrile neutropenia, $p = 0.05$; and platelets, $p = 0.05$). Grade 3–4 neuropathy ($p = 0.05$), asthenia and pain were also high in the Ox arm.

No quality of life results were presented.

Discussion of results

Strength of the evidence (internal validity)
There were no serious concerns about the internal validity of the trial, aside from that an unspecified number of patients in the 5-FU monotherapy arm had access to "an oxaliplatin treatment access program" (salvage treatment with Ox + 5-FU) after disease progression.[91]

Applicability of the results (external validity)
The study populations had a median age of only 59, around 15 years younger than the median age of the NHS population of people with

TABLE 39 *Second-line Ox: haematological toxicity*

Treatment/study	Toxicity (grade 3–4)									
	Neutropenia (%)		Anaemia (%)		Leucopenia (%)		Febrile neutropenia (%)		Platelets (%)	
Ox + 5-FU vs 5-FU	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**
Rothenberg *et al.*, 2003[91a]	48	6	5	2	NR	NR	5	1	5	0

[a] Infusional administration.

TABLE 40 *Second-line Ox: neurological and other toxicity*

Treatment/study	Toxicity (grade 3–4)											
	Neuropathy (%)		Asthenia (%)		Pain (%)		Alopecia (%)		Fatigue (%)		Hand–foot syndrome (%)	
Ox + 5-FU vs 5-FU	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**	**Ox+ 5-FU**	**5-FU**
Rothenberg *et al.*, 2003[91a]	6 (G3)	0 (G3)	5	2	5	4	NR	NR	NR	NR	NR	NR

[a] Infusional administration.

colorectal cancer. The concern that study populations in clinical trials represent younger, fitter populations than is representative of the NHS has been expressed above (see the section 'Discussion of results', p. 24). However, the literature suggests that combination Ox + 5-FU can be safe and effective in second-line treatment of older people with ACRC.

Assessment of effectiveness

The published evidence suggests the following.

- In comparison with second-line 5-FU monotherapy, the improvement conferred by combination oxaliplatin was not significant for median OS (around 1 month, $p < 0.07$), PFS was not reported.
- Oxaliplatin combination therapy in second line therapy provided a response in significantly more (8.9%) people than 5-FU ($p < 0.0001$), but with more serious toxicities. There is no evidence for a significant difference in quality of life between second-line oxaliplatin combination therapy and 5-FU monotherapy.
- It is unknown to what extent the results for OS are confounded by some trial participants receiving unplanned second-line therapy.
- Although the best data are based on an atypically young and fit population, other available evidence suggests that there is no significant difference between the efficacy and toxicity of second-line oxaliplatin monotherapy in older people.

Results: raltitrexed

Quantity and quality of research available

Number of studies identified

The search retrieved 2,105 citations.

Number and type of studies included

Four Phase III RCTs were retrieved that compared first-line raltitrexed (Ral) with 5-FU. In three studies, 5-FU was delivered by bolus injection.[94] In the fourth, 5-FU was delivered by continuous infusion.[95]

Number and type of studies excluded, with reasons for specific exclusions

No studies included in the original review[1] or industry submissions[52] were excluded from this review.

Quality and characteristics of studies

All four studies were large multicentre studies. In three cases, mature results were written up in peer-reviewed journal articles.[96] In one case, only 1-year follow-up data in abstract form was available from 1997; that it has not been subsequently published in a peer-reviewed journal is cause for concern.[97]

No trials reported upper age limits (*Table 41*). Two trials recruited participants aged over 80[96] and one recruited participants over 75 years old[95] (*Table 42*). The median age of the treatment arms across the three studies where it was reported was between 60 and 63 years. One trial did not report age composition.[97] Once more, the trials present a substantially younger population than the NHS population of colorectal cancer patients (see the sections 'Epidemiology', p. 3, and 'Quality and characteristics of studies', p. 16).

Baseline performance status was generally well balanced; however, in two trials, only 10% or less of participants had a performance status of 2.[94,96] In another, 22% of participants had a performance status of 2.[95] This is more representative than the others of the UK population of people with ACRC.[1] One trial did not report composition by performance status.[97]

In the three trials where the site of primary tumour was reported, it was the colon for the majority of participants in all arms.[96] In one of the studies, there seemed some imbalance in terms of the proportion of subjects in each arm in whom the rectum was the site of the primary tumour,[94] although it is unclear as to what effect, if any, this may have on the treatment effect size.

An assessment of the quality of the studies is given in *Table 43*.

Only one trial reported an adequate method of allocation concealment (central randomisation by telephone after confirmation of eligibility);[95] in the other cases the method of allocation concealment was unclear. One trial reported an adequate method of randomisation.[96] Withdrawals were accounted for in three trials.[96] No trials reported blinding; one reported open-label status.[96]

In summary, as far as can be ascertained from the published literature, three of the trials were relatively well designed and conducted, but there was too little information about the fourth to make an informed judgement. The populations in two

TABLE 41 *Ral: study characteristics*

Study	Participants	Interventions	Outcomes	Comments
Cocconi *et al.*, 1998 (Italy)[96]	Age ⩾18 years; at least one measurable or assessable lesion (according to WHO recommendations); WHO PS ⩽2, no other malignancies or serious illness; no evidence of significant renal or hepatic insufficiency; use of folate-containing vitamin preparations and colony-stimulating factors not permitted; written informed consent	*Arm 1* (Ral): Ral 3 mg m^{-2} once every 21 days (n = 247) *Arm 2* (5-FU): LV 200 mg m^{-2} (100 mg m^{-2} of levo-LV in South Africa and Italy), followed immediately by 400 mg m^{-2} 5-FU, both given once daily on 5 consecutive days every 4 weeks (Mayo) (n = 248)	Response rate; time to progression; OS; QoL; palliative benefits; adverse events	The randomisation scheme in the ratio 1:1 was computer generated. All efficacy analyses by ITT
Cunningham *et al.*, 1996 (UK)[94]	Aged ⩾18 years; advanced recurrent metastatic adenocarcinoma of the colon or rectum; at least one measurable or evaluable lesion; WHO PS <2, not received adjuvant chemotherapy within the previous year; not receiving folic acid; no other malignancies or serious illnesses, no evidence of significant renal or hepatic insufficiency	*Arm 1* (Ral): Ral 3 mg m^{-2} once every 3 weeks (n = 233) *Arm 2* (5-FU): LV 20 mg m^{-2} and 5-FU 425 mg m^{-2} as rapid i.v. injection once daily for 5 days every 4 weeks for the first 3 courses and every 5 weeks thereafter (Mayo) (n = 216)	Time to progression; objective response rate; Toxicity; QoL	Cross-over between treatments not permitted. Analysis by ITT. All treatments were continued until disease progression or unacceptable toxicity
Maughan *et al.*, 2002 (UK)[95]	Histologically confirmed adenocarcinoma of the colon or rectum, and locally advanced or metastatic disease at presentation; if systemic chemotherapy had been given previously, it must have been 5-FU-based adjuvant therapy completed >6 months before trial entry; adequate bone-marrow and renal function; WHO PS ⩽2	*Arm 1* (5-FU): 2-weekly cycles of i.v. FA 200 mg m^{-2} (maximum 350 mg) given over 2 h, followed by 5-FU as a 400 mg m^{-2} bolus over 5 minutes, and a 5-FU infusion of 600 mg m^{-2} over 22 h, repeated on day 2 (de Gramont) (n = 303) *Arm 2* (Ral): 3 mg m^{-2} i.v. over 15 minutes every 3 weeks (n = 301) *Arm 3* (5-FU): protracted venous infusion of 300 mg m^{-2} 5-FU daily given via an ambulatory pump plus warfarin 1 mg per day by mouth (Lokich) (n = 301)	OS; PFS; response rate; toxicity; QoL; costs and acceptability of treatment to patients	Patients were randomly assigned to one of the study regimens by a telephone call, and stratification by clinician, status of disease and WHO PS. Analyses by ITT
Pazdur and Vincent, 1997 (USA)[97]	ACRC	*Arm 1* (Ral1): Ral 3 mg m^{-2} every 3 weeks (n = 217) *Arm 2* (Ral2): Ral 4 mg m^{-2} (n = 32) *Arm 3* (5-FU): Mayo regimen (n = 210)	Objective response rate; survival; time to disease progression; toxicity	The 4 mg m^{-2} arm was closed down prematurely following three therapy-related deaths, and the ITT analysis was carried out on the remaining two arms

***TABLE 42** Ral: population characteristics*

Study	Median age	Male (%)	WHO PS	Site of primary tumour	Site of metastases	Previous 5-FU
Cocconi *et al.*, 1998[96]	*Arm 1* (Ral): 60 (23–79) *Arm 2* (5-FU): 62 (36–83)	*Arm 1* (Ral): 61.5 *Arm 2* (5-FU): 66.1	*Arm 1* (Ral): 0 = 49%, 1 = 41.3%, 2 = 9.7% *Arm 2* (5-FU): 0 = 42.7%, 1 = 50.4%, 2 = 6.9%	*Arm 1* (Ral): colon 65%, rectum 35 *Arm 2*: colon 67, rectum 33%	*Arm 1* (Ral): liver 76.9%, lung 27.1%, lymph nodes 22.7%, residual primary 18.2%, intraabdominal extension 18.6%, bone 2.4%, skin/soft tissue 3.2%, other 11.7% *Arm 2* (5-FU): liver 77.4%, lung 30.2%, lymph nodes 23.4%, residual primary 17.7%, intra-abdominal extension 12.1%, bone 4.4%, skin/soft tissue 3.6%, other 11.3% (Patients may be included in more than one category)	Adjuvant chemotherapy: *Arm 1* (Ral): 11.7% *Arm 2* (5-FU): 12.9%
Cunningham *et al.*, 1996[94]	*Arm 1* (Ral): 61 (27–82) *Arm 2* (5-FU): 61 (27–80)	*Arm 1* (Ral): 60 *Arm 2* (5-FU): 59	*Arm 1* (Ral): 0 = 45%, 1 = 44%, 2 = 10% *Arm 2* (5-FU): 0 = 39%, 1 = 49%, 2 = 12%	*Arm 1* (Ral): colon 59%, rectum 40%, unknown 0% *Arm 2* (5-FU): colon 68%, rectum 32%, unknown 0%	*Arm 1* (Ral): colon 64.8%, rectum 35.2% *Arm 2* (5-FU): colon 66.9%, rectum 33.1% *Arm 1* (Ral): liver 78%, lung 25%, lymph nodes 20%, colon/rectum 14%, local recurrence 14%, skin/soft tissue 4%, bone 2%, other 15% *Arm 2* (5-FU): liver 77%, lung 29%, lymph nodes 19%, colon/rectum 13%, local recurrence 15%, skin/soft tissue 5%, bone 6%, other 17%	Adjuvant chemotherapy: *Arm 1* (Ral): 5% *Arm 2* (5-FU): 5%
Maughan *et al.*, 2002[95]	*Arm 1* (5-FU): 63 *Arm 2* (Ral): 63	*Arm 1* (5-FU): 69 *Arm 2* (Ral): 66	*Arm 1* (5-FU): 0 = 34%, 1 = 44%, 2 = 22% *Arm 2* (Ral): 0 = 33%, 1 = 45%, 2 = 22%	*Arm 1* (5-FU): colon 63%, rectum 37% *Arm 2* (Ral): colon 65%, rectum 35%	*Arm 1* (5-FU): liver only 22%, extrahepatic only 22%, both hepatic and elsewhere 32%, no evidence of metastases 2% *Arm 2* (Ral): liver only 43%, extrahepatic 23%, both hepatic and elsewhere 34%, no evidence of metastases 0.3%	Adjuvant chemotherapy: *Arm 1* (5-FU): 13% *Arm 2* (Ral): 13%
Pazdur and Vincent, 1997[97]	NR	NR	NR	NR	NR	NR

NR, not reported.

TABLE 43 *Ral: quality assessment*

Study	Allocation concealment	Randomisation	Blinding	Withdrawals	Comments
Cocconi *et al.*, 1998[96b]	Unclear	Adequate	Inadequate	Adequate	Computer-generated randomisation. Patients in the Ral arm had more intra-abdominal extensions than patients in the 5-FU arm. Seven (1%) participants did not complete treatment. Reasons were not given for all patients
Cunningham *et al.*, 1996[94b]	Unclear	Unclear	Unclear	Adequate	Withdrawals: five participants (1%): violation of entry criteria; withdrawal of consent; deterioration in health; death prior to treatment; error in treatment
Maughan *et al.*, 2002[95a]	Adequate	Unclear	Unclear	Adequate	Allocation concealment: central randomisation. 584 (71%) completed treatment. 162 had delayed/modified doses (toxic effects and i.v. lines problems). 208 (26%) had treatment stopped and 29 (4%) received no protocol treatment (toxic effects, death, disease progression). ITT analysis on primary end-point
Pazdur and Vincent, 1997[97b]	Unclear	Unclear	Unclear	Unclear	Abstract only

[a] Infusional administration; [b] bolus administration.

trials contained imbalances and a third had a large quantity of withdrawals. As with other trials discussed in this report, the trial populations were relatively young, with the consequences discussed above.

Outcomes: OS and PFS

Survival outcomes for studies assessing first-line Ral are summarised in *Table 44*. In no case was the difference in median OS significant. In the only study to report PFS, the direction of effect favoured 5-FU, although this difference was not statistically significant.[96]

Trials that compared Ral with 5-FU were meta-analysed. The analysis of OS (*Figure 8*), using hazard ratios derived from the literature and published survival curves, involved three trials (1538 participants). One study was excluded from the meta-analyses, due to a lack of usable data.[97]

In the analysis of OS (*Figure 8*), the direction of effect favoured 5-FU, rather than Ral, although the effect was not significant (HR = 1.10, 95% CI 0.97 to 1.25, $p = 0.14$). There was no significant heterogeneity ($\chi^2 = 1.15$, df = 2, $p = 0.56$, $I^2 = 0\%$). In the analysis of prospectively identified intervention subsets, the direction of effect again favoured 5-FU when delivered via bolus injection (HR = 1.15, 95% CI 0.99 to 1.34, $p = 0.07$).[96] When 5-FU was delivered via continuous infusion there was no significant difference in treatment effect between 5-FU and Ral.[95] There was no heterogeneity within intervention subsets.

Outcomes: response rates

Response rates are reported in *Table 45*.

None of the trials that compared the response rates of Ral and 5-FU found any significant differences between study arms.

Outcomes: toxicities

Gastrointestinal, haematological and neurological toxicities are reported in *Tables 46*, *47* and *48*, respectively. In terms of gastrointestinal toxicities, trial participants in Ral arms generally had a higher incidence of grade 3–4 vomiting and nausea, but less diarrhoea and mucositis. In one trial, there was significantly less grade 3–4 stomatitis and leucopenia in the Ral group, but significantly more grade 3–4 neutropenia and

TABLE 44 Ral: survival outcomes

Treatment/study	Follow-up (months)	OS (months)			
Ral vs 5-FU		**Ral**	**5-FU**	**HR (95% CI)**	***p***
Cocconi *et al.*, 1998[96b]	17	10.9	12.3	1.15 (0.93 to 1.42)	0.197
Cunningham *et al.*, 1996[94b]	18	10.3	10.3	1.06 (0.85 to 1.32)	0.44
Maughan *et al.*, 2002[95a]	17	9.8	8.9	0.99 (0.79 to 1.25)	0.94
Pazdur *et al.*, 1997[97b]	12	12.7	9.7	NR	0.0109
Treatment/study	**Follow-up (months)**	**PFS (months)**			
Ral vs 5-FU		**Ral**	**5-FU**	**HR (95% CI)**	***p***
Maughan *et al.*, 2002[95a]	17	5.3	6.2	1.18 (0.94 to 1.46)	0.057

[a] Infusional administration; [b] bolus administration.

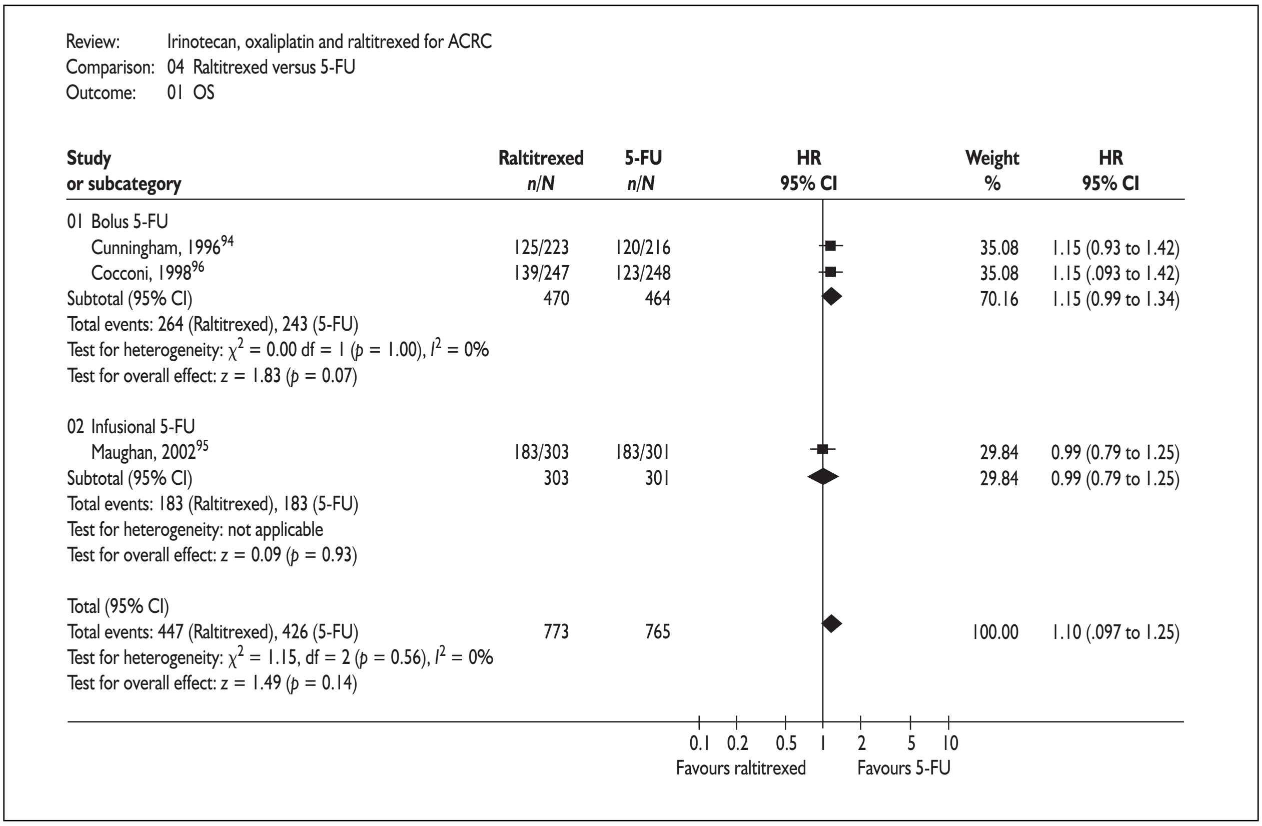


***FIGURE 8** Ral versus 5-FU (first line): OS*

TABLE 45 Ral: response rates

Treatment/study	Response rate (%)		
Ral vs 5-FU	**Ral**	**5-FU**	***p***
Cocconi *et al.*, 1998[96b]	18.6	18.1	0.90
Cunningham *et al.*, 1996[94b]	19.3	16.7	NR
Maughan *et al.*, 2002[95a]	18	23	0.20
Pazdur and Vincent, 1997[97b]	14	15	NS

[a] Infusional administration; [b] bolus administration.

TABLE 46 *First-line Ral: gastrointestinal toxicity*

Treatment/study	Toxicity (grade 3–4)							
	Vomiting (%)		Nausea (%)		Diarrhoea (%)		Stomatitis (mucositis) (%)	
Ral vs 5-FU	**Ral**	**5-FU**	**Ral**	**5-FU**	**Ral**	**5-FU**	**Ral**	**5-FU**
Cocconi *et al.*, 1998[96b]	9	9	–	–	10	19	NR	NR
Cunningham *et al.*, 1996[94b]	13	9	–	–	14	14	NR (2)	NR (22)
Maughan *et al.*, 2002[95a]	7.7	3.3	9.5	2.9	12.4	3.3	1.5	0.4
Pazdur and Vincent, 1997[97b]	13	8	–	–	10	13	NR (3)	NR (10)

[a] Infusional administration; [b] bolus administration. –, Percentage of nausea same as vomiting.

anaemia (p not stated).[96] In another, there was significantly less leucopenia, mucositis and pain in the Ral group ($p < 0.001$), but grade 3–4 asthenia was higher.[94] A third trial reported significantly increased nausea ($p < 0.01$), diarrhoea ($p < 0.01$) and neutropenia ($p < 0.01$). In one trial, there were significantly more treatment-related deaths in the Ral arm than in the de Gramont 5-FU monotherapy arm (18 versus 2, $p = 0.0002$).[95]

Outcomes: quality of life

Quality of life outcomes are reported in *Table 49*. Three trials reported quality of life data; only one trial found a significant difference between regimens favouring the de Gramont infusional 5-FU regimen over Ral. In one study, there was no overall difference in quality of life, assessed by the EORTC QLQ-C30, but a greater impact on quality of life due to nausea and vomiting ($p = 0.001$) in patients treated with Ral.[94] Another study reported significant benefits on the EQ-5D associated with Ral in the first treatment cycle, but not thereafter (p not specified).[96] A third trial reported significantly better results in all EORTC QLQ-C30 subscales for people treated with the de Gramont infusional 5-FU regimen than for people treated with Ral. There were no significant differences between the Lokich regimen and Ral.[95]

Discussion of results

Strength of the evidence (internal validity)

Variation in treatment schedules between arms offers cause for concern. Across trials, the median duration of treatment ranged from 12 to 15 weeks in the raltitrexed group and from 12 to 22 weeks in the 5-FU group.[94–97] The pooled analysis of OS favoured 5-FU, rather than raltitrexed, although this difference was not statistically significant. These results may be due to the longer duration of treatment in the 5-FU arm. The poorer outcomes experienced by patients receiving raltitrexed may be related to the early termination of the 4 mg m^{-2} raltitrexed treatment programme because of the high rate of toxic deaths.[97] High rates of toxic deaths were also reported in another study.[95] In the other included studies, OS was shorter in the raltitrexed arm, although this was not statistically significant.

With the exception of blinding, no trial reported clearly inadequate approaches to generic components of clinical trial design that minimise systematic error (see the section 'Discussion of results', p. 24, for comments on blinding in oncology trials). In one study, variations in the baseline comparability of populations may have affected internal validity to an unknown extent.[94] There was no information in any of the trial papers on the use of unplanned second-line therapies. Imbalances between arms in the proportions of patients receiving unplanned second-line therapy may affect the internal validity of study results, although three of these trials were ongoing at a time when irinotecan and oxaliplatin were not widely available.

Applicability of the results (external validity)

The issue of unplanned second-line therapies also affects the applicability of the results (see the section 'Discussion of results', p. 24, for further comment).

There was some concern that baseline PS in two trials was not reflective of the wider population, having a small proportion of participants with a WHO PS score of 2.[96]

Although no study reported excluding older people, and at least one trial recruited people aged over 80 years, the median age of the study populations was considerably younger than that of the UK NHS population to which this review aims

TABLE 47 *First-line Ral: haematological toxicity*

Treatment/study	Toxicity (grade 3–4)									
	Neutropenia (%)		Anaemia (%)		Leucopenia (%)		Febrile neutropenia (%)		Platelets (%)	
Ral vs 5-FU	**Ral**	**5-FU**	**Ral**	**5-FU**	**Ral**	**5-FU**	**Ral**	**5-FU**	**Ral**	**5-FU**
Cocconi *et al.*, 1998[96b]	NR	NR	5	2	6	13	NR	NR	NR	NR
Cunningham *et al.*, 1996[94b]	NR	NR	9	2	14	30	NR	NR	NR	NR
Maughan *et al.*, 2002[95a]	8	2.6	2.9	1.5	5.1	1.8	NR	NR	NR	NR
Pazdur and Vincent, 1997[97b]	NR	NR	NR	NR	18	41	NR	NR	NR	NR

[a] Infusional administration; [b] bolus administration.

TABLE 48 *First-line Ral: neurological and other toxicity*

Treatment/study	Toxicity (grade 3–4)											
	Neuropathy (%)		Asthenia (%)		Pain (%)		Alopecia (%)		Fatigue (%)		Hand–foot syndrome (%)	
Ral vs 5-FU	**Ral**	**5-FU**	**Ral**	**5-FU**	**Ral**	**5-FU**	**Ral**	**5-FU**	**Ral**	**5-FU**	**Ral**	**5-FU**
Cocconi *et al.*, 1998[96b]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cunningham *et al.*, 1996[94b]	NR	NR	6	2	5	7	NR	NR	NR	NR	NR	NR
Maughan *et al.*, 2002[95a]	NR	NR	NR	NR	NR	NR	0	0	NR	NR	NR	NR
Pazdur and Vincent, 1997[97b]	NR	NR	18	10	NR	NR	NR	NR	NR	NR	NR	NR

[a] Infusional administration; [b] bolus administration.

TABLE 49 *First-line Ral: quality of life*

Study	Methods of assessment	Findings
Cocconi *et al.*, 1998[96b]	RSCL EQ-5D	QoL data assessed at weeks 2, 5, and 15. 85% completion of RSCL and 60% completion of EQ-5D. Significant benefit on RSCL for Ral compared with 5-FU/LV at week 2 for physical, activity level and overall. EQ-5D showed significant benefits of Ral at week 2 for mobility, usual activities and general health. Significant benefits on EQ-5D for Ral compared with 5-FU/LV patients at week 2. No significant differences between treatments in weeks 5 and 15 on RSCL or EuroQol EQ-5D
Cunningham *et al.*, 1996[94b]	EORTC QLQ-C30	Longitudinal analysis showed significantly greater impact of nausea/vomiting in patients treated with Ral compared with 5-FU/LV
Maughan *et al.*, 2002[95a]	EORTC QLQ-C30 Hospital Anxiety and Depression Scale	Ral was inferior on almost all QoL domains and no less intrusive than either de Gramont or Lokich regimens. De Gramont and Lokich regimens produced similar QoL scores
Pazdur and Vincent, 1997[97b]	Type of measure not reported	Ral compared with 5-FU/LV group had lower incidences of grades 3 and 4 oral mucositis, diarrhoea and leucopenia, but a higher incidence of severe asthenia and grades 3 and 4 nausea/vomiting and liver transaminase elevations

[a] Infusional administration; [b] bolus administration.
RSCL, Rotterdam Symptom Checklist.

to generalise. Single-arm studies with no comparative element used raltitrexed in patients older than 70 years and found it to be an effective treatment with moderate toxicity and disease stabilisation.[98] One study administered a 33% dose reduction of raltitrexed to 13 people aged 75–90 years and found it to be effective, with acceptable toxicity.[99]

Assessment of effectiveness

The synthesis of published and unpublished evidence suggests the following.

- There is no evidence that raltitrexed improves overall or PFS when compared to 5-FU.
- The toxicity profiles of raltitrexed and 5-FU are different, with results varying across trials. Raltitrexed is associated with more vomiting and nausea, but less diarrhoea and mucositis. In the only trial which reported consistent, statistically significant differences in quality of life outcomes between arms, the direction of effect favoured 5-FU rather than raltitrexed.
- Although the best data are based on an atypically young and fit population, other available evidence suggests that raltitrexed can be a safe and efficacious treatment in older people.

Sequencing of treatment

Introduction

The preceding sections evaluated the clinical effectiveness of chemotherapies at specific stages in the treatment pathway. As has been noted, the frequent use of unplanned second-line or salvage chemotherapy subsequent to disease progression compromises the internal validity of such study outcomes. This section evaluates the clinical effectiveness of treatment sequences. It examines studies, the outcomes of which should be more robust, because they planned cross-over treatments and analysed accordingly, minimising the potential for bias. Results from the Fluorouracil, Oxaliplatin, CPT-11 Use and Sequencing (FOCUS) trial are AIC.

Quantity and quality of research available

Number of studies identified

The search retrieved 2105 citations.

Number and type of studies included

Only two Phase III RCTs were retrieved that compared sequences of treatments (these studies have also been discussed previously, in the sections 'Results: irinotecan – first-line combination', p. 12 and 'Results: oxaliplatin – first-line combination', p. 32).[51]

Number and type of studies excluded, with reasons for specific exclusions

All other studies were excluded on the grounds that they did not prospectively plan and subsequently analyse sequences of treatments. A non-systematic literature review was excluded from the main analysis as it did not conform with the inclusion criteria, but is discussed in the section 'Discussion of results' (p, 55).[100] The analysis attempted to correlate the percentage of patients receiving second-line therapy and the percentage of patients receiving three active chemotherapies (5-FU, Ir and Ox) with the reported median OS, using a weighted linear regression of published data from seven Phase III trials.

Quality and characteristics of studies

Both studies were large multicentre studies, but only one, the Groupe d'Étude et de Recherche en Oncologie-Radiothérapie (GERCOR) trial, had published mature results in a peer-reviewed journal article.[51] Two-year follow-up data for the other study, the FOCUS trial, were mature, but had only recently been analysed and presented at a conference.[42] Most of the outcome data presented on the FOCUS trial in this section were submitted as AIC. Further information is reported in the section 'Quality and characteristics of studies' (p. 16).

The GERCOR trial[51] was designed to evaluate two regimens of combination therapy (i.e. they received all three active chemotherapies: 5-FU, Ir and Ox) and to determine the best sequence to treat patients with metastatic colorectal cancer. Participants were randomised to either: (A) Ir + 5-FU followed by Ox + 5-FU at progression; or (B) Ox + 5-FU followed by Ir + 5-FU at progression.

The FOCUS trial[42] was set up to test the hypothesis that first-line two-drug combination therapy improves survival compared with the same two drugs used as sequential single agents, or the same two drugs used a staged single agent/combination therapy. Participants were randomised to one of five arms: (A) 5-FU alone followed by Ir alone at progression; (B) 5-FU alone followed by Ir + 5-FU at progression; (C) Ir + 5-FU; (D) 5-FU alone followed by Ox + 5-FU at progression; or (E) Ox + 5-FU.

During the course of the trial, a protocol amendment was made, allowing discretionary third-line salvage therapy where clinicians deemed it necessary. This was Ox + capecitabine for arms A–C and Ir + capecitabine for arms D–E. This was not measured in the analysis of the secondary outcome, time to failure of entire treatment plan, which included only the treatments listed above, and was not, a priori, a facet of the trial for all patients.

Arm A of the FOCUS trial (5-FU alone followed by Ir alone) represents the 2002 NICE recommendation, as discussed in the section 'Current licensed indications and NICE guidance' (p. 7).[2]

Outcomes: OS and PFS

Table 50 describes the outcomes of the two trials by arm.

Table 51 reports summary statistics from the comparison of treatment arms. In the FOCUS trial, staged single agents (5-FU then Ir, the current NICE recommendation) were inferior to any other plan. Staged combination (5-FU then Ir + 5-FU or Ox + 5-FU) was as effective as first-line combination.[42] In the GERCOR trial, there were no significant differences between the treatment sequences.[51]

Data for time to second progression (second PFS as defined by the GERCOR study[51]) were not available from the FOCUS study.[60] The reader should note that the outcome presented here, failure free on whole treatment policy, is different to second PFS, as censorship will include change to cross-over treatment without evidence of progression (e.g. because of severe adverse events).

Survival curves describing OS for arms from both trials are presented together in *Figure 9*. FOCUS arms are shown in black and GERCOR arms are shown in grey.

Outcomes: response rates

Response rates are reported in *Table 52*. In the FOCUS trial there were significantly more first-line responders where 5-FU was combined with either Ir or Ox ($p < 0.001$).[42] In the GERCOR trial, there was no significant difference between Ir + 5-FU and Ox + 5-FU in first-line therapy, but in second-line therapy there were significantly more responders to Ox + 5-FU ($p = 0.05$).[51]

Outcomes: toxicities

The FOCUS trial confirmed the higher toxicity profile of combination chemotherapies. It also confirmed a similar lifetime probability of toxicity whether participants received combination chemotherapy in a first-line combination or a staged approach.[42]

TABLE 50 *Sequences: OS and PFS*

Arm	Regimen	Median (months)	1-year OS	2-year OS
OS				
FOCUS A	5-FU then Ir	13.7	56%	21%
FOCUS B[a]	5-FU then Ir + 5-FU	14.8	60%	21%
FOCUS C	Ir + 5-FU	16.2	65%	27%
FOCUS D	5-FU then Ox + 5-FU	15.1	63%	25%
FOCUS E	Ox + 5-FU	15	64%	19%
GERCOR A	Ir + 5-FU then Ox + 5-FU	21.5	NR	NR
GERCOR B	Ox + 5-FU then Ir + 5-FU	20.6	NR	NR
Arm	**Regimen**	**Median (months)**	**1-year PFS**	
PFS (time to first progression)				
FOCUS A	5-FU then Ir	6.3	15%	
FOCUS B[a]	5-FU then Ir + 5-FU	6.7	16%	
FOCUS C	Ir + 5-FU	8.6	21%	
FOCUS D	5-FU then Ox + 5-FU	6.4	13%	
FOCUS E	Ox + 5-FU	8.8	21%	
GERCOR A	Ir + 5-FU then Ox + 5-FU	8.5	NR	
GERCOR B	Ox + 5-FU then Ir + 5-FU	8.0	NR	
PFS (time to failure of sequence)				
FOCUS A	5-FU then Ir	10.1	39%	
FOCUS B[a]	5-FU then Ir + 5-FU	11.5	47%	
FOCUS C	Ir + 5-FU	9	29%	
FOCUS D	5-FU then Ox + 5-FU	11.6	48%	
FOCUS E	Ox + 5-FU	9.2	31%	
GERCOR A	Ir + 5-FU then Ox + 5-FU	14.2	NR	
GERCOR B	Ox + 5-FU then Ir + 5-FU	11.8	NR	

[a] Not within licensed indication.

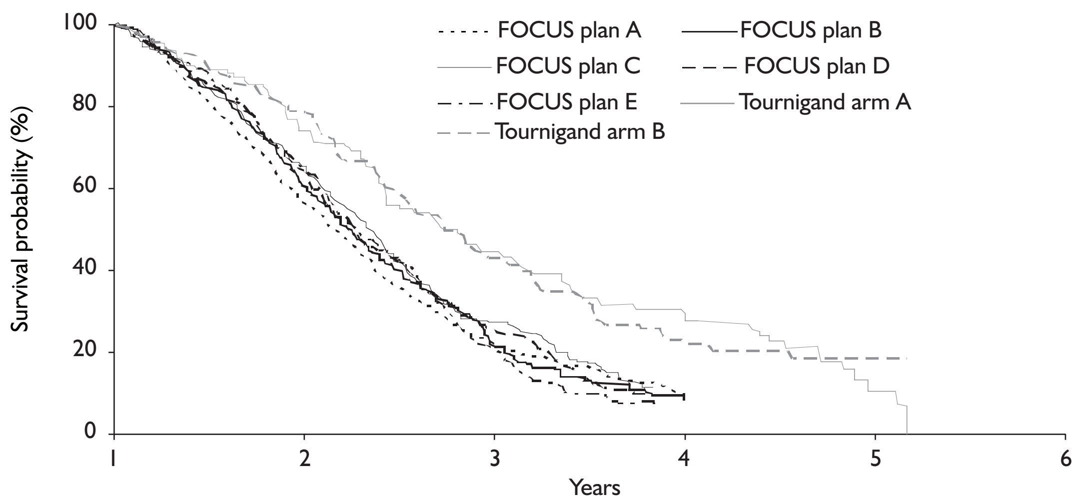


FIGURE 9 *GERCOR and FOCUS studies: OS*

TABLE 51 *Sequences: survival comparisons*

Comparison	Log-rank HR (95% CI)	*p*
OS		
[5-FU then Ir + 5-FU] (B[a]) vs [5-FU then Ir] (A)[60]	0.92 (0.79 to 1.07)	0.282
[Ir + 5-FU] (C) vs [5-FU then Ir] (A)[60]	0.86 (0.74 to 1.00)	0.058
[5-FU then Ox + 5-FU] (D) vs [5-FU then Ir] (A)[60]	0.91 (0.78 to 1.06)	0.225
[Ox + 5-FU] (E) vs [5-FU then Ir] (A)[60]	0.96 (0.83 to 1.12)	0.608
[Ir + 5-FU] (C) vs [5-FU then Ir + 5-FU] (B[a])[60]	0.94 (0.78 to 1.12)	0.478
[Ox + 5-FU] (E) vs [5-FU then Ox + 5-FU] (D)[60]	1.07 (0.90 to 1.29)	0.428
[Ir + 5-FU then Ox + 5-FU] vs [Ox + 5-FU then Ir + 5-FU][51]	NR	0.99
PFS (time to first progression)		
[5-FU then Ir + 5-FU] (B[a]) vs [5-FU then Ir] (A)[60]	0.99 (0.86 to 1.13)	0.863
[Ir + 5-FU] (C) vs [5-FU then Ir] (A)[60]	0.77 (0.67 to 0.88)	<0.001
[5-FU then Ox + 5-FU] (D) vs [5-FU then Ir] (A)[60]	1.05 (0.92 to 1.21)	0.463
[Ox + 5-FU] (E) vs [5-FU then Ir] (A)[60]	0.75 (0.66 to 0.86)	<0.001
[Ir + 5-FU] (C) vs [5-FU then Ir + 5-FU] (B[a])[60]	0.78 (0.66 to 0.91)	0.002
[Ox + 5-FU] (E) vs [5-FU then Ox + 5-FU] (D)[60]	0.71 (0.60 to 0.83)	<0.001
[Ir + 5-FU then Ox + 5-FU] vs [Ox + 5-FU then Ir + 5-FU][51]	NR	0.26
Failure free on whole treatment policy (FOCUS)/second PFS (GERCOR)		
[5-FU then Ir + 5-FU] (B[a]) vs. [5-FU then Ir] (A)[60]	0.86 (0.74 to 1.01)	0.063
[Ir + 5-FU] (C) vs [5-FU then Ir] (A)[60]	1.27 (1.09 to 1.49)	0.002
[5-FU then Ox + 5-FU] (D) vs [5-FU then Ir] (A)[60]	0.85 (0.73 to 1.00)	0.049
[Ox + 5-FU] (E) vs [5-FU then Ir] (A)[60]	1.19 (1.01 to 1.39)	0.028
[Ir + 5-FU] (C) vs [5-FU then Ir + 5-FU] (B[a])[60]	1.49 (1.24 to 1.79)	<0.001
[Ox + 5-FU] (E) vs [5-FU then Ox + 5-FU] (D)[60]	1.42 (1.19 to 1.70)	<0.001
[Ir + 5-FU then Ox + 5-FU] vs [Ox + 5-FU then Ir + 5-FU][51]	NR	0.64

[a] Not within licensed indication.

TABLE 52 *Sequences: response rates*

First-line response rates	Responders/randomised	%
5-FU alone (FOCUS A, B, D)[42]	327/1132	29
Ir + 5-FU (FOCUS C)[42]	141/275	51
Ir + 5-FU (GERCOR A)[51]	61/109	56
Ox + 5-FU (FOCUS E)[42]	166/291	57
Ox + 5-FU (GERCOR B)[51]	59/111	54
Second-line response rates	***n/N***	**%**
Ox + 5-FU (GERCOR A)[51]	21/91	15
Ir + 5-FU (GERCOR B)[51]	3/69	4
(FOCUS A, B, C, D and E)	No data	No data

The GERCOR trial confirmed that, in first-line therapy trial participants receiving Ir + 5-FU experienced significantly fewer grade 3–4 toxicities (53% versus 74%, $p = 0.001$), but significantly more patients had serious adverse events than those in the Ox + 5-FU (14% versus 5%, $p = 0.03$). Elderly patients did not experience increased toxicity compared with younger patients. There were no significant differences between treatments in overall toxicity or the number of serious adverse events during second-line therapy.[51]

Outcomes: quality of life

At the time of writing, full quality of life outcomes have not been published by either the GERCOR or the FOCUS study.[51] A conference presentation by the FOCUS trial stated that there was no appreciable quality of life gain on the EORTC

QLQ-C30 instrument from the higher response rates of first-line combinations.[42]

Discussion of results

Strength of the evidence (internal validity)
In that both the FOCUS and the GERCOR trials planned second-line therapy, their estimates of treatment effect in terms of survival outcomes are less likely to be compromised than other studies discussed in this review. Small numbers of participants in each trial crossed over to third-line salvage therapies, but the potential for confounding was not on the same scale as discussed in the section 'Discussion of results', p. 24, and throughout. The precise numbers are not known, but it is likely that only small numbers from FOCUS arms A, B and D will have crossed to discretionary third-line treatments. However, for plans C and E, which only incorporate one stage of treatment, one might speculate that larger numbers will require discretionary further treatment. Therefore, it is important to remember that the reported median OS from arms C and E is likely to be exaggerated by a majority of participants crossing to capecitabine and either oxaliplatin (arm C) or irinotecan (arm E).

Applicability of the results (external validity)
Although several of the trials discussed in this report set out to compare the outcomes of patients receiving two active chemotherapies (e.g. Ir + 5-FU versus 5-Fu alone or Ox + 5-FU versus 5-FU alone), none has compared the effects of three active chemotherapies versus only two over a planned sequence. Data presented in *Tables 9* and *50*, seem to indicate that a planned strategy of three active chemotherapies (GERCOR) delivers improved survival over two (FOCUS), although the FOCUS trial outcomes are confounded to an unknown extent by a midtrial protocol amendment allowing salvage with a third chemotherapy.

A non-systematic literature review of published data from seven Phase III trials incorporated a weighted linear regression to correlate the number of patients receiving all three active drugs with OS.[100] For each trial, the number of patients in each arm receiving all three drugs and the percentage of patients with any second-line therapy were calculated and median OS were extracted from published papers. The main analysis was a simple linear regression; sensitivity analysis was undertaken using a weighted linear regression, whereby weights were proportional to the trial sample size. The analysis found that median OS was significantly correlated with the percentage of patients who received all three drugs in the course of their disease ($p = 0.0008$), but not with the percentage of patients who received any second-line therapy ($p = 0.19$). In addition, the use of combination protocols as first-line therapy was associated with a significant improvement in median survival of 3.5 months (95% CI 1.27 to 5.73 months, $p = 0.0083$).

The method of this analysis is not ideal, as it is unclear which of the trial participants received all three drugs and what the difference in survival was compared to those who did not. A more robust solution would be to use IPD to generate separate survival curves for patients who received all three active agents and patients who did not and to compare these using standard statistical tests such as a log-rank analysis. This methodology would also have allowed for an analysis of the mean rather than the median OS. There is also an assumption that the baseline characteristics of all trial participants are homogeneous, which is not assessed in the paper.

However, bearing these criticisms in mind, the analysis appears adequate and its findings are consistent with the gap observed between the median OS reported by the GERCOR study and that reported by other studies, in which only two active chemotherapies were planned (*Tables 9* and *50*).

Assessment of effectiveness

The FOCUS trial demonstrates that using staged single agents (5-FU then irinotecan after disease progression, the current NICE recommendation) is inferior to any other plan. The most effective plan in terms of OS was irinotecan and 5-FU as first-line therapy (plan C), which significantly improved OS and time to first progression, compared with staged single agents. However, it should be noted that on completion of plan C, an unknown quantity of participants will have crossed to oxaliplatin and capecitabine (oral 5-FU), which will have affected the treatment effect size for OS to an unknown extent.

The GERCOR trial demonstrates that staged combination therapies extend median OS by longer than 20 months.

Downstaging of patients with liver metastases

Introduction

Liver metastases occur in approximately half of patients diagnosed with colorectal cancer.[101]

Surgical resection remains the only treatment that provides a potential long-term cure for hepatic metastases of colorectal cancer.[41] Despite this, only 10–20% of patients with liver metastases are amenable to potential curative resection.[102] In the remaining 80–90%, the 5-year survival rate is poor, even after partial response to chemotherapy.[103] Therefore, it is considered important to maximise the number of patients undergoing resection through the use of neoadjuvant and induction chemotherapy.[52]

Although some patients with colorectal metastatic disease confined to the liver are operable at assessment, the majority are inoperable. In these cases chemotherapy is used to downstage tumours in an attempt to render them operable. For those whose tumours become operable and on whom a resection is attempted, there is no guarantee of complete resection; tumour removal may be found to be technically impossible for a variety of reasons, and even where complete removal of metastases is macroscopically confirmed, it is often found to be incomplete on microscopic inspection. Even if this is not the case, individuals may relapse following attempts at curative surgery. With this in mind, 5-year follow-up is usually taken as an appropriate point at which to judge long-term survival.

In previous guidance, NICE has encouraged the use of oxaliplatin in combination with 5-FU/folinic acid in patients with ACRC with liver metastases (see sections 'Oxaliplatin', p. 6, and 'Current licensed indications and NICE guidance', p. 7).[2] The following sections evaluate the evidence for the clinical effectiveness of irinotecan and oxaliplatin for the downstaging of liver metastases with the intent of surgical resection.

