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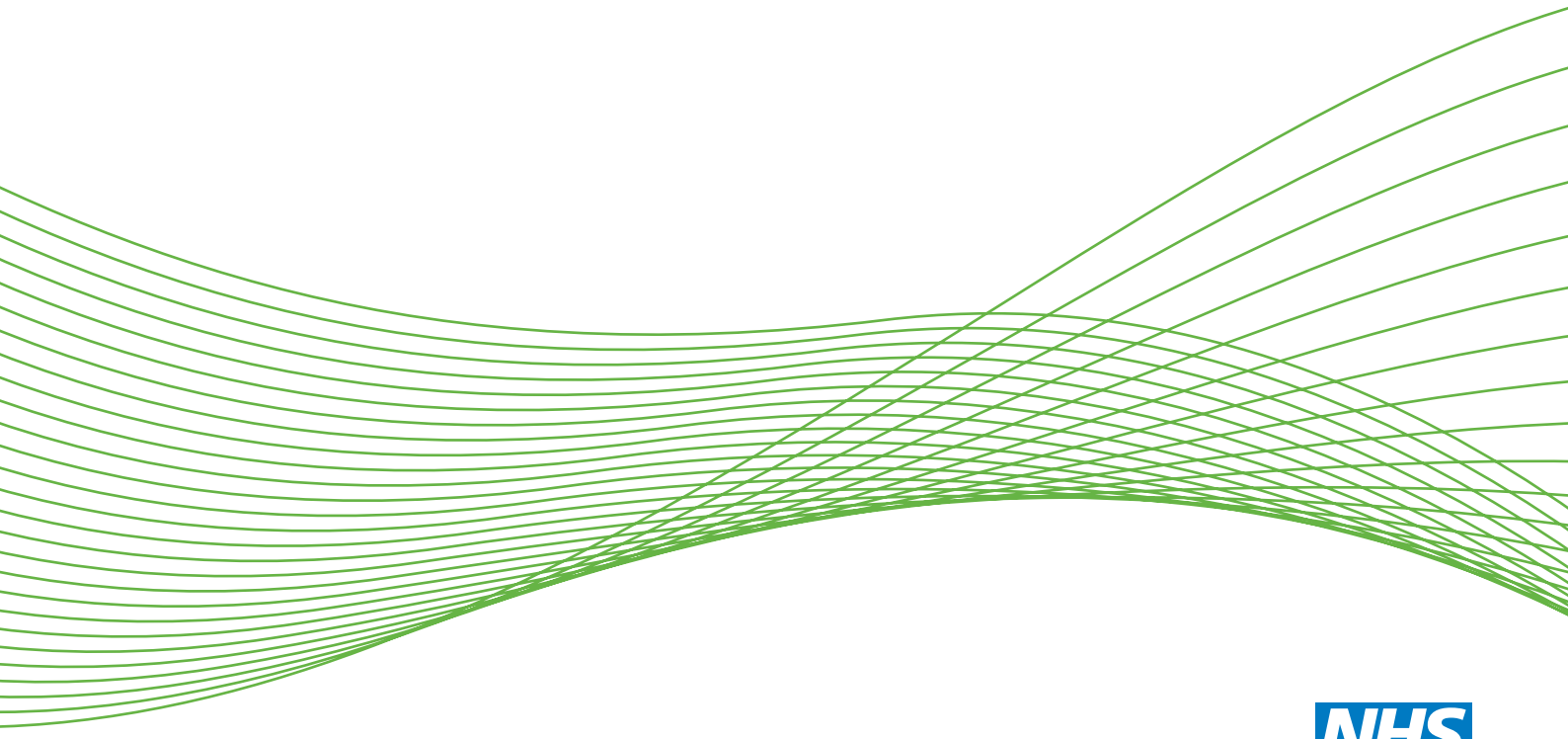

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Abstract

Computed tomographic colonography compared with colonoscopy or barium enema for diagnosis of colorectal cancer in older symptomatic patients: two multicentre randomised trials with economic evaluation (the SIGGAR trials)

Steve Halligan,[1]* Edward Dadswell,[2] Kate Wooldrage,[2] Jane Wardle,[3] Christian von Wagner,[3] Richard Lilford,[4,5] Guiqing L Yao,[4,6] Shihua Zhu[4] and Wendy Atkin[2]

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Background: Computed tomographic colonography (CTC) is a relatively new diagnostic test that may be superior to existing alternatives to investigate the large bowel.

Objectives: To compare the diagnostic efficacy, acceptability, safety and cost-effectiveness of CTC with barium enema (BE) or colonoscopy.

Design: Parallel randomised trials: BE compared with CTC and colonoscopy compared with CTC (randomisation 2 : 1, respectively).

Setting: A total of 21 NHS hospitals.

Participants: Patients aged ≥ 55 years with symptoms suggestive of colorectal cancer (CRC).

Interventions: CTC, BE and colonoscopy.

Main outcome measures: For the trial of CTC compared with BE, the primary outcome was the detection rate of CRC and large polyps (≥ 10 mm), with the proportion of patients referred for additional colonic investigation as a secondary outcome. For the trial of CTC compared with colonoscopy, the primary outcome was the proportion of patients referred for additional colonic investigation, with the detection rate of CRC and large polyps as a secondary outcome. Secondary outcomes for both trials were miss rates for cancer (via registry data), all-cause mortality, serious adverse events, patient acceptability, extracolonic pathology and cost-effectiveness.

Results: A total of 8484 patients were registered and 5384 were randomised and analysed (BE trial: 2527 BE, 1277 CTC; colonoscopy trial: 1047 colonoscopy, 533 CTC). Detection rates in the BE trial were 7.3% (93/1277) for CTC, compared with 5.6% (141/2527) for BE ($p = 0.0390$). The difference was due to better detection of large polyps by CTC (3.6% vs. 2.2%; $p = 0.0098$), with no significant difference for cancer (3.7% vs. 3.4%; $p = 0.66$). Significantly more patients having CTC underwent additional investigation (23.5% vs. 18.3%; $p = 0.0003$). At the 3-year follow-up, the miss rate for CRC was 6.7% for CTC (three missed cancers) and 14.1% for BE (12 missed cancers). Significantly more patients randomised to CTC than to colonoscopy underwent additional investigation (30% vs. 8.2%; $p < 0.0001$). There was no significant difference in detection rates for cancer or large polyps (10.7% for CTC vs. 11.4% for colonoscopy; $p = 0.69$), with no difference when cancers ($p = 0.94$) and large polyps ($p = 0.53$) were analysed separately. At the 3-year follow-up, the miss rate for cancer was nil for colonoscopy and 3.4% for CTC (one missed cancer). Adverse events were uncommon for all procedures. In 1042 of 1748 (59.6%) CTC examinations, at least one extracolonic finding was reported, and this proportion increased with age ($p < 0.0001$). A total of 149 patients (8.5%) were subsequently investigated, and extracolonic neoplasia was diagnosed in 79 patients (4.5%) and malignancy in 29 (1.7%). In the short term, CTC was significantly more acceptable to patients than BE or colonoscopy. Total costs for CTC and colonoscopy were finely balanced, but CTC was associated with higher health-care costs than BE. The cost per large polyp or cancer detected was £4235 (95% confidence interval £395 to £9656).

Conclusions: CTC is superior to BE for detection of cancers and large polyps in symptomatic patients. CTC and colonoscopy detect a similar proportion of large polyps and cancers and their costs are also similar. CTC precipitates significantly more additional investigations than either BE or colonoscopy, and evidence-based referral criteria are needed. Further work is recommended to clarify the extent to which patients initially referred for colonoscopy or BE undergo subsequent abdominopelvic imaging, for example by computed tomography, which will have a significant impact on health economic estimates.

Trial registration: Current Controlled Trials ISRCTN95152621.

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List of abbreviations

2D	two-dimensional
3D	three-dimensional
BE	barium enema
BNF	*British National Formulary*
CI	confidence interval
CRC	colorectal cancer
CRF	case report form
CT	computed tomography
CTC	computed tomographic colonography
df	degrees of freedom
E1	E-RADS category 1
E2	E-RADS category 2
E3	E-RADS category 3
E4	E-RADS category 4
E-RADS	Extracolonic Reporting And Data System
ESGAR	European Society of Gastrointestinal and Abdominal Radiology
FS	flexible sigmoidoscopy
GI	gastrointestinal
GP	general practitioner
HES	Hospital Episode Statistics
ICD	*International Classification of Diseases and Related Health Problems*
ICD-10	*International Classification of Diseases and Related Health Problems*, Tenth Edition
ICER	incremental cost-effectiveness ratio
IMD	Index of Multiple Deprivation
IQR	interquartile range
IRR	incidence rate ratio
NHSCR	National Health Service Central Register
NHSIC	National Health Service Information Centre
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
SIGGAR	Special Interest Group in Gastrointestinal and Abdominal Radiology

Plain English summary

Computed tomographic colonography (CTC) is a relatively new diagnostic test that uses an X-ray scanner to examine the large bowel for cancer and polyps (which can turn into cancer). We did this research to determine if CTC is more accurate than the existing alternatives used in the NHS for patients who have abdominal symptoms: colonoscopy (for which a flexible camera is inserted into the bowel) and barium enema (BE) (where the bowel is filled with barium liquid and radiographs taken). We investigated whether or not patients preferred CTC and whether or not it is cost-effective. CTC also examines the whole abdomen, whereas colonoscopy and BE do not, so we investigated how much disease outside the bowel was found by CTC.

A total of 5384 patients in 21 NHS hospitals participated in two trials: CTC compared with BE (3804 patients) and CTC compared with colonoscopy (1580 patients). We found that CTC detected significantly more cancers and large polyps than BE, but there was no difference between CTC and colonoscopy. However, about one-third of patients having CTC needed a colonoscopy afterwards to check on possible abnormalities. On average, patients preferred CTC to BE or colonoscopy. About two-thirds of patients having CTC had an abnormality outside the bowel, but this was usually unimportant; fewer than 1 in 10 needed further tests to check whether or not the abnormality was important. CTC detected cancers outside the bowel in about 2% of patients. Our analysis of whether or not CTC is better value for money than BE or colonoscopy was very challenging and our results are subject to very considerable uncertainty which suggests further research should be a priority.

Scientific summary

Background

Colorectal cancer (CRC) is a UK health-care priority: 1 in 20 people will develop the disease and approximately half will die as a result. An ageing population also means that these proportions are increasing. Diagnosis is usually by colonoscopy or barium enema (BE) when a whole-colon examination is deemed necessary. However, symptoms of CRC (e.g. abdominal pain and change in bowel habit) are common and non-specific, with the result that most investigated patients will ultimately prove to be normal. Diagnosis must therefore be accurate, acceptable, safe and cost-effective. Colonoscopy is the most accurate test, as it examines the endoluminal surface directly, via an endoscope. However, it requires considerable operator experience, is relatively expensive, is uncomfortable for patients (requiring intravenous sedation) and is associated with potentially serious adverse events. BE requires no sedation, is safer and is performed by technicians (making it less expensive), but has a lower sensitivity for cancer than colonoscopy.

Computed tomographic colonography (CTC) is a relatively new technology that uses a computed tomography scanner to examine the colon. After bowel preparation (as for BE and colonoscopy), the colon is distended with gas and the patient undergoes two scans of approximately 5 seconds each. The CTC data are interpreted subsequently by a radiologist using modern medical image displays that mimic the endoluminal view obtained at colonoscopy, hence the alternative term 'virtual colonoscopy'. CTC is promoted as a safe, rapid and accurate test for CRC screening, particularly in the USA, but meta-analysis suggests it is also sensitive in symptomatic patients. CTC potentially combines the sensitivity of colonoscopy with the safety of BE and may be more acceptable to patients than either of the other tests. Furthermore, because CTC can image organs outside the bowel, it could potentially combine intra- and extracolonic diagnosis at a single examination and so be more cost-effective in patients with non-specific abdominopelvic symptoms. However, there have been no randomised controlled trials (RCTs) of CTC in symptomatic patients; therefore, high-quality evidence to guide implementation is unavailable.

Objective

Our objective was to examine the diagnostic efficacy, acceptability, safety and cost-effectiveness of CTC compared with BE or colonoscopy.

Methods

We performed two RCTs: CTC compared with colonoscopy and CTC compared with BE. Ethics approval was granted in 2004 and an independent Trial Steering Committee and Data Monitoring Committee monitored the research. We recruited from 21 NHS hospitals, including both teaching and general hospitals to increase the generalisability of the results. Consenting patients aged ≥ 55 years with symptoms suggestive of CRC were referred for either colonoscopy or BE (the 'default' examinations), depending on whether the clinician preferred radiological or endoscopic investigation for the patient in question in their normal clinical practice. Patients were then randomised in a 2 : 1 ratio between the default examination or CTC, respectively. Demographic and baseline clinical information was collected on all potentially eligible patients.

All procedures were performed following full bowel preparation. BE was interpreted by 82 experienced practitioners. Colonoscopy was performed and interpreted by 217 experienced practitioners. CTC was interpreted by 46 subspecialty radiologists, representative of those likely to report CTC in the NHS. We collected details of suspected cancers and polyps, lesion diameter, location, diagnostic confidence, technical quality and adverse events.

After the randomised procedure, we collected details of confirmed cancers or polyps and additional referrals for bowel tests (usually performed either to confirm lesions suspected at BE or CTC, or to continue investigation in cases which diagnosis remained uncertain because of technical failure or continuing unexplained symptoms). Procedure costs and downstream costs were collected. Acceptability was assessed via psychological questionnaires completed the day after and 3 months after the randomised procedure. National databases were used to identify missed colonic and extracolonic cancers.

The primary outcome in the BE trial was the detection rate of CRC or large polyps (≥ 10 mm), with an estimated sample size of 3402 giving 80% power to detect a significant difference. The primary outcome in the colonoscopy trial was the proportion of patients undergoing additional colonic investigation after the randomised procedure, with a sample size of 1430 giving 80% power to detect a significant difference.

Secondary outcomes for the BE trial were referral rates for additional colonic investigation and positive predictive values. A secondary outcome for the colonoscopy trial was the detection rate of CRC or large polyps. Secondary outcomes for both trials were patient acceptability, cost-effectiveness, time to diagnosis, serious adverse events and diagnoses of cancer within 3 years. Extracolonic findings at CTC were also analysed.

Analyses were performed on a per-patient basis, using the most advanced colonic lesion. Lesions were matched between procedures based on size and location. Lesions detected at flexible sigmoidoscopy prior to the randomised procedure were excluded. All tests were two-tailed, with significance assigned at the 5% level. For the economic analysis, unit costs of procedures and all associated downstream costs were obtained to calculate total costs per patient. Cost per additional cancer or large polyp detected by CTC was compared with BE and colonoscopy.

Results

Recruitment ran from March 2004 to December 2007. A total of 8484 patients were registered, and 3036 were ultimately not randomised, usually because the clinician demanded a specific test (72%). A total of 5384 patients were randomised and ultimately analysed: 3804 in the BE trial (2527 BE and 1277 CTC) and 1580 in the colonoscopy trial (1047 colonoscopy and 533 CTC).

Barium enema trial

A significantly lower proportion of patients randomised to BE had the procedure (91.0% vs. 94.4%; $p = 0.0002$). Prior flexible sigmoidoscopy was performed in 199 patients (7.9%) in the BE arm and 89 (7.0%) in the CTC arm ($p = 0.32$). Significantly more BE examinations were judged difficult to perform (24.1% vs. 9.0%; $p < 0.0001$). In a significantly higher proportion of BE examinations visualisation was rated as 'poor' in at least one segment (22.3% vs. 16.1%; $p < 0.0001$).

A total of 141 patients randomised to BE had a CRC or large polyp diagnosed, compared with 93 randomised to CTC. In an intention-to-treat analysis, the overall detection rate was 7.3% (93/1277) in the CTC arm compared with 5.6% (141/2527) in the BE arm ($p = 0.0390$). The difference was mainly because of the higher detection rates of large polyps by CTC (3.6% vs. 2.2%; $p = 0.0098$). There was no

significant difference for CRC (3.7% vs. 3.4%; $p = 0.66$). Analysing per protocol, a cancer or large polyp was diagnosed in 7.0% (85/1206) of patients undergoing CTC and 5.2% (119/2300) undergoing BE ($p = 0.0243$).

A significantly higher proportion of patients who received CTC underwent a second colonic investigation (23.5% vs. 18.3%; $p = 0.0003$) because of the higher detection rates. Conversely, a significantly lower proportion required further investigation because of technical inadequacy or clinical uncertainty (5.2% vs. 8.5%; $p = 0.0005$). The positive predictive value for suspected cancers or large polyps was similar for CTC and BE (56% vs. 62%). Of those referred because of suspected smaller lesions, a cancer or large polyp was diagnosed in 10% following CTC and 7% following BE. Of the 195 patients who had a second procedure because of clinical uncertainty after BE, four had cancers and four had large polyps. No cancers or large polyps were detected in the 63 patients referred because of clinical uncertainty after CTC. Five serious adverse events occurred that were possibly attributable to the randomised procedure: four for BE and one for CTC.

In the 3 years following randomisation, the miss rate for patients undergoing the randomised procedure was 6.7% for CTC (45 cancers diagnosed, of which three were missed) and 14.1% for BE (85 cancers diagnosed, of which 12 were missed).

Colonoscopy trial

There was no significant difference in the proportion of patients undergoing their randomised procedure (92.4% for colonoscopy vs. 94.4% for CTC; $p = 0.14$) but significantly more patients randomised to colonoscopy refused their procedure or did not attend (6.0% vs. 3.0%; $p = 0.0093$). Flexible sigmoidoscopy was performed in eight patients randomised to CTC and none randomised to colonoscopy. A significantly higher proportion of colonoscopy examinations were rated as 'difficult' (27.4% vs. 8.3%; $p < 0.0001$). Colonoscopy was incomplete in 12.2% and, of those undergoing CTC, at least one segment was poorly visualised in 16.1%.

A total of 30% of patients (160/533) randomised to CTC underwent further colonic investigation, compared with 8.2% (86/1047) patients randomised to colonoscopy [relative risk (RR) 3.65, 95% confidence interval (CI) 2.87 to 4.65; $p < 0.0001$]. In the 1% randomised to colonoscopy, referral was because of a suspected cancer or large polyp for which biopsy was inadequate or absent. In the 16% randomised to CTC, referral was to confirm a suspected cancer or large polyp and in 9% to investigate smaller lesions. There was no significant difference in referrals precipitated by clinical uncertainty (7% for colonoscopy vs. 5% for CTC; $p = 0.19$).

All cancers confirmed following CTC occurred in patients in whom a cancer or large polyp was suspected; three large polyps were found in patients in whom smaller polyps were suspected. Of 28 patients having a second procedure because of clinical uncertainty after CTC, one had a large polyp. Of the 73 patients having a second procedure because of clinical uncertainty after colonoscopy, three had cancers and one had a large polyp.

A total of 10.7% of patients (57/533) randomised to CTC had a CRC or large polyp diagnosed, compared with 11.4% (119/1047) randomised to colonoscopy. There was no significant difference in detection rates (RR 0.94, 95% CI 0.70 to 1.27; $p = 0.69$), nor was there any difference when cancers ($p = 0.94$) and large polyps ($p = 0.53$) were analysed separately. Similar results were obtained when analysing per protocol, that is 10.7% for CTC compared with 12% for colonoscopy (RR 0.89, 95% CI 0.66 to 1.21; $p = 0.47$), with no difference when cancers ($p = 0.92$) and large polyps ($p = 0.38$) were analysed separately. Three serious adverse events possibly attributable to colonoscopy occurred; there were none for CTC. In the 3 years following randomisation, there was no new CRC diagnosis after discharge in patients who had colonoscopy. One patient was diagnosed with CRC 15 months after an apparently normal CTC.

Extracolonic findings

A total of 1748 CTC examinations were analysed; 1042 (59.6%) had at least one extracolonic finding reported (1945 individual findings) and the number of findings per patient rose with age ($p < 0.0001$). A total of 149 patients (8.5%) underwent subsequent investigation, 52 (34%) of whom underwent multiple procedures and 32 (21.5%) had surgery. Seventy-nine extracolonic neoplasms were ultimately diagnosed, 29 of which were malignant. Overall, extracolonic neoplasia was diagnosed in 79 patients (4.5%) having CTC and malignancy in 29 (1.7%). However, the positive predictive value of presenting symptoms for extracolonic disease was low. When registry data were examined, the proportion of patients diagnosed with extracolonic malignancy did not differ significantly between the three diagnostic procedures within 3 years of randomisation. Fourteen patients (0.8%) had extracolonic abdominopelvic cancer diagnosed within 3 years of an apparently normal CTC.

Patient acceptability

In the BE trial, 921 patients (606 BE, 315 CTC) returned the post-test questionnaire completed on the day following the procedure. Patients having a BE were significantly less satisfied ($p = 0.003$) and experienced more discomfort ($p < 0.001$) than those having CTC. After the test, patients having a BE were significantly more likely to experience unpleasant side effects (e.g. abdominal pain, soreness, nausea/vomiting).

In the colonoscopy trial, 547 patients (362 colonoscopy and 185 CTC) returned the post-test questionnaire. Patients having colonoscopy were significantly less satisfied ($p = 0.008$) and significantly more worried ($p = 0.007$) than those having CTC; they also experienced more physical discomfort and more adverse events. However, at 3 months, patients having colonoscopy were more satisfied with how their results had been given ($p < 0.0005$). No differences were observed in longer-term psychological consequences at 3 months.

Health economic assessment

The total costs associated with each procedure were considerably higher than the unit cost of each procedure itself. This is because total costs included those of follow-up procedures (especially colonoscopy). Total costs for BE were £460, compared with £532 for CTC, in the BE trial. Total costs for colonoscopy were £739, compared with £674 for CTC, in the colonoscopy trial. Patients originally referred for colonoscopy were likely to be at higher risk than those referred for BE. The cost of follow-up investigations made the overall cost of CTC higher in the colonoscopy trial than in the BE trial.

In the BE trial, the incremental cost-effectiveness ratio (ICER) per neoplasm detected by CTC was £4235 (95% CI £395 to £9656). The corresponding ratio for detection of an additional three cases of colon cancer per 1000 patients was £24,000 per cancer.

The ICER per significant lesion detected by colonoscopy compared with CTC was £9543, and £650,000 per cancer, but these estimates are subject to considerably statistical uncertainty. The health gains and costs, contingent on bringing forward the time of diagnosis of serious treatable extracolonic lesions by means of CTC, are hard to compute.

Conclusions

Implications for patient care

- Computed tomographic colonography detects more cancers and large polyps than BE, misses fewer cancers and improves patient experience, but also precipitates more follow-up investigations.
- Computed tomographic colonography is a safe alternative to colonoscopy in symptomatic patients, with similar sensitivity and improved patient experience short term. The way in which the results are conveyed (i.e. quicker and face to face) favours colonoscopy. CTC precipitates significantly more follow-up examinations – which, in a limited sample, did not adversely impact on patient experience – but criteria for subsequent referral are needed.
- Most patients have extracolonic findings reported at CTC and 8.5% undergo further investigation for these. Approximately 2% overall have an extracolonic malignancy detected.
  Offering CTC as the primary procedure did not significantly alter the proportion of patients diagnosed with extracolonic malignancy at 3 years, compared with colonoscopy or BE.
- When compared with BE, CTC detected one extra serious colonic neoplasm for approximately £4000. However, the detection rates were similar for CTC and colonoscopy and costs were also similar, such that there was little evidence on which a firm recommendation could be based.

Recommendations for research

1. The benefits of CTC observed in both trials will improve if referrals for clinically unnecessary subsequent investigations are diminished: there is a need to develop evidence-based guidelines for referral after CTC. This applies especially to patients for whom the normal default examination would be colonoscopy. A multivariate analysis should be performed on the data set generated by these trials in order to identify combinations of both symptoms and imaging findings on CTC that best predict a need for subsequent colonoscopy.
2. No difference was found between tests regarding the proportion of extracolonic cancers detected within 3 years. The reasons for this are unclear, but it appears that many patients undergoing BE or colonoscopy also have subsequent extracolonic investigation if no colonic abnormality was found. How and why this happens merits further research to clarify the clinical effectiveness and cost-effectiveness of CTC.
3. Detection of extracolonic pathology by CTC should be modelled beyond the trial data set over an extended time horizon and combined with detection of intracolonic pathology to estimate if CTC is cost-effective overall compared with colonoscopy. This is not a trivial undertaking.
4. Research is needed to guide implementation of CTC, especially the training needed for competent interpretation.
5. The acceptability to patients of increased referrals following CTC needs further investigation.
6. In the context of the NHS Bowel Cancer Screening Programme, research on what determines the acceptability of further investigations following positive faecal occult blood test and the potential role of CTC and other less invasive diagnostic technologies are warranted.

Trial registration

This trial is registered as ISRCTN95152621.

Funding

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Chapter 1 Introduction

Background

Along with lung cancer, colorectal cancer (CRC) is one of the most commonly diagnosed cancers in the developed world, and around 1.2 million cases were diagnosed worldwide in 2008.[1] Roughly 40,000 new cases are reported in the UK each year[2] and, with an ageing population, this number is increasing. Since 1 July 2000, the Department of Health has made recommendations that any patients with suspected cancer should be seen by a specialist within 2 weeks of referral from their general practitioner (GP).[3] This has led to the development of guidelines for referral of patients with suspected CRC, taking account of factors such as age (patients over 60 years are considered to be at increased risk) and symptoms including change in bowel habit, rectal bleeding and anaemia.[4] However, as these symptoms are non-specific and common in the general population, most patients who are investigated will not have the disease.[5,6] This places a considerable burden on diagnostic services and highlights the need for diagnostic tests that are not only sensitive and specific, but widely available, safe and acceptable to patients.

The currently established tests for examining the whole colon are colonoscopy and barium enema (BE). Colonoscopy is generally considered to be the most accurate examination for the detection of CRC and has the advantage of allowing biopsies to be taken in order to confirm the presence of cancer or other abnormalities within the bowel, and enabling the complete removal of precancerous polyps. However, colonoscopy is not without limitations. It is an invasive and technically demanding procedure and carries a small risk of serious adverse events, including bowel perforation and bleeding.[7] A study of 53,220 outpatients undergoing colonoscopy found that the risk of perforation and bleeding increased with age,[8] yet older people constitute the majority of those with symptoms. Sedation is also usually required and this conveys additional risk.[9]

Barium enema is safer than colonoscopy in elderly patients, but has been found in audits to miss a greater proportion of cancers in routine practice.[10] This has led to recommendations that its use be reduced.[11] However, for patients with a low index of suspicion for serious disease, avoidance of colonoscopy may be desirable, particularly in the elderly for whom the risks of sedation are greatest. BE is inexpensive, there is considerable experience with its use and it remains widely available, with an estimated 4 million procedures performed worldwide in 2009 (Mr Maurizio Franchini, Bracco International, 2009, personal communication).

Computed tomographic colonography (CTC) or 'virtual colonoscopy' is a relatively new health technology, potentially combining the sensitivity of colonoscopy with the safety of BE.

Existing research on the new technology

Computed tomographic colonography was first described in 1994.[12] The examination consists of a helical computed tomography (CT) scan of the cleansed and gas-distended large bowel, with evaluation of the resulting images by a radiologist. Complex image analysis techniques are used to aid interpretation, including three-dimensional (3D) rendering that simulates the colonoscopist's endoluminal view of the colon.

Computed tomographic colonography has already received considerable attention in the context of CRC screening, as there is evidence that it is safer than colonoscopy[13,14] and it does not require the patient to be sedated. It has a similar high sensitivity for cancer and large polyps in asymptomatic populations examined by experienced radiologists.[15–17] However, a role for symptomatic diagnosis has been relatively ignored.

One disadvantage of CTC when compared with colonoscopy is that it requires an additional endoscopic procedure to biopsy or remove any significant lesions detected, increasing inconvenience and cost. CTC may also detect small incidental lesions within the colon that are unlikely to be the cause of symptoms but which, once identified, will require endoscopic removal. Any patients with such lesions will not avoid colonoscopy and will need to undergo a second bowel preparation (unless colonoscopy can be performed on the same day, which is rare in normal clinical practice). However, the majority of patients having CTC will not need colonoscopy and there is evidence that CTC may be more acceptable to patients.[18–20]

Because of its high sensitivity for CRC, it has been suggested that CTC should replace BE as an alternative to colonoscopy.[21] However, few studies have directly compared BE and CTC,[22,23] and until now there have been no randomised trials. As a result, robust data to guide health policy have been lacking.

As CTC and colonoscopy have similar sensitivity for cancer and large polyps,[15–17] the choice between these two procedures is likely to depend on other factors. For example, it is not known what proportion of patients presenting with symptoms of CRC require subsequent colonic investigation to verify findings at CTC, compared with colonoscopy. This is an important consideration if CTC is to be regarded as an alternative diagnostic test.

In the NHS it is possible that CTC will find a role in cancer detection in elderly patients, in whom the risks of colonoscopy-related adverse events (oversedation, colonic perforation) are greatest and the risks of exposure to ionising radiation less important. Unlike colonoscopy or BE, CTC can also image organs outside the colon, which may aid diagnosis in patients whose symptoms are extracolonic in origin. However, this also results in incidental findings[24] with associated medical, psychological and financial consequences. If an extracolonic abnormality is identified it may prompt further investigation without any ultimate benefit to the patient, so careful evaluation is required.[25,26]

We felt that such equipoise was the ideal point at which to conduct a trial,[27] so that recommendations could be evidence based and any future implementation would be sensible, balanced and informed.

Objectives of the Special Interest Group in Gastrointestinal and Abdominal Radiology trials

Our aim was to examine the diagnostic efficacy, acceptability and cost of CTC compared with BEs or colonoscopy, by carrying out two parallel randomised trials. In the trial of CTC compared with BEs, this comparison was based primarily on detection rates for significant neoplasia, whereas in the trial of CTC compared with colonoscopy, it was based on rates of referral for a confirmatory diagnostic procedure, because the similar sensitivities of CTC and colonoscopy would have made a trial powered on detection rates impractical (see *Chapter 2*, *Sample size*). We also compared other outcomes, including miss rates for CRC and rates of serious adverse events.

The acceptability to patients of CTC, BEs and colonoscopy was assessed by giving psychological questionnaires to a sample of participants in the study, documenting their experiences on the day after the test and at 3 months after the test (see *Chapter 5*).

Finally, an economic analysis was undertaken to estimate the costs and cost-effectiveness of the three procedures (see *Chapter 6*).

Chapter 2 Methods

Study design

The study consisted of two multicentre randomised trials (International Standard Randomised Controlled Trials Number 95152621), conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice.[28] Ethics approval was obtained from the Northern and Yorkshire Multi-Centre Ethics Committee in January 2004 and subsequently from all participating hospitals. The trial was supervised by an independent Data Monitoring Committee and a Trial Steering Committee. All patients gave informed written consent.

Patients with symptoms suggestive of CRC were initially seen in clinic and referred for either colonoscopy or a BE (the 'default' examinations) by the clinician seeing the patient, depending on whether they preferred radiological or endoscopic investigation in normal clinical practice for the particular patient in question. This decision depended on factors such as expectation of cancer, perceived frailty and locally available diagnostic resources. BEs and colonoscopy are not considered clinically equivalent in normal clinical practice. To design a three-way randomised controlled trial (RCT) of BE compared with colonoscopy compared with CTC would have been unethical because of a lack of equipoise between BE and CTC, and would have suffered from poor recruitment. As a result, the study was split into two separate trials: one for CTC compared with BE (the 'BE trial') and one for CTC compared with colonoscopy (the 'colonoscopy trial').

Within each trial, patients were randomised in a 2 : 1 ratio in favour of the 'default' whole-colon examination, in accordance with the algorithm shown in *Figure 1*. A 2 : 1 ratio was chosen in order to maximise recruitment within the constraints of provision for the new technology and the study was powered accordingly.

Centres

We recruited patients from 21 NHS hospitals in England. To increase generalisability, both teaching and general hospitals were included. Participating centres were expected to have an established and efficient fast-track referral system for patients with symptoms of CRC, usually an identifiable diagnostic clinic, to facilitate recruitment. Each centre had to have a named colorectal nurse specialist or researcher attached to the clinic who would take responsibility for recruitment. Centres were also required to nominate a lead clinician who would supervise the work of the colorectal nurse specialist and a lead radiologist [and a Special Interest Group in Gastrointestinal and Abdominal Radiology (SIGGAR) member] who was willing to undergo central training in CTC according to accreditation guidelines issued by the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) (see *Computed tomographic colonography training*). A final criterion for selection was agreement by the participating site that use of CTC as a primary diagnostic test would only be offered to eligible patients as part the trial.

Participating hospitals were chosen from interested centres via a 'sham randomisation' that identified centres likely to achieve a monthly recruitment target of at least 18 patients.[29] Over a 2-month period each centre was asked to identify patients who satisfied the trial eligibility criteria and to enter simple demographics (age, sex, symptoms, route of referral and type of whole-colon investigation requested) on a secure, password-protected online database. No patients were approached directly, but this 'sham randomisation' provided an estimate of how each centre might perform once the trial was in progress.

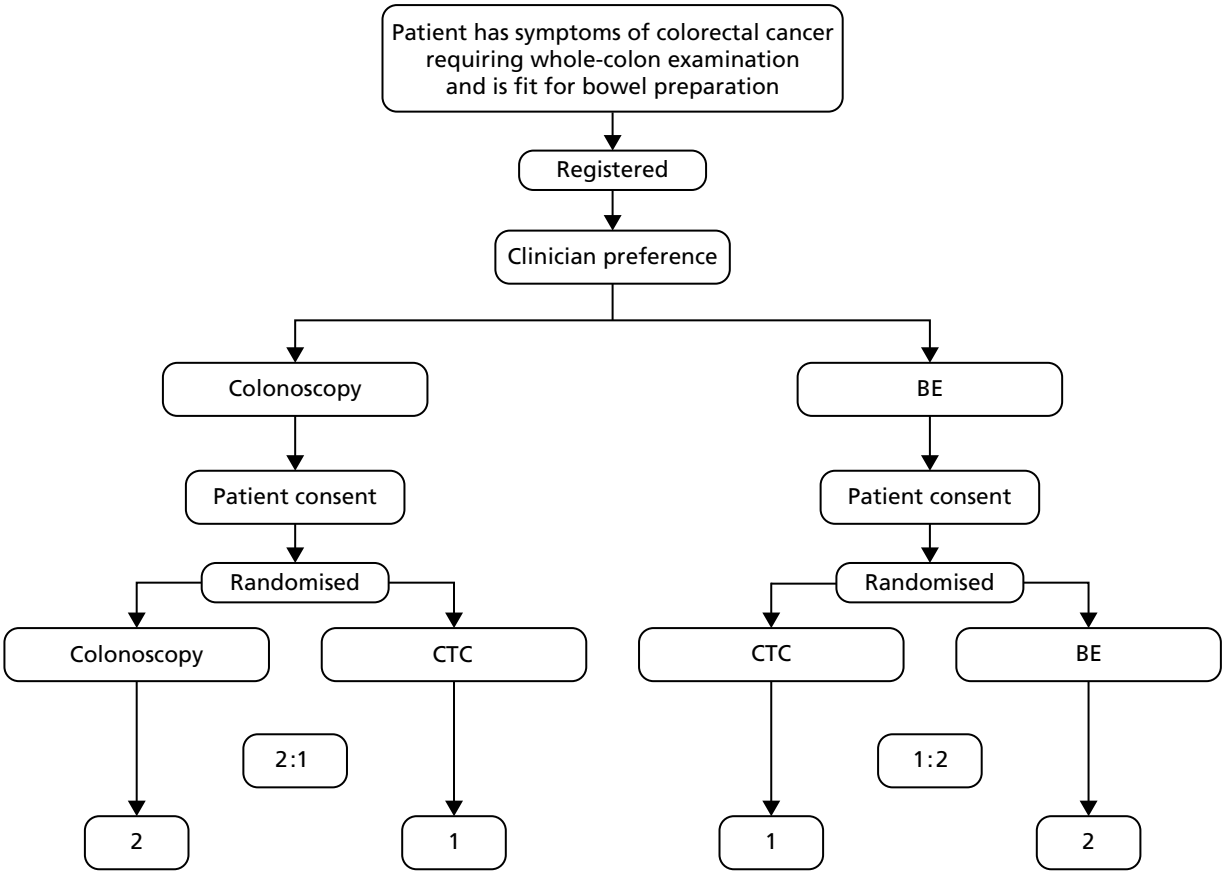

FIGURE 1 Study design. Lower boxes refer to randomisation ratio numbers.

