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Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer

Review of Technology Appraisal 33

Technology Appraisal Guidance 93 Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer

Ordering information

You can download the following documents from www.nice.org.uk/TA093

- The full guidance for this technology appraisal (this document).
- A quick reference guide, which has been distributed to health professionals working in the NHS in England.
- Information for people with advanced colorectal cancer, their families and carers, and the public.
- The assessment report – details of all the studies that were looked at.

For printed copies of the quick reference guide or information for the public, phone the NHS Response Line on 0870 1555 455 and quote:

- N0906 (quick reference guide)
- N0907 (information for the public).

This guidance is written in the following context

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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NOTE: This guidance replaces Technology Appraisal Guidance No. 33 issued in March 2002.

The Institute reviews each piece of guidance it issues. The review and re-appraisal of the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer has resulted in a change in the guidance. Specifically there has been:

- a recommendation of the use of irinotecan in combination with 5-fluorouracil and folinic acid as first-line therapy, and irinotecan alone in subsequent therapy
- a recommendation of the use of oxaliplatin in combination with 5-fluorouracil and folinic acid as first-line therapy.

1 Guidance

1.1 Irinotecan and oxaliplatin, within their licensed indications, are recommended as treatment options for people with advanced colorectal cancer as follows:

- irinotecan in combination with 5-fluorouracil and folinic acid as first-line therapy, or irinotecan alone in subsequent therapy
- oxaliplatin in combination with 5-fluorouracil and folinic acid as first-line or subsequent therapy.

1.2 Raltitrexed is not recommended for the treatment of patients with advanced colorectal cancer. Its use for this patient group should be confined to appropriately designed clinical studies.

2 Clinical need and practice

2.1 Colorectal cancer is a malignant neoplasm in the large intestine and is the third most common cancer in the UK. Almost 30,000 new cases were registered in England and Wales in 2001, representing more than 12% of all

new cancer cases. The annual incidence of colorectal cancer increases with age, from 25 per 100,000 in people aged between 45 and 55, to more than 300 per 100,000 in those older than 75 years. About 30% of patients with colorectal cancer present with advanced disease, which is defined as either metastatic or locally invasive to the extent that surgical resection with curative intent is unlikely to be carried out.

- 2.2 The overall 5-year survival rate in England is 35% but there are large differences according to the stage of disease. The 5-year survival rate for advanced colorectal cancer is less than 5%. Without treatment, the approximate survival period after diagnosis of metastatic disease is 6–9 months.
- 2.3 About 70% of patients diagnosed with colorectal cancer undergo surgery. Many have an improved prognosis after surgery (with adjuvant chemotherapy in some cases), but about 30% of those who have undergone surgery with apparently complete excision will eventually develop advanced disease and distant metastases.
- 2.4 About half of people with advanced disease have liver metastases. For these patients, surgery potentially provides a long-term cure for hepatic metastases of colorectal cancer. Reported 5-year survival rates after resection of liver metastases range from 16 to 48%, and are considerably better than survival rates associated with systemic chemotherapy. However, postoperative complications are common and often serious: operative mortality rates range from 0 to 14%, although they are reported as being less than 5% in modern liver units.
- 2.5 Treatments for advanced colorectal cancer are mainly palliative and aim to increase both the duration and the quality of the patient's remaining life while controlling symptoms. For this reason, it is important to assess how treatment-related toxicity will affect the patient's quality of life.

2.6 The management of patients with advanced colorectal cancer usually involves a combination of specialist active treatments (palliative surgery, cytotoxic chemotherapy and radiation), symptom control and psychosocial support. Patients with advanced disease who are sufficiently fit can be treated with systemic chemotherapy as first- or second-line therapy, typically with an established regimen containing 5-fluorouracil (5-FU). 5-FU inhibits thymidylate synthase, a key enzyme involved in pyrimidine biosynthesis. It is usually given in combination with folinic acid (FA) to enhance thymidylate synthase inhibition by increasing the pool of intracellular folate. The 5-FU/FA combination is usually administered intravenously, but oral analogues of 5-FU (capecitabine and tegafur with uracil) are also used in the treatment of colorectal cancer. NICE guidance issued in May 2003 (*Technology Appraisal* No. 61) states:

‘Oral therapy with either capecitabine or tegafur with uracil (in combination with FA) is recommended as an option for the first-line treatment of metastatic colorectal cancer; the choice of regimen (intravenous 5-FU/FA or one of the oral therapies) should be made jointly by the individual and the clinician(s) responsible for treatment.’

2.7 About 60% of patients experience an improvement in their condition or a stabilisation of the disease after first-line 5-FU/FA therapy, but this is always temporary as patients eventually develop resistance to the drug. There is evidence from randomised controlled trials (RCTs) that early chemotherapy for advanced disease improves survival by 3–6 months compared with deferring chemotherapy until symptom relief is required. Compared with best supportive care, the early administration of 5-FU-based regimens on diagnosis of advanced disease increases median survival time from 5–9 months to between 7.5 and 14 months.

2.8 There are various intravenous 5-FU regimens requiring either infusion or bolus injections. Regimens requiring infusion are more complex and costly to administer and often require permanent vascular access technology and admission to hospital. However, they are reported to be superior to bolus

regimens in terms of progression-free survival periods, safety, toxicity and quality of life, but equally effective in terms of overall survival. The modified de Gramont infusion regimen is often used in the UK. This involves a 2-hour infusion of FA (175 mg levofolinate as calcium salt or 350 mg folinate as disodium or calcium salt) followed by a bolus injection of 400 mg/m² 5-FU and a continuous infusion of 2800 mg/m² 5-FU over 46 hours, and allows patients to be treated on an outpatient basis.