Caution is urged in the use of the results presented in this section, as the included studies have not been through the same rigorous process of critical appraisal as the studies reviewed in the preceding sections of this chapter.

Quantity of research available

Number of studies identified

The 2207 citations retrieved by the search described in the section 'Search strategy' (p. 11) were searched for studies that evaluated at least the primary end-point, the percentage of any cohort of previously unresectable patients who were resected following systemic therapy. Secondary outcomes were response rates, the number of complete resections, OS and PFS or disease-free survival, as reported, of the downstaged cohort against the whole. Studies with populations that had already been successfully downstaged using systemic therapy were rejected, as these would only be testing the effectiveness of the surgery, rather than the neoadjuvant chemotherapy followed by the surgery.

Number of studies included

Three RCTs discussed in previous sections reported the number of participants who were rendered resectable by systemic therapy. Two compared Ox + 5-FU with 5-FU alone,[77,78] and a third compared Ir + 5-FU with Ox + 5-FU.[51] However, none of these comparative studies reported survival outcomes for the downstaged subgroup in isolation. Therefore, the retrieved citations were screened for studies from further down the hierarchy of evidence (see the section 'Inclusion and exclusion criteria', p. 11).

Six single-arm studies that reported on the efficacy of Ir + 5-FU were included. Of these, four were Phase II clinical trials,[104–107] one was a prospective case series,[108] and one was a case series in which it was unclear whether the data had been gathered prospectively or retrospectively.[109]

Two single-arm studies that reported on the efficacy of Ox + 5-FU were included. One was a Phase II clinical trial[110] and the other was a prospective case series.[41]

The characteristics of and results from the included studies are reported in *Table 79*, (Appendix 9). Quality assessment of randomised studies is reported in the sections 'Results: irinotecan – first-line combination' (p. 12) and 'Results: oxaliplatin – first-line combination' (p. 32). Quality assessment of non-randomised studies was not undertaken owing to resource constraints.

Response rates

Out of seven cohorts receiving Ir + 5-FU, six reported response rates, and these were between 47.5 and 56%. Out of five cohorts receiving Ox + 5-FU, three reported response rates, and these were between 50 and 54%. The one study in which these regimens were compared found no significant difference between them.[51]

Percentage of patients resected

All seven studies with cohorts receiving Ir + 5-FU reported resection rates, which ranged from 9 to 35%. All five cohorts receiving Ox + 5-FU reported resection rates, which ranged from 7 to 51%. In the one study in which these regimens were compared, significantly more individuals were resected in the Ox + 5-FU arm [Ox + 5-FU, $n = 24$ (22%); Ir + 5-FU, $n = 10$ (9%), $p = 0.02$].[51]

One study reported a complete resection rate of 7% in a cohort receiving Ir + 5-FU.[51] Three studies reported complete resection rates of 21–32% in cohorts receiving Ox + 5-FU.[51,78,110] In the one study in which these regimens were compared, there was no significant difference between arms in the complete resection rate.[51]

Survival outcomes

Only two studies followed up resected individuals for 5 years, a suitable proxy time-point for long-term survival.

A prospective case series of 701 previously unresectable patients followed up a cohort of 87 patients for 5 years. After treatment with Ox + 5-FU, 13.6% (95/701 patients) were resected. Five-year OS was 4.6% (19/701) and disease-free survival was 2.7% (19/701). In a Phase II trial 77/151 previously unresectable patients were treated with Ox + 5-FU. Five-year OS was 26% (39/151) and disease-free survival was 16/151 (11%).[110]

Discussion of results

Strength of the evidence (internal validity)

Although three RCTs included data on the downstaging of previously unresectable metastases with intent to operate curatively, none was designed with this as the primary outcome, and none reported long-term survival statistics.

Although all the single-arm studies were designed with the evaluation of chemotherapies in the neoadjuvant setting in mind, such studies are often subject to patient selection and other biases that can result in exaggerated effect sizes and may explain the diversity of results in the section 'Percentage of patients resected' (p. 57).

Applicability of the results (external validity)

Response rates to Ir + 5-FU and Ox + 5-FU are relatively consistent and it is therefore probably safe to generalise from these results. Resection and long-term survival rates vary considerably and more data would be desirable to validate the results presented here.

Anecdotally, while working on this subject, the review team has most frequently been referred to the large French case series ($n = 701$),[41] which also informed parts of the the treatment algorithm in Chapter 2 (*Figure 1*) and seems to inform most clinical understanding of the issue of liver resection in ACRC. The series is reliable in that it is large, and it is the only paper that specifically states that all ACRC patients who presented over a certain period were included in the study, regardless of patient characteristics. However, the study was undertaken in a single hospital in a healthcare system outside the UK, using a 5-FU regimen rarely used in the UK (a chronomodulated schedule) between between 1988 and 1996. With this in mind, it is unclear how transferable these data would be to the NHS of today.

Assessment of effectiveness

Where chemotherapy is used to downstage patients with previously unresectable liver metastases, randomised and non-randomised studies using either irinotecan with 5-FU or oxaliplatin with 5-FU consistently show tumour response rates of around 50%.

Resection rates for irinotecan combination therapy range from 9 to 35%; resection rates for oxaliplatin combination therapy range from 7 to 51%. In the only study to compare the regimens, significantly more individuals treated with oxaliplatin combination therapy were resected ($p = 0.02$).

Five-year OS rates of between 5 and 26% and 5-year disease-free survival rates of between 3 and 11% were reported in studies using oxaliplatin combination therapy.

Fluorouracil-containing treatment: differential effects

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

Caution is urged in the use of the results presented in this section, as the included studies have not been through the same rigorous process of critical appraisal as the studies reviewed in the preceding sections of this chapter.

The 2207 citations retrieved by the literature search described in the section 'Search strategy' (p. 11) were searched. A meta-analysis, performed outside the context of a systematic review, was retrieved.[111] It incorporated individual patient-level data from four Phase II and as two Phase III trials. For that reason, it did not meet the inclusion criteria of this review and a decision was made to undertake a meta-

***TABLE 53** Studies comparing bolus and infusional schedules of 5-FU*

	Infusional	Bolus	*p*
OS, months (95% CI)			
Lokich *et al.*, 1989[25]	10.3 (NR)	11.2 (NR)	0.379
de Gramont *et al.*, 1997[26]	14.3 (NR)	13.1 (NR)	0.067
Köhne *et al.*, 2003[112]	13.7 (12.0 to 16.4)	11.9 (10.2 to 15.0)	0.7
PFS, months (95% CI)			
Lokich *et al.*, 1989[25]	NR	NR	NR
de Gramont *et al.*, 1997[26]	6.4 (NR)	5.1 (NR)	0.001
Köhne *et al.*, 2003[112]	5.6 (4.4 to 6.7)	4.0 (3.4 to 4.9)	0.029
Response rates (CR + PR), %			
Lokich *et al.*, 1989[25]	30	7	<0.001
de Gramont *et al.*, 1997[26]	32.57	14.45	0.004
Köhne *et al.*, 2003[112]	17	12	ns
All grade 3–4 toxicities, %			
Lokich *et al.*, 1989[25]	NR	NR	NR
de Gramont *et al.*, 1997[26]	11.1	23.9	0.0004
Köhne *et al.*, 2003[112]	NR	NR	NR

analysis of Phase III trials using the methods and outcomes described in the section 'Analysis' (p. 12).

Only three Phase III RCTs (n = 938) involving unconfounded, direct comparisons of bolus and infusional regimens were identified (*Table 53*).[25]

Trials that compared infusional with bolus 5-FU were meta-analysed. The analysis of OS and PFS (*Figures 10* and *11*), using hazard ratios derived from the literature and published survival curves, involved three trials (938 participants).[48]

OS was not significantly better for individuals treated with infusional than for those treated with bolus 5-FU (HR=0.89, 95% CI 0.88 to 1.03, p = 0.11). There was no significant heterogeneity (χ^2 = 0.30, df = 2, p = 0.86, I^2 = 0%). PFS was significantly better for individuals treated with infusional than for those treated with bolus 5-FU alone (HR = 0.78, 95% CI 0.66 to 0.91, p = 0.001). There was no significant heterogeneity (χ^2 = 0.00, df = 1, p = 0.96, I^2 = 0%).

The results for median OS show the same direction and same size of effect as those presented by the published meta-analysis noted above (only the confidence intervals are wider). That study included two of the trials presented here, as well as a number of other studies of poorer quality. It reported significantly higher median OS (HR = 0.88, 95% CI 0.78 to 0.99, p = 0.04) and response rates (OR = 0.55, 95% CI 0.41 to 0.75, p = 0.0002) in the infusional arm.[111]

It is worth noting that a further Phase III RCT found no significant difference between two infusional regimens, the Lokich and de Gramont, in terms of either OS (HR = 0.88, 95% CI 0.70 to 1.12, p = 0.17) or PFS (HR = 0.99, 95% CI 0.80 to 1.23, p = 0.92).[95]

Summary

Irinotecan

The addition of irinotecan to first-line 5-FU significantly improves: median OS by between 2 and 4 months (p = 0.0007), median PFS by between 2 and 3 months (p <0.00001) and response rates (p <0.001). Irinotecan and 5-FU have different toxicity profiles, but there is no evidence that either confers a significant difference in quality of life.

There is no significant difference in OS or PFS between first-line irinotecan with 5-FU and oxaliplatin with 5-FU, except when 5-FU is delivered by bolus injection, when oxaliplatin provides better OS (p = 0.032) and response rates (p = 0.032), but not PFS (p = 0.169). The regimens have different toxicity profiles and there is no evidence that either confers a significant difference in quality of life.

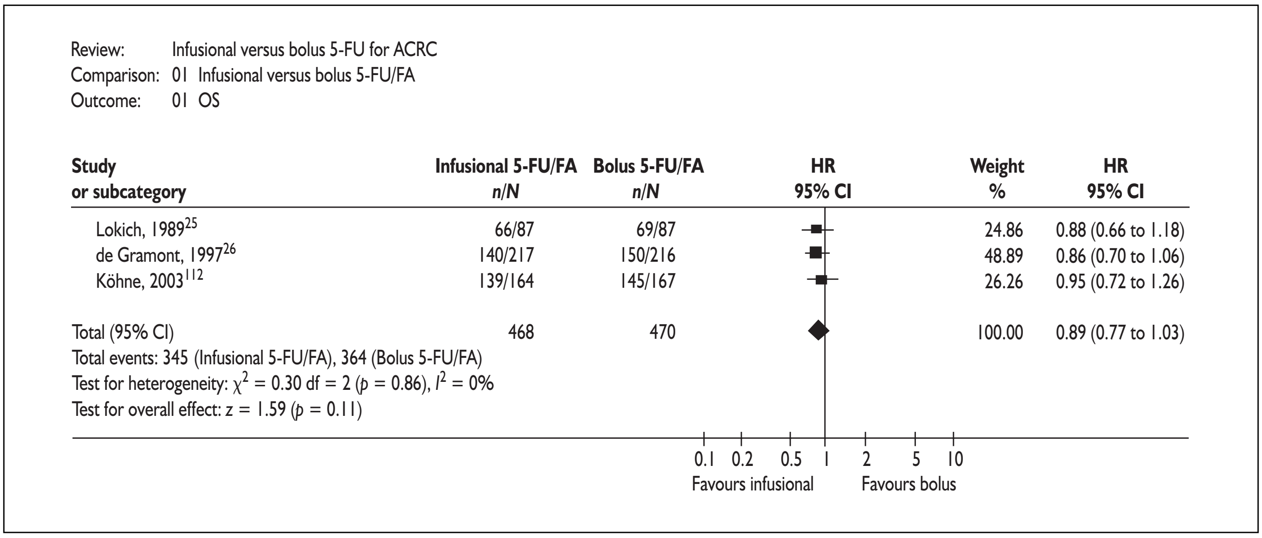


FIGURE 10 *Infusional versus bolus 5-FU: OS*

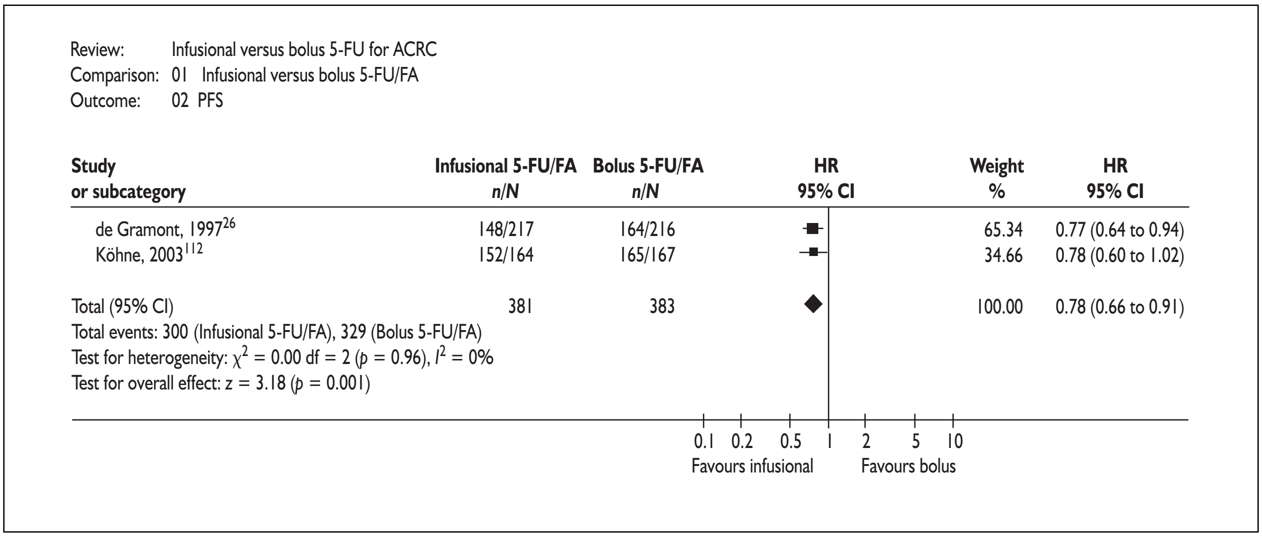


FIGURE 11 *Infusional versus bolus 5-FU: PFS*

In comparison with second-line 5-FU, irinotecan significantly improves median OS by over 2 months ($p = 0.035$) and median PFS by over 1 month ($p = 0.03$). It appears to provide a response in more people, but with more toxicities, and there is no evidence either drug provides a significant quality of life advantage.

In comparison with second-line BSC, irinotecan improves median OS by over 2.5 months ($p = 0.0001$). It causes more serious gastrointestinal and haematological toxicities than BSC, but less asthenia ($p = 0.006$) and pain ($p = 0.008$). Irinotecan maintains baseline quality of life longer than BSC alone.

Oxaliplatin

The addition of oxaliplatin to first-line 5-FU is associated with no significant difference in OS (but see caveat below), significantly improved PFS ($p < 0.00001$), significantly higher response rates ($p < 0.0001$), more serious gastrointestinal and haematological toxicities, and no significant overall improvement of quality of life. Schedules that offer treatment breaks do not appear to reduce clinical effectiveness, but may reduce toxicity. A caveat is that confounding by cross-over from 5-FU monotherapy to oxaliplatin combination in all trials may mask a real survival advantage for the latter.

The addition of oxaliplatin to second-line 5-FU is associated with a borderline significant improvement in overall survival ($p < 0.07$); a significantly higher response rate (<0.0001); and more serious toxicities. There is no evidence for a significant difference in QoL.

Raltitrexed

When compared to 5-FU, raltitrexed is associated with no significant difference in overall or progression-free survival; no significant difference in response rates; more vomiting and nausea, but less diarrhoea and mucositis; no significant difference in, or worse QoL. Raltitrexed treatment was cut short in two out of four included trials due to excess toxic deaths.

Optimum sequencing

The current NICE recommendation, 5-FU monotherapy followed by irinotecan monotherapy, appears to be inferior to any other planned sequence in preliminary data from the FOCUS study. Combination irinotecan and 5-FU as first-line therapy significantly improved OS and time to first progression. However, although this plan did not have an official second-line therapy some patients received salvage oxaliplatin and capecitabine (oral 5-FU), which will have affected the treatment effect size for OS to an unknown extent. Staged combination therapy using all active chemotherapy agents (oxaliplatin and 5-FU followed by irinotecan and 5-FU or vice versa) appears to provide the best OS and PFS, although there has been no head-to-head comparison against other treatment plans.

Downstaging

Where chemotherapy is used to downstage patients with previously unresectable liver metastases, randomised and non-randomised studies using either irinotecan with 5-FU or oxaliplatin with 5-FU consistently show tumour response rates of around 50%. Resection rates for irinotecan combination therapy range from 9 to 35%; resection rates for oxaliplatin/5-FU combination therapy range from 7 to 51%. In the only study to compare the regimens, significantly more individuals treated with oxaliplatin combination therapy were resected ($p = 0.02$). Five-year OS rates of between 5 and 26% and 5-year disease-free survival rates of between 3 and 11% were reported in studies using oxaliplatin/5-FU combination therapy (there are no such statistics for irinotecan).

Optimum 5-FU schedule

5-FU is significantly more effective and less toxic when delivered by continuous infusion rather than bolus injection, whether or not it is used in combination with other technologies.

Methodological issues

Over half of the first-line trial participants across all studies except for two were treated with unplanned second-line therapies. It is unknown to what extent estimates of OS are confounded as a result.

Although the best data are based on an atypically young and fit population, other available evidence suggests that there is no significant difference between the efficacy and toxicity of first-line irinotecan combination therapy in younger and in older people.

Chapter 4

Economic analysis

Introduction

This chapter aims to address the question 'What is the cost-effectiveness of irinotecan, oxaliplatin and raltitrexed as compared with established treatment and best supportive care in the treatment of advanced colorectal cancer?' The previous systematic review of clinical effectiveness and cost-effectiveness undertaken in 2000[1] identified a number of full and partial economic evaluations of irinotecan, oxaliplatin and raltitrexed in the treatment of ACRC. However, the majority of these economic studies were based on results reported within first- or second-line chemotherapy trials in which large numbers of patients received further chemotherapy following disease progression. As a result, either the scope of the economic analyses was limited to PFS, which may be considered at best a surrogate outcome, or the evaluations were subject to confounding owing to patients crossing over to alternative chemotherapy agents following disease progression. None of the economic studies included in the earlier NICE assessment[1] attempted to capture the cost-effectiveness of planned sequences of chemotherapy.

The next section presents a review of alternative benefit measures that may be used in the economic evaluation of chemotherapies for ACRC. Then the methods of a systematic review and critical appraisal of existing economic evidence identified within the literature and industrial submissions to NICE are presented. The following section details the methods of an independent economic evaluation of irinotecan, oxaliplatin and raltitrexed in the treatment of ACRC using newly available data from the MRC-sponsored FOCUS trial.[42] The reader should note that following the NICE appraisal, the Centre for Health Economics at the University of York undertook an economic evaluation of alternative chemotherapy regimens based on the final data from the FOCUS trial. Results of this analysis are available from http://www.york.ac.uk/inst/che/research/focus.ppt. The results of the systematic review and independent economic evaluation are then presented, followed by a report of estimates of the annual cost to the NHS associated with irinotecan and oxaliplatin-containing sequences. The final section in this chapter presents conclusions based on the findings of the cost-effectiveness review and independent economic evaluation.

Review of alternative benefit measures

There are several alternative benefit measures that may be used in the economic evaluation of chemotherapies for ACRC. Benefit measures used in previously identified economic evaluations include overall survival, quality-adjusted survival, progression-free survival, quality-adjusted progression-free survival, tumour response and adverse events avoided. A brief discussion of the advantages and disadvantages of these benefit measures is presented below; these issues should be borne in mind when interpreting the results of the systematic review of existing economic evidence.

Overall survival

OS is a highly relevant and unambiguous outcome measure in the economic evaluation of cancer treatments. OS refers to the time from randomisation to the death of the patient. Median survival is consistently reported as the primary end-point in the majority of the clinical trials of first- and second-line irinotecan, oxaliplatin and raltitrexed. However, as noted in Chapter 3, the overall survival results from these trials are particularly difficult to interpret.

Median survival may not represent true survival benefits

The true survival benefit of one intervention compared to another relates to the area between two survival curves, the mean survival difference. While median improvements in survival have the clear benefit of avoiding assumptions regarding survival distributions, this may not reflect the actual survival difference between treatments. Mean survival may be estimated by calculating the area under the survival curve using the trapezium rule. However, survival curves are typically incomplete (censored) as the duration of clinical trials is rarely sufficient to follow up all patients until death. The final portion of the survival curve may be extrapolated using statistical curve-fitting techniques such as Weibull, exponential or Gompertz curves. However, the process of fitting survival curves to empirical survival data requires assumptions concerning the shape of the final portion of the curve, and a degree of error between the fitted and empirical curves is inevitable.

Observed OS benefits in patients cannot be uniquely related to their allocated therapy

Following disease progression, it is unethical not to offer a patient with ACRC further treatment using an alternative chemotherapy regimen. The central difficulty in interpreting OS data from existing trials concerns the number of patients who cross over to alternative chemotherapies following disease progression or treatment failure. As a result, the effect of second-line therapy on OS is unknown, thus the survival of these patients cannot be uniquely related to the allocated therapy. In such cases, estimates of OS are confounded as it is unclear how much of the observed benefit is attributable to the first-line therapy or subsequent therapies. Thus, OS can be evaluated only as a measure of sequences of chemotherapy regimens. Only the trial reported by Tournigand and colleagues[51] and the FOCUS[42] trial have evaluated the overall survival benefits of planned chemotherapy sequences in ACRC. It should be noted, however, that while the FOCUS trial[42] incorporated a protocol change that resulted in sequences whereby all three drugs were used, this was not initially planned; hence only the trial reported by Tournigand[51] planned from the outset to compare sequences containing all three active agents. To illustrate the magnitude of this problem, *Table 54* shows the percentage of patients who received further chemotherapy with a different agent following disease progression. Of the eight trials that reported the number of patients who received further chemotherapies following progression, in all but one trial[69] this proportion was greater than 50%.

***TABLE 54** Unplanned chemotherapy following disease progression*

Trial[a]	Treatment setting	Allocated treatment group	Percentage of patients receiving further chemotherapy	Percentage of patients receiving Ir	Percentage of patients receiving Ox
de Gramont, 2000[77]	First line	Ox + 5-FU/FA	60%	30%	
		5-FU/FA	58%	20%	28%
Giacchetti, 2000[78]	First line	Ox + 5-FU/FA chronomodulated	Some[b]		
		5-FU/FA chronomodulated	Some[b]		57%
Grothey, 2002[85]	First line	5-FU/FA		68%	67%
		Ox + 5-FU/FA		75%	
Goldberg, 2004[55]	First line	Ox + 5-FU/FA	75%	60%	8%
		Ir + 5-FU/FA	67%	25%	24%
		Ox + Ir	70%	32%	9%
Köhne, 2004[56]	First line	5-FU/FA	65%	62%	36%
		Ir + 5-FU/FA	56%	34%	54%
Douillard, 2000[47]	First line	5-FU/FA	65%	34%	
		Ir + 5-FU/FA	49%		
Saltz, 2000[49]	First line	5-FU/FA	70%	56%	
		Ir + 5-FU/FA	52%		
Cunningham, 1999[69]	Second line	Ir (PS <2)	21%		
		BSC (PS <2)	31%	1%	
		Ir (PS = 2)	21%		
		BSC (PS = 2)	31%	1%	
Rothenberg, 2003[91]	Second line	5-FU/FA	Some[b]		
		Ox	NR		
		FOLFOX	NR		

[a] The table includes only those trials that reported that patients received further chemotherapy following disease progression.
[b] Unspecified number of patients.

Health-related quality of life

The purpose of chemotherapy for advanced (metastatic) colorectal cancer is as much for palliation of symptoms as for relatively modest survival benefits. It is thus important that chemotherapy treatment does not negate these palliative and survival benefits. The interpretation of quality of life data collected within the trials is, however, difficult, for several reasons.

Absence of utility estimates within clinical trials

Most commonly, health-related quality of life associated with ACRC has been evaluated in clinical trials using the cancer-specific EORTC QLQ-C30 questionnaire (see Appendix 10). However, there currently exists no preference-scaling method through which to translate QLQ-C30 results into an index utility score; as a result, existing quality of life data cannot be used in the context of comparative economic evaluation. Only one study[113] has attempted to assess utilities for patients undergoing chemotherapy for metastatic colorectal cancer; this study used the standard gamble technique to elicit preference scores from 30 UK nurses. However, the use of indirect utility estimates is not ideal; more robust estimates may be obtained from patients undergoing chemotherapy in a clinical trial setting. The FOCUS trial[42,114] has measured health-related quality of life using the EQ-5D questionnaire; the EQ-5D is broadly held as the preferred quality of life instrument within NICE's technology appraisals reference case.[115]

The timing of the questionnaire in relation to the chemotherapy regimen and the period to which quality of life data relate may influence the results

The EORTC QLQ-C30 quality of life instrument asks patients to assess their well-being over the previous week, whereas the EQ-5D asks patients about their state of health on the day the questionnaire is administered. The time at which the questionnaire is administered may influence the results; if the time profiles of the toxic effects of chemotherapies are very different, quality of life data may be further difficult to interpret.

Non-random censoring of quality of life data

There is evidence from some trials that censoring of quality of life data is not random, an effect known as informative censoring. This means that completion rates are not independent of the quality of life of the patient, and quality of life data for very ill patients may not be represented within the results of the study. This problem is illustrated by van Cutsem and Blijham,[116] who reported that 86% of patients still on treatment (i.e. with stable disease or tumour response) compared with only 26% of patients who were no longer on treatment completed the quality of life questionnaire. Such non-random censoring would inevitably bias quality of life results.

Quality of life changes in patients cannot be uniquely related to their allocated therapy

Owing to the large numbers of patients who cross over to alternative chemotherapies following disease progression or treatment failure, quality-adjusted survival in patients observed in clinical trials cannot be uniquely related to their allocated therapy.

Progression-free survival

PFS relates to the time from randomisation to the documented progression of disease. The WHO criteria define disease progression as an increase in the size of the primary tumour of by more than 25% and/or the appearance of new lesions, whereas the more recent RECIST criteria define progressive disease as at least a 20% increase in the sum of the longest diameters of the target lesions, or unequivocal progression of non-target lesions, or the appearance of new lesions.[117] PFS has been shown to be related to quality of life and reduced hospital stays.[113] The clinical relevance of PFS as a benefit measure derives from the notion that patients who do not respond to treatment, but whose disease is stabilised, derive benefit from chemotherapy. PFS is commonly reported within most clinical trials of chemotherapies for ACRC. The primary advantage of this outcome measure is that it is not confounded by patients receiving other chemotherapy agents following disease progression. However, there are problems in interpreting PFS results from existing clinical trials.

Time to progression is dependent on the frequency of check-ups

Disease progression results reported in the clinical trials relate to the documented time of progression; confirmation of disease progression is thus dependent on the frequency of check-ups received.

Median PFS may not represent true PFS benefits

The true PFS benefit relates to the area between two PFS curves; using median estimates of PFS may not reflect the actual benefits.

Tumour response

Tumour response may be either complete or partial. Complete response is defined by both the WHO response evaluation criteria and RECIST response evaluation criteria as the disappearance of all detectable tumours.[117] The WHO criteria define partial response as a decrease of 50% or more in the tumour surface area without the appearance of new lesions, whereas the more recent RECIST criteria define this as a decrease of 30% or more in the surface area of the tumour.[117] It has been suggested that tumour response may be an important prognostic factor for the determination of overall survival in patients with ACRC.[118]

Tumour response is a weak predictor of overall survival

Several studies have inadequately explored the relationship between response and overall survival.[119] Buyse and colleagues[120] used patient-level data from 3791 patients enrolled in 25 previously reported RCTs to explore whether an improvement in tumour response rate leads to better survival in patients with ACRC. Using regression analysis, the authors reported that only 38% (9–69%) of the variation in survival was explained by the variation in response rate. This suggests that tumour response is only a weak predictor of overall survival.

Avoidance of chemotherapy-related adverse events

Given the relatively modest survival advantages of chemotherapy observed in existing clinical trials, the avoidance of adverse events may be considered a relevant measure of the benefits attributable to alternative chemotherapies. It should be noted that offering only BSC may also impair quality of life owing to disease progression. Where survival benefits between alternative regimens are modest, the toxicity profile of individual chemotherapy regimens may be an important factor that may influence patient choice. However, the avoidance of adverse events is not an ideal benefit measure for use in economic evaluation.

Adverse events may not be an adequate surrogate measure of health-related quality of life

Although the avoidance of adverse events is a clinically relevant end-point, the central issue concerns the quality of life impact associated with chemotherapies. It is unlikely that the full breadth of treatment effects on quality of life will be captured by this end-point alone.

Adverse events reported may not be uniquely related to the allocated treatment

Similar to the problems in evaluating overall survival and quality-adjusted survival benefits attributable to individual chemotherapies, existing clinical trials have reported adverse events according to the ITT principle. It is thus unclear how many adverse events are attributable to the allocated therapy, and how many are attributable to alternative chemotherapeutic agents received following disease progression.

Summary of benefit measures

The most useful measures of the clinical benefit attributable to chemotherapy in patients with advanced colorectal cancer are OS and quality-adjusted survival as these, if measured appropriately, should capture the full breadth of effect attributable to alternative chemotherapy regimens. These outcomes cannot, however, be reliably estimated using the results reported with the majority of clinical trials owing to the confounding that arises from patients crossing over to alternative regimens following disease progression, and the unknown benefits attributable to second-line therapies. To date, only two trials[114] have used planned sequences of chemotherapies; these studies allow for the analysis of OS data (although owing to the late amendment to the study protocol, there remains some confounding within the results of the FOCUS trial[42,114]). Of these two studies of sequences of chemotherapies, only the FOCUS trial[114] has included quality of life assessments using the EQ-5D, which means that both cost-effectiveness and cost–utility may be evaluated.

Methods for cost-effectiveness review

Identification of economic studies

Systematic literature searches were undertaken to identify all relevant studies relating to the economics of irinotecan, oxaliplatin and raltitrexed in the treatment of ACRC compared with established 5-FU/FA-containing regimens and BSC. Details of the search strategies are reported in the section 'Search strategy' (p. 11). Handsearching of retrieved articles and industrial submissions to NICE was also undertaken.

Inclusion and exclusion criteria for cost-effectiveness review

Studies that aimed to evaluate the cost-effectiveness of oxaliplatin, irinotecan or raltitrexed compared with 5-FU/FA were included in the review. Economic studies were only included in the review if a full economic evaluation was reported; that is, those studies in which both the costs and benefits of chemotherapy were

TABLE 55 *First- and second-line chemotherapies included in the economic evaluation undertaken by the assessment group*

Treatment arm	First-line chemotherapy regimen	Second-line chemotherapy regimen	Subsequent salvage chemotherapy
FOCUS treatment plan A[114]	5-FU/FA (MdG)	Ir	Ox + capecitabine or Ox + 5-FU/FA (MdG)
FOCUS treatment plan B[114]	5-FU/FA (MdG)	Ir + 5-FU/FA (MdG)	Ox + capecitabine or Ox + 5-FU/FA (MdG)
FOCUS treatment plan C[114]	Ir +5-FU/FA (MdG)	BSC	Ox + capecitabine or Ox + 5-FU/FA (MdG)
FOCUS treatment plan D[114]	5-FU/FA (MdG)	Ox + 5-FU/FA (MdG)	Ir + capecitabine or Ir + 5-FU/FA (MdG)
FOCUS treatment plan E[114]	Ox + 5-FU/FA	BSC	Ir + capecitabine or Ir + 5-FU/FA (MdG)
Tournigand *et al.*, arm A[51]	Ir + 5-FU/FA (FOLFIRI)	Ox + 5-FU/FA (FOLFOX6)	None
Tournigand *et al.*, arm B[51]	Ox + 5-FU/FA (FOLFOX6)	Ir + 5-FU/FA (FOLFIRI)	None

estimated. Partial evaluations in which either costs or benefits were estimated in isolation, and reviews of existing economic studies were excluded from the review of cost-effectiveness but were retained for use in the economic evaluation undertaken by the assessment group. In addition, studies in which the methods of analysis were unclear were excluded from the review. All included studies were appraised using the checklist for assessing the quality of economic evaluations as proposed by Drummond and colleagues (see Appendix 11).[121]

Methods for the economic evaluation undertaken by the assessment group

Overview of economic analysis

The principal aim of the economic evaluation was to evaluate the cost-effectiveness of irinotecan- and oxaliplatin-containing chemotherapy regimens in the treatment of ACRC compared with first-line 5-FU/FA followed on progression by second-line single-agent irinotecan, as recommended within guidance issued by NICE in 2002.[2] Raltitrexed was not included in the economic analysis as there is no evidence to suggest that this agent improves overall survival compared with 5-FU/FA.[122]

The analysis improves on previous economic evaluations of irinotecan- and oxaliplatin-containing chemotherapy regimens (see the section 'Health economic results', p. 73) as it synthesises published and unpublished evidence on overall survival and resource use relating to sequences of chemotherapies from the current FOCUS trial[114] and the GERCOR trial reported by Tournigand and colleagues.[51] The annual cost to the NHS associated with each chemotherapy sequence is also estimated.

Health economic outcomes included in analysis

The following health economic outcomes are estimated in the model:

- cost per life-year gained (LYG)
- cost per quality-adjusted life-year (QALY) gained.

The analysis also reports on the cost-effectiveness of relevant first- and second-line chemotherapy regimens in terms of PFS for comparison with existing economic evaluations of irinotecan- and oxaliplatin-containing chemotherapy regimens (see Appendix 12). As PFS is at best a surrogate clinical end-point, cost per progression-free LYG results should not be considered central to this analysis and are thus reported in Appendix 12.

Interventions included in economic evaluation

Seven chemotherapies sequences are evaluated in the model; these are shown in *Table 55*.

The aim of the FOCUS trial[114] was to determine whether there is an advantage associated with the use of combination chemotherapy for ACRC (i.e. 5-FU/FA plus oxaliplatin or irinotecan) compared with the standard approach of sequential single-agent therapy (5-FU/FA followed on progression by irinotecan), and to determine whether combination therapy is best used in first-line management or reserved for planned second-line management following progression on first-line single-agent 5-FU/FA. The aim of the Tournigand trial[51] was to determine whether 5-FU/FA in combination with irinotecan followed on progression by 5-FU/FA in combination with oxaliplatin, or the reverse sequence, is optimal. A summary of the chemotherapy regimens evaluated within these two trials is shown in *Table 56*.

***TABLE 56** Chemotherapy regimens included in the economic analysis*

Chemotherapy regimen	Cycle duration (weeks)	Chemotherapy regimen components and protocol dose
MdG (FOCUS treatment arms)	2	400 mg m^{-2} 5-FU (bolus) 2800 mg m^{-2} 5-FU (infusion) 175 mg (flat dose) FA (infusion)
Ox +MdG (FOCUS treatment arms)	2	85 mg m^{-2} Ox (infusion) 400 mg m^{-2} 5-FU (bolus) 2800 mg m^{-2} 5-FU (infusion) 175 mg (flat dose) FA (infusion)
Ir + MdG (FOCUS treatment arms)	2	180 mg m^{-2} Ir (infusion) 400 mg m^{-2} 5-FU (bolus) 2800 mg m^{-2} 5-FU (infusion) 175 mg (flat dose) FA (infusion)
Ir (FOCUS treatment arms)	3	350 mg m^{-2} Ir (infusion)
FOLFOX6 (Tournigand treatment arms)	2	100 mg m^{-2} Ox (infusion) 400 mg m^{-2} 5-FU (bolus) 2400–3000 mg m^{-2} 5-FU (infusion) 200 mg m^{-2} l-LV or 400 mg m^{-2} dl-LV (infusion)
FOLFIRI (Tournigand treatment arms)	2	180 mg m^{-2} Ir (infusion) 400 mg m^{-2} 5-FU (bolus) 2400–3000 mg m^{-2} 5-FU (infusion) 200 mg m^{-2} l-LV or 400 mg m^{-2} dl-LV (infusion)

***TABLE 57** Scope of economic comparisons within the analysis*

Treatment regimens	OS period	First-line PFS period	Second-line PFS period
FOCUS plan A (MdG + Ir)	✓	✓	×
FOCUS plan B (MdG + IrMdG)	✓	✓	×
FOCUS plan C (IrMdG)	✓	✓	×
FOCUS plan D (MdG + OxMdG)	✓	✓	×
FOCUS plan E (OxMdG)	✓	✓	×
Tournigand FOLFIRI/FOLFOX6	✓	✓	✓
Tournigand FOLFOX6/FOLFIRI	✓	✓	✓

The analysis includes economic comparisons of irinotecan and oxaliplatin using three clinical benefit measures: OS, quality-adjusted survival and PFS. At the time of writing, PFS curves for second-line chemotherapy regimens within the FOCUS trial[114] were not available. Consequently, the economic evaluation of second-line chemotherapy regimens includes only FOLFOX6 in comparison to FOLFIRI, using survival curves reported by Tournigand.[51] *Table 57* shows the scope of the economic analysis.

A central issue that should be borne in mind when interpreting the results of this economic evaluation concerns whether a comparison of clinical evidence from the FOCUS trial[114] and the Tournigand trial[51] is valid and appropriate. While the inclusion criteria for the FOCUS trial[114] and the Tournigand trial[51] were broadly similar (Radstone D, Weston Park Hospital, Sheffield: personal communication), there is a possibility that the substantial differences observed in terms of overall survival were not solely due to the chemotherapy sequence received. These differences in overall survival may be a result of potential differences between the two clinical trials in terms of heterogeneity of the underlying patient populations, unbalanced protocol-driven intensity biases (e.g. frequency of clinical check-ups), or other random or non-random differences between underlying health service delivery systems.

Cost-effectiveness analysis methods

Methods for estimating OS and PFS benefits

Kaplan–Meier curves giving empirical estimates of OS and PFS in each treatment arm were obtained from the trial reported by Tournigand and colleagues[51] and from unpublished data made available to the assessment group (Griffiths G, MRC Clinical Trials Unit (CTU), London: personal communication). All survival curves and PFS curves were digitally scanned using TECHDIG™ software, and subsequently imported into Microsoft Excel™. As some patients were still alive at the end of the trials (i.e. right censored), the final portion of each survival curve was extrapolated using regression analysis to estimate the parameters of a Weibull survival curve. The results of this regression analysis are presented in Appendix 13.

The sequence of chemotherapies recommended within the 2002 NICE Guidance[2] (FOCUS treatment plan A: first-line 5-FU/FA followed on progression by second-line irinotecan) was taken as the baseline for the Weibull regression analysis of OS and first-line PFS. Owing to the absence of evidence on the effectiveness of second-line therapies from the FOCUS trial,[60] the FOLFOX6/FOLFIRI sequence evaluated within the trial reported by Tournigand and colleagues[51] was taken as the baseline for the regression analysis of second-line PFS. The Weibull survivor function $S(t)$ is given by the formula:

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

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

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

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

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

The application of this transformation to the Kaplan–Meier survival estimates results in an approximately straight line, whereby $\ln\{-\ln S(t)\} = y$, $\ln\lambda$ = intercept, γ = gradient and $\ln t = x$. The results of the regression analysis are detailed in Appendix 13.

To take account of correlations between the effectiveness of regimens and sequences of chemotherapy regimens, survival curves and first-line PFS curves for the remaining six sequences (i.e. FOCUS treatment plans B–E and the two Tournigand treatment arms) were estimated using the Weibull survivor function for the baseline FOCUS treatment plan A together with a log-rank hazard ratio describing the survival difference between the experimental curve and the baseline curve. The log-rank hazard ratios were treated as relative hazards between the experimental arms compared to the baseline. The same approach was used in the analysis of second-line therapies, but using second-line FOLFIRI as the baseline survivor function. Thus, the survivor functions $S(t)$ for the experimental treatment arms were estimated as:

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

where α = log-rank hazard ratio of sequence/regimen versus baseline, λ = scale parameter for baseline survivor function, t = time, and γ = shape parameter for baseline survivor function.

The analysis of OS and PFS in the model makes an explicit assumption of proportional hazards between the patients evaluated in the FOCUS trial[114] and patients evaluated in the Tournigand trial.[51] Put simply, the analysis is based on the assumption that the hazard of death at any given time for an individual in the Tournigand trial[51] is proportional to the hazard of death at that time for a similar individual in the FOCUS trial.[114] Log-rank hazard ratios for FOCUS treatment plans B–E versus FOCUS plan A (MdG + Ir) in terms of overall survival and first-line PFS were made available to the assessment group by the MRC (Griffiths G, MRC CTU, London: personal communication). Log-rank hazard ratios comparing the FOLFOX6/FOLFIRI and FOLFIRI/FOLFOX6 sequences evaluated in the Tournigand study[51] to the baseline FOCUS plan A (MdG + Ir) were not available, thus an implied relative risk for each of the Tournigand[51] treatment arms was estimated using a least-squares approach, and was tested by undertaking a separate regression analysis for the Tournigand[51] treatment arms.

As discussed in the section ‘Review of alternative benefit measures’ (p. 61), the best measure of survival is the mean, rather than the median. Mean OS and PFS benefits were calculated for each of the seven treatment arms using the formula:

$$\text{Mean survival} = (1/\alpha.\lambda)^{(1/\gamma)} \times \Gamma\{1 + (1/\gamma)\}$$

where Γ is the mathematical gamma function.

Additional analyses were undertaken using only the empirical Kaplan–Meier curves (thus ignoring the missing final portion of the curve), and mean OS and PFS were estimated by calculating the area under each curve (AUC) using the trapezium rule.

Methods for estimating quality-adjusted survival benefits

The FOCUS trial included a direct assessment of utility as measured using the EQ-5D.[114] Summary statistics on health outcomes for each chemotherapy sequence were made available to the assessment group (Sculpher M, Centre for Health Economics, University of York: personal communication); these detailed the mean EQ-5D index scores at baseline, and at 6, 12, 24, 36 and 48 weeks. However, it should be noted that at the time of writing, these data had not been subject to full checking and validation, nor had the data been adjusted for the effects of either informative or uninformative censoring within the trial. Consequently, the resulting cost–utility estimates are presented as a secondary analysis and should be interpreted with caution.

A straight-line relationship was assumed between consecutive EQ-5D utility scores to produce a profile of quality of life adjustments for each of the FOCUS treatment plans over the 48-week period, as shown in *Figure 12*. Beyond 48 weeks, a utility score equivalent to the mean of each treatment sequence utility profile was assumed. The resulting time-specific utility weights were then multiplied by the probability of survival across the entire Weibull curve. Mean quality-adjusted survival gains were estimated by calculating the area under the quality-adjusted survival curve.

The EQ-5D utility data suggest very little difference between the FOCUS treatment arms, and very little change in mean utility over the 48-week assessment period; mean EQ-5D scores remain around 0.72–0.80 throughout the 48-week period. As the EQ-5D scores appear very similar between treatment arms and do not appear to be largely affected by the treatment received, a constant utility score of 0.76 (the mean of all utility estimates for FOCUS plans A–E) was assumed for the FOLFOX6/FOLFIRI and FOLFIRI/FOLFOX6 treatment sequences.

Methods for estimating costs

Ten groups of costs are included in the economic model:

- drug acquisition costs
- infusional pumps
- pharmacy costs
- Hickman/peripherally inserted central catheter (PICC) line insertion
- administration

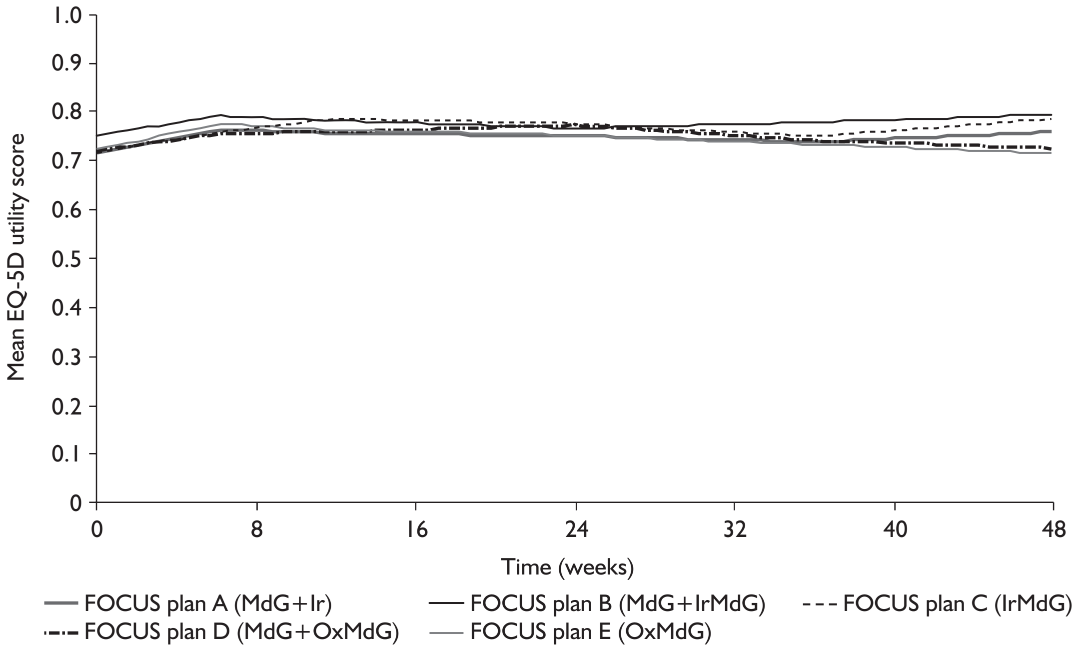


FIGURE 12 *EQ-5D profiles for FOCUS treatment sequences over time*

- hospital admissions for adverse events
- drug costs for adverse events
- diagnostic tests
- clinician consultations
- primary care costs.