Participants

Following referral from their GP, suitable patients were identified from clinics and procedure waiting lists by the colorectal nurse specialist.

Inclusion criteria

Patients were eligible for the study if they were:

- experiencing symptoms suggestive of CRC (this included both patients who fulfilled a 2-week wait criterion and those considered less urgent)
- aged ≥ 55 years
- clinically judged to need a whole-colon examination
- clinically judged fit to undergo full bowel preparation
- able to give fully informed consent.

Exclusion criteria

Patients could not be included in the study if they had:

- a known genetic predisposition to cancer, for example familial adenomatous polyposis or hereditary non-polyposis CRC
- a known diagnosis of ulcerative colitis or Crohn's disease
- undergone a previous whole-colon examination in the past 6 months
- been referred for whole-colon examination to follow up a previously diagnosed CRC.

Flexible sigmoidoscopy

It became clear during piloting that many patients were being given a flexible sigmoidoscopy (FS) examination prior to their randomised procedure. Excluding these patients would have made it difficult to recruit adequately to the study, as many hospitals make use of FS and this is likely to increase in future. Patients having FS were therefore eligible for the study if a strong clinical suspicion of right-sided cancer remained and if BE or colonoscopy would usually be the next test.

Interventions

Barium enema

Technical parameters

Exams were performed after full bowel preparation, with all centres using sodium picosulphate and magnesium citrate (Picolax®, Ferring Pharmaceuticals) as the primary laxative. An intravenous spasmolytic was administered routinely, usually 20 mg of hyoscine butylbromide (Buscopan®, Boehringer Ingelheim Ltd) unless contraindicated. Air or carbon dioxide was used for insufflation. Digital fluoroscopic images of the double-contrasted colorectum were obtained to the caecum, supplemented by overcouch decubitus films. A minimum 512 × 512 matrix was required for all images.

Interpretation

Scans were interpreted by radiologists with a subspecialty interest in gastrointestinal (GI) radiology or by fully trained radiographic technicians. Radiologists had to be performing an average of three or more BEs each week in routine clinical practice and were required to have performed at least 50 enemas unaided. Radiographers had to have completed an accredited course in double-contrast BE techniques and since that time to have performed unaided an average of at least three enemas per week for at least 6 months. Radiographers' practice had to be kept under regular audit.

Reporting

In total, 82 practitioners (including radiologists and fully trained radiographic technicians) interpreted BE scans in the study. Examinations could not be reported solely by a trainee radiologist without a subspecialty interest in GI radiology, so as to maintain parity with the CTC and colonoscopy groups. However, dual reporting was allowed, provided that one of the reporting clinicians fulfilled the criteria described above. In practice, all reports were either written or verified by a radiologist, except in a single centre, where dual reporting by senior radiographers was sometimes used. Radiologists or radiographers issued a report in accordance with normal clinical practice and completed a case report form (CRF) (see *Appendix 1*), which made it possible to capture additional information that would not routinely be mentioned in the report. Items recorded on the CRF included estimated size (mm) and location of detected lesions, the presence and site of diverticulosis, time taken for interpretation, technical difficulties (e.g. incontinence to barium or gas), quality of visualisation and any adverse events. Procedures were assessed as 'very easy', 'quite easy', 'quite difficult' or 'very difficult'. The quality of the bowel preparation

was rated as 'excellent', 'good', 'adequate' or 'poor'. Visualisation of the six major large bowel segments (rectum, sigmoid, descending colon, transverse colon, ascending colon and caecum) was rated as 'excellent', 'good', 'adequate', 'poor' or 'not seen'. The presence of diverticulosis in each segment was graded as 'none', 'mild', 'moderate' or 'severe'. If a polyp or cancer was visualised, confidence for its presence was rated as 'excellent', 'good', 'adequate' or 'poor'.

Colonoscopy

Technical parameters

Colonoscopy was performed after full bowel preparation using video endoscopes. Sedation (usually 1–5 mg of midazolam) and analgesia (usually 50 µg of fentanyl or 25–50 mg of pethidine) were administered as judged clinically necessary. Examinations were carried out according to usual practice and any detected lesions were measured and either biopsied or excised where indicated.

Interpretation

A total of 217 gastroenterologists or colorectal surgeons who had satisfied criteria for competence performed colonoscopies in the study. After the trial obtained funding, the government announced three national training centres for endoscopy, one of which is the Wolfson Unit at St Mark's Hospital in Harrow, UK, where the trial office was originally based. The aim of the national centres is to establish baseline and widespread competence in colonoscopy, and the training and accreditation procedures for the national centre were developed by trial collaborator Dr Brian Saunders. Assessment criteria for the GI endoscopists participating in the SIGGAR study were based on the accreditation procedures in place at the national training centres.

Reporting

A report was issued in line with normal clinical practice and an additional CRF completed, recording maximal diameter (mm) and location of detected lesions, information on any biopsies taken, presence and site of diverticulosis, depth of intubation and details of any adverse events. Procedures were assessed as 'very easy', 'quite easy', 'quite difficult' or 'very difficult'. The quality of the bowel preparation was rated as 'excellent', 'good', 'adequate' or 'poor'. The presence of diverticulosis in each segment was graded as 'none', 'mild', 'moderate' or 'severe'.

Computed tomographic colonography

Technical parameters

Computed tomographic colonography was performed in accordance with international guidelines for good practice,[30,31] after full bowel preparation. Most centres used Picolax as the primary laxative, although one used macrogol (Klean-Prep®, Norgine Pharmaceuticals Ltd) and one used diatrizoate (Gastrografin®, Bayer Healthcare). In general, 'dry' preparations (e.g. Picolax) are better suited to CTC than wetter preparations, which are generally used for colonoscopy and can impair interpretation of CTC because lesions may be obscured by excess residual fluid.[32] Positive faecal tagging could be used if this was local practice or preferred. Examinations were performed following administration of intravenous spasmolytic, usually 20–40 mg of Buscopan, unless contraindicated. Insufflating gas could be either room air or carbon dioxide, according to local preference, and an automatic insufflator could be used. Intravenous contrast was administered at the discretion of the supervising radiologist, depending on local practice, their interpretation of the clinical circumstances of the patient and the probability that symptoms were due to extracolonic pathology.

Multidetector row machines were required, with a minimum capacity of four detector rows and individual slice collimation not exceeding 2.5 mm. A pitch that allowed abdominal coverage (40 cm) within a single breath hold (20 seconds at most) was used. Scans were usually obtained in two patient positions, normally prone and supine, but occasionally one of these plus lateral decubitus if the patient found it difficult to lie

prone. In particularly frail patients, a single position could suffice if the supervising radiologist or CTC radiographer felt satisfied that distension was adequate to exclude a carcinoma.

Interpretation

In total, 46 radiologists registered by the Royal College of Radiologists and subspecialising in GI radiology interpreted CTC procedures in the trial. All were members of SIGGAR (now the British Society of Gastrointestinal and Abdominal Radiology), so as to reflect the type of radiologist likely to report CTC if implemented widely in UK practice (i.e. a subspecialist with an interest in GI imaging). All had prior experience of CTC, supplemented by a 2-day course for those who were judged to be relatively inexperienced (< 100 prior cases) and for more experienced radiologists who desired additional training (see *Computed tomographic colonography training*). The reading platform was determined by local preference but a minimum standard was primary analysis of the two-dimensional (2D) axial prone and supine CTC data sets, with volume-to-surface rendering for problem-solving. Visualisation software was provided [Voxar Colonscreen (Barco, Edinburgh, UK) and V3D (Viatronix, High Wycombe, UK)], but commercial alternatives were acceptable. Readers used 2D and 3D visualisation as required. Computer-assisted detection was also available (Medicsight PLC, London, UK). The primary focus was on identification/exclusion of significant colorectal neoplasia, defined as CRC or any polyp measuring ≥ 10 mm in maximal diameter, using electronic callipers on the 2D or 3D image, according to local preference.

Reporting

Radiologists issued a report and completed a CRF recording the same information as that for reporting BE examinations (see *Barium Enema, Reporting*). For CTC, the CRF included an additional section in which the radiologist could record details of extracolonic findings, including recommendations for any follow-up investigations that might be needed. Technical details of the scan were also recorded, including slice collimation (mm), number of detector rows, patient positioning (usually prone and supine), use of carbon dioxide or air for colon insufflation, use of mechanical insufflators, use of intravenous contrast or oral labelling, reading platform used and the proportion of 2D to 3D reading for interpretation.

Computed tomographic colonography training

Computed tomographic colonography is a new health technology with a steep learning curve. It is generally accepted that somewhere between 30 and 100 studies need to be analysed to achieve competence. In the UK, at the time recruitment began, relatively few radiologists possessed the requisite skills, although these skills are probably over-represented in the SIGGAR membership. ESGAR asked one of the present authors (SH) to formally assess the levels of training needed for competent CTC interpretation via a multicentre pan-European trial.[33] What is clear from the ESGAR study is that competence is variable and that some individuals can attain (and occasionally surpass) the median competence of very experienced readers after training on 50 endoscopically validated cases. Although many readers in the SIGGAR trial were very competent, it was clear from testing that others needed additional training, some of which was delivered by a 2-day course in June 2005 and some by one-to-one instruction at individual centres.

Recruitment

Suitable patients were identified from outpatient clinics and procedure waiting lists by the colorectal nurse specialist, who was responsible for checking the details of the referral and establishing that each patient met the trial entry criteria. Patients were then seen by the consulting physician, who assessed their need for a whole-colon examination and decided whether this should be a BE or colonoscopy. No patients could participate in the trial without the consultant's consent. If consultant consent was given, the nurse specialist met the patient to explain the purpose of the study and describe the tests involved. Patient information sheets relating to the trial into which the patient was to be randomised (i.e. CTC vs. BE or CTC vs. colonoscopy) were given to the patient (see *Appendix 2*). All patients who wished to participate were

given a consent form to complete. Patients recruited from outpatient departments were asked to complete the form in clinic, to ensure they could receive an appointment for their investigation on the day they were consented, and so would not be disadvantaged by having to return to the hospital to sign the form and arrange the procedure. For patients recruited from BE or colonoscopy waiting lists, the consent form and relevant patient information sheet were sent with an explanatory letter, inviting the patient to participate in the study. This was possible only if there was sufficient time for the consent form to be sent by post and returned, and (if necessary) for the patient's procedure to be changed from a BE or colonoscopy to CTC, depending on the outcome of randomisation.

Once the consent form had been signed, the colorectal nurse specialist telephoned the trial office to randomise the patient. The patient's name, sex, date of birth and the procedure for which they were originally referred (BE or colonoscopy) were recorded on the trial database and the randomised procedure was allocated and disclosed to the nurse specialist, who then booked the patient's appointment. The trial office also sent an explanatory letter to the patient's GP, informing them of the patient's participation in the study.

Patients retained a copy of their consent form and the relevant patient information sheet and were given the telephone number of the trial office in case they had any further questions. They were informed that they could withdraw from the study at any time, in which case the consent form would be destroyed by the nurse specialist and the patient allocated their original test.

Data collection

Demographic and baseline clinical information was collected on all potentially eligible patients, including those ultimately not randomised (the term 'registered patients' will be used here to refer to all patients who were registered as eligible for the trial but not subsequently randomised). Data at initial recruitment were recorded on a specially designed CRF (see *Appendix 1*), recording information such as the patient's sex and date of birth, symptoms at presentation, urgency of the referral, details of the outpatient clinic, investigation requested and whether or not sigmoidoscopy was performed.

Details of the main trial procedures – BE, colonoscopy and CTC – were also recorded on CRFs, as were flexible sigmoidoscopies, surgical procedures and details of any outpatient appointments (see *Appendix 1*). Copies of the relevant radiology and endoscopy reports were also requested, along with copies of any pathology reports relating to endoscopy or surgery. Data on any other relevant procedures such as abdominal CT or gastroscopy were obtained by requesting a copy of the hospital report. Copies of patients' discharge letters were also requested, to assist in determining their final diagnosis from the trial.

All documentation was collected by the local colorectal nurse specialist and sent to the trial office by post or fax. Forms were entered on a bespoke Oracle database (Oracle UK, Reading, UK) and any missing fields queried with the centre, to make the data as complete as possible.

Follow-up

After the randomised procedure, patients were referred for additional tests as judged clinically necessary, taking account of the patient's status and symptoms, findings from the randomised procedure, and local policy. If cancer was detected by CTC or BE, options included referral for endoscopy and subsequent histological confirmation, or direct referral for staging examinations and/or surgery if the diagnosis of cancer was felt to be certain (which occurs more often in the case of CTC, as it has the capability to visualise the extramural extent of the cancer or to detect metastases outside the colon). Patients with lesions $\geq$ 10 mm at radiology exams were usually referred to endoscopy for excision and histological

diagnosis. The decision to refer patients with smaller lesions was left to the clinician in charge, taking account of the patient's age, wishes, nature of symptoms and the overall quality of the radiological examination. Further colonic investigation (usually endoscopy) was also requested where diagnostic uncertainty persisted following the randomised procedure, either owing to poor visualisation of one or more segments of the bowel, or when no cause for the patient's symptoms had been found. Extracolonic lesions detected by CTC were also investigated if considered significant by the clinician in charge and details of these additional procedures were obtained.

If cancer was histologically confirmed at colonoscopy, patients could be referred directly for staging examinations and surgery. However, in cases for which lesions could not be histologically confirmed, if the examination was incomplete or if there was persistent clinical uncertainty, patients might be referred for additional tests.

If any adverse events occurred during or shortly after the randomised procedure, they could be reported by radiologists or endoscopists on the relevant trial CRF, or by patients themselves on a questionnaire completed the following day. Details of unplanned hospitalisations and deaths within 30 days of the randomised procedure were also collected, using hospital records and the NHS Information Centre (NHSIC), respectively. These were reviewed independently by a gastroenterologist, a radiologist and a surgeon, who each gave their opinion on whether or not the hospitalisation could be attributed to the patient's randomised procedure (reviewers were blinded to the procedure type).

In order to identify any cancers missed by the trial procedures (including extracolonic cancers), all patients in the study were identified on the NHS Central Register (NHSCR) and details of new cancer diagnoses and deaths were obtained from NHSIC. Patients were also matched with national data from Hospital Episode Statistics (HES) to reduce the time lag between cancer diagnosis and the time of notification. Cancers were confirmed using pathology and imaging reports obtained from the hospital where the cancer was diagnosed.

Outcomes

The primary outcome in the BE trial was the detection rate of CRC or large polyps (≥ 10 mm), confirmed histologically where possible. In a small number of cases, cancers were not confirmed histologically, for example because the presence of distant metastases was confirmed at CTC, or when staging scans showed the tumour to be unresectable. Secondary outcomes were referral rates for additional colonic investigation, time to diagnosis, miss rates for CRC, diagnoses of extracolonic cancer within 3 years, all-cause mortality and serious adverse events. Extracolonic findings at CTC were also analysed.

Evidence suggests that CTC and colonoscopy are similarly sensitive for the detection of cancer and polyps ≥ 10 mm,[17] so a RCT powered on detection rates would be unfeasibly large (see *Sample size*). The primary outcome in the colonoscopy trial was therefore the proportion of patients undergoing additional colonic investigation following the randomised procedure, an important consideration if CTC is to become a suitable alternative to colonoscopy. Secondary outcomes were detection rates of CRC or large polyps, time to diagnosis, miss rates for CRC, other colorectal diagnoses, diagnoses of colonic and extracolonic cancer within 3 years, all-cause mortality and serious adverse events. Extracolonic findings at CTC were also analysed.

Sample size

In the BE trial, the sample size was initially calculated assuming a detection rate for cancers or large polyps of 15% for CTC and 10% for BE. With 2 : 1 randomisation in favour of BE, a sample size of 2160 gave 90% power to detect a significant difference in detection rates at 0.05 alpha (two-tailed). The 2 : 1 ratio was chosen so as not to overwhelm facilities for CTC and results in only a small loss of statistical power compared with the more usual 1 : 1 ratio.

In December 2005, an interim analysis performed for the external Data Monitoring Committee showed that the prevalence of significant neoplasia was lower than expected. It had been anticipated that this would differ between the two trials, as high-risk patients are more likely to be referred for colonoscopy (and, therefore, more likely to enter the colonoscopy than the BE trial). However, this difference was even larger than expected, with a prevalence of 12% in the colonoscopy trial and only 5% in the BE trial. The sample size, therefore, had to be increased and the power was dropped at the same time from 90% to the more conventional 80%. The revised calculation assumed detection rates for cancers and large polyps of 5% for BE and 7.5% for CTC.[34] With randomisation in a 2 : 1 ratio in favour of BE, a sample size of 3402 gave 80% power to detect a significant difference in detection rates at 0.05 alpha (two-tailed).

Powering the colonoscopy trial on detection rates would not have been practical. Assuming a detection rate of 15% for colonoscopy and a sensitivity of 93% for CTC relative to colonoscopy, with an inferiority margin equating to approximately 87% sensitivity, such a trial would require a total of 39,000 patients. The colonoscopy trial was, therefore, powered instead on the proportion of patients having additional colonic investigation following the randomised procedure. Assuming that symptomatic patients would need additional colonic tests in 20% of cases following CTC and 14% following colonoscopy, and with randomisation in a 2 : 1 ratio in favour of colonoscopy, a sample size of 2160 gave 90% power to detect a significant difference in referral rates at 0.05 alpha (two-tailed). However, as recruitment to the colonoscopy trial was proceeding at a lower rate than expected, it was decided to lower the power to 80% at the same time that this was done for the BE trial. Keeping all other assumptions as before, the new sample size required was 1430. The external Data Monitoring Committee approved all modifications.

Randomisation

The randomisation codes were generated by a programmer unconnected with the study and kept concealed until interventions were assigned. Randomisation was performed in blocks of six, stratified by centre, sex and diagnostic pathway (BE or colonoscopy). Details of the randomisation blocking, etc. were concealed from participating centres by excluding them from the study protocol for distribution.

Implementation

Once patients had agreed to take part in the study and signed the consent form, the colorectal nurse specialist contacted the trial office by telephone and gave the patient's name, sex, date of birth and the procedure recommended by the clinician (BE or colonoscopy). These details were entered onto the trial database and the patient's allocated test was then revealed.

Blinding

Given the nature of the interventions involved, there could be no blinding for either patients or medical staff.

Statistical methods

In the BE trial, both intention-to-treat and per-protocol analyses were performed for the primary outcome. Intention-to-treat analyses considered the 2527 and 1277 patients randomised to BE and CTC, respectively, excluding those who withdrew consent. Per-protocol analyses considered the 2300 and 1206 patients who had their randomised procedure (BE and CTC respectively). Secondary outcomes were analysed only on a per-protocol basis, except for extracolonic cancers and overall mortality, which were analysed by intention to treat.

In the colonoscopy trial, both intention-to-treat and per-protocol analyses were performed for the primary outcome, as well as for the secondary outcome of the detection rate of CRC or large polyps. All other secondary outcomes were analysed only on an intention-to-treat basis, except for CRC miss rates, adverse events and time to diagnosis, which were analysed by on a per-protocol basis. Intention-to-treat analyses considered the 1047 and 533 patients randomised to colonoscopy and CTC, respectively, excluding those who withdrew consent. Per-protocol analyses considered the 967 and 503 patients who had their randomised procedure (colonoscopy and CTC, respectively).

In patients who had FS prior to the randomised procedure, it was impossible to be certain whether or not the radiologist performing the randomised procedure was aware of the FS results. If any such lesions were seen again at the randomised procedure, we therefore had to assume that the radiologist was aware of the FS findings and these lesions were not counted as being detected at the randomised procedure. As a result, lesions found at sigmoidoscopy prior to randomisation were excluded from all analyses. Lesions found at FS between randomisation and the randomised procedure were included in the intention-to-treat analysis because these lesions were found in patients who were part of the randomised group, but were excluded from per-protocol analyses.

Detection rates were analysed on a per-patient basis, using the most advanced colonic lesion diagnosed. Lesions identified on successive procedures were matched based on size and location. The size measured at endoscopy was used as a reference standard unless it was unavailable or was exceeded by a measurement at pathology or surgery, in which case the latter was used. As in previous studies,[15,16] lesions seen at randomised and subsequent procedures were considered to be the same if they were in the same or an adjacent colonic segment and the size was within 50% of the endoscopic measurement. For lesions not meeting these criteria, a consensus was reached by members of the research team.

When patients had a cancer or large polyp found during the trial, the date of diagnosis was defined as the date of the examination at which histological confirmation was first obtained (the date of first sighting on radiology was used for cancers that were not histologically confirmed). In the case of patients in whom no cancer or large polyp detected, the date of the final colonic examination was used (the date of the randomised procedure in patients with no subsequent referrals).

A CRC was defined as missed if it was identified through the NHSCR or the HES database within 36 months of randomisation but was not detected at the randomised procedure or mentioned in the patient's final discharge letter.

Included extracolonic cancers were all reported primary malignant neoplasms, excluding CRCs [*International Classification of Diseases and Related Health Problems, Tenth Edition* (ICD-10) site codes C18–C20] and non-melanoma malignant neoplasms of the skin (C44), diagnosed within 36 months of randomisation. The expected number of extracolonic cancers was calculated by applying age- and sex-specific cancer incidence rates for the general population to our cohort, having adjusted for reported mortality. Incidence rates were compared assuming a Poisson distribution.

Comparisons of categorical outcomes were made using Pearson's chi-squared test or Fisher's exact test, as appropriate. Relative risks (RRs) or risk differences with 95% confidence intervals (CIs) were calculated to estimate differences between groups. RRs by age group (< 65 years and ≥ 65 years) and sex were illustrated using forest plots and tests of interaction (Mantel–Haenszel) were used to identify significant differences. Trial participants were randomised individually but we expected some natural clustering by centre. To check whether or not clustering by trial centre affected results, we also analysed the primary outcomes using random-effects logistic models allowing for heterogeneity in the outcome and intervention effects by centre (odds ratios were compared). All tests were two-tailed, with significance assigned at 5%. Analysis was performed using Stata 9.1 (StataCorp LP, College Station, TX, USA).

Chapter 3 Results

This chapter contains information reprinted with permission from Elsevier, *The Lancet*, 2013, vol. 381, Halligan S, Wooldrage K, Dadswell E, Kralj-Hans I, von Wagner C, Edwards R, *et al.* Computed tomographic colonography versus barium enema for diagnosis of colorectal cancer or large polyps in symptomatic patients (SIGGAR): a multicentre randomised trial, pp. 1185–93;[35] and *The Lancet*, 2013, vol. 381, Atkin W, Dadswell E, Wooldrage K, Kralj-Hans I, von Wagner C, Edwards R, *et al.* Computed tomographic colonography versus colonoscopy for diagnosis of colorectal cancer or large polyps in symptomatic patients (SIGGAR): a multicentre randomised clinical trial, pp. 1194–202.[36]

Patient recruitment and randomisation

Patient recruitment began in March 2004 and was completed in December 2007, by which time the number of patients randomised in each trial had exceeded the target sample size. In total, 8484 patients were registered to the trial from 21 centres. *Table 1* shows registration and randomisation by centre (centres ordered by date of joining the trial). The proportion of registered patients varied significantly by centre and may have been due to inadequate reporting of all eligible patients at some centres. In addition, centres relying heavily on recruitment from procedure waiting lists may have had lower rates of registration as they were only identifying patients who had already been referred for a whole-colon examination.

Baseline patient characteristics

Of the 8484 patients considered potentially eligible for the trial, 3036 were ultimately not randomised. Reasons why these patients were not included are given in *Table 2*. In most cases (72%), it was the clinician in charge of the patient's care who made the decision not to enter the patient into the trial, usually because the clinician felt that a specific examination was needed and, therefore, could not allow the patient to be randomised. A smaller group of patients (7% of those excluded) met the eligibility criteria but were judged by the clinician to be unfit for a whole-colon examination. In 27% of cases it was the patient who declined consent, usually because they wanted to have a specific procedure, for example because they felt colonoscopy was too invasive or they were attracted by the possibility of extracolonic imaging at CTC.

Table 3 shows the baseline characteristics of patients in the BE trial compared with those patients who were not randomised in either trial. The proportion of women in the BE trial was significantly higher than in the non-randomised group. There was a significant difference in the age profile of the two groups, with patients in the BE trial being younger overall. There were also significant differences in all symptoms between the two groups, with patients in the BE trial more likely to present with a change in bowel habit or abdominal pain and less likely to present with rectal bleeding, anaemia or weight loss. The BE trial contained a significantly lower proportion of 2-week-wait patients than the non-randomised group.

A comparison of the baseline characteristics of patients in the colonoscopy trial and those who were not randomised is given in *Table 4*. The colonoscopy trial had a significantly lower proportion of female patients than the non-randomised group. There was also a significant difference in the age of patients, with those in the colonoscopy trial being younger overall. The colonoscopy trial contained a higher proportion of patients presenting with a change in bowel habit, rectal bleeding, or abdominal pain and a lower proportion with anaemia. There was no significant difference in the proportion of patients with weight loss as one of the presenting symptoms.

Comparing patients randomised in the BE trial with those randomised in the colonoscopy trial (*Table 5*), patients in the BE trial were older and more likely to be female. They were less likely to present with rectal bleeding and more likely to present with abdominal pain and change in bowel habit. There was

TABLE 1 Total registration and randomisation by centre

	Total registered		Registered only, excluded from randomisation		Randomised		Randomised within the BE vs. CTC trial		Randomised within the colonoscopy vs. CTC trial	
Centre	*n*	%	*n*	% of centre total	*n*	% of centre total	*n*	% of centre total	*n*	% of centre total
St Mark's	1721	20	1012	59	709	41	216	13	493	29
Birmingham	441	5	25	6	416	94	310	70	106	24
Bradford	766	9	217	28	549	72	433	57	116	15
Oldham	454	5	270	59	184	41	151	33	33	7
Portsmouth	882	10	316	36	566	64	524	59	42	5
Cornwall (Truro)	536	6	73	14	463	86	366	68	97	18
Lancaster	451	5	84	19	367	81	358	79	9	2
Nottingham City Hospital	251	3	138	55	113	45	95	38	18	7
Bath	477	6	38	8	439	92	344	72	95	20
Nottingham Queen's Medical Centre	410	5	186	45	224	55	210	51	14	3
Crewe	655	8	224	34	431	66	413	63	18	3
Charing Cross	256	3	115	45	141	55	5	2	136	53
Plymouth	250	3	16	6	234	94	33	13	201	80
Hammersmith	47	0.6	3	6	44	94	0	0	44	94
Withington	179	2	49	27	130	73	119	66	11	6
Wythenshawe	32	0.4	12	37	20	63	20	63	0	0
Furness	112	1	24	21	88	79	73	65	15	13
Frimley Park	59	0.7	18	31	41	69	17	29	24	41
Oxford	162	2	13	8	149	92	147	91	2	1
Paddington (St Mary's)	271	3	164	61	107	39	0	0	107	39
North Tees	72	0.8	39	54	33	46	4	6	29	40
Total	8484	100	3036	36	5448	64	3838	45	1610	19

TABLE 2 Reasons for exclusion of eligible patients prior to randomisation

Reason	*n*	%
Clinician reasons for declining consent		
Colorectal or other cancer already diagnosed		
CRC diagnosed	56	1.8
Other cancer diagnosed	69	2.3
Specific procedure requested		
Colonoscopy	731	24.1
CT	303	10.0
FS	230	7.6
Oesophagogastroduodenoscopy	218	7.2
BE	19	0.6
Ultrasonography	16	0.5
Magnetic resonance imaging	5	0.2
Unknown	39	1.3
Clinical situation too urgent or waiting list too long	52	1.7
Patient unfit for whole-colon examination	215	7.1
Patient unable to give informed consent	75	2.5
No reason given	148	4.9
Total where clinician declined consent	**2176**	**71.7**
Patient reasons for declining consent		
Patient wanted a specific procedure		
Colonoscopy	15	0.5
CT	3	0.1
BE	2	0.07
Unknown	128	4.2
Patient did not want a specific procedure		
CT as claustrophobic	13	0.4
CT for other reasons	2	0.07
Colonoscopy	1	0.03
BE	1	0.03
Patient had difficulty comprehending	84	2.8
Patient died before consent obtained	2	0.07
No reason given	583	19.2
Total where patient declined consent	**834**	**27.5**
Reason for exclusion unknown	26	0.9
Total excluded	**3036**	**100.0**

TABLE 3 Baseline demographic and clinical characteristics of patients randomised within the BE vs. CTC trial and patients excluded from both the BE vs. CTC trial and colonoscopy vs. CTC trial

	Randomised within BE vs. CTC trial ($n = 3838$)		Excluded from both BE vs. CTC trial and colonoscopy vs. CTC trial ($n = 3036$)		
	n	%	*n*	%	*p*-value
Sex					
Male	1483	39	1251	41	0.031
Female	2355	61	1785	59	
Age (years)					
55–64	1253	33	802	26	< 0.001
65–74	1498	39	1045	34	
75–84	980	26	930	31	
85 +	107	3	259	9	
Symptoms					
Change in bowel habit	2909	76	1926	63	< 0.001
Harder, less frequent	490	13	297	10	
Looser, more frequent	1557	41	1049	35	
Variable frequency	355	9	180	6	
Unspecified	507	13	400	13	
Rectal bleeding	1167	30	1169	39	< 0.001
Abdominal pain	1235	32	574	19	< 0.001
Anaemia	476	12	620	20	< 0.001
Weight loss	523	14	500	16	0.001
Other symptoms	431	11	585	19	< 0.001
Route of referral					
Outpatient clinic					< 0.001
Colorectal surgical clinic	2964	77	2733	90	
Gastroenterology	462	12	192	6	
Geriatrics	5	0.1	6	0.2	
Other clinic type	59	2	46	2	
Unknown clinic type	9	0.2	4	0.1	
GP	237	6	32	1	
Other	93	2	21	0.7	
Unknown	9	0.2	2	0.1	
Urgency of referral					
2-week wait	1682	44	1851	61	< 0.001
Urgent	649	17	511	17	
Soon	484	13	179	6	
Routine	686	18	315	10	
Not recorded	337	9	180	6	

TABLE 4 Baseline demographic and clinical characteristics of patients randomised within the colonoscopy vs. CTC trial and patients excluded from both the BE vs. CTC trial and colonoscopy vs. CTC trial

	Randomised within colonoscopy vs. CTC trial ($n = 1610$)		Excluded from both BE vs. CTC trial and colonoscopy vs. CTC trial ($n = 3036$)		
	n	%	*n*	%	*p*-value
Sex					
Male	729	45	1251	41	0.0075
Female	881	55	1785	59	
Age (years)					
55–64	609	38	802	26	< 0.001
65–74	576	36	1045	34	
75–84	372	23	930	31	
85 +	53	3	259	9	
Symptoms					
Change in bowel habit	1175	73	1926	63	< 0.001
Harder, less frequent	194	12	297	10	
Looser, more frequent	635	39	1049	35	
Variable frequency	182	11	180	6	
Unspecified	164	10	400	13	
Rectal bleeding	686	43	1169	39	0.0066
Abdominal pain	357	22	574	19	0.0081
Anaemia	208	13	620	20	< 0.001
Weight loss	240	15	500	16	0.17
Other symptoms	280	17	585	19	0.12
Route of referral					
Outpatient clinic					< 0.001
Colorectal surgical clinic	1401	87	2733	90	
Gastroenterology	106	7	192	6	
Geriatrics	0	0	6	0.2	
Other clinic type	12	0.7	46	2	
Unknown clinic type	0	0	4	0.1	
GP	62	4	32	1	
Other	29	2	21	0.7	
Unknown	0	0	2	0.1	
Urgency of referral					
2-week wait	963	60	1851	61	< 0.001
Urgent	333	21	511	17	
Soon	94	6	179	6	
Routine	105	7	315	10	
Not recorded	115	7	180	6	

TABLE 5 Baseline demographic and clinical characteristics of patients randomised within the BE vs. CTC trial and patients randomised within the colonoscopy vs. CTC trial

	Randomised within BE vs. CTC trial ($n = 3838$)		Randomised within colonoscopy vs. CTC trial ($n = 1610$)		
	n	%	*n*	%	*p*-value
Sex					
Male	1483	39	729	45	< 0.001
Female	2355	61	881	55	
Age (years)					
55–64	1253	33	609	38	0.001
65–74	1498	39	576	36	
75–84	980	26	372	23	
85 +	107	3	53	3	
Symptoms					
Change in bowel habit	2909	76	1175	73	0.029
Harder, less frequent	490	13	194	12	
Looser, more frequent	1557	41	635	39	
Variable frequency	355	9	182	11	
Unspecified	507	13	164	10	
Rectal bleeding	1167	30	686	43	< 0.001
Abdominal pain	1235	32	357	22	< 0.001
Anaemia	476	12	208	13	0.60
Weight loss	523	14	240	15	0.21
Other symptoms	431	11	280	17	< 0.001
Route of referral					
Outpatient clinic					< 0.001
Colorectal surgical clinic	2964	77	1401	87	
Gastroenterology	462	12	106	7	
Geriatrics	5	0.1	0	0	
Other clinic type	59	2	12	0.7	
Unknown clinic type	9	0.2	0	0	
GP	237	6	62	4	
Other	93	2	29	2	
Unknown	9	0.2	0	0	
Urgency of referral					
2-week wait	1682	44	963	60	< 0.001
Urgent	649	17	333	21	
Soon	484	13	94	6	
Routine	686	18	105	7	
Not recorded	337	9	115	7	

no significant difference between the two trials in the proportion of patients presenting with anaemia or weight loss.

Flexible sigmoidoscopies

Among randomised patients, the proportion of patients having FS before recruitment differed in the two groups, with the highest rate in the BE trial [25.1% (963/3838) vs. 9.1% (147/1610) for the colonoscopy trial; $p < 0.0001$]. This was probably as a result of variations in the use of FS between centres because the proportion of patients from each centre varied substantially between the two trials, as shown in *Table 1*.

