A randomised controlled trial to assess the cost-effectiveness of intensive versus no scheduled follow-up in patients who have undergone resection for colorectal cancer with curative intent

David Mant, Alastair Gray, Siân Pugh, Helen Campbell,
Stephen George, Alice Fuller, Bethany Shinkins,
Andrea Corkhill, Jane Mellor, Elizabeth Dixon, Louisa Little,
Rafael Perera-Salazar and John Primrose

A randomised controlled trial to assess the cost-effectiveness of intensive versus no scheduled follow-up in patients who have undergone resection for colorectal cancer with curative intent

David Mant,[1] Alastair Gray,[2] Siân Pugh,[3]
Helen Campbell,[2] Stephen George,[4] Alice Fuller,[1]
Bethany Shinkins,[5] Andrea Corkhill,[6] Jane Mellor,[6]
Elizabeth Dixon,[6] Louisa Little,[6] Rafael Perera-Salazar[1]
and John Primrose[3]*

[1]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[2]Nuffield Department of Population Health, University of Oxford, Oxford, UK
[3]University Surgery, University of Southampton, Southampton, UK
[4]Faculty of Medicine, University of Southampton, Southampton, UK
[5]Leeds Institute of Health Sciences, University of Leeds, Leeds, UK
[6]Southampton Clinical Trials Unit, University of Southampton, Southampton, UK

*Corresponding author

Declared competing interests of authors: none

Health Technology Assessment

Criteria for inclusion in the *Health Technology Assessment* journal
Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme
The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

Abstract

A randomised controlled trial to assess the cost-effectiveness of intensive versus no scheduled follow-up in patients who have undergone resection for colorectal cancer with curative intent

David Mant,[1] Alastair Gray,[2] Siân Pugh,[3] Helen Campbell,[2] Stephen George,[4] Alice Fuller,[1] Bethany Shinkins,[5] Andrea Corkhill,[6] Jane Mellor,[6] Elizabeth Dixon,[6] Louisa Little,[6] Rafael Perera-Salazar[1] and John Primrose[3]*

[1]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[2]Nuffield Department of Population Health, University of Oxford, Oxford, UK
[3]University Surgery, University of Southampton, Southampton, UK
[4]Faculty of Medicine, University of Southampton, Southampton, UK
[5]Leeds Institute of Health Sciences, University of Leeds, Leeds, UK
[6]Southampton Clinical Trials Unit, University of Southampton, Southampton, UK

*Corresponding author J.N.Primrose@soton.ac.uk

Background: Intensive follow-up after surgery for colorectal cancer is common practice but lacks a firm evidence base.

Objective: To assess whether or not augmenting symptomatic follow-up in primary care with two intensive methods of follow-up [monitoring of blood carcinoembryonic antigen (CEA) levels and scheduled imaging] is effective and cost-effective in detecting the recurrence of colorectal cancer treatable surgically with curative intent.

Design: Randomised controlled open-label trial. Participants were randomly assigned to one of four groups: (1) minimum follow-up ($n = 301$), (2) CEA testing only ($n = 300$), (3) computerised tomography (CT) only ($n = 299$) or (4) CEA testing and CT ($n = 302$). Blood CEA was measured every 3 months for 2 years and then every 6 months for 3 years; CT scans of the chest, abdomen and pelvis were performed every 6 months for 2 years and then annually for 3 years. Those in the minimum and CEA testing-only arms had a single CT scan at 12–18 months. The groups were minimised on adjuvant chemotherapy, gender and age group (three strata).

Setting: Thirty-nine NHS hospitals in England with access to high-volume services offering surgical treatment of metastatic recurrence.

Participants: A total of 1202 participants who had undergone curative treatment for Dukes' stage A to C colorectal cancer with no residual disease. Adjuvant treatment was completed if indicated. There was no evidence of metastatic disease on axial imaging and the post-operative blood CEA level was ≤ 10 µg/l.

Main outcome measures: *Primary outcome* Surgical treatment of recurrence with curative intent. *Secondary outcomes* Time to detection of recurrence, survival after treatment of recurrence, overall survival and quality-adjusted life-years (QALYs) gained.

Results: *Detection of recurrence* During 5 years of scheduled follow-up, cancer recurrence was detected in 203 (16.9%) participants. The proportion of participants with recurrence surgically treated with curative intent was 6.3% (76/1202), with little difference according to Dukes' staging (stage A, 5.1%; stage B, 7.4%; stage C, 5.6%; $p = 0.56$). The proportion was two to three times higher in each of the three more intensive arms (7.5% overall) than in the minimum follow-up arm (2.7%) (difference 4.8%; $p = 0.003$). Surgical treatment of recurrence with curative intent was 2.7% (8/301) in the minimum follow-up group, 6.3% (19/300) in the CEA testing group, 9.4% (28/299) in the CT group and 7.0% (21/302) in the CEA testing and CT group. Surgical treatment of recurrence with curative intent was two to three times higher in each of the three more intensive follow-up groups than in the minimum follow-up group; adjusted odds ratios (ORs) compared with minimum follow-up were as follows: CEA testing group, OR 2.40, 95% confidence interval (CI) 1.02 to 5.65; CT group, OR 3.69, 95% CI 1.63 to 8.38; and CEA testing and CT group, OR 2.78, 95% CI 1.19 to 6.49. *Survival* A Kaplan–Meier survival analysis confirmed no significant difference between arms (log-rank $p = 0.45$). The baseline-adjusted Cox proportional hazards ratio comparing the minimum and intensive arms was 0.87 (95% CI 0.67 to 1.15). These CIs suggest a maximum survival benefit from intensive follow-up of 3.8%. *Cost-effectiveness* The incremental cost per patient treated surgically with curative intent compared with minimum follow-up was £40,131 with CEA testing, £43,392 with CT and £85,151 with CEA testing and CT. The lack of differential impact on survival resulted in little difference in QALYs saved between arms. The additional cost per QALY gained of moving from minimum follow-up to CEA testing was £25,951 and for CT was £246,107. When compared with minimum follow-up, combined CEA testing and CT was more costly and generated fewer QALYs, resulting in a negative incremental cost-effectiveness ratio (–£208,347) and a dominated policy.

Limitations: Although this is the largest trial undertaken at the time of writing, it has insufficient power to assess whether or not the improvement in detecting treatable recurrence achieved by intensive follow-up leads to a reduction in overall mortality.

Conclusions: Rigorous staging to detect residual disease is important before embarking on follow-up. The benefit of intensive follow-up in detecting surgically treatable recurrence is independent of stage. The survival benefit from intensive follow-up is unlikely to exceed 4% in absolute terms and harm cannot be absolutely excluded. A longer time horizon is required to ascertain whether or not intensive follow-up is an efficient use of scarce health-care resources. Translational analyses are under way, utilising tumour tissue collected from Follow-up After Colorectal Surgery trial participants, with the aim of identifying potentially prognostic biomarkers that may guide follow-up in the future.

Contents

List of tables

List of figures

List of abbreviations

CEA	carcinoembryonic antigen	ICER	incremental cost-effectiveness ratio
CI	confidence interval	ITT	intention to treat
CONSORT	Consolidated Standards of Reporting Trials	MI	multiple imputation
		MRC	Medical Research Council
CRF	case report form	MRI	magnetic resonance imaging
CT	computerised tomography	NCRN	National Cancer Research Network
DMEC	Data Monitoring and Ethics Committee	NIHR	National Institute for Health Research
EORTC	European Organisation for Research and Treatment of Cancer	ONS	Office for National Statistics
		OR	odds ratio
EQ-5D	EuroQol-5 Dimensions	PET	positron emission tomography
EQ-5D-3L	EuroQol-5 Dimensions, three-level version	PPI	patient and public involvement
		QALY	quality-adjusted life-year
FACS	Follow-up After Colorectal Surgery	R0 resection	$\geq$ 1-mm clearance at lateral margins
GP	general practitioner		
HADS	Hospital Anxiety and Depression Scale	SE	standard error
		SPSS	Statistical Product and Service Solutions
HR	hazard ratio		
HRG	Healthcare Resource Group	TNM	tumour, node, metastasis
HRQoL	health-related quality of life		
HTA	Health Technology Assessment		

Plain English summary

Bowel cancer is the second most common cause of cancer death in the UK. When the cancer is confined to the bowel and/or surrounding lymph nodes (early bowel cancer), it can often be treated with an operation. Following surgery, many patients will be cured; however, for others, the cancer may come back (recur) either locally in the bowel or in another organ such as the liver. Consequently, after surgery for early bowel cancer, clinicians often follow up patients in the hope of detecting any recurrent cancer at an early and treatable stage. The way in which patients are followed up is variable. Some patients have regular computerised tomography (CT; detailed radiography) scans and/or blood tests to look for signs of cancer. Others are simply advised to report any concerning symptoms.

The FACS (Follow-up After Colorectal Surgery) trial was undertaken to determine the most effective form of follow-up. Patients were allocated to one of four follow-up regimens: (1) minimal follow-up with a single CT scan, (2) regular CT scans, (3) regular blood tests with a single CT scan or (4) both regular CT scans and blood tests. The results demonstrate that regular follow-up with either CT scans or blood tests is better than minimal follow-up at detecting recurrent cancer at a treatable stage. There was no benefit of having both CT scans and blood tests. Of the intensive follow-up strategies, regular blood tests with a single CT scan appears to be both economical and well accepted by patients.

Scientific summary

Background

The original protocol for the FACS (Follow-up After Colorectal Surgery) trial specified the main outcome as overall mortality based on 1200 patients randomised to each intervention arm and followed up for 5 years. It was planned to recruit 2400 participants in each factorial group (4800 total) to detect a 4% improvement from 49% to 53% in each factorial comparison [carcinoembryonic antigen (CEA) testing vs. no CEA testing, computerised tomography (CT) vs. no CT]. Difficulties in recruitment were encountered from the outset. Despite a major expansion in the number of centres recruiting and a substantial protocol amendment to reflect changing clinical views on the position of equipoise (a single CT scan at the investigator's discretion 12–18 months post randomisation was added to the follow-up schedule for the minimum follow-up arm), many clinicians and patients had concerns regarding participation. In addition, it was noted that the overall mortality was much lower than expected. On this basis, after interim review of 500 participants, the Data Monitoring and Ethics Committee (DMEC) advised that the sample size be reduced to 1180 in total and that the primary outcome be changed to 'surgical treatment of recurrence with curative intent'. Finally, owing to a significant interaction, the primary analysis was altered from factorial to a three-way comparison between each of the three intensively monitored groups and the group with no additional monitoring (apart from a single CT scan).

The Health Technology Assessment programme accepted this proposal for a surrogate end point and recruitment was stopped in July 2009, when just over 1200 participants had entered the trial. In August 2012, when all participants had completed 3 years of scheduled follow-up, the randomisation code was broken at the recommendation of the DMEC and an interim analysis was conducted. This analysis showed that intensive follow-up increased, by approximately threefold, the number of patients with recurrence who could be treated surgically with curative intent, but there was no significant difference in overall survival. The further analysis reported here is based on data collected up to the end of November 2014, when all surviving participants had completed the scheduled 5 years of follow-up and the median time elapsed since the recruitment of each participant was 8.7 years (range 5.5 to 11.9 years). The one exception is the observational analysis of recurrence, which is based on the data available at the time of the interim analysis.

Aim and objectives

Aim
To assess whether or not augmenting symptomatic follow-up in primary care with two intensive methods of follow-up (monitoring of blood CEA levels in primary care and scheduled imaging in hospital) is clinically effective and cost-effective in detecting the recurrence of colorectal cancer treatable surgically with curative intent and in improving survival.

Specific objectives

1. To estimate the effect of 3- to 6-monthly measurement of blood CEA levels and 6- to 12-monthly CT imaging plus an additional colonoscopy on:

    i. the number and cost of detecting recurrences treatable surgically with curative intent
    ii. overall and colorectal cancer-specific mortality
    iii. cost per quality-adjusted life-year (QALY) saved.

2. To describe in trial participants:

    i. the frequency and pattern of recurrence by site and stage of the primary tumour
    ii. the length of post-recurrence survival by treatment intent
    iii. the cost of NHS services utilised
    iv. health-related quality of life (HRQoL) during follow-up.

Methods

Design
A randomised controlled trial with a 2 × 2 factorial design; participants were randomised independently to (1) CT imaging every 6–12 months or at minimum follow-up and (2) blood testing to measure CEA levels every 3–6 months or at minimum follow-up.

Participants
The trial was conducted in 39 NHS hospitals in England that had access to high-volume regional services geared towards offering surgical treatment for metastatic recurrence. The participants were recruited between January 2003 and August 2009. All of the participants had undergone curative treatment for primary colorectal cancer with no residual disease, microscopically clear margins and Dukes' A to C stage (tumour, node, metastasis stage I–III). Patients were excluded if they had concurrent serious illness, dominantly inherited colon cancer or an inability to give written informed consent or if they were involved in a primary treatment trial with conflicting follow-up requirements.

Interventions
Follow-up was scheduled for 5 years from trial entry. Patients received one of four types of follow-up: (1) CEA testing follow-up – 3-monthly measurement of blood CEA for 2 years and then 6-monthly measurement for 3 years, with a single chest, abdominal and pelvic CT scan at 12–18 months; (2) CT follow-up – chest, abdominal and pelvic CT scan 6-monthly for 2 years and then annually for 3 years; (3) CEA testing and CT follow-up – both blood CEA measurement and CT imaging as above; and (4) minimum follow-up – no scheduled follow-up except a single chest, abdominal and pelvic CT scan at 12–18 months if requested at study entry by the hospital clinician (187, 62% received a CT scan). All patients were offered an end-of-trial colonoscopy at 5 years; in the two CT arms, a colonoscopy to check for luminal recurrence or metachronous primary cancer was also undertaken at 2 years.

Primary clinical outcome
Surgical treatment of identified recurrence with curative intent. Data on treatment of recurrence and treatment intent were recorded on case report forms (CRFs) by local National Cancer Research Network staff (who had access to the full clinical records).

Secondary clinical outcomes
(1) Overall survival, (2) deaths from colorectal cancer, (3) time to detection of recurrence and (4) post-recurrence survival. Information on deaths was collected by flagging each participant at the Office for National Statistics (ONS) central registry; cause of death was abstracted from death certificates.

Economic outcomes
The discounted total number of QALYs gained over the 5 years of follow-up was the primary outcome measure for the cost-effectiveness analysis. The secondary outcomes were (1) resource use, (2) NHS costs and (3) HRQoL. QALYs were calculated by applying the average index score of HRQoL to the observed survival in each year.

Sample size

To detect a 6% absolute difference in the primary outcome between minimum follow-up and any of the three other more intensive follow-up arms with 80% power (two-sided alpha 0.05) was estimated to require 205 patients in each of the four follow-up arms; 590 subjects allocated to each factorial group (CEA measurement and CT imaging) were estimated to provide 80% power to detect a 3% absolute difference in the factorial comparison. We therefore planned to stop recruitment when we reached a minimum of 1180 participants.

Randomisation

Patients were independently allocated at random on a 1 : 1 ratio to receive or not receive each of the factorial interventions (CEA measurement and hospital-based imaging) using the telephone randomisation service provided by the Oxford Clinical Trials Unit. A computerised algorithm was applied using the method of minimisation to balance patient characteristics within each centre; the balancing variables were adjuvant chemotherapy, gender and age group (three strata).

Statistical methods for clinical analyses

When feasible, crude data are presented with statistical comparison made between randomisation arms based on chi-squared tests for binary or categorical data, the *t*-test or analysis of variance as appropriate for comparing group means and the Kruskal–Wallis test for comparing medians. Time to recurrence was analysed by the Kaplan–Meier method, to take account of both time-censoring and the difference in the number of recurrences detected in each arm. The plots of time to recurrence are compared by the log-rank Mantel–Cox statistic. Adjusted odds ratios (ORs) for the main outcome were calculated by binary logistic regression; Cox HRs are also reported for comparison of overall mortality. The primary analysis was undertaken using IBM Statistical Product and Service Solutions (SPSS) version 20 (IBM Corporation, Armonk, NY, USA).

Statistical methods for economic analyses

The analysis was conducted from the perspective of the UK NHS, with national average unit costs (expressed in 2012–13 UK pounds sterling) obtained from a variety of sources and applied to patient-level resource-use volumes to derive costs per patient. As the time horizon for the analysis was 5 years, costs and QALYs were discounted to present values at an annual rate of 3.5%. Multiple imputation using chained regression equations were used to impute missing values. An incremental cost-effectiveness ratio (ICER) was computed and compared against the cost-effectiveness threshold specified by the National Institute for Health and Care Excellence (£20,000–30,000 per QALY). Non-parametric bootstrapping was used to generate cost-effectiveness acceptability curves. All economic analyses were performed using Stata® version 12 (StataCorp LP, College Station, TX, USA).

Protocol adherence and withdrawal

Adherence to protocol was ascertained through NHS hospital and laboratory records. A secondary per-protocol analysis is reported that excludes the 308 patients who received any unscheduled investigation or had missed more than one scheduled examination. Reasons for withdrawal were sought. All patients who withdrew gave their consent for continued follow-up through ONS mortality records. The analysis of other clinical outcomes (including recurrence and recurrence treated surgically with curative intent) is censored on the date of withdrawal.

Clinical results

Detection of recurrence

During the 5 years of scheduled follow-up, cancer recurrence was detected in 203 (16.9%) participants. Two-thirds of recurrences (134, 66.0%) were detected by a scheduled follow-up investigation: 88 (64.7%) by CT, 43 (31.6%) by CEA testing and five at colonoscopy (either by colonoscopy or by another investigation

initiated at the consultation) (2.98%). Fewer recurrences were detected in the minimum arm than in the intensive follow-up arms (12.6% vs. 18.3%; $p = 0.02$).

Recurrence treatable with curative intent

The proportion of participants with recurrence surgically treated with curative intent was 6.3% (76/1202) overall, with little difference according to Dukes' staging (stage A, 5.1%; stage B, 7.4%; stage C, 5.6%; $p = 0.56$). The proportion was two to three times higher in each of the three more intensive follow-up arms (7.5% overall) than in the minimum follow-up arm (2.7%) (absolute difference 4.8%; $p = 0.003$). The adjusted OR in the factorial comparison was 2.5 for CEA testing only ($p = 0.04$) and 3.7 for CT only ($p = 0.002$). There was no evidence of any additive effect (the adjusted OR for the combined CT and CEA testing arm was not significantly different from that for CT or CEA testing alone).

Post-recurrence survival

The number of patients with recurrence detected during scheduled follow-up who were still alive at the time of analysis was higher in intensive follow-up arms (4.8% vs. 2.3%; $p = 0.07$), as was the median post-recurrence survival (27.3 vs. 14.6 months; $p = 0.11$), but neither difference is statistically significant. Of the patients with recurrence treated with curative intent, 53% were alive at the end of follow-up.

Overall survival

Total mortality at a median of 8.7 years post randomisation in each group was as follows: CEA testing, 63 deaths (33%); CT, 80 deaths (32%); CEA testing and CT, 63 deaths (27%); and minimum follow-up, 52 deaths (28%). There were no significant differences in the total number of deaths, or in the number of deaths attributed to colorectal cancer, between the four randomisation arms or two factorial groups. The Kaplan–Meier overall survival analysis showed no significant difference in survival over time between arms (log-rank $p = 0.45$). The baseline-adjusted Cox hazard ratio (HR) comparing the minimum and intensive arms showed a non-significant survival advantage for minimum follow-up of 0.87 [95% confidence interval (CI) 0.67 to 1.15]. These CIs suggest an upper limit to the absolute mortality benefit from intensive follow-up of 3.8%; the lower limit means that it is impossible to exclude the possibility of harm, although this is unlikely to be based on the survival of patients treated with curative intent.

Observational analysis of recurrence by site

This analysis was based on 189 patients with recurrence in the 2012 data set. The incidence of recurrence varied according to the site of the primary (right colon, 51/379, 14%; left colon, 68/421, 16%; rectum, 70/332, 21%; $p = 0.023$) and initial stage (Dukes' A, 26/249, 10%; Dukes' B, 81/537, 15%; Dukes' C, 82/346, 24%; $p < 0.0001$). Recurrences from lower-stage cancers were more likely to be treatable with curative intent (Dukes' A, 13/26, 50%; Dukes' B, 32/81, 40%; Dukes' C, 20/82, 24%; $p = 0.03$). Those with rectal cancers benefited most from follow-up (proportion with treatable recurrence: rectum, 30/332, 9%; left colon, 23/421, 6%; right colon, 12/379, 3%; $p = 0.003$). Both initial stage (log-rank $p = 0.005$) and site of primary cancer (log-rank $p = 0.01$) influenced post-recurrence survival.

Economic results

The incremental cost per patient treated surgically with curative intent compared with minimum follow-up was £40,131 with CEA testing, £43,392 with CT and £85,151 with CEA testing and CT. However, the lack of differential impact on survival means there was little difference in QALYs saved between the minimum follow-up [3.61, standard error (SE) 0.07] and intensive arms (CEA testing 3.66, SE 0.06; CT 3.62, SE 0.07; CEA testing and CT 3.59, SE 0.07). Consequently, the overall mean (SE) patient costs per QALY saved were lower in the minimum follow-up arm [£3138 (£334)] than in the more intensive arms [£4613 (£438) CEA testing; £6048 (£393) CT; £6796 (£618) CEA testing and CT]. The additional cost per QALY gained of moving from minimum follow-up to CEA testing was £25,951 and for CT was £246,107. When compared with minimum follow-up, combined CEA testing and CT was more costly and generated fewer QALYs resulting in a negative ICER (–£208,347) and a dominated policy.

Conclusion

The proportion of participants with recurrence treated with curative intent was lower than predicted from previous trials (6.0% overall), but it was three times higher in the more intensive follow-up arms than in the minimum follow-up arm. Both CEA testing (with a single CT scan) and regular CT imaging are effective modes of follow-up, but combining regular CEA testing and CT imaging provided no additional benefit. There was no statistical difference in overall deaths or colorectal cancer deaths in the minimum compared with the intensive follow-up arms after a median of 8.7 years of observation. The CIs around the HR show that if there is a survival benefit from intensive follow-up in the first 10 years it is very unlikely to exceed 4% in absolute terms and harm cannot be excluded. Of the intensive follow-up strategies, CEA testing has the lowest cost per treatable recurrence detected and the lowest cost per QALY gained when compared with minimum follow-up. However, a longer time horizon is required to ascertain whether or not identifying more curatively treatable recurrences offers a survival benefit and thus a more efficient use of scarce health-care resources than minimum follow-up.

Trial registration

This trial is registered as ISRCTN41458548.

Funding

Chapter 1 Introduction

Background

Colorectal cancer is a major health problem. In the UK, around 32,000 cases are diagnosed annually and 16,000 deaths are attributed to the disease.[1] Surgery is the mainstay of treatment and most cases cured are cured by surgery alone. Adjuvant chemotherapy reduces the risk of relapse in high-risk patients and radiotherapy reduces the local recurrence rate in patients with high-risk rectal cancer. For selected patients who develop either local recurrence or distant metastases following surgery for primary disease, resection of recurrent disease, most commonly in the liver, may still result in cure. In a meta-analysis of > 20,000 patients, 40% of patients having liver resection were alive after 5 years and 30% were alive at 10 years.[2] Similar, if less well-documented, results are seen in surgery for local recurrence or lung metastases.[3,4] In those not considered to have upfront resectable recurrent disease, the early initiation of chemotherapy may prolong survival[5] or, importantly, may downsize metastases to operability.[6]

Traditionally, patients who have curative surgery for colorectal cancer are subject to long-term follow-up, the detection of treatable recurrence being one of the objectives. Curatively treated cancer in this setting is commonly held to refer to a patient without metastatic disease other than in local lymph nodes in whom all disease has been removed. Clinicians use various protocols, but few, if any, are evidence based. The costs to the NHS of follow-up are substantial and they need to be justified by evidence of cost-effectiveness. Although a number of studies have assessed the value of follow-up of patients with curatively resected colorectal cancer, none provides a definitive answer, for a variety of reasons.

At the time this study was developed, a number of randomised trials of colorectal cancer follow-up had been published.[7–10] The largest of these[7] showed no benefit of follow-up, but the protocol did not include intensive imaging. Two small and underpowered studies appeared to show benefit of follow-up, but these did not achieve statistical significance.[8,9] Only one of these trials[8] included intensive liver imaging. A study[10] of 325 patients compared intensive follow-up with computerised tomography (CT) and colonoscopy, with a structured clinical review and simple tests. More patients with asymptomatic metastases were detected in the investigational arm, but the number of potentially curative hepatectomies was not different. However, this study may not have been powerful enough to detect a difference between the two active follow-up schedules.

Preliminary results of a further trial to evaluate the effect of undertaking 'second-look' surgery in response to a rise in carcinoembryonic antigen (CEA) during follow-up were reported in 1984.[11] At the time that the Follow-up After Colorectal Surgery (FACS) trial was designed, this trial had not demonstrated any benefit from the intervention, and a subsequent publication confirmed this.[12] However, the trial suffers from the criticism that patients who developed recurrence were not commonly offered treatments that could impact on survival, such as liver/lung resection. Of the non-randomised trials, a meta-analysis suggested benefit if the follow-up strategy included CEA testing.[13] A Cochrane review concluded that there may be a benefit of imaging follow-up (around 8%), but that further adequately powered studies were necessary[14] as publication bias was likely.

It is recognised that most of the trials performed in this area preceded the common use of liver resection and modern effective chemotherapy in patients found to have metastatic disease. However, there is sufficient clinical and scientific uncertainty about a potentially important clinical treatment to justify a trial on ethical grounds. A pre-trial economic model was devised to assist in the development of the trial protocol and was used to assess the probable costs, effects and cost-effectiveness of each of the trial options. The results of this modelling (shown in *Appendix 1* along with the parameter values) indicated that relatively small gains in survival could well be cost-effective, that it was important to include a primary

care-based follow-up option with CEA monitoring in the study, that accurate information was required on palliative care alongside other aspects of resource use and that the cost-effectiveness results would be strongly influenced by the duration of follow-up and analytic horizon.

Four objectives of follow-up were considered in developing the trial.

1. *Early detection of metastatic disease*. There is unambiguous evidence that the resection of colorectal liver metastases may result in cure. Approximately 40% of patients who have a R0 (≥ 1-mm clearance at lateral margins) resection performed (no residual disease, microscopically clear margins) will survive for 5 years and 30% will survive to 10 years.[2,15] Recurrence after 10 years is not reported. The data for lung metastases are similar, although somewhat more contentious.[3,16] Although it is not absolutely certain how many patients with liver metastases are suitable for resectional surgery, the only prospective analysis suggests that the figure may be as high as 20%.[17] There is also some evidence of a survival benefit (beyond lead time) from early diagnosis and pre-symptomatic treatment with cytotoxic chemotherapy in patients not suitable for resection.[5] Furthermore, cytotoxic chemotherapy increases in a number of patients suitable for resectional liver surgery[18] and also improves the outlook of those with resectable disease.[19]
2. *Removal of further adenomatous polyps and metachronous cancer*. Patients who have developed colorectal cancer are at increased risk of further adenomatous polyps and metachronous cancer. The detection and removal of metachronous polyps or early cancer may benefit the patient in survival terms. However, it is held that if a 'clean colon' (no polyps) is achieved during initial treatment, then follow-up colonoscopy after several years is adequate for patients without specific genetic susceptibility.[20]
3. *Early detection of surgically treatable luminal recurrence*. Endoscopy may detect luminal recurrence. However, luminal recurrence is uncommon[21] and can be a manifestation of more extensive local recurrence. At the time of trial design, there was uncertainty regarding whether or not this is commonly curable.[22]
4. *Improvement in quality of life*. One randomised study suggested that follow-up has a small quality-of-life advantage over no follow-up.[23] However, a randomised trial of hospital- and community-based follow-up of patients with breast cancer in the UK, comparing quality of life and diagnostic delay, showed no advantage of hospital follow-up and found that patient satisfaction with care was higher in the general practice arm.[24]

Audit evidence suggests that follow-up, as normally practised in the early 2000s, when the trial was designed, seldom included surveillance with tumour markers or regular imaging.[25] Such practice was unlikely to achieve any of the four ends detailed above. Clinical examination may provide reassurance, but clinical examination is not clear that this reassurance is best provided in a hospital setting and it is unlikely to detect many cases of treatable recurrence. The use of colonoscopy in the detection of metachronous polyps is also established,[26] and will ultimately impact on the incidence of metachronous cancer,[20] but this need not be frequent. Anastomotic and missed synchronous cancer may also be detected (in spite of apparently complete colonic imaging), but the detection rate is low.[21] The follow-up modalities most likely to influence the primary end point were intensive imaging and serial tumour marker measurements. There was evidence that these could detect recurrence at an early and treatable stage.[14]

At the time of developing the trial, spiral CT imaging was probably the best non-invasive, widely available method of detecting colorectal metastases. Even so, the sensitivity reported varied between approximately 75% and 94%,[27,28] depending on the gold standard used. Spiral CT imaging is expensive and involves a considerable ionising radiation dose. Magnetic resonance imaging (MRI) does not involve ionising radiation and is more sensitive for detecting liver metastases (around 80%),[27] but it is much less effective for the detection of lung and other metastases, is more expensive and is less widely available. Transabdominal ultrasound is widely available and inexpensive, but it is less sensitive for the detection of hepatic metastases (77%)[28] and generally unhelpful in the detection of most extrahepatic metastases. Six-monthly CT is affordable in service terms and is currently used, with variable frequency, in most colorectal cancer units.