3 The technologies

Irinotecan

- 3.1 Irinotecan inhibits topoisomerase I, a DNA unwinding enzyme essential for cell division, resulting in inhibition of replication and breaks in single-strand DNA. In the UK, irinotecan is indicated for the treatment of patients with advanced colorectal cancer in combination with 5-FU/FA in patients without prior chemotherapy for advanced disease, and as a single agent in patients who have failed an established 5-FU-containing treatment regimen. It is associated with acute cholinergic symptoms, severe late-onset diarrhoea, myelosuppression and alopecia. Contraindications for irinotecan include chronic inflammatory bowel disease and bowel obstruction, bilirubin more than three times the upper limit of the normal range, WHO performance status more than 2, and severe bone marrow failure.
- 3.2 The recommended dose for first-line combination therapy with irinotecan is 180 mg/m² given once every 2 weeks as an intravenous infusion, administered over 30–90 minutes and followed by an infusion of 5-FU/FA. For second-line monotherapy, the recommended dose is 350 mg/m² given every 3 weeks, administered over 30–90 minutes. For full details of side effects and contraindications, see the Summary of Product Characteristics.
- 3.3 Vials containing 40 mg/2 ml and 100 mg/5 ml cost £53 and £130 respectively (excluding VAT, *British National Formulary* 49th edition [BNF 49]). For a person with a surface area of 1.75 m² the cost of irinotecan at the dose used

in the first-line regimen is about £419 per cycle. The cost at the dose used in second-line monotherapy is about £833 per cycle. Costs may vary in different settings because of negotiated procurement discounts.

Oxaliplatin

- 3.4 Oxaliplatin is a water-soluble platinum-based cytotoxic drug that prevents DNA replication, and hence cell division, by cross-linking DNA. Oxaliplatin in combination with 5-FU/FA is indicated for treatment of metastatic colorectal cancer. Neurotoxic side effects, which include cumulative sensory peripheral neuropathy, are dose limiting. Other side effects include gastrointestinal disturbances and myelosuppression. Oxaliplatin is contraindicated in patients who have myelosuppression before starting first course, as evidenced by baseline neutrophils less than 2×10^9 per litre and/or a platelet count of less than 100×10^9 per litre, and in patients who have a peripheral neuropathy with functional impairment prior to first course. For full details of side effects and other contraindications, see the Summary of Product Characteristics.
- 3.5 The recommended dose for oxaliplatin is 85 mg/m^2 when given in combination with 5-FU/FA. It is administered as an intravenous infusion over 2–6 hours every 2 weeks and followed by an infusion of 5-FU/FA.
- 3.6 Vials containing 50 mg and 100 mg cost £165 and £330 respectively (excluding VAT, *BNF* 49). For a person with a surface area of 1.75 m^2 the cost of treatment with oxaliplatin is £495 per cycle. Costs may vary in different settings because of negotiated procurement discounts.

Raltitrexed

- 3.7 Raltitrexed inhibits the enzyme thymidylate synthase, which is involved in DNA synthesis. This is the same enzyme that 5-FU targets. It is licensed in the UK for the palliative treatment of advanced colorectal cancer where 5-FU/FA based regimens are either not tolerated or inappropriate. It is contraindicated in severe renal impairment. It can cause marked

myelosuppression and gastrointestinal side effects. For full details of side effects and contraindications, see the Summary of Product Characteristics.

- 3.8 The recommended dose of raltitrexed is 3 mg/m² given intravenously as an intravenous infusion over 15 minutes every 3 weeks.
- 3.9 Raltitrexed costs £121.86 per 2 mg vial (excluding VAT, *BNF* 49). For a person with a surface area of 1.75 m² the cost of treatment is about £366 per cycle. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (Appendix A) considered evidence from a number of sources (Appendix B).

4.1 *Clinical effectiveness*

- 4.1.1 The evidence base for the management of advanced colorectal cancer includes a number of randomised controlled trials. However, results for overall survival from RCTs need cautious interpretation because the disease is often managed with sequences of either mono- or combination therapy, with the frequent use of unplanned second- or third-line salvage chemotherapy. Another caveat is that in many of the RCTs identified, the populations were relatively young and fit in comparison with the majority of people in the UK who receive second-line chemotherapy for advanced colorectal cancer.

Irinotecan in first-line combination therapy with 5-FU/FA

- 4.1.2 The Assessment Group identified seven well-designed and conducted RCTs, including four studies in which irinotecan in combination with 5-FU/FA was compared with 5-FU/FA alone, and four studies in which irinotecan in combination with 5-FU/FA was compared with oxaliplatin in combination with 5-FU/FA as first-line therapy.

- 4.1.3 In trials that compared the first-line combination of irinotecan with 5-FU/FA alone, median overall survival was improved by between 2.2 and 3.3 months and median progression-free survival by between 2.1 and 2.7 months. A meta-analysis conducted by the Assessment Group included four trials (2340 participants) and demonstrated a significantly better overall survival for irinotecan in combination with 5-FU/FA compared with 5-FU/FA alone; with a hazard ratio (HR) of 0.84 (95% confidence interval [CI] 0.76–0.93). Progression-free survival was also significantly improved (HR 0.76; CI 0.70–0.82). Response rates were 18–23% higher in the study arms that received the combination of irinotecan with 5-FU/FA.
- 4.1.4 Quality of life was reported in two RCTs that compared irinotecan and 5-FU/FA in combination with 5-FU/FA alone. No statistically significant difference was found between treatment arms, although in one RCT deterioration in quality of life and performance status occurred significantly later in the study arm receiving irinotecan.

Oxaliplatin in first-line combination therapy with 5-FU/FA

- 4.1.5 Four RCTs were identified by the Assessment Group. Two RCTs were considered by the Assessment Group to be relatively well-designed and conducted.
- 4.1.6 The addition of oxaliplatin to first-line 5-FU/FA had no statistically significant effect on median overall survival in the individual studies or in the meta-analysis (1939 participants) conducted by the Assessment Group (HR 0.93; CI 0.83–1.03), but it significantly improved median progression-free survival by 2.5–2.8 months (HR 0.75; CI 0.69–0.82). Response rates were 27–38% higher in the oxaliplatin arm. The outcomes may have been confounded by unplanned second-line therapy in more than half of trial participants in three of the trials, that is, those on 5-FU/FA monotherapy receiving second-line oxaliplatin.