Barium enema trial

Numbers analysed

As seen in *Figure 2*, a total of 5448 patients were randomised in the study, with 1610 entering the colonoscopy trial and 3838 entering the BE trial, who were randomised between BE ($n = 2553$) and CTC ($n = 1285$). Thirty-four patients withdrew consent [26 (1%) in the BE and eight (1%) in the CTC arm],

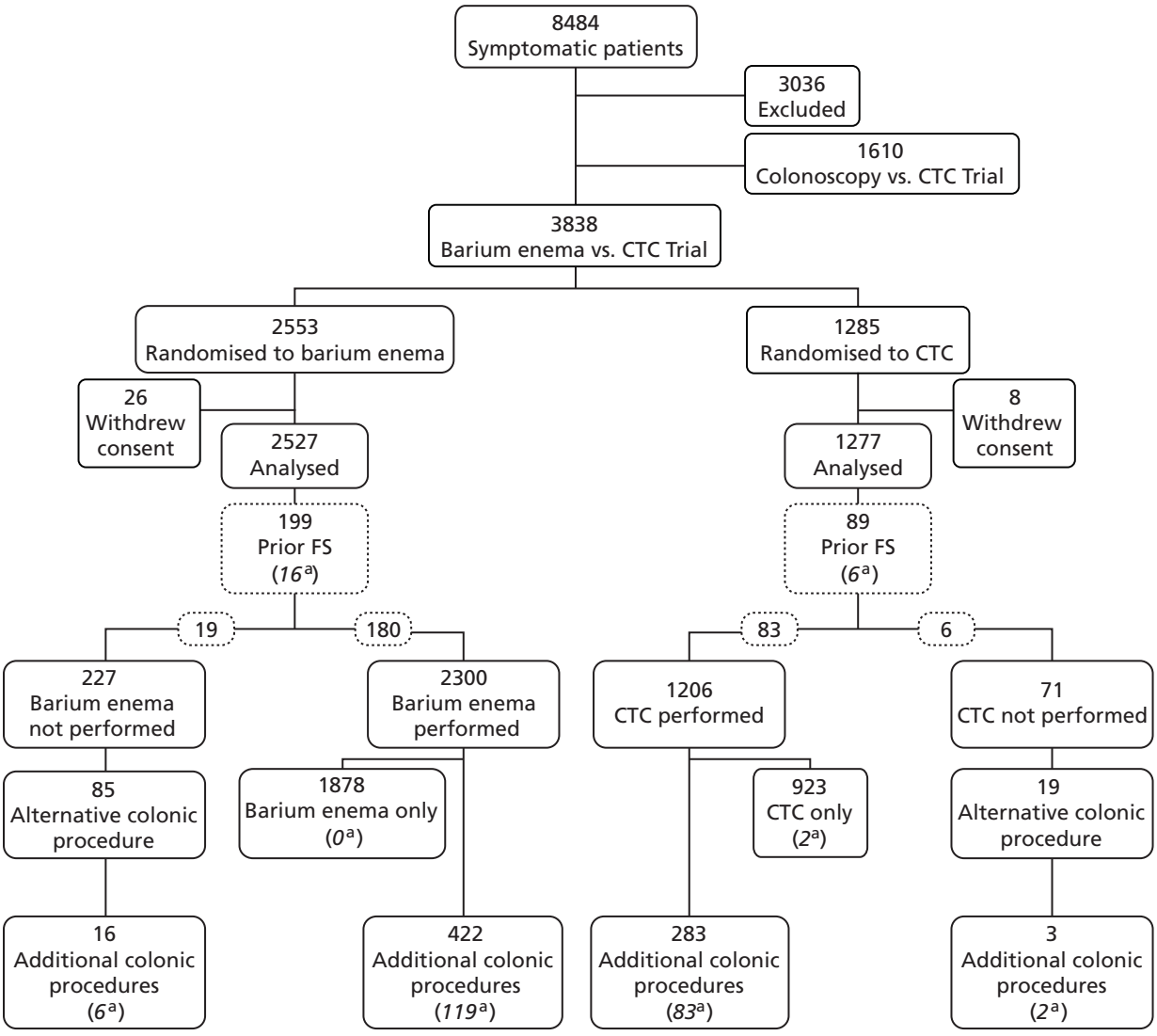

FIGURE 2 Participants' progress through the BE vs. CTC trial and selected outcomes. a, Number of patients with cancers or large polyps diagnosed at that procedure.

leaving 3804 for analysis (2527 BE and 1277 CTC). The proportion of patients withdrawing consent did not differ significantly between the two procedures.

Centres varied in the number of patients randomised to the BE trial [median 151, interquartile range (IQR) 33–358]. There were no significant differences in the demographic or clinical characteristics of patients randomised to BE or CTC (*Table 6*) (this is also true if patients who withdrew consent are included). The median age of patients was 69 years (IQR 62–75 years), and 61% were women. The most frequent presenting symptoms were change in bowel habit (76%), abdominal pain (32%) and rectal bleeding (30%); patients could report more than one symptom.

The number of patients who went on to have their randomised procedure is shown in *Table 7*, along with reasons why the procedure did not occur. A lower proportion of patients randomised to BE had their randomised procedure [91.0% (2300/2527) for BE vs. 94.4% (1206/1277) for CTC; $p = 0.0002$]. The main reason for this is that a larger proportion of patients were judged by the clinician to be unable to tolerate the examination (2.2%), which was rare for CTC (0.3%). There were also a substantial proportion of patients who did not want to have their randomised procedure, but this did not differ significantly between groups (3.2% for BE vs. 2.5% for CTC). Of those patients randomised to BE who did not have their assigned procedure, 37% (85/227) had an alternative procedure, usually CTC (62%, 53/85) or colonoscopy (21%, 18/85). Of those randomised to CTC who did not have their procedure, 27% (19/71) had an alternative examination usually BE (74%, 14/19) or colonoscopy (11%, 2/19).

TABLE 6 Baseline demographic and clinical characteristics of patients with symptoms of CRC in the BE vs. CTC trial

	Randomised to BE ($n = 2527$)		Randomised to CTC ($n = 1277$)		Total ($n = 3804$)		Excluded ($n = 3036$)		
Characteristic	*n*	%	*n*	%	*n*	%	*n*	%	*p*-value[a]
Sex									
Male	983	39	490	38	1473	39	1251	41	0.0371
Female	1544	61	787	62	23311	61	1785	59	
Age (years)									
55–64	826	33	416	33	1242	33	802	26	< 0.0001
65–74	993	39	494	39	1487	39	1045	34	
75–84	640	25	330	26	970	25	930	31	
85 +	68	3	37	3	105	3	259	9	
Symptoms[b]									
Change in bowel habit	1910	76	975	76	2885	76	1926	63	< 0.0001
Harder, less frequent	321	13	166	13	490	13	297	10	
Looser, more frequent	1007	40	535	42	1557	41	1049	35	
Variable frequency	240	9	113	9	355	9	180	6	
Unspecified	342	14	161	13	507	13	400	13	
Rectal bleeding	767	30	388	30	1155	30	1169	39	< 0.0001
Abdominal pain	819	32	406	32	1225	32	574	19	< 0.0001
Anaemia	319	13	153	12	472	12	620	20	< 0.0001
Weight loss	331	13	185	14	516	14	500	16	0.0008
Other symptoms	289	11	138	11	427	11	585	19	< 0.0001

a *p*-value for the comparison of patients randomised within the BE vs. CTC trial compared with excluded patients.
b Some patients reported more than one symptom.

TABLE 7 Occurrence of randomised procedures in the BE vs. CTC trial

Status	BE ($n = 2527$)		CTC ($n = 1277$)		
	n	%	*n*	%	*p*-value
Occurrence of randomised procedure					
Occurred	2300	91.0	1206	94.4	0.0002
Did not occur	227	9.0	71	5.6	
Reasons did not occur					
Patient's decision					
Patient refused randomised procedure	81	3.2	32	2.5	0.27
Patient did not attend scheduled procedure	27	1.1	13	1.0	
Total	108	4.3	45	3.5	
Medical decision					
Patient unable to tolerate randomised procedure	55	2.2	4	0.3	< 0.0001
Finding at prior FS	10	0.4	2	0.2	
Consultant requested alternative procedure	29	1.0	11	0.9	
Patient became too ill	16	0.6	1	0.1	
Patient's symptoms resolved	4	0.2	2	0.2	
Patient died	4	0.2	3	0.2	
Total	118	4.7	23	1.8	
Other reasons					
Equipment failure	1	0.03	3	0.2	0.11
Total	1	0.03	3	0.2	

Prior FS was performed in 199 patients (7.9%) in the BE arm and 89 (7.0%) in the CTC arm ($p = 0.32$) (see *Figure 2*). The performance of prior FS did not affect the occurrence of the randomised procedure (91.3% in those who had prior FS, vs. 92.2% in those who did not; $p = 0.58$).

Performance of the examinations

A greater proportion of BE examinations were judged to be difficult to perform, with 24.1% (554/2300) rated as 'quite' or 'very' difficult, compared with 9.0% (109/1206) for CTC ($p < 0.0001$). Similarly, in a significantly higher proportion of BE examinations there was at least one segment that was not seen or for which the radiologist rated visualisation as 'poor': 22.3% (514/2300) for BE and 16.1% (194/1206) for CTC ($p < 0.0001$). In the left colon, there was no significant difference in the quality of visualisation between BE and CTC. However, poor visualisation in the right colon was more than twice as likely to be reported at BE (12.1%) as at CTC (4.9%) ($p < 0.0001$).

Outcomes

Detection of colorectal cancer and large polyps

Among 2527 patients randomised to BE, a CRC or large polyp was diagnosed in 141: in 119 following BE, in 16 at FS prior to BE and in six patients who had an alternative procedure (see *Figure 2*). Among 1277 patients randomised to CTC, a CRC or large polyp was diagnosed in 93: in 85 following CTC, in six at prior FS and in two patients having an alternative whole-colon investigation. The 141 lesions diagnosed in patients randomised to BE included 86 CRCs (including one carcinoid tumour and five non-pathologically confirmed cancers) and 55 large polyps (51 adenomas, two hyperplastic polyps, one juvenile polyp and a polyp ≥ 10 mm which was excised but not retrieved). The 93 lesions diagnosed in patients randomised to CTC included 47 CRCs (including two non-pathologically confirmed cancers) and 46 large polyps (41 adenomas, one hyperplastic polyp, one serrated adenoma and three polyps ≥ 10 mm which were excised but not retrieved). Analysing by intention to treat, the overall detection rate of CRC or large polyps was 7.3% (93/1277) in the CTC arm and 5.6% (141/2527) in the BE arm ($p = 0.0390$) (*Table 8*). The difference was mainly as a result of a higher detection rate of large polyps in the CTC arm (3.6% vs. 2.2%; $p = 0.0098$). There was no significant difference in detection rates of CRC (3.7% vs.3.4%; $p = 0.66$). Analysing per protocol, a cancer or large polyp was diagnosed in 7.0% (85/1206) of patients having CTC and 5.2% (119/2300) having a BE ($p = 0.0243$).

TABLE 8 Intention-to-treat and per-protocol analyses of detection rates of cancer and large polyps in the BE vs. CTC trial, according to randomised procedure[a]

Analysis	BE group		CTC group		Comparison of detection rates between procedures (CTC vs. BE)		
	N = 2527		*N* = 1277				
Intention to treat	*n*	%	*n*	%	RR	95% CI	*p*-value
CRC	86[b]	3.4	47[c]	3.7	1.08	0.76 to 1.53	0.6600
≥ 10-mm polyp[d]	55[e]	2.2	46[f]	3.6	1.66	1.13 to 2.43	0.0098
CRC or ≥ 10-mm polyp[d]	141[b,e]	5.6	93[c,f]	7.3	1.31	1.01 to 1.68	0.0390
	N = 2300		*N* = 1206				
Per protocol	*n*	%	*n*	%			
CRC	73[b]	3.2	42[c]	3.5	1.10	0.76 to 1.59	0.6300
≥ 10-mm polyp[d]	46[e]	2.0	43[f]	3.6	1.78	1.18 to 2.69	0.0051
CRC or ≥ 10-mm polyp[d]	119[b,e]	5.2	85[c,f]	7.0	1.36	1.04 to 1.78	0.0243

a Only the most advanced end point per patient is presented.
b Includes five patients with non-pathologically confirmed cancers and one patient with a carcinoid tumour.
c Includes two patients with non-pathologically confirmed cancers diagnosed at randomised procedure with no further procedures performed.
d ≥ 10-mm polyp is defined as a pathologically confirmed adenoma, serrated adenoma, hyperplastic polyp, juvenile polyp or excised but not retrieved polyp with a size ≥ 10 mm at endoscopy.
e Includes one patient with a ≥ 10-mm juvenile polyp, two patients with a ≥ 10-mm hyperplastic polyp and one patient with ≥ 10-mm excised but not retrieved polyp.
f Includes one patient with a ≥ 10-mm hyperplastic polyp, one patient with a ≥ 10-mm serrated adenoma and three patients with ≥ 10-mm excised but not retrieved polyps.

The difference in detection rates between BE and CTC is probably due to the greater sensitivity of CTC for small lesions. BE and CTC have similar sensitivity for cancer, but most cancers in the trial were larger than 30 mm in size (*Table 9*). CTC was significantly better at detecting small lesions; the proportion of patients for whom the largest confirmed lesion was < 10 mm was 2.5% (58/2300) for BE and 4.3% for CTC (52/1206) ($p = 0.0039$) (see *Table 9*).

Comparing results from models ignoring clustering to those controlling for clustering by trial centre showed that odds ratios were very similar in size and significance (*Table 10*).

TABLE 9 Sizes of lesions from the per-protocol analysis of the BE vs. CTC trial, by type of lesion

	BE ($N = 2300$)		CTC ($N = 1206$)	
Type of lesion and size	*n*	%	*n*	%
CRCs				
≥ 30 mm	62	2.7	33	2.7
20–29 mm	9	0.4	6	0.5
15–19 mm	1	0.04	1	0.08
10–14 mm	1	0.04	2	0.2
Total	73	3.2	42	3.5
Large polyps				
≥ 30 mm	7	0.3	7	0.6
20–29 mm	5	0.2	6	0.5
15–19 mm	13	0.6	9	0.7
10–14 mm	21	0.9	21	1.7
Total	46	2.0	43	3.6
Small polyps				
6–9 mm	16	0.7	15	1.2
≤ 5 mm	42	1.8	37	3.1
Total	58	2.5	52	4.3
No polyps or cancers detected	2123	92.3	1069	88.6

TABLE 10 Effect of clustering on estimates of the odds ratio (CTC vs. BE) for the detection of CRC or large polyps in the BE vs. CTC trial

	No clustering			With clustering[a]		
Analysis	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
Intention-to-treat analysis	1.33	1.01 to 1.74	0.0390	1.44	1.04 to 2.01	0.0302
Per-protocol analysis	1.39	1.04 to 1.85	0.0243	1.47	1.01 to 2.14	0.0455

a Results from random-effects model allowing for heterogeneity in the detection rate and odds ratio by centre.

There was a significant difference by age in the relative detection rate following CTC compared with BE ($p = 0.0159$); in younger patients, the detection rate following CTC was double that for BE, whereas in older patients the RR did not differ from that found overall (age < 65 years: RR 2.32, 95% CI 1.36 to 3.94; age ≥ 65 years: RR 1.10, 95% CI 0.82 to 1.47) (*Figure 3*). There was no significant difference in relative detection rates between men and women ($p = 0.66$).

Further colonic investigation

The proportion of patients undergoing a second colonic investigation was significantly higher in the CTC group [23.5% (283/1206)] than in the BE group [18.3% (422/2300); $p = 0.0003$] (*Table 11* and see *Figure 2*). This was true whether the referral was for a suspected cancer or large polyp (11.0% vs. 7.5%; $p = 0.0005$) or for suspected smaller polyps (7.2% vs. 2.3%; $p < 0.0001$). Conversely, a lower proportion required further investigation because of an inadequate examination or clinical uncertainty (5.2% vs. 8.5%; $p = 0.0005$).

Of the 422 patients referred following BE, 368 (87%) had colonoscopy (complete or limited as appropriate), 29 had a radiological procedure and 25 were referred straight to surgery. Of the 283 patients referred following CTC, 259 (91%) had colonoscopy, six had a radiological procedure and 18 were referred straight to surgery.

The probability of diagnosing a cancer or large polyp at a subsequent procedure (positive predictive value) was similar for patients referred because of findings at CTC or BE (29% vs. 28%, respectively) (*Table 12*). Among patients referred because of a suspected cancer or large polyp, the proportion in whom the lesion was confirmed was also similar for CTC and BE (56% vs. 62%). Of those referred because of smaller lesions at the randomised procedure, important end points were diagnosed in 10% referred after CTC (9/87; one cancer, eight polyps ≥ 10 mm) and 7% referred after BE (4/54; one cancer, three polyps ≥ 10 mm). Of 195 patients who had a second procedure because of clinical uncertainty after BE, four were found to have cancers and four had large polyps. No cancers or large polyps were detected in the 63 patients referred because of clinical uncertainty after CTC. Among patients not referred for an additional procedure, there remained a number of patients with incomplete or inadequate examinations: in BE 18.2% (341/1878) and in CTC 13.2% (122/923).

Time to diagnosis

Among patients who had their randomised procedure, the median time from the date of randomisation to the date of diagnosis was 23 days (IQR 14–40 days); the time was significantly longer for patients having CTC ($n = 1206$, median 28 days, IQR 16–47 days vs. BE $n = 2300$, median 21 days, IQR 14–37 days; $p < 0.0001$). The time to the randomised procedure was slightly longer for CTC (median 22 days, IQR 15–34 days vs. BE: median 18 days, IQR 12–28 days; $p < 0.0001$), but for subjects who had an additional referral after the randomised procedure there was no difference between procedures in the time from the randomised procedure to the second procedure [CTC ($n = 283$ patients) median 50 days, IQR 28–94 days vs. BE ($n = 422$ patients) median 49.5 days, IQR 27–94 days; $p = 0.84$]. For patients who had a diagnosis of cancer or a large polyp, the time to diagnosis for those having CTC was significantly longer [CTC ($n = 93$ patients) median 64 days, IQR 38–99 days vs. BE ($n = 141$ patients) median 47 days, IQR 30–72 days; $p = 0.0045$].

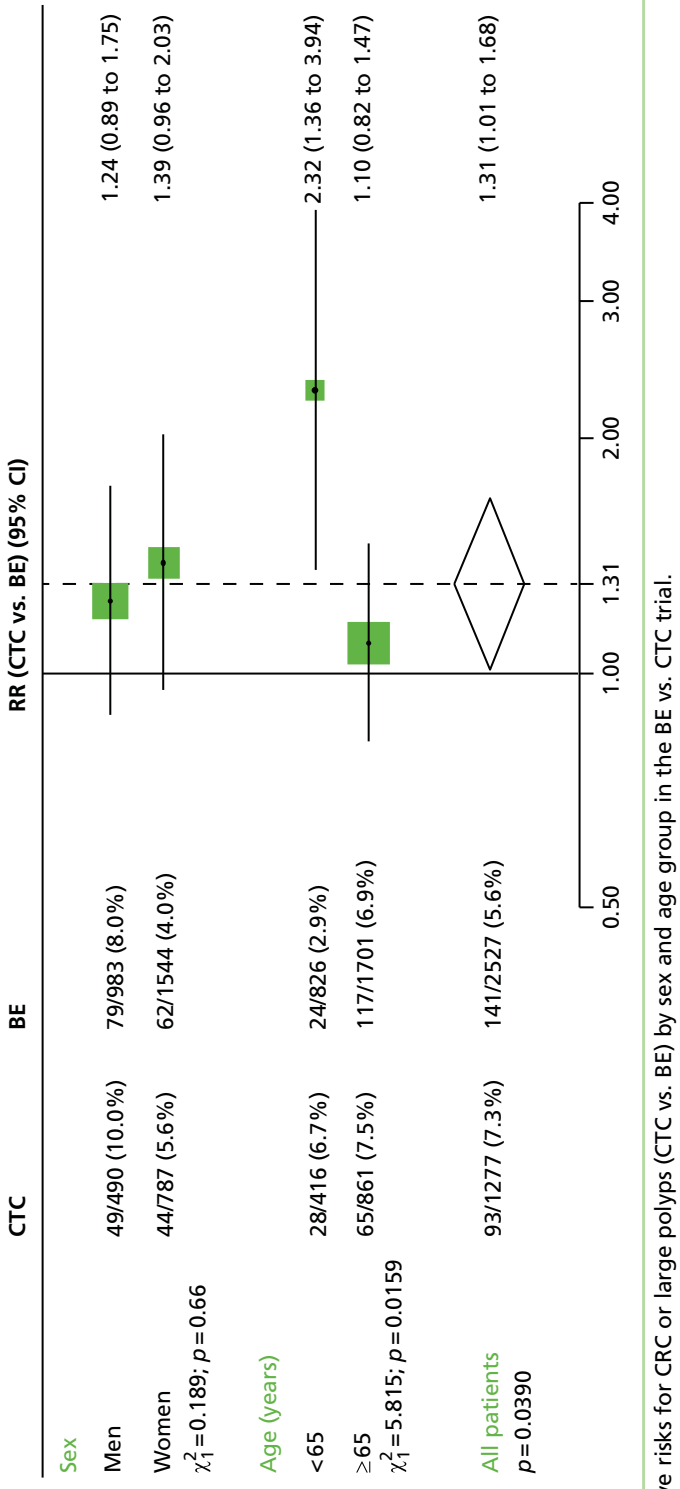

FIGURE 3 Relative risks for CRC or large polyps (CTC vs. BE) by sex and age group in the BE vs. CTC trial.

TABLE 11 Rates of referral for a second colonic procedure following the randomised procedure in the BE vs. CTC trial; overall and according to reason for referral

	BE performed ($N = 2300$)		CTC performed ($N = 1206$)		Comparison of referral rates between procedures (CTC vs. BE)		
Reason for referral	*n*	%	*n*	%	RR	95% CI	*p*-value
Cancer or large (≥ 10 mm) polyp suspected							
Cancer	86	3.7	68	5.6			0.0005
Polyp ≥ 10 mm	87	3.8	65	5.4			
Total with cancer or large (≥ 10 mm) polyp suspected	173	7.5	133	11.0	1.47	1.18 to 1.82	
Smaller polyp suspected							
Polyp 8–9 mm	18	0.8	18	1.5			< 0.0001
Polyp 6–7 mm	12	0.5	34	2.8			
Polyp ≤ 5 mm	24	1.0	35	2.9			
Total with smaller polyp suspected	54	2.3	87	7.2	3.07	2.20 to 4.28	
Clinical uncertainty (no polyps seen)							
Inadequate examination	116	5.0	34	2.8	0.56	0.38 to 0.81	0.0020
Adequate examination	79	3.4	29	2.4			
Total with clinical uncertainty	195	8.5	63	5.2	0.62	0.47 to 0.81	0.0005
Total having second procedure	422	18.3	283	23.5	1.28	1.12 to 1.46	0.0003

TABLE 12 Detection rates of cancer or large polyps among patients having a second colonic procedure following the randomised procedure in the BE vs. CTC trial; overall and according to the reason for referral[a]

	BE							CTC						
		Lesions diagnosed at second procedure							Lesions diagnosed at second procedure					
Randomised procedure undertaken	Second colonic procedure undertaken	CRC		Polyp ≥ 10 mm[b]		Cancer or polyps ≥ 10 mm[b]		Second colonic procedure undertaken	CRC		Polyp ≥ 10 mm[b]		Cancer or polyps ≥ 10 mm[b]	
Reason for referral	*N*	*n*	%	*n*	%	*n*	%	*N*	*n*	%	*n*	%	*n*	%
Cancer or large (≥ 10 mm) polyp suspected														
Cancer	86	64[c]	74	7	8	71	83	68	36	53	2	3	38	56
Polyp ≥ 10 mm	87	4	5	32	37	36	41	65	3	5	33	51	36	55
Total with cancer or large (≥ 10 mm) polyp suspected	173	68[c]	39	39	23	107	62	133	39	29	35	26	74	56
Smaller polyp suspected														
Polyp 8–9 mm	18	0	0	0	0	0	0	18	1	6	5	28	6	33
Polyp 6–7 mm	12	0	0	0	0	0	0	34	0	0	2	6	2	6
Polyp ≤ 5 mm	24	1	4	3	13	4	17	35	0	0	1	3	1	3
Total with smaller polyp suspected	54	1	2	3	6	4	7	87	1	1	8	9	9	10
Clinical uncertainty (no polyps seen)														
Inadequate examination	116	4	3	2	2	6	5	34	0	0	0	0	0	0
Adequate examination	79	0	0	2	3	2	3	29	0	0	0	0	0	0
Total with clinical uncertainty	195	4	2	4	2	8	4	63	0	0	0	0	0	0
Total having second procedure	422	73[c]	17	46	11	119	28	283	40	14	43	15	83	29

a The most advanced end point per patient is presented.
b ≥ 10-mm polyp is defined as a pathologically confirmed adenoma, serrated adenoma, hyperplastic polyp, juvenile polyp, or excised but not retrieved polyp with a size ≥ 10 mm at endoscopy.
c Includes five patients with non-pathologically confirmed cancers.

Extracolonic findings following computed tomographic colonography

At least one previously unknown extracolonic finding was reported in 58% (673/1161) of patients having CTC who did not have CRC diagnosed during the trial (patients with CRC were excluded from the analysis because it is not always possible to be sure that extracolonic findings are unrelated to the CRC and the presence of CRC will also influence the rate of subsequent investigation for extracolonic findings that are considered less important). Eighty-seven of these (7.5%) were referred for additional procedures, leading to diagnosis of extracolonic malignancy in 13 patients (*Table 13*). A more detailed analysis of extracolonic findings is given in *Chapter 4*.

Cancers diagnosed during 3 years' follow-up

When analysis was performed in June 2012, registration was reported to be 97% complete for all cancers diagnosed until December 2010 (at which point all patients had been followed up for at least 36 months) and all deaths until December 2011 had been registered. By that time (median follow-up for deaths 5.4 years, IQR 4.7–6.0 years), 400 patients (15.8%) assigned to BE and patients 201 (15.7%) assigned to CTC patients had died ($p = 0.94$), and three patients (two BE and one CTC) who did not have their randomised procedure had been diagnosed with CRC. A further 12 CRCs were diagnosed following apparently normal BE (five distal – rectum or sigmoid colon – and seven proximal) and three following CTC (one distal and two proximal). In one of the CTC patients, a 6-mm caecal polyp was detected at CTC, but colonoscopy was not performed and a 12-mm caecal adenocarcinoma was diagnosed 28 months later. The miss rate among patients having their randomised procedure was, therefore, 6.7% for CTC (45 cancers diagnosed, of which three were missed) and 14.1% for BE (85 cancers diagnosed, of which 12 were missed) (difference –7.5%, 95% CI –17.8% to 2.9%; $p = 0.21$). Combining the two procedures, this gives a miss rate of 7.8% for distal cancers (6/77) and 17.0% for proximal cancers (9/53).

During the 3-year follow-up of the trial cohort, 78 primary extracolonic cancers were diagnosed in the CTC group and 131 in the BE group [21.3 per 1000 person-years in the CTC group vs. 18.0 per 1000 person-years in the BE group; incidence rate ratio (IRR) 1.18, 95% CI 0.89 to 1.57; $p = 0.24$]. In the first year, rates of primary extracolonic cancer diagnosis in the trial cohort were nearly twice as high as expected (IRR 1.88, 95% CI 1.33 to 2.65; $p = 0.0002$), but rates did not differ significantly between the CTC and BE groups (IRR 0.84, 95% CI 0.54 to 1.30; $p = 0.43$). CTC detected 11 (39%) of the 28 extracolonic cancers that were diagnosed within the first year in the CTC group and BE detected 4 of 66 (6%).

Adverse events

An unplanned hospital admission within 30 days of the randomised procedure occurred in 14 patients following CTC and in 25 following a BE. Reasons for admission were reviewed independently by a gastroenterologist, radiologist and surgeon, who concluded that five were possibly attributable to the randomised procedure (reviewers were blinded to the procedure type). One patient was admitted directly after CTC with a possible perforation and was treated conservatively. Four hospitalisations occurred after a BE (reasons for admission were cardiac arrest, abdominal pain, rectal bleeding and patient collapsed after procedure). Three patients died within 30 days of a BE, one at 5 days (cardiac failure), one at 25 days (liver failure) and one at 28 days (perforated viscus), and one following CTC at 30 days (obstructive pulmonary disease).

TABLE 13 The number of extracolonic cancers diagnosed within 3 years of randomisation in the BE vs. CTC trial

	CTC ($n = 1277$)					BE ($n = 2527$)				
		Month of diagnosis			Found by CTC		Month of diagnosis			Found by BE
	Total	1–12	13–24	25–36		Total	1–12	13–24	25–36	
All extracolonic cancers[a]	78	28	31	19	11[b]	131[c]	66	37	28	4
Person-years of follow-up[d]	3663	1259	1219	1185		7275	2489	2424	2362	
Incidence (per 1000 person-years)	21.3	22.2	25.4	16.0		18.0	26.5	15.3	11.9	
Cancer type (ICD-10)										
Stomach (C16)	2		2			10	5	4	1	
Small intestine (C17)	0					3	2	1		
Hepatobiliary system (C22, C24)	2		2		1	3	2	1		
Pancreas (C25)	5	3	2		2	9	7	1	1	
Digestive organs, other and ill defined (C26)	0					1			1	
Bronchus and lung (C34)	16	5	5	6	1	23	9	9	5	
Mesothelial and soft tissue (C45, C46, C48)	3	3			1	5	2	1	2	1
Breast (C50)	14	3	6	5		14	6	5	3	
Cervix uteri (C53)						1	1			
Ovary (C56)	2	2			1	4	4			
Prostate (C61)	7	4	1	2	1	20	10	7	3	2
Kidney (C64, C65)	6	3	2	1	3	5	2	1	2	

continued

TABLE 13 The number of extracolonic cancers diagnosed within 3 years of randomisation in the BE vs. CTC trial (*continued*)

	CTC ($n = 1277$)					BE ($n = 2527$)				
		Month of diagnosis			Found by CTC		Month of diagnosis			Found by BE
	Total	1–12	13–24	25–36		Total	1–12	13–24	25–36	
Bladder (C67)						4	1	1	2	
Lymphoid or haematopoietic tissue (C81, C82, C83, C85, C90, C91, C92)	7	2	5			12	6	4	2	1
Primary site unknown (C80)	5	2	3		1	3	3			
Other[e]	9	1	3	5		14	6	2	6	

Data are numbers, unless otherwise specified.

a All primary malignant neoplasms, excluding colorectal cancers (C18–C20) and non-melanoma malignant neoplasms of the skin (C44).

b Two further extracolonic cancers, detected by CTC but not verified by the NHSIC, are excluded from this table.

c Four patients randomised to BE had two extracolonic cancers diagnosed within 36 months: one stomach and prostate; one small intestine and biliary tract; one melanoma of skin and lymphoid leukaemia; and one prostate and bladder. No patients randomised to CTC had more than one extracolonic cancer diagnosed.

d Adjusted for reported mortality.

e Comprises cancers of other and unspecified parts of the tongue (C02); oesophagus (C15); bone and articular cartilage of other and unspecified sites (C41); vulva (C51); brain (C71); spinal cord, cranial nerves and other parts of central nervous system (C72); thyroid (C73); and malignant melanoma of the skin (C43).

Colonoscopy trial

Numbers analysed

Of the 1610 patients in the colonoscopy trial, 1072 were randomised to colonoscopy and 538 to CTC. Thirty patients withdrew consent. The proportion of patients withdrawing consent differed between the two arms of the trial, just reaching the level of statistical significance [25 (2.3%) in the colonoscopy arm and 5 (0.9%) in the CTC arm; $p = 0.0496$].

The number of randomised patients at each site varied (median 37.5, IQR 16.5–106.5). There were no significant differences in the demographic or clinical characteristics of patients randomised to colonoscopy or CTC (*Table 14*). The median age of patients was 68 years (IQR 61–75 years) and 55% were women. The most frequent presenting symptoms were change in bowel habit (73%), rectal bleeding (43%) and abdominal pain (22%).

TABLE 14 Baseline demographic and clinical characteristics of patients with symptoms of CRC in the colonoscopy vs. CTC trial

	Colonoscopy (*N* = 1047)		CTC (*N* = 533)		Total (*N* = 1580)		Trial participants excluded (*N* = 3036)		
Characteristic	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***p*-value[a]**
Sex									
Male	476	45	240	45	716	45	1251	41	0.0074
Female	571	55	293	55	864	55	1785	59	
Age (years)									
55–64	384	37	217	41	601	38	802	26	<0.0001
65–74	377	36	186	35	563	36	1045	34	
75–84	253	24	113	21	366	23	930	31	
85 +	33	3	17	3	50	3	259	9	
Symptoms[b]									
Change in bowel habit	772	74	383	72	1155	73	1926	63	<0.0001
Harder, less frequent	126	12	66	12	192	12	297	10	
Looser, more frequent	410	39	214	40	624	39	1049	35	
Variable	124	12	54	10	178	11	180	6	
Unspecified	112	11	49	9	161	10	400	13	
Rectal bleeding	432	41	240	45	672	43	1169	39	0.0080
Abdominal pain	227	22	124	23	351	22	574	19	0.0077
Anaemia	140	13	60	11	200	13	620	20	<0.0001
Weight loss	155	15	82	15	237	15	500	16	0.19
Other symptoms	172	16	102	19	274	17	585	19	0.11

a *p*-value for the comparison to total patients within the colonoscopy trial.
b Patients may have reported multiple symptoms.

The number of patients who had their randomised procedure is shown in *Table 15*, along with reasons the procedure did not occur. There was no significant difference between the two arms in the proportion of patients having their randomised procedure [92.4% (967/1047) for colonoscopy and 94.4% (503/533) for CTC; $p = 0.14$]. Significantly more patients refused their procedure or did not attend among those randomised to colonoscopy than CTC [6.0% (63/1047) vs. 3.0% (16/533); $p = 0.0093$]. Of those patients randomised to colonoscopy who did not have their assigned procedure, 20% (16/80) had an alternative procedure, which was usually CTC (8/16, 50%). Of those randomised to CTC who did not have their procedure, 37% (11/30) had an alternative examination, which was usually colonoscopy (10/11, 91%).

As expected, no patients randomised to colonoscopy had FS performed prior to the randomised procedure, but eight patients randomised to CTC had prior FS (see *Figure 2*). Randomised CTC procedure occurred in 75.0% (6/8) of patients following FS, whereas CTC occurred in 94.7% (497/525) of patients without prior FS.

TABLE 15 Occurrence of randomised procedures in the colonoscopy vs. CTC trial

	Colonoscopy ($N = 1047$)		CTC ($N = 533$)		
Status	***n***	**%**	***n***	**%**	***p*-value**
Occurrence of randomised procedure					
Occurred	967	92.4	503	94.4	0.1373
Did not occur	80	7.6	30	5.6	
Reasons did not occur *Patient's decision*					
Patient refused randomised procedure	48	4.6	12	2.3	
Patient did not attend scheduled procedure	15	1.4	4	0.7	
Total	63	6.0	16	3.0	0.0093
Medical decision					
Patient unable to tolerate randomised procedure	5	0.5	1	0.2	
Consultant requested alternative procedure	4	0.4	8	1.5	
Patient became too ill	5	0.5	2	0.4	
Patient's symptoms resolved	2	0.2	0	0.0	
Patient died	1	0.1	2	0.4	
Total	17	1.6	13	2.4	0.26
Other reasons					
Equipment failure	0	0.0	1	0.2	
Total	0	0.0	1	0.2	

Performance of the examinations

A greater proportion of colonoscopy examinations were judged to be difficult, with 27.4% (265/967) rated as 'quite' or 'very' difficult, compared with 8.3% (42/503) for CTC ($p < 0.0001$). A total of 12.2% of patients (118/967) had an incomplete colonoscopy and 16.1% (81/503) of patients had an inadequate CTC, defined as at least one segment not seen or for which visualisation was rated as 'poor'.

Outcomes

Further colonic investigation

Of the 1047 patients randomised to colonoscopy, 86 had a further colonic investigation; these included 83 of 967 who had an additional procedure following colonoscopy and 3 of 16 who had an alternative whole-colon examination (*Figure 4*). Of the 533 patients randomised to CTC, 160 had a further colonic examination; these included 159 of 503 having CTC and 1 of 11 having an alternative procedure. Thus, additional colonic investigation was performed in 30% (160/533) randomised to CTC, compared with 8.2% (86/1047) randomised to colonoscopy (RR 3.65, 95% CI 2.87 to 4.65; $p < 0.0001$) (*Table 16*).