In order to satisfy Ionising Radiation (Medical Exposure) Regulations 2000 regulations,[29] and to reflect the findings published in *Radiation Protection Dosimetry*,[30] the patient information sheet indicated probable radiation doses and the cancer risk associated with CT imaging during the study. The patients randomised to the CT and CEA testing plus CT arms who completed all seven CT scans were exposed to a total effective radiation dose of about 140 mSv, associated with a lifetime risk of induction of a fatal cancer of about 1 in 2000. For the small group of younger (aged < 70 years) participants, the risk is higher, approximately 1 in 300. Risk from a particular radiation dose increases with younger age because there is more time for any genetic damage caused by the radiation to progress to a clinical problem.

The International Commission on Radiological Protection report on 'Radiological Protection in Biomedical Research' categorises the level of radiation involved in this study as 'moderate', with a 'substantial' societal benefit expected.[31] If a participating centre was unable to comply with these dose constraints, the co-ordinating centre (Southampton) would be informed. A local amendment of the patient information sheet would then be produced and submitted for approval by the main Research Ethics Committee (South West Multi-centre Research Ethics Committee).

Although a number of tumour markers are expressed in patients with colorectal cancer, CEA levels are most frequently detected.[32] It has been shown to be a useful adjunct to the detection of recurrent disease in colorectal cancer[32] and can be used to monitor the progress of patients undergoing chemotherapy for colorectal cancer.[33] CEA monitoring is risk free and has the advantage of being able to be used in primary care. At the time the protocol was developed, an elevated CEA level was thought to have a 77% sensitivity for recurrence (100% for liver metastases) combined with a 98% specificity,[27] although a recently published Cochrane review suggests poorer diagnostic performance.[34] The elevation in CEA level usually occurs prior to progression appearing on imaging.[33]

In the context of the radically different follow-up modalities that were being proposed, we considered that assessment of quality of life was essential. The EuroQol-5 Dimensions (EQ-5D) is a generic measure that assesses five broad dimensions of health status: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[35] The EQ-5D also provides utility scores for use in cost–utility analyses. The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (quality of life) is a disease-specific instrument widely used in European oncology trials that provides assessments of physical function, role function, cognitive function, emotional function, social function, symptoms and a global judgement of quality of life.[36] The Hospital Anxiety and Depression Scale (HADS) is also widely used in oncology trials, providing assessments of two dimensions of psychological well-being, anxiety and depression, with items that avoid physical symptoms that may arise from physical, rather than psychological, health.[37] Acceptability of follow-up regimes would then be assessed by a modified form of a College of Health Questionnaire that has proved sensitive to differences in follow-up regimes in patients with breast cancer.[38] The instrument addresses patients' perceptions of three aspects of health care: service delivery, consultations and continuity. A small number of items were also selected and piloted from the seven-item questionnaire used by Kjeldsen *et al.*[23] in their study of follow-up after radical colorectal surgery. These items more directly address issues of the perceived value and distress of follow-up visits for patients after colorectal surgery.

Health-related quality-of-life (HRQoL) instruments (EQ-5D, EORTC QLQ-C30, HADS) were selected because they have been validated for use in oncology trials; their content is appropriate to assess the impact of follow-up regimes and the number of items (49) should impose a relatively modest burden on respondents. Two more condition-specific instruments were published at the time of writing the FACS trial protocol assessing HRQoL for colorectal cancer, but they were not considered to address any important issues ignored by the selected battery of instruments and did not appear to be developed to address problems experienced by patients during the period following surgery.[39,40]

Objective

The study objective was to assess the effect on the number of recurrences treated surgically with curative intent of augmenting symptomatic follow-up in primary care with two intensive methods of follow-up: monitoring of a tumour marker in primary care and intensive imaging in hospital.

Chapter 2 Methods

Trial design

This was a factorial 2 × 2 pragmatic randomised controlled trial to assess the outcome of scheduled follow-up following primary curative treatment of colorectal cancer with blood CEA testing and/or CT imaging (plus additional colonoscopy) for 5 years, compared with minimal symptomatic follow-up. Participants were randomised independently (on a 1 : 1 allocation ratio) to 6- to 12-monthly CT imaging or minimum follow-up and to 3- to 6-monthly CEA testing or minimum follow-up. The minimum and CEA testing arms were permitted a single CT scan at 12–18 months.

Participants

The trial was conducted in 39 NHS hospitals in England that had access to high-volume regional services geared towards offering surgical treatment for metastatic recurrence. Participants were recruited between January 2003 and August 2009. All participants had undergone curative treatment for primary colorectal cancer with no residual disease, microscopically clear margins and Dukes' A to C stage [tumour, node, metastasis (TNM) stage I–III]. They were disease free on colonic imaging with no evidence of metastatic disease (confirmed by CT or MRI liver scan and chest CT scan) and with a post-operative blood CEA level of ≤ 10 µg/l. For patients having adjuvant therapy, CEA level was measured after the completion of chemotherapy and a CT scan was performed.

For a patient to enter the trial, their primary curative treatment had to be complete. Patients were excluded if they had concurrent serious illness, dominantly inherited colon cancer or an inability to give written informed consent or if they were involved in a primary treatment trial with conflicting follow-up requirements. Potential participants who were aged < 50 years or were > 6 months from completion of primary or adjuvant treatment were included only if a case for their inclusion was agreed by the chief surgical investigator.

Interventions

Follow-up was scheduled for 5 years from trial entry. The factorial design, with independent allocation to the CEA testing and CT interventions, meant that patients received one of four types of follow-up:

1. CEA testing follow-up – 3-monthly measurement of blood CEA level for 2 years, and then 6-monthly for 3 years, with a single chest, abdominal and pelvic CT scan at 12–18 months
2. CT follow-up – 6-monthly chest, abdominal and pelvic CT scan for 2 years, and then annually for 3 years
3. CEA testing and CT follow-up – both blood CEA measurement and CT imaging as above
4. minimum follow-up – no scheduled follow-up except a single chest, abdominal and pelvic CT scan at 12–18 months if requested at study entry by the hospital clinician.

The discretional CT scan in the minimum arm was adopted as a protocol amendment in May 2005 to reflect changing clinical opinion among many participating clinicians on the position of equipoise following publication of new national guidance on follow-up.[41]

All patients had been investigated by colonoscopy at trial entry (to ensure that there was no residual or metachronous intraluminal disease) and were offered an end-of-trial colonoscopy at 5 years; in the two CT arms, a colonoscopy to check for luminal recurrence was also undertaken at 2 years.

For those undergoing CEA testing follow-up, blood collection kits were sent directly to the patient, who then attended their own general practice for phlebotomy. The blood was sent by post to the biochemistry laboratory at John Radcliffe Hospital; the CEA testing analysis was carried out using a ADVIA Centaur XP analyser (Siemens Healthcare Limited, Camberley, UK). If the blood CEA level was ≥ 7 µg/l above the patient's baseline level at trial entry, the test was repeated as soon as possible; if the second test was also above this threshold, the general practitioner (GP) was asked to refer the patient urgently to the local hospital.

Outcomes

The original protocol specified overall survival as the primary clinical outcome. However, by 2006 (after 3 years of recruitment) it was clear that we would fall far short of our original recruitment target. The Data Monitoring and Ethics Committee (DMEC) also conducted an analysis of outcomes in the first 500 patients, which showed that the recurrence and survival rates were substantially better than predicted from routine data. They therefore advised the Health Technology Assessment (HTA) programme in 2007 that the trial would have insufficient power to assess mortality within the projected time scale (i.e. when all participants had completed the 5-year follow-up) and that the primary outcome should be changed to surgical treatment of recurrence with curative intent.

Surgical treatment of recurrence with curative intent is, therefore, reported here as the primary clinical outcome. Overall mortality is reported here as the main secondary clinical outcome. Other pre-specified secondary clinical outcomes reported are deaths from colorectal cancer, time to detection of recurrence and post-recurrence survival.

Data on treatment of recurrence and treatment intent were recorded on case report forms (CRFs) by local National Cancer Research Network (NCRN) staff (who had access to the full clinical records).

Information on deaths was collected by flagging each participant at the Office for National Statistics (ONS) central registry; cause of death was abstracted from death certificates.

Sample size

The trial originally set out to recruit 4800 participants in order to detect a 4% improvement in survival from 49% to 53% in any of the more intensive follow-up arms (CEA testing, CT or CEA testing and CT), compared with the minimum follow-up arm. In advising the change in main outcome from mortality to recurrence treated surgically with curative intent, the DMEC estimated that to detect a 6% absolute difference between minimum follow-up and any of the three other more intensive follow-up arms with 80% power (two-sided alpha 0.05) would require 205 patients in each of the four follow-up arms; 590 subjects allocated to each factorial group (CEA measurement and CT imaging) would provide 80% power to detect a 3% absolute difference in the factorial comparison. We therefore planned to stop recruitment when we reached a minimum of 1180 participants.

Randomisation and blinding

Patients were independently allocated at random in a 1 : 1 ratio to receive or not receive each of the factorial interventions (CEA measurement and CT imaging) using the telephone randomisation service

provided by the Oxford Clinical Trials Unit. Research staff at the local centres telephoned the unit, giving patient details and answering a checklist of questions to confirm eligibility. A computerised algorithm was applied using the method of minimisation to balance the patient characteristics within each centre. The balancing variables were adjuvant chemotherapy, gender and age group (three strata).

As this was a pragmatic open trial, it was not possible to conceal allocation arm either to the participants or to the clinical team involved in patient management. However, the research staff who abstracted the outcome data from the clinical notes were employed by the local NCRN teams, independent of the investigators.

The initial protocol had specified that the primary analysis would be undertaken when all patients had completed 5 years' follow-up. As a result of the extended period of recruitment and the change in the main outcome measure, the DMEC subsequently advised that an interim analysis should be undertaken (and randomisation code broken) in September 2012, when all participants had completed a minimum of 3 years' scheduled follow-up. This interim analysis programme was undertaken first using dummy variables for the allocation arms and the code was not broken until the syntax was agreed. The analysis reported here (based on outcome data collected up to November 2014) applies the same syntax as for the interim analysis but necessarily was not blinded to allocation arm.

Statistical methods for clinical analyses

The primary analysis was undertaken using IBM Statistical Product and Service Solutions (SPSS) Statistics version 20 (IBM Corporation, Armonk, NY, USA). When feasible, crude data are presented with statistical comparison made between randomisation arms based on chi-squared tests for binary or categorical data, the t-test or analysis of variance as appropriate for comparing group means and the Kruskal–Wallis test for comparing medians. Time to recurrence was analysed by the Kaplan–Meier method, to take account of both time-censoring and the difference in the number of recurrences detected in each arm. The plots of time to recurrence are compared by the log-rank Mantel–Cox statistic. Adjusted odds ratios (ORs) for the main outcome were calculated by binary logistic regression, entering all the baseline characteristics, reported in *Table 1*, into the model. Cox HRs are also reported for comparison of overall mortality. As there was significant interaction between the CEA testing and CT factorial groups ($p = 0.013$), the main comparison made in presenting the results is between the three intensive arms and the minimum follow-up arm.

Protocol adherence and withdrawal

Adherence to protocol was ascertained through NHS hospital and laboratory records. A secondary per-protocol analysis is reported that excludes the 308 patients who received any unscheduled investigation or had missed more than one scheduled examination. Reasons for withdrawal were sought. All patients who withdrew gave consent for continued follow-up through ONS mortality records. The analysis of other clinical outcomes (including recurrence and recurrence treated surgically with curative intent) is censored on the date of withdrawal.

Protocol amendments

The two significant amendments to the original 2003 protocol during the trial have been described above. The initial protocol did not specify the single CT scan at 12–18 months in the minimum follow-up arm; 66 patients were randomised before this change took effect in May 2005. Surgical treatment with curative intent rather than overall survival was specified as the main outcome in 2007, when it became clear that we could not recruit the number of participants necessary to estimate an effect on overall survival with adequate statistical power.

Chapter 3 Results

Characteristics of participants

The allocation of the 1202 participants recruited between January 2003 and August 2009 to each randomisation arm and subsequent drop-out is shown in the Consolidated Standards of Reporting Trials (CONSORT) diagram (*Figure 1*). The characteristics of participants at trial entry are shown in *Table 1*. The mean age of participants was 69 years, 61.2% were male, 29.1% had significant comorbidity, 40.5% had received adjuvant chemotherapy and 11.6% had received pre-operative radiotherapy (for rectal cancer) before randomisation. The randomisation method was successful in achieving a good balance between randomisation arms and factorial comparison groups, with no statistically significant or important difference in age, gender, ethnicity, tumour site and stage, adjuvant treatment or smoking habit.

Length and completeness of follow-up

The duration of scheduled follow-up to detect recurrence was 5 years and the median time elapsed since trial entry during which we collected mortality data was 8.7 years at the data lock in the autumn of 2014. As mortality data were collected through ONS flagging of death certificates, follow-up is complete except for three participants who have emigrated from the UK. As the CONSORT diagram (see *Figure 1*) shows, clinical follow-up continued until a trial end point (death, recurrence or end of scheduled follow-up), except in the 145 patients who withdrew during the study. The main reasons for withdrawal were deteriorating health (40.0%), dislike of the allocated mode of follow-up (41.4%) and moving away (13.8%). Although *Table 2* shows that there was no significant difference between arms in the number of withdrawals, there were more withdrawals from dislike of the allocated mode of follow-up in the minimum arm (27/301, 9.0%) than in the more intensive arms (32/901, 3.5%), and the median length of follow-up was shorter.

Detection of recurrence

During the 5 years of scheduled follow-up, cancer recurrence was detected in 203 (16.9%) participants (see *Table 2*). Two-thirds of recurrences (134, 66.0%) were detected by a scheduled follow-up investigation: 87 (64.9%) by CT, 43 (32.1%) by CEA measurement and four at colonoscopy (either by colonoscopy or other investigation initiated at the consultation) (2.98%). Fewer recurrences were detected in the minimum arm than in the intensive follow-up arms (12.6% vs. 18.3%; *p* = 0.02).

The Kaplan–Meier plots in *Figure 2* show the detection of recurrence over time. The difference between the three more intensive arms and the minimum arm in detection of recurrence does not reach statistical significance (log-rank *p* = 0.07), but the difference in detection of recurrence treatable with curative intent is significant (log-rank *p* = 0.005), with none detected in the minimum follow-up arm after the end of year 2.

Curative treatment and survival

The proportion of participants with recurrence surgically treated with curative intent was 6.3% (76/1202) overall, with little difference according to Dukes' stage (stage A, 5.1%; stage B, 7.4%; stage C, 5.6%; *p* = 0.56). *Table 3* shows that surgical treatment of recurrence with curative intent was two to three times higher in each of the three more intensive follow-up arms (7.5% overall) than in the minimum follow-up
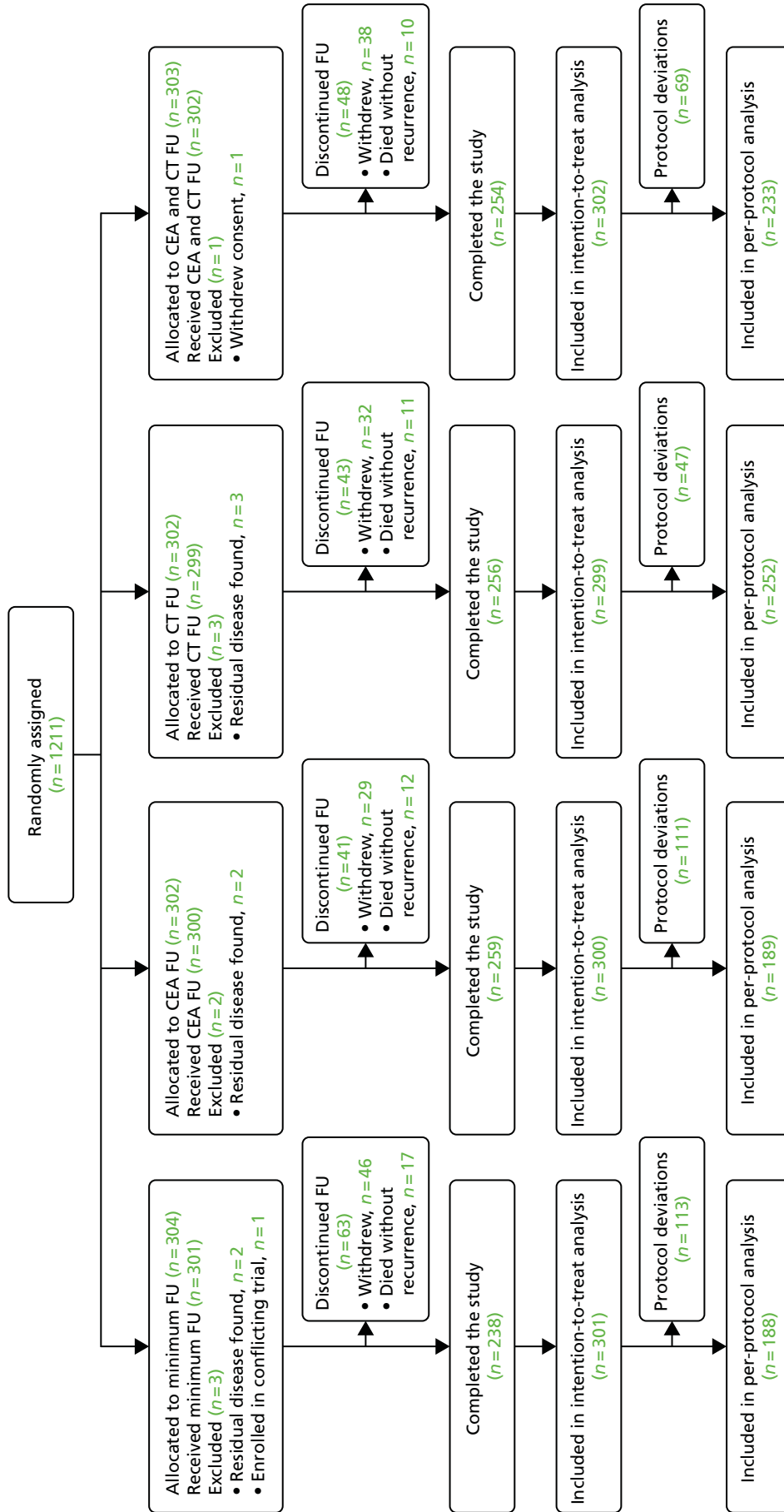
FIGURE 1 Consolidated Standards of Reporting Trials diagram. FU, follow-up.

TABLE 1 Characteristics of participants at trial entry by randomisation arm and factorial group

Characteristics	Individual randomisation arm				Factorial comparison group			
	CEA testing only (N = 300)	CT only (N = 299)	CEA testing and CT (N = 302)	Minimum (N = 301)	CEA testing (N = 602)	No CEA testing (N = 600)	CT (N = 601)	No CT (N = 601)
Age (years)								
Mean (SD)	68.8 (8.3)	69.0 (8.9)	69.5 (8.1)	69.3 (8.5)	69.2 (8.2)	69.1 (8.7)	69.2 (8.5)	69.1 (8.4)
Median (IQR)	69 (63–75)	69 (62–76)	70 (64–76)	70 (63–75)	69 (63–75)	70 (63–76)	70 (63–76)	69 (63–75)
Male gender, n (%)	184 (61.3)	183 (61.2)	185 (61.3)	184 (61.1)	369 (61.3)	367 (61.2)	368 (61.2)	368 (61.2)
Concurrent treatment for other illness, n (%)	90 (30.0)	81 (27.1)	86 (28.5)	93 (30.9)	176 (29.2)	174 (29.0)	167 (27.8)	183 (30.4)
Pre-treated with chemotherapy, n (%)	121 (40.3)	118 (39.5)	125 (41.4)	123 (40.9)	246 (40.9)	241 (40.2)	243 (40.4)	244 (40.6)
Pre-treated with radiotherapy, n (%)	32 (10.7)	34 (11.4)	38 (12.6)	35 (11.7)	70 (11.6)	69 (11.6)	72 (12.1)	67 (11.2)
Site of cancer,[a] n (%)	(N = 293)	(N = 290)	(N = 292)	(N = 295)	(N = 585)	(N = 585)	(N = 582)	(N = 588)
Right colon	93 (31.7)	96 (33.1)	90 (30.8)	103 (34.9)	183 (31.3)	199 (34.0)	186 (32.0)	196 (33.3)
Left colon	118 (40.3)	96 (33.1)	110 (37.7)	105 (35.6)	228 (39.0)	201 (34.4)	206 (35.4)	223 (37.9)
Rectum	82 (28.0)	98 (33.8)	92 (31.5)	87 (29.5)	174 (29.7)	185 (31.6)	190 (32.6)	169 (28.7)
Dukes' stage,[b] n (%)	(N = 289)	(N = 293)	(N = 287)	(N = 292)	(N = 576)	(N = 585)	(N = 580)	(N = 581)
A	54 (18.7)	71 (24.2)	60 (20.9)	69 (23.6)	114 (19.8)	140 (23.9)	131 (22.6)	123 (21.2)
B	144 (49.8)	132 (45.1)	146 (50.9)	131 (44.9)	290 (50.3)	263 (45.0)	278 (47.9)	275 (47.3)
C	91 (31.5)	90 (30.7)	81 (28.2)	92 (31.5)	172 (29.9)	182 (31.1)	171 (29.5)	183 (31.5)
Smoking status,[c] n (%)	(N = 290)	(N = 288)	(N = 294)	(N = 290)	(N = 584)	(N = 578)	(N = 582)	(N = 580)
Current smoker	20 (6.9)	16 (5.6)	18 (6.1)	14 (4.8)	38 (6.5)	30 (5.2)	34 (5.8)	34 (5.9)
Ex-smoker	145 (50.0)	154 (53.5)	162 (55.1)	155 (53.4)	307 (52.6)	309 (53.5)	316 (54.3)	300 (51.7)
Never smoked	125 (43.1)	118 (41.0)	114 (38.8)	121 (41.7)	239 (40.9)	239 (41.3)	232 (39.9)	246 (42.4)

IQR, interquartile range; SD, standard deviation.
a Site not specified precisely for 32 participants (2.7%).
b Dukes' stage not recorded for 41 participants (3.4%).
c Smoking status not recorded for 40 participants (3.3%).

TABLE 2 Withdrawal from follow-up and diagnosis of recurrence during the 5-year intervention period by randomisation arm and factorial group

Description	Individual randomisation arms					Factorial comparison groups					
	CEA testing only	CT only	CEA testing and CT	Minimum	p-value	CEA testing	No CEA testing	p-value	CT	No CT	p-value
Withdrawn without diagnosis of recurrence, n (%)	29 (9.7)	32 (10.7)	38 (12.6)	46 (15.3)	0.16	67 (11.1)	78 (13.0)	0.32	70 (11.6)	75 (12.5)	0.66
Median duration of observation (months)	26.9	20.1	24.7	7.9		19.5	20.7		20.0	20.3	
Died without diagnosis of recurrence, n (%)	12 (4.0)	11 (3.7)	10 (3.3)	17 (5.6)	0.96	22 (3.7)	28 (4.7)	0.80	21 (3.5)	29 (4.8)	0.93
Diagnosed with recurrence											
All sites, n (%)	56 (18.7)	61 (20.4)	48 (15.9)	38 (12.6)	0.06	104 (17.3)	99 (16.5)	0.72	109 (18.1)	94 (15.6)	0.25
Liver, n	23	30	19	15		42	45		49	38	
Lung, n	23	18	17	11		40	29		35	34	
Locoregional, n	18	19	15	14		33	33		34	32	
Other, n	12	8	9	14		21	22		17	26	
Recurrences detected by a scheduled follow-up examination, n (%)	35 (11.7)	52 (16.1)	40 (13.2)	9 (3.0)	< 0.001	75 (12.5)	61 (10.2)	0.21	92 (15.3)	44 (7.3)	< 0.001
Blood CEA level, n	30	0	13	0		43	0		13	30	
CT imaging, n	3	49	26	9		29	58		75	12	
Colonoscopy, n	0	3	1	0		1	3		4	0	

Note
Recurrence is often detected at more than one site so numbers do not sum to total number of participants with recurrence.

(a)

Number at risk

Symptomatic follow-up	299	261	235	224	211	199
CEA testing	300	271	249	232	215	203
CT imaging	299	264	236	225	209	198
CT imaging and CEA	302	265	247	230	216	206

Log-rank overall comparison, $p = 0.18$; intensive vs. minimum, $p = 0.07$

(b)
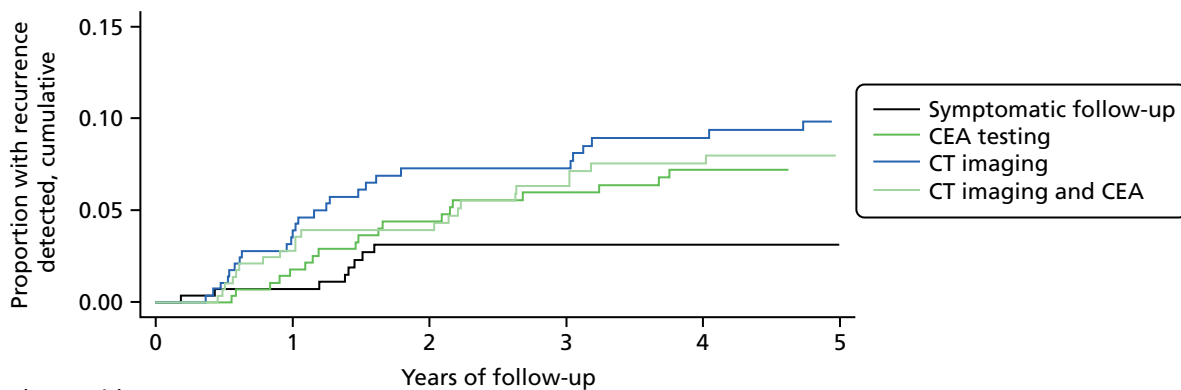
Number at risk

Symptomatic follow-up	299	261	235	224	211	199
CEA testing	300	271	249	232	215	203
CT imaging	299	264	236	225	209	198
CT imaging and CEA	302	265	247	230	216	206

Log-rank overall comparison, $p = 0.016$; intensive vs. minimum, $p = 0.005$

FIGURE 2 Kaplan–Meier plots of time to diagnosis of (a) any recurrence and (b) any recurrence surgically treatable with curative intent by follow-up group.

arm (2.7%) (absolute difference 4.8%; $p = 0.003$). The adjusted OR was 2.5 for CEA measurement only ($p = 0.04$) and 3.7 for CT only (0.002).

Both CT and CEA testing were significantly more effective than minimum follow-up in detecting recurrence treatable with curative intent, but there was no evidence of any additive effect (the adjusted OR for the combined CT + CEA testing arm was not significantly different from that for CT or CEA testing alone). More recurrences were detected in the CT arm than in the CEA testing arm (9.4% vs 6.3%; $p = 0.16$). Although the difference between CEA testing and CT was not statistically significant, the factorial comparison showed a significant absolute benefit only for CT (absolute difference 3.7%; $p = 0.01$).