- 4.1.7 Gastrointestinal, haematological and neurological toxicities were generally more frequent in the group receiving oxaliplatin, but pain and alopecia were less frequent.
- 4.1.8 Data on quality of life was available for only one RCT. In this trial, the time to deterioration of global health status was prolonged in the study arm receiving oxaliplatin, but there was no significant difference in overall quality of life between study arms.

Irinotecan in first-line combination therapy with 5-FU/FA compared with oxaliplatin in first-line combination therapy with 5-FU/FA

- 4.1.9 Studies comparing the combination of irinotecan and 5-FU/FA as first-line therapy with the combination of oxaliplatin and 5-FU/FA show mixed results. However, the meta-analysis conducted by the Assessment Group that included all four trials (1740 participants) showed no significant difference in overall survival between the two regimens when used as first-line therapy. For progression-free survival, the meta-analysis showed a significant difference in favour of the combination therapy including oxaliplatin (HR 1.10; CI 1.01–1.19). However, this could have been due to the inclusion of studies using bolus 5-FU/FA regimens, and in particular one study that included bolus 5-FU/FA in the irinotecan arm and 5-FU/FA infusion in the oxaliplatin arm. Similarly, response rates showed a difference in favour of oxaliplatin arms only when bolus regimens were used in the irinotecan arm. The submissions from the manufacturer and from professional organisations included an additional RCT that was not included in the Assessment Report because no abstract was available. This study found no significant differences for the endpoints of overall survival, progression-free survival and response rate between combination therapy containing irinotecan and combination therapy containing oxaliplatin.
- 4.1.10 There were differences in toxicity between the study arms that received irinotecan or oxaliplatin. Overall, gastrointestinal toxicities (vomiting, nausea, diarrhoea, stomatitis and mucositis) were seen more often in the study arms

containing irinotecan. Generally, haematological or neurological toxicities were seen less often in the study arms containing irinotecan.

Irinotecan in second-line monotherapy

4.1.11 Two RCTs were identified by the Assessment Group; one compared irinotecan with best supportive care and the other compared it with 5-FU/FA. The RCTs were judged by the Assessment Group to be well designed and conducted. However, the treatment arm populations in one trial appeared to be unbalanced, with unknown consequences for the estimation of treatment effect.

4.1.12 In the comparison with second-line 5-FU/FA, irinotecan significantly improved median overall survival by 2.3 months (HR 0.70; $p = 0.035$), median progression-free survival by 1.3 months (HR 0.78; $p = 0.03$), and response rates. In the comparison with best supportive care, irinotecan improved median overall survival by 2.7 months (HR 0.54; $p = 0.0001$). Progression-free survival and response rate were not reported.

4.1.13 Serious gastrointestinal and haematological toxicities were observed more often with irinotecan monotherapy than with best supportive care, but fewer neurological problems were seen.

4.1.14 Quality of life was reported in both RCTs. There was no evidence for a significant difference in quality of life between second-line irinotecan and 5-FU/FA. Compared with best supportive care, irinotecan maintained baseline quality of life longer, despite causing additional toxicity.

Oxaliplatin in second-line combination therapy with 5-FU/FA

4.1.15 One RCT was identified by the Assessment Group. In this study the combination of oxaliplatin and 5-FU/FA improved median overall survival by 1.1 months (HR 0.84, not statistically significant) compared with 5-FU/FA alone. Median progression-free survival was significantly improved by

2.1 months (HR 0.60, $p = 0.0001$), and response rates were significantly higher in the study arm receiving oxaliplatin.

4.1.16 The incidence of gastrointestinal, haematological and neurological toxicities (including asthenia and pain) was higher in the oxaliplatin arm. Quality of life results were not presented.

4.1.17 Two further RCTs, in which oxaliplatin combination therapy was part of a treatment sequence, are described below (Sections 4.1.23 to 4.1.29).

Raltitrexed

4.1.18 The Assessment Group identified four RCTs, three of which were considered to be relatively well designed and conducted. There was insufficient information about the fourth study to make an informed assessment. The populations in two trials were unbalanced and a third had a large number of withdrawals.

4.1.19 Raltitrexed did not improve overall survival or progression-free survival when compared with 5-FU/FA, and no RCT reported a significant improvement in response rates using raltitrexed. Raltitrexed was associated with more vomiting and nausea, but less diarrhoea and mucositis than 5-FU/FA. One study reported consistent, statistically significant differences in quality of life outcomes between arms, favouring the 5-FU/FA arm.

Comparison of infusional and bolus regimens for 5-FU/FA

4.1.20 Three RCTs were included in a meta-analysis by the Assessment Group (938 participants) that showed no significant difference in terms of overall survival (HR 0.89; CI 0.77–1.03), but infusional regimens were significantly better in terms of progression-free survival (HR 0.78; CI 0.66–0.91). Response rates were significantly higher with infusional regimens than with bolus administration in two out of three studies (in the third the same trend was seen, but it was not significant).

4.1.21 The results for overall survival show the same direction and size of effect as those presented in another published meta-analysis, which included additional studies of poor quality. A further RCT found no significant difference between two different infusional regimens for overall survival or progression-free survival.

4.1.22 All grade 3–4 toxicities were significantly less frequent with infusional than with bolus administration in the study where these outcomes were reported.

Treatment sequences

4.1.23 Two RCTs were identified that investigated the effect of treatment sequences and included among other outcomes, overall survival and progression-free survival. The FOCUS study included two active treatments in each of the five arms and the GERCOR study included three active treatments in a planned sequence in each arm.

4.1.24 In the FOCUS study, 2135 patients were randomised into five arms and followed up for 36 months. Treatments in the five study arms (A–E) were as follows: A – 5-FU/FA alone followed by irinotecan alone at progression (current NICE guidance); B – 5-FU/FA alone followed by the combination of irinotecan and 5-FU/FA at progression (not a licensed indication); C – a combination of irinotecan and 5-FU/FA; D – 5-FU alone followed by the combination of oxaliplatin and 5-FU/FA at progression; E – a combination of oxaliplatin and 5-FU/FA. The FOCUS study also included third-line salvage therapy where clinicians deemed it necessary. The Committee was made aware that FOCUS investigators had been discouraged from recruiting patients whose disease could have become downstaged to operability after chemotherapy.