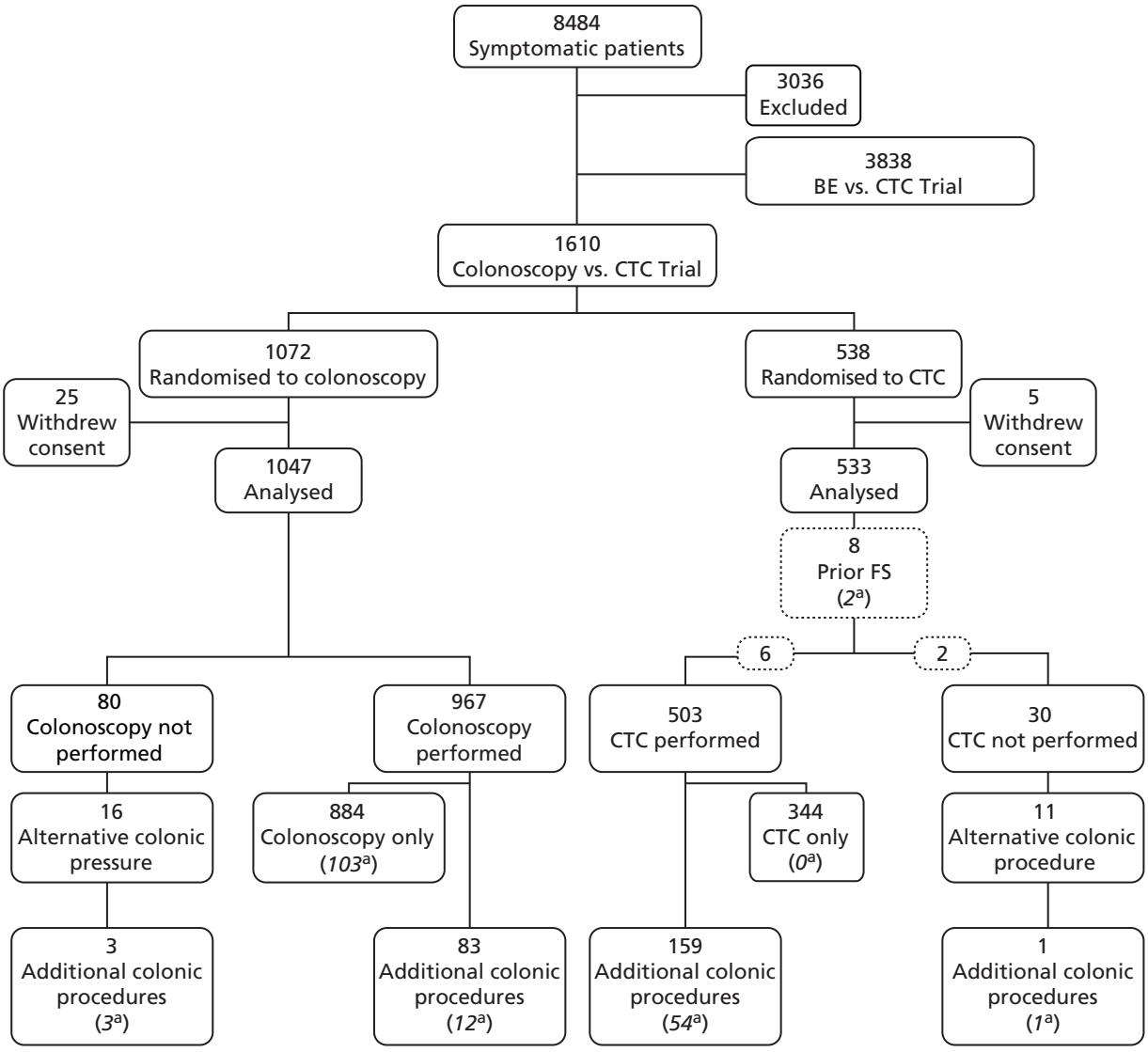

FIGURE 4 Participants' progress through the colonoscopy vs. CTC trial and selected outcomes. a, Number of patients with cancers or large polyps diagnosed.

TABLE 16 Intention-to-treat analysis of rates of subsequent colonic investigation overall and according to reason for referral in the colonoscopy vs. CTC trial

	Randomised procedure							Colonoscopy ($N = 1047$)				CTC ($N = 533$)			
	Colonoscopy ($N = 1047$)		CTC ($N = 533$)		RR (CTC vs. colonoscopy)			Men ($n = 476$)		Women ($n = 571$)		Men ($n = 240$)		Women ($n = 293$)	
Reason for referral	*n*	%	*n*	%	RR	95% CI	*p*-value	*n*	%	*n*	%	*n*	%	*n*	%
Cancer or large (≥ 10-mm) polyp suspected															
Cancer	10	1.0	47	8.8				4	0.8	6	1.0	25	10.4	22	7.5
Polyp ≥ 10 mm	2	0.2	36	6.8				0	0.0	2	0.4	20	8.3	16	5.5
Total with cancer or large (≥ 10 mm) polyp suspected	12	1.1	83	15.6	13.59	7.48 to 24.66	< 0.0001	4	0.8	8	1.4	45	18.7	38	13.0
Smaller polyp suspected															
Polyp 8–9 mm	1	0.1	14	2.6				1	0.2	0	0.0	8	3.3	6	2.0
Polyp 6–7 mm	0	0.0	22	4.1				0	0.0	0	0.0	14	5.8	8	2.7
Polyp ≤ 5 mm	0	0.0	13	2.4				0	0.0	0	0.0	5	2.1	8	2.7
Total with smaller polyp suspected	1	0.1	49	9.2	–		< 0.0001	1	0.2	0	0.0	27	11.2	22	7.5
Clinical uncertainty (no polyps seen)															
Inadequate examination	72	6.9	18	3.4				21	4.4	51	8.9	10	4.2	8	2.7
Adequate examination	1	0.1	10	1.9				1	0.2	0	0.0	5	2.1	5	1.8
Total with clinical uncertainty	73	7.0	28	5.3	0.75	0.49 to 1.15	0.19	22	4.6	51	8.9	15	6.3	13	4.4
Total having second procedure	86	8.2	160	30.0	3.65	2.87 to 4.65	< 0.0001	27	5.7	59	10.3	87	36.2	73	24.9

Of the 86 patients in the colonoscopy group who had an additional diagnostic procedure, 63 (73%) had radiological investigation, 16 (19%) had a second colonoscopy (complete or limited as appropriate) and seven were referred straight to surgery without prior histological diagnosis. Of the 160 patients in the CTC group who had an additional investigation, 150 (94%) had colonoscopy and 10 had surgery. *Table 17* describes reasons for referral: 1% of patients (12 cases) randomised to colonoscopy were referred because of a suspected cancer or large polyp, when biopsies either had not been taken or were inadequate for histological confirmation; 16% of patients randomised to CTC were referred to investigate a suspected cancer or large polyp and 9% to investigate a smaller polyp. There was no significant difference between the procedures in the proportion of patients referred because of clinical uncertainty (7% for colonoscopy vs. 5% for CTC; $p = 0.19$). All cancers identified at colonic investigations following CTC were in patients in whom a cancer or large polyp had been suspected at CTC (see *Table 17*) and three large polyps were found in people in whom smaller polyps had been suspected. Of the 28 patients who had a second procedure because of clinical uncertainty after CTC, one was found to have a large polyp. Of 73 patients who had a second procedure because of clinical uncertainty after colonoscopy, three were found to have cancers and one had a large polyp.

Comparing results for the primary outcome from models ignoring clustering with those controlling for clustering by trial centre showed that the odds ratios were quite similar in size and significance (*Table 18*).

There was a significant difference in relative referral rates between men and women. Men were more than six times as likely to have an additional examination after CTC as after colonoscopy, while women were just over twice as likely to do so (men: RR 6.39, 95% CI 4.27 to 9.56; women: RR 2.41, 95% CI 1.76 to 3.30; $p = 0.0002$) (*Figure 5*). These differences arose because men were more likely to require a second examination following CTC (36% of men vs. 25% of women), largely owing to detection of polyps (see *Table 16*), and women were more likely to require a second examination following colonoscopy (10% of women vs. 6% of men), usually because colonoscopy was incomplete. There was no significant difference in relative referral rates between the two procedures by age group (< 65 years and ≥ 65 years; $p = 0.32$) (see *Figure 5*).

Detection of colorectal cancer and large polyps

Among 1047 patients randomised to colonoscopy, a CRC or large polyp was diagnosed in 119: in 103 at initial colonoscopy, in 13 at subsequent colonic investigation and in three patients who had an alternative procedure (see *Figure 4*). Among 533 patients randomised to CTC, a CRC or large polyp was diagnosed in 57: in 54 following CTC, in two at FS prior to CTC and in one a patient undergoing an alternative whole-colon investigation. The 119 lesions diagnosed in patients randomised to colonoscopy comprised 58 CRCs and 61 large polyps (52 adenomas, four hyperplastic polyps, three serrated adenomas, one juvenile polyp and one polyp which was excised but not retrieved). The 57 lesions diagnosed in patients randomised to CTC comprised 30 CRCs and 27 large polyps (24 adenomas and three hyperplastic polyps). The overall detection rate of CRC or large polyps did not differ between groups: 10.7% (57/533) for CTC compared with 11.4% (119/1047) for colonoscopy (RR 0.94, 95% CI 0.70 to 1.27; $p = 0.69$). There was no difference in detection rates when cancers ($p = 0.94$) and large polyps ($p = 0.53$) were analysed separately. Similar results were obtained when the analysis was restricted to patients having the randomised procedure (per-protocol analysis): 10.7% (54/503) for CTC compared with 12% (116/967) for colonoscopy (RR 0.89, 95% CI 0.66 to 1.21; $p = 0.47$) and no difference in detection rates when cancers ($p = 0.92$) and large polyps ($p = 0.38$) were analysed separately (*Table 19*).

TABLE 17 Detection rates of cancer or large polyps among patients having a second colonic procedure in the colonoscopy vs. CTC trial; overall and according to reason for referral[a]

Randomised procedure group	Colonoscopy					CTC				
	Subsequent colonic procedure undertaken	Lesions seen at subsequent procedure				Subsequent colonic procedure undertaken	Lesions seen at subsequent procedure			
		CRC	Polyp ≥ 10 mm[b]	Cancer or polyps ≥ 10 mm[b]			CRC	Polyp ≥ 10 mm[b]	Cancer or polyps ≥ 10 mm[b]	
Findings at first procedure	*N*	*n*	*n*	*n*	%	*N*	*n*	*n*	*n*	%
Cancer or large (≥ 10 mm) polyp suspected										
Cancer	10	9	0	9	90	47	27	3	30	64
Polyp ≥ 10 mm	2	0	1	1	50	36	2	19	21	58
Total	12	9	1	10	83	83	29	22	51	61
Smaller polyp suspected										
Polyp 8–9 mm	1	0	0	0	0	14	0	2	2	14
Polyp 6–7 mm	0					22	0	0	0	0
Polyp ≤ 5 mm	0					13	0	1	1	8
Total	1	0	0	0	0	49	0	3	3	6
Clinical uncertainty (no polyps seen)										
Inadequate examination	72	3	1	4	6	18	0	1	1	6
Adequate examination	1	0	0	0	0	10	0	0	0	0
Total	73	3	1	4	5	28	0	1	1	4
Total having subsequent colonic procedure	86	12	2	14	16	160	29	26	55	34

a The most advanced end point per patient is presented.
b ≥ 10-mm polyp included adenoma, serrated adenoma, hyperplastic polyp, juvenile polyp, or excised but not retrieved polyp with a size ≥ 10 mm at endoscopy.

TABLE 18 Effect of clustering on estimates of the odds ratio (CTC vs. colonoscopy) for additional colonic investigation in the colonoscopy vs. CTC trial

	No clustering			With clustering[a]		
Analysis	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
Intention-to-treat analysis	4.79	3.59 to 6.39	< 0.0001	4.43	3.03 to 6.46	< 0.0001
Per-protocol analysis	4.92	3.67 to 6.60	< 0.0001	4.40	2.90 to 6.67	< 0.0001

a Results from random-effects model allowing for heterogeneity in the rate of additional colonic investigation and odds ratio by centre.

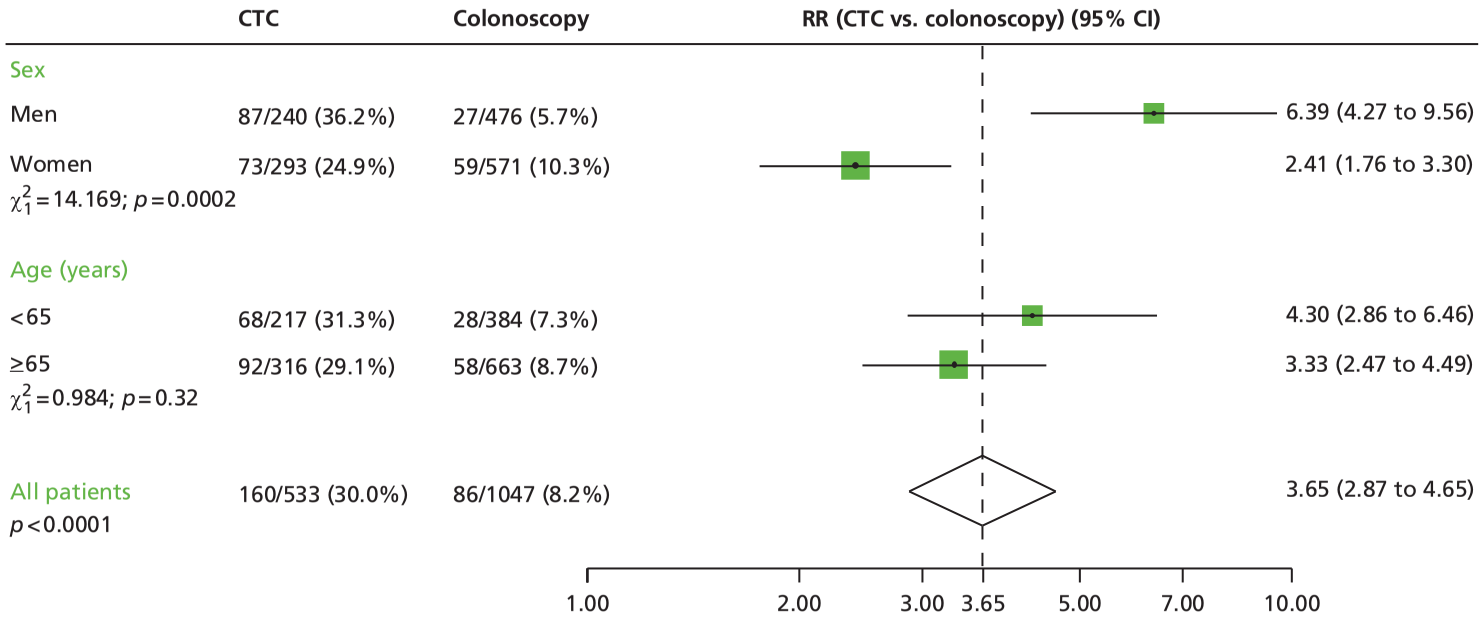

FIGURE 5 Relative risks for referral for additional colonic procedure (CTC vs. colonoscopy) by sex and age group in the colonoscopy vs. CTC trial.

TABLE 19 Intention-to-treat and per-protocol analyses of detection rates of cancer and large polyps according to randomised procedure in the colonoscopy vs. CTC trial[a]

	Colonoscopy group		CTC group		Comparison of detection rates between procedures (CTC vs. colonoscopy)		
	N = 1047		*N* = 533				
Analysis	*n*	%	*n*	%	RR	95% CI	*p*-value
Intention to treat							
CRC[b]	58	5.5	30	5.6	1.02	0.66 to 1.56	0.94
≥ 10-mm polyp[c]	61[d]	5.8	27[e]	5.1	0.87	0.56 to 1.35	0.63
CRC or ≥ 10-mm polyp[c]	119[d]	11.4	57[e]	10.7	0.94	0.70 to 1.27	0.69
	N = 967		*N* = 503				
	n	%	*n*	%			
Per protocol							
CRC	55	5.7	28	5.6	0.98	0.63 to 1.52	0.92
≥ 10-mm polyp[c]	61[d]	6.3	26[e]	5.2	0.82	0.52 to 1.28	0.38
CRC or ≥ 10-mm polyp[c]	116[d]	12.0	54[e]	10.7	0.89	0.66 to 1.21	0.47

a Only the most advanced end point per patient is presented.
b This includes one carcinoid tumour and one non-Hodgkin's lymphoma.
c ≥ 10-mm polyp is defined as a pathologically confirmed adenoma, serrated adenoma, hyperplastic polyp, juvenile polyp or excised but not retrieved polyp with a size ≥ 10 mm at endoscopy.
d Includes four patients with a ≥ 10-mm hyperplastic polyp, three patients with a ≥ 10-mm serrated adenoma, one patient with a ≥ 10-mm juvenile polyp and one patient with a ≥ 10-mm excised but not retrieved polyp.
e Includes three patients with a ≥ 10-mm hyperplastic polyp.

Colorectal diagnoses other than cancer or polyps were analysed. Diverticular disease was detected in significantly more patients having CTC than colonoscopy [54% (287/533) and 35% (366/1047) respectively; $p < 0.0001$]. Diagnoses that were significantly more frequent in patients having colonoscopy included inflammatory bowel disease [1% (4/533) vs. 3% (934/1047); $p = 0.0022$] and anal findings [2% (13/533) vs. 7% (73/1047); $p = 0.0002$]. Other findings occurred in numbers too low to be analysed.

Time to diagnosis

Among patients who had their randomised procedure or an alternative procedure, the median time from date of randomisation to date of diagnosis was 21 days (IQR 12–43 days); the time was longer for subjects randomised to CTC than for those randomised to colonoscopy [CTC ($n = 514$ patients) median 24 days, IQR 13–49 days; colonoscopy ($n = 983$ patients) median 20 days, IQR 11–41 days; $p = 0.0001$]. The time to the randomised procedure was similar for the two procedures [CTC ($n = 514$ patients) median 16 days, IQR 11–27 days; colonoscopy ($n = 983$ patients) median 17 days, IQR 11–35 days; $p = 0.0133$], but for subjects who had an additional referral after the randomised procedure, the time from the randomised procedure to the second procedure was longer for CTC [CTC ($n = 160$ patients) median 43 days, IQR 25.5–83 days; colonoscopy ($n = 86$ patients) median 25 days, IQR 12–42 days; $p < 0.0001$]. For patients who had a diagnosis of cancer or a large polyp, the delay for those having CTC was considerably longer (CTC median 42 days, IQR 29–79 days; colonoscopy median 15 days, IQR 11–41 days; $p < 0.0001$).

Extracolonic findings following computed tomographic colonography

At least one previously unknown extracolonic finding was reported in 61% (287/474) of patients having CTC who did not have CRC diagnosed during the trial. Forty-eight of these (10%) were referred for additional procedures, leading to diagnosis of extracolonic malignancy in nine patients (*Table 20*). A more detailed analysis of extracolonic findings is given in *Chapter 4*.

Cancers diagnosed during 3-years' follow-up

When analysis was performed in June 2012, registration was reported to be 97% complete for all cancers diagnosed until December 2010 (at which point all patients had been followed up for at least 36 months) and all deaths until December 2011 had been registered. By that time (median follow-up for deaths 5.2 years, IQR 4.6–5.9 years), 154 patients (14.7%) assigned to colonoscopy and 63 patients (11.8%) assigned to CTC had died ($p = 0.11$). Sixty-one patients in the colonoscopy group had a CRC diagnosis, including three who had refused colonoscopy; there were no CRC diagnoses after discharge in patients who had their colonoscopy. Thirty-one patients in the CTC group had a CRC diagnosis, including one patient who was diagnosed 15 months after an apparently normal CTC; the miss rate among patients with CTC performed was 3.4% (1/29).

During the 3-year follow-up of the trial cohort, 27 extracolonic cancers were diagnosed in the CTC group and 56 in the colonoscopy group (17.6 per 1000 person-years in the CTC group vs. 18.7 per 1000 person-years in the colonoscopy group; IRR 0.94, 95% CI 0.59 to 1.49; $p = 0.79$). In the first year, rates of primary extracolonic cancer diagnosis in the trial cohort were more than twice as high as expected (IRR 2.33, 95% CI 1.40 to 3.89; $p = 0.0007$), but rates did not differ significantly between the CTC and colonoscopy groups (IRR 0.95, 95% CI 0.53 to 1.73; $p = 0.88$) CTC detected 9 of 16 (56%) extracolonic cancers diagnosed within the first year in the CTC group, while colonoscopy detected one extracolonic cancer in the colonoscopy group (a lung primary diagnosed via a colonic metastasis).

Adverse events

An unplanned hospital admission within 30 days of the randomised procedure occurred in 12 patients following colonoscopy and in six following CTC. Reasons for admission were reviewed independently by a gastroenterologist, a radiologist and a surgeon, who concluded that three were possibly attributable to the randomised procedure (reviewers were blinded to the procedure type). All three followed colonoscopy [reasons for admission were abdominal pain ($n = 1$), rectal bleeding ($n = 1$), and diarrhoea and vomiting ($n = 1$)]. Another patient had polyps detected at CTC and experienced a possible perforation after polypectomy at colonoscopy; the patient was treated conservatively and discharged the following day. There was one death within 30 days of a patient who underwent surgery for a CRC seen at CTC.

TABLE 20 Number of patients with extracolonic cancers diagnosed within 3 years of randomisation in the colonoscopy vs. CTC trial

	CTC (*N* = 533)					Colonoscopy (*N* = 1047)				
		Month of diagnosis					Month of diagnosis			
	Total	1–12	13–24	25–36	Found by CTC	Total	1–12	13–24	25–36	Found by colonoscopy
All extracolonic cancers[a]	27	16	3	8	9	56[b]	33	9	14	1
Person-years of follow-up[c]	1536	523	512	501		2992	1030	994	968	
Incidence (per 1000 person-years)	17.6	30.6	5.9	16.0		18.7	32.0	9.1	14.5	
Cancer type (ICD-10)										
Stomach (C16)	4	2		2	1	3	1	1	1	
Small intestine (C17)	1	1				1	1			
Hepatobiliary system (C22, C23)	1	1				4	1	2	1	
Pancreas (C25)	2	1		1	1	7	6	1		
Bronchus and lung (C34)	2	2			1	12	8	2	2	1[d]
Mesothelioma (C45)						1			1	
Breast (C50)	2			2		7	4	1	2	
Ovary (C56)	1			1						
Prostate (C61)	3		2	1		10	4	2	4	
Kidney (C64, C65)	5	5			4	4	3		1	
Bladder (C67)	2	1		1						
Lymphoid or haematopoietic tissue (C82, C85, C90)	2	2			2	3	1		2	
Other[e]	2	1	1			4	4			

Data are numbers, unless otherwise specified.

a All primary malignant neoplasms, excluding colorectal cancers (C18–C20) and non-melanoma malignant neoplasms of the skin (C44).

b One patient randomised to colonoscopy had two extracolonic cancers diagnosed within 36 months: lung and kidney cancer. No patients randomised to CTC had more than one extracolonic cancer diagnosed.

c Adjusted for reported mortality.

d Secondary CRC found at colonoscopy, leading to diagnosis of primary lung cancer.

e Comprises cancers of the oesophagus (C15); vulva (C51); other and ill-defined sites (C76); and malignant melanoma of the skin (C43).

Chapter 4 Extracolonic findings

An updated and more recent analysis of the data is available in Halligan *et al.*[37]

Introduction

Symptoms suggestive of CRC include a change in bowel habit, rectal bleeding, anaemia, weight loss and abdominal pain. However, these symptoms are non-specific and (with the likely exception of rectal bleeding) may originate from pathology outside the colon.[38] A potential advantage of CTC for investigating symptomatic patients is that it can examine both the large bowel and other abdominopelvic organs at a single examination. A study of 1077 CTC examinations performed in frail elderly patients (median age 80 years), with symptoms suggestive of CRC, found extracolonic disease in 106 patients (10%) that was ultimately believed to be the cause of symptoms.[38] Another study of 400 symptomatic patients aged ≥ 70 years found extracolonic abnormalities in 67%, including 23 malignancies.[39] The authors concluded that CTC should replace a BE because it is a more comprehensive investigation.

However, although CTC can detect extracolonic pathology in patients with suspected CRC, it is uncertain if this is always beneficial. Although some patients will have clinically important abnormalities outside the colon, in other cases the detection of extracolonic lesions can precipitate follow-up investigations that increase morbidity and anxiety, are costly and ultimately offer no clinical benefit. A systematic review of 3488 patients from 17 studies found that 14% underwent further investigation, leading to detection of an extracolonic cancer in 2.7% overall.[40] An economic analysis of 225 patients by the same group found that the average cost incurred to investigate extracolonic pathology exceeded the cost of the initial CTC examination.[26] Researchers have assessed the clinical impact of extracolonic findings via chart review,[24,39,41] but this may introduce bias as the decision on whether or not a detected lesion is important is made retrospectively. In addition, the largest studies have been performed in asymptomatic individuals being screened for CRC.[42,43] Until now there has been no prospective, randomised study examining the consequences of detecting extracolonic lesions in symptomatic patients having CTC. We collected data on the frequency and nature of extracolonic pathology detected at CTC, subsequent investigations and resource use and ultimate clinical outcome.

Methods

Data collection

Radiologists interpreting the procedures issued a report in line with normal clinical practice and completed a specially designed trial CRF (see *Appendix 1*), noting any suspected colonic lesions (e.g. cancers or polyps) that might explain a patient's presenting symptoms. Space was also provided on the CRF for radiologists to describe any significant extracolonic lesions identified during their interpretation.

Follow-up

Extracolonic lesions recorded on the CTC report were investigated if considered clinically relevant by the clinician in charge, in light of the patient's presenting symptoms, status and personal wishes. Details of subsequent procedures requested to investigate or treat potential extracolonic pathology were collected from trial centres, as described in *Chapter 2*.

In order to identify cancers (both intracolonic and extracolonic) that were missed by the procedures, all participating patients were identified on the NHSCR and information on new cancer diagnoses and deaths was obtained from the NHSIC. Trial patients were also matched with national HES to reduce the time lag between cancer diagnosis and the time of notification. Cancers were confirmed using pathology and imaging reports obtained from the hospital where the cancer was diagnosed.

Statistical analysis

The analysis of extracolonic lesions was prespecified in the trial protocol. Patients with proven CRC were excluded from this analysis as it is not always possible to be sure that such patients' extracolonic findings were unrelated to their CRC and referral patterns for follow-up of extracolonic lesions are likely to be different for patients in whom CRC is also present.

A data manager examined the radiology reports from CTC examinations, extracting references to extracolonic lesions and placing them in a spreadsheet. Each extracolonic finding was subsequently assigned an Extracolonic Reporting And Data System (E-RADS) score[44] by a radiologist (SH) blind to study arm, patient, reporting radiologist, centre and ultimate clinical diagnosis. E-RADS scores categorise the perceived clinical importance of an extracolonic finding detected at CTC as follows: E-RADS category 1, normal examination or anatomic variant (E1) – 'normal exam or anatomic variant'; E-RADS category 2, clinically unimportant finding (E2) – 'clinically unimportant finding'; E-RADS category 3, likely unimportant finding, incompletely characterised (E3) – 'likely unimportant finding, incompletely characterised'; and E-RADS category 4, potentially important finding (E4) – 'potentially important finding'.[44] Patients' E-RADS scores were then matched with their demographic data, presenting symptoms and details of their subsequent diagnostic/therapeutic procedures. In cases for which a potential extracolonic abnormality was conclusively diagnosed, a data manager assigned it a code according to the *International Classification of Diseases and Related Health Problems* (ICD) classification. A senior surgeon, gastroenterologist and radiologist independently reviewed these diagnoses by ICD code, together with the presenting clinical symptoms in patients assigned that code, noting for each symptom whether or not they thought it could be related to the final diagnosis. When there was any difference in opinion, a majority vote was used to reach a final decision on whether or not the symptom was likely to be related.

Results

Patient flow through the trial is shown in *Figure 6*. Of 8484 patients, 3100 were excluded (*Table 21* shows the reasons), 3804 were randomised within the BE trial and 1580 were randomised within the colonoscopy trial. There were 1297 CTC examinations performed in the BE trial and 545 performed in the colonoscopy trial. Fifty-six patients and 38 patients in the BE trial and the colonoscopy trial, respectively, were excluded because of a diagnosis of CRC, leaving 1241 CTC studies for analysis of extracolonic lesions in the BE trial and 507 in the colonoscopy trial.

Reporting of extracolonic findings

In both trials, change in bowel habit was the most common presenting symptom (76.1% of all patients analysed), followed by abdominal pain (BE trial) and rectal bleeding (colonoscopy trial) (*Table 22*). Of the 1748 CTC studies analysed overall, 1039 (59.4%) had at least one extracolonic finding described by the reporting radiologist; 728 (58.7%) from the BE trial and 311 (61.3%) from the colonoscopy trial (see *Figure 6*). There was no association between sex and reporting of an extracolonic finding; however, patients were significantly more likely to have an extracolonic finding reported if they were older ($p < 0.0001$). In both trials, the proportion of patients with at least one extracolonic finding increased with age, rising in the BE trial from 48% for those aged 55–64 years to 74% for those aged ≥ 85 years, and from 55% to 91%, respectively, in the colonoscopy trial (see *Table 22*).

A total of 1945 individual extracolonic findings were reported: 22 (1.13%) findings were categorised as E1 ('normal exam or anatomic variant'), 1472 (75.7%) were categorised as E2 ('clinically unimportant'), 362 (18.6%) were categorised as E3 ('likely unimportant, incompletely characterised) and 89 (4.6%) were categorised as E4 ('potentially important'). The proportion of findings falling into each category was similar in the BE and colonoscopy trials (E2: 37% vs. 42%; E3: 16% vs. 15%; E4: 5% vs. 5%, respectively).

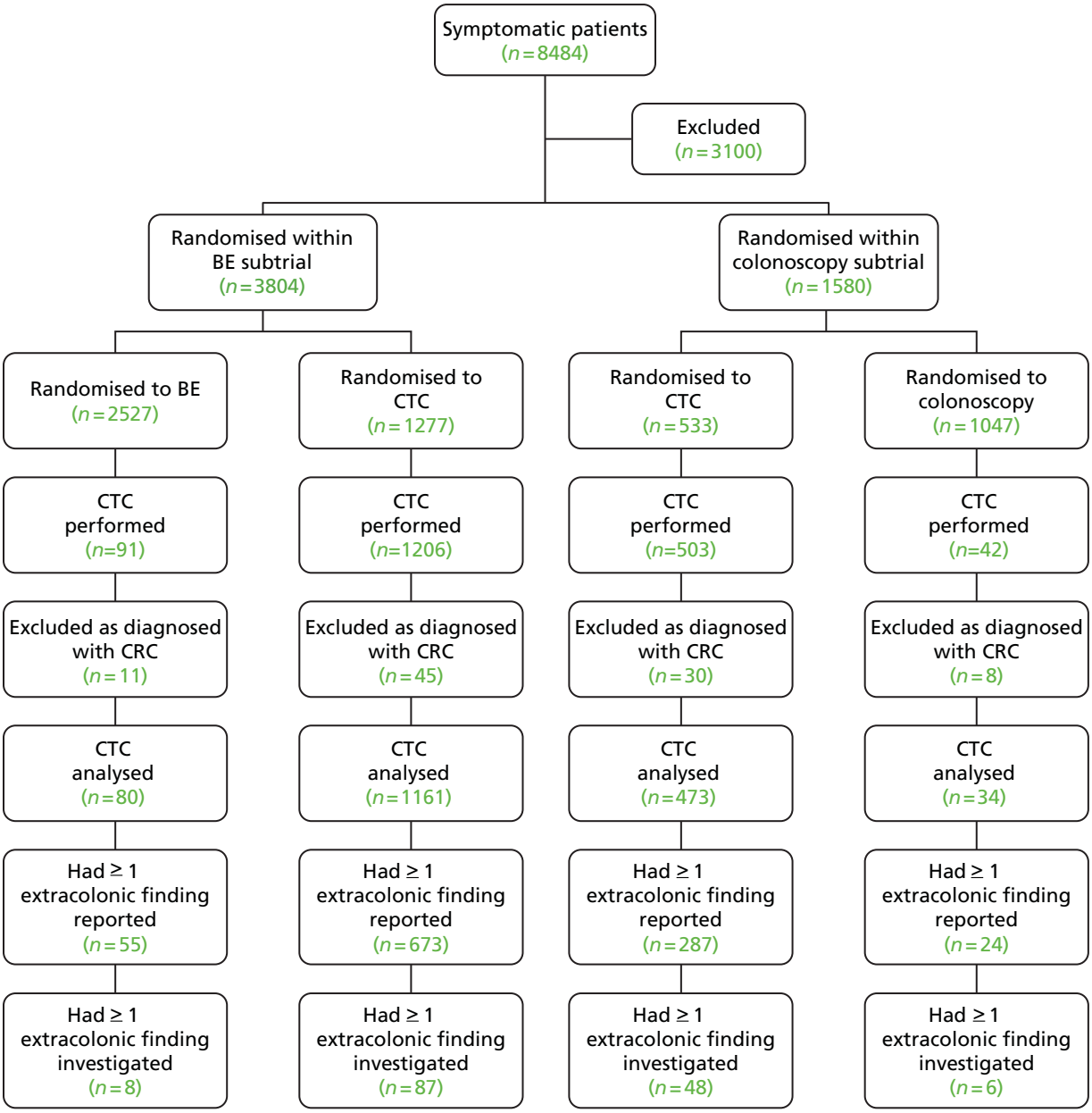

FIGURE 6 Patient flow through the trial.

TABLE 21 Reasons for exclusions

Reason	*n*	(%)
Clinician reasons for declining consent		
Colorectal or other cancer already diagnosed		
CRC diagnosed	56	1.8
Other cancer diagnosed	69	2.2
Specific procedure requested		
Colonoscopy	731	23.6
CT	303	9.8
FS	230	7.4
Oesophagogastroduodenoscopy	218	7.0
BE	19	0.6
Ultrasonography	16	0.5
Magnetic resonance imaging	5	0.2
Unknown	39	1.3
Clinical situation too urgent or waiting list too long	52	1.7
Patient unfit for whole-colon examination	215	6.9
Patient unable to give informed consent	75	2.4
No reason given	148	4.7
Total for which clinician declined consent	**2176**	**70.2**
Patient reasons for declining consent		
Patient wanted a specific procedure		
Colonoscopy	15	0.5
CT	3	0.1
BE	2	0.06
Unknown	128	4.1
Patient did not want a specific procedure		
CT as claustrophobic	13	0.4
CT for other reasons	2	0.06
Colonoscopy	1	0.03
BE	1	0.03
Patient had difficulty comprehending	84	2.7
Patient died before consent obtained	2	0.06
No reason given	583	18.8
Total for which patient declined consent	**834**	**26.9**
Reason for exclusion unknown	26	0.8
Patient withdrew consent following randomisation	64	2.1
Total excluded	**3100**	**100.0**

TABLE 22 Baseline demographic and clinical characteristics of patients with symptoms of CRC in whom CTC was performed (patients ultimately diagnosed with CRC are excluded)

	BE trial					Colonoscopy trial				
	CTC performed and analysed[a]	At least one extracolonic finding		Referred		CTC performed and analysed[a]	At least one extracolonic finding		Referred	
Characteristic	*n*	*n*	%	*n*	%	*n*	*n*	%	*n*	%
Total	1748	1039	59	149	9	1241	728	59	95	8	507	311	61	54	11
Sex															
Male	689	414	60	61	9	465	279	60	39	8	224	135	60	22	10
Female	1059	625	59	88	8	776	449	58	56	7	283	176	62	32	11
Age (years)															
55–64	618	313	51	47	8	407	196	48	27	7	211	117	55	20	9
65–74	655	384	59	52	8	478	281	59	32	7	177	103	58	20	11
75–84	421	300	71	45	11	313	219	70	32	10	108	81	75	13	12
≥ 85	54	42	78	5	9	43	32	74	4	9	11	10	91	1	9
Symptoms/signs[b]															
Change in bowel habit	1330	787	59	108	8	960	553	58	70	7	370	234	63	38	10
Rectal bleeding	599	352	59	50	8	373	215	58	24	6	226	137	61	26	12
Abdominal pain	513	293	57	46	9	400	227	57	32	8	113	66	58	14	12
Anaemia	193	138	72	24	12	142	102	72	15	11	51	36	71	9	18
Weight loss	253	163	64	28	11	179	115	64	19	11	74	48	65	9	12
Other	228	135	59	20	9	133	77	58	10	8	95	58	61	10	11

a Patients with CRC diagnosed were excluded.
b Patients may have reported multiple symptoms/signs.