TABLE 3 Treatment of recurrence with curative intent and survival by randomisation arm and factorial group (intention-to-treat analysis)

Description	Individual randomisation arms					Factorial comparison groups					
	CEA testing only (N = 300)	CT only (N = 299)	CEA testing and CT (N = 302)	Minimum (N = 301)	p-value	CEA testing (N = 602)	No CEA testing (N = 600)	p-value	CT (N = 601)	No CT (N = 601)	p-value
Surgical treatment with curative intent, n (%)	19 (6.3)	28 (9.4)	21 (7.0)	8 (2.7)	0.008	40 (6.6)	36 (6.0)	0.65	49 (8.2)	27 (4.5)	0.009
Adjusted OR[a]	2.40	3.69	2.78	1		1.13	–		1.87	–	
95% CI	1.02 to 5.65	1.63 to 8.38	1.19 to 6.49			0.70 to 1.82			1.14 to 3.07		
Wald's p-value	0.041	0.002	0.020			0.63			0.014		
Mortality											
Total deaths, n (%)	81 (27.0)	83 (27.8)	72 (23.8)	70 (23.3)	0.49	153 (25.4)	153 (25.5)	0.97	155 (25.8)	151 (25.1)	0.79
Deaths attributed to colorectal cancer, n (%)	48 (16.0)	45 (15.1)	38 (12.6)	38 (12.6)	0.73	86 (14.3)	83 (13.8)	0.84	83 (13.8)	86 (14.3)	0.92
Patients with recurrence still surviving, n (%)	14 (4.7)	14 (4.7)	15 (5.0)	7 (2.3)	0.33	29 (4.8)	21 (3.5)	0.25	29 (4.8)	21 (3.5)	0.25
Patients with recurrence treated with curative intent still surviving, n (%)	11 (3.7)	11 (3.7)	13 (4.3)	5 (1.7)	0.29	24 (4.0)	16 (2.7)	0.20	24 (4.0)	16 (2.7)	0.20
Median survival post recurrence (months)											
All patients with recurrence	23.7 (n = 56)	25.5 (n = 61)	38.0 (n = 48)	14.6 (n = 38)	0.16	27.7 (n = 104)	23.1 (n = 99)	0.44	29.2 (n = 109)	20.7 (n = 94)	0.08
Treated surgically with curative intent	51.2 (n = 19)	43.6 (n = 28)	58.7 (n = 21)	76.9 (n = 8)	0.18	56.0 (n = 40)	51.3 (n = 36)	0.82	52.0 (n = 49)	59.1 (n = 27)	1.00
Not treated surgically with curative intent	19.0 (n = 37)	13.0 (n = 33)	22.2 (n = 27)	10.6 (n = 30)	0.11	19.1 (n = 64)	12.6 (n = 63)	0.04	15.6 (n = 60)	12.6 (n = 67)	0.54

CI, confidence interval.
a The adjusted ORs and associated confidence intervals were estimated using logistic regression, including all the baseline variables listed in *Table 1* in the model. The standard p-values are based on the chi-squared test for heterogeneity (which tests whether or not the overall distribution in proportions could have occurred by chance). The Wald p-values test whether or not the odds of detecting recurrence in each of the intensive follow-up arms is significantly different from that in the minimum follow-up arm. The p-values for comparison of median survival are based on the non-parametric test for k-medians.

The number of patients with recurrence detected during scheduled follow-up who were still alive at the time of analysis was also higher in the intensive follow-up arms (4.8% vs. 2.3%; $p = 0.07$), as was the median post-recurrence survival (27.3 vs. 14.6 months; $p = 0.11$), but neither difference is statistically significant. Of the 76 patients treated surgically with curative intent, around half (40, 52.6%) were still surviving at a median of 4 years and 4 months from time of surgery. Median survival after surgical treatment of recurrence with curative intent was 52.3 months (compared with 14.2 months in those treated without curative intent). The absolute difference in the proportion of patients surviving after curative intent treatment in the intensive arms compared with the minimum arm was 2.2% ($p = 0.29$); the absolute difference in the factorial comparison was 1.3% for both CEA testing and CT ($p = 0.20$).

There were no significant differences in the total number of deaths, or in the number of deaths attributed to colorectal cancer (see *Appendix 2*), between the four randomisation arms or two factorial groups. The Kaplan–Meier overall survival curve by randomisation arm (*Figure 3*) confirms that there was no significant difference in survival over time between arms (log-rank $p = 0.45$). The Cox hazard ratio (HR) comparing the minimum and intensive arms and adjusting for the characteristics in *Table 1* showed a non-significant advantage to minimum follow-up of 0.87 [95% confidence interval (CI) 0.67 to 1.15]. These CIs imply an upper limit to the absolute mortality benefit from intensive follow-up of 3.8%; the lower limit means that it is impossible to exclude the possibility of harm. However, the outcome of patients treated for recurrence with curative intent is favourable.

Adherence to protocol

The extent of adherence to the follow-up protocol is shown in *Table 4*. Patient adherence to follow-up was good. For imaging, 85% attended for every CT scan and only 3% missed more than one scheduled CT. For CEA testing, 70% of patients attended for every scheduled blood test and only 9% missed more than one test. Although clinician adherence appears less impressive (with 10.5% of participants receiving unscheduled blood CEA level tests, 12.0% receiving unscheduled CT scans and 10.1% receiving unscheduled colonoscopies without documented evidence that these investigations had been triggered by symptomatic presentation), the protocol required investigation of any symptoms presenting between scheduled follow-up tests. Substantially more unscheduled tests were carried out in patients not receiving regular CT scans, with 16.3% compared with 4.7% receiving one or more unscheduled CEA tests ($p < 0.001$), 18.6% compared with 3.7% receiving one or more unscheduled CT scans ($p < 0.001$) and 16.0% compared with 4.3% receiving one or more unscheduled colonoscopies ($p < 0.001$).

Per-protocol analysis

The results of a per-protocol analysis are shown in *Table 5*, excluding the 340 (28.3%) patients who missed more than one scheduled investigation or received any unscheduled investigation. The results are consistent with the intention-to-treat (ITT) analysis but effect estimates are higher: the rate of detection of treatable recurrence in the more intensive arms compared with the minimum follow-up was 9.3% versus 2.1% ($p = 0.001$). As with the ITT analysis, *Table 4* and *Figure 3* show that there is no difference in overall survival between arms (log-rank $p = 0.36$). The Cox HR comparing the minimum and intensive arms and adjusting for the characteristics in *Table 1* again showed no significant difference in survival (HR 0.97, 95% CI 0.72 to 1.32).

Summary of main findings

The proportion of participants with recurrence treated with curative intent was lower than predicted from earlier trials (6.0% overall) but it was three times higher in the more intensive arms than in the minimum follow-up arm. The proportion of recurrences treatable with curative intent was not related to stage at

(a)
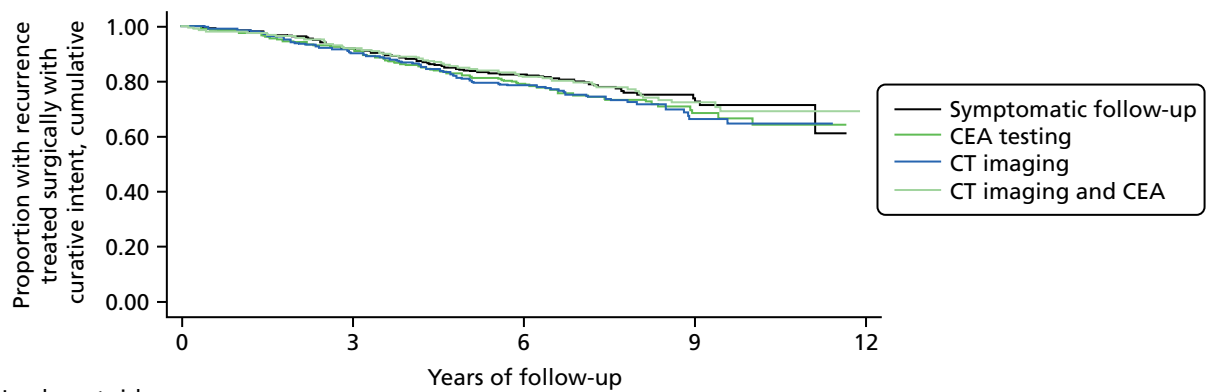
Number at risk

Symptomatic follow-up	301	276	216	58	0
CEA testing	300	274	203	55	0
CT imaging	299	270	202	55	0
CT imaging and CEA	302	279	218	55	0

Log-rank overall comparison, $p = 0.18$; intensive vs. minimum, $p = 0.07$

(b)
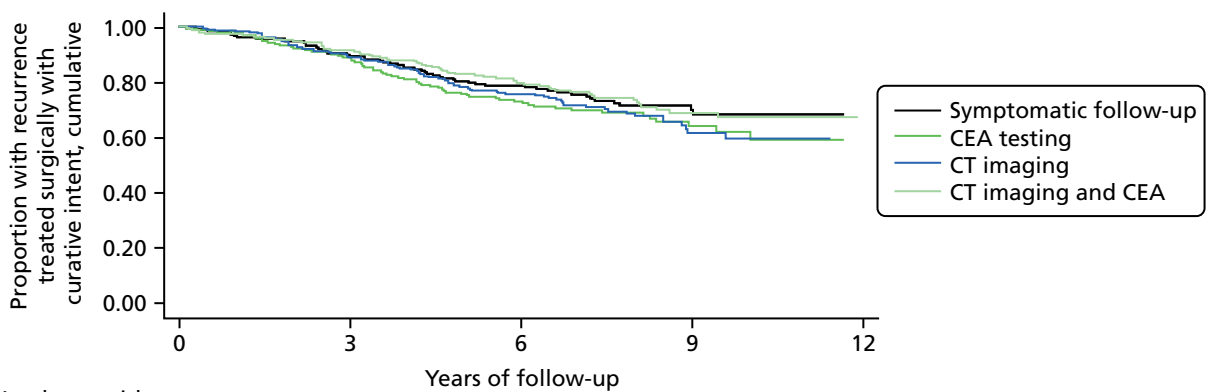
Number at risk

Symptomatic follow-up	188	168	132	44	0
CEA testing	189	167	123	40	0
CT imaging	252	224	164	43	0
CT imaging and CEA	233	213	163	47	0

Log-rank overall comparison, $p = 0.016$; intensive vs. minimum, $p = 0.005$

FIGURE 3 Kaplan–Meier plots of overall survival of the cohort by follow-up group for (a) the intention-to-treat population and (b) the per-protocol population.

diagnosis of the primary cancer. Both CEA testing (with a single CT scan) and regular CT are effective modes of follow-up, but conducting CEA testing and CT imaging in parallel provided no additional benefit. There was no statistical difference in overall deaths or colorectal cancer deaths in the minimum compared with the intensive follow-up arms after a median of 8.7 years of observation. If there is a survival benefit from intensive follow-up in the first 10 years, it is very unlikely to exceed 4% in absolute terms and harm cannot be excluded, although this seems unlikely as the survival rate of patients treated for recurrence is high.

TABLE 4 Adherence to follow-up protocol

Description	Individual randomisation arms					Factorial comparison groups					
	CEA testing only (N = 300)	CT only (N = 299)	CEA testing and CT (N = 302)	Minimum (N = 301)	p-value	CEA testing (N = 602)	No CEA testing (N = 600)	p-value	CT (N = 601)	No CT (N = 601)	p-value
Patients receiving less than specified follow-up											
Missed ≥ 1 scheduled CEA, n (%)	78 (26.0)	n/a	99 (32.8)	n/a	n/a	177 (29.4)	n/a	n/a	99 (16.5)	78 (13.0)	0.09
Missed ≥ 1 scheduled CT scan, n (%)	3 (1.0)[a]	55 (18.4)	56 (18.5)	3 (1.0)[a]	n/a	59 (9.8)	58 (9.7)	0.94	111 (18.5)	6 (1.0)[a]	n/a
Patients receiving more than specified follow-up											
Received ≥ 1 unscheduled CEA, n (%)	40 (13.3)	17 (5.7)	11 (3.6)	58 (19.3)	<0.001	51 (8.5)	75 (12.5)	0.023	28 (4.7)	98 (16.3)	<0.001
Received ≥ 1 unscheduled CT scan, n (%)	56 (18.7)	14 (4.7)	8 (2.6)	56 (18.6)	<0.001	64 (10.6)	70 (11.7)	0.57	22 (3.7)	122 (20.3)	<0.001
Received ≥ 1 unscheduled colonoscopy, n (%)	43 (14.3)	13 (4.3)	13 (4.3)	53 (17.6)	<0.001	56 (9.3)	66 (11.0)	0.33	26 (4.3)	96 (16.0)	<0.001
Total excluded from per-protocol analysis as had missed > 1 scheduled test or had received any unscheduled test, n (%)	111 (37.0)	47 (15.7)	69 (22.8)	113 (37.5)	<0.001	180 (29.9)	160 (26.7)	0.21	116 (19.3)	224 (37.3)	<0.001

n/a, not applicable.
a Participants randomised to the CEA testing and minimum follow-up arms were scheduled to receive a single CT scan at 12–18 months.

TABLE 5 Treatment of recurrence with curative intent and survival by randomisation arm and factorial group (per-protocol analysis)

Description	Individual randomisation arms					Factorial comparison groups					
	CEA testing only (N = 189)	CT only (N = 252)	CEA testing and CT (N = 233)	Minimum (N = 188)	p-value	CEA testing (N = 422)	No CEA testing (N = 440)	p-value	CT (N = 485)	No CT (N = 377)	p-value
Surgical treatment with curative intent, n (%)	16 (8.5)	27 (10.7)	20 (8.6)	4 (2.1)	0.008	36 (8.5)	31 (7.0)	0.42	47 (9.7)	20 (5.3)	0.017
Adjusted OR[a]	3.29	4.11	3.77	1		1.22	–		1.87	–	
95% CI	1.09 to 9.96	1.43 to 11.8	1.43 to 11.1			0.73 to 2.06			1.07 to 3.26		
Wald's p-value	0.016	0.003	0.020			0.45			0.027		
Mortality at median 8.7 years post randomisation											
Total deaths, n (%)	63 (33.3)	80 (31.7)	63 (27.0)	52 (27.7)	0.42	126 (29.9)	132 (30.0)	0.96	143 (29.5)	115 (30.5)	0.75
Deaths attributed to colorectal cancer, n (%)	40 (21.2)	43 (17.1)	37 (15.9)	30 (16.0)	0.47	77 (18.2)	73 (16.6)	0.48	80 (16.5)	70 (18.6)	0.73
Patients with recurrence still surviving, n (%)	9 (4.8)	14 (5.6)	14 (6.0)	5 (2.7)	0.41	23 (5.5)	19 (4.3)	0.44	28 (5.8)	14 (3.7)	0.16
Median length of survival after recurrence (months)											
All patients with recurrence	23.2 (n = 45)	27.1 (n = 60)	38.0 (n = 46)	10.6 (n = 28)	0.051	27.3 (n = 91)	23.0 (n = 88)	0.44	29.5 (n = 106)	19.8 (n = 973)	0.039
Treated surgically with curative intent	48.7 (n = 16)	43.8 (n = 27)	57.8 (n = 20)	95.3 (n = 4)	0.082	51.7 (n = 36)	52.0 (n = 31)	0.91	52.0 (n = 47)	51.7 (n = 20)	0.85
Not treated surgically with curative intent	19.0 (n = 29)	13.0 (n = 33)	22.2 (n = 26)	9.4 (n = 24)	0.035	19.1 (n = 55)	11.3 (n = 57)	0.02	15.6 (n = 59)	11.0 (n = 53)	0.326

a The adjusted ORs and associated CIs were estimated using logistic regression, including all the baseline variables listed in *Table 1* in the model. The standard *p*-values are based on the chi-squared test for heterogeneity (which tests whether or not the overall distribution in proportions could have occurred by chance). The Wald *p*-values test whether or not the odds of detecting recurrence in each of the intensive follow-up arms is significantly different from that in the minimum follow-up arm. The *p*-values for comparison of median survival are based on the non-parametric test for *k*-medians.

Chapter 4 Economic evaluation

Introduction

The FACS trial included a prospective economic analysis, which was designed to be integral to the trial, collecting information on resource use, survival and HRQoL to investigate the cost-effectiveness of each policy. This chapter reports an analysis of the FACS health economic data collected up to 5 years post randomisation for each patient. The details of the study design and interventions have been reported previously in this report.

Methods

Resource use

The planned economic evaluation was a cost–utility analysis conducted from the perspective of the UK NHS. Given the trial's modified primary end point, cost-effectiveness results were additionally expressed using recurrence treated surgically with curative intent (henceforth referred to as treatable recurrence) as the outcome measure.

The analyses used trial data collected for the duration of the 5-year clinical follow-up period; survival data were also censored at 5 years for all patients. CEA testing was organised centrally by the research team and the number of tests performed was calculated from laboratory test reports received. Numbers of CT scans, colonoscopies, radiography and MRI scans performed were extracted from hospital records by NCRN nurses in each centre and reported on CRFs. Information on confirmed recurrences and treatments (curative or palliative surgery, radiotherapy and chemotherapy) was also obtained from hospital records. Using questionnaires sent at 12, 24, 36, 48 and 60 months post randomisation, patients reported health-care services that they had used over the previous 12 months, including visits to GPs, practice nurses, stoma care nurses, hospital outpatient clinics and visits from district nurses. Patients also reported if they had been admitted to hospital, how many times they had been admitted and their total number of hospital inpatient nights.

Costs

Patient-level resource-use data were costed using national average unit costs (expressed in 2012–13 UK pounds sterling) obtained from a variety of sources.[42–44] The unit costs used are shown in *Table 15*, *Appendix 3*. Full details of the costing methods used can also be found in *Appendix 3*, with abridged information given below. As the time horizon for the analysis was 5 years, costs (and outcomes) were discounted to present values at an annual rate of 3.5%.[45]

For each patient, and for each follow-up year, each CEA test, CT scan, colonoscopy, radiography and MRI scan was costed by applying the appropriate unit cost. The associated visits to practice nurses and hospital outpatient clinics for each of these screens/scans were costed by adding the relevant visit cost. Additional practice nurse and outpatient clinic visits, together with visits to GPs and stoma nurses, and home visits from district nurses, were also costed using the appropriate per-visit costs. When costing inpatient hospital admissions for reasons other than surgery for recurrence, an average oncology bed-day cost was used to multiply the number of hospital inpatient days reported.[44]

For each patient with recurrence who underwent surgery, the type of surgical procedure performed was recorded and mapped to its corresponding Healthcare Resource Group (HRG) code(s). This code was then located in the NHS Reference Cost database and a weighted average was taken of the cost (and length of stay) across all specialties and subcategories within that code.[44] When a patient's recorded hospital stay

exceeded the average length of stay for their particular procedure, additional days were costed using an excess bed-day cost for an oncology ward.[44]

For radiotherapy and/or chemotherapy administered following recurrence, expert clinical opinion provided information on standard regimens (drug doses, frequency and duration) for curative and palliative management; these were then costed (see *Table 15*, *Appendix 3*) and assigned to patients accordingly.

Recurrence treated surgically with curative intent
Local NCRN staff extracted data on recurrences and treatment intent (curative vs. non-curative) from hospital clinical records.

Survival
Each patient entered into the study was flagged with the ONS central registry; monitoring is ongoing, but for this analysis it is censored at 5 years post randomisation. Cause of death was abstracted from death certificates.

Health-related quality of life
At baseline and at 12, 24, 36, 48 and 60 months, patients completed the EQ-5D, three-level version (EQ-5D-3L), a questionnaire assessing levels of generic HRQoL and containing questions on five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[35] Responses to the EQ-5D-3L were converted into a single HRQoL index score on a scale where 0 is representative of dead and 1 of full health with an algorithm developed using data from a sample of the UK general population.[46,47]

Quality-adjusted life-years
For each patient in the study, quality-adjusted life-years (QALYs) were generated by adjusting observed survival time in each year for the average level of EQ-5D HRQoL reported during the same year (e.g. 1 year survived with an average level of HRQoL of 0.6 gives 0.6 QALYs). These calculations were repeated for each of the 5 years, discounted and then summed to give the total number of QALYs experienced.

Statistical analysis
Data were missing on 11% of resource-use and EQ-5D data items at 5 years. Data were assumed to be missing at random and multiple imputation (MI) using chained regression equations was used to impute missing values (for additional details see *Appendix 3*). In line with recommendations, imputation was performed separately for each trial arm and five values were predicted for each missing data point, essentially creating five different data sets.[48] Rubin's rule, which acknowledges and accounts for variability within as well as between imputed data sets, was used when summarising data across the five data sets.[49,50]

Continuous resource use data, costs and QALYs were summarised as means and standard errors (SEs), and categorical data were summarised as numbers and percentages. The three imaging follow-up policies were each compared with minimum follow-up and with each other using mean costs, cases of recurrence treated surgically with curative intent and QALYs. Parametric 95% CIs were estimated around mean differences, and incremental cost-effectiveness ratios (ICERs) were calculated.[51] The ICER is estimated by dividing the difference in cost by the difference in effect between policies and provides an estimate of the additional cost of producing one additional unit of effect (here, an additional treatable recurrence or a QALY) when moving from one policy to another. To interpret an ICER reporting the incremental cost of detecting an additional treatable recurrence, knowledge is required about whether or not such an 'intermediate' end point translates into actual patient benefit, such as improved life expectancy, quality of life, or both. ICERs already encompassing 'final' end points such as the QALY are more readily interpretable and, with much research already conducted to suggest that society's maximum willingness to pay for a QALY in England and Wales lies between £20,000 and £30,000, can be compared against this threshold.[45] Policies with ICERs below this threshold are generally considered cost-effective.

Non-parametric bootstrapping was used to explore the uncertainty surrounding the QALY-based cost-effectiveness results and to construct cost-effectiveness acceptability curves, which describe a range of possible cost-effectiveness thresholds.[52]

The analyses were performed using Stata® version 12 (StataCorp, College Station, TX, USA).

Sensitivity analysis

To assess the influence of the MI procedure, an alternative complete-case analysis was performed. Uncertainty around the mode of delivery and processing costs of the CEA test was also examined; the baseline test cost of £7.50 was increased (decreased) to £10 (£5).

Results

Table 6 reports the demographic and clinical characteristics for patients in each arm of the trial; the groups were well balanced.

TABLE 6 Baseline demographics, clinical characteristics and 5-year recurrence and survival by randomisation group

Characteristics	Minimum follow-up (*N* = 301)	CEA testing follow-up (*N* = 300)	CT follow-up (*N* = 299)	CEA testing and CT follow-up (*N* = 302)
Age (years), mean (SD)	69.3 (8.5)	68.8 (8.3)	69.0 (8.9)	69.5 (8.1)
Gender (male), *n* (%)	184 (61.1)	184 (61.3)	183 (61.2)	185 (61.3)
Treated comorbidity, *n* (%)	93 (30.9)	90 (30.0)	81 (27.1)	86 (28.5)
Pre-treated with chemotherapy, *n* (%)	123 (40.9)	121 (40.3)	118 (39.5)	125 (41.4)
Pre-treated with radiotherapy, *n* (%)	35 (11.7)	32 (10.7)	34 (11.4)	38 (12.6)
Site of cancer, *n* (%)	(*N* = 295)	(*N* = 293)	(*N* = 290)	(*N* = 292)
Right colon	103 (34.9)	93 (31.7)	96 (33.1)	90 (30.8)
Left colon	105 (35.6)	118 (40.3)	96 (33.1)	110 (37.7)
Rectum	87 (29.5)	82 (28.0)	98 (33.8)	92 (31.5)
Dukes' stage, *n* (%)	(*N* = 292)	(*N* = 289)	(*N* = 293)	(*N* = 287)
A	69 (23.6)	54 (18.7)	71 (24.2)	60 (20.9)
B	131 (44.9)	144 (49.8)	132 (45.1)	146 (50.9)
C	92 (31.5)	91 (31.5)	90 (30.7)	81 (28.2)
Recurrence diagnosed at 5 years, *n* (%)	38 (12.6)	56 (18.7)	61 (20.8)	48 (15.9)
Treated surgically, *n* (%)	14 (36.8)	25 (44.6)	30 (49.2)	22 (45.8)
Surgery was with curative intent, *n* (%)	8 (21.1)	19 (33.9)	28 (45.9)	21 (43.8)
Deaths at 5 years, *n* (%)[a]	48 (16.0)	53 (17.7)	57 (19.1)	46 (15.2)
Attributable to colorectal cancer, *n* (%)[a]	28 (58.3)	35 (66.0)	36 (63.2)	28 (60.9)

SD, standard deviation.
a　Numbers for these events vary from those presented in the FACS clinical paper as survival is censored at 5 years for this analysis.

Recurrence treated surgically with curative intent

Table 6 also shows the number of patients diagnosed with recurrence in each trial arm after 5 years of clinical follow-up. This figure was 38 (12.6%) in the minimum follow-up arm, 56 (18.7%) in the CEA testing arm, 61 (20.4%) in the CT arm and 48 (15.9%) in the CEA testing and CT arm. The numbers of treatable recurrences were 8 (21.1%), 19 (33.9%), 28 (45.9%) and 21 (43.8%), respectively. When averaged across all patients in each trial arm, the mean numbers of treatable recurrences per patient were 0.027, 0.063, 0.094 and 0.070, respectively.

Resource use and costs

Table 7 summarises the mean resource use by trial arm over the 5-year follow-up period and *Table 8* reports the corresponding mean total costs by trial arm. A more detailed version of these tables by year of follow-up is shown in *Table 16* in *Appendix 3*.

The mean total undiscounted 5-year cost per patient in the minimum follow-up arm was lower than in the other three arms. Setting aside the costs of implementing the different intensive follow-up policies, *Table 8* shows that much of this cost difference arose because fewer recurrences were diagnosed and treated with minimum follow-up. The CT policy was on average £1516 (95% CI £292 to £2740; $p = 0.02$) per patient more costly than the CEA testing policy, with much of this additional cost attributable to the CT scans and associated hospital outpatient visits. The combined CEA testing and CT policy was the most costly alternative, being on average £798 (95% CI –£674 to £2270; $p = 0.29$) per patient more costly than the CT arm. Much of this difference arose because of higher costs of (non-surgery related) hospital readmissions.

TABLE 7 Mean (SE) resource use per patient by trial arm at 5 years

Description	Minimum follow-up (*N* = 301), mean (SE)	CEA testing follow-up (*N* = 300), mean (SE)	CT follow-up (*N* = 299), mean (SE)	CEA testing and CT follow-up (*N* = 302), mean (SE)
CEA tests at 5 years	0.70 (0.12)	11.55 (0.26)	0.12 (0.05)	11.03 (0.26)
CT scans at 5 years	1.09 (0.06)	1.01 (0.06)	5.44 (0.13)	5.47 (0.13)
Colonoscopies at 5 years	0.57 (0.04)	0.50 (0.04)	1.10 (0.04)	1.15 (0.05)
Radiography at 5 years	0.04 (0.01)	0.03 (0.01)	0.35 (0.08)	0.33 (0.07)
MRI scans at 5 years	0.01 (0.01)	0.01 (0.01)	0.03 (0.02)	0.01 (0.01)
≥ 1 surgeries for recurrence at 5 years, *n* (%)	14.00[a] (4.7)	25.00 (8.3)	30.00 (10.0)	22.00 (7.3)
Radiotherapy for recurrence at 5 years, *n* (%)	7.00 (2.3)	4.00 (1.3)	9.00 (3.0)	9.00 (3.0)
Chemotherapy for recurrence at 5 years, *n* (%)	14.00 (4.7)	32.00 (10.7)	32.00 (10.7)	32.00 (10.6)
GP visits at 5 years	2.95 (0.33)	3.15 (0.31)	3.39 (0.72)	3.74 (0.55)
Practice nurse visits at 5 years	2.19 (0.74)	13.48 (0.67)	1.95 (0.65)	12.01 (0.27)
District nurse visits at 5 years	0.75 (0.22)	3.89 (0.97)	1.86 (0.39)	2.71 (0.85)
Stoma nurse visits at 5 years	0.65 (0.15)	0.39 (0.10)	0.68 (0.11)	0.85 (0.21)
Outpatient clinic attendances at 5 years	6.49 (0.62)	6.17 (0.63)	11.65 (0.48)	12.07 (0.58)
Other inpatient bed-days at 5 years	1.98 (0.40)	2.68 (0.51)	2.14 (0.46)	4.52 (1.41)

a One patient known to have had two surgeries.