4.1.25 In the GERCOR trial 226 patients were randomised into two arms and followed up for 44 months. One group received first-line therapy with a combination of irinotecan and 5-FU/FA, followed by a combination of oxaliplatin and 5-FU/FA on disease progression. The other group received the

combination therapies in the opposite order. The GERCOR study did not allow third-line salvage therapy.

4.1.26 In the FOCUS trial, median overall survival ranged from 13.7 to 16.2 months and the differences between treatment arms were not statistically significant. Statistically significant differences of 2.3–2.5 months were seen only for the outcome of progression-free survival between the first-line combination sequence plan and plan A (first-line 5-FU/FA followed by irinotecan – currently recommended by NICE). Staged second-line combination treatment regimens were as effective as first-line combination sequences in median overall survival, but there was better median progression-free survival for the first-line combination therapies.

4.1.27 In the GERCOR trial, median overall survival was 20.6–21.5 months, which was considerably longer than in the FOCUS trial. However, a direct comparison of the GERCOR and FOCUS data is difficult because it is not certain whether the baseline characteristics of participants in the two RCTs were similar. In the GERCOR study the treatment sequences were not significantly different in terms of survival.

4.1.28 The FOCUS trial confirmed the higher toxicity profile of combination chemotherapy, and a similar lifetime probability of toxicity whether participants received combination chemotherapy in a first-line combination or staged approach. The GERCOR trial confirmed that in first-line therapy the combination of irinotecan and 5-FU led to significantly fewer grade 3–4 toxicities, but significantly more serious adverse events (although not defined in the trial) than the combination of oxaliplatin and 5-FU. During second-line therapy there were no significant differences between treatments in overall toxicity or the number of serious adverse events. It was also found that elderly patients did not experience more toxicity than younger patients.

4.1.29 No full quality of life outcomes were available for either the GERCOR or the FOCUS studies.

Irinotecan and oxaliplatin in ‘downstaging’ otherwise unresectable liver metastases

4.1.30 The Assessment Group identified six single-arm studies for irinotecan and 5-FU/FA (two of which were case series) and two for oxaliplatin and 5-FU/FA (one case series).

4.1.31 Reported response rates were around 50% for both irinotecan and oxaliplatin combination therapies. The percentage of people for whom resections were carried out varied from 9–35% for the combination of irinotecan and 5-FU/FA and from 7–51% for the combination of oxaliplatin and 5-FU/FA. In the one head-to-head study, significantly more resections occurred in the oxaliplatin-containing arm (22%) than in the irinotecan-containing arm (9%), although ‘secondary surgery to remove metastases’ was not a pre-specified outcome measure. One study for irinotecan in combination with 5-FU/FA reported a ‘complete resection’ rate of 7%. Although the ‘complete resection’ rates for cohorts of patients receiving oxaliplatin in combination with 5-FU/FA were higher in the three studies that reported these rates (21–32%), in the one head-to-head study between irinotecan in combination with 5-FU/FA and oxaliplatin in combination with 5-FU/FA, the ‘complete resection’ rate was not significantly different between the irinotecan- and oxaliplatin-containing arms.

4.1.32 The submissions received from patient and professional organisations include studies that show patients with metastases at sites other than the liver may also benefit from treatment that shrinks the tumour to a size where surgical resection is possible. The submissions from the manufacturer of oxaliplatin and from professional organisations included a prospective non-randomised study that was not included by the Assessment Group, showing tumour reduction in 62% of patients and a 42% resection rate, which is broadly consistent with the findings summarised in 4.1.31.

Summary of clinical effectiveness

4.1.33 For individual therapies, the combination of irinotecan or oxaliplatin with 5-FU/FA in first-line therapy is significantly more effective in terms of median

progression-free survival than 5-FU/FA alone, but there is more toxicity. The irinotecan combination has been shown to result in statistically significant improved median overall survival compared with 5-FU/FA alone; this has not been demonstrated for the combination of 5-FU/FA with oxaliplatin. However, head-to-head comparisons of irinotecan with oxaliplatin suggest the two drugs (each in combination with 5-FU) are of similar effectiveness.

4.1.34 When progression occurs on 5-FU/FA alone, a switch to irinotecan monotherapy or addition of oxaliplatin to 5-FU/FA is more effective in terms of progression-free survival than staying on 5-FU/FA alone (with irinotecan monotherapy, overall survival is also better).

4.1.35 Raltitrexed is not more effective than 5-FU/FA.

4.1.36 Staged combination plans are not different from first-line combination plans in terms of overall survival. First-line combination therapy is more effective in terms of progression-free survival than the therapy plan involving first-line 5-FU/FA. However, there is no statistically significant difference for overall survival. Therapy sequences using three active chemotherapy agents appear to lead to the longest median overall survival, but there are no direct comparisons of plans using three chemotherapy agents with plans using two chemotherapy agents.

4.1.37 Infusional regimens are more effective than bolus regimens.

4.1.38 Irinotecan and oxaliplatin show some effectiveness in downstaging of liver metastasis for resection.

4.2 Cost effectiveness

4.2.1 The Assessment Group identified seven published economic evaluations relevant to the review (excluding the Assessment Report prepared for the original appraisal). Two manufacturers submitted economic analyses and the Assessment Group developed an economic model.

4.2.2 Most economic analyses for irinotecan in combination with 5-FU/FA in first-line therapy used a median overall progression-free survival of 2.3 months. The economic analyses for the first-line oxaliplatin combination used a median progression-free survival estimate of 2.8 months, except for the manufacturer's submission that used a much larger estimate of 4.5 months.

4.2.3 The published analyses showed the following.

- First-line combination therapy of irinotecan with 5-FU/FA versus 5-FU/FA alone: cost per life year gained of £15,000 and cost per progression-free life year gained of £30,000–£58,000.
- Second-line monotherapy with irinotecan versus 5-FU/FA alone: cost per life year gained between dominating (that is, achieving more life years for a lower cost) and £12,000.
- First-line combination therapy of oxaliplatin with 5-FU/FA: cost per progression-free life year gained of £23,000–£27,000.
- Combination therapy of oxaliplatin with 5-FU/FA for the treatment of unresectable liver metastasis: cost per life year gained of £12,000.
- Raltitrexed compared with 5-FU/FA: cost per life year gained of £97,000 (US \$154,611, converted to pounds sterling at 1999 rates).