Rate and nature of subsequent investigation

A total of 149 patients (8.5% of those analysed) underwent subsequent procedures to investigate and/or treat extracolonic findings. Three of these patients had two unrelated findings investigated (i.e. there were 152 individual findings in total). In the E-RADS categories, 26 findings were classified as E2, 60 as E3, and 66 as E4, and the proportion investigated in each category was 1.8% for E2, 16.6% for E3 and 74.2% for E4. In total, 97 of the 149 patients (65%) underwent a single procedure and 52 (35%) underwent multiple procedures, with 31 patients having two procedures, 14 having three procedures, four having four procedures and one having five procedures.

The follow-up procedures undertaken to investigate or treat extracolonic findings are shown in *Table 23*. Follow-up was most frequently by non-invasive imaging (80 cases). There were 68 invasive follow-up procedures, 32 of which were surgical, including some that combined investigation and therapy (e.g. excision biopsy, vascular repair). There was a positive correlation between E-RADS category and invasiveness of follow-up procedure, with most surgical procedures performed to investigate and/or treat E4 findings whereas most radiological procedures were performed to investigate E2 findings (see *Table 23*). E3 detections were intermediate, with most procedures in this category invasive but non-surgical (e.g. endoscopy). The type and frequency of surgical and non-surgical procedures is shown in *Table 24*. The most frequently performed surgical procedure was nephrectomy (nine cases), followed by salpingo-oophorectomy and/or hysterectomy (eight cases). The most common invasive, non-surgical procedure was transvaginal ultrasonography (nine cases) followed by upper GI endoscopy (six cases).

TABLE 23 The most invasive follow-up procedure performed to investigate all individual extracolonic findings according to the E-RADS category assigned to the finding[a]

Most invasive procedure performed as a result of finding	E-RADS category of finding						
	E4 ($n = 66$)		E3 ($n = 60$)		E2 ($n = 26$)		
	n	%	*n*	%	*n*	%	Total ($n = 152$)
Surgical	23	34.8	7	11.7	2	7.7	32
Invasive, non-surgical	15	22.7	17	28.3	4	15.4	36
Non-invasive imaging	25	37.9	36	60.0	19	73.1	80
Other[b]	3	4.5	0	0.0	1	3.8	4

a Three patients had two unrelated findings investigated and included in the table.
b Includes three blood tests and one urine test.

TABLE 24 Invasive procedures performed to investigate and/or treat extracolonic findings

Procedure	Frequency
Surgical procedure	
Radical nephrectomy	9
Oophorectomy with or without salpingectomy with or without hysterectomy	8
Aneurysm repair (three endovascular, two open)	5
Laparotomy	3
Whipple procedure	1
Inguinal hernia repair	1
Laparoscopic cholecystectomy	1
Right upper lobectomy	1
Splenectomy	1
Adrenalectomy	1
Video-assisted thoracoscopy	1
Total surgical procedures	**32**
Non-surgical procedure	
Ultrasound transvaginal	9
Oesophagogastroduodenoscopy	6
Hysteroscopy	4
Ultrasound-guided biopsy	3
Bronchoscopy	2
Lymph node biopsy	2
CT-guided biopsy	1
Endoscopic retrograde cholangiopancreatography	1
Endoscopic ultrasound of pancreas	1
Extracorporeal shock wave lithotripsy	1
Flexible cystoscopy	1
Fluid aspiration and culture of uterus	1
Prostate biopsy	1
Renal biopsy	1
Ultrasound-guided drainage of ascites	1
Ultrasound-guided fine-needle aspiration of pancreas	1
Total non-surgical, invasive procedures	**36**

Final extracolonic diagnosis, predictive value of presenting symptoms and missed extracolonic cancers

An extracolonic diagnosis was reached in 133 of the 149 referred patients (89%). A list of the final diagnoses is given in *Table 25*. In total, 79 extracolonic neoplasms were diagnosed, 29 of which were malignant. Extracolonic neoplasms were therefore diagnosed in 4.5% of those having CTC overall (excluding those diagnosed with CRC) and an extracolonic malignancy was diagnosed in 1.7%. The most frequent extracolonic primary malignancies were renal (nine cases), pancreatic (four cases) and ovarian (three cases). The most frequent extracolonic benign tumour was ovarian (16 cases). A total of 26 of the 29 malignancies (90%) had been assigned to the E4 category and the remaining three were E3. In all, 21 of the 50 benign tumours (42%) were assigned an E4 rating, 24 (48%) were E3 and 5 (10%) were E2. The most frequent non-neoplastic diagnosis was abdominal aortic aneurysm (14 cases).

TABLE 25 Final diagnosis of extracolonic findings by ICD category

ICD code	Pathology	Frequency	Number of patients with ≥ 1 symptom related to diagnosis
Malignant neoplasms			
C64	Malignant neoplasm of the kidney, except renal pelvis	8	5
C25	Malignant neoplasm of the pancreas	4	4
C56	Malignant neoplasm of the ovary	3	3
C78	Secondary malignant neoplasm of respiratory and digestive organs	2	2
C34	Malignant neoplasm of the bronchus and lung	2	1
C61	Malignant neoplasm of the prostate	2	2
C16	Malignant neoplasm of the stomach	1	1
C17	Malignant neoplasm of the small intestine	1	1
C22	Malignant neoplasm of the liver and intrahepatic bile ducts	1	1
C65	Malignant neoplasm of the renal pelvis	1	1
C77	Secondary and unspecified malignant neoplasm of lymph nodes	1	1
C80	Malignant neoplasm without specification of site	1	1
C82	Follicular (nodular) non-Hodgkin's lymphoma	1	1
C90	Multiple myeloma and malignant plasma cell neoplasms	1	1
Total		29	25
Benign neoplasms			
D27	Benign neoplasm of the ovary	16	7
D18	Haemangioma and lymphangioma, any site	10	0
D14	Benign neoplasm of the middle ear and respiratory system	9	0
D25	Leiomyoma of the uterus	5	4
D30	Benign neoplasm of urinary organs	4	0

TABLE 25 Final diagnosis of extracolonic findings by ICD category (*continued*)

ICD code	Pathology	Frequency	Number of patients with ≥ 1 symptom related to diagnosis
D35	Benign neoplasm of other and unspecified endocrine glands	2	0
D36	Benign neoplasm of other and unspecified sites	2	0
D13	Benign neoplasm of other and ill-defined parts of the digestive system	1	1
D44.1	Adrenal neoplasm of uncertain or unknown behaviour	1	1
Total		50	13
Other diagnoses			
D50.9	Iron deficiency anaemia, unspecified	1	1
B90.9	Sequelae of respiratory and unspecified tuberculosis	1	1
I71.9	Abdominal aortic aneurysm, without mention of rupture	14	7
I72.3	Aneurysm of the iliac artery	1	0
J92	Pleural plaque, with presence of asbestos	3	0
J20.8	Acute bronchitis due to other specified organisms	1	0
J98.9	Respiratory disorder, unspecified	1	0
K83.5	Biliary cyst	7	0
K44.9	Diaphragmatic hernia without obstruction or gangrene	4	1
K80.2	Calculus of the gallbladder, without cholecystitis	3	0
K80.1	Calculus of the gallbladder, with other cholecystitis	1	1
K86.1	Other chronic pancreatitis	1	1
K50.0	Crohn's disease of small intestine	1	1
K91.5	Post-cholecystectomy syndrome	1	1
K76	Fatty liver, not elsewhere classified	2	0
K40.9	Inguinal hernia, without obstruction or gangrene	1	1
N28.1	Cyst of the kidney, acquired	6	0
N71.9	Inflammatory disease of the uterus, unspecified	1	0
N20	Calculus of the kidney	1	0
N13	Hydronephrosis with ureteropelvic junction obstruction	1	1
N13.5	Kinking and stricture of the ureter without hydronephrosis	1	0
Q60	Renal agenesis, unilateral	1	0
R59	Localised enlarged lymph nodes	2	0
Total		56	16

Twenty-five of 29 patients (86%) with an extracolonic malignancy had presenting symptoms that were attributable to the tumour (see *Table 25*), compared with 13 of 50 patients (26%) with a benign extracolonic tumour. Sixteen of the 56 patients (29%) with a non-neoplastic extracolonic finding had symptoms attributable to this.

Overall, 3% of patients having CTC had presenting symptoms attributable to an extracolonic finding (*Table 26*). This proportion was equal for males and females and for all ages except patients aged ≥ 85 years (of whom only five were referred). The positive predictive value of individual symptoms for an extracolonic diagnosis was low; for example, of the 1330 patients presenting with altered bowel habit, only 13 (1%) had an extracolonic finding to which this symptom could be attributed (see *Table 26*). Abdominal pain had the highest positive predictive value and rectal bleeding the lowest (7% and 0.3% of patients, respectively, had an extracolonic finding that explained their symptoms).

TABLE 26 Proportion of patients referred for further investigation as a consequence of an extracolonic finding, the proportion in whom a diagnosis was made and the proportion who had presenting symptoms attributable to the diagnosis

	Patients with CTC performed[a]	Patients referred for further investigations		Patients with an extracolonic diagnosis made		Patients with at least one symptom attributable to extracolonic diagnosis	
Characteristic	*N*	*n*	%	*n*	%	*n*	%
Total	1748	149	9	133	8	54	3
Sex							
Male	689	61	9	55	8	20	3
Female	1059	88	8	78	7	34	3
Age (years)							
55–64	618	47	8	42	7	19	3
65–74	655	52	8	45	7	20	3
75–84	421	45	11	41	10	11	3
≥ 85	54	5	9	5	9	4	7
Symptoms/signs[b]							
Change in bowel habit	1330	108	8	96	7	13	1
Rectal bleeding	599	50	8	45	8	2	0.3
Abdominal pain	513	46	9	44	9	34	7
Anaemia	193	24	12	22	11	7	4
Weight loss	253	28	11	26	10	8	3
Other	228	20	9	17	7	7	3

a Patients with CRC diagnosed were excluded.
b Patients may have reported multiple symptoms/signs.

Analysis of registry data showed that there was no significant difference in the proportion of patients diagnosed with an extracolonic cancer within 3 years of randomisation, regardless of the original randomised procedure. In the BE trial, 34 of 2427 patients (1.4%) randomised to BE were diagnosed with an extracolonic cancer within 3 years, compared with 20 of 1226 (1.6%) randomised to CTC ($p = 0.689$). In the colonoscopy trial, 17 of 983 patients (1.7%) randomised to colonoscopy were diagnosed with an extracolonic cancer, compared with 9 of 501 (1.8%) randomised to CTC ($p = 0.926$) (*Table 27*). For all randomised procedures, the greatest proportion of extracolonic tumours was diagnosed within the first 6 months, compared with subsequent 6-month blocks (see *Table 27*). There was also no significant difference by randomised procedure in the prevalence of extracolonic malignancies potentially detectable by CTC: in the BE trial, 35 of 2441 patients (1.4%) randomised to BE compared with 21 of 1230 (1.7%) randomised to CTC ($p = 0.523$); in the colonoscopy trial, 17 of 986 patients (1.7%) randomised to colonoscopy compared with 9 of 502 (1.8%) randomised to CTC ($p = 0.924$). Registry data revealed that 14 patients had an extracolonic abdominopelvic cancer diagnosed within 3 years of CTC that had not been detected by the procedure: seven prostate, three pancreatic, two renal, one ovarian and one jejunal.

Six patients died within 60 days of a follow-up procedure for an extracolonic finding: four from metastatic disease, one following a Whipple procedure for pancreatic carcinoma and one following open repair of an aortic aneurysm. There was no significant difference by randomised procedure in the proportion of patients dying within 3 years of randomisation (excluding those with CRC): in the BE trial, 158 of 2441 patients (6.5%) randomised to BE compared with 96 of 1230 (7.8%) randomised to CTC ($p = 0.13$); and in the colonoscopy trial, 66 of 988 patients (6.7%) randomised to colonoscopy compared with 26 of 503 (5.2%) randomised to CTC ($p = 0.25$).

TABLE 27 Extracolonic cancer diagnosed within 3 years of randomisation, by ICD-10 code. Patients could have more than one cancer diagnosed. Only newly diagnosed primary cancers are included and patients with CRC are excluded

	BE								CTC							
	N = 2427		Months to diagnosis				Cancer death	Found at CTC	*N* = 1226		Months to diagnosis				Cancer death	Found at CTC
BE trial (patients with missed CRC also excluded)	*n*	%	0–6	6–12	12–24	24–36			*n*	%	0–6	6–12	12–24	24–36		
C17 Malignant neoplasm of the small intestine	3	0.1	2	0	1	0	2		1	0.1	1	0	0	0	0	1
C25 Malignant neoplasm of the pancreas	8	0.3	5	1	1	1	6	1	5	0.4	3	0	2	0	4	2
C56 Malignant neoplasm of the ovary	4	0.2	4	0	0	0	3	1	2	0.2	1	1	0	0	2	1
C61 Malignant neoplasm of the prostate	16	0.7	4	5	5	2	2		7	0.6	3	1	2	1	0	2
C64 Malignant neoplasm of the kidney, except the renal pelvis	3	0.1	2	0	0	1	1	1	5	0.4	2	0	2	1	2	4
C65 Malignant neoplasm of the renal pelvis	0	0.0	0	0	0	0	0		0	0.0	0	0	0	0	0	
Total	34	1.4	17	6	7	4	14	3	20	1.6	10	2	6	2	8	10
	Colonoscopy								CTC							
	N = 983		Months to diagnosis				Cancer death	Found at CTC	*N* = 501		Months to diagnosis				Cancer death	Found at CTC
Colonoscopy trial	*n*	%	0–6	6–12	12–24	24–36			*n*	%	0–6	6–12	12–24	24–36		
C17 Malignant neoplasm of the small intestine	0	0.0	0	0	0	0	0		1	0.2	0	1	0	0	0	
C25 Malignant neoplasm of the pancreas	8	0.8	4	2	1	1	6		2	0.4	1	0	0	1	2	1
C56 Malignant neoplasm of the ovary	1	0.1	1	0	0	0	1	1	0	0.0	0	0	0	0	0	
C61 Malignant neoplasm of the prostate	7	0.7	2	1	2	2	0		2	0.4	0	0	2	0	0	
C64 Malignant neoplasm of the kidney, except the renal pelvis	1	0.1	0	0	0	1	0		3	0.6	3	0	0	0	0	3
C65 Malignant neoplasm of the renal pelvis	0	0.0	0	0	0	0	0		1	0.2	1	0	0	0	1	1
Total	17	1.7	8	3	3	4	7	1	9	1.8	5	1	2	1	3	5

Chapter 5 Health psychology assessment

This chapter contains information reproduced from Von Wagner C, Ghanouni A, Halligan S, Smith S, Dadswell E, Lilford RJ, *et al.* Patient acceptability and psychologic consequences of CTC compared with those of colonoscopy: Results from a multicenter randomized controlled trial of symptomatic patients. *Radiology* 2012;**263**:723–31[45] with permission from the Radiological Society of North America; and information reproduced with kind permission from Springer Science + Business Media: *European Radiology*, Patient acceptability of CTC compared with double contrast barium enema: results from a multicentre randomised controlled trial of symptomatic patients, vol. 21, 2011, 2046–55, von Wagner C, Smith S, Halligan S, Ghanouni A, Power E, Lilford RJ, *et al.*[46] © European Society of Radiology 2011. The final publication is available on http://link.springer.com.

Introduction

If any test is to become widely adopted for the diagnosis of CRC, its acceptability to patients is an important consideration. Existing research suggests that CTC may be more acceptable than BE in both symptomatic[18,47] and asymptomatic patients,[48] and that it is possibly more acceptable than colonoscopy.[20,49] However, most evidence is based on intraindividual comparisons in which patients experience both CTC and another test. Acceptability judgements are, therefore, relative rather than absolute, which could exaggerate differences in patient experience. To date, studies comparing acceptability of each of the procedures alone have been small and typically non-randomised, and have compared very different samples.[18] In comparing CTC and colonoscopy, there are additional complications because any lesions detected at colonoscopy can be biopsied or removed at the same examination, whereas for CTC (like BE) an additional endoscopic procedure is required. Patients may view these additional referrals negatively. Prospective preference studies have investigated attitudes towards hypothetical referral rates,[50] but there is no available evidence on patients' retrospective appraisals of follow-up investigations. Researchers have also highlighted important differences regarding result delivery: face to face at the time of the procedure (which is typical for colonoscopy) is perceived by patients to be superior to communication later (as is usually the case for BE or CTC).[51] This has not been assessed quantitatively. Finally, little is known about whether or not intertest differences are associated with longer-term psychological outcomes.

To address these limitations, we aimed to determine the acceptability of BE, colonoscopy and CTC by carrying out a post-examination survey of reported experiences for a sample of patients in the SIGGAR study. This enabled differences in test acceptability, post-test complications and both short- and longer-term experiences to be assessed in a sizeable population for whom the impact of clinician preference on outcomes had been reduced by randomisation. Moreover, as patients in the study follow normal clinical pathways after the primary randomised procedure (i.e. receive usual care), the results are more likely to reflect experience in everyday practice than designs in which all patients undergo CTC and another test.

Methods

The psychological evaluation took place during the last 12 months of recruitment to the SIGGAR study, after a series of qualitative interviews – used to design the questionnaires – had been conducted and analysed.[51] Questionnaire administration began at 18 hospitals on 1 December 2006 and at a further three hospitals on 12 February 2007.

Questionnaires

Copies of the psychological questionnaires can be seen in *Appendix 3*.

Post-test questionnaire

The post-test questionnaire was either given directly to patients by a research nurse or sent by post, according to centre preference. Patients were asked to complete the questionnaire at home on the morning after their test and to return it in a prepaid envelope. A reminder was sent by post if the patient had not responded within 14 days of the randomised procedure.

Patients were asked to rate the acceptability of the bowel preparation ('how acceptable did you find the bowel preparation?') using a four-item scale ranging from 'not at all acceptable' (score 1) to 'very acceptable' (score 4). The questionnaire also asked patients to identify the least acceptable part of their investigation: 'bowel preparation', 'bowel test', or 'other – please specify'. Acceptability of the randomised procedure was assessed using an adapted version of a previously validated scale to assess satisfaction with colonoscopy.[52] There were 29 items, each rated on a 7-point scale anchored at the end point (e.g. 'felt out of control' to 'felt in control'). Several items were added to make the scale more relevant for participants having a BE or CTC (see bold items in *Table 28*). In accordance with previous research,[18] we divided the scale into three subcomponents – satisfaction, worry and physical discomfort – each of which met the standard threshold for adequate internal reliability (Cronbach's alpha = 0.84, 0.72 and 0.87, respectively, for patients in the BE trial, and 0.85, 0.72 and 0.85, respectively, for patients in the colonoscopy trial). Higher scores reflected greater degrees of the construct being measured by each subscale. The questionnaire also assessed patients' experience in the 24 hours following the test with respect to the following eight complaints: 'abdominal pain/cramps', 'nausea/vomiting', 'faint feeling or dizziness', 'wind', 'bottom soreness', 'soiling', 'sleep difficulties' and 'anxiety'. Four response options ranged from 'none' to 'severe'.

TABLE 28 Patient experience questionnaire by subscale

Satisfaction	
Dissatisfied	***Satisfied***
Staff were not interested in me	Staff were interested in me
I was not pleased with how it went	I was pleased with how it went
Staff were cold	Staff were warm
Staff were not informative	Staff were informative
Undignified	Dignified
I was not interested	I was interested
Not confident in staff	Confident in staff
Not enough privacy	**Enough privacy**
Loss of modesty	**No loss of modesty**

TABLE 28 Patient experience questionnaire by subscale (*continued*)

Worry	
Worried	***Not worried***
Agitated	Calm
I was worried about what they would find	Not worried about what they would find
Did not understand what was happening	Understood what was happening
I felt puzzled	I did not feel puzzled
I was confused	I was not confused
Discomfort	
Painful	***Not painful***
I'd have preferred to been less awake	I'd have preferred to be more awake
Uncomfortable	Comfortable
A bad experience	A good experience
Felt out of control	Felt in control
Soreness	No soreness
Afraid of making a fool of myself	Not afraid of making a fool of myself
Bloated afterwards	**Not bloated afterwards**
Intrusive	**Not intrusive**
Hard to cope with	**Easy to cope with**
Tired afterwards	**Not tired afterwards**
Claustrophobic	**Not claustrophobic**

Items in bold were added to make scale more relevant for patients undergoing CTC or BE.

Follow-up questionnaire

A further questionnaire was sent to patients by post, 3 months after the randomised procedure, excluding any patients who had died or received a diagnosis of cancer. Reminders were posted to all patients who did not respond within 14 days.

Follow-up questionnaires asked patients to indicate when they had received their test results (10 options ranging from 'during the test' to 'I have not had the results yet'), how results had been relayed ('face to face', 'on the phone', 'in a letter', 'can't remember') and from whom ('the hospital', 'my GP', 'can't remember'). Patients were asked to rate satisfaction with the way results had been explained (using a 4-point scale from 'very satisfied' to 'very dissatisfied'). Patients indicating that they had been referred for a follow-up colonic examination were asked 'did you mind having the follow-up test?' (using a 4-point scale ranging from 'not at all' to 'very much'). Details of follow-up tests were obtained from the main trial data set and referrals precipitated by extracolonic findings were excluded.

Positive psychological consequences of the diagnostic episode were assessed using a six-item adapted version of the Psychological Consequences of Screening Questionnaire positive emotional subscale.[53] Items were measured on a 4-point scale with higher scores indicating superior outcomes. One item regarding anxiety reduction related to bowel cancer included an option of 'did not feel anxious'. Negative affect was assessed using 10 items from the Positive and Negative Affect Schedule,[54] rated on a 5-point scale ranging from 'very slightly or not at all' to 'extremely'.

Statistical analysis

Basic patient information (randomised procedure, age, sex, post code) was obtained from data recorded in the main trial data set. Each patient's post code was used to derive a marker of area-based socioeconomic deprivation,[55] the Index of Multiple Deprivation (IMD). The IMD uses census-derived indicators of income, education, employment, environment, health and housing at a small-area level to generate a scale from 0 (least deprived) to 80 (most deprived). We grouped IMD scores into tertiles of lower, medium and higher levels of deprivation.

Full data were available for patient age, sex, post code and procedures. Missing values in the patient acceptability scales were imputed for individuals who had completed at least 50% of the scale using the expectation maximisation method.[56] This uses regression analyses to estimate missing values based on individuals with complete data and other significant variables (chosen by the researcher).

Initial analysis revealed that responses were skewed towards the upper end of the distribution (indicating high levels of acceptability), therefore non-parametric methods were used to test for differences between groups and for any influence of patient characteristics, including age (< 70 years vs. ≥ 70 years), sex and level of patient-reported acceptability of bowel preparation (acceptable vs. unacceptable). The Mann–Whitney *U*-test was used to compare two groups and the Kruskal–Wallis test was used to examine differences between three or more groups (i.e. deprivation tertiles). Post-test complications were reported using frequency statistics and analysed using Pearson's chi-squared test.

Results

Post-test questionnaire

During the period in which the questionnaires were administered, a total of 1018 patients were randomised in the BE trial (675 BE and 343 CTC) (*Figure 7*). Ninety-seven patients were excluded because they did not undergo the randomised procedure ($n = 84$) or because they had withdrawn consent ($n = 13$). The final sample therefore comprised 921 patients (606 BE, 315 CTC), of whom 674 responded to the questionnaire (61% female, median age 68 years), giving a response rate of 73% (450 randomised to BE and 224 to CTC).

In the same period, 595 patients were randomised in the colonoscopy trial (397 colonoscopy and 198 CTC). Forty-eight were excluded because they did not undergo the randomised procedure ($n = 33$), withdrew consent ($n = 13$) or died before the procedure ($n = 2$). Therefore, the final sample comprised 547 patients (362 colonoscopy and 185 CTC), of whom 388 responded to the questionnaire (55% female, median age 67 years), giving a response rate of 71% (258 randomised to colonoscopy and 130 to CTC).

In both trials, patients were more likely to return the post-test questionnaire if they were from a less socioeconomically deprived area (BE trial, IMD median score = 13.9 for responders vs. 16.6 for non-responders, $p = 0.004$; colonoscopy trial, IMD median score = 17.5 for responders vs. 21.0 for non-responders, $p = 0.002$). Response status was unaffected by age, sex or randomised procedure. Patients who failed to complete at least 50% of the satisfaction, worry and discomfort scales were excluded from imputation (16 in the BE trial and nine in the colonoscopy trial).

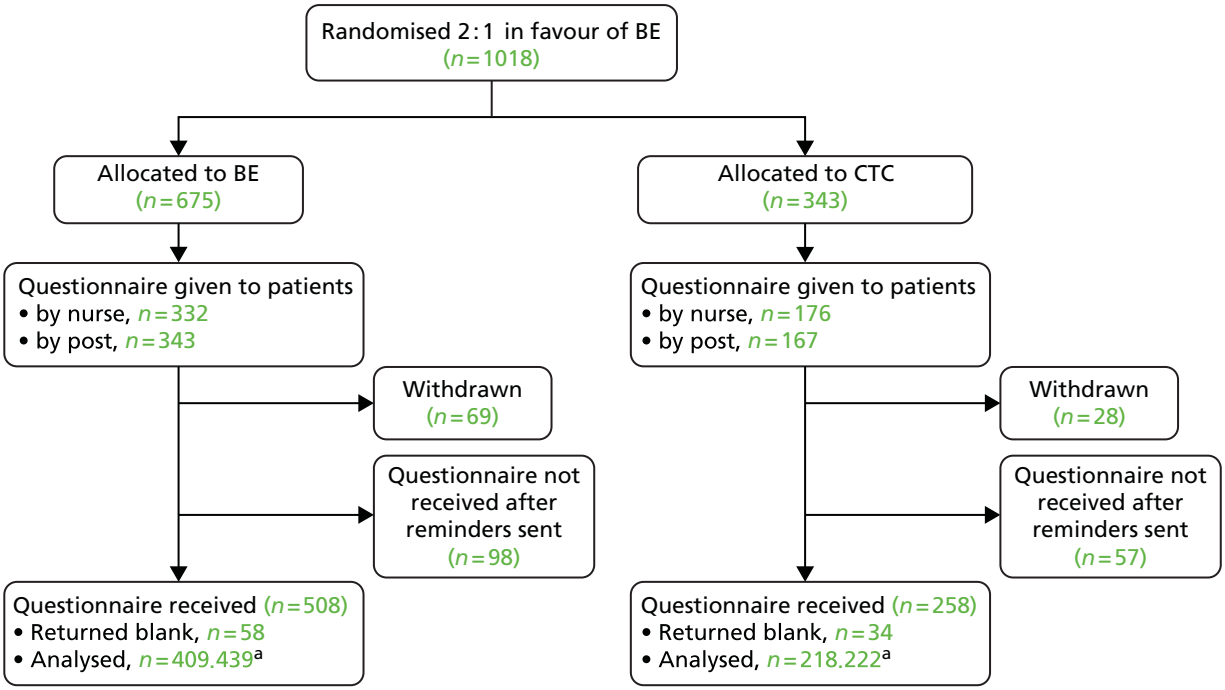

FIGURE 7 A Consolidated Standards of Reporting Trials (CONSORT) diagram of participant flow through the BE vs. CTC trial. a, Total number analysed varied by measure.

Acceptability of bowel preparation

In both trials, the median score for tolerability of bowel preparation was 3, indicating a response of 'fairly acceptable'. A substantial proportion of patients rated bowel preparation as either 'not at all acceptable' or only 'slightly acceptable' (BE trial, 23% of patients having a BE and 17% of patients having CTC; colonoscopy trial, 23% of patients having colonoscopy and 18% having CTC).

Patient satisfaction, worry and discomfort

Individuals having a BE were slightly less satisfied than those having CTC (median 61, IQR 54–67 vs. median 64, IQR 56–69, respectively; $p = 0.003$). Two individual items on this scale reached significance – 'dignity' and 'modesty' – with patients having a BE responding less favourably than those having CTC (*Table 29*). Similarly, individuals having colonoscopy were slightly less satisfied than those having CTC (median 61, IQR 55–67, vs. median 64, IQR 58–70; $p = 0.008$). The two individual items that reached significance were 'staff were interested in me' and 'confident in staff', with patients having colonoscopy responding less favourably (*Table 30*).

There were no significant differences between BE and CTC with regard to reported worry overall (median 15, IQR 10–20, vs. median 15, IQR 9.75–19, respectively; $p = 0.617$); nor were there significant differences between BE and CTC on any of the individual items (see *Table 29*). There were, however, significant differences in reported worry between colonoscopy and CTC (median 16, IQR 12–21 vs. median 15, IQR 9–19; $p = 0.007$). The two individual items that reached significance were 'worried' and 'worried about what they would find', with patients having colonoscopy responding less favourably (see *Table 30*).

TABLE 29 Scores on the patient experience scale by randomised procedure in the BE vs. CTC trial. A 7-point score was used with higher scores reflecting greater degrees of the construct being tested

	BE ($n = 436$)		CTC ($n = 222$)		
Item	Median	IQR	Median	IQR	*p*-value
Satisfaction scale					
Satisfied	7	5–7	7	5–7	0.131
Staff were interested in me	7	6–7	7	7–7	0.279
I was pleased with how it went	7	6–7	7	6–7	0.087
Staff were warm	7	6–7	7	7–7	0.290
Staff were informative	7	6–7	7	6–7	0.343
Dignified	4	2–6	5	3–7	0.000
I was interested	7	6–7	7	6–7	0.111
Confident in staff	7	7–7	7	7–7	0.629
No loss of modesty	5	3–7	6	4–7	0.001
Enough privacy	7	6–7	7	6–7	0.692
Worry scale					
Worried	3	1–5	4	1–5	0.984
Agitated	2	1–4	2	1–4	0.127
I was worried about what they would find	4	3–6	4	2–7	0.850
Did not understand what was happening	1	1–2	1	1–2	0.749
I felt puzzled	1	1–2	1	1–2	0.494
I was confused	1	1–2	1	1–2	0.567
Physical discomfort scale					
Painful	3	1–4	2	1–4	0.005
I would have preferred to be less awake	4	2–4	4	2–4	0.739
Uncomfortable	4	3–6	4	2–5	0.003
A bad experience	4	2–4	3	1–4	0.000
Felt out of control	4	1–4	3	1–4	0.071
Soreness	2	1–4	1	1–4	0.000
Afraid of ‘making a fool of myself’	2	1–4	2	1–4	0.012
Claustrophobic	1	1–2	1	1–2	0.206
Bloated afterwards	5	3–7	4	2–7	0.031
Intrusive	3	1–5	3	1–4	0.004
Hard to cope with	2	1–4	2	1–3	0.000
Difficult to do what was required	2	1–3	1	1–2	0.000
Tired afterwards	3	1–5	2	1–5	0.135

TABLE 30 Scores on the patient experience scale by randomised procedure in the colonoscopy vs. CTC trial. A 7-point score was used with higher scores reflecting greater degrees of the construct being tested

	Colonoscopy ($n = 251$)		CTC ($n = 128$)		
Item	Median	IQR	Median	IQR	*p*-value
Satisfaction scale					
Satisfied	7	5–7	7	6–7	0.122
Staff were interested in me	**7**	**6–7**	**7**	**7–7**	**0.038**
I was pleased with how it went	7	6–7	7	6–7	0.123
Staff were warm	7	6–7	7	7–7	0.076
Staff were informative	7	6–7	7	6–7	0.335
Dignified	4	3–7	5	4–7	0.157
I was interested	7	6–7	7	6–7	0.263
Confident in staff	**7**	**6–7**	**7**	**7–7**	**0.019**
No loss of modesty	6	4–7	6	4–7	0.224
Enough privacy	7	6–7	7	6–7	0.066
Worry scale					
Worried	**4**	**2–6**	**3**	**1–5**	**0.017**
Agitated	2	1–4	2	1–4	0.579
I was worried about what they would find	**5**	**4–7**	**4**	**2–6**	**< 0.0005**
Did not understand what was happening	1	1–2	1	1–2	0.727
I felt puzzled	1	1–2	1	1–2	0.610
I was confused	1	1–2	1	1–2	0.160
Physical discomfort scale					
Painful	**2**	**1–5**	**2**	**1–4**	**0.010**
I would have preferred to have been less awake	**4**	**4–6**	**4**	**2–4**	**< 0.0005**
Uncomfortable	4	2–6	4	2–5	0.931
A bad experience	**4**	**2–4**	**3**	**1–4**	**0.003**
Felt out of control	4	1–5	3	1–4	0.175
Soreness	2	1–4	2	1–4	0.149
Afraid of making a fool of myself	2	1–4	2	1–4	0.235
Claustrophobic	1	1–2	1	1–1	0.609
Bloated afterwards	3	1–5	4	2–5	0.318
Intrusive	3	1–4	2	1–4	0.241
Hard to cope with	**2**	**1–4**	**2**	**1–3**	**0.001**
Hard to do what was required	1	1–3	1	1–2	0.103
Tired afterwards	**3**	**1–6**	**2**	**1–5**	**0.003**

Items in bold are significant.

Overall, physical discomfort was rated as significantly worse by patients having a BE than by those undergoing CTC (median 40, IQR 29–52 vs. median 35.5, IQR 25–47, respectively; $p < 0.001$). Significant differences were observed for nine individual items on the discomfort subscale – 'painful', 'uncomfortable', 'a bad experience', 'soreness', 'afraid of "making a fool of myself" ', 'bloated afterwards', 'intrusive', 'hard to cope with' and 'difficult to do what was required' – with patients having a BE responding less favourably (see *Table 29*). Physical discomfort was also rated as significantly worse by patients having colonoscopy than by those undergoing CTC (median 39, IQR 29–51, vs. median 35, IQR 24–44; $p = 0.001$). The five individual items for which significant differences were observed for were 'painful', 'would have preferred to be less awake', 'a bad experience', 'hard to cope with' and 'tired afterwards', with patients having colonoscopy responding less favourably (see *Table 30*).

Regarding patient demographics, only age was associated with differences in patient experience in the BE trial; there was no effect of sex or IMD. Specifically, among participants randomised to CTC, older patients reported less physical discomfort and worry than younger patients. No such differences were found for patients randomised to BE (*Table 31*). In the colonoscopy trial, only sex was associated with differences in patient experience. Among participants randomised to colonoscopy, women reported less satisfaction, more worry and more physical discomfort. No such differences were found for patients randomised to CTC (*Table 32*).

TABLE 31 Patient demographics and experience of the randomised procedure in the BE vs. CTC trial

	BE ($n = 436$)			CTC ($n = 222$)		
	Satisfaction score (median, IQR)	Worry score (median, IQR)	Discomfort score (median, IQR)	Satisfaction score (median, IQR)	Worry score (median, IQR)	Discomfort score (median, IQR)
Age (years)						
< 70	60, 54–66	15, 10.5–20	41, 31–53.5	63, 55–68	16, 11–20	37, 27–50
≥ 70	62, 55–68	15, 10–21	38, 28–52	65, 57–70	13, 8–18	33, 23–45
p-value	0.057	0.889	0.130	0.138	0.017	0.009
Sex						
Male	62, 54–66	14, 10–20	38.5, 29–49.3	63, 55.8–69	14, 9–19	32.5, 22–45
Female	61, 54–67	15, 10–21	41, 29–56	64, 57.3–69	16, 10–19	37, 26–48
p-value	0.859	0.491	0.104	0.343	0.544	0.066
IMD						
Low	61, 54–67	15, 10.5–20	41, 29.5–54	63, 56–68	14.5, 9–19	35.5, 25.3–47
Mid	60.5, 54–66	15, 10–20.3	40, 30–52.3	64, 58.3–68	15, 10–19.8	37, 26–48.8
High	63, 57–67.5	15, 10–21	39, 28–51.5	65, 55.8–70	17, 9–19	33.5, 22–44.5
p-value	0.254	0.841	0.883	0.518	0.825	0.194

TABLE 32 Patient demographics and experience of the randomised procedure in the colonoscopy vs. CTC trial

	Colonoscopy ($n = 251$)			CTC ($n = 128$)		
	Satisfaction (median, IQR)	Worry (median, IQR)	Discomfort (median, IQR)	Satisfaction (median, IQR)	Worry (median, IQR)	Discomfort (median, IQR)
Age (years)						
< 70	61, 54–67	17, 12–21	41, 30–53	63, 58–70	16, 11–19	36, 24–45
≥ 70	63, 58–69	15, 12–20	39, 25–48	67, 59–70	11, 9–20	33, 23–44
p-value	0.256	0.224	0.059	0.253	0.324	0.595
Sex						
Male	63, 58–69	14, 11–19	36, 25–45	64, 59–70	12, 9–18	34, 24–41
Female	61, 53–66	18, 13–22	44, 33–57	65, 57–70	16, 9–20	36, 24–48
p-value	**0.008**	**0.001**	**< 0.0005**	0.606	0.232	0.350
IMD						
Low	61, 54–67	15, 11–20	40, 30–51	65, 58–70	12, 8–18	33, 23–43
Mid	62, 56–68	17, 13–21	38, 28–48	65, 56–69	16, 11–21	36, 26–47
High	61, 53–68	17, 12–21	44, 30–58	63, 59–70	15, 11–20	37, 24–44
p-value	0.651	0.505	0.300	0.747	0.212	0.643

Note
p-values in bold are significant.