TABLE 8 Mean (SE) costs (£) per patient by trial arm at 5 years (undiscounted and discounted)

Description	Minimum follow-up (N = 301), mean (SE)	CEA testing follow-up (N = 300), mean (SE)	CT follow-up (N = 299), mean (SE)	CEA testing and CT follow-up (N = 302), mean (SE)
CEA tests at 5 years	5.28 (0.88)	86.65 (1.94)	0.88 (0.35)	82.72 (1.95)
CT scans at 5 years	142.88 (8.06)	131.59 (7.20)	711.31 (17.06)	714.63 (17.31)
Colonoscopies at 5 years	295.42 (21.33)	258.71 (19.34)	567.29 (22.96)	590.59 (24.13)
Radiography at 5 years	1.46 (0.43)	1.07 (0.37)	13.91 (3.03)	13.25 (2.92)
MRI scans at 5 years	1.90 (1.10)	1.91 (1.10)	6.39 (4.60)	2.53 (1.26)
Subtotal: tests/scans	446.95 (25.48)	479.93 (23.13)	1299.78 (37.90)	1403.72 (40.24)
≥ 1 surgeries for recurrence at 5 years, n (%)	423.96 (114.07)	760.80 (152.64)	1042.49 (191.40)	613.61 (128.45)
Radiotherapy for recurrence at 5 years, n (%)	37.21 (18.39)	29.97 (18.00)	37.46 (18.52)	49.53 (22.10)
Chemotherapy for recurrence at 5 years, n (%)	492.27 (134.59)	1199.36 (203.61)	1224.99 (208.08)	1206.70 (205.39)
Subtotal: treatment for recurrence	953.44 (206.43)	1990.13 (296.99)	2304.93 (323.66)	1869.85 (291.44)
GP visits at 5 years	132.67 (14.84)	141.72 (14.11)	152.55 (32.54)	168.17 (24.97)
Practice nurse visits at 5 years	29.42 (9.89)	181.09 (8.98)	26.14 (8.71)	161.28 (3.66)
District nurse visits at 5 years	29.28 (8.41)	151.89 (37.91)	72.60 (15.33)	105.84 (33.15)
Stoma nurse visits at 5 years	27.91 (6.49)	16.86 (4.37)	29.25 (4.78)	36.74 (9.06)
Outpatient clinic attendances at 5 years	935.19 (88.75)	888.86 (91.26)	1677.34 (68.43)	1737.63 (83.33)
Other inpatient bed-days at 5 years	730.73 (148.76)	989.31 (190.43)	793.01 (170.91)	1670.18 (520.73)
Subtotal: health-care contacts	1885.21 (208.89)	2369.73 (259.95)	2750.88 (202.60)	3879.83 (576.04)
Mean total costs at 5 years	3285.60 (344.99)	4839.80 (458.05)	6355.60 (411.54)	7153.40 (652.70)
Of which: year 1	1062.80 (189.74)	1558.17 (227.07)	1925.07 (226.04)	2018.09 (252.35)
Year 2	1038.66 (183.29)	1363.56 (227.26)	2024.73 (207.47)	1876.54 (184.15)
Year 3	477.66 (81.83)	758.13 (159.95)	764.63 (149.44)	1672.28 (436.85)
Year 4	336.31 (43.47)	623.87 (144.29)	756.35 (156.58)	698.35 (130.26)
Year 5	370.16 (34.57)	536.06 (85.40)	884.82 (136.60)	888.14 (98.30)
Mean total 5-year discounted costs at 5 years	3138.15 (333.72)	4613.19 (438.35)	6048.37 (393.22)	6796.10 (617.78)

The final row in *Table 8* shows mean (SE) total discounted 5-year costs of £3138 (£334), £4613 (£438), £6048 (£393) and £6796 (£618) for the minimum, CEA testing, CT and combined CEA testing and CT follow-up arms, respectively.

Survival

At 5 years, 48 (16.0%) patients in the minimum follow-up arm had died, as had 53 (17.7%) in the CEA testing arm, 57 (19.1%) in the CT arm and 46 (15.2%) in the CEA testing and CT arm. The mean (SE) total number of discounted life-years in each of these arms at 5 years was 4.37 (0.05), 4.32 (0.05), 4.33 (0.05) and 4.37 (0.05), respectively.

Health-related quality of life

Table 9 shows the mean (SE) self-reported HRQoL of survivors by arm and year of follow-up. HRQoL appeared lower from year 2 onwards with both minimum and combined CEA testing and CT follow-up. However, only in the year 5 EQ-5D scores was any significant difference observed (and then only between minimum and CEA testing follow-up). *Appendix 3*, *Table 17* shows additional EQ-5D-3L data by domain and indicates that a slightly higher proportion of patients in the minimum follow-up and combined CEA testing and CT arms reported problems with pain and discomfort.

Figure 4 shows the mean EQ-5D scores and 95% CIs across all study patients. The mean scores in all trial arms declined over time as the number of deaths increased.

Quality-adjusted life-years

The mean (SE) estimated discounted QALYs for the minimum follow-up arm, the CEA testing arm, the CT arm and the combined CEA and CT arm were 3.61 (0.07), 3.66 (0.06), 3.62 (0.07) and 3.59 (0.07), respectively (see *Table 9*).

Cost-effectiveness

Table 10 shows the cost-effectiveness results based on a treatable recurrence end point. The ICERs are shown in the final row of the table and reveal that the lowest cost of detecting an additional treatable recurrence is achieved when moving from minimum follow-up to CEA testing-only follow-up (£40,131). The cost of detecting an additional treatable recurrence with CT over minimum follow-up, however, was only slightly higher, at £43,392. When compared with CT, follow-up with CEA testing and CT was, on average, more costly but detected fewer treatable recurrences.

The first row of *Table 11* shows the mean total cost and QALY differences and associated ICERs for each of the imaging policies compared with minimum follow-up. A move from minimum follow-up to CT or to combined CEA testing and CT follow-up was, on average, more costly and produced fewer QALYs than a move from minimum follow-up to CEA testing follow-up. This is reflected in the ICERs, with the additional cost per QALY gained by moving from minimum follow-up to CEA (£25,951), lower than the ICER for CT (£246,107). When compared with minimum follow-up, combined CEA testing and CT was more costly and generated fewer QALYs, resulting in a negative ICER (–£208,347) and a dominated policy.

TABLE 9 Mean (SE) reported EQ-5D-3L HRQoL of survivors by trial arm and year and mean (SE) QALYs for whole cohort

Description	Minimum follow-up (*N* = 301)			CEA testing follow-up (*N* = 300)			CT follow-up (*N* = 299)			CEA testing and CT follow-up (*N* = 302)		
	n	Mean	SE	*n*	Mean	SE	*n*	Mean	SE	*n*	Mean	SE
Year 1	294	0.84	0.01	296	0.86	0.01	295	0.85	0.01	296	0.85	0.01
Year 2	290	0.82	0.01	282	0.84	0.01	282	0.85	0.01	290	0.81	0.02
Year 3	276	0.82	0.02	274	0.84	0.01	270	0.84	0.01	279	0.81	0.02
Year 4	265	0.83	0.01	258	0.85	0.01	260	0.82	0.02	269	0.81	0.02
Year 5	253	0.81	0.02	247	0.87[a]	0.01	242	0.85	0.02	256	0.81	0.02
Mean total 5-year QALYs, adjusted for survival		3.85	0.07		3.91	0.07		3.86	0.07		3.83	0.08
Mean total 5-year discounted QALYs, adjusted for survival		3.61	0.07		3.66	0.06		3.62	0.07		3.59	0.07

a Difference compared to minimum follow-up = 0.068, *p* < 0.001.
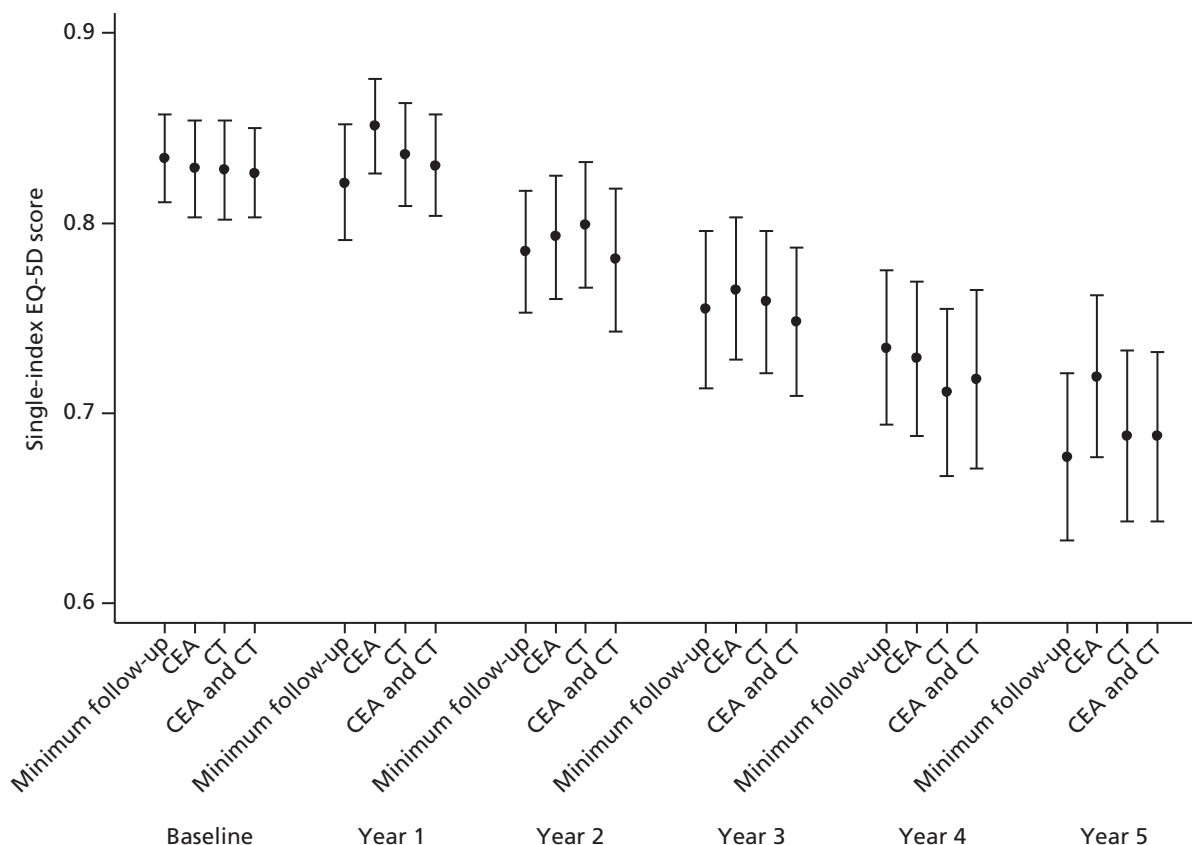
FIGURE 4 Mean (95% CI) EQ-5D-3L single-index scores for all patients in each trial arm at each year.

TABLE 10 Cost-effectiveness results based on recurrences treated surgically with curative intent as the outcome measure

Description	Minimum follow-up (*n* = 301)	CEA testing follow-up (*n* = 300)	CT follow-up (*n* = 299)	CEA testing and CT follow-up (*n* = 302)	
Cost per patient, mean (SE)	£3138.15 (£333.72)	£4613.19 (£438.35)	£6048.37 (£393.22)	£6796.10 (£617.78)	
Number of recurrences treated surgically with curative intent, per patient, mean (SE)	0.027 (0.009)	0.063 (0.014)	0.094 (0.017)	0.070 (0.015)	
Incremental results	**CEA testing vs. minimum**	**CT vs. minimum**	**CEA testing vs. CT**	**CEA testing and CT vs. minimum**	**CEA testing and CT vs. CT**
Difference in mean costs (95% CI)	£1475 (£405 to £2545)*	£2910 (£1894 to £3926)**	£1435 (£265 to £2605)***	£3658 (£2258 to £5058)**	£748 (–£650 to £2145)
Difference in mean number of recurrences treated surgically with curative intent, per patient (95% CI)	0.037 (0.004 to 0.070)***	0.067 (0.029 to 0.105)*	0.030 (–0.013 to 0.073)	0.043 (0.009 to 0.077)***	–0.024 (–0.068 to 0.020)
Incremental cost per recurrence treated surgically with curative intent detected	£40,131	£43,392	£47,347	£85,151	–£31,014 (dominated)

*p < 0.01, **p < 0.001, ***p < 0.05.

TABLE 11 Base-case and sensitivity analysis average and incremental results

Description	Minimum follow-up (n = 301)	CEA testing-only follow-up (n = 300)	CT-only follow-up (n = 299)	CEA testing and CT follow-up (n = 302)
Base-case analysis				
Mean total costs (£)	3138 (334)	4613 (438)	6048 (393)	6796 (618)
Mean total QALYs	3.61 (0.07)	3.66 (0.06)	3.62 (0.07)	3.59 (0.07)
CEA test cost £5				
Mean total costs (£)	3136 (334)	4586 (439)	6048 (393)	6770 (618)
Mean total QALYs	3.61 (0.07)	3.66 (0.06)	3.62 (0.07)	3.59 (0.07)
CEA test cost £10				
Mean total costs (£)	3140 (334)	4641 (438)	6049 (393)	6822 (618)
Mean total QALYs	3.61 (0.07)	3.66 (0.06)	3.62 (0.07)	3.59 (0.07)
Outliers removed arm 4				
Mean total costs (£)	3138 (334)	4613 (438)	6048 (393)	6064 (391)
Mean total QALYs	3.61 (0.07)	3.66 (0.06)	3.62 (0.07)	3.59 (0.07)
Complete-case analysis	**(n = 129)**	**(n = 151)**	**(n = 147)**	**(n = 146)**
Mean total costs (£)	2771 (434)	3354 (505)	5413 (489)	5463 (722)
Mean total QALYs	3.73 (0.10)	3.78 (0.09)	3.72 (0.10)	3.89 (0.09)
Incremental results	**CEA testing vs. minimum follow-up**	**CT vs. minimum follow-up**	**CEA testing and CT vs. minimum follow-up**	
Base-case analysis				
Mean cost difference (95% CI)	£1475 (£405 to £2545)*	£2910 (£1894 to £3926)**	£3658 (£2258 to £5058)**	
Mean QALY difference (95% CI)	0.06 (–0.12 to 0.24)	0.01 (–0.17 to 0.19)	–0.02 (–0.20 to 0.17)	
ICER (probability cost-effective at £20,000 per QALY)	£25,951 (41.95%)	£246,107 (3.70%)	–£208,347 (dominated) (0.15%)	
CEA test cost £5.00				
Mean cost difference (95% CI)	£1449 (£379 to £2520)*	£2912 (£1896 to £3928)**	£3633 (£2233 to £5034)**	
Mean QALY difference (95% CI)	0.06 (–0.12 to 0.24)	0.01 (–0.17 to 0.19)	–0.02 (–0.20 to 0.17)	
ICER (probability cost-effective at £20,000 per QALY)	£25,499 (42.45%)	£246,225 (3.65%)	–£206,952 (dominated) (0.15%)	
CEA test cost £10.00				
Mean cost difference (95% CI)	£1501 (£431 to £2570)*	£2909 (£1893 to £3925)**	£3682 (£2283 to £5082)**	
Mean QALY difference (95% CI)	0.06 (–0.12 to 0.24)	0.01 (–0.17 to 0.19)	–0.02 (–0.20 to 0.17)	
ICER (probability cost-effective at £20,000 per QALY)	£26,404 (41.60%)	£245,990 (3.75%)	–£209,742 (dominated) (0.15%)	

TABLE 11 Base-case and sensitivity analysis average and incremental results (*continued*)

Incremental results	CEA testing vs. minimum follow-up	CT vs. minimum follow-up	CEA testing and CT vs. minimum follow-up
Outliers removed arm 4			
Mean cost difference (95% CI)	£1475 (£405 to £2545)*	£2910 (£1894 to £3926)**	£2926 (£1913 to £3938)**
Mean QALY difference (95% CI)	0.06 (–0.12 to 0.24)	0.01 (–0.17 to 0.19)	–0.02 (–0.21 to 0.17)
ICER (probability cost-effective at £20,000 per QALY)	£25,591 (41.15%)	£246,107 (3.15%)	–£151,716 (dominated) (1.55%)
Complete-case analysis			
Mean cost difference (95% CI)	£583 (–£751 to £1918)	£2642 (£1339 to £3945)**	£2692 (£980 to £4404)*
Mean QALY difference (95% CI)	0.05 (–0.21 to 0.32)	–0.01 (–0.30 to 0.27)	0.16 (–0.10 to 0.42)
ICER (probability cost-effective at £20,000 per QALY)	£10,730 (35.15%)	–£232,771 (Dominated) (3.05%)	£17,034 (34.60%)

*$p < 0.01$, **$p < 0.001$.

Figure 5 plots 2000 bootstrapped estimates of the mean discounted 5-year cost and QALY differences for each imaging policy versus minimum follow-up. *Figure 6* plots the associated cost-effectiveness acceptability curves. CEA testing appears to offer the greatest potential for being cost-effective when compared with minimum follow-up; however, uncertainty surrounds these 5-year results. At a threshold of £20,000 per QALY, the probability of CEA testing being cost-effective is 41.95%, increasing to 49.85% at a threshold of £30,000 per QALY.

Sensitivity analyses

Table 11 also shows results for the sensitivity analyses. The findings were not sensitive to changes in the cost of the CEA test. However, a complete-case analysis showed combined CEA testing and CT to be more cost-effective than in the base-case analysis. In particular, the mean (SE) discounted 5-year QALYs for combined CEA testing and CT at 3.89 (0.09) were higher than for the other three arms [mean 3.74 (0.06)]. This was because, for patients with complete data, 5-year mortality was lower in the combined CEA testing and CT arm (7.5%) than in the other three arms (mean 16.4%).

Correspondingly, then, the larger reduction in QALYs seen in the combined CEA testing and CT arm following imputation was attributable to higher levels of mortality in patients with incomplete data in that arm (26% compared with just 17% with minimum follow-up, 18% with CT and 22% with CEA testing) and also to lower levels of HRQoL (e.g. in year 2 mean EQ-5D scores for surviving patients with incomplete data in the minimum, CEA testing and CT follow-up arms were 0.78, 083 and 0.83, respectively, but in the combined CEA testing and CT arm the level was 0.76).

Finally, two patients receiving combined CEA testing and CT follow-up reported substantially higher inpatient bed-days (120 days and 200 days) than other patients being admitted to hospital, and this resulted in unexpectedly high inpatient costs. After removing both patients and re-estimating the results, the cost in the combined CEA testing and CT arm fell from £6796 to £6064, but the mean QALYs were also reduced by 0.0017 and the policy remained dominated, with a low probability of being cost-effective (1.55%).
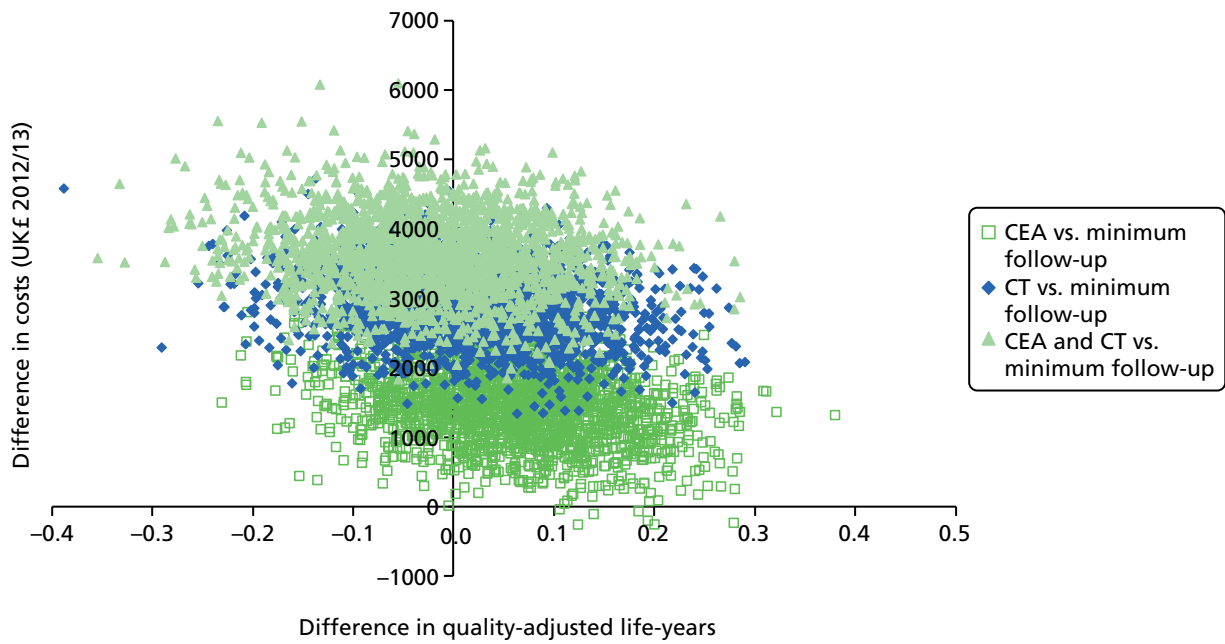
FIGURE 5 Incremental cost-effectiveness plane showing 2000 bootstrapped mean total discounted 5-year costs and QALY differences for each intensive follow-up arm vs. minimum follow-up.
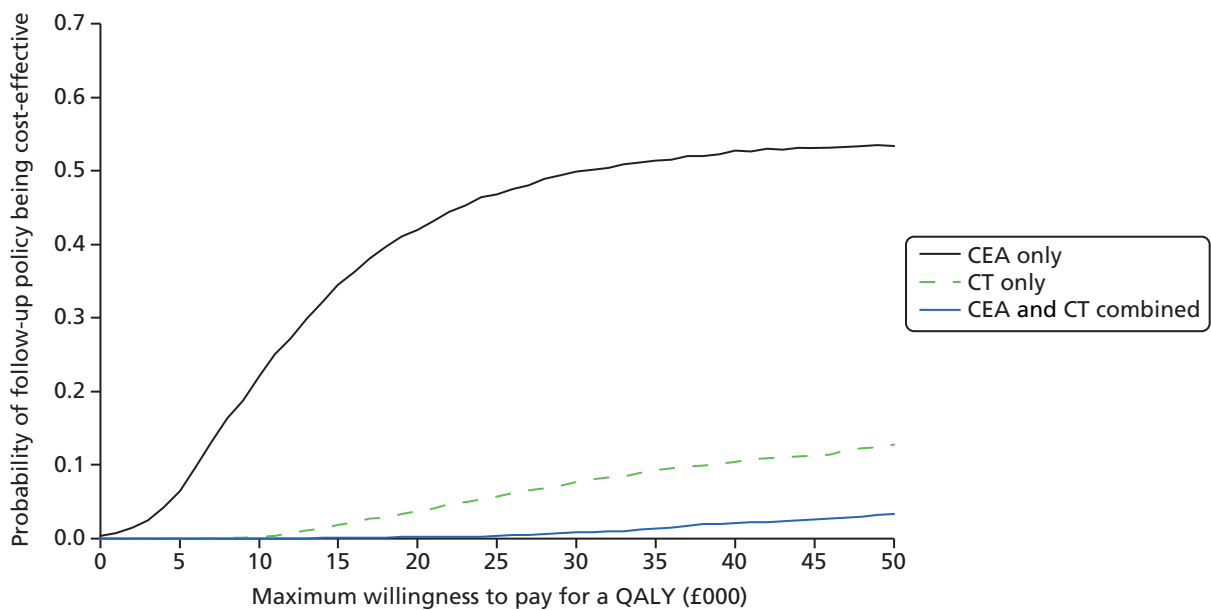
FIGURE 6 Cost-effectiveness acceptability curves showing the probability that each intensive follow-up policy is cost-effective compared with minimum follow-up for different levels of the threshold ICER.

Discussion

The follow-up tests assessed in this trial – CEA testing and CT imaging – have been identified in meta-analyses as the most promising current methods of detecting curatively treatable metastatic recurrence in patients with colorectal cancer.[14,53] However, the economic evidence assembled to date is quite meagre. Secco *et al.*[54] reported some costs for patients in a randomised trial of risk-adapted FACS, but the analysis was not comprehensive in economic methods or costs included and related to only a subset of patients.

The one detailed published cost-effectiveness analysis of intensive versus conventional follow-up after curative resection for colorectal cancer derived its effectiveness estimates from a meta-analysis of five randomised trials, and reported that the number of life-years gained through intensive surveillance over standard care was between 0.73 and 0.82 per patient depending on the trials included, with a resulting ICER of £3402 per life-year gained.[55] However, there was considerable heterogeneity in the follow-up regimens across the trials included, an absence of patient-level data on resource use and costs and no HRQoL information. This study is therefore the first comprehensive analysis able to draw on patient-level cost and HRQoL data and with a reasonable sample size and 5-year follow-up.

Although this study has clear advantages over previous evaluations, a number of issues make it difficult to draw definitive conclusions on the cost-effectiveness of intensive follow-up. First, there were no clear differences in HRQoL between the trial arms. This is of interest in itself, as it does not support the perception that more intensive follow-up may be associated with increased anxiety and hence lower quality of life. The results from this trial show no evidence that patients in the CEA testing, CT or combined arms were more likely to report problems on the anxiety domain of the EQ-5D (see *Table 17, Appendix 3*), with some suggestion that, despite the slightly higher number of detected recurrences in the CEA testing and CT arms, quality of life was slightly, albeit non-significantly, higher in these arms than in the minimum follow-up arm (see *Table 9*) at most follow-up points. However, the absence of significant differences in HRQoL also meant that quality-adjusted survival was primarily influenced by the observed survival differences, which then directly influenced the cost-effectiveness analysis. As detailed above, however, the trial was not powered for survival, and a first analysis of the data when all patients had completed a minimum of 3 years' scheduled follow-up showed not only no significant differences in the number of deaths between the intensive follow-up arms and the minimum follow-up arm [18.2% (164/901) vs. 15.9% (48/301), respectively; difference 2.3%, 95% CI –2.6% to 7.1%], but an unexpected 2% aggregate survival advantage with minimum follow-up.[56] Although longer-term follow-up (median 8.7 years) has shown that survival in the minimum follow-up arm has now fallen below that of the intensive follow-up arms (albeit not statistically so), the short-term survival advantage associated with minimum follow-up has influenced the cost-effectiveness results presented in this paper. The increase in recurrences treated with curative intent observed in the FACS trial would have been expected to translate into a small survival advantage and, as shown above and in *Table 11*, the CIs around total mortality and QALYs are still consistent with a survival advantage being possible with intensive follow-up.

In an attempt to provide a somewhat fairer representation of the cost-effectiveness of intensive follow-up, results were also presented using the trial's primary end point of treatable recurrences detected. When compared with minimum follow-up, CEA testing detected additional treatable recurrences (mean 0.037 recurrences per patient) at the lowest additional cost (mean £1475 per patient), giving an ICER of £40,131. Whether or not this represents good value for money, however, can really be determined only by extrapolating the associated patient benefit. For example, if detection of a recurrence at a stage at which it could be managed surgically with curative intent was known to afford a patient an additional 2.5 QALYs, then the equivalent cost per QALY gained from moving from minimum follow-up to using CEA testing would be around £15,950 [£1475/(0.037 × 2.5)]. Threshold analyses (not shown) suggest that a benefit of at least an additional two discounted QALYs over the course of a patient's lifetime would be needed for an ICER < £20,000. As noted above, however, there are few data available on life-years gained through early identification of recurrence.

A second difficulty encountered is that an assessment of cost-effectiveness at 5 years is almost certainly premature. Data in *Table 6* showed fewer recurrences with minimum follow-up and suggest that, in that arm, there may be a number of undetected recurrences that are still to present. With no new curatively treatable recurrences presenting in that arm beyond 2 years, the majority of these as yet undiagnosed recurrences will probably be incurable.[56] In the longer term, therefore, mortality might be expected to increase in the minimum follow-up arm and a survival advantage from intensive follow-up could manifest with no additional intensive surveillance costs. Although data from this study show that it is unlikely that CT or combined CEA testing and CT will be cost-effective, it is still possible that follow-up with CEA testing could be proven to be cost-effective in the longer term.

This economic analysis has some limitations. For example, 11% of data were missing on resource use and HRQoL. A complete-case analysis suggested combined CEA testing and CT to be substantially more cost-effective than in the base-case analysis; however, patients with complete data in that arm were not representative of all patients in the combined CEA testing and CT arm. By imputing what may be considered a relatively small number of missing data, it was possible to include all patients in the analysis and, thus, to generate more reliable estimates.

A further limitation is that, in the case of patients with recurrence, data were not collected on therapies given beyond those used to treat the initial recurrence. This should be mitigated to some extent, however, by the inclusion of costs for health-care contacts with hospitals (outpatient clinics and inpatient admissions).