4.2.4 The economic analysis submitted by Aventis suggested costs per progression-free life year gained (compared with 5-FU/FA alone) of £44,000 for combination therapy consisting of irinotecan with 5FU/FA, and £25,000 for combination therapy consisting of oxaliplatin with 5FU/FA.

4.2.5 The economic analysis from the Sanofi-Synthelabo submission for combination of oxaliplatin and 5-FU/FA (compared with 5-FU/FA alone) suggested a cost per progression-free life year gained of £23,000, a cost per quality-adjusted progression-free life year of £26,000, and a cost per quality-adjusted life year gained of £22,000 (note that both arms were followed by irinotecan on disease progression). Second-line combination therapy with oxaliplatin and 5-FU/FA compared with irinotecan (both after first-line

5-FU/FA) was found to be dominating, that is it was more effective and cost less than the comparator.

4.2.6 The Assessment Group noted the following concerns with these published and submitted economic models.

- Median rather than mean survival is used in economic analyses because it avoids assumptions regarding survival distributions. However, the mean survival difference (the area between two survival curves) more correctly represents the actual survival difference between treatments.
- In trials without planned second-line or salvage therapies, comparisons using overall survival are misleading.
- Where health-related quality of life has been evaluated using cancer-specific questionnaires, completion rates are not independent of the quality of life of the patient, and quality-of-life data for the very ill patients may not be represented within the results of the study. Furthermore, no preference-scaling method exists with which to translate scores on these cancer-specific scales into a utility score. Where cost per QALY has been estimated, utility estimates were taken from a study in which specialist nurses were asked to rate quality-of-life benefits of disease stabilisation in advanced colorectal cancer.
- Information about the cost of treatment based on the actual treatment time is scarce, and is often only based on the median treatment duration and the costs of an infrequently used 5-FU regimen.
- In the case of the Sanofi-Synthelabo submission, the progression-free survival estimate modelled does not match those found in other studies.

4.2.7 The Assessment Group analysed the cost-effectiveness of therapy sequences including irinotecan or oxaliplatin. The shortcomings of the other available models were addressed as follows: data on effectiveness were obtained from the GERCOR trial and from (unpublished) data for the

individual arms in the FOCUS trial made available by the MRC in confidence; to take account of correlations between the effectiveness of regimens and sequences of chemotherapy regimens, survival curves and first-line progression-free survival curves for the six regimens were estimated; survival curves were extrapolated to represent people who were still alive at the end of trials; additional costs were included and updated; data on the mean number of cycles used and mean dosage of chemotherapy were made available by the authors for the GERCOR and FOCUS studies; data from FOCUS were obtained from an unpublished ad hoc analysis of a subset of 1200 patients and 18% of patients were assumed to receive treatment on inpatient basis; and utility estimates from the FOCUS study using EQ-5D were made available by the MRC/Centre for Health Economics, York, in confidence. All treatment options listed below were compared with first-line monotherapy using 5-FU/FA and second-line monotherapy using irinotecan, as recommended in current NICE guidance.

4.2.8 For the first-line combination of irinotecan and 5-FU/FA, the analysis resulted in costs of £12,000 per life year gained, £45,000 per progression-free life year, and £14,000 per QALY gained.

4.2.9 For the first-line combination of oxaliplatin and 5-FU/FA, the analysis resulted in costs of £44,000 per life year gained, £40,000 per progression-free life year gained, and £68,000 per QALY gained.

4.2.10 For staged combination therapy of oxaliplatin with 5-FU/FA (after failure of 5-FU/FA monotherapy), the model resulted in costs of £24,000 per life year gained and £32,000 per QALY gained. The analysis of staged combination therapy of irinotecan with 5-FU/FA (after failure of 5-FU/FA monotherapy), resulted in £13,000 per life year gained and £10,000 per QALY gained.

4.2.11 The Assessment Group model also considered an indirect comparison of the treatment sequences used in the GERCOR study with the treatment sequence currently recommended by NICE (5-FU/FA monotherapy followed by irinotecan monotherapy on progression). Under the 'cautious' assumption

of comparability of patients that entered in the two trials, the combination of first-line irinotecan with 5-FU/FA followed by the combination of oxaliplatin with 5-FU/FA resulted in costs of £13,000 per life year gained, £96,000 per progression-free life year gained, and £17,000 per QALY gained. The combination of first-line oxaliplatin with 5-FU/FA followed by the combination of irinotecan with 5-FU/FA resulted in costs of £17,000 per life year gained, £63,000 per progression-free life year gained, and £22,000 per QALY gained.

4.2.12 In interpreting the results of the indirect comparison between the GERCOR and FOCUS studies, the Assessment Group noted that although the inclusion criteria of both studies were broadly similar, it is possible that the differences in overall survival reported in the two studies were not solely due to the chemotherapy received. Furthermore, in reviewing the full results of the economic analysis, the Assessment Group noted that the data on utility sourced from FOCUS had not been subject to full validation, nor had the data been adjusted for the effects of either informative or uninformative censoring within the trial. Moreover, since salvage chemotherapy was available to a substantial percentage of people in the FOCUS trial, the cost estimates for drug treatment were likely to be underestimated. The degree to which the costs are underestimated would be greatest for the first-line combinations because these patients did not receive planned second-line treatment. Finally, because of limited evidence, the Assessment group held the differential costs of hospitalisation between treatment arms constant; and noted that therefore uncertainty in the cost of regimens and sequences may be underestimated.

4.2.13 In summary, evidence from published economic evaluations, manufacturers' submissions and the Assessment Group model suggests that combination of irinotecan or oxaliplatin with 5-FU/FA leads to costs per progression-free life year gained greater than £25,000. In most of the published economic evaluations, estimates of costs and benefits were accompanied by considerable uncertainty. Only the Assessment Group model calculated costs per QALY for combination therapies and sequences. This analysis suggests a favourable cost effectiveness estimate for irinotecan in first-line combination

therapy. However, it should be noted that the FOCUS treatment costs for all study arms are underestimated, most notably for the first-line combination arms. The cost-effectiveness estimates for the GERCOR treatment sequences were favourable in comparison with the FOCUS baseline of 5-FU/FA alone followed by irinotecan, but this analysis was based on a non-randomised comparison of arms of two different trials.