With the exception of Hickman and PICC line insertion for outpatient 5-FU/FA regimens, all costs were calculated on a cyclical basis such that mean costs for PFS and OS periods could be estimated for each chemotherapy regimen and sequence, and subsequently related to OS/PFS benefits.

Drug acquisition costs

Unit costs of irinotecan, oxaliplatin, 5-FU and FA were taken from the BNF.[123] In instances where multiple products were listed, the least expensive was used within the analysis. In keeping with recent guidance issued by NICE on the methods of health technology appraisal,[115] VAT was not added to unit costs within the economic evaluation. Data relating to the mean number of treatment cycles of FOLFOX6 and FOLFIRI regimens received as first- and second-line therapy were made available to the assessment group by the corresponding author of the Tournigand trial (de Gramont A, Hôpital Saint-Antoine, Paris: personal communication). Data relating to the mean number of treatment cycles received within each treatment plan during first-line therapy and during the entire follow-up period of the FOCUS trial were made available to the assessment group. These data related to an unpublished ad hoc analysis of a subset of 1200 patients enrolled within the FOCUS trial (Griffiths G, MRC CTU, London: personal communication).

The mean doses of FOLFOX6 and FOLFIRI received during first- and second-line therapy were obtained from the paper reported by Tournigand and colleagues.[51] Mean dosage data for each chemotherapy regimen for the first-line PFS and OS periods in the FOCUS trial were also obtained from the analysis of 1200 patients enrolled in the FOCUS trial (Griffiths G, MRC CTU, London: personal communication).

The mean acquisition cost of each chemotherapy component received was calculated as:

Mean number of cycles received × Mean dose received × Cost per mg × Mean body size

Data on mean dosage of each chemotherapy regimen received were available from the FOCUS trial.[114] Mean acquisition costs in the Tournigand trial[51] were calculated based on the assumption that the mean body size of trial subjects was 1.75 m^2; this assumption is in line with previous cost-effectiveness studies. Mean acquisition costs were calculated for each chemotherapy regimen received in each treatment arm and summed to give the mean cost of chemotherapy acquisition per patient in each trial arm.

Importantly, a number of patients in the FOCUS trial received further salvage therapies following disease progression on first- or second-line therapy. For FOCUS treatment plans A–C, patients may have received oxaliplatin plus either capecitabine or 5-FU/FA as salvage therapy, while for FOCUS treatment plans D and E, patients may have received irinotecan plus either capecitabine or 5-FU/FA as salvage therapy. Unfortunately, data concerning the mean number of cycles of salvage therapy received were not collected in the trial. *Table 58* shows the estimated proportion of patients who received subsequent salvage therapies in each of the five FOCUS treatment arms (Griffiths G, MRC CTU, London: personal communication).

Table 58 suggests that between 25.5% and 50.0% of patients received further salvage chemotherapy for an unknown duration. This proportion is higher (46.0–50.0%) in treatment plan C (IrMdG) and plan E (OxMdG) as patients were not allocated a second-line therapy within the sequence. As a result, the mean costs of treatment for all treatment plans are likely to be substantially underestimated in the economic analysis of OS. The true cost impact of these subsequent salvage therapies in the FOCUS trial is not known,

***TABLE 58** Proportion of patients who received salvage therapies in the FOCUS trial*

Salvage treatment	Treatment plan A (MdG + Ir) (*n* = 400)	Treatment plan B (MdG + IrMdG) (*n* = 200)	Treatment plan C (IrMdG) (*n* = 200)	Treatment plan D (MdG + OxMdG) (*n* = 200)	Treatment plan E (OxMdG) (*n* = 200)
Chemotherapy	25.5%	29.5%	50.0%	27.0%	46.0%
Radiotherapy	17.0%	18.0%	18.5%	16.0%	21.0%
Surgery	12.8%	9.0%	17.5%	11.5%	10.0%

although the degree of underestimation of costs is expected to be greatest for treatment plan C (IrMdG) and plan E (OxMdG). This limitation of these data should be borne in mind when interpreting the results of the economic analysis.

Infusional pumps

The cost of disposable infusional pumps was taken from a study reported by Iveson and colleagues.[32] This was estimated as a weekly cost and included the cost of the pharmacist's time. The model assumes that a new pump is required for each cycle of chemotherapy received. This cost is applied only to outpatient 5-FU/FA regimens in the model. A cost of £62.00 was used in the analysis and uplifted to 2004 prices using health service inflation indices.[124]

Pharmacy costs

The estimated pharmacy costs per cycle of treatment are shown in *Table 59*. It was assumed that the cost for a simple intravenous infusion was £23.00 and the cost for a complex intravenous infusion was £38.00 (Michelle Rowe M, Clinical Services, The Christie Hospital NHS Trust, Manchester: personal communication). Therefore, the total pharmacy cost for a cycle of MdG (consisting of 5-FU bolus, 5-FU infusion, FA infusion) is estimated as 3 × £38.00 = £114. These costs include the pharmacist's time for checking and the technician's time for dispensing. It should be noted that these costs are considerably higher than other published estimates.[125]

TABLE 59 *Pharmacy costs used in the economic model*

Chemotherapy regimen	Pharmacy cost per cycle
MdG	£114.00
IrMdG	£152.00
OxMdG	£152.00
Ir	£23.00

Pharmacy costs were not available for FOLFOX6 or FOLFIRI. It was assumed in the analysis that the pharmacy cost for FOLFOX6 was the same as the cost for OxMdG, and the pharmacy cost for FOLFIRI was assumed to be the same as the cost for IrMdG.

Hickman/PICC line insertion

The cost of line insertion was taken from the results of an RCT comparing image-guided Hickman line insertion versus unguided Hickman line insertion.[126] The cost of an unguided, rather than image-guided, Hickman line insertion was used in the economic analysis. Cost estimates in the trial included the basic costs of insertion as well as unplanned events, costs associated with misplaced insertions, serious adverse events and infections, and the costs of nurse, oncologist and radiologist assistance. A mean cost of £440.40 was used in the model and uplifted using health service inflation indices.[124]

Administration costs

Unit costs of inpatient days and outpatient attendances were obtained from an earlier Personal Social Services Research Unit (PSSRU) report;[127] these costs are reported at 1999 prices, and were uplifted to 2004 values using health service inflation indices.[124] It was assumed that these costs included nursing time for the administration of chemotherapy. The cost per medical oncology day case was not available and was hence assumed to be the same as a medical oncology outpatient attendance.[1] A medical oncology inpatient day was reported to be £356 and a medical oncology outpatient day was assumed to be £109.[127] The hospitalisation resource use per cycle for each chemotherapy regimen assumed in the model is reported in *Table 60*.

The number of patients who receive chemotherapy for colorectal cancer on an

TABLE 60 *Hospitalisation resource use per cycle for chemotherapy regimens included in the economic analysis*

Treatment regimen	Resource per cycle	
	Chemotherapy given as inpatient	Chemotherapy given as outpatient
MdG	2 inpatient days	1 outpatient day
Ox + MdG	2 inpatient days	1 outpatient day
Ir + MdG	2 inpatient days	1 outpatient day
Ir	1 inpatient day	1 outpatient day
FOLFOX6	2 inpatient days	1 outpatient day
FOLFIRI	2 inpatient days	1 outpatient day

TABLE 61 *Proportion of patients receiving chemotherapy as inpatients/outpatients*[52]

Treatment regimen	Number inpatient	Percentage inpatient	Number outpatient	Percentage outpatient	Total
MdG	15	21%	56	79%	71
Ir	7	25%	21	75%	28
FOLFOX6	3	7%	38	93%	41
FOLFIRI	4	17%	19	83%	23
Total	29	18%	134	82%	163

inpatient basis in the UK is uncertain. The proportion of patients treated as inpatients and outpatients was estimated using data reported in the Aventis submission to NICE.[52] The submission detailed the proportion of a sample of 163 UK patients who received treatment on an inpatient and outpatient basis in previous chemotherapy trials. These data are shown in *Table 61*. No information was available concerning how this sample of patients was constructed.

Table 61 suggests that around 7–25% of UK patients in the FOCUS trial[114] and the Tournigand trial[51] received chemotherapy on an inpatient basis. It is unlikely that the setting for chemotherapy is dependent on the regimen received, but is more likely to be a result of geographical variation, the availability of local resources and patient considerations (Radstone D, Weston Park Hospital, Sheffield: personal communication). In the base-case analysis, the economic model assumes that 18% (29/163) of patients receive chemotherapy as inpatients, while the remaining 82% of patients are assumed to receive chemotherapy on an outpatient basis.

Hospital admissions for chemotherapy-related adverse events

The economic evaluation reported in the earlier assessment of irinotecan and oxaliplatin[1] estimated hospitalisation costs using data reported by Schmitt[128] and unpublished resource-use data from the de Gramont trial,[77] which were reported in the Sanofi-Synthelabo submission to NICE.[130] Schmitt[128] reported the mean number of days in hospital per patient per month, estimated via a retrospective case-note review. The Sanofi-Synthelabo submission estimated the mean number of hospital days per patient per month based on the estimated treatment time (using the PFS curve). Schmitt[128] estimated the mean number of days in hospital per month to be 1.2 and 0.8 days for irinotecan and 5-FU/FA, respectively. Analysis of the de Gramont trial data[77] resulted in a lower estimate of 0.38 days per month.

Data on the proportion of hospitalisations by ward type were reported by both Schmitt[128] and the Sanofi-Synthelabo submission;[130] these data were used together with the estimated days in hospital to calculate hospitalisation costs for chemotherapy-related adverse events. The higher cost estimate of £258 and longer mean duration of 1 day per month were used in the model and applied to all chemotherapy regimens; the impact of the lower cost estimate on cost-effectiveness was explored in the sensitivity analysis. The calculations underpinning these estimates are shown in *Table 62*.

A limitation of this approach is that hospitalisation costs are assumed to be the same for each chemotherapy regimen. Unpublished data relating to all hospitalisation resources during the entire FOCUS trial period were made available to the assessment group (Sculpher M, Centre for Health Economics, York: personal communication). However, hospitalisations relating specifically to serious adverse events could not be distinguished from planned hospitalisations and thus could not be used in the framework of the economic analysis. Summary data relating to hospitalisations for serious adverse events during first- and second-line FOLFOX6/FOLFIRI and FOLFIRI/FOLFOX6 were also made available to the assessment group (de Gramont A, Hôpital Saint-Antoine, Paris: personal communication). These data suggested a similar number of unplanned hospitalisation days per month for patients receiving first-line therapy to the estimate reported by Schmitt[128] (1.0–1.5 hospital days per month for FOLFOX6/FOLFIRI and FOLFIRI/FOLFOX6). However, hospital days per month on second-line therapy appeared to be higher (around 3 days per month on treatment) than the estimate reported by Schmitt.[128] As no additional information was available relating to ward type, these data were not used in the economic analysis.

Drug costs for managing adverse events

Drug costs used to manage adverse events were estimated from a study reported by Kerr and

TABLE 62 *Proportion of hospital days and unit costs by specialty*

Department	Proportion of hospital days by specialty						Cost per day
	Schmitt *et al.*[128]			de Gramont *et al.*[77]			
	Ir (*n* = 127)	5-FU (*n* = 129)	Average	Ox + 5-FU (*n* = 210)	5-FU (*n* = 210)	Average	Unit cost (Netten *et al.*,[127])
Medicine	51.5%	58.9%	55.2%	41.4%	15.1%	28.2%	£222
Oncology	21.7%	10.1%	15.9%	28.2%	47.6%	37.9%	£356
Surgery	19.3%	16.2%	17.8%	28.0%	32.7%	30.3%	£301
ICU	0.4%	0.4%	0.4%	2.5%	4.6%	3.5%	£359
Other	7.0%	14.2%	10.6%	0.0%	0.0%	0.0%	£222
Average cost			£257.54			£299.91	

ICU, intensive care unit.

O'Connor,[129] taking the average of the 5-FU and raltitrexed costs. An estimate of £9.74 per month was used in the model, and uplifted to 2004 prices using health service inflation indices.[124]

Cost of diagnostic tests
The cost of diagnostic tests was taken from a study by Kerr and O'Connor[129] and included the cost of X-rays, blood tests and computed tomographic (CT) scans. A cost of £64.55 was assumed for each of the chemotherapy regimens, calculated as the mean of the raltitrexed and 5-FU/FA treatment arms reported by Kerr and O'Connor.[129]

Clinician consultations
The cost of clinical consultations per cycle was estimated from the study reported by Iveson and colleagues.[32] A cost of £79.81 was used in the model and uplifted to 2004 prices using health service inflation indices.[124]

Primary care costs
Primary care costs were taken from Kerr and O'Connor;[129] an estimate of £10.42 per month was assumed for all chemotherapy regimens.

Discounting
Current guidance from NICE on the methods of technology appraisal[115] recommends that costs and benefits that occur in the future are given less weight than those that occur in the present. However, no information was available on the distribution of treatment cycles over time; therefore, discounting was not possible within this economic analysis. Owing to the short time horizon for the analysis, it is unlikely that the incorporation of discounting would substantially impact upon the cost-effectiveness results.

Uncertainty analysis
The economic evaluation includes two types of sensitivity analysis: simple scenario analysis to explore alternative costing assumptions in the analysis, and more sophisticated probabilistic sensitivity analysis to explore second order uncertainty surrounding mean parameter values.

Scenario analysis
There is a paucity of good-quality evidence concerning resources required in the delivery of alternative chemotherapy regimens for ACRC (see the section 'Methods for estimating costs', p. 68). The earlier assessment of irinotecan, oxaliplatin and raltitrexed[1] identified several estimates of resources required, and grouped these in terms of high and low costs. In this analysis, base-case estimates relate to the higher reported costs. Scenario analysis was undertaken to explore the impact of assuming lower cost estimates on central estimates of cost-effectiveness. As noted earlier, there is limited evidence on the number of patients who receive chemotherapy as inpatients or outpatients. An additional scenario analysis was undertaken whereby it was assumed that all patients received chemotherapy on a less expensive outpatient basis.

Probabilistic sensitivity analysis
Probabilistic sensitivity analysis was undertaken to explore the impact of second order uncertainty surrounding mean parameter values on the cost-effectiveness. This was undertaken by describing parameter values in the model using probability distributions, and by randomly sampling from all uncertain distributions simultaneously using Monte Carlo simulation techniques. The results of these simulations are presented as cost-effectiveness

planes and cost-effectiveness acceptability curves (CEACs).

The baseline OS curve and baseline PFS curve in the model were described by multivariate normal distributions of the form $X \sim N(\mathbf{m},\mathbf{V})$ where $\mathbf{m}$ is the vector of means (the scale and shape parameters of the baseline Weibull survivor function) and $\mathbf{V}$ is the covariance matrix of these means. As the logs of the standard errors for the hazard ratios between OS and PFS curves from the FOCUS trial[114] were symmetrical, these were sampled from a normal distribution. Standard errors associated with the log-rank hazard ratios for comparisons between the Tournigand treatment sequences[51] and the FOCUS baseline (MdG + Ir)[60] were not available; additional uncertainty was incorporated by assuming that the standard error for these log-rank hazard ratios was twice as large as the greatest standard error of the FOCUS hazard ratios.[60]

Standard errors surrounding the mean number of treatment cycles were estimated from unpublished data from the FOCUS trial and the Tournigand trial; these parameters were described by normal distributions. 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 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 included in the sample.[52]

As uncertainty in health economic models is ubiquitous, all model parameters should ideally be described by uncertain distributions. However, limited evidence was available on the differential hospital resources required to manage serious adverse events between treatment arms in the model. Mean estimates of hospital resource use (presented in *Table 62*) were held constant during the simulations; therefore, uncertainty in the cost of regimens and sequences of chemotherapies may be underestimated in the economic evaluation.

Health economic results

Number and type of economic studies identified

A summary of the results of the economic literature searches is presented in *Figure 13*. The systematic searches identified 100 potentially relevant studies relating to the health economics of irinotecan, oxaliplatin or raltitrexed in the treatment of ACRC. Alongside the electronic searches, submissions from Sanofi-Synthelabo[130] and Aventis[52] were also retained for inclusion in the review. An industrial submission was not received from Astra Zeneca. Two additional potentially relevant studies[131,132] were identified by handsearching identified studies and submissions. Of these 104 studies, 21 were retrieved for further evaluation. Three of these studies were excluded as the methods used were not reported in sufficient detail.[131,133,134] Four studies were excluded as they were partial evaluations that considered only the costs of chemotherapies in isolation of improvements in survival.[132,135–137] A further study reported only medical care consumption related to treatment with irinotecan in combination with 5-FU/FA and was also excluded from this review.[128] One of the retrieved studies was a review of cost and cost-effectiveness evaluations and did not present any new evidence;[74] this study was also excluded from the cost-effectiveness review. One study[138] related to adjuvant chemotherapy and was also excluded from the review. In total, 11 full economic evaluations which estimated both the costs and benefits of irinotecan, oxaliplatin and/or raltitrexed in the treatment of ACRC were included in the review. Only two of the included studies[130,139] attempted to estimate the cost-effectiveness of chemotherapy in the treatment of patients with initially unresectable liver metastases. The characteristics of the included studies are shown in *Table 63*.

Review of existing health economic studies

This section presents a detailed critical appraisal of existing health economic studies. The checklist proposed by Drummond and colleagues[121] is presented in Appendix 11.

Economic evaluations of irinotecan

Cunningham *et al.* (2002) *Clinical and economic benefits of irinotecan in combination with 5-fluorouracil and folinic acid as first-line treatment of metastatic colorectal cancer*[140]

Cunningham and colleagues[140] report a cost-effectiveness analysis of first-line irinotecan in combination with 5-FU/FA versus 5-FU/FA alone for patients with metastatic colorectal cancer. The analysis was undertaken from the perspective of the UK NHS and included only direct costs and benefits. The authors report the use of life-years gained as the measure of clinical benefit, which

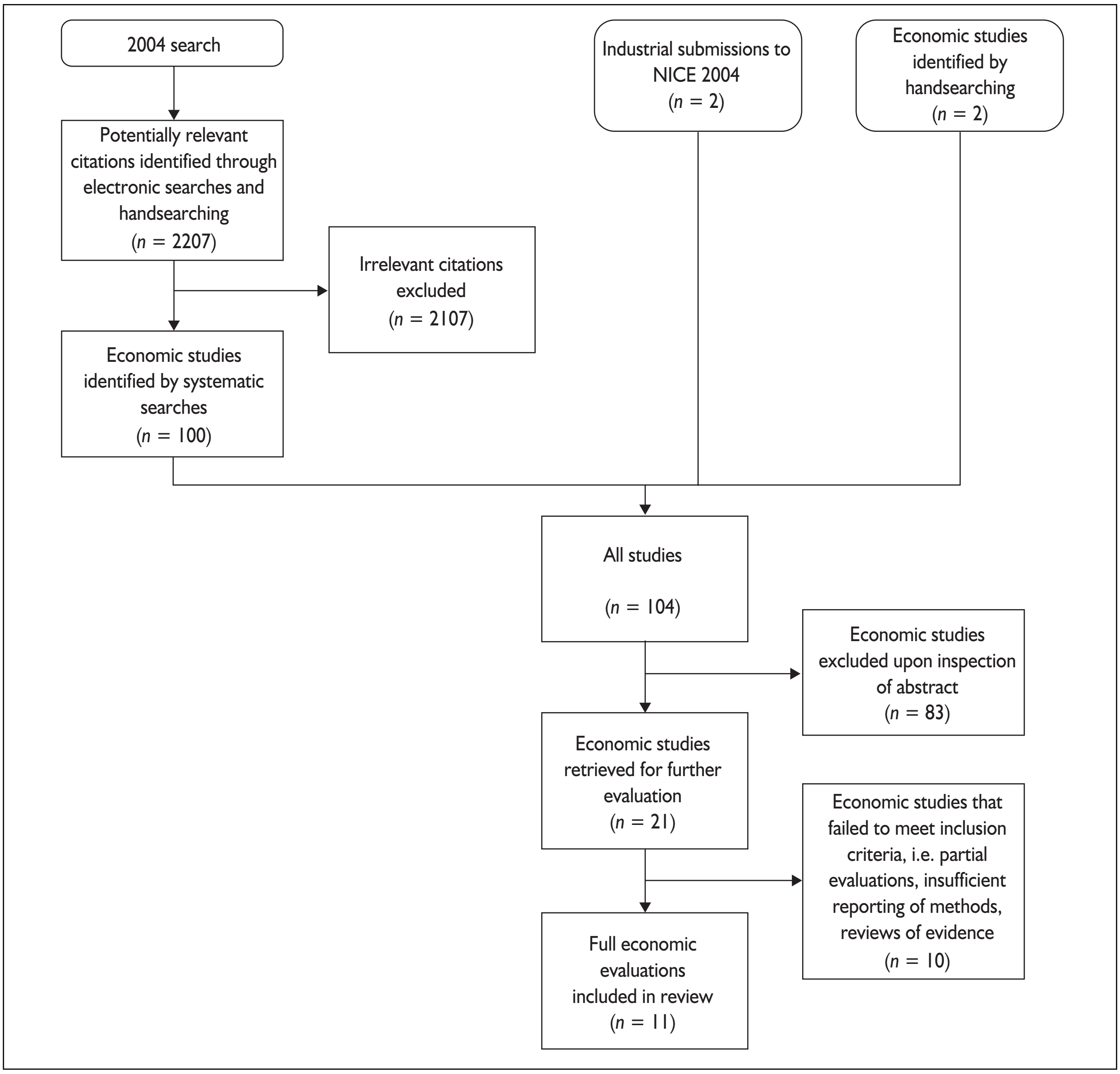


FIGURE 13 *Studies included in cost-effectiveness review*

implies a comparison of overall survival between the treatment arms.

Survival results and the majority of resource-use data used in the economic evaluation were taken from the Douillard trial,[47] although further resource-use data following disease progression were collected retrospectively. The authors report that only cost data relating to patients who received the de Gramont regimen were included in the evaluation, as the AIO regimen which was also used in the trial is not used in the UK. However, survival data reported in the trial paper relate to both 5-FU regimens; this suggests a degree of incompatibility of the survival and cost data.

The authors included three main groups of costs: drug acquisition costs, treatment administration costs, and costs incurred as a result of complications due to treatment or the disease. The costs of drug acquisition were calculated using median treatment durations reported in the trial, and unit costs for chemotherapies were derived from the BNF,[123] with some allowance for wastage. It should be noted that mean treatment durations would be more accurate for use in economic evaluation. In instances where more than one alternative treatment was available, the lowest cost was used. The costs of treatment administration included costs of inpatient and outpatient hospitalisation, nursing time and equipment use. Treatment with 5-FU/FA and irinotecan in

TABLE 63 *Characteristics of studies included in the cost-effectiveness review*

Study	Evaluation of first-/second-line therapies or sequences of chemotherapies	Intervention(s) included in primary analysis	Comparator(s)	Study design	Economic perspective	Source of clinical effectiveness data	Benefit measure(s)	Resource and cost data included	Analysis of unresectable liver metastases?
Cunningham *et al.*, 2002[140]	First line (including postprogression costs)	Ir + 5-FU/FA	5-FU/FA	Cost-effectiveness analysis	UK NHS	Douillard[47]	LYG	Drug acquisition and administration; adverse events due to disease or therapy; hospitalisations	No
Aventis, 2004[52]	First line and sequences	*PFS analysis* First-line Ir + 5-FU/FA; first-line Ox + 5-FU/FA *OS analysis* First-line Ir + 5-FU/FA; first-line Ox + 5-FU/FA First-line FOLFIRI followed on progression by second-line FOLFOX	*PFS analysis* First-line 5-FU/FA *OS analysis* First-line 5-FU/FA followed on progression by second-line Ir First-line FOLFOX followed on progression by second-line FOLFIRI	Cost-effectiveness analysis	UK NHS	de Gramont,[77] Giacchetti,[78] Douillard,[47] Saltz,[49] Köhne,[29] Goldberg,[55] Tournigand,[51] FOCUS[114]	(a) LYG; (b) PFLYG	Drug acquisition; chemotherapy administration; adverse events; pharmacy costs; fixed costs (line insertion and pump); hospital tests; primary care; consultations with clinicians	No
Lloyd-Jones *et al.*, 2001[1]	First and second line	*First line* Ir + 5-FU/FA Ox + 5-FU/FA *Second line* Ir	*First line* 5-FU/FA *Second line* 5-FU/FA	Cost-effectiveness analysis	UK NHS	Rougier,[68] de Gramont,[77] Saltz,[49] Douillard[47]	PFLYG (sensitivity analysis to adjust for QoL)	Drug acquisition; chemotherapy administration; adverse events; pharmacy costs; fixed costs (line insertion and pump); hospital tests; primary care; consultations with clinicians	No

continued

TABLE 63 *Characteristics of studies included in the cost-effectiveness review (cont'd)*

Study	Evaluation of first-/second-line therapies or sequences of chemotherapies	Intervention(s) included in primary analysis	Comparator(s)	Study design	Economic perspective	Source of clinical effectiveness data	Benefit measure(s)	Resource and cost data included	Analysis of unresectable liver metastases?
Levy-Piedbois *et al.*, 2000[141]	Second line	Ir	5-FU/FA	Cost-effectiveness analysis	French hospital	Rougier[68]	LYG	Chemotherapy; hospital admissions for administration of chemotherapy and subsequent complications; hospital outpatient visits	No
Iveson *et al.*, 1999[32]	Second line	Ir	5-FU/FA	Cost-effectiveness analysis	UK NHS	Rougier[68]	LYG	Drug acquisition costs; chemotherapy administration; hospitalisation costs; consultations with clinicians; service costs	No
Poston *et al.*, 2001[139]	First line	Ox + 5-FU/FA	5-FU/FA	Cost-effectiveness analysis	UK NHS	de Gramont,[77] Giacchetti[78]	LYG	Drug acquisition; liver resection; postsurgery inpatient stay	Yes
Nicholls *et al.*, 2001[142]	First line	Ox + 5-FU/FA	5-FU/FA	Cost-effectiveness analysis	UK NHS	de Gramont[77]	PFLYG	Drug acquisition; premedications; hospitalisations	No
Nicholls *et al.*, 2001[143]	First line	Ox + 5-FU/FA Ir + 5-FU/FA	5-FU/FA	Cost-effectiveness analysis	NR	de Gramont,[77] Douillard[47]	PFLYG	Drug acquisition	No

continued

TABLE 63 *Characteristics of studies included in the cost-effectiveness review (cont'd)*

Study	Evaluation of first-/second-line therapies or sequences of chemotherapies	Intervention(s) included in primary analysis	Comparator(s)	Study design	Economic perspective	Source of clinical effectiveness data	Benefit measure(s)	Resource and cost data included	Analysis of unresectable liver metastases?
Sanofi-Synthelabo, 2004[130]	First line and sequences	*OS analysis* First-line 5-FU/FA + Ox followed on progression by second-line Ir *PFS analysis* First-line 5-FU/FA + Ox	*OS analysis* First-line 5-FU/FA followed on progression by Ir *PFS analysis* First-line 5-FU/FA	Cost-effectiveness analysis	UK NHS	de Gramont,[77] Goldberg,[55] Douillard,[47] Saltz,[49] Cunningham,[69] Rougier,[68] Andre,[92] Rothenberg,[91]	(a) PFLYG; (b) LYG; (c) QAPFLYG; (d) QALY	Drug acquisition and administration; treatment of chemotherapy-related toxicities; hospitalisations	Yes
Groener, 1999[144]	First line	Ral	5-FU/FA	Cost-effectiveness analysis	Dutch (societal perspective inferred)	Cunningham[94]	(a) LYG; (b) additional patients free of mucositis, leucopenia, anaemia and asthenia	*Chemotherapy regimen-related costs* Drugs and preparation; drug administration at the outpatient day-case department; diagnostics related to treatment (laboratory tests); transport from and to hospital *Non-chemotherapy regimen-related costs* Hospitalisations (at the oncology ward and ICU); treatment of chemotherapy-related side-effects; non-treatment-related diagnostics; hospital outpatient visits; GP visits; transport to and from hospital	No

continued

TABLE 63 *Characteristics of studies included in the cost-effectiveness review (cont'd)*

Study	**Evaluation of first-/second-line therapies or sequences of chemotherapies**	**Intervention(s) included in primary analysis**	**Comparator(s)**	**Study design**	**Economic perspective**	**Source of clinical effectiveness data**	**Benefit measure(s)**	**Resource and cost data included**	**Analysis of unresectable liver metastases?**
Kerr and O'Connor, 1999[129]	First line	Ral	5-FU/FA	Cost-minimisation analysis	UK NHS	Cunningham[94]	Cost difference	Acquisition; pharmacy charges; tests; adverse events; inpatient stays; outpatient stays; community health visits; dose delay	No

PELYG, progression-free life-year gained; QAPFLYG, quality-adjusted progression-free life-year gained.

combination with 5-FU/FA required insertion of a central line catheter by a doctor as well as an infusional device.

Prospective data collection provided an estimate of the proportion of inpatient hospitalisations and day hospital attendances required per infusion in each treatment arm. The costs of managing complications were categorised as unplanned hospitalisation, consultation costs, and costs for clinical and diagnostic services. GP and nurse visits were also documented on the case-report forms in the main trial; these unit costs were derived from the PSSRU.[124] Unit costs for hospitalisation, specialist consultations and diagnostic costs derived from Qost database (1997/98). The authors assumed that nurse and healthcare professional consultations would take 30 minutes each.

The authors report the use of sensitivity analysis whereby only patients from the UK were included in the analysis, "to reflect the local situation".

Overall costs per patient in the first-line irinotecan plus 5-FU/FA treatment group were higher compared with those allocated to 5-FU/FA alone (£13,550 versus £10,098, cost difference of £3452). Douillard and colleagues[47] reported a median difference in PFS of 2.8 months in favour of the irinotecan plus 5-FU/FA group; the analysis uses an estimate of 0.23 incremental LYG attributable to the irinotecan group. The base-case results suggest that irinotecan has a cost-effectiveness of £14,794 per life-year saved. The sensitivity analysis resulted in a cost-effectiveness of £16,015 per life-year saved when only data from UK patients were included in the analysis. The authors suggest that the results of the analysis demonstrate that the cost-effectiveness of irinotecan plus 5-FU/FA lies within the acceptable range for cancer treatments.

Industrial submission from Aventis (2004)
Submission to the National Institute of Clinical Excellence (NICE) on Campto® (irinotecan) for colorectal cancer (advanced) – irinotecan, oxaliplatin and raltitrexed [review][52]
The economic analysis presented by Aventis[52] is based on the earlier economic analysis undertaken by the School of Health and Related Research, University of Sheffield (ScHARR) in the first NICE assessment of irinotecan, oxaliplatin and raltitrexed.[1] The Aventis submission to NICE[52] reports the results of a cost-effectiveness analysis of irinotecan in combination with 5-FU/FA in the first-line treatment of patients with ACRC compared with oxaliplatin in combination with 5-FU/FA and 5-FU/FA alone (de Gramont regimen). The analysis was undertaken from the perspective of the UK NHS. The economic outcome for the analysis of first-line therapies was cost per progression-free LYG. The analysis was extended to consider the cost-effectiveness of these regimens compared with the existing NICE guidance of 5-FU/FA as first-line therapy (modified de Gramont regimen), followed on progression by single-agent irinotecan;[2] the economic outcome for the analysis of sequences of chemotherapies was cost per LYG. The analysis of sequences of chemotherapies was undertaken using preliminary data from the FOCUS trial[114] and the trial reported by Tournigand.[51] However, as the analysis of sequences compares first-line therapies only versus sequences of therapies, the clinical and economic relevance of this comparison is difficult to justify. The submission describes the increasing role of first-line irinotecan in combination with 5-FU/FA in the downstaging of initially unresectable liver metastases; however, this is not included in the cost-effectiveness analysis. Cost–utility was not estimated; the authors state that "insufficient data were available to derive reliable utility estimates for the competing therapeutic arms."[52]

The submission model draws on efficacy data from a number of recent clinical trials[77] in addition to preliminary data from the MRC CR08 FOCUS trial.[114] Mean PFS was estimated using Weibull curves and AUC analysis.

For the analysis of sequences of chemotherapies, the model is divided into six distinct time phases:

1. time on first-line treatment
2. time following treatment cessation until disease progression
3. time from first-line disease progression until start of second-line treatment
4. time on second-line treatment
5. time following cessation of second-line treatment until disease progression
6. time from disease progression until death.

The mean and median time on treatment (measured in months) for each study were estimated at 3 and 6 months, respectively, using Kaplan–Meier survival curves (extrapolated using Weibull curves to account for censoring). The analysis of sequences draws on two studies that evaluated planned sequences of chemotherapies.[51] However, there are important problems with the use of these data; first, the preliminary results from FOCUS reported only grouped data for first- and second-line irinotecan/oxaliplatin. Thus, the analysis presented in the submission makes the explicit assumption that oxaliplatin in combination with 5-FU/FA and irinotecan in combination with 5-FU/FA are equivalent in terms of OS and PFS, and that the two drugs have identical adverse event profiles. The key difficulty in using the Tournigand trial[51] is that the time on first- and second-line therapies is unknown and must therefore be estimated. These difficulties lead to important weaknesses in the analysis of sequences of chemotherapies.

Cost and resource data included in the analysis were derived from a number of studies[32] and were calculated on a monthly basis. These estimates were uplifted to current prices where necessary, using the Hospital and Community Health Services (HCHS) cost index.[124] The key cost components used in the model can be divided into four categories:

- drug acquisition costs: these are calculated by multiplying the drug cost per cycle by the number of cycles per month
- drug administration costs: these include the costs of both inpatient and outpatient administration, pump costs and clinician consultations
- costs associated with adverse events, hospital tests, plus primary care and pharmacy costs
- fixed costs: these include the cost of line insertion for patients treated on an outpatient basis. However, they are excluded from the estimate of the total cost per patient.

Given the different costs associated with chemotherapy administration in an inpatient and an outpatient setting, costs were based on the estimated mean proportion of inpatient and outpatient visits from the UK studies. Costs were then related to the effectiveness of different treatments (in terms of OS or PFS) to produce cost-effectiveness estimates.

The analysis includes three different costing scenarios based on different assumptions concerning time on treatment and time until progression following cessation of treatment:

- scenario 1 (base case): costs calculated using mean time on treatment and mean post-treatment time until progression
- scenario 2: costs calculated using median time on treatment and the difference between the mean time to progression and the median time on treatment
- scenario 3: costs calculated using estimated mean time to progression.

The latter scenario assumes that patients stay on treatment until disease progression, which is likely to overestimate overall treatment time. This would be offset slightly by the implicit assumption that no costs are incurred between cessation of treatment and disease progression. The results from scenario 2 may be unreliable, as the distribution of treatment times may be skewed. While not ideal, results from the base-case scenario are likely to be the most robust.

Sensitivity analysis was undertaken using 'low' and 'high' scenarios for the monthly costs associated with hospitalisations due to adverse events, hospital tests, primary care and pharmacy costs, in an attempt to estimate an upper and lower bound for the cost-effectiveness of irinotecan and oxaliplatin. These two costing scenarios were based on different estimates from the literature. These sensitivity analyses incorporate the various scenarios regarding calculation of time on treatment and time to progression outlined above. The 'low' scenario cost-effectiveness estimates combined the use of low cost estimates and median time to disease progression, and defined post-treatment time to progression by the difference between the mean time to progression and the median time on treatment. Such an approach is therefore likely to underestimate the costs of treatment. The high scenario used the high cost estimates from the literature and defined time on treatment as the mean time to progression, with post-treatment time to progression assumed to be zero. This approach would therefore be expected to overestimate costs. The base-case analysis cost results are estimated as the mean of the low and high cost estimates.

Two further sensitivity analyses were also carried out using the assumption that all patients were treated entirely on an inpatient or an outpatient basis, rather than as a combination of the two as per the base-case analysis. Probabilistic sensitivity analysis was not undertaken as part of the submission. A further minor limitation of the model concerns the absence of discounting.

The submission reports that irinotecan in combination with 5-FU/FA as first-line therapy is associated with 2.3 additional progression-free months compared with 5-FU/FA alone. The irinotecan regimen was associated with an additional cost of £8592. This results in a marginal cost-effectiveness of £43,712 per progression-free life year gained LYG. If all patients are assumed to be treated on an outpatient basis, the marginal cost per progression-free LYG for irinotecan in combination with 5-FU/FA compared with 5-FU/FA alone is reduced to £39,743.

Lloyd-Jones *et al.* (2001) *The clinical and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer*[1]

The earlier assessment of irinotecan, oxaliplatin and raltitrexed for NICE reported by Lloyd-Jones and colleagues[1] included an assessment of the cost-effectiveness of irinotecan and oxaliplatin. The analysis estimated the marginal cost-effectiveness of first-line irinotecan plus 5-FU/FA, and first-line oxaliplatin plus 5-FU/FA versus first-line 5-FU/FA alone. The analysis also estimated the marginal cost-effectiveness of second-line irinotecan alone versus second-line 5-FU/FA. The analysis was undertaken from the perspective of the NHS, and included only direct costs. The analysis used PFS as the benefit measure. Effectiveness data were taken from three RCTs.[49] PFS curves were projected by fitting Weibull curves to account for censoring. Mean PFS was estimated using AUC analysis. Utility scores were derived from the study reported by Petrou and Campbell.[113]

The analysis included the following cost components:

- drug acquisition costs: these are calculated by multiplying the drug cost per cycle by the number of cycles per month
- drug administration costs: these include the costs of both inpatient and outpatient administration, pump costs and clinician consultations
- costs associated with adverse events and hospital tests, plus primary care and pharmacy costs
- fixed costs: these include the cost of line insertion for patients treated on an outpatient basis. However, they are excluded from the estimate of the total cost per patient.

All costs were valued in 2000 UK pounds sterling. Owing to the absence of good-quality evidence on costs for use in the analysis, costs were estimated using three scenarios based on different assumptions concerning resource use:

- scenario 1 (base case): costs were calculated using mean time on treatment and mean post-treatment time until progression
- scenario 2: costs were calculated using median time on treatment and the difference between the mean time to progression and the median time on treatment
- scenario 3: costs were calculated using estimated mean time to progression.

As with the Aventis model,[52] sensitivity analysis was undertaken using 'low' and 'high' scenarios for the monthly costs associated with hospitalisations due to adverse events, hospital tests, primary care and pharmacy costs in an attempt to estimate an upper and a lower bound for the cost-effectiveness of irinotecan and oxaliplatin. The analysis did not include any discounting of health effects or costs.

The marginal cost-effectiveness of first-line oxaliplatin plus 5-FU/FA versus 5-FU/FA alone was reported to range from £23,047 to £67,856 per progression-free LYG depending on the costing assumptions used. The marginal cost-effectiveness of first-line irinotecan plus 5-FU/FA versus 5-FU/FA alone was reported to be in the range £47,989–94,713 per progression-free LYG. For second-line single-agent irinotecan, the cost per progression-free LYG was estimated to be in the range £26,416 to dominating.

Although some adjustments for quality of life effects were explored in the analysis, the authors stated that the results were too uncertain to draw conclusions from these. The key limitations of this analysis, and of the analysis submitted by Aventis,[52] are that the analysis is based on PFS, effective treatment durations on first- and second-line therapies were unknown, and the adverse event profiles of the different chemotherapy regimens were assumed to be identical.

Levy-Piedbois *et al.* (2000) *Cost-effectiveness of second-line treatment with irinotecan or infusional 5-fluorouracil in metastatic colorectal cancer*[141]

Levy-Piedbois and colleagues[141] report the cost-effectiveness of second-line treatment with irinotecan compared with three alternative infusional regimens of 5-FU/FA in patients with metastatic colorectal cancer. The analysis was undertaken from the perspective of a French hospital. Health benefits were measured in terms of life-years gained, using median survival estimates from the trial reported by Rougier and colleagues.[68]

Resource-use data were collected prospectively in the trial, and estimated costs were converted into US dollars using the purchasing power parity (PPP) index. The costing analysis included the cost of chemotherapy, hospital admissions for administration of chemotherapy and for subsequent complications, and hospital outpatient visits. Other drug treatments for symptom palliation were excluded from the analysis under the assumption that they would be equivalent in each treatment arm.[141] The time horizon over which costs were included is ambiguous: the authors initially suggest that costs were computed over the total duration of patient survival, or 3-year follow-up, and subsequently suggest that OS and costs were estimated from the time of randomisation until the death of the patient, or the last visit.[142] However, some of the resource-use quantities reported are the same as those reported by Schmitt,[128] who stated a maximum 16-month follow-up. As a result, it is difficult to interpret the cost-effectiveness results presented. Discounting was not undertaken in the analysis; however, it is unlikely that this exclusion would have a substantial impact on the results of the economic analysis.

Levy-Piedbois and colleagues[141] report that the total cost of treatment for irinotecan patients was $14,135 versus $12,192–12,344 for patients receiving infusional 5-FU/FA chemotherapy regimens. The central estimates of cost-effectiveness for irinotecan versus 5-FU/FA regimens ranged from $9344 to $10,137 per LYG. Basic one-way sensitivity analysis was undertaken to explore the impact of the alternative survival benefits on the cost per LYG. The authors report that when survival benefits ranged between 0.5 and 3.5 months, the cost-effectiveness ratio ranged from $3000 to $45,000 per LYG.

Iveson *et al.* (1999) *Irinotecan in second-line treatment of metastatic colorectal cancer: improved survival and cost-effect compared with infusional 5-FU*[32]

Iveson and colleagues[32] report on the cost-effectiveness of replacing conventional 5-FU/FA with single-agent irinotecan in the second-line treatment of metastatic colorectal cancer, using final results from the trial reported by Rougier and colleagues.[68] Two-hundred and fifty-six patients were randomised into the two treatment groups, all of whom had previously received first-line 5-FU/FA therapy (which for the majority of patients had been palliative). The primary end-point used in the trial was OS, with patients remaining on treatment until disease progression, unacceptable toxicity or patient refusal. Iveson and colleagues[32] used efficacy data from the trial together with prospective economic data and data from an investigator questionnaire concerning resource use in each treatment arm to compare the economic implications of the two treatments.

A range of cost components was used in the evaluation, including drug acquisition costs, administration costs, costs associated with complications of disease and treatment (e.g. hospital consultations with oncologists, radiologists and surgeons) and nursing and equipment costs. Cost estimates were derived from a number of sources, including the BNF[123] for drug acquisition costs, extracontractual referral tariffs for hospital costs, unit costs from the Department of Health for general medicine and ward tariffs, the Qost database for laboratory costs and diagnostic tests, and the PSSRU[124] for costs of professional expenses. It is unclear whether costs were uplifted to a formal price year. Neither costs nor benefits were discounted, owing to the short time horizon under consideration.

The cost-effectiveness analysis used the mean total cost and the median survival for each treatment arm. A more appropriate approach would be to compare the mean survival associated with the two interventions, which takes into account the spread of survival times and makes no assumptions about the distribution of survival. The authors justified their choice of parameters by carrying out sensitivity analyses to consider the lifetime estimates of survival and costs, using non-parametric methods to extrapolate beyond the data observed in the trial.

An incremental cost-effectiveness ratio (ICER) was calculated for irinotecan compared with each of the 5-FU/FA regimens. The incremental cost per LYG was estimated to be £7695 when irinotecan was compared with the de Gramont regimen, while the corresponding value for the Lokich regimen was £11,947. The results of these sensitivity analyses did not change the conclusions of the primary cost-effectiveness analysis. These cost-effectiveness results were compared with those from other cancer studies, and considered in the context of expected cost-effectiveness thresholds upon which previous adoption decisions have been made. Comparison is made between these results and those from studies that used different methods for deriving total costs. The resource-use analysis was not extended to assess the feasibility of treating all patients with irinotecan as opposed to 5-FU/FA.

Poston *et al.* (2001) *Costs of neoadjuvant chemotherapy and surgery in patients with liver metastases from advanced colorectal cancer*[139]

Poston and colleagues[139] report the cost-effectiveness of oxaliplatin in combination with 5-FU/FA versus 5-FU/FA alone in the treatment of patients with ACRC with initially unresectable liver metastases. Cost-effectiveness estimates were derived from mean overall survival estimates, drug acquisition costs and subsequent costs associated with surgical resection. Health benefits were measured in terms of life-years gained.