Conclusion

This study has generated detailed data on the costs and HRQoL of patients undergoing minimum and intensive follow-up regimes for the detection of recurrence following colorectal cancer. However, drawing definitive conclusions on cost-effectiveness using the FACS trial is impossible because the FACS data lack the necessary statistical power to determine whether or not the benefit in detecting treatable recurrence translates into a survival benefit. Analyses using both treatable recurrences and QALYs as end points suggest CEA testing to be the most promising of the intensive follow-up regimes, but, with the former approach, the longer-term data required to extrapolate from treatable recurrence to a final end point (life-years or QALYs) so as to facilitate an assessment of value for money are difficult to find, while the latter approach is influenced by overall survival in the FACS trial, which the trial was not powered to detect. The longer-term follow-up of patients and the monitoring of new recurrences and survival should help to ascertain whether or not CEA testing represents an efficient use of scarce health-care resources. Meanwhile, it is recommended that an economic evaluation of follow-up in colorectal cancer should follow good practice guidelines in viewing data from the FACS trial as being complementary to and used alongside information from all other relevant data sources.[57]

Chapter 5 Observational analysis of participants with recurrence in the Follow-up After Colorectal Surgery study

Introduction

The FACS trial provides an opportunity to evaluate the characteristics of those who develop recurrence in a population of well-staged prospectively followed-up patients treated for colorectal cancer. Knowledge of those patients most likely to relapse is informative with respect to follow-up and planning adjuvant treatment strategies. For example, rectal cancer has a well-established tendency to recur locally; however, the combination of total mesorectal excision and optimal chemoradiotherapy has reduced rates to < 10% in modern series.[58–61] Existing evidence on the pattern of recurrence after curative resection of colorectal cancer is limited to retrospective audits,[62–64] and data from high-quality randomised controlled trials are lacking. Trials of adjuvant therapies for colon and rectal cancer reveal certain information on patterns of recurrence, but these are by definition limited to more advanced-stage cancers requiring such treatments.[65]

The present lack of evidence has resulted in conflicting guidance with respect to whether or not the same surveillance strategy should be offered to patients irrespective of the site and stage of the primary tumour. Some guidance suggests additional follow-up strategies for rectal cancer,[66,67] whereas others recommend much less intensive follow-up for rectal cancer than for colon cancer.[68,69] Furthermore, much uncertainty exists with respect to whether or not early-stage cancers should be followed up at all, owing to the low likelihood of recurrence. Consequently, there is a need to advance understanding of the pattern of recurrence and benefit of follow-up in the era of modern management of both primary colorectal cancer and recurrence.

Methods

This retrospective cohort analysis aggregates data from all four trial arms and is restricted to 1132 patients (94.2%) for whom complete detailed data are available on initial stage and site of recurrence. The cut-off date used for this analysis is 31 August 2012, by which time all patients had reached a minimum of 3 years of follow-up, with a median follow-up of 4.4 years since randomisation.

Categorical variables are presented as frequencies (percentages) and the chi-squared test used for comparisons. The Kaplan–Meier method was utilised for survival analyses and the log-rank test used to compare survival between groups; $p < 0.05$ was considered significant. Tables were produced using SPSS version 22 and survival analyses were carried out using the 'survival' package in R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Incidence of recurrence

A total of 189 participants (17%) developed recurrence during the median follow-up period of 4.4 years (interquartile range 3.1–5.0 years). The mean age of participants with recurrence was 67.8 years, and 63% were male (*Table 12*). Predictably, recurrence was more frequent in those with a more advanced-stage primary tumour [Dukes' A primary, 10% (26/249); Dukes' B, 15% (81/537); Dukes' C, 24% (82/346); $p < 0.0001$] (*Table 13*). The incidence of recurrence also varied according to the site of the original tumour

TABLE 12 Characteristics of participants who went on to develop recurrence at trial entry by site of primary tumour

Characteristic	All (*N* = 189)	Right colon (*N* = 51)	Left colon (*N* = 68)	Rectum (*N* = 70)
Age (years), mean (SD)	67.8 (8.9)	69.3 (9)	65.8 (9.6)	68.6 (7.9)
Male, *n* (%)	119 (63)	29 (56.9)	41 (60.3)	49 (70)
Concurrent treatment for other illness, *n* (%)	47 (24.9)	12 (23.5)	16 (23.5)	19 (27.1)
Chemotherapy prior to trial entry, *n* (%)	93 (49.2)	25 (49)	32 (47.1)	36 (51.4)
Radiotherapy prior to trial entry, *n* (%)	27 (14.3)	0	3 (4.4)	24 (34.3)
Dukes' stage, *n* (%)				
A	26 (13.8)	3 (5.9)	9 (13.2)	14 (20)
B	81 (42.9)	24 (47.1)	29 (42.6)	28 (40)
C	82 (43.4)	24 (47.1)	30 (44.1)	28 (40)
Smoking status, *n* (%)				
Never smoked	74 (41.8)	21 (45.7)	27 (41.5)	26 (39.4)
Ex-smoker	87 (49.2)	22 (47.8)	32 (49.2)	33 (50)
Current smoker	16 (9)	3 (6.5)	6 (9.2)	7 (10.6)
Unknown	12 (6.3)	5 (9.8)	3 (4.4)	4 (5.7)

SD, standard deviation.

TABLE 13 Site of recurrence by site and stage of original tumour

| Description | Site of primary tumour | | | |
	Total	Right colon	Left colon	Rectum
All patients in the trial, *n*	1132	379	421	332
Recurrences, *n* (%)	189	51	68	70
Liver only	50	9 (18.0)	23 (46.0)	18 (36.0)
Lung only	33	3 (9.1)	8 (24.2)	22 (66.7)
Liver and lung only	11	3 (27.3)	6 (54.5)	2 (18.2)
Locoregional only	41	14 (34.1)	14 (34.1)	13 (31.7)
Multisite/other	54	22 (40.7)	17 (31.5)	15 (27.8)
Description	Stage of cancer (Dukes')			
	Total	A	B	C
All patients in the trial, *n*	1132	249	537	346
Recurrences, *n* (%)	189	26	81	82
Liver only	50	10 (20.0)	25 (50.0)	15 (30.0)
Lung only	33	8 (24.2)	14 (42.4)	11 (33.3)
Liver and lung only	11	1 (9.1)	4 (36.4)	6 (54.4)
Locoregional only	41	4 (9.8)	22 (53.7)	15 (36.6)
Multisite/other	54	3 (5.6)	16 (29.6)	35 (64.8)

[right-colonic primary, 14% (51/379); left-colonic primary, 16% (68/421); rectal primary, 21% (70/332); $p = 0.023$] (see *Table 13*).

Site of recurrence

Two-thirds of the recurrences detected (124/189) were at a single site (liver, 50; lung, 33; and locoregional, 41), with the remainder having recurrence at other or multiple sites. Overall, the liver was the most frequent site of recurrence, with 42% (79/189) of all recurrences involving the liver. Interestingly, the distribution of recurrent disease varied according to the stage and location of the primary tumour. Both locoregional recurrence and recurrence at multiple/other sites were most frequently associated with more advanced-stage primary tumours (see *Table 13*). Recurrence involving just the lung was most frequently associated with rectal primary tumours (right colon, 3/33, 9%; left colon, 8/33, 24%; rectum, 22/33, 67%; $p < 0.0001$). In addition, recurrence at sites other than the lung, liver or locoregionally or at more than one of those sites varied according to the site of primary tumour (right colon, 25/65, 38%; left colon, 23/65, 35%; rectum, 17/65, 26%; $p = 0.018$).

Incidence of recurrent disease treatable surgically with curative intent

The primary outcome of the FACS trial was treatment of recurrence surgically with curative intent. When the analysis is restricted to the 189 participants with complete data on site and stage of the primary cancer, a total of 65 (34%) are known to have undergone treatment with curative intent (*Table 14*). Those participants with recurrence from a lower-stage primary tumour were more likely to be resectable (Dukes' A, 13/26, 50%; Dukes' B, 32/81, 40%; Dukes' C, 20/82, 24%; $p = 0.08$). Although there was no significant difference in the likelihood of recurrent disease being amenable to curative resection according to the site of original tumour, a trend was apparent (right colon, 12/51, 24%; left colon, 23/68, 34%; rectum, 30/70, 43%; $p = 0.086$).

Benefit of follow-up

The proportion of participants with recurrence surgically treated with curative intent taken as a proportion of the whole trial cohort was similar for each Dukes' stage (A, 13/249, 5%; B, 32/537, 6%; C, 20/346, 6%; $p = 0.80$). As such, a key finding of the FACS trial was that the benefit of follow-up is independent of stage; that is, although recurrence is less frequent in those with Dukes' A primary tumours, it is more likely to be treatable.[56] By contrast, the benefit of follow-up did vary according to the site of the primary tumour. Those participants with a rectal primary tumour were more likely to have a treatable recurrence detected during the follow-up period (right colon, 12/379, 3%; left colon, 23/421, 6%; rectum, 30/332, 9%; $p = 0.003$).

TABLE 14 Proportion of patients with recurrence treatable with curative intent according to stage and site of primary tumour

Description	Site of primary tumour				
	Total	Right colon	Left colon	Rectum	*p*-value[a]
Recurrences, *n*	189	51	68	70	
Treatable with curative intent, *n* (%)	65	12 (23.5)	23 (33.8)	30 (42.9)	0.086
Description	Stage of cancer (Dukes')				
	Total	A	B	C	*p*-value[a]
Recurrences, *n*	189	26	81	82	
Treatable with curative Intent, *n* (%)	65	13 (50)	32 (39.5)	20 (24.4)	0.03

a *p*-value based on chi-squared statistic.

Survival post recurrence

Of the 189 diagnosed with recurrent disease, 113 (60%, 106 specifically from recurrence and seven from other causes) died during the follow-up period. Survival post recurrence differed according to both the site (log-rank $p = 0.01$) and stage (log-rank $p = 0.005$) of the primary tumour (*Figure 7a* and *b*).

Survival post recurrence also differed according to the site of recurrent disease. Those with multisite recurrence or metastatic recurrence at other sites had an inferior survival to those with single-site recurrence in the liver, lung or locoregionally (see *Figure 7c*; log-rank $p < 0.0001$), consistent with the high proportion of patients with these single-site recurrences undergoing surgical treatment with curative intent (liver only, 30/50, 60%; lung only, 13/33, 40%; locoregionally only, 16/41, 40%; multisite/other recurrence, 6/65, 9%).

Of those amenable to treatment with curative intent, around three-quarters (44/65, 67.7%) were still alive at the end of the follow-up period. Neither the site nor the stage of the primary tumour influenced the survival of those with recurrent disease treated with curative intent, although there was a trend towards worse survival in those with a higher-stage primary tumour (*Figure 8*).

Discussion

This observational analysis reports on patterns of recurrence and post-recurrence survival in the prospectively followed-up large cohort of patients curatively treated for Dukes' A to C colorectal cancer in the FACS trial. The rigour of investigative procedures undertaken to ensure that patients were free of disease prior to recruitment affords an accurately staged population in which to assess the true incidence of disease recurrence.

The pattern of recurrence observed in the FACS cohort is similar to that reported by other studies, with the liver being the most common site of disease recurrence. The results also demonstrate a preponderance of isolated lung recurrence from rectal tumours, supporting the contention that haematogenous spread occurs from the rectum to the lungs via the iliac veins. The relatively low incidence of locoregional recurrence from rectal primary tumours is consistent with modern management combining total mesorectal excision with selective use of chemoradiotherapy. Indeed, locoregional recurrence was no more frequent in rectal tumours than in colonic tumours. This is at odds with certain guidance that recommends the use of regular proctosigmoidoscopy in the follow-up of rectal cancer patients.[67]

This analysis demonstrates clear differences between right-colonic, left-colonic and rectal primary tumours. Right-colonic tumours resulted in fewer isolated recurrences in the liver, in the lung or locally than recurrences from left-colonic or rectal tumours. This is in agreement with data demonstrating more peritoneal and distant lymph node metastases in BRAF mutated and microsatellite unstable tumours,[71] two features most commonly associated with right-sided cancers. The less favourable pattern of relapse from right-colonic tumours plausibly extends to an inferior survival post relapse for these patients in the FACS cohort. Indeed, in a recent consensus subtyping of colorectal cancer, the group with the highest proportion of right-colonic tumours had the worse survival after relapse, whereas those with the lowest proportion had the most favourable survival.[72]

Recurrence was, predictably, more frequent in those who were followed up with a higher-stage primary tumour. However, as already noted,[56] the benefit of follow-up was independent of the stage of the primary tumour. That is, although participants with a higher-stage primary tumour were more likely to have a recurrence detected during the follow-up period, it was less likely to be treatable. Indeed, it may be that a higher-stage tumour at original diagnosis reflects not simply a later stage in the developmental pathway of colorectal cancer, but rather a more aggressive tumour type, the prognostic implications of which remain if recurrence occurs. These results support the use of equivalent follow-up strategies in patients with early-stage cancers, as they derive equal benefit. This is a key finding, given that some

(a)

Dukes' A	26	22	17	14	7	3	2
Dukes' B	81	61	45	35	28	17	10	6
Dukes' C	82	57	35	20	10	4	3

(b)

Right colon	51	31	16	12	10	4	2
Left colon	68	51	39	27	14	9	5	3
Rectum	70	58	42	30	21	11	8	3

(c)

Liver only	50	46	34	25	16	10	7	3
Lung only	33	26	20	17	11	5	3	1
Locoregional only	41	32	24	18	12	6	4	2
Multisite/other	65	36	19	9	6	3	1
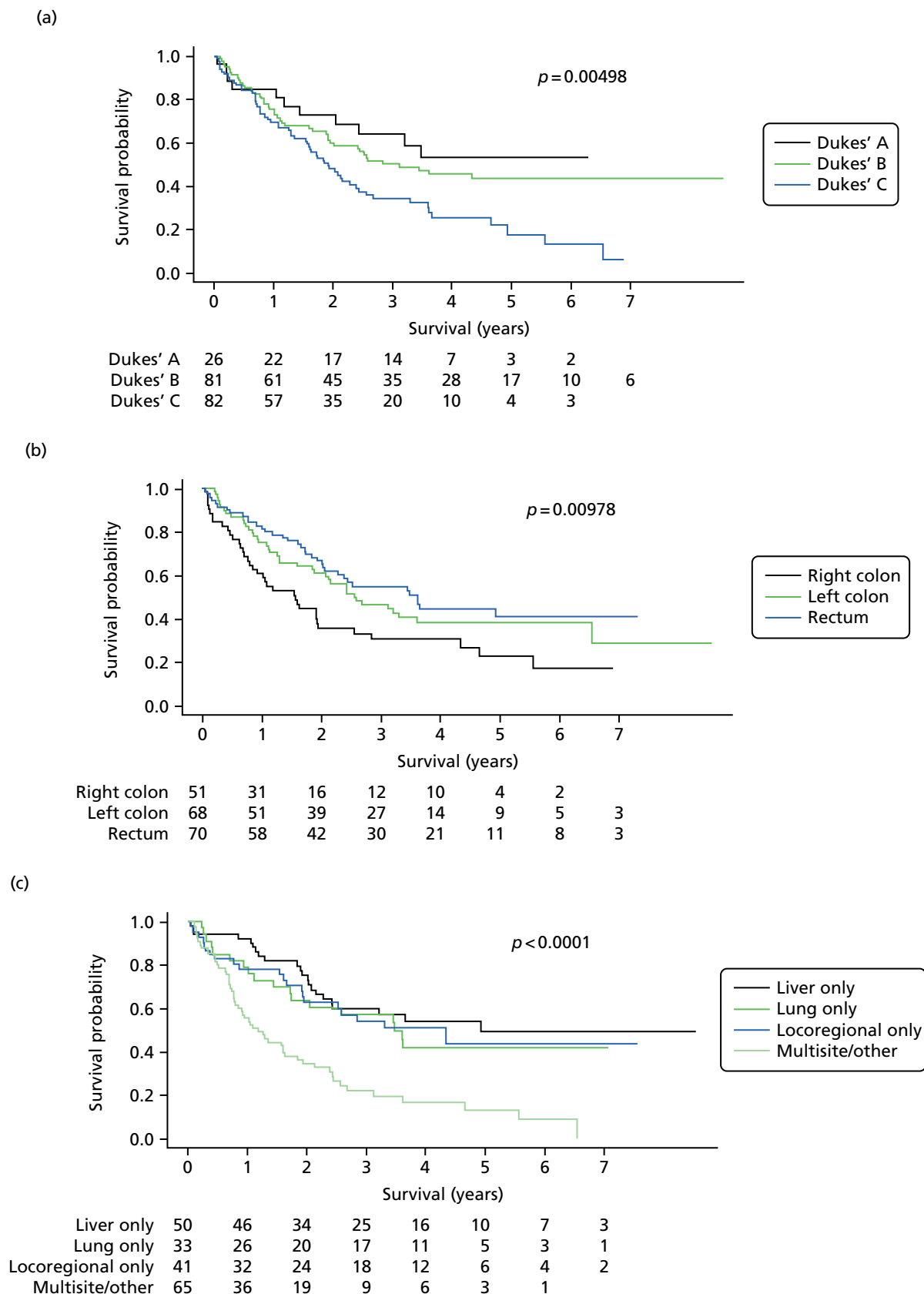
FIGURE 7 Kaplan–Meier curves for post-recurrence survival for all participants with disease recurrence. (a) Dukes' stage; (b) site of primary cancer; and (c) site of recurrence. Reprinted with permission, copyright © 2015 Wolters Kluwer Health. From Pugh SA, Shinkins B, Fuller A, Mellor J, Mant D, Primrose JN. Site and stage of colorectal cancer influence the likelihood and distribution of disease recurrence and postrecurrence survival: data from the FACS randomized controlled trial. *Ann Surg* 2016;**263**:1143–7.[70]

(a)

	0	1	2	3	4	5	6	7
Dukes' A	13	13	12	10	5	2	2	
Dukes' B	32	30	27	23	19	13	9	6
Dukes' C	20	20	16	11	7	3	2	

(b)

	0	1	2	3	4	5	6	7
Right colon	12	12	7	7	6	3	2	
Left colon	23	21	20	14	9	6	4	3
Rectum	30	30	28	23	16	9	7	3
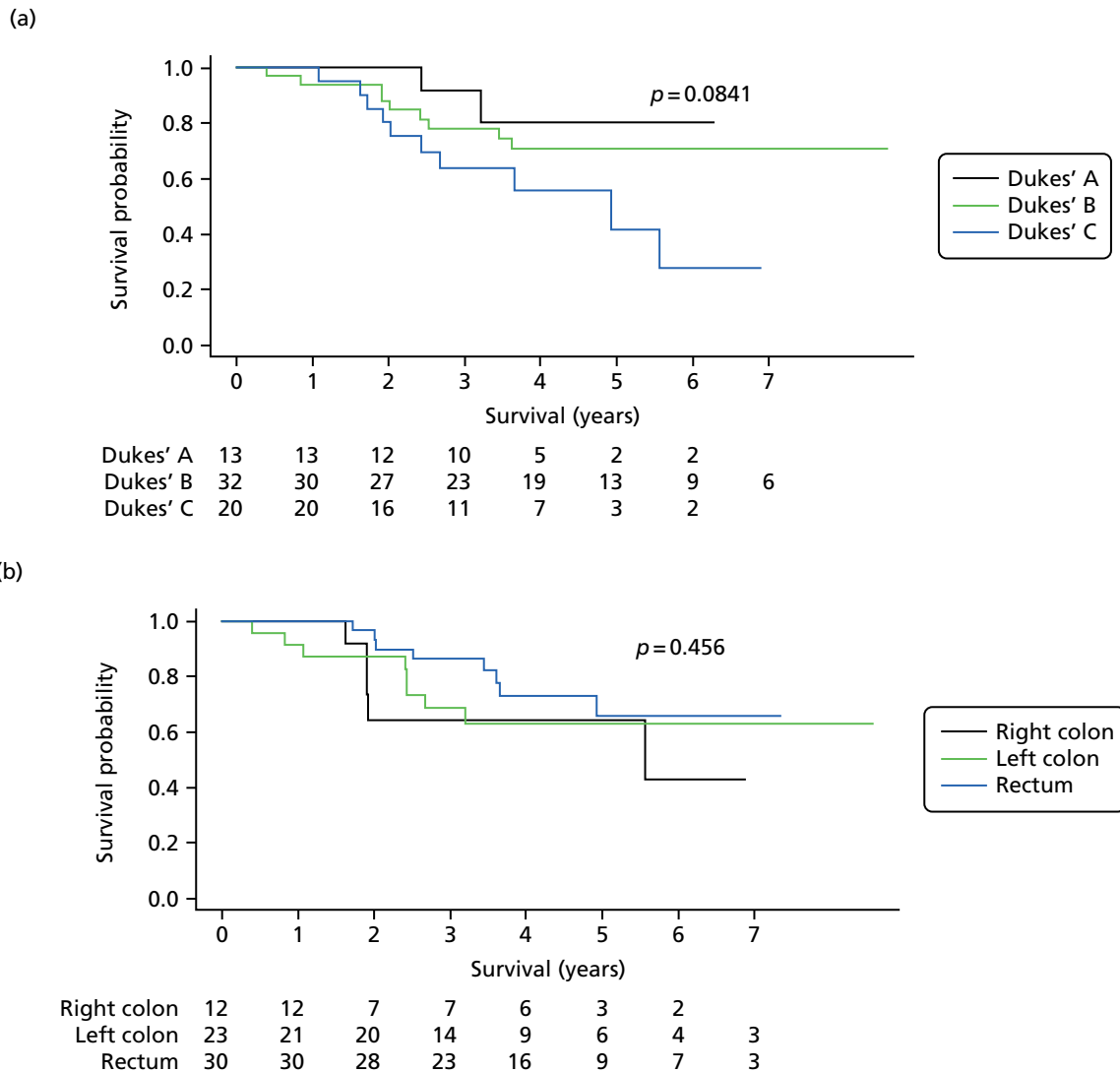
FIGURE 8 Kaplan–Meier curves for post-recurrence survival for just those participants who underwent surgical treatment of recurrence with curative intent. (a) Stage of primary tumour; and (b) site of primary tumour. Reprinted with permission, copyright © 2015 Wolters Kluwer Health. From Pugh SA, Shinkins B, Fuller A, Mellor J, Mant D, Primrose JN. Site and stage of colorectal cancer influence the likelihood and distribution of disease recurrence and postrecurrence survival: data from the FACS randomized controlled trial. *Ann Surg* 2016;**263**:1143–7.[70]

guidance currently states that there is a lack of evidence for follow-up after resection of stage I/Dukes' A colorectal cancer.[66]

In contrast to the observation for Dukes' stage, the benefit of follow-up was dependent on the site of the primary tumour. Patients with rectal tumours were three times as likely as those with right-colonic tumour to have a treatable recurrence detected during the follow-up period. This supports the practice of undertaking intensive follow-up for patients with rectal tumours similar to that for those with colonic tumours, which is contrary to certain guidance.[68,69]

In conclusion, the FACS cohort demonstrates that characteristics of the primary colorectal tumour, specifically site and stage, influence not only the likelihood of recurrence, but the distribution of recurrent disease and post-recurrence survival. The influence of stage on outcome, even post recurrence, suggests that the stages of primary colorectal cancer represent different disease biology rather than simply points on the timeline of disease progression.

The post-recurrence survival of participants with recurrence is shown according to stage of primary tumour (see *Figure 7a*), site of primary tumour (see *Figure 7b*) and site of recurrent disease (see *Figure 7c*). All include the number of patients at risk and *p*-value calculated using the log-rank method.

The post-recurrence survival of participants with recurrence treated surgically with curative intent is shown according to stage of primary tumour (see *Figure 8a*) and site of primary tumour (see *Figure 8b*). All include the number of patients at risk and the *p*-value calculated using the log-rank method.

Chapter 6 Discussions and conclusions

Principal findings

This trial investigated two different strategies in the follow-up of patients having treatment for primary colorectal cancer with curative intent: hospital-based imaging and CEA measurement in primary care in a 2 × 2 trial design. The two follow-up strategies were chosen because meta-analyses suggest that CEA testing and CT imaging are the only practical and available modalities with significant potential to detect curatively treatable recurrence. Endoscopy is well established in follow-up and its use is evidence based[73] in the detection of metachronous polyps and rarely luminal recurrence. However, it is commonly only performed 5 years after the initial resection, assuming that the colon is free of polyps at the time of treatment of primary disease. The hospital-based imaging arms therefore had an additional 2-year endoscopic examination scheduled in order to determine whether or not any additional recurrence may be detected.

Other follow-up modalities were considered and rejected. Liver ultrasound lacks sensitivity and specificity, as does clinical examination, and although MRI imaging is very sensitive in the detection of liver metastases, it has limited utility elsewhere.[14,53] CT–positron emission tomography (PET) was not widely available when this trial was designed, is complex and expensive, and would be used only if it were shown to be superior to the results obtained from modern CT scanners. No such evidence exists even from the perspective of 2016 and, thus, the modalities chosen in the FACS trial remain the only practical and useful tests.

Our results show that the proportion of patients treated with curative intent was around 6%, with little difference according to stage. Intensive follow-up by either scheduled CEA testing, imaging or both increased the likelihood of detecting such recurrences by around two to three times. The absolute difference in the proportion of participants treated with curative intent was 3.6–6.7% in the ITT analysis and 6.4–8.6% in the per-protocol analysis, indicating that between 12 and 20 patients need to be followed up to identify one potentially curable recurrence. Over 50% of the patients treated surgically with curative intent were still alive at a median of 8.7 years from trial entry and 4.4 years post recurrence, somewhat higher than would be expected from prior reports.[2,3]

Although the proportion of recurrences treated with curative intent (and the success of such treatment) is high compared with earlier reports, the absolute number of treatable recurrences detected is lower.[14] This is not explicable by differences in stage-specific case mix (detection of recurrences treatable with curative intent was similar irrespective of stage) and neither is there any evidence that FACS trial participants were at low risk of recurrence within stage (84.5% of stage C participants had received adjuvant chemotherapy). Stage-specific overall survival of FACS trial participants is comparable with that reported in trials of adjuvant chemotherapy such as MOSAIC.[74]

The probable explanation for the lower detection of treatable recurrence is the rigour of the investigative procedures undertaken to ensure that no residual cancer was present at trial entry. It suggests that the high rate of early recurrence reported from routine cancer statistics in England and Scandinavia[75] reflects residual disease that would have been detected with fastidious imaging. Before entry to the trial, all patients had to have a CT scan of the chest, abdomen and pelvis and also a CEA test that was within normal limits. Although this would now be the standard of care for most patients with colorectal cancer, it certainly was not at the time that the trial was set up. It is, therefore, inevitable that many patients who were classed by superficial staging as having Dukes' stage A to C colorectal cancer would actually have been in stage D and that these 'occult' metastases declared themselves relatively early after the patients were managed for the primary cancer. Fastidious staging to detect metastatic disease will inevitably reduce

the number of patients with recurrent disease detected by follow-up, hence reducing its cost-effectiveness. It is one of the most important findings of the study that full staging of patients with primary colorectal cancer is essential if they are to be managed optimally.

The comparison between intervention arms suggests that monitoring with CEA testing combined with a single CT scan at 12–18 months is equally as effective as undertaking regular CT scanning. As CEA testing can be done in primary care, it is likely to be more cost-effective than regular CT imaging, and this is confirmed by the health economic analysis discussed in summary below. However, imaging is still necessary to confirm recurrence, and, in the combined CEA testing and CT arm, two-thirds of recurrences were first detected by CT. Indeed, in the factorial analysis, CT significantly outperformed CEA testing in the detection of recurrence. The diagnostic performance of CEA as a monitoring test depends on the frequency of testing and the algorithm used to interpret the result. The algorithm applied in the FACS trial (refer for imaging if blood CEA level is ≥ 7 µg/l above baseline) achieves good specificity, but at the cost of modest sensitivity.[76] We are currently now investigating whether or not a higher sensitivity can be achieved at an acceptable level of specificity by applying a diagnostic algorithm that takes account of change over time and that has been applied successfully in interpreting CA125 levels when screening for ovarian cancer.[77]

The decision on whether or not the absolute benefit of follow-up is sufficient to justify its opportunity cost will differ between health economies. The benefits of follow-up appear to be independent of diagnostic stage because although there are fewer recurrences with earlier-stage tumours, they are more likely to be curable, and so it makes no sense to apply stage-specific follow-up strategies.[66] Because of the meticulous investigation carried out before trial entry to exclude residual disease, our results also provide useful new data on the timing of recurrence, which can strengthen the evidence base for choosing the optimal frequency of testing. Duplication of monitoring tests does not appear to add value; the participants in our CEA testing arm had a single CT scan at 12–18 months, when three recurrences were detected, but otherwise there was no suggestion of benefit from monitoring with both CEA testing and CT.

Despite the size of the trial, it provides very limited precision in estimating survival. The observed 2–3% apparent survival advantage in the minimum and maximal (CT plus CEA testing) follow-up arm is certainly correct and it is based on ONS data. However, our sample size means that the survival estimates for each arm are also imprecise. Even if 50% of the additional treatable recurrences detected in the more intensive intervention arms were cured, the overall survival advantage would be very small (and the 95% CIs would include the results we have actually observed). Even the possibility of harm cannot be excluded, although, bearing in mind the excellent survival in the patients treated for single-site metastatic disease, this seems unlikely. Furthermore, owing to the efficacy of modern treatments for advanced colorectal cancer, differences in overall survival at 5 years may not be evident in any case.

