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-Salazar1 and John Primrose3*

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

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

Declared competing interests of authors: none

Published May 2017
DOI: 10.3310/hta21320

Scientific summary

The FACS RCT
Health Technology Assessment 2017; Vol. 21: No. 32
DOI: 10.3310/hta21320

NIHR Journals Library www.journalslibrary.nihr.ac.uk
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 arm [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

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.
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

The research reported in this issue of the journal was funded by the HTA programme as project number 99/10/99. The contractual start date was in April 2004. The draft report began editorial review in January 2016 and was accepted for publication in January 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

© Queen’s Printer and Controller of HMSO 2017. This work was produced by Mant et al. under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).
Health Technology Assessment Editor-in-Chief

Professor Hywel Williams  Director, HTA Programme, UK and Foundation Professor and Co-Director of the Centre of Evidence-Based Dermatology, University of Nottingham, UK

NIHR Journals Library Editor-in-Chief

Professor Tom Walley  Director, NIHR Evaluation, Trials and Studies and Director of the EME Programme, UK

NIHR Journals Library Editors

Professor Ken Stein  Chair of HTA Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

Professor Andree Le May  Chair of NIHR Journals Library Editorial Group (EME, HS&DR, PGfAR, PHR journals)

Dr Martin Ashton-Key  Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

Professor Matthias Beck  Chair in Public Sector Management and Subject Leader (Management Group), Queen's University Management School, Queen's University Belfast, UK

Dr Tessa Crilly  Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin  Senior Scientific Advisor, Wessex Institute, UK

Ms Tara Lamont  Scientific Advisor, NETSCC, UK

Dr Catriona McDaid  Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

Professor William McGuire  Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads  Professor of Health Sciences Research, Health and Wellbeing Research Group, University of Winchester, UK

Professor John Norrie  Chair in Medical Statistics, University of Edinburgh, UK

Professor John Powell  Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

Professor James Raftery  Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma  Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts  Professor of Child Health Research, UCL Institute of Child Health, UK

Professor Jonathan Ross  Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks  Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Jim Thornton  Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Professor Martin Underwood  Director, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK

Please visit the website for a list of members of the NIHR Journals Library Board: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: journals.library@nihr.ac.uk