The study used a theoretical cohort of 2000 patients with unresectable liver metastases. Patients were assigned equally between the two treatment regimens, to be treated with chemotherapy for a period of 6 months. At this stage, each patient was assessed for suitability for resection, based on the scale of any reduction in the size of the liver tumour. Resectability rates of 11.4% and 4.1% were applied to the oxaliplatin plus 5-FU/FA and 5-FU/FA arms, respectively, based on data from the trial reported by de Gramont.[77] Kaplan–Meier survival curves were obtained from a retrospective study of patients with initially unresectable liver metastases who had been treated with oxaliplatin plus 5-FU/FA to reduce tumour size.[110] Mean postsurgery survival was estimated as the area under these curves. Mean OS for patients undergoing resection was estimated to be 9.0 years; for patients considered unsuitable for resection, mean survival was estimated to be 1.7 years. These figures include patients still alive at the end of the follow-up period, whose survival is assumed to be equal to that of an age-matched normal population (21.6 years). This may represent an overestimate given the likelihood of recurrent disease.

The cost analysis includes the acquisition costs of chemotherapies (over a period of 6 months), an assessment of each patient's suitability for resection and the costs of liver resection (including preoperative evaluation, surgery cost, postoperative intensive care, inpatient hospital stay and subsequent outpatient appointment). Drug administration costs were excluded from the analysis, on the basis that no additional training, pharmacy services or staff time would be required to administer combination oxaliplatin therapy, compared with 5-FU/FA alone. All other postsurgical costs, including further chemotherapy/surgery and palliative care, were excluded. It should be noted that as the mean survival benefits for neoadjuvant chemotherapy were estimated to be 9.0 and 1.7 years for the two treatment arms, the use of a 6-month time horizon for costs is likely to underestimate total costs of treatment in both arms. Costs were not discounted in the cost-effectiveness analysis.

Survival gains were discounted at 1.5% in the main analysis; the authors do not report the discounting of treatment costs.

The ICER of oxaliplatin in combination with 5-FU compared with 5-FU/FA is estimated to be £11,985 per LYG in the base-case analysis. Sensitivity analyses were conducted to assess the sensitivity of the results to changes in assumptions regarding resection rates on the two treatment arms, survival of censored patients and the discounting of health benefits (at 1.5% per annum, in line with NICE guidelines). These analyses give a range of ICER of between £5489 and £15,624 per LYG.

Nicholls *et al.* (2001) *Cost-effectiveness of combination chemotherapy (oxaliplatin or irinotecan in combination with 5-FU/FA) compared with 5-FU/FA alone*[143]

Nicholls and colleagues[143] report the cost-effectiveness of irinotecan and oxaliplatin in combination with 5-FU/FA compared with 5-FU/FA alone. The perspective for the analysis was not reported. The outcome for the analysis was cost per progression-free LYG. Evidence of effectiveness, measured in terms of median first-line PFS, was derived from a Phase III trial of oxaliplatin with 5-FU/FA[77] and a Phase III trial of irinotecan with 5-FU/FA.[47] Secondary analysis was also undertaken to estimate the cost per additional responding patient.

The authors included only drug acquisition costs in the analysis; the exclusion of the costs of chemotherapy administration and hospitalisations due to treatment-related toxicities suggests that it is likely that the costs of the combination chemotherapy arms were underestimated.

The authors report the use of simple sensitivity analysis, whereby costs were allowed to vary by ±10% of the estimated mean cost and PFS was allowed to vary by ±2.5% of the estimated median survival. It should be noted that varying the narrow ranges used in the sensitivity analysis may underestimate the uncertainty within the model. Each sensitivity analysis compared the lower confidence interval limit (or estimate) of the active arm with the upper confidence interval limit (or estimate) for the control arm, "to give the full range of costs incurred during the study period."[143] However, the range for costs used was arbitrary, as was the variation in PFS from the Douillard trial;[47] thus, it is difficult to confirm whether the true uncertainty in costs and effects was explored. Furthermore, the sensitivity analysis did not include simultaneous variations in both costs and effects.

The authors report the incremental cost per progression-free LYG for oxaliplatin in combination with 5-FU/FA versus 5-FU/FA alone to be £26,655 (range £21,421–31,909). The equivalent estimate for irinotecan in combination with 5-FU/FA was reported to be £30,171 (range £23,691–36,651). The cost per additional responding patient is reported to be £31,065 (range £24,852–43,491) for oxaliplatin in combination with 5-FU/FA and £46,343 (range £23,171 to dominated) for irinotecan in combination with 5-FU/FA. It should be noted that the exclusion of other important costs besides those associated with acquisition is likely to bias these analyses in favour of irinotecan and oxaliplatin compared with 5-FU/FA alone. Furthermore, it is likely that if uncertainty in both costs and effects had been evaluated simultaneously, this would result in greater uncertainty around the mean cost-effectiveness estimates.

Economic evidence for oxaliplatin

Nicholls *et al.* (2001) *Cost-effectiveness of oxaliplatin in combination with 5-FU/FA compared with 5-FU/FA alone*[142]

Nicholls and colleagues[142] report the cost-effectiveness of oxaliplatin in combination with 5-FU/FA in comparison with 5-FU/FA alone. The analysis was undertaken from the perspective of the UK NHS. Estimates of effectiveness were derived from a Phase III trial reported by de Gramont and colleagues;[77] effectiveness was measured in terms of PFS. Mean PFS was calculated as the AUC using the trapezium rule. The authors adjusted for censoring due to patients surviving beyond the follow-up time by reducing survival to 0% by 30 months in equal increments for the censored data.

The evaluation included direct costs only; these included the costs of drug acquisition and hospital resources used in the management of treatment-related toxicities. The authors did not include the costs of chemotherapy administration, as they suggest that oxaliplatin combination therapy with 5-FU/FA requires no additional training, pharmacy costs or staff time compared with that for 5-FU/FA alone. However, this exclusion is not warranted as combination therapy may differ from 5-FU/FA alone in terms of the mean number of cycles received, which ultimately may lead to different costs. The impact of this exclusion is that total costs may be biased in favour of combination therapy with oxaliplatin.

Drug acquisition costs were taken from the BNF[123] and the Monthly Index of Medical Specialities (MIMS).[145] Costs resulting from hospitalisation were taken from the PSSRU[124] and NHS Reference Costs.[146] The costs of premedications were derived from the Royal Marsden Drug and Therapeutics Advisory Committee's prescribing guidelines,[147] Devita and colleagues,[148] MIMS[145] and the BNF.[123] Drug costs were estimated to include wastage. Hospitalisation costs were calculated according to the type of ward to which patients were admitted; these included surgical, oncology, medical and intensive care wards.

The authors report that discounting was not used, as "the studies and projections did not extend beyond one year";[142] however, this is unclear as the authors clearly report that follow-up data from the de Gramont trial[77] were approximately 24 months, and PFS was extrapolated to up to 30 months in the analysis.

Sensitivity analysis was undertaken on drug acquisition costs and PFS separately by varying estimates according to their 95% confidence interval limits. As with Nicholls,[143] varying costs and effects separately is likely to underestimate the true uncertainty in cost-effectiveness. The authors report an incremental cost per progression-free LYG to be £25,600 (range £12,055 to dominated).

Industrial submission from Sanofi-Synthelabo (2004) *The use of oxaliplatin for the treatment of advanced colorectal cancer (review of NICE guidance no. 33)*[130]

The model reported within the Sanofi-Synthelabo submission to NICE[130] details the use of a Markov-based economic model to evaluate the cost-effectiveness of two oxaliplatin-based chemotherapy regimens versus the current NICE recommendation of 5-FU/FA followed on progression by irinotecan monotherapy in patients with ACRC. The cost-effectiveness of combination chemotherapy in patients who have initially unresectable liver metastases was also evaluated as a separate analysis.

The analysis reports the cost per progression-free LYG and cost per quality-adjusted progression-free LYG for first-line oxaliplatin-containing regimens as well as the cost per QALY gained for three sequences of chemotherapies:

- sequence A: oxaliplatin plus 5-FU/FA followed on progression by irinotecan monotherapy
- sequence B: 5-FU/FA alone followed on progression by irinotecan monotherapy
- sequence C: 5-FU/FA alone followed on progression by oxaliplatin plus 5-FU/FA.

The economic evaluation was conducted from the perspective of the NHS in England and Wales and thus includes only direct costs and benefits. The authors used a state transition approach to simulate chemotherapy sequences using data from both first- and second-line clinical trials in an attempt to remove the confounding in trial data that resulted from treatment cross-overs and mixed salvage treatments. The model included five health states, which were evaluated using a 3-month cycle length:

1. progression free on first-line therapy
2. progression on first-line therapy
3. progression free on second-line therapy
4. progression on second-line therapy
5. dead.

The analysis of first-line therapies used a time horizon from baseline (initiation of first-line chemotherapy) until the point of disease progression. The analysis of chemotherapy sequences, which included both first- and second-line therapies, used a time horizon from baseline to death.

Estimates of the effectiveness of first- and second-line chemotherapy regimens were derived from PFS curves and OS curves reported in clinical trials.[77] OS and PFS curves were extrapolated using survival analysis, in which Weibull curves were fitted to empirical OS and PFS data using a least squares approach to estimate the final portion of each curve.

The model assumes that the entire cohort enters the model in state 1, that is, receiving first-line therapy with no progression. Extrapolated PFS curves from trials of first-line chemotherapy were used to model the probability of remaining in this initial health state; the probability of remaining on first-line chemotherapy during the current model cycle was calculated by dividing the proportion of patients without progression at time $t + 1$ by the proportion of patients without progression at time t. During any given model cycle, patients receiving first-line therapy could either progress (and thus enter into a temporary state before receiving second-line therapy) or die. The 3-month probability of dying while on first-line therapy was calculated using extrapolated OS curves reported in first-line clinical trials of 5-FU/FA and oxaliplatin. The probability of dying was calculated as 1 minus the proportion of patients surviving at time $t + 1$ divided by the proportion of patients surviving at time t. However, the use of survival curves for individual chemotherapies to estimate the probability of death during each Markov cycle results means that the results remain confounded; it is unknown how much of the observed survival benefit was actually attributable to the allocated treatment.

The model assumes that all surviving patients who progress on first-line therapy meet the inclusion criteria for second-line therapy; that is, the patients progress to the second-line progression-free health state.

The model includes three categories of cost:

- *Chemotherapy administration*: the cost of first-line chemotherapy was calculated as the estimated number of cycles (observed in first-line chemotherapy trials) multiplied by the cost per cycle. This cost was applied to 100% of patients. The cost of second-line chemotherapy following disease progression was calculated as the number of chemotherapy cycles observed in the second-line trials multiplied by cost per chemotherapy cycle. This cost was applied to all surviving patients who enter the second-line progression-free health state. However, as noted above, this cost is likely to be an overestimate.
- *Treatment of chemotherapy-related toxicities:* the costs of treatment-related adverse events were calculated as the mean percentage of adverse events taken from trials over the entire period of treatment multiplied by unit costs for indicated therapies for each type of adverse event. However, as with the OS benefits, adverse event data reported within the trials are similarly confounded as they cannot be uniquely related to the allocated treatment.
- *Hospitalisations:* the cost of hospitalisations was estimated using data on hospitalisations before disease progression obtained from patient charts collected in the de Gramont trial.[77] This cost was calculated as the number of hospitalisations associated with progression-free and progression health states, multiplied by unit costs from the PSSRU.[124]

Utilities in the model were derived from a study in which 30 specialist nurses were asked to rate the quality of life benefits of stabilisation in the treatment of advanced metastatic colorectal cancer using the standard gamble technique.[113] The utility associated with six health states was estimated (best possible health, worst possible health, partial response, stable disease, progressive disease and terminal disease).

The analysis used baseline discount rates of 6% and 1.5% for costs and health outcomes, respectively, in line with current NICE recommendations.

Alternative discounting scenarios were explored in the sensitivity analysis.

Cost-effectiveness results were presented for first-line therapies, as well as for sequences of therapies. For first-line oxaliplatin plus 5-FU/FA versus 5-FU/FA alone, the cost per progression-free LYG was reported to be £22,576. When the analysis included adjustments for quality of life, the cost per quality-adjusted progression-free LYG was reported to be £25,951. For first-line oxaliplatin in combination with 5-FU/FA followed on progression by irinotecan versus 5-FU/FA followed on progression by irinotecan, the cost per QALY was estimated to be £22,302 (note that this includes a correction to second-line treatment durations in the model). The model suggests that 5-FU/FA followed on progression by oxaliplatin plus 5-FU/FA is cost-saving in comparison to 5-FU/FA followed on progression by irinotecan (note that this includes a correction to second-line treatment durations in the model).

A range of one-way sensitivity analyses was undertaken to explore the impact of using alternative discount rates, alternative costs for 5-FU/FA and alternative assumptions concerning the utility associated with the model's health states. The one-way sensitivity analysis suggested that the choice of discount rate has only a minor impact on the cost-effectiveness of oxaliplatin; this is unsurprising given the short time horizon for the analysis. Additional sensitivity analysis was undertaken whereby the cost of 5-FU/FA was replaced with the cost of capecitabine (Xeloda®, Roche Pharmaceuticals); this had only a limited impact on the cost-effectiveness ratio. Further sensitivity analysis was undertaken to explore the sensitivity of the utility values used in the model; again, the analysis suggested that cost–utility was not sensitive to alternative values for these parameters. However, the authors stated that the choice of these utility values was arbitrary.[130]

The authors claimed to have undertaken probabilistic sensitivity analysis, and presented the results of the uncertainty analysis as CEACs and cost-effectiveness planes. The authors report that transition probabilities in the Markov model were unaltered, but each actual transition was governed by chance. However, probability distributions were not assigned to any of the uncertain parameters in the model; instead, the authors have re-created the base-case model at the level of the individual patient, which does not allow for an analysis of the uncertainty surrounding the mean parameter estimates in the model. The uncertainty analysis is theoretically incorrect and should be ignored.

In summary, while the approach adopted in the submission to NICE from Sanofi-Synthelabo[130] attempted to prevent the confounding arising from patients crossing over to other chemotherapy regimens following disease progression, the use of a Markov approach does not overcome this problem. The cost-effectiveness results relating to sequences of chemotherapies remain confounded and should be considered unreliable. Therefore, the cost-effectiveness results for first-line therapies are more likely to be robust, although these are restricted to the use of PFS as the measure of clinical benefit.

Economic evidence for raltitrexed

Groener (1999) ***An economic evaluation of Tomudex (raltitrexed) and 5-fluorouracil plus leucovorin in advanced colorectal cancer***[144]

Groener[144] reports on an economic evaluation of raltitrexed versus 5-FU/FA in patients with ACRC. The economic perspective of the analysis was not stated; however, the inclusion of indirect costs suggests that the analysis was undertaken using a Dutch societal viewpoint. Costs were valued in dollars, although the country of origin was not reported. Clinical results and resource-use data were obtained directly from the trial reported by Cunningham and colleagues.[94] While the Cunningham trial[94] failed to demonstrate a statistically significant improvement in survival for raltitrexed over 5-FU/FA, a statistically significant improvement in side-effects was observed within the trial. The authors postulate that such improvements may lead to cost savings compared with 5-FU. However, it should be noted that Cunningham and colleagues[94] reported overall survival results and adverse events on an ITT basis.

Health outcomes were measured in two ways; first, using OS at 6 and 12 months; and second, as the percentage of patients without leucopenia, mucositis, anaemia (all WHO grade 3 and 4) or any episodes of asthenia. The analysis included costs associated with drugs and preparation, administration at the outpatient day-case department, diagnostics, hospitalisations, treatment of chemotherapy-related side effects, outpatient visits, GP visits, and transport to and from hospital. All resource-use data were collected alongside the trial, with the exception of volumes relating to transport and laboratory tests. Unit costs of day-case days, hospitalisations, laboratory tests and outpatient visits were derived from studies performed by the Institute for Medical

Technology Assessment. Drug costs were derived from the Dutch pharmaceutical price list. Drug preparation costs were based on additional research among hospital pharmacists. Transport costs were estimated from the literature. Discounting was not undertaken in this study; however, given the short time horizon for the economic analysis, the exclusion of time preference is unlikely to bias the results.

The central estimates of cost-effectiveness are reported to be $15,086 per additional 6 months of life saved, $154,611 per additional 12 months of life saved, and $3936 per additional patient free of mucositis, leucopenia, anaemia and asthenia. Sensitivity analysis was undertaken using Fieller's method to generate 95% confidence intervals around the central estimates of cost-effectiveness. However, as the 95% confidence interval for cost-effectiveness crosses both the *x*- and *y*-axes, the cost-effectiveness ranges from dominated to dominating.

Groener[144] suggests that the unit costs of chemotherapy and its administration are the main cost drivers in the analysis. However, the author acknowledges that the setting of the trial may not reflect current practice patterns and that other 5-FU regimens should be included in economic evaluations.

Kerr and O'Connor (1999) ***An economic comparison of the net clinical benefit and treatment costs of raltitrexed and 5-fluorouracil + leucovorin (Mayo regimen) in advanced colorectal cancer***[129]

Kerr and O'Connor[129] report the methods and results of an economic evaluation to assess the clinical benefit and treatment costs of raltitrexed and 5-FU/FA under the Mayo regimen in ACRC. The authors used a cost-minimisation approach assuming equivalent effectiveness between the two chemotherapy regimens. The analysis was undertaken from the perspective of the UK NHS.

Evidence on effectiveness was derived from Cunningham and colleagues,[94] in which median survival was shown to be similar (median time to death reported as 10.1 months for raltitrexed and 10.2 months for 5-FU/FA). The cost and resource-use analysis included the acquisition costs of the chemotherapy regimens,[94] pharmacy preparation,[125] diagnostic tests,[94] costs of treating chemotherapy-related adverse events[132] and outpatient stays.[94] Resource utilisation relating to inpatient stays, GP visits and dose delays were taken from clinical trial data held on file.[94] Unit costs were derived from a range of sources, including the BNF[123] and the PSSRU.[124] Costs were uplifted to 1999 prices using the HCHS price index.[124] The authors did not mention the use of discounting, and no sensitivity analyses were undertaken.

Results of the study were reported in terms of the average cost of chemotherapy per month; disaggregated mean resource-use estimates were not reported. The authors reported that the monthly cost of treatment with raltitrexed is similar to that with the Mayo 5-FU/FA regimen (£781 versus £834). However, as the de Gramont 5-FU/FA regimen is more commonly used in the UK, the results of this study should be interpreted with caution.

Summary of existing economic evidence

The existing economic evaluations of irinotecan, oxaliplatin and raltitrexed in the management of ACRC included in this review are subject to a number of important weaknesses. The principal limitation of existing economic evidence relates directly to flaws in the design and reporting of the clinical trials from which evidence of effectiveness is drawn. *Table 64* presents the central estimates of cost-effectiveness, together with a summary of the limitations of each study. A summary of the most important limitations of the existing economic evaluations is presented below.

Limitations concerning OS and PFS

The most notable weakness concerns the potential confounding in OS due to patients crossing over to alternative chemotherapy agents following disease progression or treatment failure on their first-line allocated therapy. For economic studies in which evidence of effectiveness is drawn from clinical trials with unplanned cross-overs following disease progression, the only means by which to avoid confounding is through the use of PFS as the measure of benefit. However, as discussed in the section 'Review of alternative benefit measures' (p. 61), this benefit measure may at best be considered a surrogate outcome; hence, the interpretation and generalisability of the cost-effectiveness results are limited.

Use of median PFS

A further limitation of several existing economic evaluations concerns the use of median PFS. The true PFS benefit relates to the AUC.

Limitations concerning resource-use data collected within clinical trials

This review has highlighted limitations in the resource-use data available for use in existing

TABLE 64 *Summary of available cost-effectiveness estimates*

Author	Economic comparison(s)	Central estimate of cost-effectiveness	Key limitations of study
Cunningham *et al.*[140]	Ir + 5-FU/FA vs 5-FU/FA alone	£14,794 per LYG	Potential incompatibility between effectiveness and cost data. Median treatment duration used to estimate costs. Median survival difference used
Industrial submission from Aventis[52]	(a) Ir + 5-FU/FA vs 5-FU/FA; (b) Ox + 5-FU/FA vs 5-FU/FA; Results for first-line therapy versus sequences not reported here	(a) £43,712 per progression-free LYG (b) £24,961 per progression-free LYG	Relevance of comparison of first-line regimen versus sequence is difficult to justify. Preliminary FOCUS data combined oxaliplatin and irinotecan arms, hence assuming identical efficacy and side-effect profiles
Lloyd-Jones *et al.*[1]	(a) First-line Ox + 5-FU/FA vs 5-FU/FA alone (b) First-line Ir + 5-FU/FA vs 5-FU/FA alone (c) Second-line Ir vs 5-FU/FA alone	(a) £23,047 per progression-free LYG (b) £58,424 per progression-free LYG (c) Dominating	Limited information on treatment durations. Adverse event profiles assumed to be identical between regimens
Levy-Piedbois *et al.*[141]	Second-line Ir vs 5-FU/FA	$9344–10,137 per LYG	French hospital perspective is of limited relevance to UK NHS. Median survival difference used. Ambiguous time horizon used for costing analysis
Iveson *et al.*[32]	Second-line Ir vs 5-FU/FA	£7965–11,974 per LYG	Median survival estimate used
Poston *et al.*[139]	Ox + 5-FU/FA vs 5-FU/FA (patients with initially unresectable liver metastases)	£11,985 per LYG	6-month time horizon used for costing: likely to underestimate long-term costs. OS may be overestimated through assumption of equality to that of an age-matched normal population
Nicholls *et al.*[143]	(a) First-line Ox + 5-FU/FA vs 5-FU/FA (b) First-line Ir + 5-FU/FA vs 5-FU/FA	(a) £26,655 per progression-free LYG; £31,065 per additional responding patient (b) £30,171 per progression-free LYG; £46,343 per additional responding patient	Chemotherapy administration costs and costs of managing adverse events excluded and thus likely to bias in favour of combination therapies. Median survival difference used
Nicholls *et al.*[142]	First line Ox + 5-FU/FA vs 5-FU/FA	25,600 per progression-free LYG	Exclusion of administration costs may favour combination therapy
Industrial submission from Sanofi-Synthelabo[130]	(a) First-line Ox + 5-FU/FA vs 5-FU/FA (b) First-line Ox + 5-FU/FA followed on progression by 2nd-line irinotecan versus 1st-line 5-FU/FA followed on progression by second-line Ir	(a) £22,576 per LYG; £25,951 per QALY gained (b) £22,302 per QALY gained	Potentially confounded survival curves used to estimate mortality
Groener[144]	Ral vs 5-FU/FA	$154,611 per life-year saved	Perspective unclear. No survival benefit demonstrated within clinical trial
Kerr and O'Connor[129]	Ral vs 5-FU/FA	Cost difference of £51 per patient	No survival benefit demonstrated within clinical trial. Mayo regimen not commonly used in UK

economic evaluations. Put simply, evidence on resource use reported in trials cannot be directly related to PFS and OS benefits. Most existing economic evaluations have estimated chemotherapy acquisition and administration costs based on the median number of treatment cycles reported in the clinical trials. This may, however, not be representative of the mean number of cycles; therefore, resulting cost-effectiveness estimates may be biased. Further, the reporting of resources used in the treatment of chemotherapy-related adverse events (concomitant medications and hospitalisations) in clinical trials is scant, and where available, these outcomes are reported on an ITT basis. As a result, these data are subject to confounding as it is unclear how many adverse events relate to the allocated therapy and how many relate to therapies received following disease progression. Several evaluations have assumed that irinotecan, oxaliplatin and raltitrexed have identical adverse event profiles; this assumption is likely to result in biases that favour irinotecan- and oxaliplatin-containing regimens compared to 5-FU/FA alone.

Absence of direct utility data

As noted in the review of alternative benefit measures, only the FOCUS trial[114] has directly measured health-related quality of life using an instrument that may be used to estimate index utility scores, within a study design that incorporates sequences of therapy. While several studies, for example the submissions to NICE from Aventis[52] and Sanofi-Synthelabo,[130] have incorporated utility data from Petrou and Campbell,[113] more robust estimates could be obtained from the direct assessment of quality of life in clinical trials.

Selective inclusion of cost components

A comparison of the cost-effectiveness of irinotecan, oxaliplatin and raltitrexed is difficult given the inclusion of different cost aspects between the studies included in this review. From the perspective of the UK NHS, economic evaluations of chemotherapies for ACRC should include costs associated with drug acquisition, administration and the treatment of chemotherapy-related toxicities. However, although several studies have purported to have adopted an NHS perspective, for example the study reported by Nicholls and colleagues,[142] some of these cost components were not included in the analysis.

Lack of robust sensitivity analysis

Existing studies have used only simplistic one- or two-way sensitivity analysis. None of these undertook probabilistic sensitivity analysis to explore second order uncertainty surrounding mean estimates of cost-effectiveness.

Suggested improvements for economic evaluations

The most significant improvement to existing economic evaluations of these therapies would be the analysis of OS, whereby evidence of effectiveness would be drawn from clinical trials that have evaluated planned sequences of chemotherapies. The use of planned sequences of chemotherapy would also enable the analysis of PFS for first- and second-line therapies. Mean OS should be estimated as the area under the survival curve. Ideally, resource and cost estimates would include all relevant cost components, namely, drug acquisition including wastage, drug administration, concomitant medications and hospitalisations due to chemotherapy-related adverse events. Such evidence should be directly related to benefits and should be collected within a clinical trial setting. Mean rather than median resource estimates should be used, and cost estimates should be adjusted for censoring where appropriate. Utility estimates should be derived directly from the trial population, and measured using validated health-related quality of life instruments such as the EQ-5D or the Short Form (SF)-6D valuation technique, which allow for the calculation of preference-based single index utilities. The inclusion of resource use associated with the treatment of adverse events should be directly related to the phase of treatment (i.e. first-line therapy, second-line therapy or both). Appropriate methods for sensitivity analysis should be used to explore the impact of uncertainty in both costs and effects simultaneously.

Results of economic evaluation undertaken by the assessment group

Overview of results

This section details the results of the health economic evaluation undertaken by the assessment group. All results are presented in terms of the marginal cost per LYG compared with the chemotherapy sequence recommended in the 2002 NICE guidance[2] (5-FU/FA followed on progression by irinotecan). The results are divided into four sections, which detail the health economic results relating to the OS period. Economic results relating to PFS periods during first- and second-line therapies are presented in

TABLE 65 *Comparison of median survival, mean empirical survival data estimated from Kaplan–Meier curves using AUC, and mean survival estimated using Weibull regression analysis*

	FOCUS[60]					Tournigand *et al.*[51]	
	Plan A: MdG + Ir	**Plan B: MdG + IrMdG**	**Plan C: IrMdG**	**Plan D: MdG + OxMdG**	**Plan E: OxMdG**	**FOLFOX6 + FOLFIRI**	**FOLFIRI + FOLFOX6**
OS (months)							
Median	13.7	14.8	16.2	15.1	15.0	20.6	21.5
Estimated AUC (mean)	16.1	16.6	17.2	17.0	16.3	24.3	24.7
Weibull model	16.6	17.6	18.4	17.7	17.1	25.7	27.3
PFS during first-line therapy (months)							
Median	6.3	6.7	8.6	6.4	8.8	8.0	8.5
Empirical data	8.1	7.7	9.4	7.4	9.4	10.4	9.3
Weibull model	8.0	8.1	9.4	7.8	9.5	10.2	9.0
PFS during second-line therapies (months)							
Median	NA	NA	NA	NA	NA	2.5	4.2
Empirical data	NA	NA	NA	NA	NA	3.6	5.0
Weibull model	NA	NA	NA	NA	NA	3.6	4.7

NA, not applicable.

Appendix 12. The following subsections report the OS and PFS benefits as estimated using AUC analysis and the Weibull regression analysis; the central estimates of cost-effectiveness under the base-case cost assumptions; the results of a series of scenario analyses used to test the assumptions in the model; and the results of the probabilistic sensitivity analysis.

Estimated OS and PFS benefits

Table 65 shows a comparison of median and estimated mean OS and PFS, together with the results of the Weibull regression analysis.

The Weibull regression analysis results in higher estimates of OS and PFS benefits as these include additional benefits extrapolated beyond the duration of the trials. *Table 65* demonstrates a considerable difference in terms of OS between the chemotherapy sequences evaluated in the Tournigand trial[51] (AUC mean overall survival = 24.3–24.7 months) and the treatment sequences evaluated in the FOCUS trial[60] (AUC mean overall survival = 16.1–17.2 months). These considerable differences in survival benefit are, however, not clearly reflected in terms of PFS (AUC mean PFS = 9.3–10.4 months for Tournigand arms versus 7.4–9.4 months for FOCUS arms). A comparison of second-line PFS between the FOCUS trial arms and Tournigand trial arms was not possible.

It should also be noted that the median OS and PFS benefits reported are consistently lower than mean benefits estimated using the AUC. This highlights the importance of using the mean benefit rather than the median as a measure of OS.

Central estimates of cost-effectiveness and cost–utility

Cost-effectiveness results

This section reports central estimates of cost-effectiveness under the base-case assumptions. *Table 66* reports the deterministic cost-effectiveness results for the OS period. These cost-effectiveness estimates are based on life-years gained and do not include adjustments for health-related quality of life.

It is standard practice to present health economic results incrementally, whereby interventions are ranked in order of effectiveness, those interventions that are dominated are ruled out of the analysis, and ICERs are calculated for the remaining interventions. However, owing to the missing costs of salvage therapies within the FOCUS treatment plans, using the conventional incremental approach could produce misleading results; some interventions could appear to be dominated and excluded from the analysis when in fact they are not. For this reason, results are presented as marginal cost-effectiveness ratios compared to FOCUS treatment plan A.

Table 66 suggests that the least expensive chemotherapy sequence is the current NICE

TABLE 66 *Central estimates of cost-effectiveness results for OS period using estimated Weibull curves*

Treatment sequence	Mean survival (years)	Mean cost	Marginal cost vs FOCUS Plan A (MdG + Ir)	Marginal LYG vs FOCUS Plan A (MdG + Ir)	Marginal cost per LYG
FOCUS plan A (MdG + Ir)	1.38	£11,458.85	–	–	–
FOCUS plan B (MdG + IrMdG)	1.47	£12,542.50	£1,083.64	0.08	£13,173.59
FOCUS plan C (IrMdG)	1.54	£13,350.75	£1,891.90	0.15	£12,417.64
FOCUS plan D (MdG + OxMdG)	1.48	£13,680.37	£2,221.52	0.09	£23,785.71
FOCUS plan E (OxMdG)	1.42	£13,186.14	£1,727.28	0.04	£43,531.39
Tournigand FOLFIRI/FOLFOX6	2.28	£22,864.46	£11,405.61	0.89	£12,761.42
Tournigand FOLFOX6/FOLFIRI	2.15	£24,231.01	£12,772.15	0.76	£16,776.07

TABLE 67 *Cost–utility results for FOCUS treatment arms: OS period*

Treatment arm	Mean QALYs gained	Mean cost	Marginal QALYs vs FOCUS plan A (MdG + Ir)	Marginal cost vs FOCUS plan A (MdG + Ir)	Cost per QALY gained
FOCUS plan A (MdG + Ir)	1.04	£11,458.85	–	–	–
FOCUS plan B (MdG + IrMdG)	1.14	£12,542.50	0.10	£1,083.64	£10,337.99
FOCUS plan C (IrMdG)	1.17	£13,350.75	0.14	£1,891.90	£13,629.54
FOCUS plan D (MdG + OxMdG)	1.11	£13,680.37	0.07	£2,221.52	£31,555.65
FOCUS plan E (OxMdG)	1.06	£13,186.14	0.03	£1,727.28	£67,661.79
Tournigand FOLFIRI/FOLFOX	1.72	£22,864.46	0.68	£11,405.61	£16,663.03
Tournigand FOLFOX/FOLFIRI	1.62	£24,231.01	0.58	£12,772.15	£21,845.27

recommendation of 5-FU/FA followed on progression by irinotecan; the mean cost for this regimen is estimated to be £11,459 per patient. The most expensive regimen is estimated to be FOLFOX6 followed on progression by FOLFIRI; the mean cost for this regimen is estimated to be £24,231 per patient. However, the interpretation of these economic results is problematic owing to the exclusion of costs associated with subsequent salvage therapies (see *Table 58*). However, assuming that it is reasonable to compare the Tournigand trial[51] to the FOCUS trial,[114] both FOLFOX6/FOLRFIRI and FOLFIRI/FOLFOX appear to have a cost-effectiveness that is better than many interventions currently funded on the NHS. The base-case analysis suggests that FOLFOX6/FOLFIRI is associated with a marginal cost of £16,776 per LYG, while FOLFIRI/FOLFOX6 is associated with a marginal cost of £12,761 per LYG. It is clear that the marginal cost-effectiveness of the FOLFOX6/FOLFIRI and FOLFIRI/FOLFOX sequences is driven by the considerably better survival observed in the Tournigand trial.

Cost–utility results

The cost-effectiveness results presented above did not include adjustments for health-related quality of life. EQ-5D utility estimates were not available for the FOLFOX6/FOLFIRI or FOLFIRI/FOLFOX6 sequences evaluated in the Tournigand trial.[51] However, owing to the small differences in utility between the FOCUS sequences and the limited changes in utility over time, a constant utility score of 0.76 was assumed for FOLFOX6/FOLFIRI and FOLFIRI/FOLFOX (see the section 'Methods for estimating quality-adjusted survival benefits', p. 68). *Table 67* presents the results of the preliminary analysis of cost–utility for the seven chemotherapy sequences. As noted previously, at the time of writing the EQ-5D utility data used to estimate QALYs in each treatment arm had not been subject to comprehensive checking, validation or adjustments for censoring, so these cost–utility results should be interpreted with caution.

The impact of incorporating these data on quality of life is that OS benefits observed in each chemotherapy sequence are down-weighted by around 25%.

Scenario analysis results

This section reports a series of scenario analyses to explore alternative assumptions in the estimation of costs and effects in the economic model.

***TABLE 68** Central estimates of cost-effectiveness for OS period using empirical Kaplan–Meier survival curves*

Treatment arm	Mean survival (years)	Mean cost	Marginal cost vs FOCUS plan A (MdG + Ir)	Marginal LYG vs FOCUS plan A (MdG + Ir)	Marginal cost per LYG
FOCUS plan A (MdG + Ir)	1.34	£11,458.85	–	–	–
FOCUS plan B (MdG + IrMdG)	1.38	£12,542.50	£1,083.64	0.04	£24,875.85
FOCUS plan C (IrMdG)	1.43	£13,350.75	£1,891.90	0.09	£20,276.32
FOCUS plan D (MdG + OxMdG)	1.42	£13,680.37	£2,221.52	0.08	£27,593.97
FOCUS plan E (OxMdG)	1.36	£13,186.14	£1,727.28	0.02	£77,326.08
Tournigand FOLFIRI/FOLFOX6	2.06	£22,864.46	£11,405.61	0.72	£15,803.00
Tournigand FOLFOX6/FOLFIRI	2.03	£24,231.01	£12,772.15	0.69	£18,470.03

***TABLE 69** Alternative cyclical costs used in scenario analysis*

Parameter	Base-case cost (high estimate)	Source	Scenario analysis cost (low estimate)	Source
Days in hospital per month	1.00	Schmitt[128]	0.38	Analysis of PFS reported in de Gramont trial[77]
Cost per hospital day	£258	Iveson *et al.*[32]	£300	Unpublished data from de Gramont trial[77]
Monthly cost of diagnostic tests	£65.00	Kerr and O'Connor[129]	£3.16	Iveson *et al.*[32]
Monthly primary care cost	£10.42	Iveson *et al.*[32]	£1.14	Kerr and O'Connor[129]
Percentage of patients treated as outpatients	82%	Aventis submission[52]	100%	Assumption
Line insertion cost	£440.40	Boland *et al.*[126]	£250.00	Iveson *et al.*[32]

Cost-effectiveness estimates using empirical Kaplan–Meier survival curves

The central estimates of cost-effectiveness reported in the base-case analysis used survival benefits estimated from the Weibull regression analysis, and thus included extrapolated survival benefits beyond the durations of the FOCUS[114] and Tournigand[51] trials. *Table 68* reports an analysis of marginal cost-effectiveness for the seven treatment sequences whereby effects are estimated as the area under the empirical Kaplan–Meier OS curves; that is, effects relate to empirical OS benefits observed in the trials and are not extrapolated.

Table 68 shows that estimating the effectiveness of the treatment sequences using the empirical Kaplan–Meier overall survival curves has only a minor impact on cost-effectiveness. The greatest departure from the cost-effectiveness results estimated in the base-case analysis is observed in the FOCUS treatment plan E (OxMdG), where the marginal OS difference is lower using the empirical survival curves (empirical OS = 0.02 LYG versus Weibull OS = 0.04 LYG). Consequently, the cost per LYG for treatment plan E is nearly double that estimated using the Weibull regression analysis (£77,326 versus £43,531).

Impact on cost-effectiveness of optimistic cyclical cost estimates

The earlier assessment of irinotecan and oxaliplatin[1] reported estimates of cost-effectiveness based on high and low cost scenarios. Where multiple cost estimates were available, the base-case results presented in the section 'Cost-effectiveness results' (p. 90) use the higher cost estimates. *Table 69* shows the lower cyclical cost estimates used in the base-case analysis.

Table 70 shows the resulting cost-effectiveness estimates using these optimistic cost assumptions.

Assuming optimistic cost estimates results in a reduction in the mean treatment cost per patient of around £2300–4000 over their lifetime. Consequently, this results in a small reduction in the cost per LYG associated with each treatment sequence. Again, it should be noted that the costs associated with the FOCUS treatment sequences

TABLE 70 *Central estimates of cost-effectiveness using optimistic cost assumptions: OS period*

Treatment arm	Mean survival (years)	Mean cost	Marginal cost vs FOCUS plan A (MdG + Ir)	Marginal LYG vs FOCUS plan A (MdG + Ir)	Marginal cost per LYG
FOCUS plan A (MdG + Ir)	1.38	£8,686.32	–	–	–
FOCUS plan B (MdG + IrMdG)	1.47	£9,549.30	£862.98	0.08	£10,491.01
FOCUS plan C (IrMdG)	1.54	£10,971.53	£2,285.21	0.15	£14,999.15
FOCUS plan D (MdG + OxMdG)	1.48	£10,520.88	£1,834.55	0.09	£19,642.48
FOCUS plan E (OxMdG)	1.42	£10,896.91	£2,210.59	0.04	£55,711.72
Tournigand FOLFIRI/FOLFOX6	2.28	£18,970.01	£10,283.68	0.89	£11,506.13
Tournigand FOLFOX6/FOLFIRI	2.15	£20,272.26	£11,585.94	0.76	£15,217.99

TABLE 71 *Central estimates of cost-effectiveness using pessimistic cost assumptions: OS period*

Treatment arm	Mean survival (years)	Mean cost	Marginal cost vs FOCUS plan A (MdG + Ir)	Marginal LYG vs FOCUS plan A (MdG + Ir)	Marginal cost per LYG
FOCUS plan A (MdG + Ir)	1.38	£16,476.58	–	–	–
FOCUS plan B (MdG + IrMdG)	1.47	£18,779.14	£2,302.56	0.08	£27,991.60
FOCUS plan C (IrMdG)	1.54	£18,178.52	£1,701.93	0.15	£11,170.77
FOCUS plan D (MdG + OxMdG)	1.48	£20,306.91	£3,830.32	0.09	£41,011.12
FOCUS plan E (OxMdG)	1.42	£17,808.07	£1,331.49	0.04	£33,556.46
Tournigand FOLFIRI/FOLFOX6	2.28	£31,181.86	£14,705.28	0.89	£16,453.34
Tournigand FOLFOX6/FOLFIRI	2.15	£32,696.31	£16,219.73	0.76	£21,304.42

are underestimated here owing to the omission of the costs associated with salvage therapies.

Impact on cost-effectiveness of all chemotherapy given on inpatient basis

The base-case analysis assumed that 18% of patients receive chemotherapy on an inpatient basis. As there is a considerable difference between the cost of delivering chemotherapy on an inpatient and an outpatient basis, scenario analysis was undertaken to explore the impact on central estimates of cost-effectiveness of assuming that all patients receive chemotherapy as inpatients. This scenario represents the most pessimistic set of costing assumptions in the model. *Table 71* shows the impact of this scenario on the cost per LYG over the entire survival duration.

Table 71 shows that, assuming all patients undergo chemotherapy in an inpatient setting, the mean cost is increased by £4600–8500 across the seven treatment sequences. The impact of this cost increase for all FOCUS treatment sequences is masked by the missing data on the costs of salvage therapy received by patients. In particular, the mean number of cycles received in FOCUS arms C (IrMdG) and E (OxMdG) relates only to first-line therapy, yet up to 50% of patients received subsequent salvage therapy, thus the marginal cost per LYG for these treatment arms appears more economically attractive compared with FOCUS plan A (MdG + Ir). This further highlights the limitations of the FOCUS resource data[60] used in the model. Under this assumption, the marginal cost per LYG for FOLFIRI/FOLFOX6 and FOLFOX6/FOLFIRI is slightly higher.

Probabilistic sensitivity analysis results

This section reports the results of the probabilistic sensitivity analysis. Results are presented first as cost-effectiveness planes and then as CEACs. *Figure 14* presents the marginal costs and effects of each treatment sequence for the OS period compared with FOCUS plan A (MdG + Ir).

The cost-effectiveness plane presented in *Figure 14* shows that the marginal costs and effects in the FOCUS chemotherapy sequences are clustered around the origin; the FOCUS treatment plans B–E are more likely to cost more than FOCUS plan A (MdG + Ir), yet there is also a possibility that these sequences will be less effective than FOCUS plan A (FOCUS plan B = 13%, plan C = 3%, plan D = 11%, plan E = 29%). The large dispersion of sample estimates of effectiveness for FOLFOX6/FOLFIRI and FOLFIRI/FOLFOX6 is a result of the large assumed standard error applied to the hazard ratio between these arms and

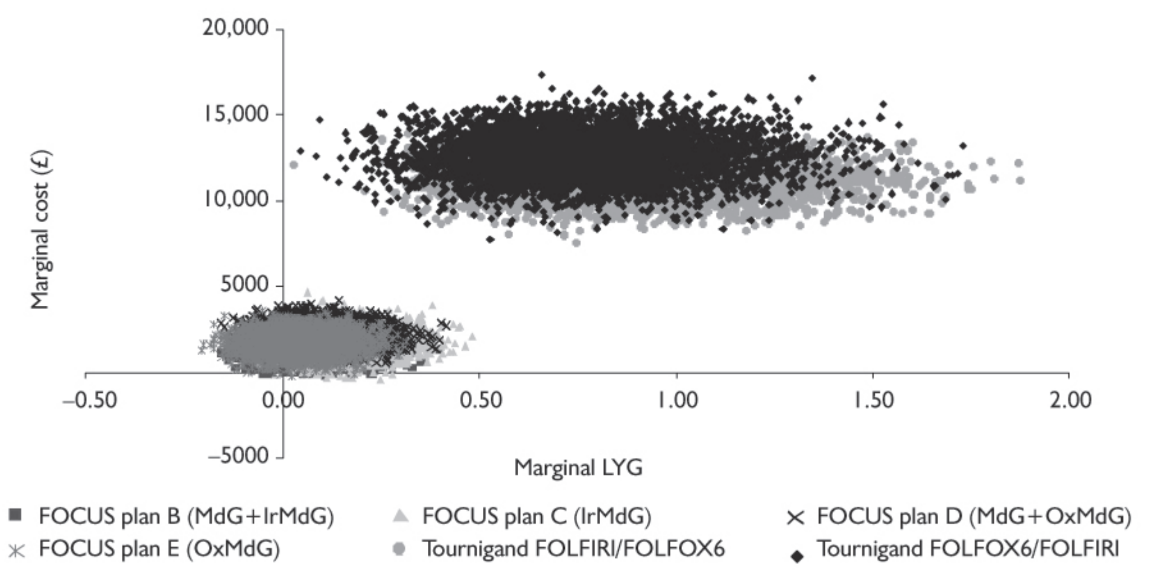


FIGURE 14 *Cost-effectiveness plane: OS period*

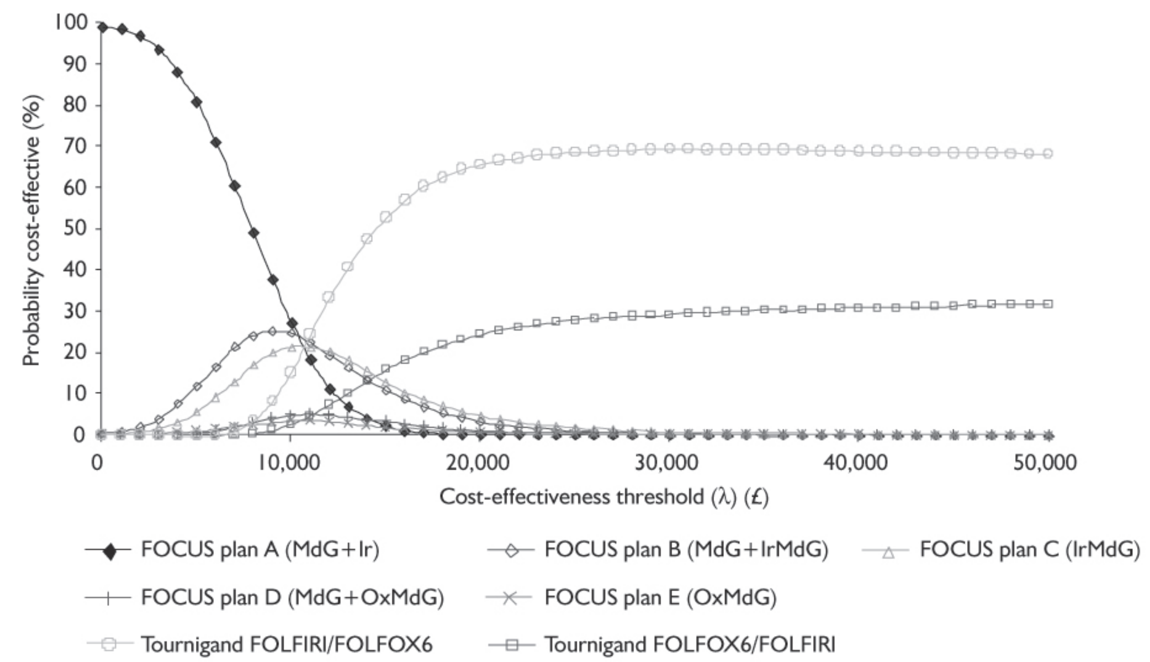


FIGURE 15 *Incremental CEACs: OS period*

FOCUS plan A. It is noteworthy that despite the assumed additional uncertainty, both FOLFOX6/FOLFIRI and FOLFIRI/FOLFOX6 are always expected to result in an improvement in OS compared with FOCUS plan A.