4.3 Consideration of the evidence

- 4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer, having considered evidence on the nature of the condition and the value placed on the benefits of these drugs by people with the condition, those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.3.2 The Committee heard testimony from the clinical and patient experts that the most important outcomes for people with advanced colorectal cancer are overall survival and quality of life. The Committee noted that time to progression is an important measure of disease processes but that improvements in this outcome are not necessarily related to increases in length or quality of life, particularly when disease progression is asymptomatic. The Committee concluded that quality-adjusted overall survival is the preferred outcome in interpreting clinical and cost-effectiveness evidence for treatment options in advanced colorectal cancer. However, the Committee was mindful of the fact that when reviewing the results of trials with first-line combination therapies, unplanned (and uncosted) second-line treatments used in the trials may have contributed to the overall survival benefits.
- 4.3.3 The Committee heard testimony from the clinical experts that the modified de Gramont regimen for administering 5-FU/FA has become the standard clinical practice in England and Wales. The Committee accepted that for the purpose

of this appraisal the modified de Gramont regimen is the most appropriate for administering 5-FU/FA, alone or in combination.

- 4.3.4 In reviewing the evidence on clinical and cost effectiveness for irinotecan in second-line monotherapy, and for raltitrexed, the Committee concluded that no new evidence had come to light since the original appraisal that would cause it to change the original recommendations for these two interventions.
- 4.3.5 In reviewing the clinical effectiveness evidence for the other treatment options, the Committee noted that irinotecan in first-line combination therapy resulted in a statistically significant increase in median overall survival compared with 5-FU/FA alone, whereas for oxaliplatin in first-line combination therapy this has not been shown. However, the evidence from head to head trials comparing first-line combination therapies including either irinotecan or oxaliplatin showed no difference in median overall survival between them. The Committee therefore concluded that it would not differentiate between these two drugs in terms of clinical effectiveness.
- 4.3.6 The Committee carefully considered the new evidence on each drug in combination with 5FU/FA, the main difference being that the previous data on progression-free survival were now supported by the results of two studies (FOCUS and GERCOR) on sequences of treatment reporting improved overall survival.
- 4.3.7 The Committee further noted the longer overall survival in the GERCOR study compared with the FOCUS study, particularly in view of the comparable first-line progression-free survival data. In seeking clarification from the clinical experts, the Committee heard that the baseline patient characteristics were similar in terms of performance status. However, the Committee was made aware that the GERCOR study may have had a higher proportion of patients with better prognosis in terms of potential for resection of metastasis than the FOCUS trial.

- 4.3.8 The difference in overall survival was interpreted by the experts as being due to the availability of three active chemotherapy drugs to all patients in the GERCOR study; in the FOCUS study a much smaller percentage of patients had access to a third chemotherapy agent as salvage therapy after failure of the first two drugs. The Committee also heard from the experts that recent (non-randomised) reanalysis of previously published trials had shown that overall survival increases with the number of patients to whom three drugs are available. The Committee noted that other components of the pathways of care in the studies could also explain the increase in overall survival.
- 4.3.9 When considering the cost effectiveness evidence, the Committee concluded that the Assessment Group's model was the most appropriate model because it incorporated quality-of-life and resource-cost estimates from the same UK dataset as the effectiveness data. The Committee also agreed that the use of the treatment sequence recommended in the 2002 NICE guidance (see Section 8) as a comparator was appropriate. However, the Committee was aware of a number of uncertainties around the modelling, such as the data on resource use and quality of life taken from the FOCUS study that were not yet validated, and – most critically – that the cost of salvage therapies was not included. The Committee heard testimony from clinical experts that a significant proportion of patients in the FOCUS trial received further treatment after progression and that the extent to which this happened was unevenly distributed between the treatment arms. However, the Committee concluded that even if the cost difference for first-line combination therapy with irinotecan and 5-FU/FA compared with the baseline arm of FOCUS was substantially increased to allow for the cost of the salvage therapies, the cost per quality-adjusted life year gained was likely to remain within acceptable limits. Therefore, the Committee concluded that first-line combination therapy with irinotecan and 5-FU/FA was cost effective.
- 4.3.10 The Committee noted that the Assessment Group's cost effectiveness estimate for first-line oxaliplatin in combination with 5-FU/FA was considerably higher than the estimate for irinotecan. But because the costs and outcomes

within the FOCUS trial had substantially overlapping confidence intervals and because the head-to-head trials showed little difference between combination therapies including either irinotecan or oxaliplatin, the Committee concluded that first-line combination of both drugs should be available. Given the different side-effect profiles of the drugs, the Committee accepted the importance of having a range of drug treatment options.

4.3.11 When considering the evidence for second-line combination therapy of oxaliplatin with 5-FU/FA, the Committee noted that the substantial benefit in overall survival seen in the GERCOR study when this treatment was given after irinotecan in combination with 5-FU/FA in first-line therapy led to a favourable cost effectiveness when compared with the FOCUS baseline arm, even though these data had to be interpreted with considerable caution because of the uncertainties about the comparability of the FOCUS and GERCOR studies. However, on balance, the Committee concluded that second-line oxaliplatin in combination with 5-FU/FA is a cost-effective option in the treatment of advanced colorectal cancer.

4.3.12 The Committee noted the economic analyses of the FOCUS and GERCOR treatment regimens which also suggested that second-line combination therapy of irinotecan with 5-FU/FA could be a cost effective treatment option. However, this use of irinotecan is not covered by the current UK licence, and the Appraisal Committee did not put forward a recommendation.

4.3.13 The Committee noted that its original recommendation for the availability of oxaliplatin where there was potential to reduce metastases to a resectable size was now subsumed by the current recommendations, in that all patients would be offered combination therapy with either irinotecan or oxaliplatin as appropriate for their clinical needs.