Health economic and quality-of-life analysis

The analysis was principally based on the trial end point, which is surgical treatment of recurrent disease with curative intent. The incremental cost per patient, compared with the minimum arm, ranged from £40,131 with CEA testing through £43,392 with hospital-based imaging to £85,151 with CEA testing and CT combined. As expected, CEA testing (combined with a single CT scan) is the most economical option, and imaging costs more per patient by around 50%. The cost of the most intensive schedule, however, is around four times that of CEA testing and, as there is no current clear advantage to using both modalities, it is obvious that, in economic terms, CEA testing or imaging appears preferable. The trial was not powered to detect a difference in overall survival. No difference was observed and by inference it could not be more than 3%. Mean quality of life was also found to differ little between the arms of the study, but, as expected, it did deteriorate over 5 years. Mean reported quality of life appeared to be significantly better in the CEA testing arm only in year 5. The consequence of these results was that there was little difference between arms in quality-adjusted survival. Combining cost and QALY differences, the incremental cost per QALY gained for CEA testing compared with minimum follow-up was £25,951,

for CT compared with minimum follow-up was £246,107, and for the combined CEA testing and CT arm was more expensive and less effective, resulting in a negative cost per QALY gained of –£208,347. A high degree of uncertainty accompanied these results, with our analysis indicating a 42% probability that the cost per QALY gained for CEA testing versus minimum follow-up was below a £20,000 threshold.

Observational analysis

The analysis of just those patients with recurrence at a median follow-up of 4.4 years demonstrates that the characteristics of the primary tumour influence not only the likelihood of recurrence but also the distribution of recurrent disease and survival post recurrence. These data suggest that disease biology present at the time of diagnosis of primary disease remains relevant even after the diagnosis of recurrence.

Interestingly, whereas a key finding of the FACS trial is that all stages of primary tumour benefit equally from follow-up, this was not the case for site of primary tumour. Patients with rectal cancers were approximately three times as likely to have a treatable recurrence identified during follow-up as those with right-colonic tumours. This directly supports undertaking equivalent follow-up in these patients, contrary to certain guidance.[68] Overall, this analysis demonstrates favourable outcomes for patients treated surgically with curative intent for recurrence, supporting the use of this as a surrogate end point for the trial.

Strengths and weaknesses of the trial

The FACS trial is the largest follow-up trial in colorectal cancer that has been performed to date that utilises modern diagnostic facilities and applies modern surgical and other management to those with detected recurrence. Importantly, the trial was undertaken in a large number of hospital settings in England, including small district general hospitals as well as large teaching centres. This aspect has ensured that the results are generalisable throughout the NHS. Although many of the centres involved in the study did not locally undertake surgery for recurrent disease, such as liver resection, it was mandated that all of the patients managed in the trial had access through the multidisciplinary teams to surgical services that would include liver and lung resection as well specialist surgery to deal with local recurrence when this was not available locally. This type of service is now routine in the UK, although when the study began it was not universal.

As well as examining the treatment modalities involved in follow-up, this trial contained economic and quality-of-life evaluations in order to be able to determine the cost-effectiveness of follow-up. The trial also enabled us to obtain tissue from the resected primary tumours that allow biomarker studies to be undertaken. The combination of the clinical trial data with the availability of tissue for biomarkers is a major advantage and one that will allow further research. In half of the study cohort (those in whom CEA measurement was performed), serum was retained. This allows for the investigation of additional markers without the need to repeat the study.

The major weakness in the study is that, although it is the largest well-designed follow-up study performed to date, it is underpowered to look for differences in mortality between the treatment arms. The original study design did envisage an overall survival end point. This, however, was based on the relapse rates available at the time and commonly reported within colorectal cancer patients in the UK. This, for instance, envisaged a relapse rate of approximately 70% at 5 years for patients in Dukes' stage C and approximately 50% relapse overall.[78] However, it was clear from the run-in phase of the study that the relapse rate was not nearly as high as had been predicted from national data. Indeed, the overall survival in the study was approximately 80% at 5 years and approximately 70% at 10 years (although the numbers reaching 10 years are very small). As detailed above, these data are entirely compatible with studies on the adjuvant treatment of resected colorectal cancer[74] and almost certainly result from the fastidious pre-trial entry staging.

Owing to the much lower recurrence rate observed during the run-in phase of the study, the primary end point was changed to the treatment of recurrence surgically with curative intent. This was felt to be a clinically meaningful end point that would still allow the benefit of follow-up to be assessed. It is accepted that this end point is subject to ascertainment bias in so much as the outcome is not independent of the method of follow-up. It is, however, generally acknowledged that the majority of recurrences will present within 5 years[79–81] and, therefore, by completion of 5 years of follow-up this should not be a major issue.

The study also suffers from a relatively high level of withdrawals and protocol deviations. With respect to withdrawals, this is perhaps to be expected in a study that lasts for many years in patients with cancer. It is noteworthy that there were more withdrawals from some arms than from others. The highest number of withdrawals was from the minimum follow-up arm, and in some cases this may represent a level of concern over the lack of continuing follow-up. The most intensive of the arms also suffered from more withdrawals, and in some cases this was documented to be because of the relatively onerous nature of the follow-up schedule, requiring both regular blood tests and CT imaging. Reassuringly, however, there is little difference in the outcome measures in the patients who were managed and analysed by the ITT method as opposed to the per-protocol analysis. All of the patients in the study were flagged with the ONS, and hence the death data, which include all patients in the study whether or not they withdrew, are known to be accurate.

The study had a pragmatic design, so most aspects of patient management, including the pathological examination of the primary tumour and the subsequent radiology, were done by local protocol. This has the advantage of ensuring that the results from the trial are applicable across the NHS, with the obvious unknown variations in practice. However, in respect of the pathology it may cause understaging (e.g. whether a patient is in Dukes' stage A or C depends on a fastidious examination for lymph nodes in the mesentery of the resected specimen). If this is not undertaken diligently, a patient who is diagnosed as being in Dukes' stage A may actually be at stage C; however, as we have demonstrated that benefit of follow-up is independent of disease stage, this appears to have made little difference to the results. There was also no central review of CT scans or, indeed, any set protocol at all for conducting the examination of these. It is commonly observed that different protocols and different scanners will have different sensitivity for picking up metastatic disease. Again, this is likely to introduce a degree of variability into the results. In addition, the multidisciplinary team process that patients go through once recurrent disease has been detected varies considerably.[82]

Findings in context

Although other studies have been performed assessing the utility of follow-up in this setting,[7–10,14,53,54,83,84] they are generally of historic significance only and, therefore, meta-analysis with the FACS trial is inappropriate. The authors of these studies did not have available modern imaging techniques and, in addition, procedures such as resection of colorectal liver metastases were usually not available. We know from this present study that examinations that bring to light recurrent or metachronous luminal cancer (five patients in total) can make only a very small contribution to the long-term outcome.

The Schoemaker study[10] compared clinical follow-up with clinical follow-up plus CT and colonoscopy. The conclusion was that, although liver metastasis was detected at an earlier stage in the intensive arm, this did not change greatly the number of liver metastases resections performed. However, as the study consisted of only 325 patients, it was underpowered to detect any difference between the two arms.

The MRC-funded UK CEA trial[12] recruited a large number of patients ($n = 1447$). It was conducted between 1982 and 1993, when patients with recurrent cancer were not managed as they are now (i.e. with detailed imaging to determine the site of recurrence and subsequent appropriate management). In the trial, patients who developed a CEA rise were randomised to either aggressive treatment that

included a second-look laparotomy or a conservative approach. It was presumed that the second-look surgery would be able to treat some patients with local recurrence, but, with hindsight, this was a flawed strategy. It would not now be accepted that second-look surgery, on the basis of a rise in CEA level, is an appropriate or adequate treatment.

Three other studies that commenced at or around the time of the FACS trial have, so far, not reported in full. The Italian GILDA study[85] examined the addition of ultrasound to CEA-based follow-up of colorectal cancer patients, although, confusingly, rectal cancer patients were also permitted a CT scan. As ultrasound is an insensitive method of examining for recurrence, and as all patients had regular CEA measurement, it is unsurprising that the experimental arm in this study did not demonstrate benefit.[85] A French study registered on ClinicalTrials.gov (NCT00199654) examines the use of PET compared with conventional imaging and CEA testing. The end point is time to diagnosis of recurrence, and the study authors planned to recruit 376 patients. However, this study started in 2005 and has yet to report. The technology of PET has changed radically since 2005 (now only CT–PET is performed); it is expensive, and with the end point chosen the investigators will be unable to determine the effectiveness or cost-effectiveness of the intervention in improving the outcome of patients with relapsed colorectal cancer. The mainly Scandinavian COLOFOL study initiated in 2005 (NCT00225641) examines the use of CT/MRI and CEA testing either twice (12 and 36 months) or more frequently (6-monthly for 2 years and then at 36 months).[86] This is a potentially large trial, with a recruitment target of 2500, so the results may be relevant to NHS practice and some meta-analysis with the FACS trial may be possible.

Since 2005, significant changes in the way in which advanced colorectal cancer is managed have increased the importance of detecting early metastatic disease. Chemotherapy, often with the addition of biological agents, has increased the survival of patients with advanced colorectal cancer up to a median of 24 months without surgical treatment.[87] Perhaps a bigger advantage of chemotherapy is that it is possible to bring patients who are found to have inoperable colorectal liver metastasis to operability; this is known to be associated with long-term survival in many cases.[88] Other treatments, including radioembolisation, are now available to treat colorectal liver metastasis that were not available when this study began.[89] Last, it has been shown that a combination of liver resection and ablation of unresectable disease, using radiofrequency or other techniques, can result in increased survival as demonstrated in a randomised trial.[90] However, all of these later treatments, which increase the length of survival even in the absence of cure, do make it more difficult to use the overall survival end point in follow-up studies. Indeed, although this study originally set out to examine outcomes at 5 years, it is clear that any survival analysis will have to be extended to 10 years or possibly beyond.

Implications for health care

This study has significant implications for the way in which patients with primary colorectal cancer are managed. It is evident that fully staging patients with primary colorectal cancer is paramount. In the case of patients presenting with synchronous metastatic disease, the management plans are likely to be radically different and may, for instance, include neoadjuvant chemotherapy prior to any surgical intervention. In relation to the methods used in this trial, pre-operative CT imaging and post-operative CEA measurement may seem to be appropriate in routine practice. Although detecting metastatic disease at presentation using CT imaging before trial entry was the most common reason for exclusion from recruitment, it was also noted that some patients were discovered not to have had full imaging of the colon prior to their colorectal resection. Endoscopic imaging mandated by trial entry picked up a number of previously unknown second primary tumours that required further surgery.

UK guidance on follow-up has suggested that patients should have at least one CT scan at 12–18 months as a matter of routine, and this was adopted in the minimum arm of the FACS trial.[41] It is the case, however, that many centres perform more CT scans than the minimum recommended in the guidelines. In this trial, we have been able to show that, with the end point of surgical treatment of recurrence with curative intent, CEA testing in combination with a single scan at 18 months *performs* equally well in this

respect. We have also been able to show that doubling up (i.e. conducting regular CT scans as well as CEA blood tests) does not detect significantly more treatable recurrences.

National Institute for Health and Care Excellence guidance[91] currently suggests that two CT scans should be performed in appropriate patients in the first 3 years in addition to regular CEA measurement. These guidelines were produced prior to the first publication from this trial. We are currently conducting a secondary analysis of the diagnostic performance of CEA testing in the trial, which will help to inform future guidance on the optimal testing interval, the threshold for initiating further investigation and the need for adjuvant CT scans.

These results should impact on how patients in the UK are managed; they also have implications overseas. We have been able to provide compelling evidence about which modalities are best at detecting treatable recurrence, thereby allowing health-care professionals to make evidence-based judgements on what is best in their particular setting. Our health economic modelling suggests that a single CT scan combined with regular CEA measurement is the most cost-effective approach.

Recommendations for research

In terms of the future, we are now in the era of genomics and biomarkers. A great deal of work has been carried out on the whole-genome sequencing of colorectal cancer, and different subtypes have been identified that have a different prognosis both in the short term and when the cancer recurs.[72] This study suffers somewhat from the context of the clinical trials from which the material for analysis was derived, and further useful insights may come from the UK GEL 100K initiative (www.genomicsengland.co.uk) and other sequencing programmes. In addition, the immune response to colorectal cancer has emerged as a key prognostic indicator. Specifically, the infiltration of T cells within the primary tumour strongly correlates with outcome. Thus, patients with tumours demonstrating a high T-cell infiltrate have a far better prognosis than those with very little, and certain data suggest that this is superior to traditional Dukes' or TNM staging.[92,93]

It seems likely in the future that follow-up of patients with colorectal cancer will be based on a combination of genetic analysis, biomarkers and traditional follow-up methodologies, as demonstrated by the FACS trial. It may be that it will be possible to identify a group of patients in whom the risk of relapse is so low that follow-up is not required. By contrast, it is also likely that patients will be identified who have a very high chance of relapse, and in whom a targeted trial of follow-up might be undertaken.

One of the major advantages of the FACS trial is the translational studies that it will permit. The trial provides a large cohort of well-staged patients with almost complete follow-up data and complete mortality data. Tissue from the primary resection has been collected, and we will go on to acquire tissue from the resection of metastases. The first translational study, funded by the HTA programme, will determine whether or not the immune infiltrate of the primary tumours can identify a cohort of patients who do not benefit from follow-up. This is of practical importance, as the techniques required to assess the immune infiltrate of tumours can be carried out in any routine histopathological laboratory in the NHS.

Conclusion

Among patients who had undergone curative surgery for primary colorectal cancer, follow-up with intensive imaging or CEA screening both provided an improved rate of recurrence treated with curative intent compared with minimal follow-up. The trial is underpowered to determine the effect of follow-up on either cancer-specific or overall survival, and no trend in favour of any strategy is evident from the perspective of 5 years of follow-up. It may be that a trend will be detected when follow-up for mortality is continued to 10 years, as we propose to do. Any survival advantage is, however, likely to be small, taking into account the whole cohort, the large majority of whom did not relapse.

Acknowledgements

The authors would like to acknowledge the key roles played by the following people and institutions.

Sponsor

This trial predated sponsorship.

Data Monitoring and Ethics Committee members

Professor Jack Hardcastle, Professor Michael Campbell and Professor David Whynes.

Current Trial Steering Committee members 2011–present

Dr Stephen Falk, Professor Andrew Protheroe, Professor Sally Stenning, Professor Roger James and Dr Mark Jeffery.

Original Trial Steering Committee members

Professor Roger James, Dr Mark Jeffery, Professor David Kerr and Maxine Stead.

Consumer representative

Lynn Faulds Wood.

Follow-up After Colorectal Surgery trial investigators

Birmingham Heartlands Hospital, Birmingham (Mr Gamal Barsoum); Castle Hill Hospital, Hull (Mr John Hartley); Charing Cross Hospital, London (Mr Peter Dawson); Cumberland Infirmary, Carlisle (Dr Jonathan Nicoll); Darent Valley Hospital, Dartford (Mr Mike Parker); Derriford Hospital, Plymouth (Mr Mark Coleman); Grantham and District Hospital, Grantham (Mr Dilip Mathur); Harrogate District Hospital, Harrogate (Mr Jon Harrison); Hillingdon Hospital, Uxbridge (Mr Yasser Mohsen); Hinchingbrooke Hospital, Huntingdon (Dr Litee Tan); King's Mill Hospital, Sutton-in-Ashfield (Mr Mukul Dube); Leeds St James, Leeds (Mr Simon Ambrose); Leeds General Infirmary, Leeds (Mr Paul Finan); Leighton General Hospital, Crewe (Mr Arif Khan); Maidstone Hospital, Maidstone (Dr Mark Hill); Mayday Hospital, Croydon (Croydon University Hospital) (Mr Muti Abulafi); Newham University Hospital, London (Mr Roger Le Fur); Oxford Radcliffe Hospitals, Oxford (Professor Neil Mortensen); Queen Alexandra Hospital, Portsmouth (Mr Daniel O'Leary); Queen Elizabeth Hospital, Birmingham (Dr Neil Steven); Queen's Hospital, Burton upon Trent (Mr Stelios Vakis); Queen's Medical Centre, Nottingham (Professor John Scholefield); Royal Cornwall Hospital, Truro (Mr Ponnandai Arumugam); Royal Derby Hospital,

Contributions of authors

Publications

Primrose JN, Perera R, Gray A, Rose P, Fuller A, Corkhill A, *et al*. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomised clinical trial. *JAMA* 2014;**311**:263–70.

Pugh SA, Shinkins B, Fuller A, Mellor J, Mant D, Primrose JN. Site and stage of colorectal cancer influence the likelihood and distribution of disease recurrence and postrecurrence survival: data from the FACS randomized controlled trial. *Ann Surg* 2016;**263**:1143–7.

Nicholson BD, Shinkins B, Pathiraja I, Roberts NW, James D, Mallett S, *et al.* Blood CEA levels for detecting recurrent colorectal cancer. *Cochrane Database Syst Rev* 2015;**12**:CD011134.

Shinkins B, Nicholson BD, James TJ, Primrose JN, Mant D. Carcinoembryonic antigen monitoring to detect recurrence of colorectal cancer: how should we interpret the test results? *Clin Chem* 2014;**60**:1572–4.

Data sharing statement

Data included in this report can be obtained by contacting the corresponding author.

References

1. Cancer Research UK. *Cancer Statistics Report: Cancer Incidence and Mortality in the UK*. Oxford: Cancer Research UK; 2014.

2. Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, *et al.* Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol* 2012;**4**:283–301. http://dx.doi.org/10.2147/CLEP.S34285

3. Gonzalez M, Poncet A, Combescure C, Robert J, Ris HB, Gervaz P. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. *Ann Surg Oncol* 2013;**20**:572–9. http://dx.doi.org/10.1245/s10434-012-2726-3

4. Colibaseanu DT, Mathis KL, Abdelsattar ZM, Larson DW, Haddock MG, Dozois EJ. Is curative resection and long-term survival possible for locally re-recurrent colorectal cancer in the pelvis? *Dis Colon Rectum* 2013;**56**:14–19. http://dx.doi.org/10.1097/DCR.0b013e3182741929

5. Nordic Gastrointestinal Tumor Adjuvant Therapy Group. Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. *J Clin Oncol* 1992;**10**:904–11. https://dx.doi.org/10.1200/jco.1992.10.6.904

6. Bismuth H, Adam R, Lévi F, Farabos C, Waechter F, Castaing D, *et al.* Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996;**224**:509–20. https://doi.org/10.1097/00000658-199610000-00009

7. Kjeldsen BJ, Kronborg O, Fenger C, Jørgensen OD. A prospective randomized study of follow-up after radical surgery for colorectal cancer. *Br J Surg* 1997;**84**:666–9. https://doi.org/10.1002/bjs.1800840523

8. Mäkelä JT, Laitinen SO, Kairaluoma MI. Five-year follow-up after radical surgery for colorectal cancer. Results of a prospective randomized trial. *Arch Surg* 1995;**130**:1062–7. https://doi.org/10.1001/archsurg.1995.01430100040009

9. Ohlsson B, Breland U, Ekberg H, Graffner H, Tranberg KG. Follow-up after curative surgery for colorectal carcinoma. Randomized comparison with no follow-up. *Dis Colon Rectum* 1995;**38**:619–26. https://doi.org/10.1007/BF02054122

10. Schoemaker D, Black R, Giles L, Toouli J. Yearly colonoscopy, liver CT, and chest radiography do not influence 5-year survival of colorectal cancer patients. *Gastroenterology* 1998;**114**:7–14. https://doi.org/10.1016/S0016-5085(98)70626-2

11. Northover JSW. A randomised trial of CEA prompted second look surgery in recurrent colorectal cancer. A preliminary report. *Dis Col Rectum* 1984;**27**:576.

12. Treasure T, Monson K, Fiorentino F, Russell C. The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted reoperation for recurrent colorectal cancer. *BMJ Open* 2014;**4**:e004385. http://dx.doi.org/10.1136/bmjopen-2013-004385

13. Bruinvels DJ, Stiggelbout AM, Kievit J, van Houwelingen HC, Habbema JD, van de Velde CJ. Follow-up of patients with colorectal cancer. A meta-analysis. *Ann Surg* 1994;**219**:174–82. https://doi.org/10.1097/00000658-199402000-00009

14. Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. *Cochrane Database Syst Rev* 2007;**1**:CD002200. http://dx.doi.org/10.1002/14651858.CD002200.pub2

15. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Br J Cancer* 2006;**94**:982–99. http://dx.doi.org/10.1038/sj.bjc.6603033

16. Treasure T, Utley M, Hunt I. When professional opinion is not enough. *BMJ* 2007;**334**:831–2. https://doi.org/10.1136/bmj.39161.403218.AD

17. Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. *World J Surg* 1995;**19**:59–71. https://doi.org/10.1007/BF00316981

18. Giacchetti S, Itzhaki M, Gruia G, Adam R, Zidani R, Kunstlinger F, *et al.* Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. *Ann Oncol* 1999;**10**:663–9. https://doi.org/10.1023/A:1008347829017

19. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, *et al.* Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008;**371**:1007–16. http://dx.doi.org/10.1016/S0140-6736(08)60455-9

20. Winawer SJ, Zauber AG, O'Brien MJ, Ho MN, Gottlieb L, Sternberg SS, *et al.* Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Workgroup. *N Engl J Med* 1993;**328**:901–6. http://dx.doi.org/10.1056/NEJM199304013281301

21. Khoury DA, Opelka FG, Beck DE, Hicks TC, Timmcke AE, Gathright JB Jr. Colon surveillance after colorectal cancer surgery. *Dis Colon Rectum* 1996;**39**:252–6. https://doi.org/10.1007/BF02049461

22. Safi F, Link KH, Beger HG. Is follow-up of colorectal cancer patients worthwhile? *Dis Colon Rectum* 1993;**36**:636–43. https://doi.org/10.1007/BF02238589

23. Kjeldsen BJ, Thorsen H, Whalley D, Kronborg O. Influence of follow-up on health-related quality of life after radical surgery for colorectal cancer. *Scand J Gastroenterol* 1999;**34**:509–15. https://doi.org/10.1080/003655299750026254

24. Grunfeld E, Gray A, Mant D, Yudkin P, Adewuyi-Dalton R, Coyle D, *et al.* Follow-up of breast cancer in primary care vs specialist care: results of an economic evaluation. *Br J Cancer* 1999;**79**:1227–33. http://dx.doi.org/10.1038/sj.bjc.6690197

25. Smith JA, King PM, Lane RH, Thompson MR. Evidence of the effect of 'specialization' on the management, surgical outcome and survival from colorectal cancer in Wessex. *Br J Surg* 2003;**90**:583–92. http://dx.doi.org/10.1002/bjs.4085

26. Neugut AI, Lautenbach E, Abi-Rached B, Forde KA. Incidence of adenomas after curative resection for colorectal cancer. *Am J Gastroenterol* 1996;**91**:2096–8.

27. Ward J, Naik KS, Guthrie JA, Wilson D, Robinson PJ. Hepatic lesion detection: comparison of MR imaging after the administration of superparamagnetic iron oxide with dual-phase CT by using alternative-free response receiver operating characteristic analysis. *Radiology* 1999;**210**:459–66. http://dx.doi.org/10.1148/radiology.210.2.r99fe05459

28. Carter R, Hemingway D, Cooke TG, Pickard R, Poon FW, McKillop JA, McArdle CS. A prospective study of six methods for detection of hepatic colorectal metastases. *Ann R Coll Surg Engl* 1996;**78**:27–30.

29. Department of Health. *Ionising Radiation (Medical Exposure) Regulations 2000 (IRMER)*. 2012. URL: www.gov.uk/government/publications/the-ionising-radiation-medical-exposure-regulations-2000 (accessed 3 May 2017).

30. Wall BF. Radiation protection dosimetry for diagnostic radiology patients. *Radiat Prot Dosimetry* 2004;**109**:409–19. http://dx.doi.org/10.1093/rpd/nch317

31. International Commission on Radiological Protection. *Radiological Protection in Biomedical Research*. Ottawa, ON: International Commission on Radiological Protection; 1992.

32. Macdonald JS. Carcinoembryonic antigen screening: pros and cons. *Semin Oncol* 1999;**26**:556–60.

33. Ward U, Primrose JN, Finan PJ, Perren TJ, Selby P, Purves DA, Cooper EH. The use of tumour markers CEA, CA-195 and CA-242 in evaluating the response to chemotherapy in patients with advanced colorectal cancer. *Br J Cancer* 1993;**67**:1132–5. https://doi.org/10.1038/bjc.1993.208

34. Nicholson BD, Shinkins B, Pathiraja I, Roberts NW, James TJ, Mallett S, *et al.* Blood CEA levels for detecting recurrent colorectal cancer. *Cochrane Database Syst Rev* 2015;**12**:CD011134. http://dx.doi.org/10.1002/14651858.CD011134.pub2

35. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;**37**:53–72. https://doi.org/10.1016/0168-8510(96)00822-6

36. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;**85**:365–76. https://doi.org/10.1093/jnci/85.5.365

37. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361–70. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

38. Grunfeld E, Fitzpatrick R, Mant D, Yudkin P, Adewuyi-Dalton R, Stewart J, *et al.* Comparison of breast cancer patient satisfaction with follow-up in primary care versus specialist care: results from a randomized controlled trial. *Br J Gen Pract* 1999;**49**:705–10.

39. Sprangers MA, te Velde A, Aaronson NK. The construction and testing of the EORTC colorectal cancer-specific quality of life questionnaire module (QLQ-CR38). European Organization for Research and Treatment of Cancer Study Group on Quality of Life. *Eur J Cancer* 1999;**35**:238–47. https://doi.org/10.1016/S0959-8049(98)00357-8

40. Ward WL, Hahn EA, Mo F, Hernandez L, Tulsky DS, Cella D. Reliability and validity of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) quality of life instrument. *Qual Life Res* 1999;**8**:181–95. https://doi.org/10.1023/A:1008821826499

41. ACPGBI Guidelines for the Management of Colorectal Cancer. *2007 CC Management Guidelines.* 2007. URL: www.acpgbi.org.uk/resources/guidelines/guidelines-for-the-management-of-colorectal-cancer (accessed 14 November 2016).

42. Royal Pharmaceutical Society of Great Britain. *British National Formulary No. 66.* London: BMJ Group and RPS Publishing; 2013.

43. Curtis L. *Unit Costs of Health and Social Care 2013*. Canterbury: Personal and Social Services Research Unit, University of Kent; 2013.

44. Department of Health. *NHS National Schedule of Reference Costs 2012–13*. London: Department of Health; 2013.

45. National Institute for Health and Care Excellence. *Guide to the Methods of Technology Appraisal 2013*. London: National Institute for Health and Care Excellence; 2013.

46. Dolan P, Gudex C, Kind P, Williams A. *A Social Tariff for EuroQol: Results from a UK General Population Survey (Discussion Paper No. 138)*. York: Centre for Health Economics, University of York; 1995.

47. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;**35**:1095–108. https://doi.org/10.1097/00005650-199711000-00002

48. Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *PharmacoEconomics* 2014;**32**:1157–70. http://dx.doi.org/10.1007/s40273-014-0193-3

49. Briggs A, Clark T, Wolstenholme J, Clarke P. Missing . . . presumed at random: cost-analysis of incomplete data. *Health Econ* 2003;**12**:377–92. http://dx.doi.org/10.1002/hec.766

50. Little R, Rubin D. *Statistical Analysis with Missing Data*. New York, NY: John Wiley and Sons; 1987.

51. Gray AM, Clarke PM, Wolstenholme JL, Wordsworth S. *Applied Methods of Cost-Effectiveness Analysis in Health Care*. Oxford: Oxford University Press; 2011.

52. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves – facts, fallacies and frequently asked questions. *Health Econ* 2004;**13**:405–15. http://dx.doi.org/10.1002/hec.903

53. Renehan AG, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. *BMJ* 2002;**324**:813. https://doi.org/10.1136/bmj.324.7341.813

54. Secco GB, Fardelli R, Gianquinto D, Bonfante P, Baldi E, Ravera G, *et al.* Efficacy and cost of risk-adapted follow-up in patients after colorectal cancer surgery: a prospective, randomized and controlled trial. *Eur J Surg Oncol* 2002;**28**:418–23. https://doi.org/10.1053/ejso.2001.1250

55. Renehan AG, O'Dwyer ST, Whynes DK. Cost effectiveness analysis of intensive versus conventional follow up after curative resection for colorectal cancer. *BMJ* 2004;**328**:81. http://dx.doi.org/10.1136/bmj.328.7431.81

56. Primrose JN, Perera R, Gray A, Rose P, Fuller A, Corkhill A, *et al.* Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. *JAMA* 2014;**311**:263–70. http://dx.doi.org/10.1001/jama.2013.285718

57. Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, *et al.* Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. *Value Health* 2015;**18**:161–72. http://dx.doi.org/10.1016/j.jval.2015.02.001

58. Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, *et al.* The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg* 2007;**246**:693–701. http://dx.doi.org/10.1097/01.sla.0000257358.56863.ce

59. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, *et al.* Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;**351**:1731–40. http://dx.doi.org/10.1056/NEJMoa040694

60. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, *et al.* Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006;**355**:1114–23. https://doi.org/10.1056/NEJMoa060829

61. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, *et al.* Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;**345**:638–46. http://dx.doi.org/10.1056/NEJMoa010580

62. Obrand DI, Gordon PH. Incidence and patterns of recurrence following curative resection for colorectal carcinoma. *Dis Colon Rectum* 1997;**40**:15–24. https://doi.org/10.1007/BF02055676

63. Ding P, Liska D, Tang P, Shia J, Saltz L, Goodman K, *et al.* Pulmonary recurrence predominates after combined modality therapy for rectal cancer: an original retrospective study. *Ann Surg* 2012;**256**:111–16. http://dx.doi.org/10.1097/SLA.0b013e31825b3a2b

64. Roth ES, Fetzer DT, Barron BJ, Joseph UA, Gayed IW, Wan DQ. Does colon cancer ever metastasize to bone first? a temporal analysis of colorectal cancer progression. *BMC Cancer* 2009;**9**:274. http://dx.doi.org/10.1186/1471-2407-9-274

65. Kornmann M, Staib L, Wiegel T, Kron M, Henne-Bruns D, Link KH, *et al.* Long-term results of 2 adjuvant trials reveal differences in chemosensitivity and the pattern of metastases between colon cancer and rectal cancer. *Clin Colorectal Cancer* 2013;**12**:54–61. http://dx.doi.org/10.1016/j.clcc.2012.07.005

66. Meyerhardt JA, Mangu PB, Flynn PJ, Korde L, Loprinzi CL, Minsky BD, *et al.* Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol* 2013;**31**:4465–70. http://dx.doi.org/10.1200/JCO.2013.50.7442

67. Steele SR, Chang GJ, Hendren S, Weiser M, Irani J, Buie WD, *et al.* Practice guideline for the surveillance of patients after curative treatment of colon and rectal cancer. *Dis Colon Rectum* 2015;**58**:713–25. http://dx.doi.org/10.1097/DCR.0000000000000410

68. Glimelius B, Tiret E, Cervantes A, Arnold D, ESMO Guidelines Working Group. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;**24**(Suppl. 6):81–8. http://dx.doi.org/10.1093/annonc/mdt240

69. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandalà M, Cervantes A, *et al.* Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;**24**(Suppl. 6):64–72. http://dx.doi.org/10.1093/annonc/mdt354

70. Pugh SA, Shinkins B, Fuller A, Mellor J, Mant D, Primrose JN. Site and stage of colorectal cancer influence the likelihood and distribution of disease recurrence and postrecurrence survival: data from the FACS randomized controlled trial. *Ann Surg* 2016;**263**:1143–7. https://doi.org/10.1097/SLA.0000000000001351

71. Tran B, Kopetz S, Tie J, Gibbs P, Jiang ZQ, Lieu CH, *et al.* Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. *Cancer* 2011;**117**:4623–32. http://dx.doi.org/10.1002/cncr.26086

72. Guinney J, Dienstmann R, Wang X, de Reyniès A, Schlicker A, Soneson C, *et al.* The consensus molecular subtypes of colorectal cancer. *Nat Med* 2015;**21**:1350–6. http://dx.doi.org/10.1038/nm.3967

73. Rex DK, Kahi CJ, Levin B, Smith RA, Bond JH, Brooks D, *et al.* Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and US Multi-Society Task Force on Colorectal Cancer. *CA Cancer J Clin* 2006;**56**:160–7. https://doi.org/10.3322/canjclin.56.3.160

74. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, *et al.* Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009;**27**:3109–16. http://dx.doi.org/10.1200/JCO.2008.20.6771

75. Morris EJ, Sandin F, Lambert PC, Bray F, Klint A, Linklater K, *et al.* A population-based comparison of the survival of patients with colorectal cancer in England, Norway and Sweden between 1996 and 2004. *Gut* 2011;**60**:1087–93. http://dx.doi.org/10.1136/gut.2010.229575

76. Tan E, Gouvas N, Nicholls RJ, Ziprin P, Xynos E, Tekkis PP. Diagnostic precision of carcinoembryonic antigen in the detection of recurrence of colorectal cancer. *Surg Oncol* 2009;**18**:15–24. http://dx.doi.org/10.1016/j.suronc.2008.05.008

77. Drescher CW, Shah C, Thorpe J, O'Briant K, Anderson GL, Berg CD, *et al.* Longitudinal screening algorithm that incorporates change over time in CA125 levels identifies ovarian cancer earlier than a single-threshold rule. *J Clin Oncol* 2013;**31**:387–92. http://dx.doi.org/10.1200/JCO.2012.43.6691

78. Morris EJ, Forman D, Thomas JD, Quirke P, Taylor EF, Fairley L, *et al.* Surgical management and outcomes of colorectal cancer liver metastases. *Br J Surg* 2010;**97**:1110–18. http://dx.doi.org/10.1002/bjs.7032

79. Cho YB, Chun HK, Yun HR, Lee WS, Yun SH, Lee WY. Clinical and pathologic evaluation of patients with recurrence of colorectal cancer five or more years after curative resection. *Dis Colon Rectum* 2007;**50**:1204–10. http://dx.doi.org/10.1007/s10350-007-0247-0

80. Broadbridge VT, Karapetis CS, Beeke C, Woodman RJ, Padbury R, Maddern G, *et al.* Do metastatic colorectal cancer patients who present with late relapse after curative surgery have a better survival? *Br J Cancer* 2013;**109**:1338–43. http://dx.doi.org/10.1038/bjc.2013.388

81. Bouvier AM, Launoy G, Bouvier V, Rollot F, Manfredi S, Faivre J, *et al.* Incidence and patterns of late recurrences in colon cancer patients. *Int J Cancer* 2015;**137**:2133–8. http://dx.doi.org/10.1002/ijc.29578

82. Jones RP, Vauthey JN, Adam R, Rees M, Berry D, Jackson R, *et al.* Effect of specialist decision-making on treatment strategies for colorectal liver metastases. *Br J Surg* 2012;**99**:1263–9. http://dx.doi.org/10.1002/bjs.8835

83. Rodríguez-Moranta F, Saló J, Arcusa A, Boadas J, Piñol V, Bessa X, *et al.* Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: a prospective, multicenter, randomized, controlled trial. *J Clin Oncol* 2006;**24**:386–93. https://doi.org/10.1200/JCO.2005.02.0826

84. Pietra N, Sarli L, Costi R, Ouchemi C, Grattarola M, Peracchia A. Role of follow-up in management of local recurrences of colorectal cancer: a prospective, randomized study. *Dis Colon Rectum* 1998;**41**:1127–33. https://doi.org/10.1007/BF02239434

85. Rosati G, Ambrosini G, Barni S, Andreoni B, Corradini G, Luchena G, *et al.* A randomized trial of intensive versus minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma. *Ann Oncol* 2016;**27**:247–80. http://dx.doi.org/10.1093/annonc/mdv541

86. Hansdotter Andersson P, Wille-Jørgensen P, Horváth-Puhó E, Petersen SH, Martling A, Sørensen HT, Syk I. The COLOFOL trial: study design and comparison of the study population with the source cancer population. *Clin Epidemiol* 2016;**8**:15–21. https://doi.org/10.2147/CLEP.S92661

87. Venook AP, Niedzwiecki D, Lenz H-J, Innocenti F, Mahoney MR, O'Neil BH, *et al.* CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). *J Clin Oncol* 2014;**32**:5s. https://doi.org/10.1200/jco.2014.32.18_suppl.lba3

88. Gruenberger T, Bridgewater J, Chau I, Garcia Alfonso P, Rivoire M, Mudan S, *et al.* Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. *Ann Oncol* 2014;**26**:702–8. http://dx.doi.org/10.1093/annonc/mdu580

89. van Hazel GA, Heinemann V, Sharma NK, Findlay MPN, Ricke J, Peeters M, *et al.* SIRFLOX: randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. *J Clin Oncol* 2016;**34**:1723–31. https://doi.org/10.1200/JCO.2015.66.1181

90. Ruers T, Punt CJA, von Coevorden F, Pierie J-P, Rinkes IB, Ledermann JA, *et al.* Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM): long-term survival results of a randomized phase II study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC). *J Clin Oncol* 2015;**26**(Suppl. 4):iv114–15. https://doi.org/10.1093/annonc/mdv235.17

91. National Institute for Health and Care Excellence. *Colorectal Cancer: Diagnosis and Management. Clinical Guideline*. London: National Institute for Health and Care Excellence; 2011. URL: www. nice.org.uk/guidance/cg131 (accessed 3 May 2017).

92. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pages C, *et al.* Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science* 2006;**313**:1960–4. http://dx.doi.org/10.1126/science.1129139

93. Galon J, Pagès F, Marincola FM, Thurin M, Trinchieri G, Fox BA, *et al.* The immune score as a new possible approach for the classification of cancer. *J Transl Med* 2012;**10**:1. http://dx.doi.org/10.1186/1479-5876-10-1

94. Department of Health. *Electronic Market Information Tool*. 2011. URL: www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit (accessed 12 April 2014).

95. NHS Digital. *HRG4 + 2012/13 Reference Costs Grouper*. 2013. URL: http://content.digital.nhs.uk/article/4698/HRG4-201213-Reference-Costs-Grouper-and-Documentation (accessed 28 October 2016).

Appendix 1 Pre-trial modelling

Introduction

A pre-trial economic model was devised to assess the probable costs, effects and cost-effectiveness of each of the trial options and to identify areas in which it was likely to be particularly important to collect information during the trial.

Methods

The model took recurrence rates over the 5 years from the primary episode, stage-specific survival and initial stage distribution rates from the Wessex Colorectal Cancer Audit (based on 4466 audited cases). As the trial protocol proposed to recruit patients in Dukes' stages A to C only, patients whose initial tumour was classified as stage D were excluded from the calculations. The overall survival rate of patients with initial colorectal cancer in Dukes' stages A to C in the Wessex data was around 50%. The cumulative recurrence rate at 5 years was around 28%. The model assumed that, in routine care, 6% of patients with recurrences would be successfully treated and survive for 5 years.

The model included initial estimates of the frequency and cost of investigative procedures (CEA tests, ultrasound and CT scans, GP consultations) in normal care and by following the proposed trial protocol. Unit costs were taken from national sources. To calculate investigative costs, the predicted number of CEA tests, GP consultations, ultrasound and CT scans according to the protocol were adjusted by expected survival, taking into account cancer- and non-cancer-related deaths. To estimate treatment costs, the model assumed that all patients who were successfully treated and approximately 5% of patients who were not successfully treated would undergo resection. It was also assumed that all patients with a recurrence who were not successfully treated would have a period of palliative care.

The model estimated the effect of improving the colorectal cancer death rate and thus increasing the proportion of patients surviving recurrence by means of each of the three active intervention groups of the proposed study: CEA testing in primary care, hospital-based follow-up and combined follow-up. In the combined follow-up group, the improvement was set to give a survival gain of 8% over no follow-up, in line with the trial hypothesis. CEA testing in primary care was set to give a survival gain of approximately 4%, as was hospital-based follow-up. To obtain a 4% gain in overall survival, it was necessary for the CEA testing or hospital-based follow-up interventions to increase the proportion of patients surviving recurrence from 6% to 20%. To obtain an 8% gain in overall survival, it was necessary for the combined interventions to increase the proportion of patients surviving recurrence from 6% to 39%.

Cost-effectiveness was calculated as the incremental cost per life-year gained of each option compared with normal practice. Different discount rates were examined for costs and effects, ranging from 6% to 1.5%. The following table gives all main model parameter values and results. *Figure 9* shows how the cost per life-year gained changes in each arm as the percentage improvement in colorectal cancer death rate alters. *Figure 10* shows the model's baseline estimate of cost-effectiveness of the three colorectal cancer follow-up strategies relative to no follow-up.
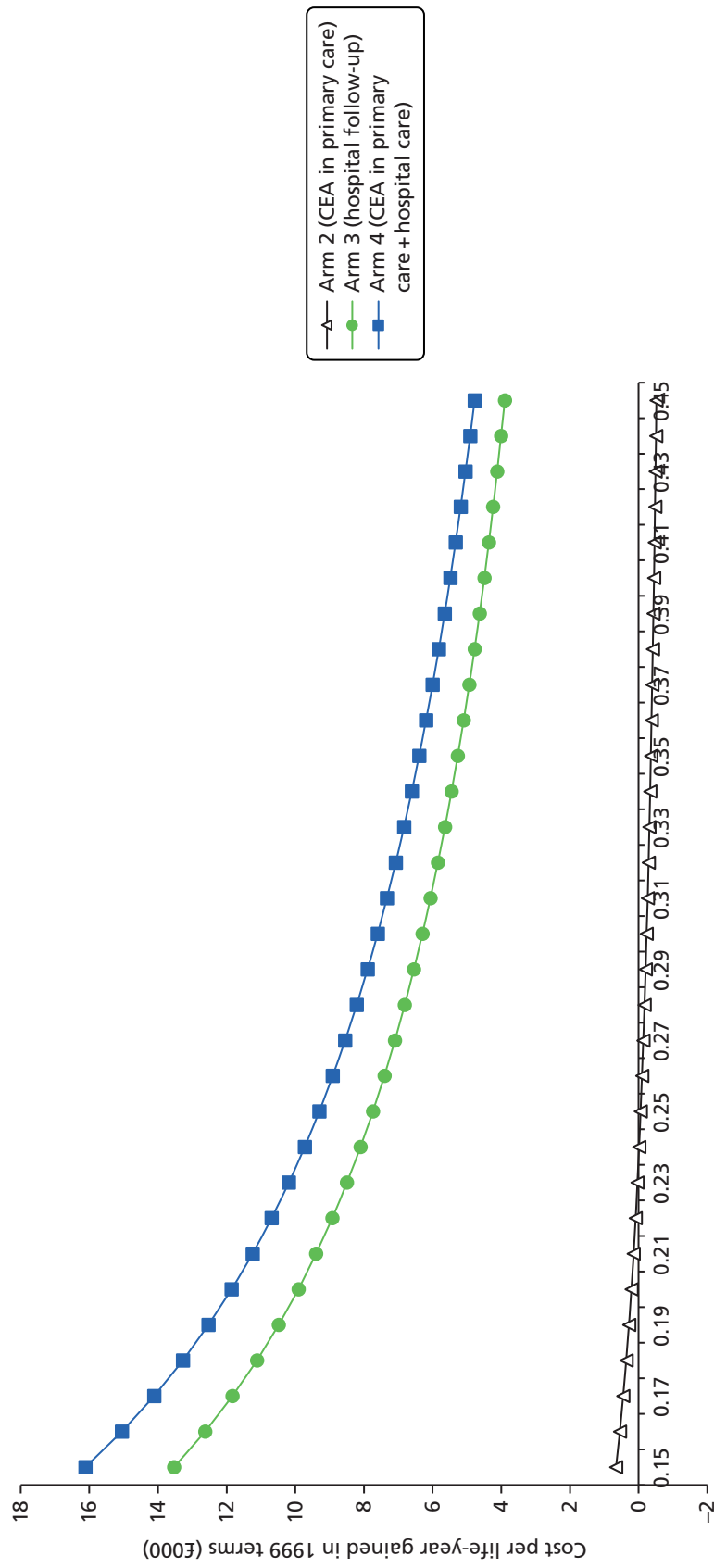
FIGURE 9 Cost per life-year gained as percentage improvement in colorectal cancer death rate alters.
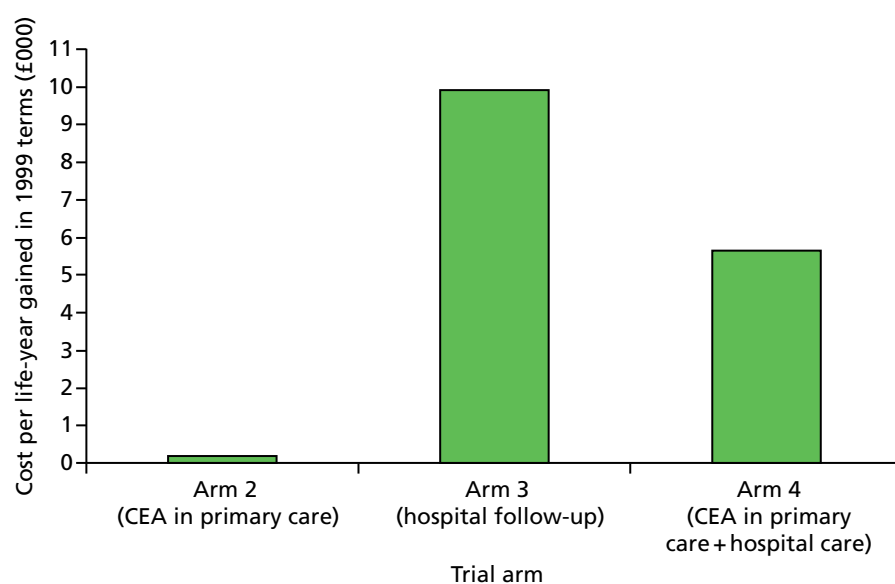
FIGURE 10 Cost-effectiveness of three colorectal cancer follow-up strategies relative to no follow-up.

Model parameter values and results

| Parameter values | Protocol | | | | | Survival adjusted |
	Year 1	Year 2	Year 3	Year 4	Year 5	5 years
Number of CEA tests						
Group 1 (normal care)	0.00	0.00	0.00	0.00	0.00	0.00
Group 2 (CEA testing in primary care)	4.00	4.00	2.00	2.00	2.00	10.40
Group 3 (hospital follow-up)	0.00	0.00	0.00	0.00	0.00	0.00
Group 4 (CEA testing and hospital care)	4.00	4.00	2.00	2.00	2.00	10.83
Number of GP consultations related to recurrence						
Group 1 (normal care) (assumed to be four times the recurrence rate)	0.33	0.33	0.33	0.07	0.07	0.81
Group 2 (CEA testing in primary care)	4.00	4.00	2.00	2.00	2.00	10.40
Group 3 (hospital follow-up)	0.33	0.33	0.33	0.07	0.07	0.85
Group 4 (CEA testing and hospital care)	4.33	4.33	2.33	2.07	2.07	11.71
Number of ultrasound and radiography scans						
Group 1 (normal care; assumed that referrals get CT)	0.00	0.00	0.00	0.00	0.00	0.00
Group 2 (CEA testing in primary care)	0.08	0.08	0.08	0.02	0.02	0.21
Group 3 (hospital follow-up)	2.00	2.00	1.00	1.00	1.00	5.20

Parameter values	Protocol					Survival adjusted
	Year 1	Year 2	Year 3	Year 4	Year 5	5 years
Group 4 (CEA testing and hospital care)	2.08	2.08	1.08	1.02	1.02	5.64
Number of CT scans						
Group 1 (normal care; assumed that 50% of consultations are referred)	0.00	0.00	0.00	0.20	0.20	0.23
Group 2 (CEA testing in primary care; assumed to be twice the actual recurrence rate)	0.16	0.16	0.16	0.03	0.03	0.42
Group 3 (hospital follow-up)	2.00	2.00	1.00	1.00	1.00	5.20
Group 4 (CEA testing and hospital care)	2.16	2.16	1.16	1.03	1.03	5.86
Number of colonoscopies						
Group 1	1.00	0.00	0.00	0.00	1.00	1.393
Group 2	1.00	0.00	0.00	0.00	1.00	1.452
Group 3	1.00	0.00	0.00	0.00	1.00	1.452
Group 4	1.00	0.00	0.00	0.00	1.00	1.511
Recurrence rate from Dukes' stage A, B and C tumours (Wessex registry)						
All	0.10	0.19	0.25	0.26	0.28	

Successful treatment rates	Assumed Improvement in colorectal cancer death rate	Proportion of recurrences surviving	Proportion of recurrences not surviving	Proportion of recurrences operated on		
Group 1 (normal care; data from Wessex Colorectal Cancer Audit)	0	0.06	0.94	0.11		
Group 2 (CEA testing in primary care)	0.20	0.26	0.74	0.30		
Group 3 (hospital follow-up)	0.20	0.26	0.74	0.30		
Group 4 (CEA testing and hospital care)	0.39	0.45	0.55	0.48		

Survival probability based on above	Year 1	Year 2	Year 3	Year 4	Year 5	(Gain)
Group 1 (normal care; Wessex registry)	0.856	0.744	0.657	0.585	0.54	
Group 2 (CEA testing in primary care)	0.876	0.775	0.695	0.625	0.58	3.96%
Group 3 (hospital follow-up)	0.876	0.775	0.695	0.625	0.58	3.96%
Group 4 (CEA testing and hospital care)	0.895	0.806	0.732	0.666	0.62	7.92%

| Parameter values | Protocol | | | | | Survival adjusted |
	Year 1	Year 2	Year 3	Year 4	Year 5	5 years
Unit costs (£)						
Cost of radiography	71					
Cost of ultrasound scan	35					
Cost of CT scan	185					
Cost of colonoscopy	175					
Cost of outpatient appointment	63					
Cost of resection	6000					
Cost of CEA testing (£6.50 + £1.50 postage/packing)	8					
Cost of palliative care	10,000					
Cost of GP consultation	14					
Five-year results: cost (£) per life-year gained compared with normal practice						
Group 2 (CEA testing in primary care)	209					
Group 3 (hospital follow-up)	9911					
Group 4 (CEA testing in primary care and hospital care)	5647					

Appendix 2 Colorectal cancer-specific survival
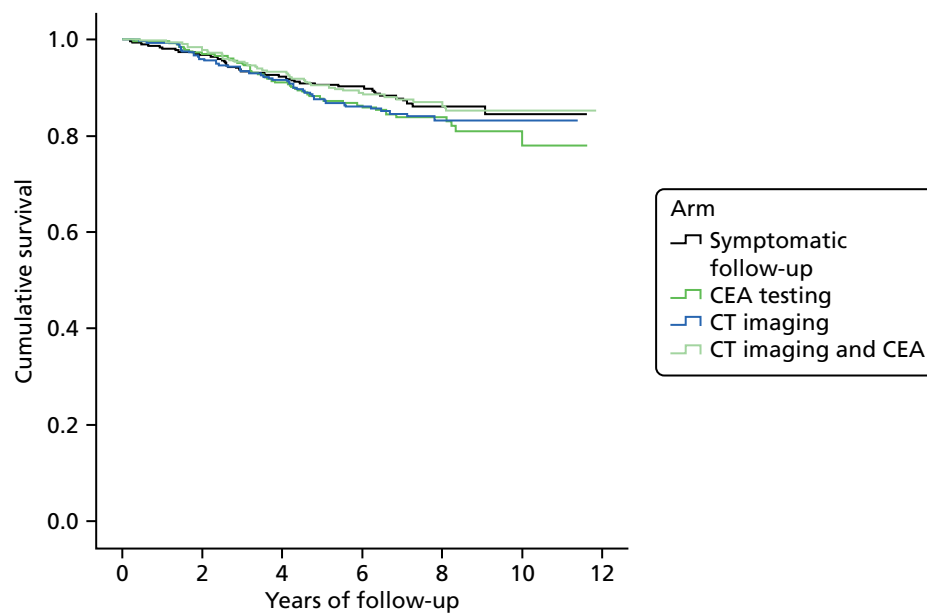
FIGURE 11 Cumulative survival by intervention arm: colorectal cancer deaths only.

Appendix 3 Follow-up After Colorectal Surgery health economics

Costing methods

The unit cost for each CEA test recorded included consumables and laboratory processing costs. CEA tests were generally conducted by practice nurses but, because patients reported visits to health-care professionals separately, a practice nurse visit was not included as part of the CEA test unit cost to avoid double-counting. Cross-checks of the annual numbers of CEA tests and patient-reported practice nurse visits were performed, and when the number of practice nurse visits reported was lower than the number of CEA tests an upwards adjustment to the number of practice nurse visits was made so that that numbers for both variables were equivalent.

Computerised tomography scans, colonoscopies, radiography and MRI scans were costed using the sources listed in *Table 15*; these investigations were conducted at hospital outpatient clinics, but as with CEA tests, the associated clinic visit was counted separately and not included as part of these investigations. Again, cross-checks were performed and when the number of outpatient clinic visits reported was lower than the sum of the number of CT scans, colonoscopies, radiography and MRI scans, an upwards adjustment to the number of visits was made so that numbers for both variables were equivalent.

TABLE 15 Unit costs (£) used in the analysis and sources of information (2012/13)

Resource-use item	Unit cost (£)	Source
Tests/investigations		
CEA test	7.50	£6.00 for laboratory analysis plus £1.50 for postage and packing – trial-participating hospital
CT scan	130.72	NHS reference costs 2012/13[44] – average of codes RA08A, RA09A, RA10Z–RA14Z, RA50Z. Diagnostic imaging outpatients, medical oncology
Chest radiography	40	Finance department, trial participating hospital
MRI	191.05	NHS reference costs 2012/13[44] – average of codes RA01A, RA02A, RA03Z–RA07Z. Diagnostic imaging outpatients, medical oncology
Colonoscopy	514.00	NHS reference costs 2012/13[44] – code FZ51Z – diagnostic colonoscopy, aged ≥ 19 years, colorectal surgery day case
Treatment for recurrence		
Surgery		Individual procedures were mapped to one or more HRG codes and the weighted average of 2012/13 NHS reference costs[44] for each mapped HRG code (elective inpatients) was calculated
	6980.80	Code AA12 – intermediate intracranial procedures except trauma with brain tumours or cerebral cysts
	8945.16	Code AA06 – major intracranial procedures except trauma with brain tumours or cerebral cysts
	7361.79	Code DZ02 – complex thoracic procedures
	3719.05	Code DZ53 – major or intermediate thoracic procedures
	5158.88	Code FZ66/FZ67 – very major/major small intestine procedures, aged ≥ 19 years
	6936.06	Code FZ66 – very major small intestine procedures, aged ≥ 19 years

TABLE 15 Unit costs (£) used in the analysis and sources of information (2012/13) (*continued*)

Resource-use item	Unit cost (£)	Source
	7471.52	Code FZ73/FZ74/FZ75 – very complex/complex large intestine procedures/proximal colon procedures
	8155.33	Code FZ73/FZ74 – very complex/complex large intestine procedures
	10,500.74	Code GA03 – very complex open hepatobiliary or pancreatic procedures
	9450.05	GA03/GA04 – very complex/complex open hepatobiliary or pancreatic procedures
	8517.09	Code GA03/GA04/GA05 – very complex/complex/very major open hepatobiliary or pancreatic procedures
	4242.29	Code GA06/GA07/GA13 – major/intermediate open hepatobiliary or pancreatic procedures/laparoscopic hepatobiliary or pancreatic procedures
	2741.87	Code GA07/GA10 – intermediate open hepatobiliary or pancreatic procedures/laparoscopic/open cholecystectomy
	4068.17	Code GB01/GB08 – very major/complex endoscopic or percutaneous, hepatobiliary or pancreatic procedures
	795.11	Code GB04 – minor endoscopic or percutaneous, hepatobiliary or pancreatic procedures, aged ≥ 19 years
	1098.63	Code GB07 – minor diagnostic endoscopic retrograde cholangiopancreatography
	3865	Code HC04 – extradural spine intermediate
	5476.86	Code LB60/LB61/LB62 – complex/major open or percutaneous, kidney or ureter procedures, aged ≥ 19 years/major laparoscopic kidney or ureter procedures, aged ≥ 19 years
	16,358.63	Code LB71 – total pelvic exenteration
	4289.45	Code – MA06/MA26 complex/major open or laparoscopic, upper or lower genital tract procedures for malignancy
Chemotherapy		
First-line therapy drugs per 21-day cycle		
Oxaliplatin 130 mg/m^2, once	18.25	100 mg/20 ml (£6.32) and 50 mg/10 ml (£5.61) from NHS eMIT.[94] Body surface area of 1.79 m^2 assumed
Capecitabine 1000 mg/m^2, twice daily, days 1–14	41.16	500-mg tablets, 120 per pack (£47.84) and 150 mg tablets, 60 per pack (£8.34) from NHS eMIT.[94] Body surface area of 1.79 m^2 assumed
Bevacizumab (Avastin, Roche) 7.5 mg/kg, once	1409.72	100 mg/4 ml (£242.66) and 400 mg/16 ml (£924.40) from the BNF 2015.[42] Average weight is assumed to be 76.5 kg
Second-line therapy drugs per 21-day cycle		
Irinotecan 180 mg/m^2, once per cycle	31.20	300 mg/15 ml (£25.58) and 40 mg/2 ml (£5.62) from NHS eMIT.[94] Body surface area of 1.79 m^2 assumed
Fluoroacil 2400 mg/m^2 infusion, once	3.47	5 g/100 ml (£3.47) from NHS eMIT.[94] Body surface area of 1.79 m^2 assumed
Fluoroacil 400 mg/m^2 bolus, once	4.46	500 mg/10 ml (£0.96) and 250 mg/10 ml (£3.50) from NHS eMIT.[94] Body surface area of 1.79 m^2 assumed
Folinic acid 300 mg, once	89.95	300 mg/30 ml (£89.95) from the BNF 2015[42]
Aflibercept (Zaltrap, Sanofi-Aventis) 4 mg/kg, once	1182.60	200 mg vial (£591.30) and 100 mg vial (£295.65) from the BNF 2015.[42] Average weight is assumed to be 76.5 kg

TABLE 15 Unit costs (£) used in the analysis and sources of information (2012/13) (*continued*)

Resource-use item	Unit cost (£)	Source
Radiotherapy		
With curative intent		
Radical radiotherapy planning session	733.92	NHS reference costs 2012/13[44] – average of codes SC40Z, SC41Z, SC51Z, SC52Z – preparation for conformal/IM radiation therapy (RAD worksheet)
Radical radiotherapy fraction cost	121	NHS reference costs 2012/13[44] – code SC23Z – deliver a fraction of complex radiotherapy (RAD worksheet)
With palliative intent		
Palliative radiotherapy planning session	281.53	NHS reference costs 2012/13[44] – average of codes SC45Z–SC50Z – preparation for simple/superficial radiotherapy (RAD worksheet)
Palliative radiotherapy fraction cost	91.00	NHS reference costs 2012/13[44] – code SC22Z, deliver a fraction of radiotherapy (RAD worksheet)
Longer-term follow-up		
GP clinic attendance	45	PSSRU 2013[43] (assuming attendance duration of 11.7 minutes), section 10.8b GP unit costs
Visits to practice nurse	13.43	PSSRU 2013[43] (assuming attendance duration of 15.5 minutes), section 10.6
District nurse at home	39.00	PSSRU 2013,[43] section 10.1 community nurse
Stoma care nurse	43.00	NHS reference costs 2012/13[44] – code N24AF – specialist nursing – stoma care services, adult, face to face
Oncology outpatient clinic attendance	144	NHS reference costs 2012/13[44] – code 370 – consultant-led medical oncology clinic attendance
Excess inpatient bed-day on oncology ward	369.79	NHS reference costs 2012/13[44] – weighted average of elective inpatient excess bed-day costs for medical oncology

BNF, *British National Formulary*; eMIT, electronic Market Information Tool; IM, intensity modulated; PSSRU, Personal Social Services Research Unit; RAD, radiotherapy.