Figure 15 shows incremental CEACs for the seven treatment sequences evaluated in the economic model. The net benefits of the chemotherapy sequences are compared incrementally; therefore, the CEACs show the probability that each

TABLE 72 *Estimated annual cost to the NHS*

Trial sequence	First-line chemotherapy	Second-line chemotherapy	Estimated mean cost over patient lifetime (excluding VAT)	Estimated annual cost to NHS (number of patients = 12,665)
FOCUS plan A	MdG	Ir	£10,411	£152,964,554
FOCUS plan B	MdG	IrMdG	£11,021	£166,628,324
FOCUS plan C	IrMdG	–	£11,893	£182,098,621
FOCUS plan D	MdG	OxMdG	£12,063	£182,431,690
FOCUS plan E	OxMdG	–	£11,799	£180,307,118
Tournigand arm A	FOLFIRI	FOLFOX6	£20,426	£313,121,064
Tournigand arm B	FOLFOX6	FOLFIRI	£21,751	£333,009,684

sequence will result in the greatest net benefit at a given cost-effectiveness threshold (λ). For the analysis of OS, net benefit is calculated as:

$$\text{Net benefit} = (\lambda \times \text{LYG}) - \text{Cost of chemotherapy sequence}$$

Figure 15 suggests that for cost-effectiveness thresholds less than £10,000, FOCUS plan A (MdG + Ir) is expected to be optimal (i.e. result in a greater net benefit than the other six sequences). However, as λ increases, the impact of survival on the net benefit function increases; for cost-effectiveness thresholds greater than £10,000, FOLFIRI followed on progression by FOLFOX6 is most likely to result in the greatest net benefit. Assuming a cost-effectiveness threshold of £20,000–30,000 per LYG, the probability that FOLFIRI/FOLFOX6 is the optimal sequence is around 70%.

Estimated cost to the NHS

Figure 1 presented a detailed algorithm to estimate chemotherapy treatment use in England and Wales. An estimated 12,665 people with 'uncured' ACRC will be given first-line treatment with chemotherapy each year, 7092 (56%) of whom will subsequently undergo second-line treatment with chemotherapy, as observed in the FOCUS trial. The annual direct cost to the NHS of providing the alternative treatment sequences was estimated using the expected number of patients who undergo first-line chemotherapy each year, together with the mean treatment cost calculated by the health economic model under the base-case assumptions. In accordance with recent NICE methodology guidance,[115] all annual cost estimates include VAT.

Table 72 presents estimates of the annual direct costs to the NHS for the seven treatment sequences included in the model. It should be noted that the cost estimates for FOCUS treatment arms A–E are underestimates owing to the absence of costs relating to subsequent salvage therapies received in the trial.

Table 72 suggests that the current NICE recommendation (5-FU/FA followed on progression by irinotecan) is the least expensive sequence of chemotherapies; this is estimated to cost around £153 million per year. The most expensive regimens are expected to be the two sequences of combination therapies (FOLFOX6 followed on progression by FOLFIRI and the reverse sequence); the annual cost to the NHS is estimated to be £313–333million for these sequences. It should be noted again that the mean patient lifetime costs for the FOCUS chemotherapy sequences are underestimates owing to the absence of cost data relating to salvage therapies. This problem is not applicable to the FOLFOX6/FOLFIRI and FOLFIRI/FOLFOX6 sequences; therefore, the annual cost differences between the FOCUS sequences and the Tournigand sequences are unlikely to be as large as suggested by *Table 72*.

Conclusions on the health economics of irinotecan, oxaliplatin and raltitrexed in the treatment of ACRC

Conclusions on the review of cost-effectiveness

Central estimates of cost-effectiveness reported in existing economic analyses suggest that first-line irinotecan plus 5-FU/FA versus 5-FU/FA alone is associated with a marginal cost of £14,794 per LYG. The marginal cost per progression-free LYG for irinotecan plus 5-FU/FA versus 5-FU/FA alone is reported to be in the range £30,171–58,424. The marginal cost-effectiveness of second-line irinotecan versus 5-FU/FA is reported to range from dominating to £11,974 per LYG. Central estimates of cost-effectiveness reported in existing economic analyses suggest that first-line oxaliplatin plus 5-FU/FA versus 5-FU/FA alone is associated with a marginal cost of £22,576 per LYG and £25,951 per QALY gained. The marginal cost per progression-free LYG for oxaliplatin plus 5-FU/FA versus 5-FU/FA alone is reported to be in the range £23,047–26,655. Owing to important differences in the scope of existing economic analyses, together with weaknesses in the methodologies used, these cost-effectiveness results should be interpreted with caution.

Conclusions on the health economic evaluation undertaken by the assessment group

The analysis of the FOCUS treatment sequences suggests that FOCUS plan C (IrMdG) results in the greatest benefit in terms of life-years gained; the least effective treatment plan was the sequence recommended in the NICE guidance in 2002.[2] However, differences in terms of overall survival between the FOCUS treatment sequences were small.[60] The economic analysis suggests that first-line 5-FU/FA followed on progression by second-line irinotecan plus 5-FU/FA (FOCUS plan B), first-line irinotecan plus 5-FU/FA (FOCUS plan C) and first-line 5-FU/FA followed on progression by second-line 5-FU/FA plus oxaliplatin (FOCUS plan D) have a cost-effectiveness profile that is favourable in comparison to many other interventions currently available on the NHS. However, between 26 and 50% of patients in each FOCUS treatment plan underwent further salvage chemotherapy (e.g. irinotecan plus capecitabine); resource-use relating to these stages of chemotherapy were not collected within the trial. Consequently, the treatment costs associated with each of these five chemotherapy sequences are underestimated in the economic model. The impact of this bias on cost-effectiveness estimates is unknown. It is possible that this additional resource use associated with salvage therapy is unbalanced across the five sequences; thus, the interpretation of cost-effectiveness results within the FOCUS trial is even more problematic.

The economic model included a comparison of costs and effects associated with the two treatment sequences evaluated in the Tournigand trial[51] against the chemotherapy sequence recommended by NICE in 2002[2] (first-line 5-FU followed on progression by single-agent irinotecan) as evaluated in the FOCUS trial.[114] First-line 5-FU/FA plus oxaliplatin followed on progression by second-line 5-FU/FA plus irinotecan was estimated to cost £16,776 per LYG compared with FOCUS plan A. The reverse sequence of first-line 5-FU/FA plus irinotecan followed on progression by second-line 5-FU/FA plus oxaliplatin was estimated to cost an additional £12,761 per LYG compared with FOCUS plan A. While the FOCUS treatment costs are clear underestimates, the two Tournigand sequences are not. Despite this problem, both Tournigand treatment sequences remain economically attractive in comparison to the FOCUS baseline. Owing to the large differences in observed OS between the Tournigand sequences and the FOCUS treatment plans, the uncertainty analysis suggests that first-line 5-FU/FA plus irinotecan followed on progression by second-line 5-FU/FA plus oxaliplatin is likely to result in the greatest net benefit over feasible willingness-to-pay thresholds. The economic attractiveness of these sequences of chemotherapies is not reflected in the economic analyses based on PFS as the measure of clinical benefit (see Appendix 12); this raises important questions concerning the reliability of previous economic analyses that have presented economic results based on progression-free life-years gained.

The central issue surrounding the results of this economic evaluation concerns whether a direct comparison between the Tournigand trial[51] and the FOCUS trial[114] is appropriate and valid. Although the inclusion criteria for the two trials appear to be similar, it is unclear whether the notable differences in OS between the trials is entirely a result of the chemotherapy sequences received, or whether this is a result of different treatment protocols for the two trials, differences in the patient populations enrolled in the trials or differences in the delivery of healthcare between the trials. Further evidence, preferably from an RCT, is required to investigate whether similar OS gains observed in the Tournigand trial[51] are replicated within a UK setting.

A further issue of relevance to the interpretation of both the cost and cost-effectiveness results presented in this chapter is that the patent for oxaliplatin is due to expire in 2006/07. 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 compared with the chemotherapy sequence recommended by the 2002 NICE guidance.[2] 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.

Chapter 5

Implications for other parties

Financial impact for patient and others

Sculpher and co-workers[149] report an analysis of the travel costs for patients and their carers for patients treated with raltitrexed and 5-FU. The analysis showed that many patients were accompanied by their carers when undergoing chemotherapy, and that between 79% (raltitrexed group) and 85% (5-FU group) of carers took time off from work or household duties to do this. Clearly, the number and duration of hospital visits will affect the burden on carers.

Quality of life for family and carers

Family members and other carers play an important role in the care of cancer patients, but may experience high levels of anxiety and depression that can adversely affect aspects of their physical and mental health as well as their social and family lives.[150,151] The impact of the therapy on family and carers will depend on their beliefs regarding its effectiveness, their perception of its favourable and adverse effects, and the logistics of the delivery of care.

Chapter 6

Factors relevant to NHS

Equity issues

There was significant overall improvement in survival for bowel cancer during the 1990s, but the deprivation gap also widened significantly. Survival for rectal cancer in the latest period analysed (1996–1999) was 9.4% higher for the richest patients than for the poorest patients in men and 8.3% higher in women. Between 1986 and 1999, this gap widened by an average of 2.5% every 5 years. The deprivation gap in survival was also large for colon cancer: 5.7% in men and 7.3% in women in the period 1996–1999. The gap widened by an average of 1.9% in men and 2.2% in women every 5 years during the three successive 5-year periods studied.[152]

Chapter 7
Discussion

Assumptions, limitations and uncertainties

There is considerable uncertainty surrounding the cost-effectiveness of these therapies. Owing to the design of the majority of the clinical trials, most economic analyses of these therapies have used PFS as the measure of clinical benefit, and have thus been restricted to the analysis of first- or second-line therapies. Ideally, economic analyses should include the evaluation of alternative sequences of chemotherapies using OS and quality-adjusted survival as the benefit measure.

Benefits

Existing economic analyses are subject to several methodological limitations. The most important limitation is due to the potential confounding in OS owing to patients crossing over to alternative chemotherapeutic agents following disease progression or treatment failure on their first-line allocated therapy. The use of PFS as a measure of clinical benefit limits the interpretation and generalisability of economic analyses.

For the purposes of economic evaluation, the mean incremental benefit is required; many existing economic studies have used median PFS or median OS. As the median may lie on either side of the mean, such analyses may be biased.

Only the FOCUS trial[114] has directly measured health-related quality of life using an instrument that may be used to estimate utility scores, within a study design that incorporates planned sequences of therapy. While several studies, for example the submissions to NICE from Aventis[52] and Sanofi-Synthelabo,[130] have incorporated utility data from Petrou and Campbell,[113] more robust estimates could be obtained from a direct assessment of quality of life.

Costs

There is limited information concerning resource use within trials. Most existing economic evaluations have estimated chemotherapy acquisition and administration costs based on the median number of treatment cycles reported in the clinical trials. This may, however, not be representative of the mean number of cycles, and thus actual treatment time is unknown. In addition, evidence concerning resources required to treat chemotherapy-related adverse events in clinical trials is limited, and in most trials it is unclear whether adverse events are a result of the allocated therapy or subsequent therapies received following disease progression or treatment failure.

An early cost-effectiveness analysis of the FOCUS trial[114] and the planned cross-over trial reported by Tournigand and colleagues[51] is anticipated subsequent to the submission of this report.

Further research

Routine NHS data collection to assess chemotherapies for downstaging

Published data on the effectiveness of combination chemotherapy regimens in the downstaging of patients with previously unresectable distant metastases vary considerably. Many of the data are also derived from outside the NHS setting and may be subject to selection bias. The collection of routine data from within the NHS would be desirable to validate the results presented in the section 'Downstaging of patients with liver metastases' (p. 55).

IPD meta-analysis to validate Grothey

Published clinical trials are mostly confounded by cross-over, making it difficult to assess the precise impact of the addition of irinotecan and oxaliplatin to 5-FU on survival outcomes. The paper by Grothey and colleagues[100] discussed in the section 'Sequencing of treatment' (p. 51) suggests that survival is increased by each addition of active chemotherapies: that is to say, 'three are better than two are better than one'. However, the analysis undertaken by Grothey and colleagues was crude and based on published data. A meta-analysis using IPD, including those from more recent trials, may give a better estimate of the survival effect, the optimal treatment sequence and a baseline against which future treatment sequences could be compared.

Requirements for future trial design

The central problem in evaluating the cost-effectiveness of chemotherapies for ACRC is not the confounding in the survival data, but rather the limited collection of data concerning the actual drugs received in each trial arm. As a result, it is unclear which patients received which drugs and for how long they received them; this presents substantial difficulties in estimating the mean cost of treatment. A further research recommendation, therefore, would be for future cancer trial protocols to incorporate more detailed resource data collection strategies and to report summary statistics that are of use in economic evaluations.

All of the trials included in this review used median OS or PFS as the primary measure of clinical benefit. As noted earlier, the median is an estimate of benefit at a single time-point and does not relate to the OS or PFS benefit observed across the entire patient group. The mean should be considered a more appropriate measure of overall clinical benefit; this may be estimated by calculating the area under the survival curve using the trapezium rule, or extrapolating the survival curve using parametric survival methods and solving the integral of this curve. This should be recommended as standard practice in the reporting of survival data from clinical trials.

Chapter 8
Conclusions

Clinical effectiveness

The addition of irinotecan to first-line 5-FU significantly improves median OS by between 2 and 4 months ($p = 0.0007$), median PFS by between 2 and 3 months ($p < 0.00001$) and response rates ($p < 0.001$). The two regimens have different toxicity profiles and there is no evidence that either confers a significant difference in quality of life.

In comparison with second-line 5-FU, irinotecan significantly improves median overall survival by over 2 months ($p = 0.035$) and median PFS by over 1 month ($p = 0.03$). It appears to provide a response in more people, but with more toxicities, and there is no evidence either drug provides a significant quality of life advantage.

In comparison with second-line BSC, irinotecan improves median OS by over 2.5 months ($p = 0.0001$). It causes more serious gastrointestinal and haematological toxicities than BSC, but less asthenia ($p = 0.006$) and pain ($p = 0.008$). Irinotecan maintains baseline quality of life longer than BSC alone.

The addition of oxaliplatin to first-line 5-FU is associated with no significant difference in OS (but see caveat below), significantly improved PFS ($p < 0.00001$), significantly higher response rates ($p < 0.0001$), more serious gastrointestinal and haematological toxicities, and no significant overall improvement of quality of life. Schedules that offer treatment breaks do not appear to reduce clinical effectiveness, but may reduce toxicity. (Caveat: confounding by cross-over from 5-FU monotherapy to oxaliplatin combination in all trials may mask a real survival advantage for the latter.)

The addition of oxaliplatin to second-line 5-FU is associated with a borderline significant improvement in overall survival ($p < 0.07$); a significantly higher response rate (<0.0001); and more serious toxicities. There is no evidence for a significant difference in QoL.

There is no significant difference in OS or PFS between first-line irinotecan with 5-FU and oxaliplatin with 5-FU, except when 5-FU is delivered by bolus injection, when oxaliplatin provides better OS ($p = 0.032$) and response rates ($p = 0.032$), but not PFS ($p = 0.169$). The regimens have different toxicity profiles and there is no evidence that either confers a significant difference in quality of life.

When compared to 5-FU, raltitrexed is associated with no significant difference in overall or progression-free survival; no significant difference in response rates; more vomiting and nausea, but less diarrhoea and mucositis; no significant difference in, or worse QoL. Raltitrexed treatment was cut short in two out of four included trials due to excess toxic deaths.

The current NICE recommendation, 5-FU monotherapy followed by irinotecan monotherapy, appears to be inferior to any other planned sequence in preliminary data from the FOCUS study. Combination irinotecan and 5-FU as first-line therapy significantly improved OS and time to first progression. However, although this plan did not have an official second-line therapy, some patients received salvage oxaliplatin and capecitabine (oral 5-FU), which would have affected the treatment effect size for OS to an unknown extent. Staged combination therapy using all active chemotherapy agents (oxaliplatin and 5-FU followed by irinotecan and 5-FU or vice versa) appears to provide the best OS and PFS, although there has been no head-to-head comparison against other treatment plans. In the only trial (GERCOR) to use all three active chemotherapies (5-FU, irinotecan and oxaliplatin), OS was over 20 months in any staged combination. In the FOCUS trial (the other study that planned sequences of treatment), the longest recorded median OS from a treatment plan using only two active agents was 16.2 months.

Where chemotherapy is used to downstage patients with previously unresectable liver metastases, randomised and non-randomised studies using either irinotecan with 5-FU or oxaliplatin with 5-FU consistently show tumour response rates of around 50%. Resection rates for irinotecan combination therapy range from 9 to 35%; resection rates for oxaliplatin/5-FU combination therapy range from 7 to 51%. In the only study to compare the regimens, significantly more individuals treated with oxaliplatin combination therapy were resected (p = 0.02). Five -year OS rates of 5–26% and 5-year disease-free survival rates of 3–11% were reported in studies using oxaliplatin/5-FU combination therapy (there are no such statistics for irinotecan).

5-FU is significantly more effective and less toxic when delivered by continuous infusion than by bolus injection, whether or not it is used in combination with other technologies.

Over half of first-line trial participants across all studies, except two, were treated with unplanned second-line therapies; it is unknown to what extent estimates of OS are confounded as a result.

Although the best data are based on an atypically young and fit population, other available evidence suggests that there is no significant difference between the efficacy and toxicity of first-line irinotecan combination therapy in younger and in older people.

Review of cost-effectiveness

Central estimates of cost-effectiveness reported in existing economic analyses suggest that first-line irinotecan plus 5-FU/FA versus 5-FU/FA alone is associated with a marginal cost of £14,794 per LYG. The marginal cost per progression-free LYG for irinotecan plus 5-FU/FA versus 5-FU/FA alone is reported to be in the range £30,171–58,424.

Existing economic studies suggest that the marginal cost-effectiveness of second-line irinotecan versus 5-FU is in the range dominating to £11,974 per LYG.

Central estimates of cost-effectiveness reported in existing economic analyses suggest that first-line oxaliplatin plus 5-FU/FA versus 5-FU/FA alone is associated with a marginal cost of £22,576 per LYG and £25,951 per QALY gained. The marginal cost per progression-free LYG for oxaliplatin plus 5-FU/FA versus 5-FU/FA alone is reported to be in the range £23,047–26,655.

Owing to important differences in the scope of existing economic analyses, together with weaknesses in the methodologies used, the cost-effectiveness results should be interpreted with caution.

Economic evaluation undertaken by the assessment group

The economic evaluation estimates the cost-effectiveness of six sequences of chemotherapy compared with first-line 5-FU/FA followed on progression by second-line irinotecan monotherapy. Using evidence from the FOCUS trial, the evaluation suggests that 5-FU/FA followed on progression by irinotecan in combination with 5-FU/FA costs £13,174 per LYG and £10,338 per QALY gained compared with 5-FU/FA followed on progression by irinotecan. 5-FU/FA in combination with irinotecan followed on progression by additional second-line therapies is estimated to cost £12,418 per LYG and £13,630 per QALY gained compared with 5-FU/FA followed on progression by irinotecan. 5-FU/FA followed on progression by 5-FU/FA plus oxaliplatin is estimated to cost £23,786 per LYG and £31,556 per QALY gained compared with 5-FU/FA followed on progression by irinotecan. 5-FU/FA in combination with oxaliplatin followed on progression by additional second-line therapies is estimated to cost £43,531 per LYG and £67,662 per QALY gained compared with 5-FU/FA followed on progression by irinotecan. The evaluation of the FOCUS treatment arms should be interpreted with caution owing to missing information on the costs of salvage therapies.

Incorporating evidence on OS observed in the Tournigand trial suggests that 5-FU/FA in combination with irinotecan followed on progression by 5-FU/FA in combination with oxaliplatin costs £12,761 per LYG and £16,663 per QALY gained compared with 5-FU/FA followed on progression by irinotecan. The reverse sequence of 5-FU/FA in combination with oxaliplatin followed on progression by 5-FU/FA in combination with irinotecan costs £16,776 per LYG and £21,845 per QALY gained. The evaluation suggests that these two sequences have a cost-effectiveness profile that is favourable in comparison to other therapies currently funded by the NHS. However, the differences in OS observed in the Tournigand and FOCUS trials may be a result of potential differences between the two clinical trials in terms of heterogeneity of the underlying patient populations, unbalanced protocol-driven intensity biases or other differences between underlying health service delivery systems.

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Danny Hind (Research Fellow) coordinated the review. Angie Ryan (Information Officer) developed the search strategy and undertook searches; Danny Hind, Indra Tumur and Paul Tappenden (Research Fellows) and Simon Eggington (Operational Research Analyst) screened the search results. Danny Hind, Indra Tumur, Paul Tappenden, Simon Eggington and Paul Sutcliffe (Research Associate) screened retrieved papers against inclusion criteria, appraised the quality of papers and abstracted data from papers. Danny Hind and Paul Tappenden wrote to authors of papers for additional information. Danny Hind, Indra Tumur, Paul Tappenden, Simon Eggington and Paul Sutcliffe analysed the data. Danny Hind wrote the background section. Danny Hind, Indra Tumur and Paul Sutcliffe wrote the section on clinical effectiveness. Paul Tappenden and Simon Eggington wrote the section on cost-effectiveness. Paul Tappenden undertook the economic evaluation.

References

1. Lloyd-Jones M, Hummel S, Bansback N, Orr B, Seymour M. A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. *Health Technol Assess* 2001;**5**(25).
2. National Institute for Clinical Excellence. *Guidance on the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.* Technology Appraisal Guidance No. 33. London: NICE; 2002
3. Cancer Research UK. *Statistics: colorectal cancer*. London: Cancer Research UK. 2004.
4. Rowan S, Gautrey M, Quinn MJ. *Cancer registrations in England, 2001*. London: Office for National Statistics; 2004.
5. Welsh Cancer Intelligence and Surveillance Unit. *Cancer incidence in Wales 1992–2001*. 2004.
6. Quinn M, Babb M, Broch A, Kirby L, Jones J. *Cancer trends in England and Wales 1950–1999.* Studies in Medical and Population Subjects No. 66. London: The Stationery Office; 2001.
7. Willett W. The search for the causes of breast and colon cancer. *Nature* 1989;**338**:389–94.
8. Reddy B, Engle A, Katsifis S, Simi B, Bartram HP, Perrino P, *et al.* Biochemical epidemiology of colon cancer: effect of types of dietary fiber on fecal mutagens, acid, and neutral sterols in healthy subjects. *Cancer Res* 1989;**49**:4629–35.
9. Potter JD. Reconciling the epidemiology, physiology, and molecular biology of colon cancer. *JAMA* 1992;**268**:1573–7.
10. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 1981; **66**:1191–308.
11. Hill MJ, Morson BC, Bussey HJ. Aetiology of adenoma–carcinoma sequence in large bowel. *Lancet* 1978;**i**:245–7.
12. American Joint Committee on Cancer. *Collaborative staging manual and coding instructions.* 2004.
13. South West Cancer Intelligence Service. *Data held on file: audit study of patients with colorectal cancer undertaken in the Wessex Region 1991–1995.* 1995.
14. Boyle P, Langman JS. ABC of colorectal cancer: epidemiology. *BMJ* 2004;**321**:805–8.
15. Centre for Reviews and Dissemination. The management of colorectal cancers. *Effective Health Care* 1997;**8**(3). York: CRD.
16. NHS Executive. *Improving outcomes in colorectal cancer: the research evidence.* London: NHS Executive; 2000.
17. Seymour MT, Stenning SP, Cassidy J, and the Colorectal Cancer Working Party of the UK Medical Research Council. Attitudes and practice in the management of metastatic colorectal cancer in Britain. *Clin Oncol (R Coll Radiol)* 1997;**9**:248–51.
18. Young A, Rea D. ABC of colorectal cancer: treatment of advanced disease. *BMJ* 2000; **321**:1278–80.
19. Ward S, Kaltenthaler E, Cowan J, Brewer N. Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation. *Health Technol Assess* 2003;**7**(32).
20. National Institute for Clinical Excellence. Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer. Technology Appraisal Guidance No. 61. London: NICE;2003.
21. Advanced Colorectal Cancer Meta-Analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992; **10**:896–903.
22. Poon MA, O'Connel MJ, Wieand HS, Krook JC, Gerstner JB, Tschetter LK, *et al.* Biochemical modulation of fluorouracil with leucovorin: confirmatory evidence of improved therapeutic efficacy in advanced colorectal cancer. *J Clin Oncol* 1991;**9**:1967–72.
23. Machover D, Goldschmidt E, Chollet P, Metzger G, Zittan J, Marquet J. *et al.* Treatment of advanced colorectal and gastric adenocarcinoma with 5-fluorouracil and high-dose folinic acid. *J Clin Oncol* 1986;**4**:685–96.
24. Madajewicz S, Petrelli N, Rustum YM. Phase I–II trial of high-dose calcium leucovorin and 5-fluorouracil in advanced colorectal cancer. *Cancer Res* 1984;**44**:4667–9.
25. Lokich JJ, Ahlgren JD, Gullo JJ, *et al.* Prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma. A Mid Atlantic

Oncology Programme Study. *J Clin Oncol* 1989; **7**:425–32.

26. de Gramont A, Bosset JF, Milan C, Rougier P, Bouche O, Etiene PL, *et al.* Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer. A French Intergroup Study. *J Clin Oncol* 1997;**15**:808–15.
27. Leonard P, Seymour MT, James R, Hochhauser D, Ledermann JA. Phase II study of irinotecan with bolus and high dose infusional 5-FU and folinic acid (modified de Gramont) for first- or second-line treatment of advanced or metastatic colorectal cancer. *Br J Cancer* 2002;**87**:1216–220.
28. Aranda E, Diaz-Rubio E, Cervantes A, Antón-Torres A, Carrato A, Massuti T, *et al.* Randomized trial comparing monthly low-dose leucovorin and fluorouracil for advanced colorectal cancer: a Spanish Cooperative Group for Gastro-Intestinal Tumor Therapy (TTD) Study. *Ann Oncol* 1998;**9**:727–31.
29. Köhne CH, Schöffski P, Wilke H, Käufer C, Andreesen R, Ohl U. Effective biomodulation by leucovorin of high-dose infusion fluorouracil given as a weekly 24-hour infusion: results of a randomized trial in patients with advanced colorectal cancer. *J Clin Oncol* 1998;**16**:418–26.
30. Levi F. Chronopharmacology of anticancer agents. In Redfern P, Lemmer B, editors. *Physiology and pharmacology of biological rhythms*. Berlin: Springer; 1997. pp 299–331.
31. National Institute for Clinical Excellence. *Guidance on cancer services: improving outcomes in colorectal cancers* (manual update). London: NICE; 2004.
32. Iveson TJ, Hickish T, Schmitt C, Van Cutsem E. Irinotecan in second-line treatment of metastatic colorectal cancer: improved survival and cost-effect compared with infusional 5-FU. *Eur J Cancer* 1999; **35**:1796–804.
33. Jonker DJ, Maroun JA, Kocha W Survival benefit of chemotherapy in metastatic colorectal cancer: a meta-analysis of randomized controlled trials. *Br J Cancer* 2000;**82**:1789–94.
34. Irinotecan: summary of product characteristics. *Electronic Medicines Compendium* 2005. http://www.medicines.org.uk
35. Joint Formulary Committee. *British National Formulary* **47**. London: British Medical Association; 2004.
36. *Electronic Medicines Compendium (eMC)*. 2004. http://www.medicines.org.uk
37. Oxaliplatin: summary of product characteristics. *Electronic Medicines Compendium* 2005.
38. Atkin WS. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. *Lancet* 2002; **359**:1291–300.
39. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) Investigators. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. *Lancet* 1995;**345**:939–44.
40. Cassidy J. Capecitabine (X) vs bolus 5-FU/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT study): efficacy results of a phase III trial. *ASCO Annual Meeting*, 2004. *J Clinical Oncology* **22**(145): July 15, Suppl. 3509.
41. Adam R, Avisar E, Ariche A, Giachetti S, Azoulay D, Castaing D, *et al.* Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. *Ann Surg Oncol* 2001;**8**:347–53.
42. Seymour MT. Optimizing the use and sequencing of fluorouracil, irinotecan and oxaliplatin in advanced colorectal cancer (ACRC): the UK MRC FOCUS (CR08) Trial. European Society of Medical Oncology; 2004. *Ann Oncol* 2004;**15**(Suppl.): Abstract SIN.
43. Moher D, Cook DJ, Eastwood S, *et al.* Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Lancet* 1999;**354**:1896–900.
44. Schulz KF, Chalmers I, Hayes RJ, Altman D. Empirical evidence of bias. *JAMA* 1995;**273**:408–12.
45. Parmar MK, Torri V, Stewart L Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;**17**:2815–34.
46. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–60.
47. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, *et al.* Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial [published erratum appears in *Lancet* 2000:**355**:1372]. *Lancet* 2000;**355**:1041–7.
48. Köhne CH, Van Cutsem E, Wils JA, Bokemeyer C, El-Serefi M, Lutz M *et al.* Irinotecan improves the activity of the AIO regimen in metastatic colorectal cancer: results of EORTC GI Group study 40986 [abstract]. *Proc Am Soc Clin Oncol* 2003;**22**:254.
49. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000;**343**:905–14.
50. Comella P, Massidda B, Farris A. Oxaliplatin vs irinotecan plus leucovorin/fluorouracil i.v. bolus as first-line treatment of advanced colorectal carcinoma. ESMO Annual Meeting, 2002.

http://www.asco.org/portal/site/asco/menuitem.34d60f5624ba07fd506fe310ee37a10d/?vgnextiod=76f8201eb61a7010VgnVCM100000ed730ad1rcrd&vmview=abst_detail_view&confid=16&absrractid=645

51. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, *et al.* FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;**22**:229–37.

52. Aventis Pharma. Submission to the National Institute of Clinical Excellence (NICE) on Campto® (irinotecan) for colorectal cancer (advanced) – irinotecan, oxaliplatin and raltitrexed [review]. Industry submission to NICE; 2004.

53. Bajetta E, Di Bartolomeo M, Mariani L, Cassata A, Artale S, Frustaci S, *et al.*, Italian Trials in Medical Oncology. Randomized multicenter Phase II trial of two different schedules of irinotecan combined with capecitabine as first-line treatment in metastatic colorectal carcinoma. *Cancer* 2004; **100**:279–87.

54. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer [see comment]. *N Engl J Med* 2004;**350**:2335–42.

55. Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, *et al.* A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004; **22**:23–30.

56. Köhne CH, Van Cutsem E, Wils J, Bokemeyer C, El-Serafi, Lutz M, *et al.* Phase III study of weekly high-dose infusional 5-fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer. [submitted as commercial in confidence]. 2004.

57. Comella P, Massidda B, Filippelli G. Oxaliplatin (OXA) plus folinic acid (FA) and 5-fluorouracil (FU) i.v. bolus (OXAFAFU) versus irinotecan (IRI) plus FA and FU i.v. bolus (IRIFAFU) in advanced colorectal carcinoma (ACC): activity and toxicity results of the SICOG 0103 randomized trial. *Proc Am Soc Clin Oncol* 2004;**22**(145): Abstract 4143.

58. Comella P. Randomized trial comparing the addition of oxaliplatin or irinotecan to high-dose leucovorin and 5-fluorouracil intravenous bolus every two weeks in metastatic colorectal carcinoma: Southern Italy Cooperative Oncology Group 0103. *Clin Colorectal Cancer* 2003;**3**:186–9.

59. Comella P, Massidda B, Filippelli G. Biweekly oxaliplatin (OXA) or irinotecan (IRI) with high dose folinic acid (FA) and 5-fluorouracil (FU) i.v. bolus in advanced colorectal carcinoma (ACC). Southern Italy Cooperative Oncology Group (SICOG 0103) randomized study. *Proc Am Soc Clin Oncol* 2003;**22**(280):Abstract 1123.

60. Medical Research Council. Academic in confidence data from the FOCUS trial submitted by the Clinical Trials Unit. 2004.

61. Saltz LB, Douillard JY, Pirotta N, Alakl M, Gruia G, Awad L, *et al.* Irinotecan plus fluorouracil/leucovorin for metastatic colorectal cancer: a new survival standard. *Oncologist* 2001; **6**:81–91.

62. Kohne CH, Grothey A, Bokemeyer C, Bontke N, Aapro M. Chemotherapy in elderly patients with colorectal cancer. *Ann Oncol* 2001;**12**:435–42.

63. Ross PJ, Popescu D, Cunningham A. Adjuvant and palliative chemotherapy for colorectal cancer in patients aged 70 years or older. *Proc Am Soc Clin Oncol* 1998;**17**;1096.

64. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment. *N Engl J Med* 1999;**341**:2061–7.

65. Marcuello E, Navarro M, Cervantes AS, Anton A, Massuti B, Carrato A, *et al.* TTD Spanish Cooperative Group Biweekly oxaliplatin (OXA) plus weekly 48 h continuous infusion (CI) of 5FU (TTD regimen) for the first-line treatment of advanced colorectal cancer (ACC). *Ann Oncol* 2000; **11**:213P.

66. Folprecht G, Cunningham D, Ross P, Glimelius B, Di Costanzo F, Wils J, *et al.* Efficacy of 5-fluorouracil-based chemotherapy in elderly patients with metastatic colorectal cancer: a pooled analysis of clinical trials. *Ann Oncol* 2004;**15**:1330–8.

67. Potosky AL, Harlan LC, Kaplan RS, Johnson KA, Lynch CF. Age, sex and racial differences in the use of standard adjuvant therapy for colorectal cancer. *J Clin Oncol* 2002;**20**:1192–202.

68. Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, *et al.* Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer [published erratum appears in *Lancet* 1998;**352**:1634]. *Lancet* 1998; **352**:1407–12.

69. Cunningham D, Glimelius B. V301 Study Group. A phase III study of irinotecan (CPT-11) versus best supportive care in patients with metastatic colorectal cancer who have failed 5-fluorouracil therapy. *Semin Oncol* 1999;**26**:6–12.

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

71. Adenis A, Douillard JY, Lacroix H-Randomized phase II–III trial of oxaliplatin (OXA) with

5-flourouracil (5FU) continuous infusion (CI) versus a control arm with either 5FU or irinotecan (CPT11) in previously treated metastatic colorectal cancer (MCRC) patients (Pts). *ASCO OnLine* 2000; 1088.

72. Rougier P, Lepille D, Bennouna J, Marre A, Ducreux M, Mignot L, *et al.* Antitumour activity of three second-line treatment combinations in patients with metastatic colorectal cancer after optimal 5-FU regimen failure: a randomised, multicentre phase II study. *Ann Oncol* 2002; **13**:1558–67.

73. Smithies A, Stein K. Wessex Institute for Health Research and Development, *Irinotecan as second-line chemotherapy in colorectal cancer*. University of Southampton; 1999.

74. Selke B, Lebrun T, Comte S [Economic assessment of adjuvant and palliative chemotherapy in colorectal cancer: a review]. *Bull Cancer* 2003; **90**:143–9.

75. Fuchs CS, Moore MR, Harker G, Villa L, Rinaldi D, Hecht JR. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. *J Clin Oncol* 2003;**21**:807–14.

76. Stewart G, Chau I, Norman A, Katopodis O, Topham C, Middleton G, *et al.* Elderly patients with fluoropyrimidine-resistant advanced colorectal cancer (CRC) derive similar benefit without excessive toxicity when treated with irinotecan monotherapy. ASCO Annual Meeting; 2004. *J Clin Oncol* [ABCO Annual Meeting Proceedings (Post Meeting Edition)] 2004;**22**(145): 3622.

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

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

79. Grothey A, Buechele T, Kroening H, Ridwelski K, Reichardt P, Kretzschmar A, *et al.* Phase III trial of bolus 5-fluorouracil (5-FU)/folinic acid (FA) (MAYO) vs weekly oxaliplatin (OXA) plus high dose 24h 5-FU infusion/FA in patients with advanced colorectal cancer (CRC). *Proc Am Soc Clin Oncol* 2002;**21**:Abstract S12.

80. Zori Comba A, Blajman C, Richardet E. Bimonthly oxaliplatin (L-OHP) with (A) or without (B) flouracil (FU) and leucovorin (FA): proven evidence of synergism in a phase II: randomised trial. *ASCO OnLine* 1999;953.

81. de Gramont A, Cervantes A, Andre T. OPTIMOX study: FOLFOX 7/LV5FU2 compared to FOLFOX 4 in patients with advanced colorectal cancer [abstract]. *ASCO Annual Meeting Proceedings 2004*. *J Clin Oncol* 2004;**22**.

82. Giacchetti S. First-line infusion of 5-fluorouracil, leucovorin and oxaliplatin for metastatic colorectal cancer: 4-day chronomodulated (FFL4-10) versus 2-day FOLFOX2. A multicenter randomized Phase III trial of the Chronotherapy Group of the European Organization for Research and Treatment of Cancer (EORTC 05963). *ASCO Annual Meeting*, 2004. 40th Annual Meeting, New Orleans, USA.

83. Levi F, Zidani R, Vannetzel JM. Chronomodulated versus fixed-infusion-rate delivery of ambulatory chemotherapy with oxaliplatin, fluorouracil, and folinic acid (leucovorin) in patients with colorectal cancer metastases: a randomized multi-institutional trial. *J Nat Cancer Inst* 1994;**86**:1608–17.

84. Cassidy J, Cunningham D, Utracka-Hutka B, Zaluski J, Glynne-Jones R, Mainwaring P. Life: longevity improvement with front-line eloxatin. A randomised trial evaluating Eloxatin (oxaliplatin) combined with 2 different 5-FU regimens followed by irinotecan in patients with previously untreated advanced colo-rectal cancer: preliminary results [abstract]. *Proc Am Soc Clin Oncol* 2003;**22**:265.

85. Grothey A, Deschler B, Kroening H. Phase III study of bolus 5-fluorouracil (5-FU)/ folinic acid (FA) (Mayo) vs weekly high-dose 24h 5-FU infusion/FA + oxaliplatin (OXA) (FUFOX) in advanced colorectal cancer (ACRC). *Proc Am Soc Clin Oncol* 2002;**21**(Issue 129a): Abstract S12; 3530.

86. Exquis B, Aapro M, Kohler S. Oxaliplatin (with 5FU and leucovorin) in patients above age 70 suffering from metastatic colorectal cancer: an observational study. *ASCO Annual Meeting*, 2004. *J Clin Oncol* **22**(145, July Suppl.):8042.

87. Botto HG. Combination of oxaliplatin (OXA) and 5-fluorouracil, leucovorin (5-FU/LV), as first-line therapy, in elderly patients >70 years, with metastatic colorectal cancer. *ASCO Annual Meeting*, 2004. *J Clin Oncol* **22**(145, July Suppl.):3717.

88. Andre T, Figer A, Cervantes A, Lledo G, Flesch M, Maindrault-Goebel F, *et al.* Folfox7 compared to Folfox4: preliminary results of the randomised optimox study [abstract]. *Proc Am Soc Clin Oncol* 2003;1016.

89. Figer A, Perez N, Carola E, Andre T, Chirivella I, Lledo G, *et al.* 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) in very old patients with metastatic colorectal cancer. *J Clin Oncol* 2004; **22**:3571.

90. Maindrault-Gœbel F, Louvet C, Andre T, Carola E, Gilles V, Garcia M, *et al.* Oxaliplatin reintroduction

in patients pretreated with leucovorin, fluorouracil and oxaliplatin for metastatic colorectal cancer (MCRC). *Ann Oncol* 2000;**11**:216P.

91. Rothenberg ML, Oza AM, Burger B, *et al.* Final results of a phase III trial of 5-FU/leucovorin versus oxaliplatin versus the combination in patients with metastatic colorectal cancer following irinotecan, 5-FU, and leucovorin [abstract]. *Proc Am Soc Clin Oncol* 2003;**22**:252.

92. Andre,T, Bensmaine MA, Louvet C, Francois E, Lucas V, Desseigne F, *et al.* Aimery Multicenter phase II study of bimonthly high-dose leucovorin, fluorouracil infusion, and oxaliplatin for metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen. *J Clin Oncol* 1999;**17**:3560–8.

93. Rothenberg ML, Oza AM, Bigelow RH, Berlin JD, Marshall JL, Ramanathan RK, *et al.* Superiority of oxaliplatin and fluorouracil–leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil–leucovorin: interim results of a phase III trial [see comment]. *J Clin Oncol* 2003; **21**:2059–69.

94. Cunningham D, Zalcberg JR, Rath U, Oliver I, Van Cutsem E, Svensson C, *et al.* Final results of a randomised trial comparing 'Tomudex' (raltitrexed) with 5-fluorouracil plus leucovorin in advanced colorectal cancer. 'Tomudex' Colorectal Cancer Study Group [published erratum appears in *Ann Oncol* 1997;**8**:407]. *Ann Oncol* 1996;**7**:961–5.

95. Maughan TS, James RD, Kerr DJ, Ledermann JA, McArdle C, Seymour MT, *et al.* Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2002;**359**:1555–63.

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

97. Pazdur R, Vincent M. Raltitrexed (Tomudex) versus 5-fluorouracil and leucovorin (5FU+LV) in patients with advanced colorectal cancer (ACC): results of a randomized, multicenter, North American trial [abstract]. *Proc Am Soc Clin Oncol* 1997;**16**:228a.

98. Mel JR, Feliu J, Camps C, Escudero P, Aparicio J, Menendez D, *et al.* Tomudex (raltitrexed) in elderly patients with advanced colorectal cancer (ACC): an effective palliative treatment. *Proc Am Soc Clin Oncol* 2000;**19**:1000.

99. Franchi F, Pastore C, Caporale A, Fabiani O, Rossi L, Seminara P. Favorable toxicity profile of raltitrexed in elderly patients treated for colorectal cancer: a case series. *Gerontology* 2003;**49**:324–7.

100. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil–leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* 2004; **22**:1209–14.

101. Adam R. Chemotherapy and surgery: new perspectives on the treatment of unresectable liver metastases. *Ann Oncol* 2003;**14**:13–16.

102. Adson MA. Resection of liver metastases. When is it worthwhile? *World J Surg* 1987;**11**:511–20.

103. Bismuth H, Adam R, Levi F, Farabos C, Waechter F. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996;**224**:509–20.

104. Ducreux M, Raoul JL, Marti P, Merrouche Y, Tigaud JM, Risse ML, *et al.* Irinotecan (CPT-11) high-dose 260 mg m^{-2} with 5-FU/FA (LV5FU2 or LF5FUS) in first-line metastatic colorectal cancer [abstract]. *Proc Am Soc Clin Oncol* 2002; **21**:639c.

105. Ho WM, Mok TS, Ma BB, Lim B, Lai PB, Chui A, *et al.* Liver resection after irinotecan (CPT-11), 5-fluorouracil (5FU) and folinic acid (FA) for patients (pts) with unresectable liver metastases (mets) from colorectal cancer (crc). *Proc Am Soc Clin Oncol* 2003;**22**:1253.

106. Piedbois P. Intravenous CPT-11/5-FU/LV and hepatic artery infusion pirarubicin in non operable liver metastases from colorectal cancer. A study of the A.E.R.O. Group [abstract]. *Ann Oncol* 2002;**13**:291P.

107. Zelek L, Bugat R, Cherqui D, Ganem G, Valleur P, Guimbaud R, *et al.* European Association for Research in Oncology, Creteil, France. Multimodal therapy with intravenous biweekly leucovorin, 5-fluorouracil and irinotecan combined with hepatic arterial infusion pirarubicin in non-resectable hepatic metastases from colorectal cancer (a European Association for Research in Oncology trial) [see comment]. *Ann Oncol* 2003;**14**:1537–42.

108. Pozzo C, Basso M, Cassano A, Quirino A, Schinzari G, Trigila N, *et al.* Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. *Ann Oncol* 2004; **15**:933–9.