4.3.14 The Committee considered the fact that participants in trials for advanced colorectal cancer are often younger than those who would be treated in clinical practice. It heard testimony from clinical experts who stated that fitness instead of age is often the criterion for inclusion in trials; that older

people show a relatively good tolerability profile to the drugs; and that overall survival is comparable with that of younger people on drug treatment.

5 Recommendations for further research

5.1 The following clinical trials are ongoing.

- FOCUS2 (CR09). Drug treatment for bowel cancer: making the best choices when a milder treatment is needed. Treatment regimens to be included are 5-FU/FA (modified de Gramont), the combination of oxaliplatin with 5-FU/FA, capecitabine alone, and the combination of oxaliplatin with capecitabine. Accrual target is 460 people with a closure date at the end of 2005.
- Genetic factors in colorectal cancer; the role of genetic factors in clinical outcome for colorectal cancer patients. Epidemiological study with sample size of 800 people. Closure date September 2005.
- Cetuximab with or without irinotecan for patients with advanced colorectal cancer (EPIC EMR 622202–025). Accrual target is 1300 people. Closure date 1 April 2005.
- LIFE: Oxaliplatin combined with two different 5-FU regimens in patients with previously untreated advanced colorectal cancer. Number of patients enrolled, 725. Data on effectiveness were released in May 2005.
- Ongoing trials involving combinations of capecitabine with irinotecan and oxaliplatin in first-line treatment, combination of irinotecan with oxaliplatin in second-line treatment, combination of irinotecan, oxaliplatin and 5-FU in first-line treatment and trials that involve bevacizumab or cetuximab. One such trial is the COIN trial, currently being set up by the MRC with a sample size of 2421 and involving cetuximab. The closure date for this is 3.5 years after opening.

- 5.2 The Committee noted the need for the full sequence of treatments to be recorded for all patients in all trials.

6 Implications for the NHS

- 6.1 The Assessment Group estimated that each year approximately 13,000 patients are treated with first-line therapy and 7000 of those are subsequently treated with second-line therapy for advanced colorectal cancer. Although specific data are not available on current use of chemotherapy for advanced colorectal cancer, two scenarios are feasible:

- 1 currently all patients requiring first-line therapy are treated with 5-FU/FA in the modified de Gramont regimen and all patients requiring second-line therapy are treated with irinotecan alone; or
- 2 50% of patients are already being offered combination therapy with either irinotecan or oxaliplatin in first- and/or second-line therapy.

The second scenario is consistent with a manufacturer's submission.

- 6.2 Because the most robust lifetime costs of treatment can be derived from the GERCOR trial, these lifetime costs are used in the resource impact calculation below. The resource impact calculation uses the standard comparator of FOCUS to calculate current baseline expenditure, but it should be noted that the costs of this regimen are likely to be an underestimate. Moreover it is also assumed that, when the recommendations in this guidance are implemented, patients will predominantly be using the GERCOR regimen in which oxaliplatin is given with 5-FU/FA as second-line therapy. This assumption is consistent with the licensed indications of oxaliplatin and irinotecan.
- 6.3 If it is assumed that scenario 1 reflects current spending on chemotherapy for advanced colorectal cancer, this equates to approximately £153 million each year. When the assumption in Section 6.2 is used to calculate lifetime costs

for the combination therapies (scenario 2) this equates to approximately £233 million each year.

- 6.4 If an equal uptake of the guidance is assumed for both scenarios, and this is between 20 and 50%, the resource impact for the NHS would equate to extra spending of between £32 million and £80 million for scenario 1, and between £32 million and £48 million for scenario 2 in the first year after publication of the guidance.

7 Implementation and audit

- 7.1 Clinicians with responsibility for treating people with advanced colorectal cancer should review their current practice and policies to take account of the guidance set out in Section 1.
- 7.2 Local guidelines, protocols or care pathways that refer to the care of people with advanced colorectal cancer should incorporate the guidance.
- 7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.
- 7.3.1 A person with advanced colorectal cancer is offered irinotecan and oxaliplatin, within their licensed indications, as treatment options as follows:
- irinotecan in combination with 5-FU/FA as first-line therapy, or irinotecan alone in subsequent therapy, or
 - oxaliplatin in combination with 5-FU/FA in first-line or subsequent therapy.
- 7.3.2 A person with advanced colorectal cancer is offered raltitrexed only as part of an appropriately designed clinical study.

- 7.4 Local clinical audits on the management of advanced colorectal cancer could also include measurement of compliance with accepted clinical guidelines or protocols or with the measures for the treatment of colorectal cancer that are suggested in 'Guidance on cancer services. Improving outcomes in colorectal cancers' (see Section 8.4 for details).

8 Related guidance

- 8.1 This guidance is a review of the following NICE guidance:

Guidance on the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. *Technology Appraisal Guidance* No.33.
Available from www.nice.org.uk

- 8.2 NICE has issued the following related technology appraisal guidance.

Guidance on the use of laparoscopic surgery for colorectal cancer.
Technology Appraisal Guidance No.17. Issued December 2000.

Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer. *Technology Appraisal Guidance* No. 61. Issued May 2003.

- 8.3 NICE is in the process of producing the following technology appraisal guidance.

The use of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer. Expected date of issue May 2006.

The use of bevacizumab and cetuximab for the treatment of advanced colorectal cancer. Expected date of issue August 2006.

The use of irinotecan for the adjuvant treatment of colon cancer. Expected date of issue January 2007.

8.4 NICE has issued the following related cancer service guidance.

Improving outcomes in colorectal cancer. *Guidance on Cancer Services*.
Issued June 2004.