Post-test complications

In the BE trial, patients in both groups reported post-test complaints: 'wind' {92% for BE vs. 84% for CTC; chi-squared [1 degree of freedom (df), $n = 647$ patients included] = 11.15; $p = 0.001$}, 'abdominal pain/cramps' [68% vs. 57%; chi-squared (1 df, $n = 645$ patients included) = 7.61; $p = 0.007$], 'bottom soreness' [57% vs. 37%; chi-squared (1 df, $n = 646$ patients included) = 21.81; $p < 0.001$], 'nausea/vomiting' [16% vs. 8%; chi-squared (1 df, $n = 636$ patients included) = 6.72; $p = 0.009$), and 'soiling' [31% vs. 23%; chi-squared (1 df, $n = 639$ patients included) = 4.67; $p = 0.034$] were all significantly more common for BE than CTC (*Table 33*). The severity of post-procedural wind was greatest for BE [27% reporting 'severe' as opposed to 15% for CTC; chi-squared (1 df, $n = 647$ patients included) = 11.47; $p = 0.001$]. No other symptoms differed significantly between the groups. In the colonoscopy trial, only one symptom differed significantly: 'faint feeling or dizziness' was significantly more common after colonoscopy than after CTC (82/246 vs. 28/122; $p = 0.039$). Rates of other post-test complaints are shown in *Table 34*.

Least acceptable aspects of the patient experience

The majority of respondents stated that bowel preparation was the least acceptable aspect of the experience (BE trial, 69% for BE and 74% for CTC; colonoscopy trial, 66% for colonoscopy and 78% for CTC). A smaller proportion rated the test itself as the least acceptable aspect (BE trial, 24% for BE and 14% for CTC; colonoscopy trial, 25% for colonoscopy and 14% for CTC). The remaining patients cited other aspects such as the waiting time after arriving for their appointment.

TABLE 33 Post-test problems by randomised procedure in the BE vs. CTC trial

Symptom	Test	None (%)	Mild (%)	Moderate (%)	Severe (%)
Abdominal pain/cramps	BE	31.8	26.6	29.3	13.2
	CTC	42.7	29.5	18.6	9.1
Nausea/vomiting	BE	84.4	8.9	4.8	1.9
	CTC	91.7	6.4	1.8	0.0
Faint feeling or dizziness	BE	76.3	16.1	7.1	0.5
	CTC	73.9	18.8	6.9	0.5
Wind	BE	7.7	22.8	42.3	27.2
	CTC	16.3	37.6	30.8	15.4
Bottom soreness	BE	43.5	28.2	21.9	6.4
	CTC	62.9	24.0	9.5	3.6
Soiling	BE	68.6	15.2	12.1	4.0
	CTC	76.7	16.4	4.6	2.3
Sleep difficulties	BE	72.4	14.0	11.7	1.9
	CTC	78.2	12.6	6.0	3.2
Anxiety	BE	61.8	21.8	13.5	2.8
	CTC	67.7	18.6	10.0	3.6

TABLE 34 Post-test problems by randomised procedure in the colonoscopy vs. CTC trial

Symptom	Test	*n*	None (%)	Mild (%)	Moderate (%)	Severe (%)	Any severity (%)	*p*-value[a]
Abdominal pain/cramps	Colonoscopy	246	48	36	13	4	53	0.507
	CTC	121	51	26	18	5	49	
Nausea/ vomiting	Colonoscopy	241	85	7	7	1	15	0.072
	CTC	121	92	5	3	1	8	
Faint feeling or dizziness	Colonoscopy	246	67	24	7	2	33	**0.032**
	CTC	122	78	16	6	1	22	
Wind	Colonoscopy	248	20	34	35	12	80	0.562
	CTC	123	23	34	32	11	77	
Bottom soreness	Colonoscopy	243	58	27	12	2	42	0.609
	CTC	124	56	21	19	5	44	
Soiling	Colonoscopy	240	81	13	5	2	19	0.629
	CTC	122	79	16	5	0	21	
Sleep difficulties	Colonoscopy	236	75	13	11	1	25	0.224
	CTC	122	80	11	5	4	20	
Anxiety	Colonoscopy	241	72	18	8	3	28	0.520
	CTC	124	69	27	4	1	32	

a Any severity vs. none.
p-values in bold are significant.

Follow-up questionnaire

Follow-up questionnaires were analysed only for patients in the colonoscopy trial, to look for any longer-term differences in experience between patients having radiological or endoscopic procedures.

A total of 337 patients responded to the follow-up questionnaire (59% female, median age 67 years), which was a response rate of 62% (230 colonoscopy, 107 CTC). As with the post-test questionnaires, patients were significantly more likely to respond if they were from less socioeconomically deprived areas (IMD median score = 17.2 for responders vs. 20.5 for non-responders; $p = 0.015$). Women were also significantly more likely to respond to the follow-up questionnaire than men ($p = 0.003$). Response was unaffected by age or procedure.

Receiving results

Patients having colonoscopy were significantly more likely to receive their results on the same day than at a later time (65% vs. 17% for CTC; $p < 0.0005$). Colonoscopy patients were also more likely to receive results via a face-to-face conversation than by telephone or post (85% vs. 50%; $p < 0.0005$) and more likely to receive them from the hospital than from their GP (94% vs. 80%; $p = 0.001$). Patients having colonoscopy were significantly more satisfied with the way results were conveyed than were those having CTC (median 4, IQR 3–4, vs. median 3, IQR 3–3; $p < 0.0005$).

Referral for follow-up investigations

Significantly more responders to the follow-up questionnaire had additional colonic tests following CTC than colonoscopy [33% (37/107) vs. 7% (17/230); $p < 0.0005$]. Among patients referred for colonic follow-up testing and responding to the appropriate question, two out of eight (25%) in the colonoscopy group reported that they did mind being referred, compared with 9 out of 23 responding patients (39%) referred following CTC. No statistical analysis was attempted because of the small sample size.

Psychological outcomes

At 3 months, there was no significant difference between CTC and colonoscopy in positive psychological consequences of the diagnostic episode (*p*-values ranged from 0.153 to 0.844 for all six items) (*Table 35*). A trend was observed towards higher levels of negative affect for patients having colonoscopy than those having CTC (median 12, IQR 10–17, for colonoscopy vs. median 11, IQR 10–15, for CTC). However, this did not reach significance ($p = 0.050$).

TABLE 35 Scores on the psychological consequences of diagnostic episode scale by randomised procedure in the colonoscopy vs. CTC trial

	Colonoscopy ($n = 224$)		CTC ($n = 102$)		
Item (scored 1–4)	Median	IQR	Median	IQR	*p*-value
Given me a sense of reassurance that I do not have bowel cancer	4	3–4	4	3–4	0.486
Made me feel more able to do the things that I normally do	3	1–3	3	1–4	0.326
Made me more hopeful about the future	3	2–4	3	2–4	0.653
Made me get on better with those around me	2	1–3	3	1–3	0.153
Given me a greater sense of well-being	3	2–4	3	2–4	0.844
Made me feel less anxious about bowel cancer[a]	3	3–4	3	3–4	0.676

a Among patients who reported feeling some degree of anxiety.

Chapter 6 Health economic assessment

Introduction

The SIGGAR study aimed to provide a detailed comparison of CTC with BE and with colonoscopy for diagnosis of CRC or large polyps in symptomatic patients. To provide a complete picture of the relative advantages of the three procedures, and to assess the feasibility of more widespread implementation of CTC within the NHS, an economic analysis is an important part of the study.

The advantage of the SIGGAR randomised trial design, over most previous studies in which patients receive both CTC and colonoscopy, is that it provides extensive data on referral rates for additional tests after BE, colonoscopy or CTC in normal clinical practice and on the nature of the follow-up tests undertaken. This allows us to calculate the cost of each procedure, taking account of the full series of tests it will typically give rise to.

This chapter is divided into two parts. In part 1, previous economic studies of diagnostic and screening tests are reviewed systematically. In part 2, we model costs and effects based on trial data that cover a minimum follow-up period of 3 years and a median follow-up duration of 5.2 years. In this section, we first model costs from resource-use data and then combine this with detection rates to calculate incremental costs per case detected for large polyps or cancer and for colon cancer alone. In subsequent work, we have modelled the consequences of polyp and colon cancer detection over the remaining lifespan to calculate incremental cost–utility ratios (submitted for publication).

Part 1: literature review on economic studies of computed tomographic colonography

Screening and diagnosis

Several systematic reviews of economic studies relating to methods for detecting CRC have been published in recent years. The majority of the literature has focused on screening rather than diagnosis in symptomatic patients. The results of economic evaluations of screening programmes cannot be translated directly into cost-effectiveness measures of the same procedures when used for diagnosis in symptomatic patients. First, the prevalence of CRC and large polyps is likely to differ between the two settings. Second, cancers identified in screening populations are likely to be systematically different (e.g. growing less rapidly) to those identified in a symptomatic setting. These factors will influence predictive values and may also influence sensitivity and specificity. Furthermore, compliance is likely to be lower in a screening programme than in a symptomatic setting. Consequently, the relative cost-effectiveness of competing detection methods in a screening setting does not necessarily reflect their relative cost-effectiveness when used as diagnostic tests in symptomatic patients. Although this limits the relevance of much of the available literature related to screening for CRC, it is not entirely inapplicable to our study. The screening literature provides information on costs and outcomes of various clinical pathways downstream of the detection of colonic lesions. Therefore, our review included both screening and symptomatic diagnosis of CRC.

Cost-effectiveness: literature

We carried out a systematic review using the following search strategy:

Economic evaluations were identified by searching PubMed for economic evaluations of CRC diagnosis or screening, in which CTC was compared with colonoscopy. The search included the keywords 'colorectal cancer', 'diagnosis', 'screening', 'CT-colonography', 'computerized tomography colonography', 'virtual colonoscopy', 'colonoscopy' and 'cost-effectiveness', 'cost-utility', 'cost benefit', 'life years', 'quality life year'. The search was restricted to articles published between July 1999 and July 2013, and in the English language.

This revealed a recent systematic review of 16 studies dealing with screening tests for colon cancer.[57] We proceeded as follows:

1. We extracted data dealing specifically with CTC compared with colonoscopy from the above systematic review. Fourteen papers satisfied this criterion.[58–71]
2. We updated the above systematic review of screening tests finding one more paper dealing with CTC compared with colonoscopy;[72] therefore, we analysed 15 papers on this topic.
3. We also repeated the search to include papers comparing CTC with colonoscopy in symptomatic diagnostic studies, finding one such paper.[73]

Cost-effectiveness: findings

The systematic review of screening tests included 14 studies comparing CTC with colonoscopy. Twelve of these 14 studies were based on Markov models[58–61,63,65–71] and two on microsimulations.[62,64] Eleven studies[58–63,66–68,70,71] provided outcomes in terms of life-years saved, while two[64,69] derived quality-adjusted life-years (QALYs) and one[65] reported both life-years and QALYs. In six studies,[61–64,69,70] colonoscopy dominated CTC. In the only study that concluded CTC dominated colonoscopy, the effects of CTC in detecting extracolonic lesions were considered.[59] The incremental cost-effectiveness ratios (ICERs) among the remaining seven studies[58,60,65–68,71] varied from US$2144 to US$498,668, with a tendency for more recent studies to yield more favourable ratios. The results were sensitive to a number of assumptions, including relative unit costs of the two tests and differences in screening uptake rates by test. They were somewhat insensitive to performance characteristics (sensitivity and specificity) within the plausible range. However, they were highly influenced by whether or not extracolonic lesions were included in the model – a point to which we will return. Lee *et al.*[71] reported that colonoscopy appeared marginally more effective than CTC but was more expensive in the UK setting, with an ICER of £34,002 per QALY (this was one of the many papers that did not consider extracolonic lesions). Knudsen *et al.*[62] used microsimulation models (MISCAN, SimCRC and CRC-SPIN) to project the natural history of polyp growth and cancer development. They concluded that CTC was dominated by colonoscopy. The additional paper by Vanness *et al.*[72] adopted the above simulation models but populated them with data from the ACRIN national CTC trial to compare three screening options: CTC, colonoscopy and flexible sigmoidoscopy plus faecal occult blood test or faecal immunochemical testing.[71] They reported that CTC is more costly and less effective than colonoscopy and was thus dominated by it.

As stated above, results were strongly influenced by the relative unit costs of CTC and colonoscopy. This may explain much of the difference in findings across the various studies. For example, the study by Lee *et al.*[71] was one to find that CTC was cost-effective in comparison with colonoscopy (albeit marginally so), and in this study CTC was also considerably less expensive (£128) than colonoscopy (£488). By contrast, Knudsen *et al.*[62] reported results in favour of colonoscopy despite similar assumptions regarding effectiveness and here the unit costs of the tests were reversed.

Extracolonic lesions

One of the important features of CTC is that it can detect lesions outside the colon. Hassan *et al.*[59] investigated the potential benefits of incidental detection of aortic aneurysms and extracolonic cancers, finding that CTC was dominant over colonoscopy[59] when these were included in the model.

Only one study compared the use of CTC with colonoscopy in symptomatic patients (i.e. for diagnostic purposes).[73] This study adopted the Markov screening model produced by the School of Health and Related Research at the University of Sheffield, UK,[74] and assumes that CTC and colonoscopy provide comparable accuracy for diagnosis of clinically significant polyps and CRC. They found that CTC (compared with colonoscopy) was a marginally cost-effective option for primary colonic imaging of symptomatic patients (ICER of £23,000).

Another study[26] investigated resource use and costs associated specifically with incidental extracolonic findings from CTC, based on a retrospective cohort study. The authors found that resources consumed as a result of extracolonic findings in symptomatic patients approximately doubled the costs of CTC. The authors modelled the potential payback from detection of extracolonic lesions and we will return to this model later.

Conclusion

Previous cost-effectiveness studies of CTC have focused on screening for CRC rather than symptomatic diagnosis. The results of cost-effectiveness analyses favour colonoscopy over CTC, but there is very wide variance in the results. To a substantial extent, this reflects difference in the unit costs of each test – a surprisingly variable quantity. More problematic still, most studies ignored the potential benefits or harms of detecting extracolonic findings at CTC (a point discussed more fully in *Part 2: health economic analysis within the trial*). Finally, we found no studies comparing the cost-effectiveness of CTC with BE, perhaps because the latter test is becoming obsolete in high-income countries.

Our economic analysis is designed to evaluate costs and cost-effectiveness of CTC compared with BE and of CTC compared with colonoscopy, for diagnosis of CRC and large polyps (≥ 10 mm) in older symptomatic patients.

Part 2: health economic analysis within the trial

Introduction

In this section, we analyse the economic data over the trial follow-up period (median 5.2 years). We calculate costs contingent on following the diagnostic pathways compared in the two trials. However, few patients would be expected to die from cancer over the follow-up period. Therefore, in this section, our analysis is based on cost per case detected. We analyse cost per case of cancer or a large polyp and also the cost per case of cancer alone.

Methods

Perspective and time horizons

The economic analysis was conducted in the context of NHS secondary care (i.e. only costs relevant to secondary care were included). The time horizon was set at 5.2 years, which is the median follow-up for patients in the trial.

Trial data used in the analysis

The outcome measures were based on primary clinical end points observed in the trials. We collected data on detection rates of cancer and large polyps and the proportion of patients referred for further investigation or treatment. The number and nature of extracolonic findings were recorded for patients undergoing CTC.

Estimating the costs

Resources considered

Resource usage included the initial assigned procedures (BE, colonoscopy or CTC), medications to prepare a patient for the procedure and any subsequent procedures required to make a diagnosis. Downstream activities resulting from detection of colonic lesions included radiological investigations, surgical procedures, outpatient attendances, treatment for cancers or large polyps and hospitalisations as a result of major adverse events. Downstream activities to investigate and treat extracolonic lesions found at CTC were also recorded.

Resource usage on medications

Information was collected on medications and dosages used during the procedures. The main medications included pethidine, midazolam, fentanyl, Buscopan and glucagon. Doses recommended by the *British National Formulary* (BNF) were used if data were missing.

Information on medications used for bowel preparation was not collected individually during the trial. However, all centres were asked to provide details of the standard bowel preparation used for BE and CTC during the period the trial was in progress. Ultimately, we assumed that every patient having a procedure was given two sachets of Picolax, which was the preparation used in most centres.

Resource usage on diagnostic procedures

Details of all diagnostic and follow-up procedures were recorded. For colonoscopy, this included information on whether or not any biopsies were taken or polyps removed.

Resource usage on surgery for colonic lesions

Information was collected on surgery related to colonic findings. Almost all surgical procedures were carried out for the treatment of cancer. Detailed information was recorded on the type of operation performed, reasons for the operation, length of hospital stay and whether or not there were any complications during or following the procedure. Costs were based on the type of operation and length of stay.

Resource usage on adverse events

Adverse events were classified as major or minor. Major adverse events were defined as those involving unplanned hospitalisation or death. The costs of hospitalisation were estimated based on the actual length of stay and the specialty concerned. Costs were not attributed to minor adverse events.

Resource usage on outpatient appointments

A trial pro forma (see *Appendix 1*) was completed to capture data on outpatient attendances resulting from initial investigation of the colon. This form included a record of any referrals for additional investigation, such as a flexible sigmoidoscopy or CT scan.

Resource usage on extracolonic findings

All procedures relating to follow-up of extracolonic abnormalities detected by CTC were collected. This included the type of procedure(s) performed and the date on which they occurred. Information was collected on operations performed. However, patients were not followed up in the longer term. For example, we did not collect information on surgery for aneurysms that might have enlarged to the point at which surgery was indicated under surveillance initiated as a result of the study. In addition, data on the

investigation of extracolonic lesions that manifested in the non-CTC arms of the trials were not collected. We will try to make good estimates of these deficiencies by staging outcomes using HES data.

Unit costs

The unit costs of medications were obtained from data published by the BNF in September 2011.[75] *Table 36* reports this information. The unit costs of BE, CTC, colonoscopy and flexible sigmoidoscopy were obtained from NHS national reference costs at 2010–11 prices.[76,77] This information is presented in *Table 37*. The costs of colonoscopy and flexible sigmoidoscopy are classified according to whether or not a biopsy was taken or a polyp removed during the procedure. There is no specific national cost for CTC; instead we used the cost of a CT scan as an approximation (the 2010–11 reference cost: RA08Z-RA14Z Computerised Tomography Scan, more than three areas).

TABLE 36 Unit costs of medications

Drug name	Preparation	Cost (£)	Standard dose for BE/CTC/colonoscopy
Buscopan (injection)	20 mg/ml, 1 ml	0.22	Intravenous injection 10–40 mg
Glucagon (injection)	1 mg	11.52	Intravenous injection 0.5–1 mg
Pethidine (injection)	50 mg/ml, 1 ml	0.43	Intravenous injection 25–50 mg
Midazolam (injection)	1 mg/ml, 2 ml	0.50	Intravenous injection 1–2 mg
Fentanyl (injection)	50 µg/ml, 2 ml	0.30	Intravenous injection 25–100 µg
Picolax	10 mg/sachet × 2	3.39	Two sachets before the procedure

The unit costs of major surgical interventions and other diagnostic procedures and the cost of associated hospitalisations were based on NHS reference costs 2010–11.[76,77] *Tables 41* and *42* in *Appendix 4* list all unit costs of these procedures. The length of stay was used to calculate the total cost of each episode associated with surgical operations or adverse events. If these data were unavailable, relevant reference costs were used. All costs have been expressed in pounds sterling at 2010–11 prices.

TABLE 37 Unit costs of main diagnostic procedures[a]

Intervention	Value (£)	Low range (£)	High range (£)	HRG4 codes	Description
Colonoscopy alone	330	287	395	FZ51Z	Diagnostic colonoscopy ≥ 19 years
Colonoscopy with biopsy	385	305	450	FZ52Z	Diagnostic colonoscopy with biopsy ≥ 19 years
Colonoscopy with polyps or CRC removed	450				Used the high range of colonoscopy with biopsy
FS alone	220	150	253	FZ54Z	Diagnostic FS ≥ 19 years
FS with biopsy	253				Used the high range of flexible sigmoidoscopy alone
FS with polyps or CRC removed	450				Assumed the same as the high range of colonoscopy with biopsy
BE	135	91	162	RA17Z	Contrast fluoroscopy procedures 20–40 minutes
CTC	160	89	186	RA14Z	CT scan, more than three areas

a Some entries do not have low or high range values or a HRG4 code because several exams attract a single cost without a range.

Analysis

The total costs per patient were calculated as the sum of the products of resources used and their unit costs.

The costs of diagnosis associated with each investigative pathway were evaluated according to the original randomised group and the differences in costs compared. The following cost comparisons were carried out:

- total costs contingent on assigned procedure, excluding the costs of investigation and treatment for incidental extracolonic lesions
- the cost per case detected for colon cancer or a large polyp and also for colon cancer alone.

Initially, we had intended to compare all the costs contingent on each diagnostic strategy. This would have included the costs of investigating and treating incidental extracolonic lesions across all groups. However, these costs were collected only for patients having CTC. It could not be assumed that there were no similar additional costs in the BE and colonoscopy arms, even within the time scale of the study. Pending further investigation using national HES data, we have presented the costs of following up extracolonic lesions after CTC in separate tables. Failure to include these costs for patients having other procedures will exaggerate the cost difference between CTC and these procedures. However, failure to collect information on surgery for extracolonic lesions in the longer term will lead to an underestimate in CTC costs. Given these uncertainties, we decided to analyse the costs and benefits of detecting extracolonic lesions separately from those of detecting colonic lesions.

The cost per additional cancer or large polyp detected by CTC was compared with that for the other two strategies. In addition, the mean intervals between presentation and diagnosis were compared for each modality. Total costs for each patient, contingent on their final diagnosis, were calculated for the trial period, with the caveat that a separate calculation was carried out for the cost of following up extracolonic lesions.

All analyses were based on the principle of intention to treat. Bootstrap methods were used to estimate costs and cost differences. ICERs with their CIs and a scatterplot were produced based on 1000 replicates. The analyses were conducted in SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Costs over diagnostic sequence (excluding extracolonic lesions)

In terms of the costs of the procedures themselves (unit costs), BE is costed at £135, CTC at £160 and colonoscopy at £330. However, the total costs associated with each procedure are higher (by over 100%) as they take into account the various contingent downstream costs such as repeat procedures, complications and operations. These total costs do not take account of those arising from detection of incidental extracolonic lesions. In the BE trial, the mean total cost per person was £460 for BE and £532 for CTC. In the colonoscopy trial, it was £739 for colonoscopy and £674 for CTC. Details of costs by procedure are presented in *Table 38*. Colonoscopy is more expensive than CTC (despite the considerably higher requirement for follow-up investigations after CTC), but the difference is £65 per patient and well within the limits of statistical precision. BE is less expensive than CTC, with a cost difference of £72 per patient, also within the limits of statistical precision. The higher costs of CTC in the colonoscopy trial than in the BE trial can be attributed to the higher risk of patients, on average, in the colonoscopy trial (see *Chapter 2*).

TABLE 38 Costs associated with the investigation and treatment of colonic lesions. All values are mean cost (£) per patient (95% CI)

	BE trial		Colonoscopy trial	
	BE ($n = 2527$)	CTC ($n = 1277$)	Colonoscopy ($n = 1047$)	CTC ($n = 533$)
Diagnostic procedure	184 (178 to 189)	231 (222 to 240)	368 (360 to 375)	266 (250 to 281)
Colonic surgery	223 (179 to 266)	242 (178 to 306)	295 (218 to 373)	323 (212 to 434)
Other examinations	1 (1 to 2)	1 (0 to 1)	1 (0 to 2)	0 (0 to 1)
Outpatient administration	48 (46 to 51)	54 (50 to 58)	71 (67 to 76)	86 (79 to 92)
Adverse event	4 (–1 to 10)	4 (–4 to 12)	4 (–2 to 10)	0
Total	460 (415 to 506)	532 (465 to 599)	739 (660 to 819)	674 (559 to 790)

Incremental cost-effectiveness ratio (excluding extracolonic lesions)

Here we consider the differences in cost per case detected as a result of the initial diagnostic sequence. CTC and colonoscopy detected a similar proportion of both cancers and large polyps, but with a slight (non-significant) trend in favour of colonoscopy, which detected an additional 6.8 such lesions per 1000 cases. Based on this difference in point estimates, the incremental cost per significant lesion detected by colonoscopy was £9543. Cancer detection rates differed by only 1 in 10,000 so the incremental cost-effectiveness is large (£650,000 per case detected).

The difference in detection rates for significant lesions in the BE trial was statistically significant and in this case CTC detected more lesions, with a difference in the point estimate of 17 significant lesions per 1000 cases. Scatter plots of differences in costs and detection rates of cancer or large polyps for CTC compared with BE are shown in *Figure 8*. The figure shows the positive correlation between increased costs and increased detection rates for CTC compared with BE. The incremental cost per neoplasm detected by CTC was £4235 (95% CI £395 to £9656).The corresponding ratio for detection of an additional three cases of colon cancer per 1000 patients (a statistically non-significant difference) was £24,000 per cancer.

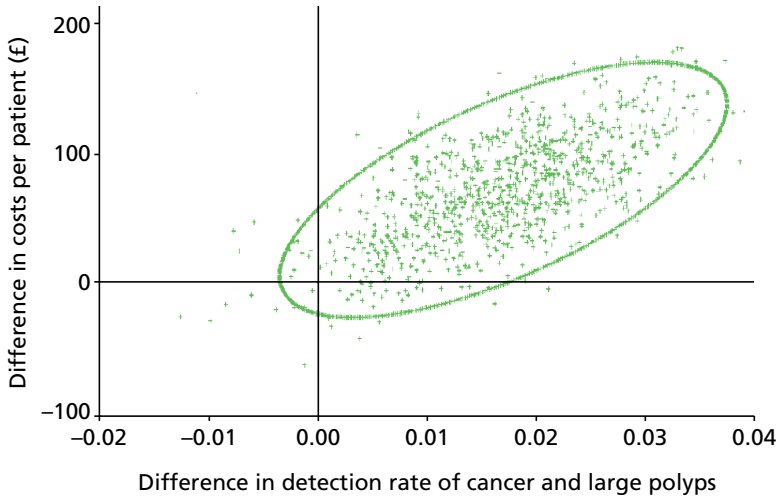

FIGURE 8 Scatter plot of difference in costs vs. difference in detection rate of cancer or large polyps for CTC compared with BE.

Costs contingent on finding extracolonic lesions

The diagnosis and treatment costs for following up extracolonic lesions (both trials) are shown in *Table 39*. The primary cancers and aneurysms are the most costly items and costs would be higher if longer-term effects were included. We have not accounted for costs in the counterfactual groups and the figures given are an overestimate the marginal gains from CTC. A summary of incremental costs per case detected for CTC and BE is given in *Table 40*.

TABLE 39 Cost of follow-up investigation and treatment for extracolonic lesions

		Cost per patient (£)			
Lesion type	Number of patients	Mean	Lower quartile	Median	Upper quartile
Primary cancer	23	2094	99	483	5175
Secondary cancer	5	470	105	276	816
Haematological	2	137	63	137	211
Aneurysm	13	1901	53	95	6609
Minor cases	89	449	53	142	794
Other	17	268	53	109	361

TABLE 40 Benefits vs. costs for CTC vs. BE

Gains in detection per 1000 cases	Incremental cost per case detected (£)
CRC[a]	24,000
CRC + polyps[a]	4235
Extracolonic lesions (primary cancers)[b]	6628
Extracolonic lesions (primary and secondary cancer, haematological and aneurysms)[b]	3545

a Excluding cost of intervening and treating extracolonic lesions.
b Cost of intervening and treating extracolonic lesions only.

Chapter 7 Discussion

Barium enema trial

This is the first randomised trial to compare the performance of CTC and BE for diagnosis of CRC and large polyps in symptomatic patients. The pragmatic design allowed us to compare referral rates for further colonic investigation and positive predictive values for the two tests when used in normal clinical practice. We found that CTC detected significantly more cancers or large polyps, confirming its higher sensitivity for significant lesions. However, referral rates for a second colonic procedure were significantly higher following CTC because of higher detection rates of both large and small polyps. The probability of diagnosing a cancer or large polyp at a second examination did not differ between the two procedures.

The diagnostic yield of CRC was relatively low in this cohort (3.5%) compared with the parallel CTC compared with colonoscopy trial (5.6%) and the detection rate for cancer in this trial did not differ significantly between the procedures (3.7% for CTC vs. 3.4% for BE). The cancer miss rate was lower for CTC than BE (6.7% vs. 14.1%), but not significantly so; however, the study was not powered to find a difference based on cancer detection alone, as the required sample size would be unfeasible, even in a symptomatic cohort. We did find a significantly higher detection rate of large polyps by CTC (3.6% vs. 2.2%), suggesting that it is more sensitive for detection of these lesions. We used large polyps as a surrogate for cancers, as it is rare to find cancers smaller than 10 mm. Therefore, our findings suggest that CTC is superior to BE for detecting smaller cancers. This is important as a recent preference study[78] found that two-thirds of participants considered sensitivity the single most important attribute for a diagnostic bowel test, with even modest improvements valued highly.

The observed CRC miss rate for BE in the present study (14%) is similar to those reported in several large audits. Defining a missed cancer as one diagnosed within 3 years of a negative procedure, a large Canadian audit found a miss rate in a hospital setting of 21%.[79] A similar audit of 20 US hospitals found a miss rate of 15%[10] and a national audit of UK hospital radiology departments examining CRCs diagnosed within 12 months of BE found an average miss rate of 15%, with variation from 0% to 50%.[80] In the present trial, 9 of the 12 cancers missed at BE were diagnosed more than 12 months after the randomised procedure, so it is likely that the prior UK audit underestimated the actual BE miss rate. There are no comparable data on miss rates following CTC in routine clinical practice. Meta-analysis of published data[17,81] suggests that its sensitivity for cancer is around 96% (95% CI 91% to 99%), but the data are derived mainly from small studies from specialist centres.

We could not determine the miss rate of large polyps at CTC or BE, as colonoscopy was not performed as a reference standard. In the only study that has compared both BE and CTC with colonoscopy, 613 high-risk patients underwent all three procedures with a per-patient sensitivity for detection of any lesion $\geq$ 10 mm of 48% for BE and 59% for CTC.[82] A similarly low sensitivity for CTC of 55% was reported in a study[83] of 600 patients undergoing CTC prior to clinically indicated colonoscopy.[83] These results conflict with other published data, mainly from asymptomatic screened populations, in which sensitivity for lesions $\geq$ 10 mm is around 90%.[15,17] Differences in radiologist expertise may account for these divergent findings.

Randomisation and a pragmatic design allowed us to observe patient pathways reflecting normal clinical practice, which is impossible in within-patient comparisons for which all participants receive colonoscopy after a radiological procedure, regardless of findings. We were therefore able to determine the proportion of patients undergoing a second diagnostic procedure either to confirm a lesion seen at the randomised procedure or to exclude pathology for which no lesion had been seen but diagnostic uncertainty persisted, for example owing to poor visualisation. Referral rates were significantly higher after CTC than BE (23% vs. 18%). Previous screening studies have reported referral rates after CTC of 8–16% using

detection of a polyp ≥ 6 mm as a threshold.[15,83–85] Although referral rates might be higher in our symptomatic cohort because of the increased prevalence of cancers and large polyps, they may also indicate lack of confidence in radiological findings. Even in patients who had FS prior to their randomised procedure (and ignoring all referrals arising from the sigmoidoscopy findings), referral rates were still high (11% after BE and 18% after CTC). The routine use of prior FS in some centres might reflect the referring clinician's judgement that CTC and BE are less reliable in the distal colon. However, the Canadian audit suggests that the miss rate of cancers following BE is higher in the right than the left colon.[79] Our findings corroborate this as 8% (6/77) of distal and 17% (9/53) of proximal cancers were missed by BE or CTC.

Significantly more referrals occurred following CTC because of suspected large polyps (11.0% vs. 7.5%) and also because of suspected smaller polyps (7.2% vs. 2.3%). Careful management of patients with suspected lesions < 10 mm is required, as the majority of these lesions have low malignant potential and are unlikely to be the cause of symptoms. However, of the significant lesions found at colonoscopy following detection of small polyps at CTC, the single cancer and five of the six large polyps were in patients with lesions measured as 8–9 mm at CTC, indicating a possible benefit of lowering the threshold for referral to 8 mm. Following detection of small polyps at BE, all four of the significant lesions found at colonoscopy (one cancer and three large polyps) were in patients with lesions measured as ≤ 5 mm at BE. This could be a result of measurement errors at BE, particularly when dealing with sessile lesions, or the lesions seen at BE and colonoscopy may not have been the same.

Factors other than sensitivity will influence test choice for both doctors and patients. BE is more physically demanding because multiple patient positions are required, while CTC requires only two (usually prone and supine). This makes CTC more suitable for frail elderly patients, who account for many of those with symptoms. Radiation dose for the two procedures is similar overall, but can be lowered for CTC if intravenous contrast is omitted.[86] The symptomatic perforation rate has been calculated at 0.03% for CTC[13] and 0.0004% for BE.[87] In the present trial, serious adverse events were rare for either procedure: four attributed to BE and one to CTC.

Patients consider the detection of extracolonic lesions to be one of the advantages of CTC.[51] We found that 1.7% of people undergoing CTC as their randomised procedure had an extracolonic lesion that was subsequently confirmed as malignant (4.5% had a neoplasm). However, in both symptomatic and asymptomatic populations, extracolonic findings are reported for the majority of CT colonographies and many precipitate unnecessary investigations with associated psychological and physical morbidity, and increased financial cost.[25,40]

Another potential advantage of CTC is that patients can be referred for same-day colonoscopy to remove any significant lesions identified in the bowel. This is impossible following BE because of residual barium suspension, so patients require a further clinic attendance and second bowel preparation. However, this advantage of CTC can be exploited only if there is prompt reporting of CTC findings and adequate spare capacity in endoscopy departments, which may limit its feasibility. In the present trial, only one patient had a follow-up colonoscopy on the same day as CTC.

A limitation of studies of all radiological colonic examinations is the requirement that lesions be confirmed at colonoscopy and it is impossible to be certain that a negative colonoscopy following a positive radiological examination is not a false negative. Furthermore, when lesions are detected at both procedures, matching them is problematic because of discrepancies in location and size. Among the polyps that were measured at both colonoscopy and radiology, size was underestimated at radiology in 23% of those identified at BE and 37% at CTC, and overestimated in 47% at BE and 41% at CTC, using colonoscopy as a reference standard. For small lesions, in particular, it was difficult to be certain that a lesion visualised by the randomised procedure was the same lesion identified subsequently at colonoscopy. The potential to introduce bias when matching lesions is therefore considerable, although less so for large lesions.