109. Slater R, Radstone D, Matthews L, McDaid J, Majeed A. Hepatic resection for colorectal liver metastases after downstaging with irinotecan improves survival. *Proc Am Soc Clin Oncol* 2003; **22**:1287.

110. Giacchetti S, Itzhaki M, Gruia G. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional

chemothrapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. *Ann Oncol* 1999;**10**:663–9.

111. Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998;**16**:301–8.

112. Köhne CH, Wils J, Lorenz M, Schoffski P, Voigtmann R, Bokemeyer C, *et al.* Randomized phase III study of high-dose fluorouracil given as a weekly 24-hour infusion with or without leucovorin versus bolus fluorouracil plus leucovorin in advanced colorectal cancer: European Organization of Research and Treatment of Cancer Gastrointestinal Group study 40952. *J Clin Oncol* 2003;**21**:3721–8.

113. Petrou S, Campbell N. Stabilisation in colorectal cancer. *International Journal of Palliative Nursing* 1997;**3**:275–80.

114. Medical Research Council. *Fluorouracil, Oxaliplatin and Irinotecan: Use and Sequencing (FOCUS) clinical protocol* (version 6). 2003;**CR08**:1-90. London: MRC.

115. National Institute for Clinical Excellence. *Guide to the methods of technology appraisal.* London: NICE; 2004.

116. van Cutsem E, Blijham GH. Irinotecan versus infusional 5-fluorouracil: a phase III study in metastatic colorectal cancer following failure on first-line 5-fluorouracil. *Semin Oncol* 1999;**26**:13–20.

117. Collett D. *Modelling survival data in medical research*. London: Chapman & Hall; 1994.

118. Graf W, Pahlman L, Bergstrom R, Glimelius B. The relationship between an objective response to chemotherapy and survival in advanced colorectal cancer. *Br J Cancer* 1994;**70**:559–63.

119. Weiss GB, Bunce H III, Hokanson JA. Comparing survival of responders and nonresponders after treatment: a potential source of confusion in interpreting cancer trials. *Control Clin Trials* 1983; **4**:43–52.

120. Buyse M, Thirion P, Carlson RW, Burzykowski T, Molenberghs G, Piedbois P. Relation between tumour response to first-line chemotherapy and survival in advanced colorectal cancer: a meta-analysis. *Lancet* 2000;**356**:373–8.

121. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes.* 2nd ed. Oxford: Oxford University Press; 1997.

122. Hind D, Tappenden P, Tumur I, Eggington S, Sutcliffe P, Ryan A. The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation (review of Guidance No. 33). Technology Assessment Report submitted to NICE; 2005.

123. British Medical Association. *British National Formulary* 48. London: BMA; 2004. URL: http://www.bnf.org/bnf/

124. Netten A, Curtis L. *Unit costs of health and social care*. Canterbury: Personal Social Services Research Unit; 2004.

125. Summerhayes M, Wanklyn SJ, Shakespeare RA, Lovell J. Reduced pharmacy resource utilization associated with raltitrexed treatment of advanced colorectal cancer. *Journal of Oncology Pharmacy Practice* 1997;**3**:24–30.

126. Boland J, Haycox A, Bagust A, Fitzsimmons L. A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses. *Health Technol Assess* 2003;**7**(36).

127. Netten A, Dennett J, Knight J. *Unit costs of health and social care*. Canterbury: Personal Social Services Research Units; 1999.

128. Schmitt C. Medical care consumption in a phase III trial comparing irinotecan with infusional 5-fluorouracil (5-FU) in patients with metastatic colorectal cancer after 5-FU failure. *Anticancer Drugs* 1999;**10**:617–23.

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

130. Sanofi-Synthelabo. The use of oxaliplatin for the treatment of advanced colorectal cancer (review of NICE guidance no. 33). Industry submission to NICE; 2004.

131. Schmitt C, Levy-Piedbois C, Frappe M, Durand-Zaleski I, Gruia G, Alakl M, Rougier P. Cost-effectiveness analysis of irinotecan+5FU/FA as first-line therapy in advanced colorectal cancer. *Ann Oncol* 2000;**11**:202P.

132. Elliott R. An analysis of drug costs in the management of chemotherapy-related side effects in advanced colorectal cancer. A comparison between raltitrexed ('Tomudex') and 5-fluorouracil plus folinic acid. *Journal of Oncology Pharmacy Practice* 1996;**2**:186–90.

133. Vaiani M, Trippoli S, Messori A. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2001;**344**:305–6.

134. Trippoli S, Vaiani M, Cattel F, Messori A. Cost-effectiveness of irinotecan in advanced colorectal cancer. *Ann Oncol* 2000;**11**:899–900.

135. Ross P. Cost of treating advanced colorectal cancer: a retrospective comparison of treatment regimens. *Eur J Cancer* 1996;**32A**(Suppl 5):S13–17.

136. Gautie L, Mogenet I, Puisset F, Bonhomme C, Canal P. The cost of palliative chemotherapies for metastatic colorectal cancer: A retrospective study

conducted at the Claudius Regaud Institute. *Journal d'Economie Medicale* 2002;**20**:401–8.

137. Focan C. Pharmaco-economic comparative evaluation of combination chronotherapy vs. standard chemotherapy for colorectal cancer. *Chronobiol Int* 2002;**19**:289–97.

138. Koperna T, Semmler D. Innovative chemotherapies for stage III colon cancer: a cost-effectiveness study. *Hepatogastroenterology* 2003;**50**:1903–9.

139. Poston G, Benjamin IS, Diamond T, Finch-Jones M, Parks RW, *et al.* Costs of neoadjuvant chemotherapy and surgery in patients with liver metastases from advanced colorectal cancer. *Journal of Medical Economics* 2001;**4**:167–77.

140. Cunningham D, Falk S, Jackson D. Clinical and economic benefits of irinotecan in combination with 5-fluorouracil and folinic acid as first-line treatment of metastatic colorectal cancer. *Br J Cancer* 2002;**86**:1677–83.

141. Levy-Piedbois C, Durand-Zaleski I, Juhel H, Schmitt C, Bellanger A, Piedbois P. Cost-effectiveness of second-line treatment with irinotecan or infusional 5-fluorouracil in metastatic colorectal cancer. *Ann Oncol* 2000;**11**:157–61.

142. Nicholls CJ, Cassidy J, Freemantle N, Harrison M, Carita P. Cost-effectiveness of oxaliplatin in combination with 5-FU/FA compared with 5-FU/FA alone. *Journal of Medical Economics* 2001;**4**:127–35.

143. Nicholls C, Cassidy J, Freemantle N, Harrison M, Carita P. Cost-effectiveness of combination chemotherapy (oxaliplatin or irinotecan in combination with 5-FU/FA) compared with 5-FU/FA alone. *Journal of Medical Economics* 2001; **4**:115–25.

144. Groener MGH. An economic evaluation of Tomudex (raltitrexed) and 5-fluorouracil plus leucovorin in advanced colorectal cancer. *Anticancer Drugs* 1999;**10**:283–8.

145. *Monthly index of medical specialties.* London: Haymarket Medical; 2000 (September)

146. Department of Health. *NHS reference costs.* 2003.

147. *Royal Marsden Drug and Therapeutics Advisory Committee. Prescribing guidelines.* London: Royal Marsden; 2000 (September).

148. Devita VT Jr, Hellman S, Rosenberg SA. *Cancer: principles and practice of oncology.* 5th ed. Philadelphia, PA: Lippincott-Raven 1997.

149. Sculpher M, Palmer MK, Heyes A. Costs incurred by patients undergoing advanced colorectal cancer therapy: a comparison of raltitrexed and fluorouracil plus folinic acid. *Pharmacoeconomics* 2000;**17**:361–70.

150. Cancer Research UK. URL: http://www.cancerresearchuk.org/images/11632/briefsheet bowel_0403.pdf. Accessed 2004.

151. http://www.cancercumbria.org.uk/hobsons_choice.pdf. Accessed 2004.

152. http://www.nature.com/bjc/press_releases/press_release_47.html. Accessed 2004.

153. Bouzid K, Khalfallah S, Tujakowski J, Piko B, Purkalne G, Plate S, *et al.* Irinotecan Study Group. A randomized phase II trial of irinotecan in combination with infusional or two different bolus 5-fluorouracil and folinic acid regimens as first-line therapy for advanced colorectal cancer. *Ann Oncol* 2003;**14**:1106–14.

154. Cheeseman SL, Joel SP, Chester JD, Wilson G, Dent JT, Richards FJ, Seymour MT. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. *Br J Cancer* 2002;**87**:393–9.

155. Graeven U, Schmiegel W. Colon carcinoma. Consensus of therapeutic strategies. *Internist* 2000; **41**:876–85.

156. Kalofonos HP, Skarlos D, Bafaloukos D, Papakostas P, Bamias A, Janinis J, *et al.* A phase II study with CPT-11 plus leucovorin and bolus IV 5-fluorouracil in patients with advanced colorectal carcinoma. *Cancer Invest* 2003;**21**: 855–62.

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

158. Pozzo C, Pyrhonen S, Bodrogi I. A randomized phase II trial assessing irinotecan (IRI) and 5FU/folinic acid (LV), 'Mayo regimen', in first-line palliative chemotherapy patients (pts) with metastatic colorectal cancer (MCRC). *Eur J Cancer* 1999;**35**:(S70):Abstract 213.

159. Recchia F, De Filippis S, Rosselli M, *et al.* Randomized phase II study of oxaliplatin (OX) or CPT-11 (CPT) combined with bimonthly leucovorin (L) and 5-flourouracil (5-FU) in metastatic colorectal cancer (MCC). Preliminary report. *ASCO OnLine* 2000.

160. Rougier P, Cunningham D, Roth AD. Irinotecan (Iri) in combination with high-dose infusional (HDI) 5FU/FA either weekly or bi-weekly: evidence of survival advantage and quality of life (QoL) improvement in metastatic colorectal cancer (MCRC). *Eur J Cancer* 1999; **35**:206.

161. Ulrich-Pur H, Brugger S, Kornek GV. Randomized phase II study of CPT-11 plus mitomycin C versus oxaliplatin plus mitomycin C in previously treated patients with advanced colorectal cancer (ACC). *Eur J Cancer* 1999;**35**:(S72): Abstract 225, 72–3.

162. Bollina R, Toniolo D, Belloni P, Cozzi C, Clerici M. Oxaliplatin (LOHP) and Irinotecan (CPT11)-Oxiri-: Phase I/II Study in 5FU (F) refractory advanced colorectal cancer (ACRC) elderly patients (pts), a second-line treatment. American Society of Clinical Oncology; 2001.

163. Chau I, Norman AR, Cunningham D, Waters JS, Topham C, Middleton G, *et al.* Elderly patients with fluoropyrimidine and thymidylate synthase inhibitor-resistant advanced colorectal cancer derive similar benefit without excessive toxicity when treated with irinotecan monotherapy. *Br J Cancer* 2004;**91**:1453–8.

164. Comella P, Farris A, Lorusso V, Palmeri S, Maiorino L, De Lucia L, *et al.* Irinotecan plus leucovorin-modulated 5-fluorouracil I.V. bolus every other week may be a suitable therapeutic option also for elderly patients with metastatic colorectal carcinoma. *Br J Cancer* 2003;**89**:992–6.

165. Lopez-Gomez L, Escudero P, Yubero A, Feliu J, Salud A, Galan A, *et al.* XELOX (capecitabine and oxaliplatin) as 1st-line treatment for elderly patients (pts) with advanced/metastatic colorectal cancer (MCRC). *J Clin Oncol* 2004;**22**:3688.

166. Rosati *et al.* A phase II trial of oxaliplatin (L-OHP) and uracil-tegafur (UFT)/folinic acid (FA) for advanced colorectal cancer (ACC) in elderly patients. ASCO *Annual Meeting,* 2004. *J Clin Oncol* **22**:2793.

167. Cortinovis D, Bajetta E, Di Bartolomeo M, Dognini G, Beretta E, Ferrario E, *et al.* Raltitrexed plus oxaliplatin in the treatment of metastatic colorectal cancer. *Tumori* 2004;**90**:186–91.

168. Facchini T, Genet D, Berdah JF, Nouyrigat P, Dutin JP, Laplaige P, Haguenauer D. Ratitrexed (Tomudex) has a manageable toxicity profile in elderly patients with metastatic colorectal cancer: final analysis of a multicentre study. *ASCO Annual Meeting*, 2000.

169. Paredes M, Garcia D, Mel JR, Escudero P, Camps C, Montalar J, *et al.* An ongoing Phase II study of tomudex (raltitrexed) in elderly patients with advanced colorectal cancer: an assessment of tolerability and clinical benefit. *ASCO Annual Meeting*, 1999.

170. Romiti A, Di Seri M, Lacava V, Oliveti A, Bonginelli P, Santuari L, *et al.* Tolerability of raltitrexed in elderly patients affected with colorectal cancer (CRC). *Ann Oncol* 2000;**11**:58–9.

Appendix 1

BNF general guidance on use of cytotoxic drugs

The chemotherapy of cancer is complex and should be confined to specialists in oncology. Cytotoxic drugs have both anticancer 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, either as neoadjuvant treatment (initial chemotherapy aimed at shrinking the primary tumour, thereby rendering local therapy less destructive or more effective) or as adjuvant treatment (which follows definitive treatment of the primary disease, when the risk of subclinical metastatic disease is known to be high). All chemotherapy drugs cause side-effects and a balance has to be struck between likely benefit and acceptable toxicity.

Continual Reassessment Method (CRM) guidelines on handling cytotoxic drugs:

- trained personnel should reconstitute cytotoxics.
- reconstitution should be carried out in designated areas.
- protective clothing (including gloves) should be worn.
- the eyes should be protected and means of first aid should be specified.
- pregnant staff should not handle cytotoxics.
- 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 antitumour activity, sites of action and toxicity. A 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 2

QUOROM checklist

Heading	Subheading	Descriptor	Reported? (Y/N)	Position
Title		Identify the report as a meta-analysis (or systematic review) of RCTs	Y	First page
Abstract		Use a structured format		
		Describe		
	Objectives	The clinical question explicitly		
	Data sources	The databases (i.e. list) and other information sources		
	Review methods	The selection criteria (i.e. population, intervention, outcome and study design): methods for validity assessment, data abstraction and study characteristics, and quantitative data synthesis in sufficient detail to permit replication		
	Results	Characteristics of the RCTs included and excluded; qualitative and quantitative findings (i.e. point estimates and confidence intervals); and subgroup analyses		
	Conclusions	The main results		
		Describe		
Introduction		The explicit clinical problem, biological rationale for the intervention and rationale for review	Y	Chapter 2
Methods	Searching	The information sources, in detail (e.g. databases, registers, personal files, expert informants, agencies, handsearching), and any restrictions (years considered, publication status, language of publication)		Chapter 3; Appendix 3
	Selection	The inclusion and exclusion criteria (defining population, intervention, principal outcomes and study design)		Chapter 3
	Validity assessment	The criteria and process used (e.g. masked conditions, quality assessment, and their findings)		Chapter 3
	Data abstraction	The process or processes used (e.g. completed independently, in duplicate)	Y	Chapter 3
	Study characteristics	The type of study design, participants' characteristics, details of intervention, outcome definitions, etc. and how clinical heterogeneity was assessed	Y	Chapter 3
	Quantitative data synthesis	The principal measures of effect (e.g. relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data; how statistical heterogeneity was assessed; a rationale for any a priori sensitivity and subgroup analyses; and any assessment of publication bias	Y	Chapter 3
Results	Trial flow	Provide a meta-analysis profile summarising trial flow	Y	Appendix 4
	Study characteristics	Present descriptive data for each trial (e.g. age, sample size, intervention, dose, duration, follow-up period)	Y	Throughout
	Quantitative data synthesis	Report agreement on the selection and validity assessment; present simple summary	Y	Throughout
Discussion		Summarise key findings; discuss clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (e.g. publication bias); and suggest a future research agenda		

Appendix 3

Search strategies

MEDLINE search using filter to identify RCTs

1 irinotecan.af.
2 100286-90-6.rn.
3 cpt 11.af.
4 cpt11.af.
5 campto.af.
6 camptosar.af.
7 oxaliplatin.af.
8 63121-00-6.rn.
9 1 ohp.af.
10 eloxatin.af.
11 raltitrexed.af.
12 tomudex.af.
13 ici d 1694.af.
14 ici d1694.af.
15 112887-68-0.rn.
16 zd 1694.af.
17 zd1694.af.
18 or/1-17
19 TEGAFUR/
20 1 2 tetrahydrofuryl 5 fluorouracil.af.
21 1 tetrahydro 2 furanyl 5 fluorouracil.af.
22 5 fluoro 1 tetrahydro-2-furanyl 2 4-pyrimidinedione.af.
23 florafur.af.
24 fluorofur.af.
25 ft207.af.
26 ft-207.af.
27 ftorafur.af.
28 futraful.af.
29 n1 2 tetrahydrofuryl 5 fluorouracil.af.
30 sunfural s.af.
31 17902-23-7.rn.
32 tegafur.af.
33 uft.af.
34 1 uft protocol.rn.
35 uftoral.af.
36 or/19-35
37 exp colorectal neoplasms/
38 neoplasms/
39 carcinoma/
40 adenocarcinoma/
41 or/38-40
42 colonic diseases/
43 rectal diseases/
44 exp colon/
45 exp rectum/
46 or/42-45
47 41 and 46
48 (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
49 (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
50 (neoplasm adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
51 (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
52 (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
53 (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
54 (tumour adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
55 (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
56 or/48-55
57 37 or 47 or 56
58 (18 or 36) and 57
59 randomized controlled trial.pt.
60 controlled clinical trial.pt.
61 randomized controlled trials/
62 random allocation/
63 double blind method/
64 single blind method/
65 or/59-64
66 clinical trial.pt.
67 exp clinical trials/
68 (clin$ adj25 trial$).tw.
69 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw.
70 placebos/
71 placebo$.tw.
72 random$.tw.
73 research design/
74 or/66-73
75 "comparative study"/
76 exp evaluation studies/
77 follow-up studies/
78 prospective studies/
79 (control$ or prospectiv$ or volunteer$).tw.
80 (control$ or prospectiv$ or volunteer$).tw.
81 or/75-80
82 65 or 74 or 81
83 "animal"/
84 "human"/
85 83 not 84
86 82 not 85
87 58 and 86

EMBASE search using filter to identify systematic reviews

#1 explode 'irinotecan-' / all subheadings in DEM,DER,DRM,DRR
#2 100286-90-6 in rn
#3 cpt 11
#4 cpt11
#5 campto
#6 camptosar
#7 oxaliplatin
#8 63121-00-6 in rn
#9 1 ohp
#10 explode 'oxaliplatin-' / all subheadings in DEM,DER,DRM,DRR
#11 eloxatin
#12 explode 'raltitrexed-' / all subheadings in DEM,DER,DRM,DRR
#13 raltitrexed
#14 tomudex
#15 ici d1694
#16 ici d 1694
#17 112887-68-0 in rn
#18 zd1694
#19 zd 1694
#20 irinotecan
#21 (explode 'irinotecan-' / all subheadings in DEM,DER,DRM,DRR) or (100286-90-6 in rn) or (cpt 11) or (cpt11) or (campto) or (camptosar) or (oxaliplatin) or (63121-00-6 in rn) or (1 ohp) or (explode 'oxaliplatin-' / all subheadings in DEM,DER,DRM,DRR) or (eloxatin) or (explode 'raltitrexed-' / all subheadings in DEM,DER,DRM,DRR) or (raltitrexed) or (tomudex) or (ici d1694) or (ici d 1694) or (112887-68-0 in rn) or (zd1694) or (zd 1694) or (irinotecan)
#22 (explode 'colorectal-cancer' / all subheadings in DEM,DER,DRM,DRR) or (explode 'colorectal-carcinoma' / all subheadings in DEM,DER,DRM,DRR) or (explode 'colorectal-disease' / all subheadings in DEM,DER,DRM,DRR) or (explode 'colorectal-tumor' / all subheadings in DEM,DER,DRM,DRR)
#23 'neoplasm-' / all subheadings in DEM,DER,DRM,DRR
#24 'carcinoma-' / all subheadings in DEM,DER,DRM,DRR
#25 'adenocarcinoma-' / all subheadings in DEM,DER,DRM,DRR
#26 ('neoplasm-' / all subheadings in DEM,DER,DRM,DRR) or ('carcinoma-' / all subheadings in DEM,DER,DRM,DRR) or ('adenocarcinoma-' / all subheadings in DEM,DER,DRM,DRR)
#27 carcinoma near3 (colorectal or colon* or rect* or intestin* or bowel)
#28 neoplasia near3 (colorectal or colon* or rect* or intestin* or bowel)
#29 neoplasm* near3 (colorectal or colon* or rect* or intestin* or bowel)
#30 adenocarcinoma near3 (colorectal or colon* or rect* or intestin* or bowel)
#31 cancer* near3 (colorectal or colon* or rect* or intestin* or bowel)
#32 tumor* near3 (colorectal or colon* or rect* or intestin* or bowel)
#33 tumour* near3 (colorectal or colon* or rect* or intestin* or bowel)
#34 malignan* near3 (colorectal or colon* or rect* or intestin* or bowel)
#35 #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34
#36 'colon-disease' / all subheadings in DEM,DER,DRM,DRR
#37 'rectum-disease' / all subheadings in DEM,DER,DRM,DRR
#38 explode 'colon-' / all subheadings in DEM,DER,DRM,DRR
#39 explode 'rectum-' / all subheadings in DEM,DER,DRM,DRR
#40 #36 or #37 or #38 or #39
#41 #26 and #40
#42 #22 or #41
#43 #21 and #42
#44 explode 'meta-analysis' / all subheadings
#45 (meta adj analy*) or metaanaly*.tw
#46 systematic* near1 review*
#47 systematic* near1 overview*
#48 (explode 'meta-analysis' / all subheadings) or ((meta adj analy*) or metaanaly*.tw) or (systematic* near1 review*) or (systematic* near1 overview*)
#49 reference list* in ab
#50 bibliograph* in ab
#51 hand-search* in ab
#52 manual search* in ab
#53 relevant journals in ab
#54 (reference list* in ab) or (bibliograph* in ab) or (hand-search* in ab) or (manual search* in ab) or (relevant journals in ab)
#55 data extraction in ab
#56 selection criteria in ab
#57 (data extraction in ab) or (selection criteria in ab)
#58 review in dt
#59 ((data extraction in ab) or (selection criteria in ab)) and (review in dt)
#60 letter in dt
#61 editorial in dt
#62 (letter in dt) or (editorial in dt)
#63 (((explode 'meta-analysis' / all subheadings) or ((meta adj analy*) or metaanaly*.tw) or (systematic* near1 review*) or (systematic* near1

overview*)) or ((reference list* in ab) or (bibliograph* in ab) or (hand-search* in ab) or (manual search* in ab) or (relevant journals in ab)) or (((data extraction in ab) or (selection criteria in ab)) and (review in dt))) not ((letter in dt) or (editorial in dt))
#64 #43 and #63

CINAHL search using filter to identify RCTs

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3 cpt 11.af.
4 cpt11.af.
5 campto.af.
6 camptosar.af.
7 oxaliplatin.af.
8 63121-00-6.rn.
9 1 ohp.af.
10 eloxatin.af.
11 raltitrexed.af.
12 tomudex.af.
13 ici d 1694.af.
14 ici d1694.af.
15 112887-68-0.rn.
16 zd 1694.af.
17 zd1694.af.
18 TEGAFUR/
19 1 2 tetrahydrofuryl 5 fluorouracil.af.
20 1 tetrahydro 2 furanyl 5 fluorouracil.af.
21 5 fluoro 1 tetrahydro-2-furanyl 2 4-pyrimidinedione.af.
22 florafur.af.
23 fluorofur.af.
24 ft207.af.
25 ft-207.af.
26 ftorafur.af.
27 futraful.af.
28 n1 2 tetrahydrofuryl 5 fluorouracil.af.
29 sunfural s.af.
30 17902-23-7.rn.
31 tegafur.af.
32 uft.af.
33 1 uft protocol.rn.
34 uftoral.af.
35 exp colorectal neoplasms/
36 neoplasms/
37 carcinoma/
38 adenocarcinoma/
39 or/36-38
40 colonic diseases/
41 rectal diseases/
42 exp colon/
43 exp rectum/
44 or/40-43
45 39 and 44
46 (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
47 (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
48 (neoplasm adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
49 (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
50 (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
51 (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
52 (tumour adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
53 (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
54 or/46-53
55 35 or 45 or 54
56 exp Clinical Trials/
57 clinical trial.pt.
58 (clinic$ adj trial$1).tw.
59 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3)).tw.
60 Randomi?ed control$ trial$.tw.
61 Random assignment/
62 Random$ allocat$.tw.
63 Placebo$.tw.
64 Quantitative Studies/
65 PLACEBOS/
66 allocat$ random$.tw.
67 or/56-66
68 or/1-34
69 55 and 67 and 68

CDSR

1 irinotecan.af.
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4 campto.af.
5 camptosar.af.
6 oxaliplatin.af.
7 1 ohp.af.
8 eloxatin.af.
9 raltitrexed.af.
10 tomudex.af.
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12 ici d1694.af.
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17 1 tetrahydro 2 furanyl 5 fluorouracil.af. (0)
18 5 fluoro 1 tetrahydro-2-furanyl 2 4-pyrimidinedione.af. (0)

19 florafur.af. (0)
20 fluorofur.af. (0)
21 ft207.af. (0)
22 ft-207.af. (0)
23 ftorafur.af. (0)
24 futraful.af. (0)
25 n1 2 tetrahydrofuryl 5 fluorouracil.af. (0)
26 sunfural s.af. (0)
27 tegafur.af. (2)
28 uft.af. (3)
29 [1 uft protocol.rn.] (0)
30 uftoral.af. (0)
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35 (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (8)
36 (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (90)
37 (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (9)
38 (tumour adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (7)
39 (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw. (12)
40 or/32-39 (98)
41 1 or 2 or 6 or 8 or 9 or 10 or 14 or 15 or 27 or 28 (14)
42 40 and 41 (7)
43 from 42 keep 1-7 (7)
44 from 42 keep 1-7 (7)
45 from 44 keep 1-7 (7)

BIOSIS (Biological Abstracts)

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3 cpt11
4 campto
5 camptosar
6 oxaliplatin
7 63121-00-6 in rn
8 1 ohp
9 eloxatin
10 raltitrexed
11 tomudex
12 ici d1694
13 ici d 1694
14 112887-68-0 in rn
15 zd1694
16 zd 1694
17 irinotecan
18 carcinoma near3 (colorectal or colon* or rect* or intestin* or bowel)
19 neoplasia near3 (colorectal or colon* or rect* or intestin* or bowel)
20 neoplasm* near3 (colorectal or colon* or rect* or intestin* or bowel)
21 adenocarcinoma near3 (colorectal or colon* or rect* or intestin* or bowel)
22 cancer* near3 (colorectal or colon* or rect* or intestin* or bowel)
23 tumor* near3 (colorectal or colon* or rect* or intestin* or bowel)
24 tumour* near3 (colorectal or colon* or rect* or intestin* or bowel)
25 malignan* near3 (colorectal or colon* or rect* or intestin* or bowel)
26 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
28 27 and 26

CCTR

1 irinotecan.af.
2 [100286-90-6.rn.]
3 cpt 11.af.
4 cpt11.af.
5 campto.af.
6 camptosar.af.
7 oxaliplatin.af.
8 [63121-00-6.rn.]
9 1 ohp.af.
10 eloxatin.af.
11 raltitrexed.af.
12 tomudex.af.
13 ici d 1694.af.
14 ici d1694.af.
15 [112887-68-0.rn.]
16 zd 1694.af.
17 zd1694.af.
18 TEGAFUR/
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20 1 tetrahydro 2 furanyl 5 fluorouracil.af.
21 5 fluoro 1 tetrahydro-2-furanyl 2 4-pyrimidinedione.af.
22 florafur.af.
23 fluorofur.af.
24 ft207.af.
25 ft-207.af.
26 ftorafur.af.
27 futraful.af.
28 n1 2 tetrahydrofuryl 5 fluorouracil.af.
29 sunfural s.af.
30 [17902-23-7.rn.]
31 tegafur.af.
32 uft.af.

33 [1 uft protocol.rn.]
34 uftoral.af.
35 exp colorectal neoplasms/
36 neoplasms/
37 carcinoma/
38 adenocarcinoma/
39 or/36-38
40 colonic diseases/
41 rectal diseases/
42 exp colon/
43 exp rectum/
44 or/40-43
45 39 and 44
46 (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
47 (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
48 (neoplasm adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
49 (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
50 (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
51 (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
52 (tumour adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
53 (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
54 or/46-53
55 54 or 45 or 35
56 or/1-34
57 55 and 56

SCI

1 TS=IRINOTECAN
2 TS=100286-90-6
3 TS=CPT 11
4 TS=CPT11
5 TS=CAMPTO*
6 TS=OXALIPLATIN
7 TS=63121-00-6
8 TS=1 OHP
9 TS=ELOXATIN
10 TS=RALTITREXED
11 TS=TOMUDEX
12 TS=ICI D1694
13 TS=ICI D 1694
14 TS=112887-68-0
15 TS=ZD1694
16 TS=ZD 1694
17 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
18 TS=(MALIGNAN* SAME (COLORECTAL OR COLON* OR RECT* OR INTESTIN* OR BOWEL))
19 TS=(TUMOUR SAME (COLORECTAL OR COLON* OR RECT* OR INTESTIN* OR BOWEL))
20 TS=(TUMOR* SAME (COLORECTAL OR COLON* OR RECT* OR INTESTIN* OR BOWEL))
21 TS=(CANCER* SAME (COLORECTAL OR COLON* OR RECT* OR INTESTIN* OR BOWEL))
22 TS=(ADENOCARCINOMA SAME (COLORECTAL OR COLON* OR RECT* OR INTESTIN* OR BOWEL))
23 TS=(NEOPLASM* SAME (COLORECTAL OR COLON* OR RECT* OR INTESTIN* OR BOWEL))
24 TS=(NEOPLASIA SAME (COLORECTAL OR COLON* OR RECT* OR INTESTIN* OR BOWEL))
25 TS=(CARCINOMA SAME (COLORECTAL OR COLON* OR RECT* OR INTESTIN* OR BOWEL))
26 #18 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
27 #26 AND #17

NHS EED/NHS HTA

1 TEGAFUR OR IRINOTECAN OR CAMPTO OR OXALIPLATIN OR ELOXATIN OR RALTITREXED OR TOMUDEX OR UFT

DARE

1 irinotecan.af.
2 cpt 11.af.
3 cpt11.af.
4 campto.af.
5 camptosar.af.
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7 1 ohp.af.
8 eloxatin.af.
9 raltitrexed.af.
10 tomudex.af.
11 ici d 1694.af.
12 ici d1694.af.
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15 tegafur.af.
16 1 2 tetrahydrofuryl 5 fluorouracil.af.
17 1 tetrahydro 2 furanyl 5 fluorouracil.af.
18 5 fluoro 1 tetrahydro-2-furanyl 2 4-pyrimidinedione.af.

19 florafur.af.
20 fluorofur.af.
21 ft207.af.
22 ft-207.af.
23 ftorafur.af.
24 futraful.af.
25 n1 2 tetrahydrofuryl 5 fluorouracil.af.
26 sunfural s.af.
27 tegafur.af.
28 uft.af.
29 [1 uft protocol.rn.]
30 uftoral.af.
31 or/1-30
32 (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
33 (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
34 (neoplasm adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
35 (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
36 (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
37 (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
38 (tumour adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
39 (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.
40 or/32-39
41 40 and31

OHE HEED

1 TEGAFUR OR IRINOTECAN OR CAMPTO OR OXALIPLATIN OR ELOXATIN OR RALTITREXED OR TOMUDEX OR UFT

Appendix 4
QUOROM trial flowchart

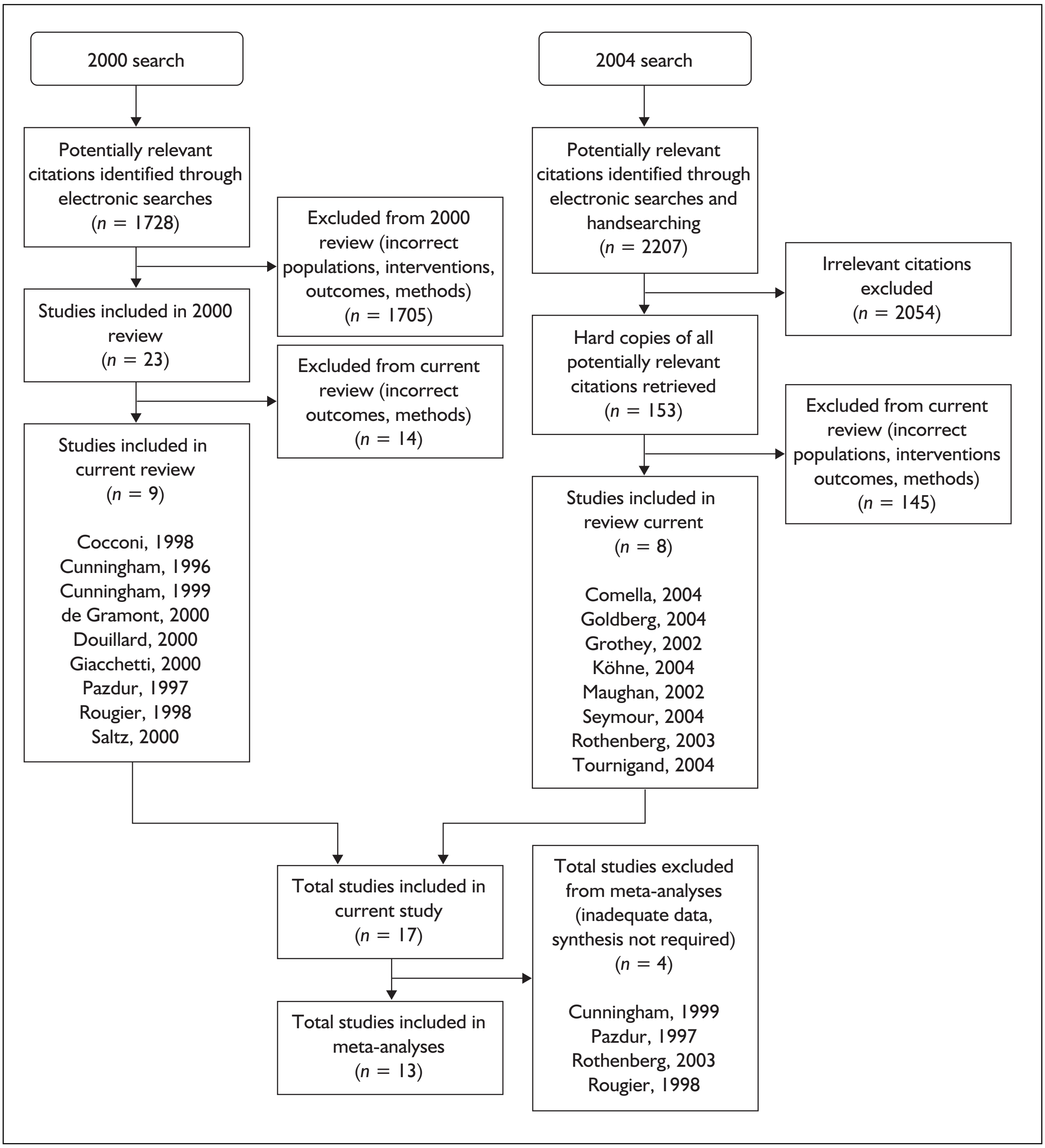

FIGURE 16 *Trial flow diagram*

Appendix 5
Exclusions

***TABLE 73** Studies excluded from the review of clinical effectiveness*

Study	Reason for exclusion
Adenis *et al.*, 2000[71]	Phase II-III trial; stopped early
Andre *et al.*, 1999[92]	Phase II trial
Bajetta *et al.*, 2004[53]	Phase II trial
Becouarn *et al.*, 1999[70]	Phase II trial
Bouzid *et al.*, 2003[153]	Phase II trial; (A) Ir + Saltz regimen; (B) Ir + Douillard regimen; (C) Ir + Mayo regimen
Cheeseman *et al.*, 2002[154]	Phase II trial
Comba *et al.*, 1999[80]	Phase II trial; first-line monotherapy; (A) first-line Ox alone; (B) Oxa + 5-FU/FA
de Gramont *et al.*, 2004[81]	Comparison of the different regimens; (A) FOLFOX4; (B) FOLFOX7
Giacchetti *et al.*, 2004[82]	(A) FOLFOX; (B) FFL4-10 (chronomodulated)
Graeven and Schmiegel, 2000[155]	Phase II trial
Hurwitz *et al.*, 2004[54]	(A) Ir + 5-FU/FA + placebo; (B) Ir + 5-FU/FA + bevacizumab
Kalofonos *et al.*, 2003[156]	Phase II trial
Levi *et al.*, 1994[83]	(A) Chronomodulated Ox + 5-FU/FA; (B) Ox + 5-FU/FA
Levi, 1997[30]	(A) Chronomodulated Ox + 5-FU/FA; (B) Ox + 5-FU/FA
Maiello *et al.*, 2000[157]	Phase II trial
Pozzo *et al.*, 1999[158]	Phase II trial
Recchia *et al.*, 2000[159]	Phase II trial
Rougier *et al.*,1999[160]	No survival data
Rougier *et al.*, 2002[72]	Phase II trial
Ulrich-Pur *et al.*, 1999[161]	Phase II trial

Appendix 6

Validity assessment

TABLE 74 *Validity assessment summary*

	Cocconi *et al.*, 1998[96]	Comella *et al.*, 2003[59]	Cunningham *et al.*, 1996[94]	Cunningham and Glimelius, 1999[69]	de Gramont *et al.*, 2000[77]	Douillard *et al.*, 2000[47]	Goldberg *et al.*, 2004[55]	Giacchetti *et al.*, 2000[78]	Grothey *et al.*, 2002[85]	Köhne *et al.*, 2003[48]	Maughan *et al.*, 2002[95]	Pazdur and Vincent, 1997[97]	Rothenberg *et al.*, 2003[91]	Rougier *et al.*, 1998[68]	Saltz *et al.*, 2000[49]	Tournigand *et al.*, 2004[51]
Was the method used to assign participants to the treatment groups really random?	Y	U	U	N	U	Y	U	Y	U	U	U	U	U	U	U	U
What method of assignment was used?	CG	U	U	N	U	CG	U	Y	U	U	U	U	U	U	U	U
Was the allocation of treatment concealed?	U	U	U	U	U	Y	U	Y	U	U	Y	U	U	U	U	U
What method was used to conceal treatment allocation?	U	U	U	U	U	CR	U	Y	Y	U	CR	U	U	U	U	U
Was the number of participants who were randomised stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y
Were details of baseline comparability presented?	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	U	U	Y	Y	Y
Was baseline comparability achieved?	N	U	Y	N	Y	U	Y	N	N	U	U	U	U	N	Y	N
Were the eligibility criteria for study entry specified?	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	U	U	Y	Y	Y
Were any co-interventions identified that may influence the outcomes for each group?	Y	Y	Y	N	Y	Y	Y	Y	U	Y	Y	U	U	Y	Y	Y
Were the outcome assessors blinded to the treatment allocations?	N	U	U	N	U	U	U	U	U	U	U	U	U	U	N	U
Were the individuals who administered the intervention blinded to the treatment allocation?	N	U	U	N	U	U	U	U	U	U	U	U	U	U	N	U
Were the participants who received the intervention blinded to the treatment allocation?	N	U	U	N	U	U	U	U	U	U	U	U	U	U	N	U
Was the success of the blinding procedure assessed?	N	U	U	N	U	U	U	U	U	U	U	U	U	U	N	U
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	N	U	U	Y	Y	Y
Were the reasons for withdrawal stated?	N	Y	Y	U	Y	Y	Y	Y	N	N	Y	U	U	Y	Y	Y
Was an intention-to-treat analysis included?	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	U	U	N	Y	Y

Y, yes; N, no; U, unclear; CG, computer-generated; CR, central randomisation.

Appendix 7

Meta-analyses: source data

TABLE 75 *Source data for meta-analyses*

Trial	Comparison	Outcome	Follow-up (months)	Parmar method	Observed events
Cocconi *et al.*, 1998[96]	Ral vs 5-FU	OS	17	3	Parmar method 10: 'effective number alive'
Cocconi *et al.*, 1998[96]	Ral vs 5-FU	PFS	17	3	Parmar method 10: 'effective number alive'
Comella *et al.*, 2004[50]	Ir + 5-FU vs Ox + 5-FU	OS	19	7	Reported in paper
Comella *et al.*, 2004[50]	Ir + 5-FU vs Ox + 5-FU	PFS	19	7	Reported in paper
Cunningham *et al.*, 1996[94] (Ral)	Ral vs 5-FU	OS	18	3	Parmar method 10: 'effective number alive'
Cunningham *et al.*, 1996[94] (Ral)	Ral vs 5-FU	PFS	18	3	Parmar method 10: 'effective number alive'
de Gramont *et al.*, 2000[77]	Ox + 5-FU vs 5-FU	OS	27.7	10	Parmar method 10: 'effective number alive'
de Gramont *et al.*, 2000[77]	Ox + 5-FU vs 5-FU	PFS	27.7	10	Parmar method 10: 'effective number alive'
Douillard *et al.*, 2000[47]	Ir + 5-FU vs 5-FU	OS	23	3	Parmar method 10: 'effective number alive'
Douillard *et al.*, 2000[47]	Ir + 5-FU vs 5-FU	PFS	23	3	Parmar method 10: 'effective number alive'
Goldberg *et al.*, 2004[55]	Ir + 5-FU vs Ox + 5-FU	OS	20.4	3	Parmar method 10: 'effective number alive'
Goldberg *et al.*, 2004[55]	Ir + 5-FU vs Ox + 5-FU	PFS	20.4	3	Parmar method 10: 'effective number alive'
Giacchetti *et al.*, 2000[78]	Ox + 5-FU vs 5-FU	OS	47	10	Parmar method 10: 'effective number alive'
Giacchetti *et al.*, 2000[78]	Ox + 5-FU vs 5-FU	OS	47	10	Parmar method 10: 'effective number alive'
Grothey *et al.*, 2002[85]	Ox + 5-FU vs 5-FU	OS	27.3	10	Parmar method 10: 'effective number alive'
Grothey *et al.*, 2002[85]	Ox + 5-FU vs 5-FU	PFS	27.3	10	Parmar method 10: 'effective number alive'
Köhne *et al.*, 2003[48]	Ir + 5-FU vs 5-FU	OS	36	2	Parmar method 10: 'effective number alive'
Köhne *et al.*, 2003[48]	Ir + 5-FU vs 5-FU	PFS	36	2	Parmar method 10: 'effective number alive'
Maughan *et al.*, 2002[95]	Ral. vs 5-FU	OS	17	3	Parmar method 10: 'effective number alive'
Maughan *et al.*, 2002[95]	Ral. vs 5-FU	PFS	17	3	Parmar method 10: 'effective number alive'
Rothenberg *et al.*, 2003[91]	Ox + 5-FU vs 5-FU	OS	20	3	Parmar method 10: 'effective number alive'
Rothenberg *et al.*, 2003[91]	Ox + 5-FU vs 5-FU	PFS	10	2	Parmar method 10: 'effective number alive'
Saltz *et al.*, 2000[49]	Ir + 5-FU vs 5-FU	OS	42	3	Parmar method 10: 'effective number alive'
Saltz *et al.*, 2000[49]	Ir + 5-FU vs 5-FU	PFS	42	3	Parmar method 10: 'effective number alive'
Seymour, 2004[42]	Ir + 5-FU vs 5-FU	OS	36	3	Reported in paper
Seymour, 2004[42]	Ir + 5-FU vs 5-FU	PFS	36	3	Reported in paper
Seymour, 2004[42] [1]	Ir + 5-FU vs Ox + 5-FU	OS	36	3	Reported in paper
Seymour, 2004[42][1]	Ir + 5-FU vs Ox + 5-FU	PFS	36	3	Reported in paper
Seymour, 2004[42] [2]	Ox + 5-FU vs 5-FU	OS	36	3	Reported in paper
Seymour, 2004[42] [2]	Ox + 5-FU vs 5-FU	PFS	36	3	Reported in paper
Tournigand *et al.*, 2004[51]	Ir + 5-FU vs Ox + 5-FU	OS	43.9	10	Parmar method 10: 'effective number alive'
Tournigand *et al.*, 2004[51]	Ir + 5-FU vs Ox + 5-FU	PFS	43.9	10	Parmar method 10: 'effective number alive'

Appendix 8

Effectiveness data specific to older people

TABLE 76 *Single-arm studies: Ir in older patients*

Study	Regimen	Age (years)	Efficacy	Safety
Bollina *et al.*, 2001[162]	T1: Ir + Ox + 5-FU/FV (n = 21)	T1: median = 73	Among 21 patients in Phase II study, 14 were evaluable for response: CR (7%), PR (21%), MR (7%), SD (36%) and DP (29%). No significant toxicity was found	Dose-limiting toxicity was found at dose level II; two patients had grade 4 (WHO/NCI grading) neutropenia, four grade 3 neutropenia, one grade 3 diarrhoea and six grade 2 alopecia
Chau *et al.*, 2004[163]	T1: Ir + 5-FU/LV (n = 339) Patients were divided into two groups: Young: <70 years (n = 267) Elderly: ⩾70 years (n = 72)	T1: median = 62 (range 29–80)	Objective response rate was 9.4% (95% CI 6.3 to 12.6%). Median survival was 9.1 months and 1-year survival was 35.3% (95% CI 30.1 to 40.5%). No significant difference in survival between patients aged <70 years and ⩾70 years (p = 0.74)	Patients aged ⩾70 years had similar benefit and toxicity to Ir as younger patients. No support for recommendations to give a reduced starting dose to elderly patients
Comella *et al.*, 2003[164]	T1: Ir + 5-FU/LV (n = 118) Patients were divided into three groups: Younger: ⩽54 years (n = 37) Middle-aged: 55–69 years (n = 64) Elderly: ⩾70 years (n = 17)	Younger: median = 48 (range 28–54) Middle-aged: median = 64 (range 55–69) Elderly: median = 68 (range 65–79)	In terms of survival, Cox analysis was unrelated to the age of patients: median OS was 13.4 months (younger), 15.3 months (middle-aged) and 13.9 months (elderly). Overall response rate was comparable in all age groups: 38% (younger), 34% (middle-aged) and 35% (elderly)	Severe toxicity was not significantly different in elderly compared with other patients. Occurrence of severe diarrhoea was lower among elderly patients. Main severe haematological toxicity was neutropenia, 46 patients: grade ⩾3 neutropenia occurred in 43% (younger), 41% (middle-aged) and 31% (elderly). Among non-haematological effects, grade ⩾3 diarrhoea in 11% (younger), 18% (middle-aged) and 6% (elderly)
Marcuello *et al.*, 2000[65]	T1: Ir + 5-FU (n = 91)	T1: median = 77 (range 72–84)	85 patients: 3 CR, 27 PR, 28 SD and 15 DP, with tumour growth control in 68% of patients. Median follow-up of 10.9 months, OS was 15.1 months (95% CI 13.3 to 16.9). Overall, T1 is a feasible treatment for patients ⩾72 years old with metastatic CRC	For 85 patients, grade 3–4 toxicity per patient: neutropenia (21%), diarrhoea (17%), asthenia (13%), leucopenia (8%), abdominal pain (7%), vomiting (6%)
Stewart *et al.*, 2004[76]	T1: Ir (n = 339)	72 patients (21%) aged ⩾70	Patients aged ⩾70 had similar objective responses (11.1% vs 9%, p = 0.585) and survival (median 9.4 vs 9 months, p = 0.74) to younger patients	No significant difference in proportions of patients developing toxicity composite end-point by age <70 years (37.8%) compared to ⩾70 years (45.8%). Elderly patients had same benefit without experiencing more toxicity with second-line Ir treatment for ACRC

CR, complete responses; DP, disease progression; MR, minor response; PR, partial responses; SD, stable disease.