For patients with recurrence who underwent one or more surgeries, the type of surgical procedure performed was recorded along with hospital admission and discharge dates. Using the HRG4 + 2012/13 Reference Costs Grouping programme from the National Casemix Office, the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures code for each type of surgery was identified and mapped to a corresponding HRG code(s).[95] HRG codes were then located in the NHS Reference Cost database, a weighted average was taken of the cost (and length of stay) across all specialties (excluding paediatrics) and subcategories within that code, and then the resulting costs were applied to the appropriate patients.[44] When a patient's hospital stay was known to exceed the average length of stay for their particular procedure, additional days were costed using an excess bed-day cost for an oncology ward.[44]

Detailed information was not collected on types of radiotherapy and/or chemotherapy received by patients with recurrence; instead, expert clinical opinion provided information on standard regimens, doses, frequency and duration of treatments, and *Table 15* shows the resulting estimated radiotherapy and chemotherapy unit costs. Radiotherapy treatment schedules varied depending upon whether a recurrence was treated with curative intent or palliatively. Radical radiotherapy was assumed to involve a complex planning session and 25 sessions of treatment. Palliative radiotherapy was assumed to consist of a simple planning session followed by five sessions of treatment. For patients recorded as having received radiotherapy, treatment was assumed to have been radical if the patient also underwent surgery with curative intent following recurrence. Radiotherapy was assumed to have been palliative if the patient underwent surgery without curative intent or if the patient

was not treated surgically for their recurrence. Patients receiving chemotherapy for recurrence and who survived at least 1 year from recurrence were assumed to have completed eight cycles of the first-line regimen shown in *Table 15*. Patients who died within 1 year of recurrence were assumed to have progressed mid-way through their remaining survival time and to have spent half of the time receiving the first-line chemotherapy regimen and half receiving the second-line regimen.

Additional practice nurse and outpatient clinic visits, together with visits to GPs and stoma nurses and home visits from district nurses, were also costed for each patient using appropriate unit costs from a variety of sources including Personal Social Services Research Unit and NHS Reference Costs (see *Table 15*).[43,44] When costing inpatient hospital admissions reported by patients, and to avoid double-counting for those patients who had undergone surgery for recurrence, one hospital admission and the appropriate number of surgery-related inpatient hospital days recorded by staff were subtracted from patients' annual self-reported data. The remaining hospital inpatient days were costed using an average oncology bed-day cost taken from the NHS Reference Costs.[44]

Multiple imputation

The MI approach uses predictions from regression models specified for each individual variable with missing data to fill in the missing data points. The form of each regression equation is dependent upon the type of data to be imputed, for example when imputing whether or not radiotherapy was given post recurrence (yes/no), a logistic regression was specified. When imputing the EQ-5D single-index score, a linear regression with prediction mean matching was used to ensure values were not predicted outside the permissible range (–0.594 to 1). Variables with complete data were used as predictors in each regression model (e.g. age and gender) along with all other variables to be imputed.

Table 16 gives a detailed breakdown, by each resource use category, of mean resource use and undiscounted costs per patient by trial arm and year of follow-up. *Table 17* shows the proportion of surviving patients reporting some or severe problems on each domain of the EQ-5D, by year and arm.

TABLE 16 Mean resource use and undiscounted costs per patient by trial arm and year of follow-up

Resource item	Mean (SE) resource use or n (%) receiving resource				Mean cost [SE (£)]			
	Minimum follow-up arm (N = 301)	CEA testing-only follow-up arm (N = 300)	CT-only follow-up arm (N = 299)	CEA testing and CT follow-up (N = 302)	Minimum follow-up arm (N = 301)	CEA testing-only follow-up arm (N = 300)	CT-only follow-up arm (N = 299)	CEA testing and CT follow-up (N = 302)
Year 1								
CEA tests	0.20 (0.04)	3.22 (0.05)	0.04 (0.02)	3.10 (0.06)	1.50 (0.28)	24.18 (0.41)	0.28 (0.12)	23.22 (0.41)
CT tests	0.30 (0.03)	0.28 (0.03)	1.37 (0.03)	1.40 (0.03)	38.65 (3.61)	37.04 (3.78)	179.25 (4.33)	183.09 (4.56)
Colonoscopy	0.08 (0.02)	0.06 (0.01)	0.12 (0.02)	0.14 (0.02)	42.69 (8.54)	30.84 (7.46)	63.61 (10.10)	73.19 (10.35)
Radiography	0.00 (0.00)	0.00 (0.00)	0.09 (0.02)	0.10 (0.02)	0.13 (0.13)	0.13 (0.13)	3.61 (0.76)	3.84 (0.84)
MRI scans	0.01 (0.00)	0.00 (0.00)	0.01 (0.01)	0.01 (0.00)	1.27 (0.90)	0.00 (0.00)	2.56 (1.27)	1.27 (0.89)
Surgery	6 (1.99%)	5 (1.67%)	7 (2.34%)	7 (2.32%)	177.09 (73.93)	142.52 (63.65)	250.79 (99.68)	184.28 (71.08)
Chemotherapy	4 (1.33%)	12 (4.00%)	15 (5.02%)	15 (4.97%)	160.01 (79.67)	470.12 (133.19)	555.22 (143.85)	549.71 (142.46)
Radiotherapy	3 (1.00%)	0 (0.00%)	4 (1.34%)	4 (1.32%)	17.38 (12.94)	0.00 (0.00)	17.50 (13.03)	17.32 (12.90)
GP visits	0.97 (0.12)	1.06 (0.12)	0.95 (0.13)	1.08 (0.14)	43.42 (5.42)	47.52 (5.43)	42.77 (5.92)	48.73 (6.51)
PN visits	1.38 (0.76)	4.27 (0.63)	0.59 (0.19)	3.26 (0.06)	18.48 (9.54)	57.41 (8.44)	7.91 (2.54)	43.81 (0.80)
DN visits	0.55 (0.17)	1.62 (0.70)	1.30 (0.36)	0.85 (0.60)	21.40 (6.53)	63.36 (27.17)	50.63 (14.15)	33.24 (23.44)
SN visits	0.34 (0.11)	0.23 (0.07)	0.36 (0.08)	0.40 (0.10)	14.49 (4.79)	9.83 (3.01)	15.42 (3.33)	17.34 (4.43)
Outpatient visits	1.42 (0.11)	1.44 (0.17)	3.17 (0.31)	3.24 (0.27)	204.66 (16.52)	207.07 (24.05)	456.75 (44.48)	466.81 (39.10)
Inpatient stays	0.13 (0.03)	0.15 (0.03)	0.19 (0.04)	0.14 (0.03)	321.63 (104.52)	468.15 (117.28)	278.76 (56.95)	372.24 (163.00)
Year 2								
CEA tests	0.16 (0.03)	3.44 (0.09)	0.02 (0.01)	3.29 (0.09)	1.17 (0.22)	25.80 (0.65)	0.18 (0.10)	24.69 (0.65)
CT tests	0.49 (0.03)	0.48 (0.03)	1.62 (0.05)	1.50 (0.05)	64.27 (4.25)	62.31 (4.30)	212.04 (6.67)	195.65 (6.68)
Colonoscopy	0.07 (0.02)	0.08 (0.02)	0.54 (0.03)	0.51 (0.03)	37.57 (8.09)	39.41 (8.27)	275.05 (14.85)	263.81 (14.81)
Radiography	0.03 (0.01)	0.02 (0.01)	0.13 (0.03)	0.10 (0.02)	1.20 (0.39)	0.93 (0.35)	5.08 (1.17)	4.11 (0.92)

TABLE 16 Mean resource use and undiscounted costs per patient by trial arm and year of follow-up (continued)

Resource item	Mean (SE) resource use or n (%) receiving resource				Mean cost [SE (£)]			
	Minimum follow-up arm (N = 301)	CEA testing-only follow-up arm (N = 300)	CT-only follow-up arm (N = 299)	CEA testing and CT follow-up (N = 302)	Minimum follow-up arm (N = 301)	CEA testing-only follow-up arm (N = 300)	CT-only follow-up arm (N = 299)	CEA testing and CT follow-up (N = 302)
MRI scans	0.00 (0.00)	0.01 (0.01)	0.01 (0.01)	0.00 (0.00)	0.63 (0.63)	1.91 (1.10)	1.92 (1.92)	0.63 (0.63)
Surgery	7 (2.33%)	10 (3.33%)	14 (4.68%)	5 (1.66%)	192.91 (80.35)	293.49 (91.96)	457.69 (126.68)	149.77 (67.02)
Chemotherapy	8 (2.66%)	9 (3.00%)	7 (2.34%)	9 (2.98%)	312.37 (109.14)	326.32 (110.14)	283.92 (106.54)	345.66 (114.77)
Radiotherapy	3 (1.00%)	1 (0.33%)	0 (0.00%)	2 (0.66%)	17.38 (12.94)	12.53 (–)	0.00 (0.00)	14.89 (12.68)
GP visits	0.70 (0.10)	0.94 (0.18)	0.50 (0.10)	0.89 (0.21)	31.37 (4.61)	42.24 (8.12)	22.67 (4.65)	40.02 (9.52)
PN visits	0.26 (0.04)	3.64 (0.09)	0.14 (0.05)	3.48 (0.09)	3.44 (0.57)	48.86 (1.26)	1.94 (0.70)	46.74 (1.25)
DN visits	0.13 (0.06)	1.98 (0.69)	0.32 (0.14)	0.87 (0.36)	5.23 (2.26)	77.40 (26.86)	12.44 (5.42)	33.89 (13.86)
SN visits	0.08 (0.04)	0.08 (0.04)	0.11 (0.04)	0.07 (0.02)	3.23 (1.87)	3.24 (1.68)	4.80 (1.54)	2.93 (0.97)
Outpatient visits	1.64 (0.18)	1.54 (0.14)	3.41 (0.16)	3.68 (0.37)	236.43 (26.25)	222.53 (20.47)	491.24 (23.41)	529.94 (53.94)
Inpatient stays	0.09 (0.03)	0.07 (0.02)	0.23 (0.08)	0.11 (0.03)	131.45 (51.42)	206.59 (70.45)	255.76 (97.24)	223.83 (70.26)
Year 3								
CEA tests	0.14 (0.03)	1.61 (0.06)	0.02 (0.01)	1.54 (0.06)	1.07 (0.21)	12.08 (0.46)	0.18 (0.09)	11.52 (0.43)
CT tests	0.11 (0.02)	0.11 (0.02)	0.76 (0.04)	0.79 (0.04)	14.33 (2.73)	14.38 (2.44)	99.68 (4.92)	103.02 (5.14)
Colonoscopy	0.07 (0.01)	0.04 (0.01)	0.11 (0.02)	0.11 (0.02)	35.86 (7.56)	20.56 (5.82)	55.01 (9.20)	57.87 (9.97)
Radiography	0.00 (0.00)	0.00 (0.00)	0.04 (0.01)	0.06 (0.02)	0.00 (0.00)	0.00 (0.00)	1.61 (0.56)	2.25 (0.68)
MRI scans	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.63 (0.63)
Surgery	2 (0.66%)	5 (1.67%)	1 (0.33%)	5 (1.66%)	53.96 (38.09)	135.71 (63.59)	47.46 (–)	142.52 (64.04)
Chemotherapy	1 (0.33%)	4 (1.33%)	4 (1.34%)	4 (1.32%)	15.01 (–)	156.71 (77.96)	150.00 (74.88)	155.67 (77.45)
Radiotherapy	0 (0.00%)	2 (0.67%)	3 (1.00%)	1 (0.33%)	0.00 (0.00)	4.91 (3.47)	4.93 (3.48)	12.45 (–)
GP visits	0.41 (0.07)	0.53 (0.11)	0.42 (0.08)	0.68 (0.21)	18.63 (3.24)	23.67 (5.14)	18.90 (3.51)	30.55 (9.63)
PN visits	0.19 (0.04)	1.77 (0.07)	0.20 (0.08)	1.71 (0.07)	2.61 (0.47)	23.71 (0.97)	2.73 (1.02)	22.96 (0.87)

Resource item	Mean (SE) resource use or n (%) receiving resource				Mean cost [SE (£)]			
	Minimum follow-up arm (N = 301)	CEA testing-only follow-up arm (N = 300)	CT-only follow-up arm (N = 299)	CEA testing and CT follow-up (N = 302)	Minimum follow-up arm (N = 301)	CEA testing-only follow-up arm (N = 300)	CT-only follow-up arm (N = 299)	CEA testing and CT follow-up (N = 302)
DN visits	0.05 (0.03)	0.07 (0.04)	0.03 (0.02)	0.69 (0.43)	2.00 (1.36)	2.70 (1.53)	1.10 (0.62)	26.76 (16.70)
SN visits	0.09 (0.03)	0.01 (0.01)	0.06 (0.03)	0.21 (0.10)	3.97 (1.25)	0.34 (0.34)	2.67 (1.35)	9.00 (4.37)
Outpatient visits	1.30 (0.31)	1.04 (0.17)	1.68 (0.15)	1.91 (0.16)	186.48 (44.04)	149.38 (25.19)	241.86 (22.29)	274.74 (23.09)
Inpatient stays	0.08 (0.02)	0.16 (0.06)	0.17 (0.17)	0.12 (0.05)	143.74 (46.68)	213.99 (73.13)	138.52 (128.89)	822.35 (414.00)
Year 4								
CEA tests	0.13 (0.03)	1.50 (0.06)	0.03 (0.01)	1.42 (0.06)	0.97 (0.20)	11.25 (0.46)	0.20 (0.09)	10.68 (0.46)
CT tests	0.09 (0.02)	0.08 (0.02)	0.70 (0.04)	0.70 (0.04)	11.73 (2.24)	10.46 (2.39)	91.81 (5.04)	90.90 (4.83)
Colonoscopy	0.06 (0.01)	0.06 (0.01)	0.03 (0.01)	0.04 (0.01)	32.45 (7.22)	30.84 (7.06)	13.75 (4.80)	22.13 (6.01)
Radiography	0.00 (0.00)	0.00 (0.00)	0.04 (0.01)	0.04 (0.01)	0.00 (0.00)	0.00 (0.00)	1.74 (0.54)	1.59 (0.49)
MRI scans	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.64 (0.64)	0.00 (0.00)
Surgery	0 (0.00%)	3 (1.00%)	4 (1.34%)	4 (1.32%)	0.00 (0.00)	118.84 (74.29)	110.52 (55.24)	102.27 (51.02)
Chemotherapy	0 (0.00%)	5 (1.67%)	4 (1.34%)	2 (0.66%)	0.00 (0.00)	191.12 (85.01)	157.23 (78.22)	77.83 (54.95)
Radiotherapy	1 (0.33%)	1 (0.33%)	1 (0.33%)	2 (0.66%)	2.45 (–)	12.53 (–)	12.57 (–)	4.88 (3.44)
GP visits	0.45 (0.10)	0.31 (0.06)	1.07 (0.61)	0.56 (0.14)	20.03 (4.45)	14.13 (2.91)	47.95 (27.63)	25.09 (6.44)
PN visits	0.20 (0.04)	1.76 (0.08)	0.87 (0.60)	1.76 (0.11)	2.66 (0.57)	23.59 (1.09)	11.67 (8.11)	23.62 (1.42)
DN visits	0.02 (0.02)	0.17 (0.11)	0.22 (0.12)	0.04 (0.03)	0.65 (0.65)	6.50 (4.38)	8.43 (4.53)	1.68 (1.16)
SN visits	0.09 (0.03)	0.04 (0.02)	0.05 (0.02)	0.12 (0.03)	3.77 (1.27)	1.58 (0.88)	1.98 (0.71)	5.21 (1.42)
Outpatient visits	1.15 (0.19)	1.17 (0.28)	1.74 (0.18)	1.31 (0.09)	165.05 (27.93)	168.77 (40.61)	251.11 (26.63)	189.20 (12.67)
Inpatient stays	0.10 (0.02)	0.03 (0.01)	0.04 (0.02)	0.06 (0.03)	96.56 (27.87)	34.27 (21.73)	46.75 (20.84)	143.26 (95.65)

TABLE 16 Mean resource use and undiscounted costs per patient by trial arm and year of follow-up (*continued*)

Resource item	Mean (SE) resource use or n (%) receiving resource				Mean cost [SE (£)]			
	Minimum follow-up arm (N = 301)	CEA testing-only follow-up arm (N = 300)	CT-only follow-up arm (N = 299)	CEA testing and CT follow-up (N = 302)	Minimum follow-up arm (N = 301)	CEA testing-only follow-up arm (N = 300)	CT-only follow-up arm (N = 299)	CEA testing and CT follow-up (N = 302)
Year 5								
CEA tests	0.08 (0.02)	1.78 (0.08)	0.01 (0.00)	1.68 (0.07)	0.57 (0.14)	13.35 (0.57)	0.05 (0.04)	12.62 (0.54)
CT tests	0.11 (0.02)	0.06 (0.01)	0.98 (0.05)	1.09 (0.05)	13.90 (2.63)	7.41 (1.85)	128.53 (6.39)	141.97 (6.82)
Colonoscopy	0.29 (0.03)	0.27 (0.03)	0.31 (0.03)	0.34 (0.03)	146.86 (13.41)	137.07 (13.15)	159.87 (13.78)	173.60 (14.22)
Radiography	0.00 (0.00)	0.00 (0.00)	0.05 (0.01)	0.04 (0.02)	0.13 (0.13)	0.00 (0.00)	1.87 (0.56)	1.46 (0.60)
MRI scans	0.00 (0.00)	0.00 (0.00)	0.01 (0.01)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	1.28 (1.28)	0.00 (0.00)
Surgery	0 (0.00%)	2 (0.67%)	4 (1.34%)	1 (0.33%)	0.00 (0.00)	70.24 (51.80)	176.03 (89.03)	34.77 (–)
Chemotherapy	1 (0.33%)	2 (0.67%)	2 (0.67%)	2 (0.66%)	4.88 (–)	55.09 (42.24)	78.62 (55.50)	77.83 (54.95)
Radiotherapy	0 (0.00%)	0 (0.00%)	1 (0.33%)	0 (0.00%)	0.00 (0.00)	0.00 (0.00)	2.46 (–)	0.00 (0.00)
GP visits	0.43 (0.14)	0.31 (0.07)	0.45 (0.14)	0.53 (0.16)	19.23 (6.34)	14.16 (3.08)	20.26 (6.18)	23.78 (7.20)
PN visits	0.17 (0.03)	2.05 (0.09)	0.14 (0.07)	1.80 (0.08)	2.22 (0.42)	27.52 (1.18)	1.89 (0.95)	24.15 (1.03)
DN visits	0.00 (0.00)	0.05 (0.03)	0.00 (0.00)	0.26 (0.18)	0.00 (0.00)	1.92 (1.04)	0.00 (0.00)	10.28 (7.11)
SN visits	0.06 (0.02)	0.04 (0.02)	0.10 (0.02)	0.05 (0.02)	2.46 (1.04)	1.86 (0.69)	4.37 (1.06)	2.25 (0.73)
Outpatient visits	0.99 (0.14)	0.98 (0.14)	1.64 (0.08)	1.92 (0.11)	142.56 (20.38)	141.12 (19.62)	236.37 (10.93)	276.94 (16.27)
Inpatient stays	0.02 (0.01)	0.05 (0.02)	0.08 (0.02)	0.05 (0.02)	37.35 (18.34)	66.32 (33.93)	73.22 (26.80)	108.49 (41.40)

DN, district nurse; PN, practice nurse; SN, stoma nurse.

TABLE 17 Proportion of surviving patients reporting some or severe problems on each domain of the EQ-5D, by year and arm

EQ-5D domain	Minimum follow-up	CEA testing only	CT only	CEA testing and CT
Mobility				
Baseline	0.24	0.23	0.23	0.28
1	0.26	0.22	0.27	0.26
2	0.30	0.27	0.25	0.24
3	0.27	0.28	0.23	0.27
4	0.27	0.30	0.25	0.27
5	0.27	0.27	0.24	0.35
Self-care				
Baseline	0.07	0.05	0.06	0.07
1	0.06	0.05	0.07	0.05
2	0.07	0.06	0.06	0.06
3	0.05	0.08	0.06	0.09
4	0.05	0.04	0.05	0.07
5	0.06	0.07	0.06	0.10
Usual activities				
Baseline	0.32	0.33	0.33	0.39
1	0.29	0.24	0.28	0.24
2	0.33	0.24	0.26	0.25
3	0.29	0.33	0.22	0.28
4	0.24	0.30	0.29	0.27
5	0.30	0.26	0.24	0.32
Pain/discomfort				
Baseline	0.38	0.39	0.35	0.38
1	0.29	0.31	0.28	0.33
2	0.36	0.29	0.23	0.34
3	0.35	0.35	0.26	0.31
4	0.35	0.34	0.30	0.35
5	0.34	0.26	0.23	0.35
Anxiety/depression				
Baseline	0.25	0.25	0.25	0.24
1	0.24	0.26	0.25	0.23
2	0.29	0.23	0.29	0.26
3	0.31	0.23	0.28	0.25
4	0.26	0.22	0.25	0.26
5	0.28	0.21	0.25	0.27

Appendix 4 Quality-of-life questionnaire

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
16.	Have you been constipated?	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
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 <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> 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 <u>health</u> during the past week?

1	2	3	4	5	6	7

Very poor   Excellent

30.   How would you rate your overall <u>quality of life</u> during the past week?

1	2	3	4	5	6	7

Very poor   Excellent

EQ-5D-3L

Health Questionnaire

English version for the UK

(Validated for Ireland)

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 ☐

UK (English) © 1990 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Best imaginable
health state

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

100

9●0

8●0

7●0

6●0

5●0

4●0

3●0

2●0

1●0

0

Worst imaginable
health state

UK (English) © 1990 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Section 3

Please tick one box per question to describe how you feel

1. **I feel tense or "wound up":**
   Most of the time

   A lot of the time
   From time to time, occasionally
   Not at all

2. **I still enjoy the things I used to enjoy:**
   Definitely as much
   Not quite so much
   Only a little
   Hardly at all

3. **I get a sort of frightened feeling as if something awful is about to happen:**
   Very definitely and quite badly
   Yes, but no too badly
   A little, but it doesn't worry me
   Not at all

4. **I can laugh and see the funny side of things:**
   As much as I always could
   Not quite so much now
   Definitely not so much now
   Not at all

5. **Worrying thoughts go through my mind:**
   A great deal of the time
   A lot of the time
   From time to time, but not too often
   Only occasionally

6. **I feel cheerful:**
   Not at all
   Not often
   Sometimes
   Most of the time

7. **I can sit at ease and feel relaxed:**
   Definitely
   Usually
   Not often
   Not at all

8. I feel as if I am slowed down:
Nearly all the time
Very often
Sometimes
Not at all

9. I get a sort of frightened feeling like "butterflies" in the stomach:
Not at all
Occasionally
Quite often
Very often

10. I have lost interest in my appearance:
Definitely
I don't take as much care as I should
I may not take quite as much care
I take just as much care as ever

11. I feel restless as I have to be on the move:
Very much indeed
Quite a lot
No very much
Not at all

12. I look forward with enjoyment to things:
As much as I ever did
Rather less than I used to
Definitely less than I used to
Not at all

13. I get sudden feelings of panic:
Very often indeed
Quite often
Not very often
Not at all

14. I can enjoy a good book or radio or TV programme:
Often
Sometimes
Not often
Very seldom

Section 4   **Your use of Health Services**

We would be grateful if you answer these questions about your use of health services over the last
12 months for reasons related to bowel cancer. If you are not sure, please give us your best guess.

1.   Over the last 12 months, <u>how many times</u> you have visited or been visited by the   following for   reasons related to bowel cancer.

GP: ……………………... ……….   District/community nurse at home: ....

Practice nurse: …………………….   Stoma nurse: …………………………………...

An out-patient clinic: ………………

2.   Over the last 12 months, have you had any overnight stays in hospital for reasons related to   bowel cancer?   (please tick as appropriate)

Yes: ☐   No: ☐

If yes, number of hospital stays: ……………………………

If yes, total number of nights in hospital: ………………….

3.   Over the last 12 months, has your home required any adaptations or aids such as bath lifts or hoists, for reasons related to bowel cancer?   (please tick as appropriate)

Yes: ☐   No: ☐

If   yes,   please   give   details   here: …………………………………………………………………..

4.   Over the last 12 months, have you relied on family or friends to provide regular care to you for   reasons related to bowel cancer?   (please tick as appropriate)

No: ☐   Yes, less than an hour a day: ☐   Yes, more than an   ☐
hour a day:

5.   Are you currently in paid employment? (please tick as appropriate)

No: ☐   Yes, full time: ☐   Yes,   ☐
part-time:

6.   Over the last 12 months, have reasons related to bowel cancer made you:

reduce your weekly working hours?   No: ☐   Yes, by: …………….. hours per week

reduce your other normal activities?   No: ☐   Yes, by: ……………..hours per week

7.   If you would like to tell us about any other costs you have incurred over the last 12 months for   reasons related to bowel cancer, please write them here:

Thank you very much for taking the time to complete this questionnaire!

Appendix 5 Patient and public involvement

The FACS trial had a patient and public involvement (PPI) member actively engaged in the development and planning of the trial. Having strong involvement in bowel cancer campaigns and patient groups, the PPI member was ideally placed to offer a patient voice to the trial and was a full member of the trial management group. Alongside this, the FACS trial was in the National Cancer Research Institute Colorectal Clinical Studies Group portfolio and was regularly discussed by the group, which included PPI representation.

EME
HS&DR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library