In conclusion, in patients with symptoms of CRC in whom a radiological examination is indicated, we show that CTC is superior to BE for detection of cancers and lesions ≥ 10 mm and there was a trend towards fewer missed cancers. CTC also offers potential benefits such as diagnosis of extracolonic disease, although this, along with its ability to detect small lesions in the colon, can lead to unnecessary follow-up tests for findings that are not clinically important. If CTC is to replace BE as the preferred radiological test, it must be implemented with a system of training and continuous audit for radiologists and rigorous guidelines on patient referral, to maximise the potential benefit of this technology.

Colonoscopy trial

We compared referral rates for additional colonic procedures following colonoscopy or CTC in patients investigated for symptoms suggestive of CRC. The observed referral rate of 30% after CTC was 3.6 times higher than that after colonoscopy (8.2%). CTC also identified extracolonic lesions, leading to further investigation in 10% of patients. CTC showed a high sensitivity similar to colonoscopy for detection of CRC; only one CRC was missed by CTC and none by colonoscopy, although there were three later cancer diagnoses in patients who had refused colonoscopy. Extracolonic cancers were diagnosed by CTC in nine patients.

In powering this study we assumed that CTC is equivalent to colonoscopy in terms of sensitivity for cancer, as has been confirmed in recent meta-analyses, so sensitivity was not the main focus of the study. Instead, we aimed to determine the proportion of patients having additional colonic tests after CTC compared with colonoscopy, which is an important consideration if CTC is to become widely used. We anticipated that the rate of additional colonic investigation would be higher after CTC than after colonoscopy because lesions detected at CTC require histological confirmation, but expected this would be offset by a lower rate of referral because of incomplete examinations, as CTC is not subject to the technical difficulties of navigating an endoscope through the colon and is better tolerated than colonoscopy. A survey undertaken prior to this study concluded that more than 20% of colonoscopies undertaken in routine practice in the UK were incomplete.[88] In response to this finding, a national quality improvement programme for colonoscopy was initiated[89] and the low rate of completion examinations observed in this trial suggests that standards, at least among the unselected clinicians performing colonoscopy in this trial, were much better than previously observed.

Although the rate of further colonic examination after colonoscopy was lower than expected, it was much higher than expected after CTC, based on the very few observational studies that had compared rates.[84,85] Most previous evaluations of CTC and colonoscopy have been within-patient comparisons in which all patients receive CTC followed by colonoscopy[15,16] and further examination rates are not observed directly but are estimated from detection rates of lesions larger than the threshold size for referral. In our trial, the rate of further colonic investigation following CTC was double that reported in a retrospective analysis of an asymptomatic screening population of a similar age.[84] In that study, 10% of patients were referred for colonoscopy for investigation of lesions ≥ 10 mm and a further 5% for 6–9-mm lesions.[84] In our cohort, 15% of patients were referred for investigation of a suspected cancer or polyp ≥ 10 mm and a further 16% for smaller polyps or clinical uncertainty. In the last group, no cancers and only three large polyps were diagnosed. The observed high referral rate following CTC demonstrates both the higher yield of potentially significant lesions and the more cautious approach of radiologists and referring clinicians when dealing with findings in a symptomatic population. Small polyps generally have low malignant potential and, with few exceptions, their removal offers no clinical benefit in this symptomatic group, but contributes to the patient and economic burden caused by the demand for additional tests following CTC. A careful assessment of patients' clinical status and risk factors is therefore needed when choosing whether or not to refer in such cases.

There were significant differences in rates of referral by sex, with men more than six times as likely to be referred after CTC than colonoscopy, while women were only twice as likely to be referred. The higher referral rate after CTC in men arose because they had more polyps detected at CTC that required investigation. Conversely, in women, colonoscopy was more likely to be incomplete. These findings confirm results from other studies that show that women do not tolerate colonoscopy as well and have fewer polyps than men.[90,91]

The ability of CTC to detect abnormalities outside the colon was also investigated. Extracolonic findings were reported in around 60% of patients undergoing CTC in both this and the parallel trial of CTC compared with BE. In 10% of cases in this trial and 8% in the parallel trial, additional investigations were deemed necessary. These rates are similar to those reported in two retrospective UK studies of symptomatic patients[26,39] and in an older asymptomatic US cohort.[24] The financial cost of investigating extracolonic lesions at CTC has been estimated at approximately £150 per patient.[26] Whether or not this expenditure is worthwhile depends on the clinical importance of the lesion detected. In this trial, nine patients had an extracolonic cancer detected by CTC; however, the proportion of patients with an extracolonic cancer diagnosed within 3 years was similar following CTC and colonoscopy (4.6%). Around half of these cancers were diagnosed within the first 6 months after the randomised procedure, indicating that the diagnoses resulted from ongoing investigation of the symptoms for which patients were initially referred. This suggests that even patients having colonoscopy must undergo additional investigation to identify an extracolonic cause of their symptoms. As this usually involves referral to a different specialty, we were not able to capture this information during the course of the study. Thus, clinicians are faced with a choice: to perform CTC which permits examination of extracolonic regions of the abdomen but results in additional investigation for lesions of uncertain importance, or to perform a specific colonic investigation such as colonoscopy and then refer for additional investigation if there is persistent concern about symptoms (which may similarly lead to detection of unimportant lesions).

Our study bears out previous evidence that adverse events are more often associated with colonoscopy than CTC. In this and the parallel BE trial, there was only one hospitalisation attributed to CTC and six to colonoscopy.[7,13] However, it is important to note that endoscopy-related adverse events may be less frequent but are not avoided if CTC is followed by a referral for colonoscopy, as happened in 30% of patients having CTC in this trial.

Our study has limitations. Since recruitment finished there have been significant improvements in CTC, which may have considerably reduced the proportion of patients requiring a subsequent investigation to confirm or exclude cancer or large polyps. For example, faecal tagging (the use of oral contrast to label residual stool) was not generally used in our study, although it is now widespread in clinical practice to improve specificity.[92] Its use, together with a more restrictive policy on referral for removal of small polyps, would reduce the proportion of patients needing subsequent endoscopy. The combination of dietary restriction with faecal tagging also means that full bowel preparation can be avoided altogether. Although this will diminish sensitivity, it has been shown to increase compliance in screening studies.[93]

With our sample size it was impossible to compare CTC and colonoscopy on the basis of sensitivity for cancer or large polyps, as meta-analyses suggest that the sensitivity of CTC is around 90%. We calculate that a trial powered to do this would require a sample of around 40,000 patients and suggest that the best way to compare sensitivity of the two procedures for cancer would be to implement a national audit programme for both CTC and colonoscopy using national administrative data sets. However, we did follow all patients for 3 years to identify cancers that were missed by either procedure. Combining data from both this and the BE trial, we found that CTC missed 4 out of 74 CRCs (5.4%), while none (0 out of 33) was missed in patients having colonoscopy, although there were three CRCs diagnosed in patients who refused colonoscopy and one in a patient who refused CTC.

The sensitivity and specificity that can be achieved with CTC depends on the expertise of the radiologists reporting the examination. Those in the current study were all experienced in interpreting CTC and their performance probably represents the best that could be achieved in older symptomatic patients at the time the study was performed. A recent study points out that CTC generally tends to be performed by a limited number of radiologists in each hospital who may, therefore, be more experienced.[94] More widespread implementation could result in a decrease in sensitivity if it is not accompanied by a thorough programme of audit and training.[95]

In conclusion, CTC may be a desirable alternative to colonoscopy if symptoms are vague, if patients are frail or elderly, and in women because they generally have fewer polyps and a higher rate of incomplete colonoscopy. The results of our trial lend weight to previous studies indicating that CTC has comparable sensitivity to colonoscopy for cancer and appears to be more acceptable to patients. However, CTC is associated with a significantly higher rate of referral for additional tests, potentially increasing inconvenience and overall cost, and – in patients referred for colonoscopy – mitigating any advantage that comes from avoiding an endoscopic examination. Despite this, for the majority of patients who are not referred for additional colonic tests, CTC offers a straightforward, non-invasive, lower-risk alternative to colonoscopy. Close attention to referral criteria and continued emphasis on radiologist training and assessment are needed if CTC is to become an effective tool for investigation of symptomatic patients.

Extracolonic findings

It was Hara *et al.*[24] who first highlighted the importance of detecting extracolonic lesions at CTC, finding that 30 of 264 consecutive patients (11%) at high risk of CRC had potentially important extracolonic lesions reported, 18 of whom underwent subsequent investigation. The authors concluded that 'the evaluation of extracolonic structures with CTC can help detect clinically important disease'. In the USA, CTC is promoted for CRC screening, with the ability to simultaneously image extracolonic organs cited as an advantage. A retrospective review of 10,286 CTC screening examinations found CRC in 22 patients (0.21%) and extracolonic cancers in 36 patients (0.35%), the most common of which was renal.[42] However, others have argued that detection of extracolonic lesions is unhelpful. A 2009 commentary concluded that CTC screening would generate a 'deluge' of incidental extracolonic findings that would inevitably cause subsequent anxiety, morbidity and mortality as well as increase costs.[96]

Detection of extracolonic lesions in symptomatic patients is perceived as less controversial because standard abdominopelvic CT is used to search for an extracolonic cause of symptoms in elderly patients from whom a reliable history cannot be obtained owing to debilitation or confusion,[97] helping to reassure clinicians that they are not missing occult disease. CTC combines intracolonic and extracolonic investigation in an acceptable format and is easier for older patients to tolerate than colonoscopy or BE.[39]

The pragmatic design of our study meant that we were in a unique position to examine how the reporting of extracolonic lesions by radiologists influenced patients' subsequent diagnostic pathway and ultimate diagnosis. We found that most CTC reports (59.6%) mentioned an extracolonic abnormality; a figure very similar to the 63% quoted by a US study of patients at high and average risk of CRC.[98] We found that the frequency of extracolonic findings rose significantly with age, also in keeping with the results of other studies: one in the USA found that extracolonic abnormalities were reported in 185 out of 250 patients (74%) aged ≥ 65 years, compared with 113 out of 204 younger patients (55.4%).[99] A UK series of 400 consecutive symptomatic patients > 70 years found that 268 (67%) had extracolonic lesions.[39] The E-RADS classification[44] was devised to clarify management of extracolonic findings by ascribing an estimate of likely clinical significance. In common with researchers working in an asymptomatic setting, we found that the highest categories (E3, E4) were least frequently reported: a US screening study of 2277 patients found that 46% had at least one extracolonic finding, but this was rated as E3 or E4 in only 250 patients (11%).[43] The combined rate for E3 and E4 detections in our study was higher (21%), likely reflecting the symptomatic nature and greater age of our cohort.

The E3 and E4 detections are important because they represent lesions that may warrant further investigation by the clinician in charge of the patient's care. Interestingly, although 365 patients (21%) were assigned these scores, only 150 (8.6%) were subsequently investigated. This difference may reflect a clinical decision that the finding is unlikely to be the cause of symptoms and is therefore not worth pursuing. It is also possible that patients may decline further investigation or are too frail to undergo it. As expected, E4 lesions were most frequently investigated but 15% were not, despite being 'potentially important'. We also found that investigation of extracolonic lesions was not straightforward: one-third of investigated patients needed two or more procedures. Although most investigation was non-invasive, a substantial minority underwent invasive procedures including surgery, usually for E4 findings.

We attempted to address the question of whether or not extracolonic findings were responsible for patients' presenting symptoms rather than being incidentally found, as is the case with screening. When the relationship between presenting symptoms and extracolonic findings was analysed, 2.9% of patients in the BE trial and 3.6% of patients in the colonoscopy trial had symptoms that were ultimately ascribed to extracolonic pathology. These figures are similar to the prevalence of CRC in the trials (3.5% and 5.6% respectively; excluded from the present analysis). It can be concluded that the predictive value of individual symptoms for both intracolonic and extracolonic disease is low. The chance of an extracolonic lesion being the cause of presenting symptoms was highest in the group aged ≥ 85 years, supporting the use of CTC in this group, although the number of such patients in our study was small (54 people). We had thought that we might be able identify symptoms associated with extracolonic disease, but anaemia was the only one significantly associated with reporting of an extracolonic finding. When the likelihood that individual symptoms could be attributed to an extracolonic finding was taken into account, abdominal pain had the strongest association with extracolonic pathology. However, abdominal pain was a common presenting complaint, therefore, clinical usefulness on a per-patient basis was limited.

We had hypothesised that the comprehensive nature of intracolonic and extracolonic diagnosis possible by CTC would lead to earlier diagnosis of intra-abdominal or pelvic extracolonic cancer than either BE or colonoscopy, especially as some cancers may be chance detections in patients whose symptoms originated elsewhere. We found extracolonic malignancy in 1.7% of patients having CTC (excluding those with CRC). However, we were surprised to find that there was no difference by randomised procedure in the incidence of newly diagnosed primary extracolonic cancers at 3 years. Furthermore, the rate of extracolonic cancer was highest within the first 6 months after the randomised procedure for all three modalities. We believe that these data suggest that many patients randomised to colonoscopy or BE will eventually undergo comprehensive abdominopelvic imaging if no colorectal cause for their symptoms is found and that this often occurs relatively soon after the initial referral. We collected details of follow-up procedures for each patient until discharge from the colorectal clinic, but do not have data on resource use beyond this, so cannot confirm this hypothesis at the time of writing.

Our study does have limitations. In all, 46 different radiologists participated and their personal thresholds for reporting extracolonic lesions will differ, especially for lesions perceived as being of lower importance. Differences may also arise depending on CTC technique, for example the use of intravenous contrast. We did not analyse centre-to-centre variation, which will form the basis of a subsequent report. However, the pragmatic nature of the study in terms of setting and radiologist experience means that our findings are generalisable to daily practice with symptomatic patients. Another limitation arises from the use of the E-RADS categories to classify the potential importance of extracolonic findings. We used this system because it is well established,[44] but there are no comprehensive classification tables linking individual findings to E-RADS scores. Therefore, the category assigned to an individual finding could vary depending on the individual making the assessment. Further, E-RADS is based on asymptomatic patients. There is a need to develop similar guidelines for symptomatic patients and to describe which scores should be assigned to the entire range of CTC findings.

Patients with proven CRC were excluded from the present analysis because it is not always possible to be certain that extracolonic findings are unrelated to the CRC and its presence will also influence the rate of subsequent extracolonic investigation. It is possible that some patients had both CRC and an important extracolonic lesion, although the number will be small.

We collected data on resource use until discharge but cancer registry data suggest that extracolonic examination was ultimately performed on a proportion of patients whose primary randomised procedure was either BE or colonoscopy. Collection of resource use by individual patients for the whole 3 years of registry follow-up is beyond available resources. We are also planning a modelling exercise that will extrapolate data beyond the trial to determine the impact of extracolonic detections in terms of lives ultimately saved compared with morbidity/mortality owing to unnecessary investigation. This will include non-neoplastic diagnoses such as abdominal aortic aneurysm (14 cases). A prior cost-effectiveness analysis of asymptomatic patients suggests that CTC is 'highly cost-effective' when used to screen for aortic aneurysm in combination with CRC.[67]

In summary, extracolonic findings are commonly identified by radiologists reporting CTC in patients referred with a suspicion of CRC and their frequency rises with patient age. A small proportion of patients are investigated subsequently. Approximately 3% of patients presenting with symptoms of CRC have extracolonic pathology that is likely to be the cause of their presenting symptoms and in approximately half of these cases, this will be owing to extracolonic malignancy. However, when used in normal clinical practice, CTC does not appear to hasten the diagnosis of extracolonic intra-abdominal or pelvic malignancy compared with either BE or colonoscopy.

Health psychology assessment

This study reports the experience of symptomatic patients randomised to undergo CTC, BE or colonoscopy in order to diagnose or exclude significant colorectal neoplasia. This is the first time a randomised design has been used rather than cohort studies in which patients undergo all tests under investigation. A randomised design is advantageous because it increases generalisability and allows us to obtain a more valid representation of patient experience in daily clinical practice.

We found that patient experience differed significantly according to the diagnostic test administered, with patients having a BE or colonoscopy reporting less satisfaction and greater discomfort than those having CTC. These data support previous findings from non-randomised cohort studies.[20,47,48] The fact that CTC is more acceptable than BE while also offering superior diagnostic sensitivity indicates that it should replace BE as the standard radiological whole-colon investigation.[100]

In the colonoscopy trial, patients having colonoscopy reported higher scores on the 'worry' subscale of the satisfaction measure than those having CTC. It is known that women perceive colonoscopy as more painful than men,[18] a finding confirmed in our study in women having colonoscopy. No significant differences were found between men and women having CTC. It was reassuring that most patients having CTC did not report claustrophobia, which had been identified by previous research as a potential drawback.[78] Our findings also support previous evidence suggesting that bowel preparation is the worst aspect of patients' overall experience.

Patients having CTC rated staff interactions significantly more favourably. This was surprising because a previous qualitative study suggested that patients regard CTC as more impersonal than colonoscopy, with less interaction.[51] However, that research was conducted in a single tertiary referral unit. The present multicenter design (including both teaching and community hospitals) is likely to better reflect day-to-day practice.

An important prespecified aim was to assess patients' experiences of receiving their test results, because delays following radiological procedures may cause uncertainty and anxiety.[51] We confirmed that patients having CTC were less likely to receive their results on the day of the test or face to face; a consequence of the fact that CTC is usually reported by a radiologist some time after the scan takes place, while colonoscopy is interpreted during the procedure itself. As a result, patients having CTC were less satisfied with the reporting of results than patients having colonoscopy. Timely delivery of results may be particularly important if CTC is used for screening, as patients will expect a standard of care equivalent to colonoscopy. The situation is more complex for symptomatic work, for which diagnosis of cancer is much more likely. Immediate delivery of a cancer diagnosis is inappropriate in radiology departments because the required support services (i.e. psychological support and discussion of treatment options, implications and prognosis) are usually unavailable. However, some units have the facility to call such services to the radiology department and immediate delivery of results face to face may be feasible in such circumstances. It should also be borne in mind that most symptomatic patients will receive a negative examination and consideration should be given to making this information rapidly available, perhaps via a subsequent telephone call to the patient.

Our study has limitations. Although a randomised design offers the opportunity to observe patient experience in normal clinical practice, it also has some drawbacks. Perhaps most importantly, patients were aware that two tests were being compared and a description of each was inevitably part of the consent process. Therefore, it is possible that a prerandomisation preference, perhaps arising from the perceived advantages of a new technology (CTC), may have biased patients who were subsequently randomised to BE or colonoscopy and impacted negatively on their reported experience.

Patients rated their experience without comprehensive information regarding relative test sensitivity. Previous research has found sensitivity to be important when patients form preferences for colorectal investigations, both in symptomatic[78] and screening contexts.[101–103] It is possible that participants would rate CTC less positively if aware that it may be less sensitive than colonoscopy.[15] Observations may also have been influenced by centre-to-centre variation in bowel preparation, sedation/analgesia and gas insufflation. We did not stipulate that carbon dioxide or air be used for colon insufflation, as both gases are used for both procedures in daily practice. However, we did stipulate that 'full bowel preparation' was used for both procedures, so the experience would be comparable despite the use of different pharmacological agents to achieve this. Although full purgation is necessary for BE, CTC is an evolving technology and it is possible that bowel preparation will be reduced or abandoned altogether in future.[104,105] As a result, the acceptability of CTC will likely improve beyond the level documented in our study.

Although it is long-established that carbon dioxide is more comfortable than air for patients having a BE,[106] we were surprised that nine centres were still using air (indeed seven were using air for CTC). This may impact on physical discomfort (the item for which we would expect the gas used to have most influence) but, at the same time, it is important that our data are generalisable to daily practice.

A number of important questions arise from our findings that warrant future research. An evaluation of the extent to which patients prefer a more convenient or comfortable test (e.g. one that avoids bowel preparation) if this means trading off some degree of diagnostic sensitivity would be of interest to both health-care professionals and policy makers. Despite preliminary qualitative evidence suggesting unwillingness to sacrifice any level of sensitivity,[78] more extensive research is required.

In conclusion, patients with symptoms suggestive of CRC perceive CTC as a more acceptable test than patients having a BE or colonoscopy. In conjunction with clinical efficacy data for CTC, our findings support the wider implementation of CTC for diagnosis of symptomatic colorectal disease.

Health economic assessment

Computed tomographic colonography compared with barium enema trial

The comparison of CTC with BE showed that CTC was superior in terms of significant colonic lesions detected. However, BE is less expensive because it has lower unit cost and is less likely to lead to follow-on investigation. For CTC, the incremental cost per case detected was nearly £4235 per significant lesion (large polyp or cancer) detected, rising to £24,000 per CRC. The estimate for significant neoplasms was significant albeit a wide confidence limits (95% CI £395 to £9656). Costs per cancer detected were unsurprisingly higher given the small number of cases, but not statistically significant. Costs vary from place to place and over time. In addition, not all costs can be included because the data were not collected, such as a change in primary care consultation rates for example. The overall cost-effectiveness of CTC relative to BE requires extrapolation beyond the trial necessarily requiring many assumptions. Such a model will be submitted for publication.

Computed tomographic colonography compared with colonoscopy trial

According to systematic reviews, CTC and colonoscopy have approximately equal sensitivity for large polyps and cancers. Therefore, the comparison between them depends on other issues. We compared costs and costs per case detected.

Computed tomographic colonography has a lower unit cost, but 30% of patients require a further test before a firm diagnosis can be made, compared with 8% of patients having colonoscopy. CTC turns out to be marginally less expensive overall, despite the need for a further test (usually colonoscopy) in nearly one-third of patients. However, costs are closely balanced and a very small increase in unit costs attributed to CTC would alter the above conclusion. In that case, colonoscopy would dominate CTC. As in the case of CTC compared with BE, the confidence limits are relatively wide, especially as far as cancer is concerned. There are further factors to be considered, such as patient acceptability (see *Chapter 5*). On the negative side, we found a slightly increased time to diagnosis for CTC compared with colonoscopy, presumably as a result of the need to refer for colonoscopy to biopsy suspicious lesions.

Extracolonic lesions

One stark difference between CTC and both colonoscopy and BE relates to the detection of extracolonic lesions. Although CTC detected CRC in 5.2% of cases (across both trials), it detected aortic aneurysms or extracolonic cancers in 2.4% – almost half as many. Primary extracolonic cancers were found in 1.3% of cases. Many of these patients would have had a poor prognosis despite detection and others would have had as good a prognosis even if their cancer had gone undetected. However, there are likely to be cases for which earlier detection would make a material difference to patient outcomes. A calculation of the net benefit (or harm) of detecting extracolonic lesions would require complex modelling and this is planned as part of a subsequent follow-on study by the investigators. Xiong *et al.*[40] calculated that if the mean cost of investigating extracolonic lesions was £150, then detecting such lesions would be cost-effective if it resulted with a gain of one life-year every 3000 CTC examinations. Whether or not this is the case is scientifically unproven at this point.

Conclusion

Neither CTC nor colonoscopy shows clear superiority in terms of either cost or cases detected. However, CTC detects more cases than BE, but at higher total cost. Extracolonic lesions remain an enigma as far as health economics of CTC is concerned. In the meantime, individual patients will have personal utilities driving individual decisions and there is an argument that leaving the decision to individual discretions maximises societal utility gain in such split choice scenarios.[107]

Conclusions

Implications for health care

- Computed tomographic colonography detects more cancers and large polyps than BE, misses fewer cancers and improves patient experience, but also precipitates more follow-up investigations. CTC could replace BE for large bowel investigation.
- Computed tomographic colonography is a safe alternative to colonoscopy in symptomatic patients, with similar sensitivity and improved patient experience in the short term. The way in which the results are conveyed (i.e. quicker and face to face) favours colonoscopy. CTC precipitates significantly more follow-up examinations – which, in a limited sample, did not adversely impact on patient experience – but criteria for subsequent referral are needed.
- Most patients have extracolonic findings reported at CTC and 8.5% undergo further investigation for these. Approximately 2% overall have an extracolonic malignancy detected. Offering CTC as the primary procedure did not significantly alter the proportion of patients diagnosed with extracolonic malignancy at 3 years compared with colonoscopy or BE.
- When compared with BE, CTC detected one extra serious colonic neoplasm for approximately £4000. However, the detection rates were similar for CTC compared with colonoscopy and costs were similar such that there was little evidence on which a firm recommendation should be based.

Recommendations for further research

1. The benefits of CTC observed in both trials will improve if referrals for clinically unnecessary subsequent investigations are diminished; there is a need to develop evidence-based guidelines for referral after CTC.
2. No difference was found between tests regarding the proportion of extracolonic cancers detected within 3 years. The reasons for this are unclear but it appears that many patients having a BE or colonoscopy have subsequent extracolonic investigation in cases where no colonic abnormality was found. How and why this happens merits further research to clarify the clinical effectiveness and cost-effectiveness of CTC.
3. The combined benefits of detecting intracolonic and extracolonic pathology by CTC should be modelled beyond the trial data set over an extended time horizon to estimate if CTC is cost-effective compared with colonoscopy overall. This is not a trivial undertaking.
4. Research is needed to guide implementation of CTC, especially the training needed for competent interpretation.
5. The acceptability to patients of increased referrals following CTC needs further investigation.
6. Implementation of CTC in the National Bowel Cancer Screening Programme warrants investigation. Detection characteristics for significant neoplasia were good in the present study but lesions are likely to be smaller in a screening group and, therefore, more difficult to detect.

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Appendix 1 SIGGAR forms

Special Interest Group In Gastrointestinal & Abdominal Radiology V.21/04/06

INITIAL RECRUITMENT FORM
Outpatient route

Study number:
Hospital number:
Patient title: Surname:
Patient forename:
Sex M F
Date of birth: d d m m y y y y
Patient telephone: Mobile:
GP Surname: GP Forname:
GP Surgery name:
GP Address:
GP Postcode: GP Telephone:

Please affix address label here

DETAILS OF REFERRAL (Please complete as appropriate and tick (✓) **ALL** that apply)

Rectal bleeding Abdominal pain Anaemia Weight loss FOBT positive
Change in bowel habit Specify:
Other Specify:
Flexible sigmoidoscopy performed: Date: d d m m y y y y
Rigid sigmoidoscopy performed: Date: d d m m y y y y

OP CLINIC REQUESTING INVESTIGATION (Please complete as appropriate)

Clinic type: Colorectal surgical clinic Gastroenterology
Other Specify:
Name of consultant: Clinician seeing patient:
Urgency: Two week wait Urgent Soon Routine
Route of Referral: GP Other Specify:
Date of clinic: d d m m y y y y Attended Clinic: Yes No
If **NO**, reason: New clinic date: d d m m y y y y

DIAGNOSES (If appropriate)

INVESTIGATION REQUESTED (Please tick (✓) **ONE** box that applies – PTO)

Colonoscopy Barium Enema Other specify:

CONSULTANT AGREEMENT (Please complete as appropriate)

Consultant agrees patient suitable for trial Yes No
If **NO**, reason:
Urgency of procedure: Fast track Urgent Soon Routine N/A Comment:

PATIENT CONSENT (Please complete as appropriate)

Consent form: given to patient person who sent form:
Patient signed consent? Yes No If **NO**, reason:
Letter sent to GP Yes Date: d d m m y y y y

RANDOMISATION (Please complete as appropriate)

Diagnostic pathway before randomisation: Colonoscopy Barium Enema
Procedure allocated after randomisation: **Colonoscopy** **Barium Enema** **CT**
Date of exam appointment: d d m m y y y y Time: am/pm
Date of outpatient appointment: d d m m y y y y Time: am/pm N/A

PERSON COMPLETING FORM

Name: Job title:
Date: d d m m y y y y

Please return **TOP** (Grey) copy to: Prof Wendy Atkin SIGGAR1, CR-UK Colorectal Unit, St Mark's Hospital, FREEPOST LON 2069, Harrow HA1 3BR

SIGAR-OP1/606

Special Interest Group in Gastrointestinal & Abdominal Radiology V.21/04/06

INITIAL RECRUITMENT FORM
Radiology/Endoscopy route

Study number:
Hospital number:
Patient title: Surname:
Patient forename:
Sex M F
Date of birth: d d m m y y y y
Patient telephone: Mobile:
GP Surname: GP Forname:
GP Surgery name:
GP Address:
GP Postcode: GP Telephone:

Please affix address label here

ASCERTAINMENT OF PATIENT (Please tick (✓) **ONE** box that applies)

Endoscopy ☐ Radiology ☐ CT clinic ☐ A&E ☐ Other ☐ Specify:

INVESTIGATION REQUESTED (Please tick (✓) **ONE** box that applies – PTO)

Colonoscopy ☐ Barium Enema ☐ Other ☐ Specify:

REASON FOR REFERRAL (Please tick (✓) **ALL** boxes that apply – PTO)

Rectal bleeding ☐ Abdominal pain ☐ Anaemia ☐ Weight loss ☐ FOBT positive ☐
Change in bowel habit ☐ Please specify:
Other ☐ Specify:

ROUTE OF REFERRAL (Please tick (✓) ONE box that applies)

Outpatient clinic ☐ GP referral ☐ Other ☐ please specify:

OP CLINIC REQUESTING INVESTIGATION (only complete this section if route of referral is outpatient clinic)

Clinic type: ☐ Colorectal surgical clinic ☐ Gastroenterology ☐ Geriatrics ☐
Other ☐ Please specify:
Name of consultant: Clinician seeing patient:
Date of clinic: d d m m y y y y
Urgency: Two week wait ☐ Urgent ☐ Soon ☐ Routine ☐

DIAGNOSES (If appropriate)

CONSULTANT AGREEMENT (Please complete as appropriate)

Letter sent to consultant Yes ☐ Date letter sent: d d m m y y y y
Consultant agrees patient suitable for trial Yes ☐ No ☐
If **NO**, reason:
Urgency of procedure: Fast track ☐ Urgent ☐ Soon ☐ Routine ☐ N/A ☐ Comment:

PATIENT CONSENT (Please complete as appropriate)

Consent form: posted to patient ☐ Date: d d m m y y y y person who sent form:
Patient signed consent? Yes ☐ No ☐ If **NO**, reason:
Letter sent to GP Yes ☐ Date: d d m m y y y y

RANDOMISATION (Please complete as appropriate)

Diagnostic pathway before randomisation: Colonoscopy ☐ Barium Enema ☐
Procedure allocated after randomisation: **Colonoscopy** ☐ **Barium Enema** ☐ **CT** ☐
Date of exam appointment: d d m m y y y y Time: : am/pm
Date of outpatient appointment: d d m m y y y y Time: : am/pm N/A ☐

PERSON COMPLETING FORM

Name: Job title:
Date: d d m m y y y y

Please return **TOP** (Grey) copy to: Prof Wendy Atkin SIGGAR1, CR-UK Colorectal Unit, St Mark's Hospital, FREEPOST LON 2069, Harrow HA1 3BR

The North West London Hospitals
NHS Trust
Northwick Park Hospital
Watford Road
Harrow
Middlesex
HA1 3UJ

Tel: 0208 235 4253
Fax: 0208 864 2693

Lead Researchers:
Prof S. Halligan Consultant Radiologist
Prof W. Atkin Clinical Epidemiologist

Please affix address label here

CONSENT FORM

Virtual colonoscopy compared with BARIUM ENEMA for diagnosis of bowel disease

	Please INITIAL box
1. I confirm that I have read and understand the information sheet dated May 2005 for the above study and have had the opportunity to ask questions.	☐ INITIAL
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐ INITIAL
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. I understand that data collected in this trial may be used for future research and that I cannot be identified from this data.	☐ INITIAL
4. In principle I agree to take part in the above study. I understand that this decision is not binding at this point in time and that I have at least 24 hours further to reconsider.	☐ INITIAL

Name of Patient	Date	Signature
Name of researcher or person taking consent	Date	Signature

Thank you.

Please return TOP COPY in the stamped, addressed envelope provided to:
Prof Wendy Atkin. SIGGAR1 Trial, Colorectal Unit, St Mark's Hospital, Level 5, Northwick Park, Harrow. HA1 3UJ

Give one copy to the patient, put one copy in the patient's medical notes and keep one copy for your records

V.1.2-19/04/05

SIGC1/BX

The North West London Hospitals
NHS Trust
Northwick Park Hospital
Watford Road
Harrow
Middlesex
HA1 3UJ

Tel: 0208 235 4253
Fax: 0208 864 2693

Lead Researchers:
Prof S. Halligan Consultant Radiologist
Prof W. Atkin Clinical Epidemiologist

Please affix address label here

CONSENT FORM

Virtual colonoscopy compared with conventional COLONOSCOPY for diagnosis of bowel disease

	Please INITIAL box
1. I confirm that I have read and understand the information sheet dated May 2005 for the above study and have had the opportunity to ask questions.	☐ INITIAL
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐ INITIAL
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. I understand that data collected in this trial may be used for future research and that I cannot be identified from this data.	☐ INITIAL
4. In principle I agree to take part in the above study. I understand that this decision is not binding at this point in time and that I have at least 24 hours further to reconsider.	☐ INITIAL

Name of Patient	Date	Signature
Name of researcher or person taking consent	Date	Signature

Thank you.