TABLE 77 *Single-arm studies: Ox in older patients*

Study	Regimen	Age (years)	Efficacy	Safety
Botto, 2004[87]	T1: Ox + 5-FU/LV (*n* = 14)	T1: median = 73 (range 70–83)	Time to DP (median 7 months; range 4–12 months) and overall survival (median 16 months; range 10–36 months). 2 weeks combination of T1, elderly patients >70 years with metastatic CRC had positive antitumoral response, acceptable toxicity and good survival time	Toxicity grade 2–3: diarrhoea 6/14, neutropenia 7/14, thrombocytopenia 4/14, paresthesia 4/14
Exquis *et al.*, 2004[86]	T1: Ox (*n* = 137)	T1: median = 62 (range 32–81) *Number of patients at each age:* ≤70 years = 104 (median = 58) >70 years = 33 (median = 75)	Age should not be a limiting factor for Ox-based chemotherapy	Oxaliplatin combined with 5-FU is safe and active in daily practice with elderly patients
Lopez-Gomez *et al.*, 2004[165]	T1: capecitabine + Ox (*n* = 32)	T1: median = 75 (range 70–82)	No data available	Grade 3–4 adverse events per patient (%): thrombocytopenia 10, fever 3, neutropenia 7, hand–foot syndrome 3, diarrhoea 3, paresthesia 3, asthenia 13, anorexia 3, nausea 13, abdominal pain 3, stomatitis 3
Rosati *et al.*, 2004[166]	T1: Ox + uracil-tegafur/FA (*n* = 46)	T1 (range 70–89)	Median OS and median time to progression were not concluded. Preliminary findings show chemotherapy combination is active and tolerated in elderly patients with ACRC	Grade 3 diarrhoea (13%) and neutropenia (2%). Most common grade 2 toxicities were thrombocytopenia (15%) nausea/vomiting (15%), and anaemia (11%). Of the evaluable patients, 20 (50%) had objective responses; 15 (37.5%) had SD and 5 (12.5%) had DP

TABLE 78 *Single-arm studies: Ral in older patients*

Study	Regimen	Age (years)	Efficacy	Safety
Cortinovis *et al.*, 2004[167]	T1: Ral + Ox (*n* = 51)	T1: median = 65 (range 43–78) Number of patients at each age: ≥65 years = 28 <65 years = 23	Number of patients: 2 CR, 12 PR, 23 SD, 8 DP	Most frequent metastatic sites were liver (18 cases), lung (10 cases), liver + lung (8 cases) and lymph nodes (3 cases). Common toxicities included: transaminitis (16 patients, grade 3–4), diarrhoea (6 patients, grade 3), nausea/vomiting (1 patient, grade 4) and asthenia (1 patient, grade 3). Adverse event profile was similar in the patients aged >65 years and <65 years
Facchini *et al.*, 2000[168]	T1: Ral (*n* = 51)	T1: median 75 (range 70–89)	Among the 35 patients evaluable for efficacy, 2 CR and 8 PR. The overall response rate was 29% and 13 patients (37%) experienced SD	Grade 3–4 adverse events included increase in transaminases (10 patients), nausea/vomiting (4 patients), anaemia (3 patients), diarrhoea (5 patients) and infectious disease (1 patient)
Franchi *et al.*, 2003[99]	T1: Ral (*n* = 13)	T1: (range 75–90)	Overall, 1 PR, 4 SD, and 2 DP were observed in seven patients with advanced CRC. Four out of six patients treated in the adjuvant setting for Dukes' C CRC remained disease free at observation periods of 15+ to 29+ months. Absence of toxicity in patients	Administration of reduced doses of Ral seems a putative therapy for elderly patients who, because of their age, are susceptible to adverse effects of chemotherapy
Mel *et al.*, 2000[98]	T1: Ral (*n* = 90)	Mean = 76 (range 70–86) *Number of patients at each age:* >75 years = 53 (59%) >80 years = 16 (17%)	Of 69 patients evaluable for efficacy 17 (25%) had PR (95% CI 15 to 36%), 37 (54%) had SD and 15 (22%) had DP. Overall benefit observed in 38% of patients (95% CI 27.6 to 49.2%)	Grade 3–4 toxicity: nausea/vomiting 6 (7%), diarrhoea 3 (3%), liver toxicity 5 (6%), neutropenia 3 (3%), anaemia 2 (2%). Risk group for nausea/vomiting and diarrhoea was female aged 70–75 years, and for liver toxicity male age >75 years
Paredes *et al.*, 1999[169]	T1: Ral (*n* = 116)	Mean = 76 (range 70–85)	In 45.8% of the patients there was a clinical improvement after the second cycle. After stopping therapy: 1 CR and 4 PR (objective response 25%) and 9 SD (45%)	Most frequent toxicities were diarrhoea (3%), asthenia (3%), nausea/vomiting (9%), liver toxicity (1%)
Romiti *et al.*, 2000[170]	T1: Ral (*n* = 45)	T1: median = 70	Low incidence of major toxicities using Ral in elderly CRC patients	Serious toxicities included: 2 (4%) grade 4 WHO diarrhoea, 1 (2%) grade 3 neutropenia, 1 (2%) grade 3 nausea/vomiting

Appendix 9

Data extraction: downstaging

TABLE 79 *Data on the effectiveness of Ir and Ox for downstaging*

Study	Study type	Regimen	No. of Patients	Response rate	No. (%) resected	No. (%) complete resection	OS	Disease-free survival/PFS
Adam *et al.*, 2001[41]	Prospective case series	700–1200 mg m^{-2} 5-FU, 300 mg m^{-2} FA and 25 mg m^{-2} Ox. Every course lasted to 4–5 days with intervals of 2–3 weeks between courses, (mean = 10) (Chronomodulated delivery)	701 consecutive, non-resectable patients were treated with neoadjuvant chemotherapy	NR. Complete pathological response in 6/701 patients (0.8%)	95/701 (13.6%) patients achieved measurable response to neoadjuvant treatment and underwent potentially curative resection	NR	5-year OS: 32/701 patients (4.6%)	19/701 (2.7%) had no evidence of disease (only 87 patients were followed up for 5 years)
de Gramont *et al.*, 2000[77]	Phase III trial	*Arm A* (5-FU): LV 200 mg m^{-2} per day as a 2-h infusion followed by bolus 5-FU 400 mg m^{-2} per day and a 22-h infusion of 5-FU 600 mg m^{-2} per day, repeated for 2 consecutive days every 2 weeks *Arm B* (Ox + 5-FU): same bimonthly regimen + Ox 85 mg m^{-2} on day 1 only, given as a 2-h infusion in 250 ml of dextrose 5%, concurrent with LV (de Gramont)	*Arm A* (5-FU): 210 *Arm B* (Ox + 5-FU): 210	NR	*Arm A*: seven patients (3.3%) *Arm B*: 14 patients (6.7%)	NR	NR	Median PFS: arm A = 6.2 months, arm B = 9.0 months
Ducreux *et al.*, 2002[104]	Phase II trial, single arm	Ir high-dose (260 mg m^{-2}) + 5-FU 600 mg m^{-2}/FA 200 mg m^{-2} + CI 600 mg m^{-2} on days 1 and 2 every 2 weeks	55: 49 were used in analysis, 42 were evaluable for response	53%	31% underwent surgery	NR	NR	NR

continued

TABLE 79 *Data on the effectiveness of Ir and Ox for downstaging (cont'd)*

Study	Study type	Regimen	No. of Patients	Response rate	No. (%) resected	No. (%) complete resection	OS	Disease-free survival/PFS
Giacchetti *et al.*, 1999[110]	Phase II trial, single arm	Ox + 5-FU 5 days every 3 weeks, 4 days every 2 weeks, (chronomodulated regimen)	151 patients with initially unresectable liver metastases	NR	77/151 (51%) of patients underwent surgery	NR	Median survival of 77 operated patients was 48 months with a 5-year OS rate of 50%. ITT figure (including the 74 non-operated patients): 39/151 (26%)	61/77 operated patients relapsed. Therefore, 5-year disease-free survival (ITT figure): 16/151 (11%)
Giacchetti *et al.*, 2000[78]	Phase III trial	*Arm A* (5-FU): 5-FU (chronomodulated, 5 days, 700 mg m^{-2} per day) + FA (300 mg m^{-2} per day) *Arm B* (Ox + 5-FU): Ox (125 mg m^{-2}) 6-h i.v. infusion; 5-FU (chronomodulated, 5 days, 700 mg m^{-2} per day) + FA (300 mg m^{-2} per day)	*Arm A* (5-FU/LV): 100 *Arm B* (Ox + 5-FU): 100	NR	*Arm A* (5-FU): 21 (21%) *Arm B* (Ox + 5-FU): 32 (32%)	*Arm A* (5-FU): 17 (17%) *Arm B* (Ox + 5-FU): 21 (21%)	NR	Median PFS: arm A = 6.1 months; arm B = 8.7 months
Ho *et al.*, 2003[105]	Phase II prospective trial, single arm	Ir 180 mg m^{-2}, FA 200 mg m^{-2}, 5-FU 400 mg m^{-2} bolus i.v. followed by continuous infusion of 5-FU 600 mg m^{-2} on days 1 and 2	46. Interim analysis based on 28 patients	55.5%	11% of patients underwent liver resection	NR	NR	NR
Piedbois, 2002[106]	Phase II trial, single arm	Ir150–180 mg m^{-2}/5-FU/FA administered every 2 weeks + HAI pirarubicin 60 mg m^{-2} on day 1 every 4 weeks	31	48%	Liver resection was made possible in 35% of patients	NR	OS 21.7 months	Median PFS 8.6 months

continued

***TABLE 79** Data on the effectiveness of Ir and Ox for downstaging (cont'd)*

Study	Study type	Regimen	No. of Patients	Response rate	No. (%) resected	No. (%) complete resection	OS	Disease-free survival/PFS
Pozzo *et al.*, 2004[108]	Prospective case series	Ir 80 mg m^{-2} i.v. on day 1, FA 200 mg m^{-2} i.v. on days 1 and 2, 5-FU 400 mg m^{-2} i.v. bolus on days 1 and 2, and 5-FU 1200 mg m^{-2} continuous 48-h i.v. infusion on day 1. The treatment was repeated every 2 weeks (de Gramont)	40	Response rate to chemotherapy was 47.5% (n = 19). SD was 27.5% (n = 11) and DP was 25.0% (n = 10). In relation to resection rate: 1 of 2 complete responses and 10 of 17 partial responses were not confirmed after 4 weeks due to surgical intervention	13 patients (32.5%) underwent potentially curative liver resection following chemotherapy	NR	NR	Median DFS in operated patients = 14.3 months
Slater *et al.*, 2003[109]	Case series	Ir 180 mg m^{-2} as a 30–90 minutes i.v. infusion on days 1 and 2 with 5-FU 200 mg m^{-2} per day	32	NR	Liver metastases were downstaged in 34%	NR	NR. Mean survival: no liver resection = 22.4 months; liver resection = 38.6 months	NR
Tournigand *et al.*, 2004[51]	Phase III RCT	*Arm A* (Ir + 5-FU): l-LV 200 mg m^{-2} or dl-LV 400 mg m^{-2} as a 2-h infusion, and Ir 180 mg m^{-2}, bolus FU 400 mg m^{-2} and a 46-h infusion FU 2400 mg m^{-2}, repeated every 2 weeks (de Gramont *Arm B* (Ox + 5-FU): same LV + FU regimen, Ox 100 mg m^{-2} on day 1, as a 2-h infusion (de Gramont)	226	Overall response rate for first line: Arm A 61 (56%); arm B 59 (54%) Overall response rate for second line: Arm A 12 (15%); arm B 3 (4%)	10 patients (9%) received surgical resection in arm A versus 24 patients (22%) in arm B (p = 0.02)	8 patients (7%) had a complete resection in arm A, and 14 (13%) in arm B (p = 0.26)	NR (2-year follow-up)	NR
Zelek *et al.*, 2003[107]	Non-randomised, multicentre, Phase II study, single arm	Ir 150 mg m^{-2} on days 1, 2 and 15, bolus 5-FU 400 mg m^{-2} FA 200 mg m^{-2} 2-h i.v. infusion followed by infusional 5-FU 600 mg m^{-2} over 22h, HAI pirarubicin 60 mg m^{-2}	31 patients with non-resectable liver metastases	48%	Liver resection was made possible in 11 patients	NR	NR Median OS = 20.5 months	Median PFS = 9.1 months

Appendix 10

Quality of life instruments

EORTC QLQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|

Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|

Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3.	Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4

<u>Please go on to the next page</u>

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EQ-5D quality of life instrument

Describing your own health today:

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

Self-Care

I have no problems with self-care ☐

I have some problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ☐

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

Anxiety/Depression

I am not anxious or depressed

I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

Appendix 11

Drummond checklist for assessing economic evaluations

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)?
   1.2 Did the study involve a comparison of alternatives?
   1.3 Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?

2. **Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often?**
   2.1 Were any important alternatives omitted?
   2.2 Was (Should) a *do-nothing* alternative (be) considered?

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?
   3.2 Was effectiveness established through an overview of clinical studies?
   3.3 Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?

4. **Were all the important and relevant costs and consequences for each alternative identified?**
   4.1 Was the range wide enough for the research question at hand?
   4.2 Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.)
   4.3 Were capital costs, as well as operating costs, included?

5. **Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life-years)?**
   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?

6. **Were costs and consequences valued credibly?**
   6.1 Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements.)
   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 or types 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?

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 to the additional effects, benefits, or utilities generated?

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 a 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)?

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?

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?

10.3 Did the study discuss the generaliseability of the results to other settings and patient/client groups?

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)?

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?

Appendix 12

Cost-effectiveness results using progression-free survival

This appendix reports the equivalent economic analysis presented within the main report using PFS as the measure of clinical benefit for comparison with existing economic evaluations of irinotecan and oxaliplatin. It should be noted that PFS is a surrogate outcome, and the generalisability and interpretation of the cost per progression-free LYG outcome are unclear.

Central estimates of cost-effectiveness: first- and second-line PFS periods

Table 80 reports central estimates of cost-effectiveness for first-line therapies in terms of marginal cost per progression-free LYG compared with FOCUS plan A.

Table 80 suggests that while mean PFS is fairly similar across all treatment arms, FOLFIRI and FOLFOX6 are considerably more expensive during the first-line treatment period. As a result, the marginal cost per progression-free LYG for these therapies is high; FOLFOX6 is estimated to cost £63,468 per progression-free LYG, while FOLFIRI is estimated to cost £95,653 per progression-free LYG. The two first-line combination therapies evaluated in the FOCUS trial, treatment plan C (IrMdG) and treatment plan E (OxMdG), resulted in slightly longer PFS with a greater mean cost per patient. The marginal cost per progression-free LYG for these therapies was estimated to be £45,408 for IrMdG and £40,002 for OxMdG.

Table 81 presents the central estimates of cost-effectiveness for the second-line PFS period. As Kaplan–Meier survival curves were not available for second-line therapies evaluated in the FOCUS trial,[5] only an economic comparison of second-line FOLFOX6 versus second-line FOLFIRI was possible.

The table suggests that second-line FOLFOX6 is associated with slightly greater costs and benefits

TABLE 80 *Central estimates of cost-effectiveness for first-line PFS period using estimated Weibull curves*

Treatment arm	Mean PFS (years)	Mean cost	Marginal cost vs FOCUS plan A (MdG + Ir)	Marginal progression-free LYG vs FOCUS plan A (MdG + Ir)	Marginal cost per progression-free LYG
FOCUS plan A (MdG+Ir)	0.67	£7,206.60	–	–	–
FOCUS plan C (IrMdG)	0.78	£12,211.48	£5,004.88	0.11	£45,407.92
FOCUS plan E (OxMdG)	0.79	£12,098.00	£4,891.40	0.12	£40,002.36
Tournigand FOLFIRI/FOLFOX6	0.75	£15,283.96	£8,077.35	0.08	£95,652.72
Tournigand FOLFOX6/FOLFIRI	0.85	£18,856.65	£11,650.05	0.18	£63,468.26

TABLE 81 *Central estimates of cost-effectiveness for second-line PFS period using estimated Weibull curves*

Treatment arm	Mean PFS (years)	Mean cost	Marginal costs vs FOLFOX/ FOLFIRI	Marginal progression-free LYG vs FOLFOX/ FOLFIRI	Marginal cost per progression-free LYG
Tournigand FOLFOX6/FOLFIRI	0.30	£8,693.81	–	–	–
Tournigand FOLFIRI/FOLFOX6	0.39	£10,168.97	£1,475.16	0.09	£16,553.16

***TABLE 82** Central estimates of cost-effectiveness for first-line PFS period using empirical Kaplan–Meier curves*

Treatment arm	Mean PFS (years)	Mean cost	Marginal cost vs FOCUS plan A (MdG + Ir)	Marginal progression-free LYG vs FOCUS plan A (MdG + Ir)	Marginal cost per progression-free LYG
FOCUS plan A (MdG+Ir)	0.68	£7,206.60	–	–	–
FOCUS plan C (IrMdG)	0.78	£12,211.48	£5,004.88	0.10	£47,982.25
FOCUS plan E (OxMdG)	0.78	£12,098.00	£4,891.40	0.10	£47,180.86
Tournigand FOLFIRI/FOLFOX6	0.77	£15,283.96	£8,077.35	0.10	£83,282.12
Tournigand FOLFOX6/FOLFIRI	0.87	£18,856.65	£11,650.05	0.19	£60,950.77

***TABLE 83** Central estimates of cost-effectiveness for second-line PFS period using empirical Kaplan–Meier curves*

Treatment arm	Mean PFS (years)	Mean cost	Marginal cost vs FOLFOX/ FOLFIRI	Marginal progression-free LYG vs FOLFOX/ FOLFIRI	Marginal cost per progression-free LYG
Tournigand FOLFOX6/FOLFIRI	0.30	£8,693.81	–	–	–
Tournigand FOLFIRI/FOLFOX6	0.42	£10,168.97	£1,475.16	0.12	£12,646.95

***TABLE 84** Central estimates of cost-effectiveness using optimistic cost assumptions: first-line PFS period*

Treatment arm	Mean PFS (years)	Mean cost	Marginal cost vs FOCUS plan A (MdG+Ir)	Marginal progression-free LYG vs FOCUS plan A (MdG + Ir)	Marginal cost per progression-free LYG
FOCUS plan A (MdG + Ir)	0.67	£5,169.80	–	–	–
FOCUS plan C (IrMdG)	0.78	£10,032.39	£4,862.59	0.11	£44,116.98
FOCUS plan E (OxMdG)	0.79	£9,994.73	£4,824.93	0.12	£39,458.73
Tournigand FOLFIRI/FOLFOX6	0.75	£12,554.05	£7,384.25	0.08	£87,444.89
Tournigand FOLFOX6/FOLFIRI	0.85	£15,840.20	£10,670.40	0.18	£58,131.22

compared with second-line FOLFIRI. The model estimates that second-line FOLFOX6 is associated with a cost of £16,553 per progression-free LYG compared with second-line FOLFIRI.

Scenario analysis: first- and second-line PFS periods

This section reports the results of the scenario analysis using PFS as the measure of clinical benefit. *Table 82* shows the cost-effectiveness results for the first-line PFS period, where effects were estimated as the area under the empirical PFS curves.

The table suggests that estimating mean PFS using AUC analysis has only a minor impact on the cost per progression-free LYG; all marginal cost-effectiveness ratios appear similar to those reported in the base-case analysis.

Table 83 shows the central estimates of cost-effectiveness for second-line therapies, where effects were estimated as the area under the second-line PFS curves.

As with the analysis of OS and first-line PFS, using empirical second-line PFS estimates has only a minor impact on the cost-effectiveness results. Using the empirical second-line PFS data observed in the Tournigand trial,[4] the model suggests that FOLFIRI/FOLFOX6 costs £12,647 per progression-free LYG.

Table 84 shows the impact of optimistic costing assumptions on the cost per progression-free LYG for first-line therapies.

As with the analysis of OS, the optimistic cost assumptions result in a minor improvement in marginal cost per progression-free LYG for all first-line therapies compared with FOCUS plan A.

TABLE 85 *Central estimates of cost-effectiveness using optimistic cost assumptions: second-line PFS period*

Treatment arm	Mean PFS (years)	Mean cost	Marginal cost vs FOLFOX/ FOLFIRI	Marginal progression-free LYG vs FOLFOX/ FOLFIRI	Marginal cost per progression-free LYG
Tournigand FOLFOX6/FOLFIRI	0.30	£7,169.52	–	–	–
Tournigand FOLFIRI/FOLFOX6	0.39	£8,606.77	£1,437.26	0.09	£16,127.84

TABLE 86 *Central estimates of cost-effectiveness using pessimistic cost assumptions: first-line PFS period*

Treatment arm	Mean PFS (years)	Mean cost	Marginal cost vs FOCUS plan A (MdG + Ir)	Marginal progression-free LYG vs FOCUS plan A (MdG + Ir)	Marginal cost per progression-free LYG
FOCUS plan A (MdG + Ir)	0.67	£11,250.23	–	–	–
FOCUS plan C (IrMdG)	0.78	£16,578.81	£5,328.58	0.11	£48,344.80
FOCUS plan E (OxMdG)	0.79	£16,294.57	£5,044.34	0.12	£41,253.07
Tournigand FOLFIRI/FOLFOX6	0.75	£20,922.17	£9,671.94	0.08	£114,535.90
Tournigand FOLFOX6/FOLFIRI	0.85	£25,154.10	£13,903.87	0.18	£75,746.81

TABLE 87 *Central estimates of cost-effectiveness using pessimistic cost assumptions: second-line PFS period*

Treatment arm	Mean PFS (years)	Mean cost	Marginal cost vs FOLFOX/ FOLFIRI	Marginal progression-free LYG vs FOLFOX/ FOLFIRI	Marginal cost per progression-free LYG
Tournigand FOLFOX6/FOLFIRI	0.30	£12,200.64	–	–	–
Tournigand FOLFIRI/FOLFOX6	0.39	£13,763.00	£1,562.36	0.09	£17,531.65

Table 85 shows the impact of the optimistic cost assumptions on the marginal cost per progression-free LYG for second-line therapies.

The table shows that the use of optimistic cost assumptions within the model leads to a reduction in second-line treatment costs of around £1500 for both FOLFOX6 and FOLFIRI. This cost difference is almost identical for both second-line FOLFOX6 and second-line FOLFIRI: thus, the marginal cost per progression-free LYG remains around £16,000.

Table 86 shows the impact of assuming that all patients undergo chemotherapy on an inpatient basis on the marginal cost per progression-free LYG.

The impact of this assumption is clearer on the cost per progression-free LYG than on OS. In the FOCUS treatment arms, the mean cost of first-line treatment is increased by around £4000. As a result, the cost per progression-free LYG for first-line IrMdG and first-line OxMdG is increased to £48,345 and £41,253, respectively. The mean cost of FOLFOX6 and FOLFIRI is increased by around £6000: the cost per progression-free LYG for first-line FOLFOX6 and first-line FOLFIRI is increased to £75,747 and £114,536, respectively.

Table 87 shows the impact of assuming that all chemotherapy is undertaken on an inpatient basis on the marginal cost per progression-free LYG for second-line FOLFOX6 compared with second-line FOLFIRI.

The table shows that this assumption raises the mean cost of treatment in both arms by around £3500; thus, the marginal cost per progression-free LYG remains similar to the base-case analysis.

Uncertainty analysis: first and second-line PFS periods

Figure 17 shows the results of the stochastic analysis for the first-line progression-free period as a cost-effectiveness plane.

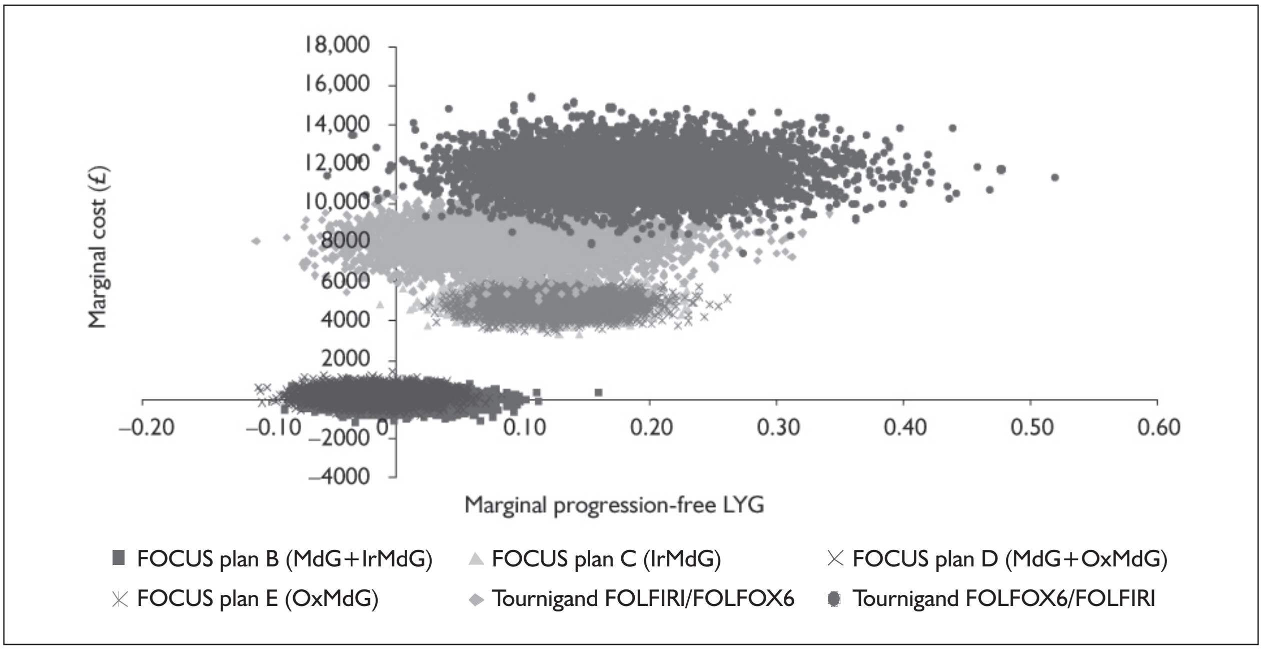

FIGURE 17 *Cost-effectiveness plane: first-line PFS*

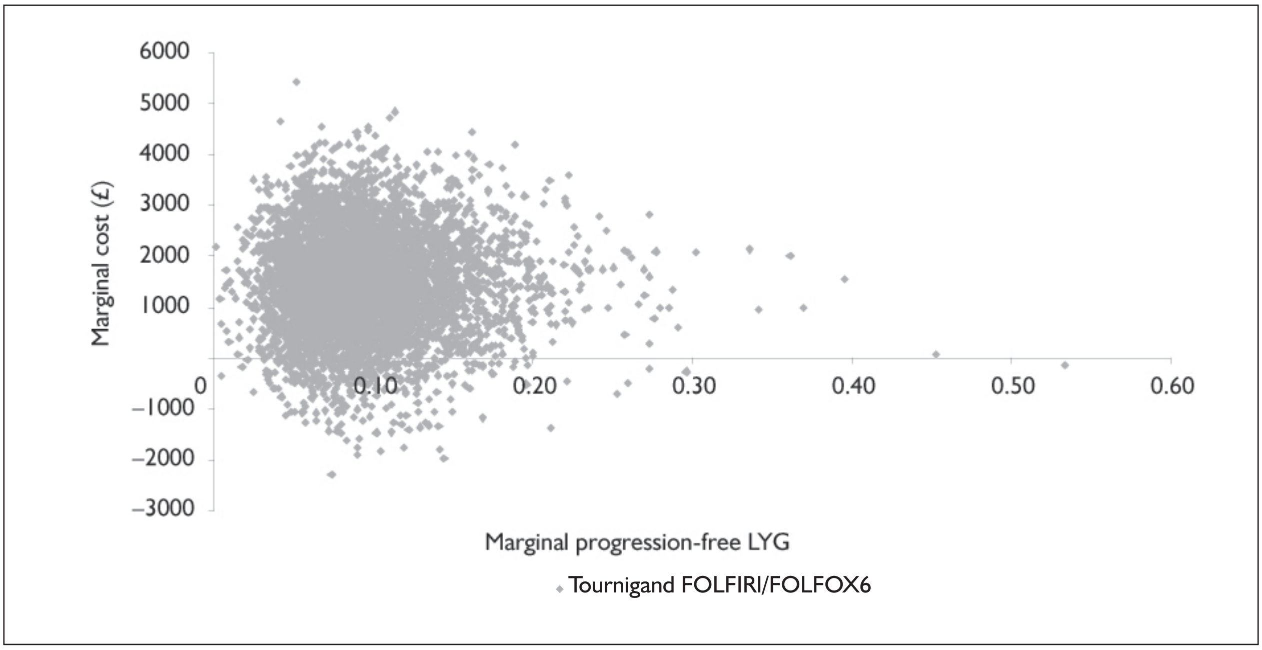

FIGURE 18 *Cost-effectiveness plane: second-line PFS period*

As one would expect, FOCUS treatment plans B and D, which both included 5-FU/FA as the planned first-line therapy in the sequence, are clustered around the origin of the plane. The plane also suggests that for the most part, offering combination therapy (oxaliplatin or irinotecan in combination with 5-FU/FA) as first-line therapy is expected to result in extended PFS, albeit at a greater cost.

Figure 18 shows the equivalent marginal costs and effects for FOLFIRI/FOLFOX6 compared with FOLFOX6/FOLFIRI.[4]

The figure suggests that offering FOLFOX6 as second-line therapy is expected to result in greater PFS than FOLFIRI, although the mean cost per patient is also expected to be greater.

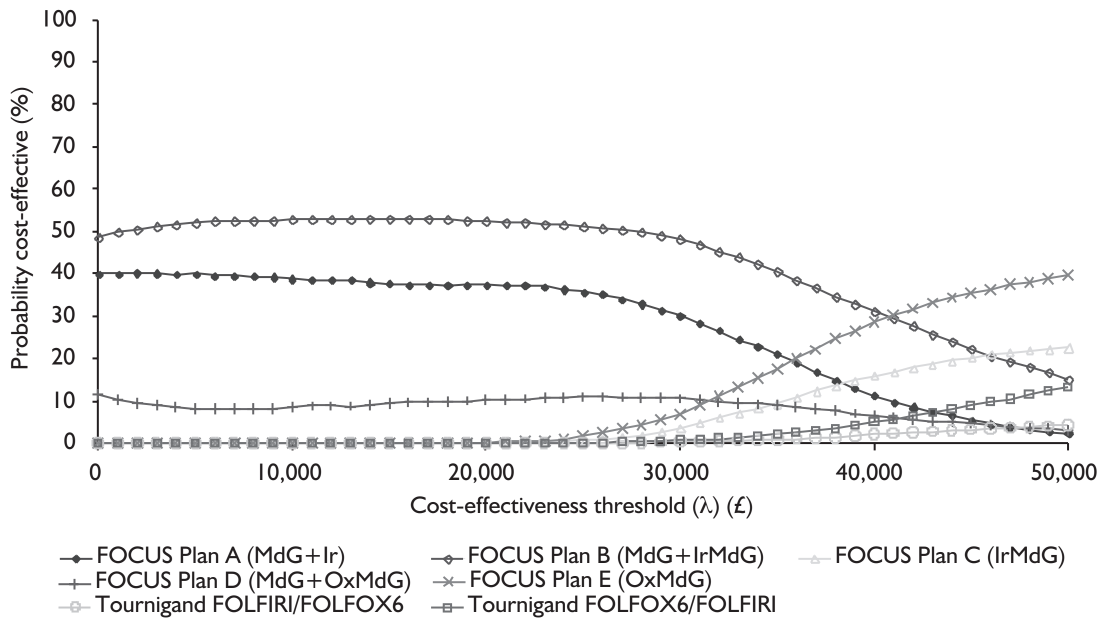

FIGURE 19 *Incremental CEACs: first-line PFS period*

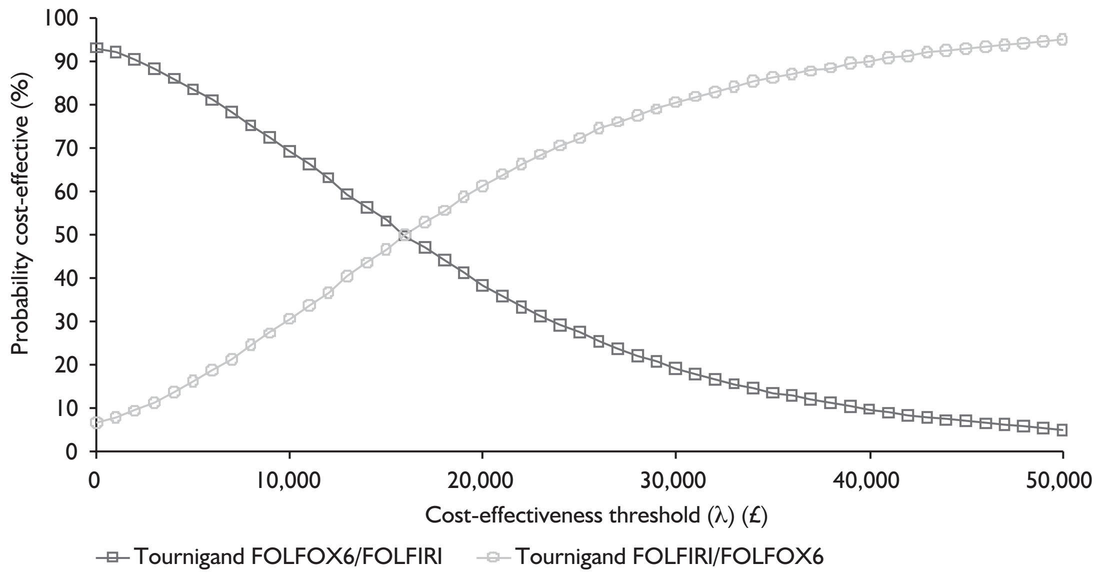

FIGURE 20 *Incremental CEACs: second-line PFS period*

Figure 19 shows the CEACs relating to the first-line PFS period. In this instance, net benefits are calculated as:

Net benefit = (λ × progression-free LYGs) – first-line therapy costs

Figure 19 suggests that if society is willing to pay up to £40,000 per progression-free LYG, offering 5-FU/FA alone is expected to result in the greatest net benefit. Beyond this willingness-to-pay threshold, 5-FU/FA in combination with oxaliplatin (FOCUS plan E) is expected to result in the greatest net benefit. It should be noted that the interpretation of CEACs where net benefit is based on PFS is difficult, as the likely range for a feasible cost-effectiveness threshold based on progression-free LYGs is unclear.

Figure 20 shows the CEACs relating to FOLFOX6 and FOLFIRI as given as second-line therapies. Again, for these CEACs, net benefit is estimated using progression-free LYGs.

The figure suggests that for cost-effectiveness thresholds of less than £16,000 per progression-free LYG, offering FOLFIRI is most likely to result in the greatest net benefit as second-line therapy. For thresholds greater than £16,000 per progression-free LYG, FOLFOX6 has a higher probability of resulting in the greatest net benefit. As with the CEACs for first-line therapies, the likely feasible range for the cost-effectiveness threshold based on PFS is unclear.

Discussion on cost per progression-free LYG results

The interpretation of economic results based on PFS is problematic. While the costs of first-line therapies can be directly attributed to the first-line PFS benefits observed in the FOCUS trial (i.e. these are not subject to underestimation due to the absence of salvage therapy costs or confounding due to treatment cross-overs following disease progression), the relationship between PFS and OS is unclear. Despite considerable differences in the mean duration of OS between the sequences evaluated by the Tournigand trial[4] and the FOCUS trial,[3] the mean duration that patients spent on first-line therapy appears to be fairly similar between the trials. While the two Tournigand sequences[4] appear economically attractive in terms of OS (see Chapter 3), these sequences appear considerably less attractive in terms of cost per first-line progression-free LYG. Consequently, it remains unclear as to how economic results based on PFS (within both this economic evaluation and previous evaluations) should be interpreted within a healthcare commissioning context.

Appendix 13

Empirical Kaplan–Meier and Weibull fitted curves

This appendix shows the results of the Weibull regression analysis used to extrapolate OS and PFS curves beyond the durations of the FOCUS[3] and Tournigand trials.[4]

Comparison of empirical Kaplan–Meier survival curves and Weibull regression analysis: OS period

Table 88 shows the results of the Weibull regression analysis using the empirical Kaplan–Meier OS curve for FOCUS treatment plan A (MdG + Ir).

Table 89 reports the log-rank hazard ratios applied to the baseline Weibull survivor function to estimate the survivor functions of FOCUS treatment plans B–E and the implied hazard ratios for the FOLFOX6/FOLFIRI and FOLFIRI/FOLFOX6 sequences for the analysis of OS.

Figures 21–27 show the survival curves estimated by the Weibull regression analysis for each of the seven treatment sequences included in the economic analysis, compared with the empirical Kaplan–Meier survival curves.

Comparison of empirical Kaplan–Meier survival curves and Weibull regression analysis: first-line PFS period

Table 90 shows the results of the Weibull regression analysis using the empirical Kaplan–Meier first-line PFS curve for FOCUS treatment plan A (MdG + Ir).

Table 91 reports the log-rank hazard ratios applied to the baseline Weibull survivor function to estimate the survivor functions for FOCUS treatment plans B–E, and the implied hazard ratios for the FOLFOX6/FOLFIRI and FOLFIRI/FOLFOX6 treatment arms for the analysis of first-line PFS.

Figures 28–34 show the first-line PFS curves estimated by the Weibull regression analysis for each of the seven treatment arms included in the economic analysis, compared with the empirical Kaplan–Meier PFS curves.