9 Review of guidance

9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

9.2 The guidance on this technology will be considered for review in August 2008.

Andrew Dillon
Chief Executive
August 2005

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets regularly and membership is split into two branches. In order to ensure consistency, the chair of each branch is also a member of a branch of which they are not chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Darren Ashcroft

Senior Lecturer, School of Pharmacy and Pharmaceutical Sciences

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Mr Brian Buckley

Vice Chairman, InContact

Dr Mark Chakravarty

Head of Government Affairs and NHS Policy, Procter and Gamble Pharmaceuticals (UK)

Ms Donna Covey

Chief Executive, National Asthma Campaign

Dr Mike Davies

Consultant Physician, University Department of Medicine and Metabolism,
Manchester Royal Infirmary

Professor Jack Dowie

Health Economist, London School of Hygiene and Tropical Medicine

Dr Fergus Gleeson

Consultant Radiologist, The Churchill Hospital, Oxford

Ms Sally Gooch

Director of Nursing and Workforce Development, Mid Essex Hospital Services NHS
Trust

Professor Peter Jones

Professor of Statistics and Dean, Faculty of Natural Sciences, Keele University

Ms Rachel Lewis

Staff Nurse (Nephrology), Hull Royal Infirmary

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Ruairidh Milne

Senior Lecturer in Public Health, National Coordinating Centre for Health Technology

Dr Neil Milner

General Practitioner, Sheffield

Mr Miles Scott

Chief Executive, Harrogate Health Care NHS Trust

Dr Ken Stein

Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens (Chair)

Professor of Public Health, University of Birmingham

B. NICE project team

Each appraisal of a technology is assigned to one or more Health Technology Analysts and a Technology Appraisal Project Manager within the Institute.

Meindert Boysen

Technical Lead, NICE project team

Elisabeth George

Technical Lead, NICE project team

Emily Marschke

Project Manager, NICE project team

Appendix B. Sources of evidence considered by the Committee

- A The assessment report for this appraisal was prepared by Danny Hind, Paul Tappenden, Indra Tumor, Simon Eggington, Paul Sutcliffe and Angie Ryan, of the School of Health and Related Research (SchHARR).

Hind D, Tappenden P, Tumor I et al. *The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation (review of Guidance No. 33)*, January 2005.

- B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope and assessment report and the appraisal consultation document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturer(s)/sponsor(s):

- AstraZeneca
- Aventis Pharma (marketing authorisation holder of irinotecan until 16 October 2004 – now Sanofi-Aventis)
- Pfizer (marketing authorisation holder of irinotecan from 16 October 2004)
- Sanofi-Synthelabo (now Sanofi-Aventis)

II Professional/specialist and patient/carer groups:

- Association of Cancer Physicians
- Beating Bowel Cancer
- British Association of Surgical Oncology
- British Oncological Association
- British Oncology Pharmacy Association
- British Psychosocial Oncology Society

- Cancer Research UK
- Cancer Research Wales
- CancerBACUP
- Colon Cancer Concern
- Help Adolescents with Cancer
- Lynn's Bowel Cancer Campaign
- Macmillan Cancer Relief
- Marie Curie Cancer Care
- National Cancer Alliance
- National Council for Hospice and Specialist Palliative Care Services
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Royal College of Radiologists
- Royal College of Surgeons
- Royal Pharmaceutical Society of GB
- Teenage Cancer Trust (UK)
- Tenovus Cancer Information Centre

III Commentator organisations (without the right of appeal):

- Association of Welsh Community Health Councils
- British Medical Association
- British National Formulary
- Health Development Agency
- National Collaborating Centre for Cancer
- National Public Health Service for Wales
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland
- MRC Clinical Trials Unit, Cancer Division

- National Cancer Research Institute
- Mayne Pharmaceuticals
- Medac UK
- Wyeth Pharmaceuticals
- Roche
- National Coordinating Centre for Health Technology Assessment
- School of Health and Related Research, Sheffield

The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on irinotecan, oxaliplatin and raltitrexed by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Tim Maughan, Consultant Clinical Oncologist and Honorary Professor of Cancer Studies, Velindre Hospital, Cardiff
- Dr Richard Wilson, Consultant, Queen's University Belfast, Belfast City Hospital; Cancer Research UK
- Ms Helen Crowe, patient expert, nominated by Colon Cancer Concern
- Ms Dorothy Gale, patient expert, nominated by Colon Cancer Concern

Appendix C. Detail on criteria for audit of the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer

Possible objectives for an audit

An audit on the treatment of people with advanced colorectal cancer could be carried out to ensure that irinotecan, oxaliplatin and raltitrexed are being used appropriately.

Possible patients to be included in the audit

An audit could be carried out on people with advanced colorectal cancer seen over a suitable time period for audit, for example, 6 months or a year.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer are as follows.

Criterion	Standard	Exception	Definition of terms
<p>1. A person with advanced colorectal cancer is offered irinotecan and oxaliplatin, within their licensed indications, as treatment options as follows:</p> <p>a. irinotecan in combination with 5-FU/FA as first-line therapy or</p> <p>b. irinotecan alone in subsequent therapy or</p> <p>c. oxaliplatin in combination with 5-FU/FA as first-line or subsequent therapy</p>	<p>100% of people diagnosed as having advanced colorectal cancer</p>	<p>A. The person has contraindications to either of:</p> <p>(1) irinotecan</p> <p>(2) oxaliplatin</p> <p>B. The clinician determines that the person is not sufficiently fit for combination chemotherapy</p>	<p>Clinicians will need to agree locally on how the offer of the treatment options and how the determination that the person is not sufficiently fit for combination chemotherapy are documented for audit purposes.</p> <p>See the Summaries of Product Characteristics for full descriptions of licensed indications.</p> <p>Contraindications for irinotecan include chronic inflammatory bowel disease and bowel obstruction, bilirubin more than three times the upper limit of the normal range, WHO performance status more than 2 and severe bone marrow failure.</p> <p>Contraindications for oxaliplatin include myelosuppression before starting first course, as evidenced by baseline neutrophils less than 2×10^9 per litre and/or a platelet count of less than 100×10^9 per litre, and peripheral neuropathy with functional impairment. For full details of contraindications, see the Summaries of Product Characteristics.</p>
<p>2. A person with advanced colorectal cancer is prescribed raltitrexed</p>	<p>0% of people diagnosed as having advanced colorectal cancer</p>	<p>A. The person is participating in an appropriately designed clinical study</p>	

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the **criteria** plus number of patients who meet any **exception** listed}{\text{Number of patients to whom the **measure** applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.