TABLE 88 *Regression results from Weibull regression analysis on FOCUS plan A: OS analysis*

Multiple *R*	0.997901
R^2	0.995806
Adjusted R^2	0.995763
Standard error	0.089056
Observations	101
Weibull gamma	0.543551
Weibull lambda	1.443989

TABLE 90 *Regression results from Weibull regression analysis on FOCUS plan A: first-line PFS analysis*

Multiple *R*	0.969331
R^2	0.939602
Adjusted R^2	0.938673
SE	0.42925
Observations	67
Weibull gamma	1.634237
Weibull lambda	1.71538

TABLE 89 *Log-rank hazard ratios used in economic model: OS period*

Comparison	Mean HR	Estimated SE	Source
FOCUS plan B vs FOCUS plan A	0.92	0.08	G. Griffiths, ESMO data[5]
FOCUS plan C vs FOCUS plan A	0.86	0.08	G. Griffiths, ESMO data[5]
FOCUS plan D vs FOCUS plan A	0.91	0.08	G. Griffiths, ESMO data[5]
FOCUS plan E vs FOCUS plan A	0.96	0.08	G. Griffiths, ESMO data[5]
Tournigand FOLFIRI/FOLFOX6 vs FOCUS plan A	0.49	0.16	Model fitted against FOCUS plan A
Tournigand FOLFOX6/FOLFIRI vs FOCUS plan A	0.53	0.16	Model fitted against FOCUS plan A

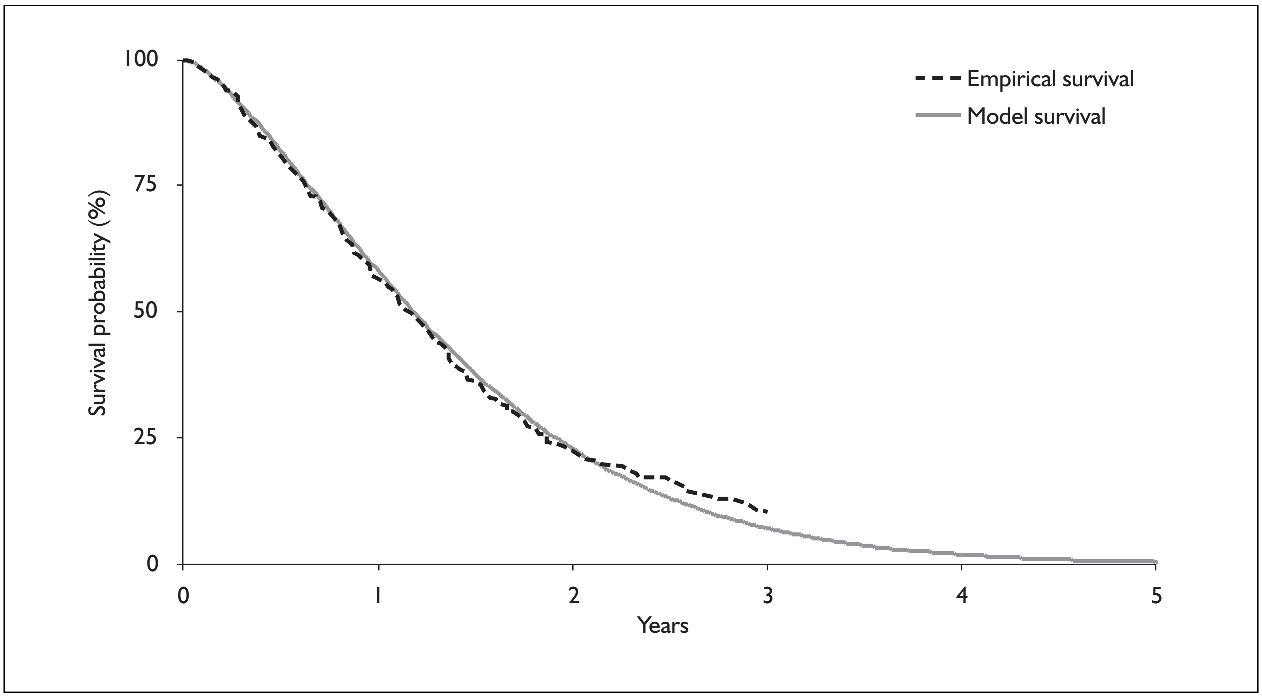

FIGURE 21 *Comparison of empirical Kaplan–Meier OS curve versus estimated Weibull survival curve: FOCUS plan A (MdG + Ir)*

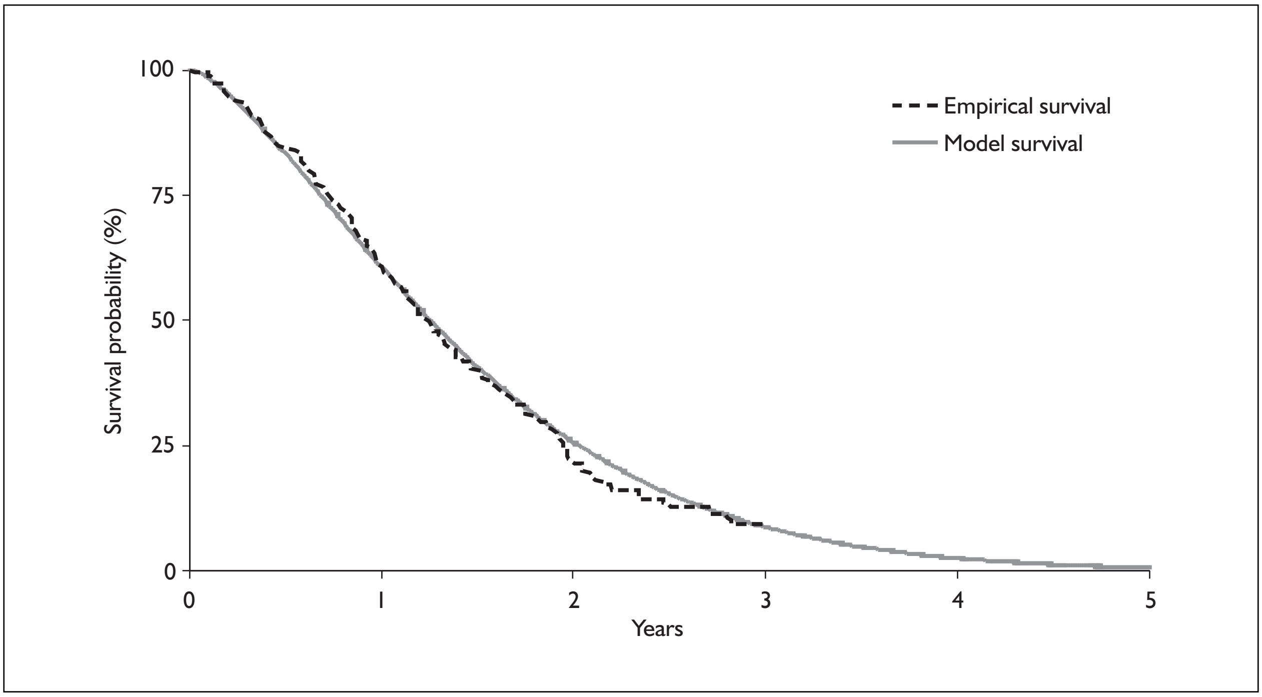

FIGURE 22 *Comparison of empirical Kaplan–Meier OS curve versus estimated Weibull survival curve: FOCUS plan B (MdG + IrMdG)*

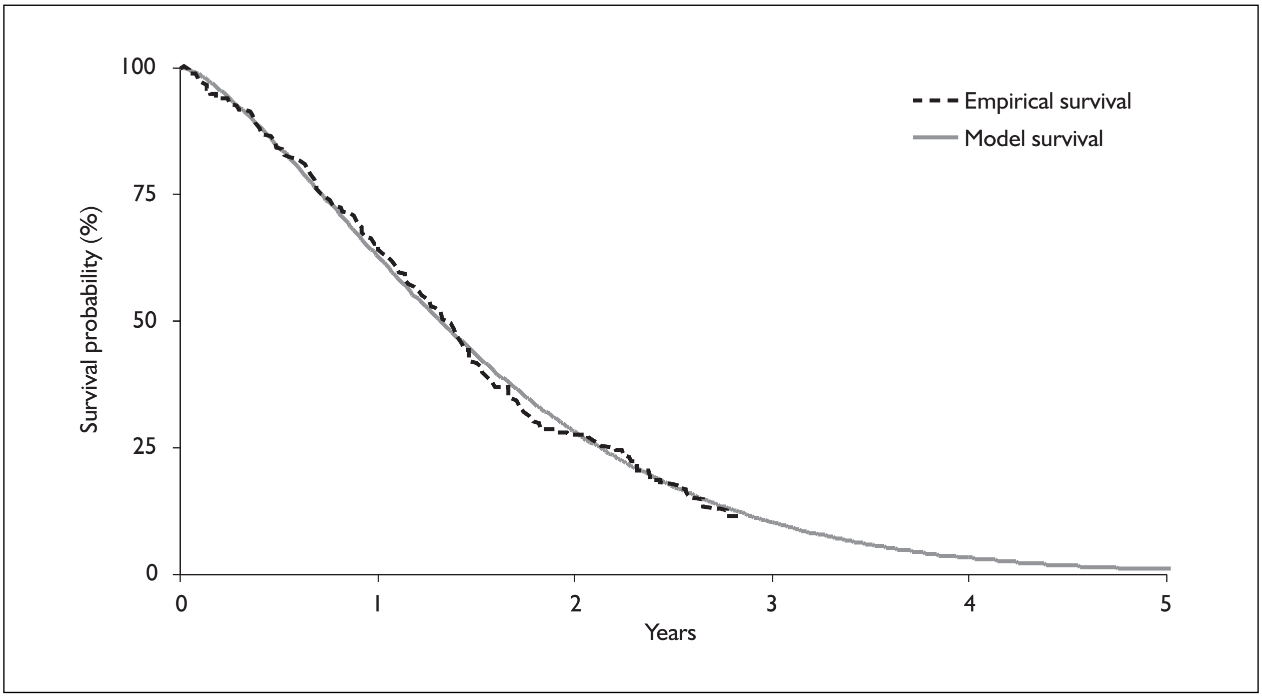

FIGURE 23 *Comparison of empirical Kaplan–Meier OS curve versus estimated Weibull survival curve: FOCUS plan C (IrMdG)*

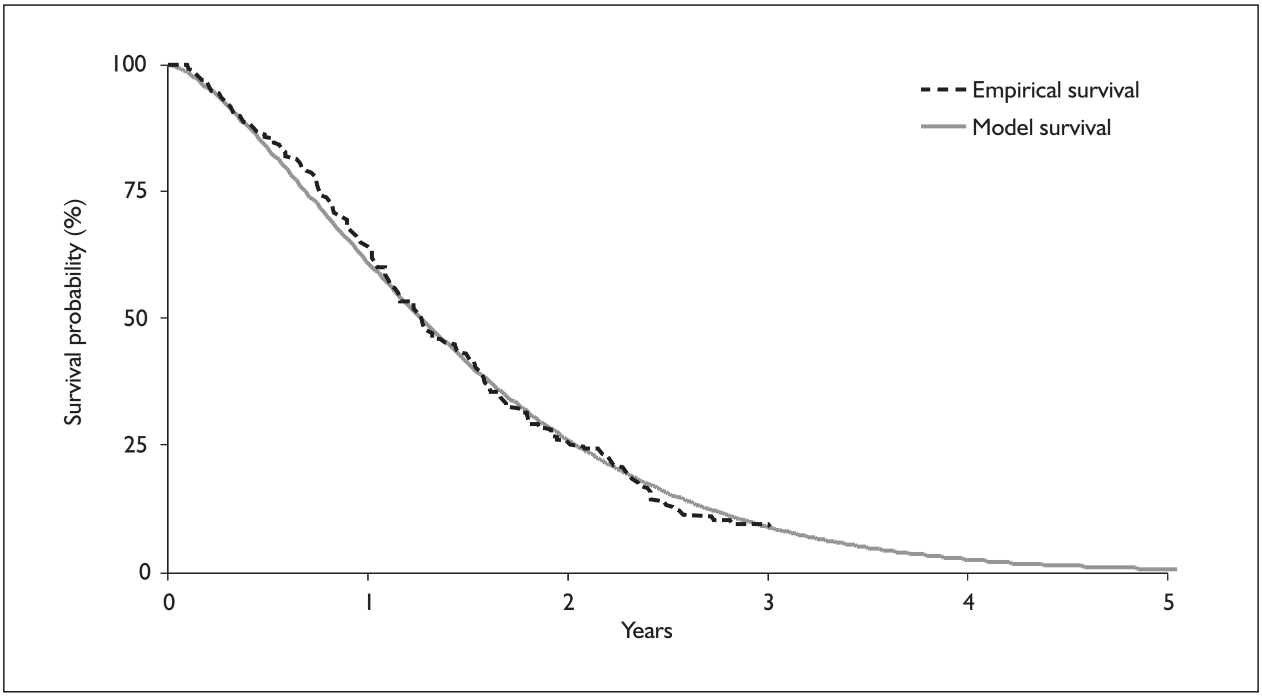

FIGURE 24 *Comparison of empirical Kaplan–Meier OS curve versus estimated Weibull survival curve: FOCUS plan D (MdG + OxMdG)*

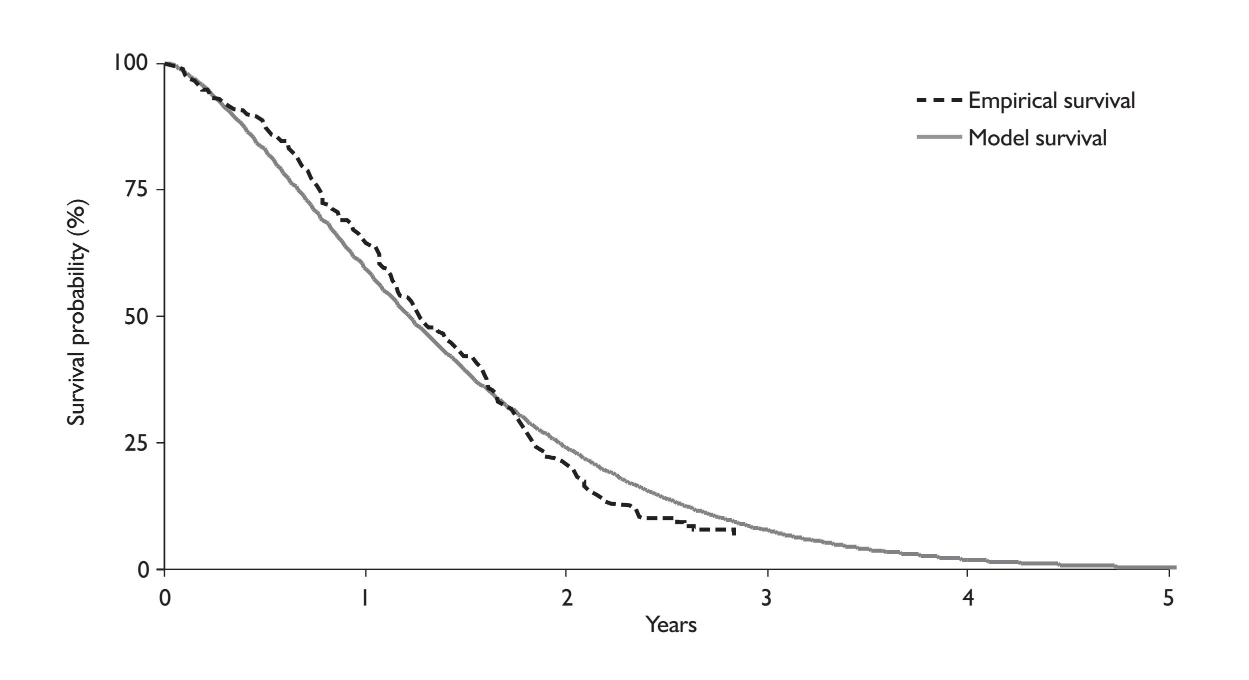

FIGURE 25 *Comparison of empirical Kaplan–Meier OS curve versus estimated Weibull survival curve: FOCUS plan E (OxMdG)*

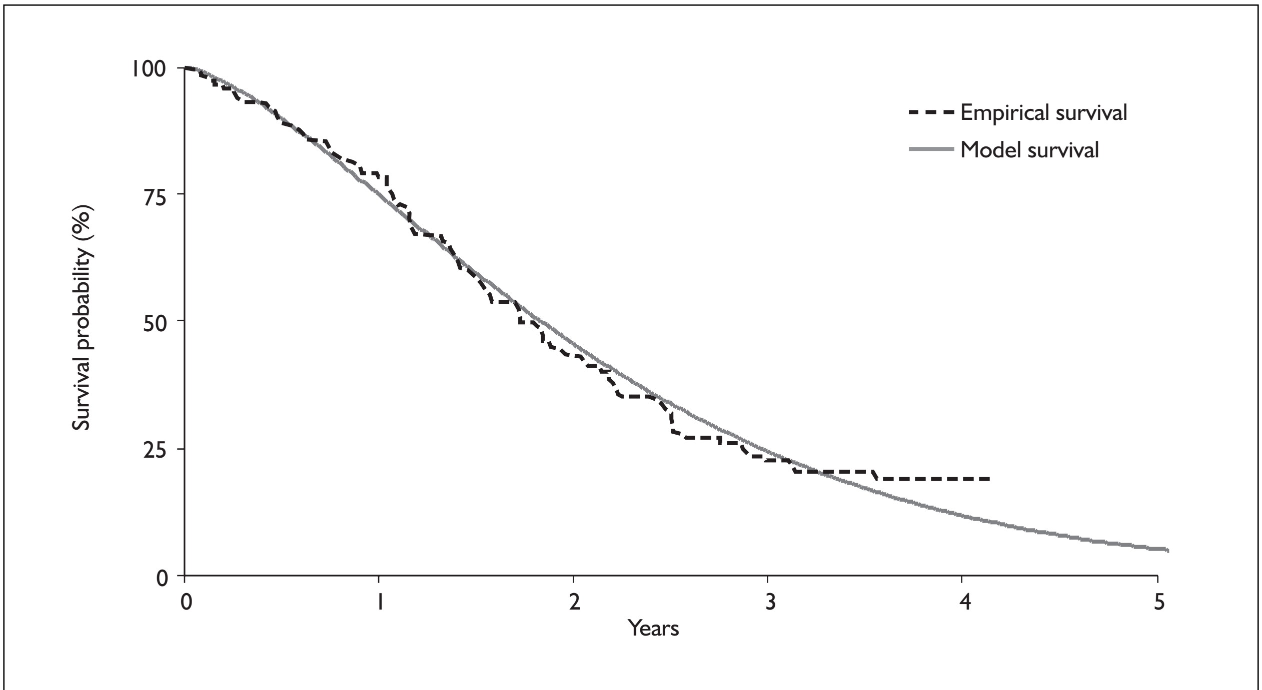

FIGURE 26 *Comparison of empirical Kaplan–Meier OS curve versus estimated Weibull survival curve: Tournigand FOLFOX6/FOLFIRI*

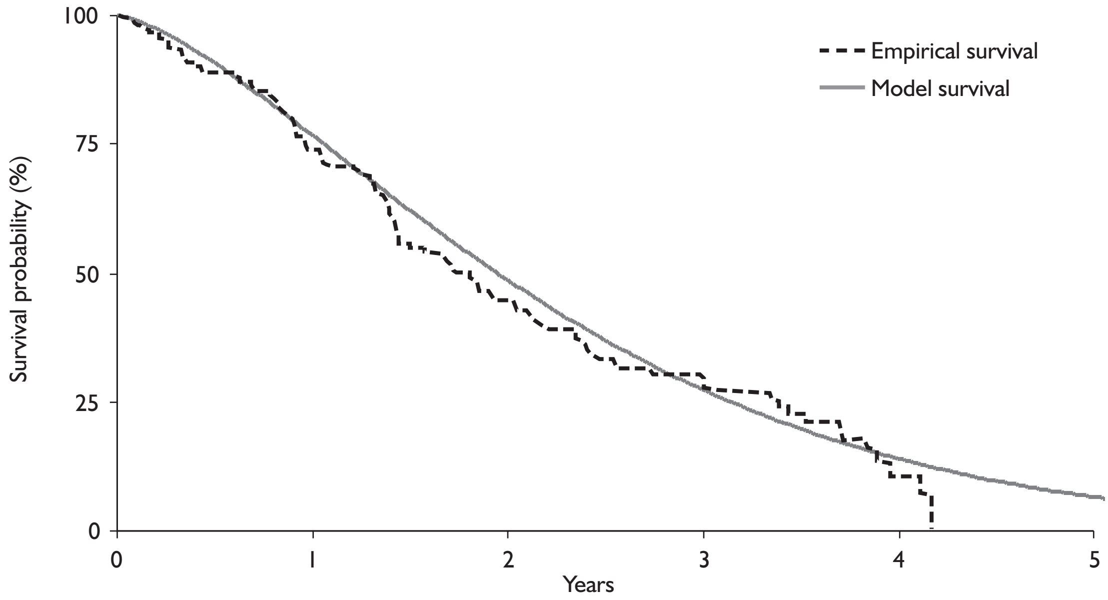

***FIGURE 27** Comparison of empirical Kaplan–Meier OS curve versus estimated Weibull survival curve: Tournigand FOLFIRI/FOLFOX6*

***TABLE 91** Log-rank hazard ratios used in economic model: first-line PFS period*

Comparison	Mean HR	Estimated SE	Source
FOCUS plan B vs FOCUS plan A	0.99	0.07	G. Griffiths ESMO data[5]
FOCUS plan C vs FOCUS plan A	0.77	0.07	G. Griffiths ESMO data[5]
FOCUS plan D vs FOCUS p A	1.05	0.07	G. Griffiths ESMO data[5]
FOCUS plan E vs FOCUS plan A	0.75	0.07	G. Griffiths ESMO data[5]
Tournigand FOLFIRI/FOLFOX6 vs FOCUS plan A	0.82	0.14	Model fitted against FOCUS plan A
Tournigand FOLFOX6/FOLFIRI vs FOCUS plan A	0.66	0.14	Model fitted against FOCUS plan A

Comparison of empirical Kaplan–Meier survival curves and Weibull regression analysis: second-line PFS analysis

Table 92 shows the results of the Weibull regression analysis using the empirical Kaplan–Meier second-line PFS curve for FOLFOX6/FOLFIRI.

Table 93 reports the log-rank hazard ratios applied to the baseline Weibull survivor function to estimate the survivor function for FOLFIRI/ FOLFOX6 for the analysis of second-line PFS.

Figures 35 and *36* show the survival curves estimated by the Weibull regression analysis for the two second-line chemotherapies evaluated within the Tournigand trial,[4] compared with the empirical Kaplan–Meier survival curves.

***TABLE 92** Regression results from Weibull regression analysis on FOLFOX6/FOLFIRI: second-line PFS*

Multiple *R*	0.957382
R^2	0.916581
Adjusted R^2	0.915511
Standard error	0.493431
Observations	80
Weibull gamma	8.514007
Weibull lambda	1.977021

TABLE 93 Log-rank hazard ratio used in economic model: second-line PFS period

Comparison	Mean HR	Estimated SE	Source
FOLFIRI/FOLFOX6 vs FOLFOX6/FOLFIRI	0.60	0.11	de Gramont A (Hôpital Saint-Antoine, Paris: personal communication)

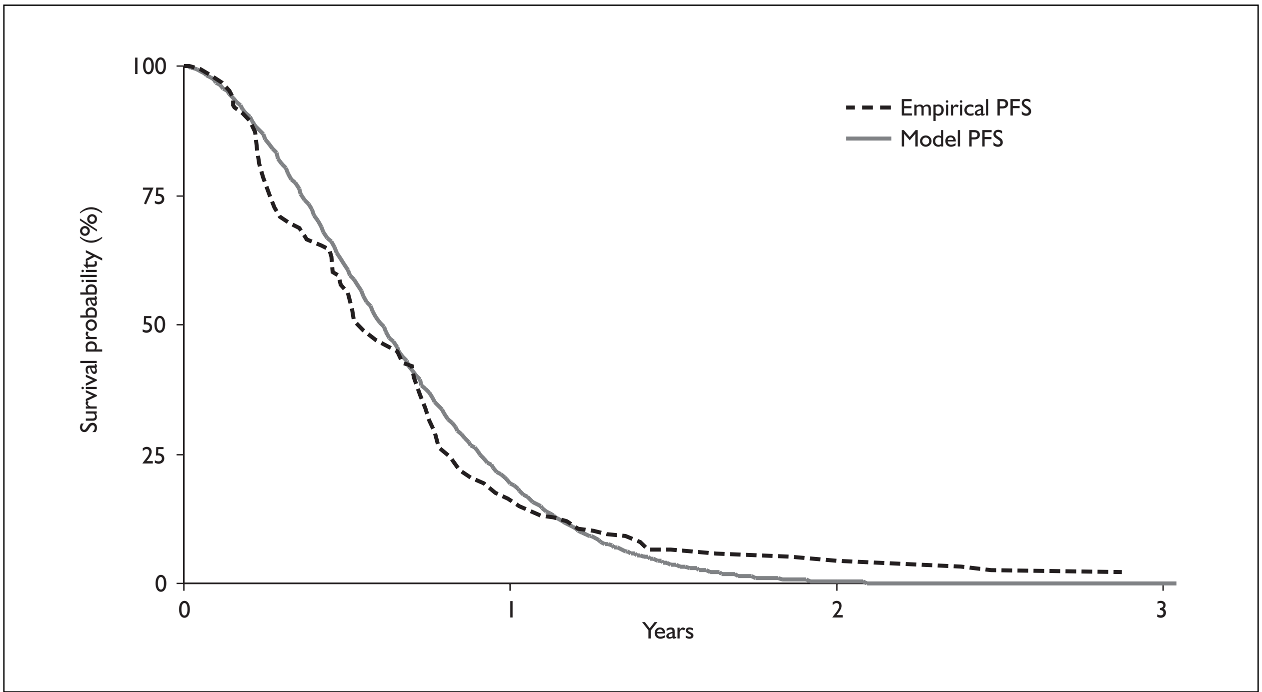

***FIGURE 28** Comparison of empirical Kaplan–Meier first-line PFS curve versus estimated Weibull survival curve: FOCUS plan A (MdG + Ir)*

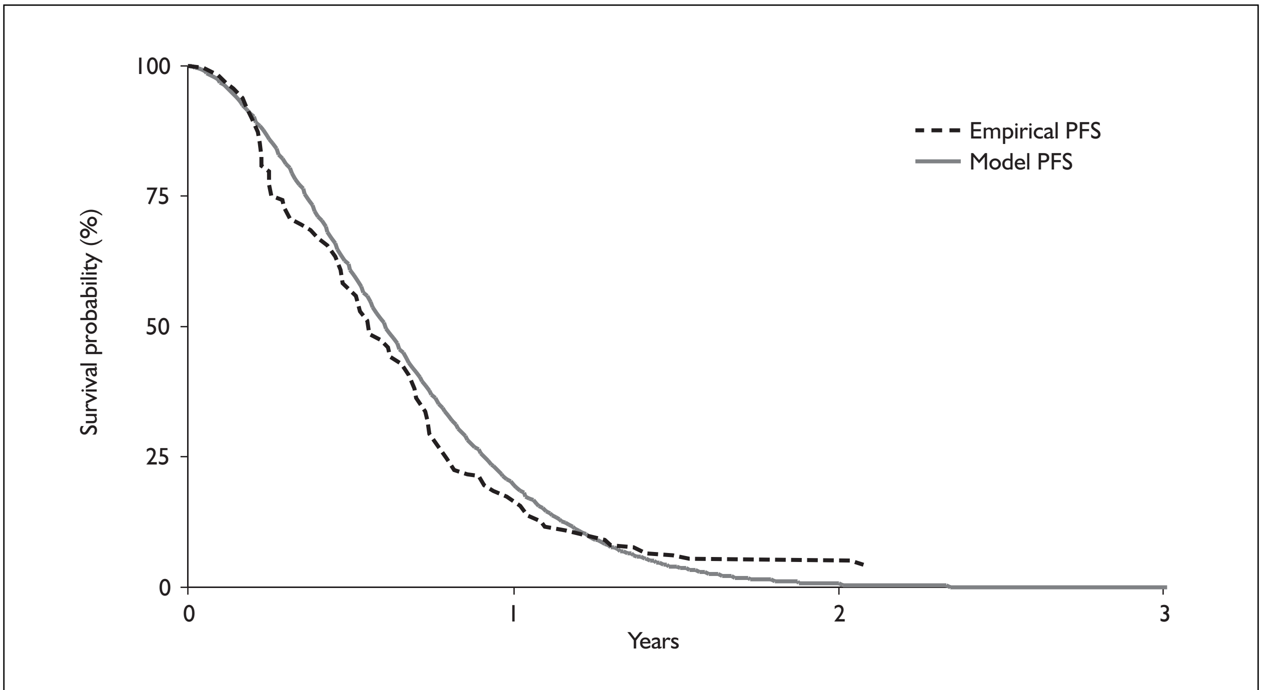

***FIGURE 29** Comparison of empirical Kaplan–Meier first-line PFS curve vs estimated Weibull survival curve: FOCUS plan B (MdG + IrMdG)*

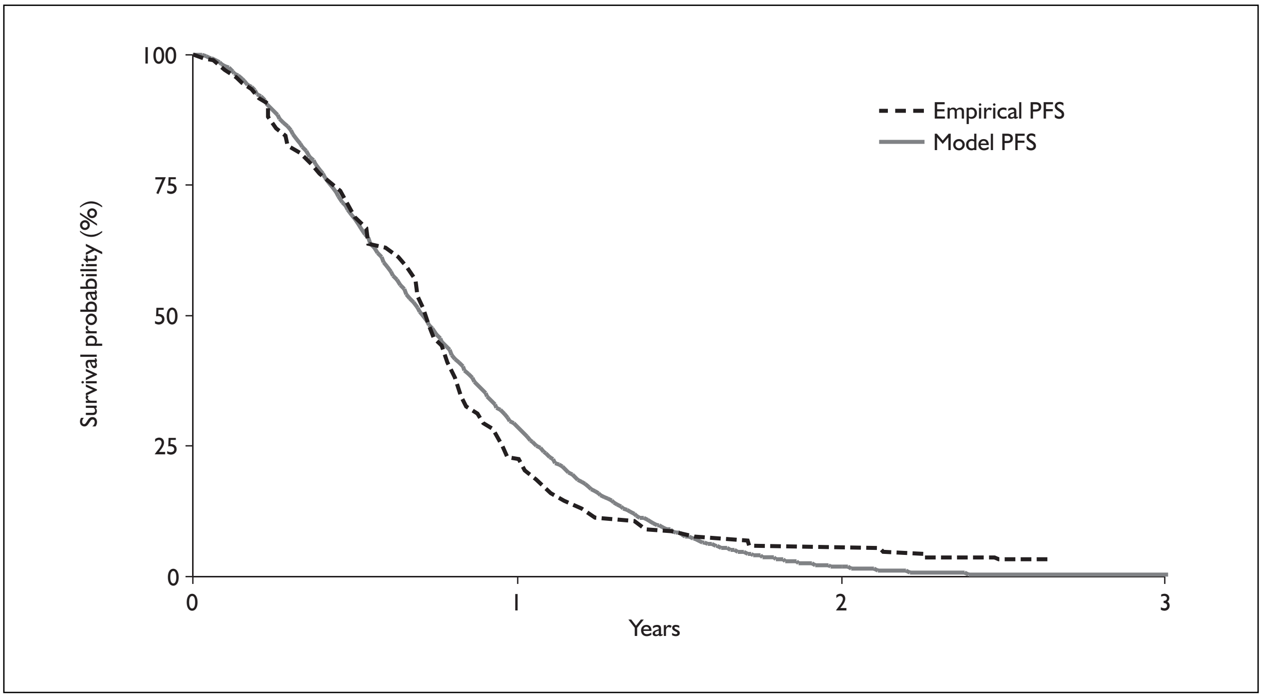

***FIGURE 30** Comparison of empirical Kaplan–Meier first-line PFS curve versus estimated Weibull survival curve: FOCUS plan C (IrMdG)*

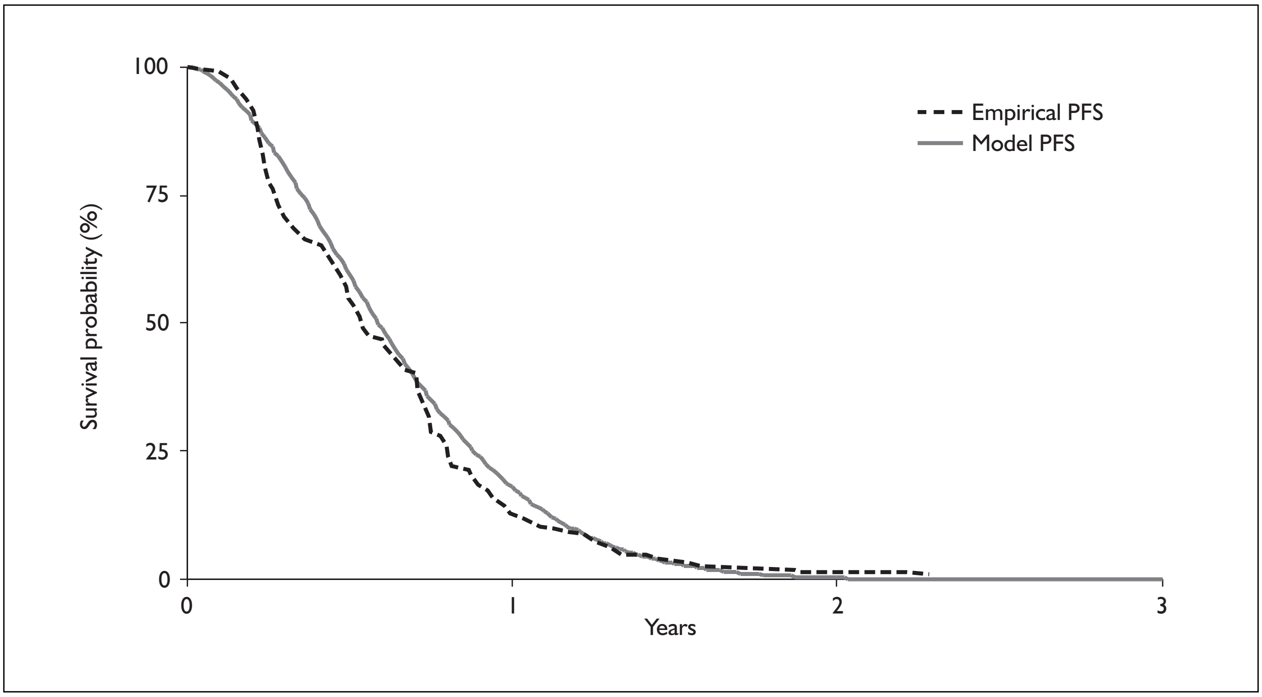

***FIGURE 31** Comparison of empirical Kaplan–Meier first-line PFS curve versus estimated Weibull survival curve: FOCUS plan D (MdG + OxMdG)*

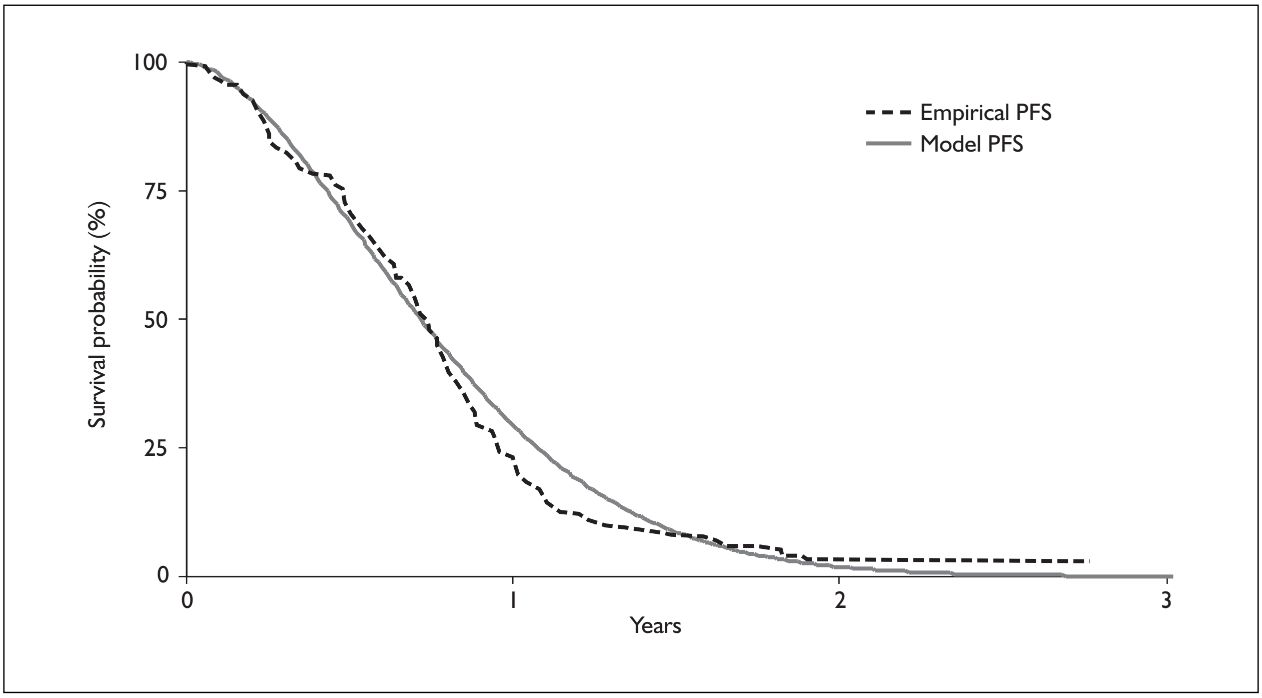

FIGURE 32 *Comparison of empirical Kaplan–Meier first-line PFS curve versus estimated Weibull survival curve: FOCUS plan E (OxMdG)*

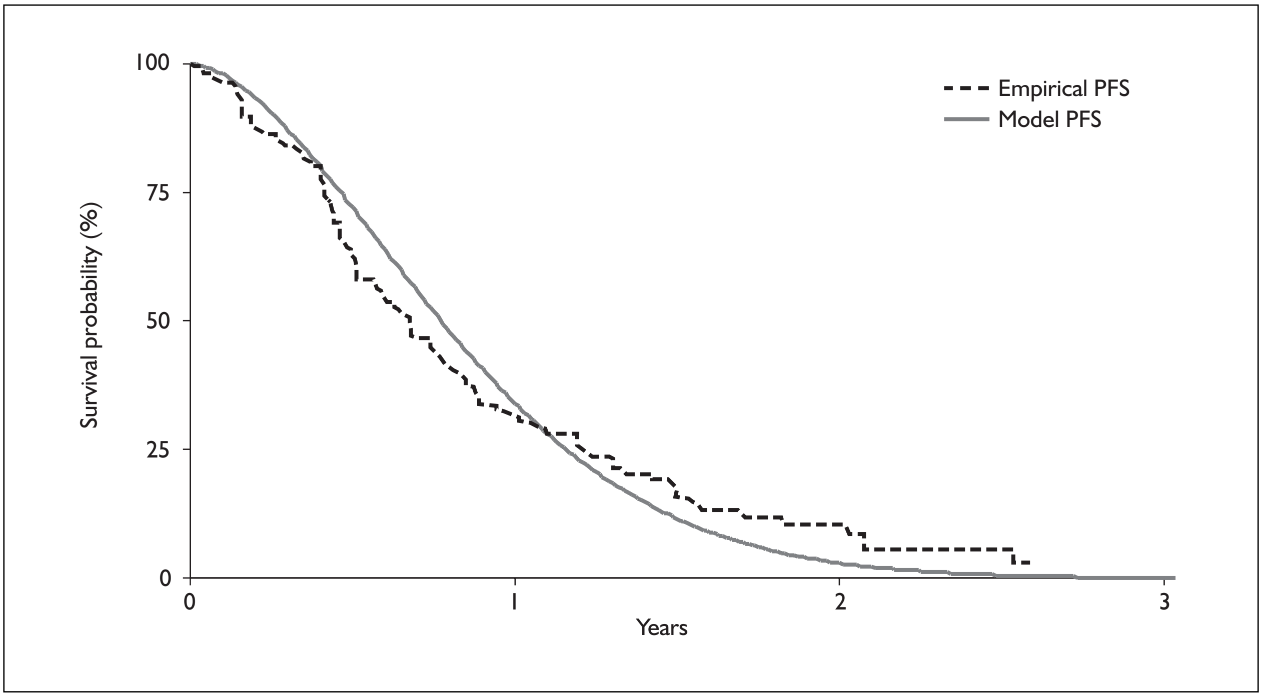

FIGURE 33 *Comparison of empirical Kaplan–Meier first-line PFS curve versus estimated Weibull survival curve: Tournigand FOLFOX6/FOLFIRI*

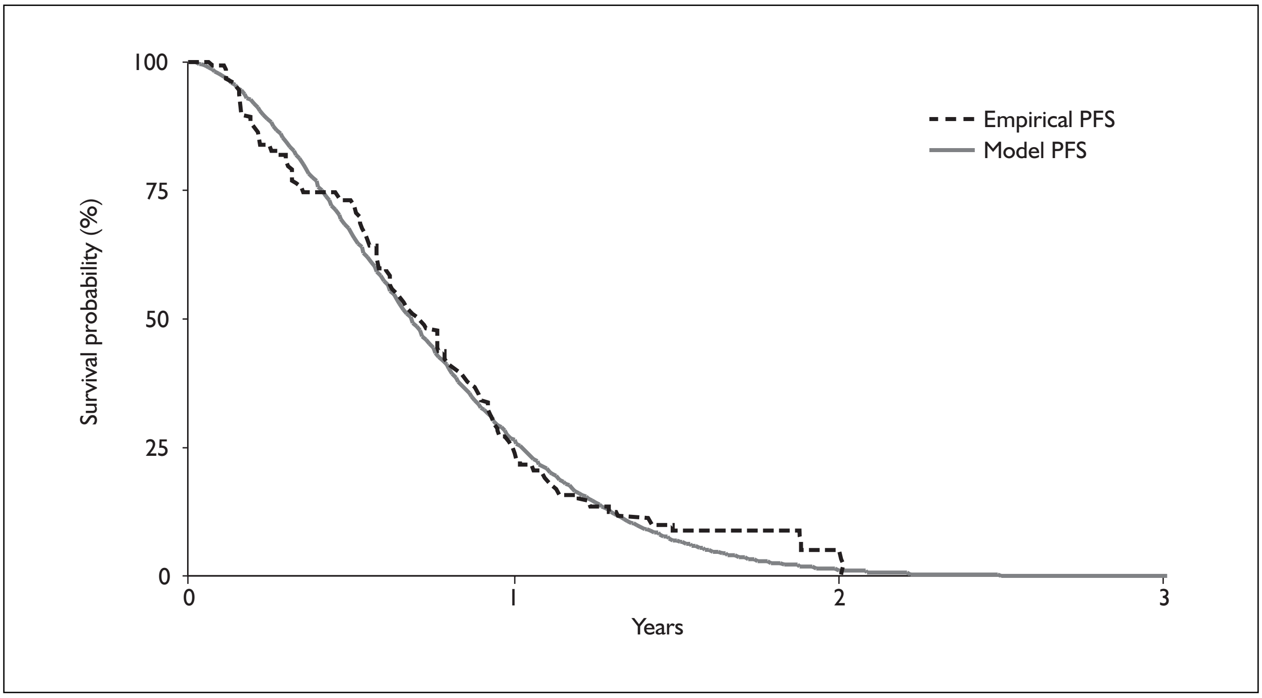

FIGURE 34 *Comparison of empirical Kaplan–Meier first-line PFS curve versus estimated Weibull survival curve: Tournigand FOLFIRI/FOLFOX6*

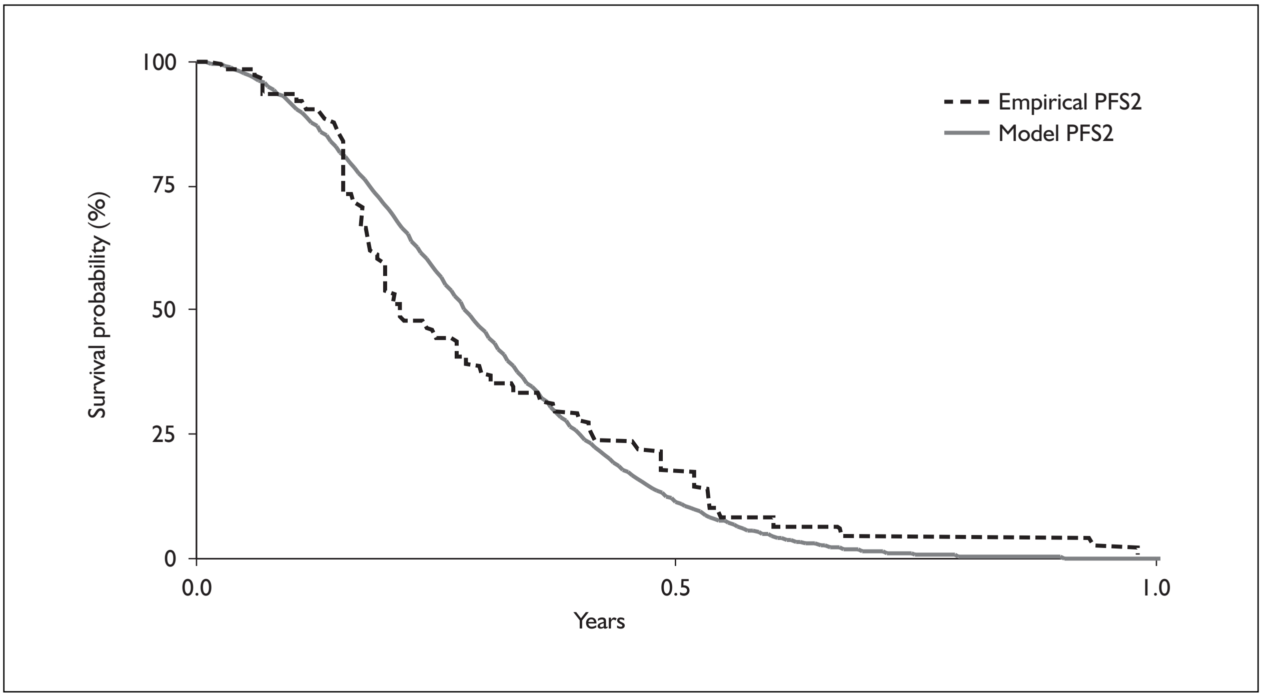

FIGURE 35 *Comparison of empirical Kaplan–Meier second-line PFS curve versus estimated Weibull survival curve: Tournigand FOLFOX6/FOLFIRI*

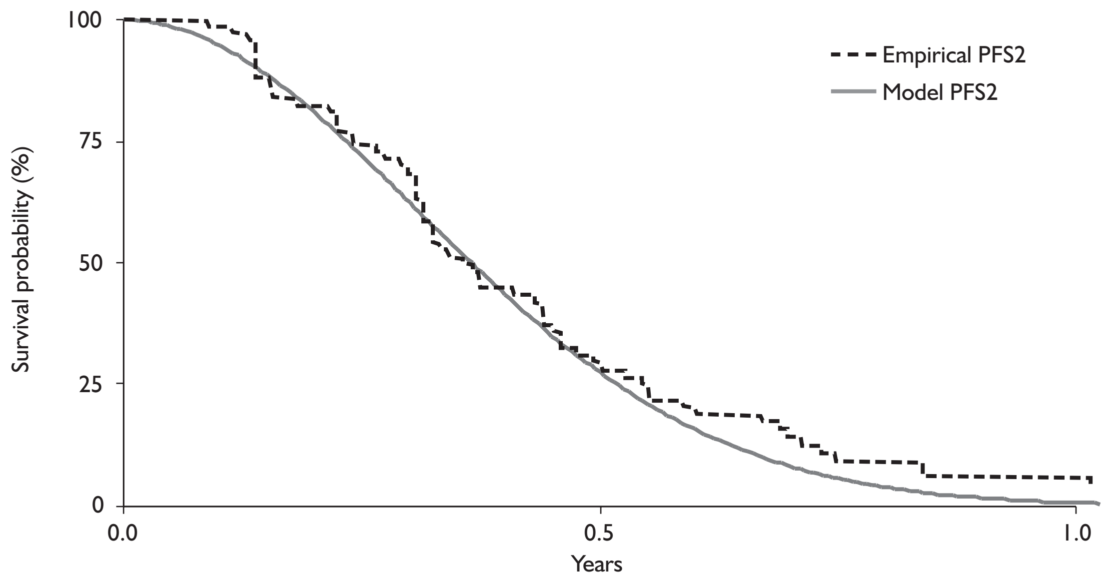

***FIGURE 36** Comparison of empirical Kaplan–Meier second-line PFS curve versus estimated Weibull survival curve: Tournigand FOLFIRI/FOLFOX6*

Discussion of Weibull regression results

Tables 88–93 and *Figures 21–36* show that a good fit was obtained from the Weibull regression analysis, particularly with respect to the OS curves. The assumption of proportional hazards between the Tournigand sequences and the FOCUS treatment plans appears to be reasonable; the implied relative hazards between the Tournigand treatment sequences provided a good fit using OS observed in the FOCUS plan A treatment group. The estimated Weibull curves for PFS were slightly less accurate; this is in part due to the uneven distribution of PFS over time. It should be noted that the apparently systematic 'bumps' in the PFS curves are likely to be a result of protocol-driven clinical assessments.

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The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.
By Hind D, Tappenden P, Tumur I, Eggington E, Sutcliffe P, Ryan A.

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The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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