Please return TOP COPY in the stamped, addressed envelope provided to:
Prof Wendy Atkin. SIGGAR1 Trial, Colorectal Unit, St Mark's Hospital, Level 5, Northwick Park, Harrow. HA1 3UJ

Give one copy to the patient, put one copy in the patient's medical notes and keep one copy for your records

V.1.2-19/04/05

SIGC/1606

Special Interest Group in Gastrointestinal & Abdominal Radiology V.21/04/06

BARIUM ENEMA FORM

GREEN

Study number:

Hospital number:

Patient title: Surname:

Patient forename:

Please affix address label here

Exam Date: d d m m y y y y Time: : am/pm

Exam not performed: Reason:

Room Time Enter: : am/pm Exit: : am/pm

Procedure Time Start: : am/pm Stop: : am/pm

Reason/Indications:

STUDY PERFORMED BY (Please tick (✓) **ONE** box)

Reporting Radiologist ☐ Radiographer ☐ Other Consultant ☐ SpR ☐

OVERALL ASSESSMENT OF EXAMINATION (Please tick (✓) **ONE** box)

Very easy ☐ Quite easy ☐ Quite difficult ☐ Very difficult ☐

TECHNICAL DIFFICULTIES (Please tick (✓) where option applies)

Incontinence to barium ☐ Poor mobility ☐ Redundant colon ☐ Other ☐ Specify:

MEDICATION (Please tick (✓) as appropriate and indicate dose)

Buscopan ☐ mg Glucagon ☐ mg Other ☐ Please specify:

BOWEL PREPARATION (Please tick (✓) **ONE** box)

Excellent ☐ Good ☐ Adequate ☐ Poor ☐

ADVERSE EVENTS (Please describe – *use overleaf if necessary*)

SEGMENTAL VISUALISATION (Please compete as appropriate)

Time taken for interpretation : mins *(To the nearest half minute)*

SEGMENT (Code each box)	RM	RS	SC	DC	SF	TC	HF	AC	CM
Quality (**1** Excellent, **2** Good, **3** Adequate, **4** Poor, **8** Not Seen)									
Diverticula (**0** None, **1** Mild, **2** Moderate, **3** Severe)									

OVERALL FINDINGS WITH RESPECT TO COLONIC NEOPLASIA (Please tick (✓) where option applies)

☐ Normal If normal, confidence that there are no significant polyps or cancer (**1** Excellent, **2** Good, **3** Adequate, **4** Poor) ☐

☐ Suspected cancer or polyps *(please record below)*

REPORT ON CANCERS OR POLYPS (Please complete for **EACH** lesion seen)

Lesion	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**
Segment **(RM, RS, SC, DC, SF, TC, HF, AC, CM)**										
Estimated size **(mm)**										
Cancer **(C)**, Polyp **(P)** or Unsure **(U)**										
Confidence for presence of lesion (**1** Excellent, **2** Good, **3** Adequate, **4** Poor)										
If cancer **(C)**, confidence in diagnosis (**1** Excellent, **2** Good, **3** Adequate, **4** Poor)										
If polyp **(P)**, confidence not cancer (**1** Excellent, **2** Good, **3** Adequate, **4** Poor)										

OTHER FINDINGS /COMMENTS (Please describe)

ACTION (Please tick (✓) **ONE** box)

☐ Discharged ☐ Referred back to clinician ☐ Referred for another procedure

If **YES**, please specify Date: d d m m y y y y

RADIOLOGIST(S) reading films (Please **PRINT** and complete as appropriate)

Name: Grade: Name: Grade:

Please return **TOP** (Green) copy to: Prof Wendy Atkin SIGGAR1, CR-UK Colorectal Unit, St Mark's Hospital, FREEPOST LON 2069, Harrow HA1 3BR

SIGBAR1/6/06

Special Interest Group in Gastrointestinal & Abdominal Radiology V.21/04/06

COLONOSCOPY FORM

YELLOW

Study number:

Hospital number:

Patient title: Surname:

Patient forename:

Please affix address label here

Exam Date: d d / m m / y y y y Time: : am/pm

Exam not performed: Reason:

Room Time Enter: : am/pm Exit: : am/pm

Procedure Time Start: : am/pm Stop: : am/pm

Reason/Indications:

OVERALL ASSESSMENT OF EXAMINATION (Please tick (✓) **ONE** box only)

Very easy ☐ Quite easy ☐ Quite difficult ☐ Very difficult ☐

MEDICATION (Please tick (✓) **ALL** boxes that apply and indicate dose)

Pethidine ☐ mg Midazolam ☐ mg Fentanyl ☐ mg Buscopan ☐ mg

Other ☐ Please specify:

BOWEL PREPARATION (Please tick (✓) **ONE** box only)

Excellent ☐ Good ☐ Adequate ☐ Poor ☐

OVERALL FINDINGS (Please tick (✓) as appropriate)

☐ Normal
☐ Suspected cancer (record below)
☐ Polyps (record below)
☐ Other, please specify below or overleaf

COMPLETENESS OF EXAMINATION

Segment reached (RM, RS, SC, DC, SF, TC, HF, AC,CM)? ☐☐

Examination complete (to caecal pole)? Yes ☐ No ☐

If **NO**, reason, please tick (✓): Pain ☐ Faeces ☐ Other ☐

If **OTHER** specify

ADVERSE EVENTS (Please describe – *use overleaf if necessary*)

POLYPS/ CANCERS/ BIOPSIES – *see overleaf for guide to filling form* (Please complete **ONE** line for each lesion)

Polyp No	SEGMENT	Distance from Anus (cm)	SIZE (mm)	Please tick (✓) **ONE** box for **EACH** question: Stalk Narrow 1	Stalk Wide 2	Sessile 3	Flat or Depressed 4	Cold Biopsy 1	Hot Biopsy 2	Cold Snare 3	Hot snare 4	No Rx 5	Clin Diag PTO	Fate Biopsy PTO
A				☐	☐	☐	☐	☐	☐	☐	☐	☐		
B				☐	☐	☐	☐	☐	☐	☐	☐	☐		
C				☐	☐	☐	☐	☐	☐	☐	☐	☐		
D				☐	☐	☐	☐	☐	☐	☐	☐	☐		
E				☐	☐	☐	☐	☐	☐	☐	☐	☐		
F				☐	☐	☐	☐	☐	☐	☐	☐	☐		
G				☐	☐	☐	☐	☐	☐	☐	☐	☐		
H				☐	☐	☐	☐	☐	☐	☐	☐	☐		
I				☐	☐	☐	☐	☐	☐	☐	☐	☐		
J				☐	☐	☐	☐	☐	☐	☐	☐	☐		

SEGMENT (Code **each** box)	RM	RS	SC	DC	SF	TC	HF	AC	CM
Diverticula: (**0** None, **1** Mild, **2** Moderate, **3** Severe)									

OTHER FINDINGS/DIAGNOSES (Please describe)

ACTION (Please tick (✓) **ALL** boxes as appropriate)

☐ **Cancer detected** (tick (✓) all as appropriate)
Refer to surgeon ☐ Procedure requested? ☐ If **YES**, please specify:

☐ **No cancer detected** (tick (✓) all as appropriate)
Refer back to clinician ☐ Exam incomplete? ☐ Specify procedure referred for:

☐ **Polyp detected:** Surveillance in years Specify exam: Check excision site in weeks

☐ **Discharged**

COMMENTS (Please describe)

Name of endoscopist: (Please PRINT) **Signature:**

Please return **TOP** (Yellow) copy to: Prof Wendy Atkin SIGGAR1, CR-UK Colorectal Unit, St Mark's Hospital, FREEPOST LON 2069, Harrow HA1 3BR

SIG/COL/1606

Special Interest Group in Gastrointestinal & Abdominal Radiology V.21/04/06

CT COLONOGRAPHY FORM

BLUE

Study number:

Hospital number:

Patient title: Surname:

Patient forename:

Please affix address label here

Exam Date: d d m m y y y y Time: am/pm

Exam not performed: Reason:

Room Time Enter: am/pm Exit: am/pm

Procedure Time Start: am/pm Stop: am/pm

Reason/Indications:

STUDY PERFORMED BY (Please tick (✓) **ONE** box)

Reporting Radiologist ☐ Radiographer ☐ Other Consultant ☐ SpR ☐

OVERALL ASSESSMENT OF EXAMINATION (Please tick (✓) **ONE** box)

Very easy ☐ Quite easy ☐ Quite difficult ☐ Very difficult ☐

MEDICATION (Please tick (✓) as appropriate and indicate dose)

Buscopan ☐ mg Glucagon ☐ mg Other ☐ Please specify:

BOWEL PREPARATION (Please tick (✓) **ONE** box)

Excellent ☐ Good ☐ Adequate ☐ Poor ☐

EXAMINATION (Please tick (✓) where option applies)

Slice Collimation: mm (1-5) No. of detector rows (4-64)

Scans obtained: Prone ☐ Supine ☐ Gas: Carbon Dioxide ☐ Air ☐

Intravenous contrast administered? ☐ Oral labeling used? ☐ Mechanical insufflators used? ☐

TECHNICAL DIFFICULTIES (Please tick (✓) where option applies)

Incontinence to gas ☐ Poor mobility ☐ Other ☐ Specify: ☐

ADVERSE EVENTS (Please describe – *use overleaf if necessary*)

SEGMENTAL VISUALISATION (for prone & supine scans combined)

Time taken for interpretation : mins Proportion of 2D to 3D reading (e.g. 80:20)

Reading platform used, please specify (e.g. Voxar, Vitrea, GE):

SEGMENT (Code each box)	RM	RS	SC	DC	SF	TC	HF	AC	CM
Quality (**1** Excellent, **2** Good, **3** Adequate, **4** Poor, **8** Not Seen)									
Diverticula (**0** None, **1** Mild, **2** Moderate, **3** Severe)									

OVERALL FINDINGS WITH RESPECT TO COLONIC NEOPLASIA (Please tick (✓) where option applies)

☐ Normal. If **normal**, confidence that there are no significant polyps or cancer (**1** Excellent, **2** Good, **3** Adequate, **4** Poor) ☐

☐ Suspected cancer or polyps *(please record below)*

REPORT ON CANCERS OR POLYPS (Please complete for **EACH** lesion seen)

Lesion	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**
Segment **(RM, RS, SC, DC, SF, TC, HF, AC, CM)**										
Estimated size **(mm)**										
Cancer **(C)**, Polyp **(P)** or Unsure **(U)**										
Confidence for presence of lesion (**1** Excellent, **2** Good, **3** Adequate, **4** Poor)										
If cancer **(C)**, confidence in diagnosis (**1** Excellent, **2** Good, **3** Adequate, **4** Poor)										
If polyp **(P)**, confidence not cancer (**1** Excellent, **2** Good, **3** Adequate, **4** Poor)										

OTHER COLONIC FINDINGS (Please describe)

EXTRA COLONIC FINDINGS (Please complete as appropriate)

	Abnormality seen (e.g. size of aortic aneurysm)	Details of any further action suggested on report
1		
2		

ACTION (Please tick (✓) **ONE** box)

☐ Discharged ☐ Referred back to clinician ☐ Referred for another procedure

If **YES**, please specify Date: d d m m y y y y

RADIOLOGIST(S) reporting CT (Please **PRINT** and complete as appropriate)

Name: Grade: Name: Grade:

Please return **TOP** (Blue) copy to: Prof Wendy Atkin SIGGAR1, CR-UK Colorectal Unit, St Mark's Hospital, FREEPOST LON 2069, Harrow HA1 3BR

SIG/CTCOL/1/606

Special Interest Group in Gastrointestinal & Abdominal Radiology V.21/04/06

FLEXIBLE SIGMOIDOSCOPY FORM

Study number:

Hospital number:

Patient title: Surname:

Patient forename:

Please affix address label here

Exam Date: d d m m y y y y Time: : am/pm

Exam not performed: Reason:

Room Time Enter: : am/pm Exit: : am/pm

Procedure Time Start: : am/pm Stop: : am/pm

Reason/Indications:

OVERALL ASSESSMENT OF EXAMINATION (Please tick (✓) **ONE** box only)

Very easy ☐ Quite easy ☐ Quite difficult ☐ Very difficult ☐

BOWEL PREPARATION (Please tick (✓) **ONE** box only)

Excellent ☐ Good ☐ Adequate ☐ Poor ☐

OVERALL FINDINGS (Please tick (✓) as appropriate)

☐ Normal
☐ Suspected cancer (record below)
☐ Polyps (record below)
☐ Other, please specify below or overleaf

COMPLETENESS OF EXAMINATION

Segment reached (RM, RS, SC, DC, SF, TC)?

Examination complete (to SC/DC junction)? Yes ☐ No ☐

If **NO**, reason, please tick (✓): Pain ☐ Faeces ☐ Other ☐

specify:

Maximum shaft insertion? cm

ADVERSE EVENTS (Please describe – *use overleaf if necessary*)

POLYPS/ CANCERS/ BIOPSIES – *see overleaf for guide to filling form* (Please complete **ONE** line for each lesion)

Please tick (✓) **ONE** box for **EACH** question

LESION	SEGMENT	Distance from Anus (cm)	SIZE (mm)	Stalk Narrow 1	Stalk Wide 2	Sessile 3	Flat or Depressed 4	Cold Biopsy 1	Hot Biopsy 2	Cold Snare 3	Hot snare 4	No Rx 5	Clin Diag PTO	Fate Biopsy PTO
A				☐	☐	☐	☐	☐	☐	☐	☐	☐		
B				☐	☐	☐	☐	☐	☐	☐	☐	☐		
C				☐	☐	☐	☐	☐	☐	☐	☐	☐		
D				☐	☐	☐	☐	☐	☐	☐	☐	☐		
E				☐	☐	☐	☐	☐	☐	☐	☐	☐		
F				☐	☐	☐	☐	☐	☐	☐	☐	☐		
G				☐	☐	☐	☐	☐	☐	☐	☐	☐		
H				☐	☐	☐	☐	☐	☐	☐	☐	☐		
I				☐	☐	☐	☐	☐	☐	☐	☐	☐		
J				☐	☐	☐	☐	☐	☐	☐	☐	☐		

SEGMENT (Code **each** box)	RM	RS	SC	DC	SF	TC	HF	AC	CM
Diverticula: (**0** None, **1** Mild, **2** Moderate, **3** Severe)									

OTHER FINDINGS/DIAGNOSES (Please describe)

ACTION (Please tick (✓) **ALL** boxes as appropriate)

☐ **Cancer detected** (tick (✓) all as appropriate)
Refer to surgeon ☐ Procedure requested? ☐ If **YES**, please specify:

☐ **No cancer detected** (tick (✓) all as appropriate)
Refer back to clinician ☐ Exam incomplete? ☐ Specify procedure referred for:

☐ **Polyp detected:** Surveillance in years Specify exam: Check excision site in weeks

☐ **Discharged**

COMMENTS (Please describe)

Name of endoscopist: (Please PRINT) **Signature:**

Please return **TOP** (Pink) copy to: Prof Wendy Atkin SIGGAR1, CR-UK Colorectal Unit, St Mark's Hospital, FREEPOST LON 2069, Harrow HA1 3BR

SIGFS/1606

Special Interest Group in Gastrointestinal & Abdominal Radiology V.21/04/06

SURGICAL RECORD FORM

Study number:
Hospital number:
Patient title: Surname:
Patient forename:
Procedure not performed ☐ Reason:
Reason/Indications:
Date of operation: d d m m y y y y
Time: : am/pm
Surgeon name: Grade:
Assistant name: Grade:

Please affix address label here

OPERATION RECORD (Please tick (✓) as appropriate)

Site(s) of lesion: RM ☐ RS ☐ SC ☐ DC ☐ SF ☐ TC ☐ HF ☐ AC ☐ CM ☐ Anus ☐ Appendix ☐

Intra-operative colonoscopy No ☐ Yes ☐

Indication: Curative ☐ Palliative ☐ Unsure ☐ Other, specify:

Specify operation type:

Please tick (✓) as appropriate:

	Specify type:		
☐ Anastomosis:			
☐ Metastasis:	☐ Liver	☐ Peritoneal	☐ Other, specify
☐ Stoma Ileostomy:	☐ Temporary	☐ Permanent	
☐ Stoma Colostomy:	☐ Temporary	☐ Permanent	

POST-OPERATIVE COURSE

Length of hospital stay days

If >16 days, give reason:

MAJOR COMPLICATIONS (Please tick (✓) as appropriate)

	Pease specify treatment
☐ Anastomotic leak	
☐ Burst abdomen (requiring resuture)	
☐ Wound infection (delaying discharge)	
☐ Other, please specify:	

OTHER COMMENTS: (attach clinical records where relevant)

Signature of Surgeon:

Please return **TOP** (Gold) copy to: Prof Wendy Atkin SIGGAR1, CR-UK Colorectal Unit, St Mark's Hospital, FREEPOST LON 2069, Harrow HA1 3BR

SIGSUR1606

Special Interest Group in Gastrointestinal & Abdominal Radiology V.21/04/06

OUTPATIENT FOLLOW-UP FORM

Study number:
Hospital number:
Patient title: Surname:
Patient forename:
Sex M F
Appointment date: d d / m m / y y y y
Appointment time: : am/pm
Did not attend Reason:

Please affix address label here

WHITE

OP APPOINTMENT DETAILS (Please complete as appropriate)

Consultant in charge of clinic:
Name of clinician seeing patient (if different from above):

CLINICAL HISTORY (Please fill in **ALL** exams that the patient has had – first procedure is initial randomised procedure)

Randomised Procedure (Please tick (✓) one): Colonoscopy ☐ Barium Enema ☐ CT ☐

List other procedures below (in the order in which they took place):

2	4	6
3	5	7

COLONIC FINDINGS AT OR AFTER RANDOMISED PROCEDURE (Pleaase tick (✓) **ALL** boxes that apply)

☐ Cancer, please specify: suspected cancer ☐ confirmed cancer ☐
☐ Polyps, please specify: polyps detected ☐ polyps removed ☐ confirmed adenomas ☐
☐ Other abnormality, please specify:
☐ No abnormality detected

EXTRA COLONIC FINDINGS FROM CT COLONOGRAPHY AT OR AFTER RANDOMISED PROCEDURE (If relevant)

Outpatient consultant/clinician's decision on extra colonic findings (Please tick (✓) **ONE** box that applies):
☐ Incidental to patient's symptoms but I feel obliged to investigate
☐ Incidental to patient's symptoms and I am going to ignore this finding
☐ Cause of symptoms, therefore pursue this line of investigation

PROCEDURES/TESTS PERFORMED AT OUTPATIENT CLINIC (Please complete overleaf if more than one)

Procedure/Test | Details or reason why test performed

ACTION (Please complete as appropriate and tick (✓) **ALL** boxes that apply)

☐ **Discharge from clinic?** ☐ **Watch and wait?** – see again in Months Date: d d / m m / y y y y
☐ Cancer found, specify treatment:
☐ Refer for colonic test(s) If **YES**, specify test, reason and date of appointment if known
Date: d d / m m / y y y y
Date: d d / m m / y y y y
☐ Refer for non colonic test(s) If Yes, specify test, reason and date of appointment if known
Date: d d / m m / y y y y
Date: d d / m m / y y y y

ANY OTHER COMMENTS

PERSON COMPLETING FORM

Name: Job title:
Date: d d / m m / y y y y

Please return **TOP** (White) copy to: Prof Wendy Atkin SIGGAR1, CR-UK Colorectal Unit, St Mark's Hospital, FREEPOST LON 2069, Harrow HA1 3BR

SIGOPSUP1A06

Appendix 2 Patient information sheets

SIGGAR 1

The North West London Hospitals
NHS Trust

NHS

Northwick Park Hospital
Watford Road
Harrow
Middlesex
HA1 3UJ

Tel: 0208 235 4253
Fax: 0208 864 2693

Lead Researchers:
Prof S. Halligan, Consultant Radiologist
Prof W. Atkin, Clinical Epidemiologist

Patient Information sheet

Virtual colonoscopy compared with barium enema for diagnosis of bowel disease

We are inviting you to take part in a research study. Before you decide, you need to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

We want to compare the effectiveness and convenience to you of two procedures that are used to diagnose bowel disease. The method that we have been using up to now at St Marks Hospital is called a barium enema. Barium enema involves filling the bowel with barium liquid and then gas, and then taking x-rays of it in order to see any abnormalities. Recently, a new type of x-ray CT scan called 'virtual colonoscopy' has been developed that is as good at diagnosing disease and may be more convenient for the patient. A few NHS hospitals are already offering virtual colonoscopy to patients instead of barium enema. The NHS has sponsored this research project in order to find out if this test should replace barium enema. The research is being carried out in 15 NHS hospitals and will involve 2,000 patients who will be allocated randomly to receive either the barium enema or the virtual colonoscopy. This way we will be able to find out which works best both for doctors and patients.

Why have I been chosen to take part in the study?

You have been chosen because your doctor has referred you for a bowel examination to find out the reason for your symptoms.

Do I have to take part?

No. It is up to you to decide whether or not to take part in this research. If you decide not to, you will get the barium enema. If you do decide to take part then there will be a random decision to give you either the barium enema or the virtual colonoscopy. We recommend that you keep this information sheet. You can withdraw at any time, or decide not to take part, which will not affect the usual standard of care you receive.

What will happen to me if I take part?

One third of our patients will be given the virtual colonoscopy and two-thirds will have the barium enema, **which is the same test you would have if you did not take part in this research. You will therefore have a one in three chance of having a virtual colonoscopy.** The test you will be offered will be decided by a computer, like in a lottery – **you cannot decide what test you will have.**

Both tests involve taking laxative medicines the day before in order to clear the bowel out. Both tests are performed with you lying down and both involve an injection to relax your bowel.

- For barium enema a doctor or nurse radiographer places a tube just inside your back passage and introduces some barium liquid and then carbon dioxide to inflate the bowel. You will turn into several different positions while x-rays of the bowel are taken. The whole examination takes about 20 to 30 minutes. You will then be free to go.

- During virtual colonoscopy a smaller tube is placed just inside your back passage and, as with barium enema, some carbon dioxide is introduced through this in order to inflate the bowel. One difference for you is that no liquid is used. Two x-ray CT scans are then taken, one with you lying on your

tummy and one with you lying on your back. Each CT scan takes about 20 seconds and you will be asked to hold your breath during this. The whole examination takes about 20 minutes. You will then be free to go.

Whichever test you have, you will need to come back for your out-patient appointment with your doctor to get the results. Whichever test you have, the results

will be handled by your doctor exactly as normal and will also be transferred to a research office at St. Mark's Hospital in London. At various stages up to **three months** after, we will ask your opinion of the test that you received. We will ask you to fill in some short questionnaires that we will send to you along with a stamped-addressed envelope for return.

What are the side effects of taking part?

Neither procedure has any common serious side-effects.

What are the possible disadvantages and risks?

Both the barium enema and virtual colonoscopy use x-rays but both are well within official safe limits for medical procedures. However, the dose of radiation for virtual colonoscopy is slightly higher than that for the barium enema. **The virtual colonoscopy also looks at organs outside the bowel. This has possible advantages (e.g. disease elsewhere may be detected earlier) and disadvantages (e.g. you may need further tests if the virtual colonoscopy shows something elsewhere that you doctor thinks is important).**

What are the benefits?

Both tests are well-established and you will get the best possible care whichever test you have.

What if new information becomes available?

If the virtual colonoscopy test comes out as being better for diagnosis, or more convenient for patients, then we will be able to switch to this test for future investigations.

What if something goes wrong?

If taking part in this research project harms you then usual NHS compensation arrangements apply. If you are harmed due to someone's negligence then you may have grounds for legal action. If you wish to complain about any aspect of the way you have been approached or treated during the course of this study, then we would like to hear from you and would ask you to contact us directly. Also, the normal National Health Service (NHS) complaints mechanisms are available to you.

Will my taking part in this study be kept confidential?

All information about you collected during the course of the research will be kept strictly confidential and available only to your hospital doctor and the study researchers. **During the trial period, your contact details and the results for your investigations will be held on a secure database at St Marks Hospital, a National hospital for Colorectal Diseases.** Any information about you that leaves your hospital will **comply with the Data Protection Act and only authorised study researchers will have access to this information**. Your GP will be notified of your participation in the trial.

What will happen to the results of the research study?

The results following completion of the study will be published in medical journals. Further information can be obtained from Professor Steve Halligan, St Marks Intestinal Imaging Centre. You will not be identified from the publication. The results of this research will be used by the NHS to decide whether to use the virtual colonoscopy test instead of barium enema.

Who is organising the research?

This research is being organised by Professor Steve Halligan, a consultant radiologist at St Mark's Hospital, London, in association with other doctors across the United Kingdom, including many working at Cancer Research UK. The research is happening at 15 hospitals.

The study has been reviewed by the NHS Central Office for Research Ethics Committees (COREC) and the NHS Health Technology Assessment (HTA) Programme is funding this research. The doctors and nurses are not being specially paid to do this research.

If you have further questions or require further information please contact Reshma Kanani (Trial Coordinator), on 020 8235 4253.

Thank you for reading this and taking part if you agree.

Patient information sheet barium enema: Version 1.3 19th May 2005

The North West London Hospitals
NHS Trust

Northwick Park Hospital
Watford Road
Harrow
Middlesex
HA1 3UJ

Tel: 0208 235 4253
Fax: 0208 864 2693

Lead Researchers:
Prof S. Halligan, Consultant Radiologist
Prof W. Atkin, Clinical Epidemiologist

Patient Information Sheet

Virtual colonoscopy compared with conventional colonoscopy for diagnosis of bowel disease

We are inviting you to take part in a research study. Before you decide, you need to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

We want to compare the effectiveness and convenience to you of two procedures that are used to diagnose bowel disease. The method that we have been using up to now at St Marks Hospital is called colonoscopy. Colonoscopy involves inserting a tube into the bowel so that the doctor can see inside in order to see any abnormalities. Recently, a new type of x-ray CT scan called 'virtual colonoscopy' has been developed that is as good at diagnosing disease and may be more convenient for the patient. A few NHS hospitals are already offering virtual colonoscopy to patients instead of conventional colonoscopy. The NHS has sponsored this research project in order to find out if this test should replace conventional colonoscopy. The research is being carried out in 15 NHS hospitals and will involve 2,000 patients who will be allocated randomly to receive either conventional colonoscopy or the virtual colonoscopy. This way we will be able to find out which works best both for doctors and patients.

Why have I been chosen to take part in the study?

You have been chosen because your doctor has referred you for a bowel examination to find out the reason for your symptoms.

Do I have to take part?

No. It is up to you to decide whether or not to take part in this research. If you decide not to, you will get conventional colonoscopy. If you do decide to take part then there will be a random decision to give you either conventional colonoscopy or the virtual colonoscopy. We recommend that you keep this information sheet. You can withdraw at any time, or decide not to take part, which will not affect the usual standard of care you receive.

What will happen to me if I take part?

One third of our patients will be given the virtual colonoscopy and two-thirds will have the conventional **colonoscopy, which is the same test you would have if you did not take part in this research You will therefore have a one in three chance of having a virtual colonoscopy**. The test you will be offered will be decided by a computer, like in a lottery – **you cannot decide what test you will have.**

Both tests involve taking laxative medicines the day before in order to clear the bowel out. Both tests are performed with you lying down and both involve an injection to relax your bowel.

- For conventional colonoscopy a doctor places the colonoscope tube inside your back passage and looks around while moving it along the bowel. You may be given a sedative injection to make you a little drowsy. The whole examination usually takes about 20 minutes but can take longer. If you have been given a sedative you will need to wait for this to wear off before you can go. This usually takes about an hour.

- During virtual colonoscopy a smaller tube is placed just inside your back passage. Some carbon dioxide is introduced through this in order to inflate the bowel. One difference for you is that no sedative is given. Two x-ray CT scans are then taken, one with you lying on your tummy and one with you

lying on your back. Each CT scan takes about 20 seconds and you will be asked to hold your breath during this. The whole examination takes about 20 minutes. You will then be free to go.

Whichever test you have, you will need to come back for your out-patient appointment with your doctor to get the results. Whichever test you have, the results will be handled by your doctor exactly as normal and will also be transferred to a research office at St. Mark's Hospital in London. At various stages up to **three months** after, we will ask your opinion of the test that you received. We will ask you to fill in some short questionnaires that we will send to you along with a stamped-addressed envelope for return.

What are the side effects of taking part?

Neither procedure has any common serious side-effects. However, very rarely, patients having conventional colonoscopy may become over-drowsy with the sedative. Even more rarely, the bowel can be torn by the colonoscope tube. This is very uncommon.

What are the possible disadvantages and risks?

The virtual colonoscopy use x-rays but is well within official safe limits for medical procedures. **The virtual colonoscopy also looks at organs outside the bowel. This has possible advantages (e.g. disease elsewhere may be detected earlier) and disadvantages (e.g. you may need further tests if the virtual colonoscopy shows something elsewhere that you doctor thinks is important).**

What are the benefits?

Both tests are well-established and you will get the best possible care whichever test you have.

What if new information becomes available?

If the virtual colonoscopy test comes out as being better for diagnosis, or more convenient for patients, then we will be able to switch to this test for future investigations.

What if something goes wrong?

If taking part in this research project harms you then usual NHS compensation arrangements apply. If you are harmed due to someone's negligence then you may have grounds for legal action. If you wish to complain about any aspect of the way you have been approached or treated during the course of this study, then we would

like to hear from you and would ask you to contact us directly. Also, the normal National Health Service (NHS) complaints mechanisms are available to you.

Will my taking part in this study be kept confidential?

All information about you collected during the course of the research will be kept strictly confidential and available only to your hospital doctor and the study researchers. **During the trial period, your contact details and the results for your investigations will be held on a secure database at St Marks Hospital, a National hospital for Colorectal Diseases.** Any information about you that leaves your hospital will **comply with the Data Protection Act and only authorised study researchers will have access to this information**. Your GP will be notified of your participation in the trial.

What will happen to the results of the research study?

The results following completion of the study will be published in medical journals. Further information can be obtained from Professor Steve Halligan, St Marks Intestinal Imaging Centre. You will not be identified from the publication. The results of this research will be used by the NHS to decide whether to use the virtual colonoscopy test instead of conventional colonoscopy.

Who is organising the research?

This research is being organised by Professor Steve Halligan, a consultant radiologist at St Mark's Hospital, London, in association with other doctors across the United Kingdom, including many working at Cancer Research UK. The research is happening at 15 hospitals.

The study has been reviewed by the NHS Central Office for Research Ethics Committees (COREC) and the NHS Health Technology Assessment (HTA) Programme is funding this research. The doctors and nurses are not being specially paid to do this research. If you have further questions or require further information please contact Reshma Kanani (Trial Coordinator) on 020 8235 4253.

Thank you for reading this and taking part if you agree.

Patient information sheet colonoscopy: Version 1.3 19th May 2005

Appendix 3 Psychological questionnaires

Study Number:	
Initials:	
Diagnostic pathway before randomisation:	Colonoscopy ☐ Barium enema ☐
Date randomised:	

AFTER THE TEST I

Dear Patient,

Thank you for helping us with this questionnaire on your experiences of the bowel test.

The questions will ask you about your experience of the bowel examination and should be completed AFTER you had your bowel test at the hospital. Ideally we would like you to complete this questionnaire ON THE MORNING **AFTER** THE BOWEL TEST or soon after.

Your answers will help us learn more about patients' experiences of different types of bowel tests. So we are very grateful for your time.

Your answers will be treated in strict confidence.

Once you have completed the questionnaire, please return it in the enclosed freepost envelope. No stamp is required.

For any questions please contact the study co-ordinator:

Study Co-ordinator
Reshma Kanani
Tel: 020 8235 4253, Fax: 020 8864 2693

SIG-PT1-1-906

Please turn to the next page...

HOW ARE YOU FEELING RIGHT NOW?

Below is a list of words that describe different feelings you might be experiencing right now. We are interested in your GENERAL mood at the moment. Please read EACH word and tick (✓) the box that best indicates the extent to which you feel this way right now. Have a look at the EXAMPLE below:

EXAMPLE: Consider the word 'sleepy'.

If you are **NOT** feeling sleepy right now you should tick (✓) 'very slightly or not at all'

	Very slightly or not at all	A little	Moderately	Quite a bit	Extremely
Sleepy	☑	☐	☐	☐	☐

Or if you feel **MODERATELY** 'sleepy', you should tick (✓) 'moderately '

	Very slightly or not at all	A little	Moderately	Quite a bit	Extremely
Sleepy	☐	☐	☑	☐	☐

Now please read **EACH** word carefully. If a word does not apply or make sense to you, please tick 'very slightly not at all'. It is important that you tick (✓) a box for **EVERY** word.

	Very slightly or not at all	A little	Moderately	Quite a bit	Extremely
Active	☐	☐	☐	☐	☐
Distressed	☐	☐	☐	☐	☐
Excited	☐	☐	☐	☐	☐
Upset	☐	☐	☐	☐	☐
Strong	☐	☐	☐	☐	☐
Guilty	☐	☐	☐	☐	☐
Scared	☐	☐	☐	☐	☐
Hostile	☐	☐	☐	☐	☐
Enthusiastic	☐	☐	☐	☐	☐
Proud	☐	☐	☐	☐	☐
Irritable	☐	☐	☐	☐	☐
Alert	☐	☐	☐	☐	☐
Ashamed	☐	☐	☐	☐	☐
Inspired	☐	☐	☐	☐	☐
Nervous	☐	☐	☐	☐	☐
Determined	☐	☐	☐	☐	☐
Attentive	☐	☐	☐	☐	☐
Jittery (on edge)	☐	☐	☐	☐	☐
Interested	☐	☐	☐	☐	☐
Afraid	☐	☐	☐	☐	☐

Please turn to the next page...

BEFORE THE TEST

How acceptable did you find the bowel preparation?			
Not at all acceptable ☐	Slightly acceptable ☐	Fairly acceptable ☐	Very acceptable ☐
Did you read the instructions for the bowel preparation?		Yes ☐	No ☐
If YES how satisfied were you with the instructions for the bowel preparation?			
Very dissatisfied ☐	Dissatisfied ☐	Satisfied ☐	Very satisfied ☐
What was the date and time of your appointment?		Time	Date
Did anyone come with you to the test?		Yes ☐	No ☐
If YES, was it difficult to find someone to come with you to the test?			
Not at all difficult ☐	Slightly difficult ☐	Fairly difficult ☐	Very difficult ☐
If you had to have the same test again in future, would you ask someone to come with you?			
Yes ☐	No ☐	Don't know ☐	
How satisfied were you with the waiting room facilities at the hospital?			
Very dissatisfied ☐	Dissatisfied ☐	Satisfied ☐	Very satisfied ☐
How satisfied were you with the changing room facilities at the hospital?			
Very dissatisfied ☐	Dissatisfied ☐	Satisfied ☐	Very satisfied ☐

Please turn to the next page...

HAVING THE BOWEL TEST

Which bowel test did you have in the hospital?

Barium enema	CT colonography (Scan)	Colonoscopy	Don't know
☐	☐	☐	☐

How satisfied were you with the test?

Very dissatisfied	Dissatisfied	Satisfied	Very satisfied
☐	☐	☐	☐

Was the test more painful or less painful than you expected?

Less painful than I expected	About the same as I expected	More painful than I expected
☐	☐	☐

Did you receive a sedative before or during the procedure? Yes ☐ No ☐ Don't know ☐

How bloated did you feel during the bowel test?

Not at all	Somewhat	Moderately	Very
☐	☐	☐	☐

How satisfied were you with the instructions from clinical staff during the bowel test?

Very dissatisfied	Dissatisfied	Satisfied	Very satisfied
☐	☐	☐	☐

How satisfied were you with the attitude of staff during the bowel test?

Very dissatisfied	Dissatisfied	Satisfied	Very satisfied
☐	☐	☐	☐

During the bowel test, were you given information about the findings of the investigation? Yes ☐ No ☐

Please turn to the next page...

THINKING ABOUT THE TEST YOU HAD

For each word or statement below, please tick (✓) the box on the scale below which best describes your experience of the test. Please begin by looking at the example below.

EXAMPLE								
FOR EXAMPLE: If you felt that **time went slowly** during the test you might tick the scale like this								
Time went slowly	☑	☐	☐	☐	☐	☐	☐	*Time went quickly*
Or If you felt that **time went neither slowly nor quickly** you might tick the scale like this								
Time went slowly	☐	☐	☐	☑	☐	☐	☐	*Time went quickly*

Felt out of control	☐	☐	☐	☐	☐	☐	☐	Felt in control
Worried	☐	☐	☐	☐	☐	☐	☐	Not worried
Undignified	☐	☐	☐	☐	☐	☐	☐	Dignified
Uncomfortable	☐	☐	☐	☐	☐	☐	☐	Comfortable
Dissatisfied	☐	☐	☐	☐	☐	☐	☐	Satisfied
Intrusive	☐	☐	☐	☐	☐	☐	☐	Not intrusive
Loss of modesty	☐	☐	☐	☐	☐	☐	☐	No loss of modesty
Agitated	☐	☐	☐	☐	☐	☐	☐	Calm
Staff were not interested in me	☐	☐	☐	☐	☐	☐	☐	Staff were interested in me
Staff were cold	☐	☐	☐	☐	☐	☐	☐	Staff were warm
I'd have preferred to be **less** awake	☐	☐	☐	☐	☐	☐	☐	I'd have preferred to be **more** awake
Did not understand what was happening	☐	☐	☐	☐	☐	☐	☐	Understood what was happening
Soreness	☐	☐	☐	☐	☐	☐	☐	No soreness
Hard to cope with	☐	☐	☐	☐	☐	☐	☐	Easy to cope with
Staff were not informative	☐	☐	☐	☐	☐	☐	☐	Staff were informative
I felt puzzled	☐	☐	☐	☐	☐	☐	☐	I did not feel puzzled

Please turn to the next page...

Afraid of "making a fool of myself"	☐	☐	☐	☐	☐	☐	☐	Not afraid of "making a fool of myself"
I was not interested	☐	☐	☐	☐	☐	☐	☐	I was interested
Took a long time for bowels to get going again	☐	☐	☐	☐	☐	☐	☐	Did not take a long time for bowels to get going again
Painful	☐	☐	☐	☐	☐	☐	☐	Not painful
Difficult to do what was required	☐	☐	☐	☐	☐	☐	☐	Easy to do what was required
Not confident in staff	☐	☐	☐	☐	☐	☐	☐	Confident in staff
I was worried about what they would find	☐	☐	☐	☐	☐	☐	☐	I was not worried about what they would find
A bad experience	☐	☐	☐	☐	☐	☐	☐	A good experience
I was confused	☐	☐	☐	☐	☐	☐	☐	I was not confused
Tired afterwards	☐	☐	☐	☐	☐	☐	☐	Not tired afterwards
Not enough privacy	☐	☐	☐	☐	☐	☐	☐	Enough privacy
Claustrophobic	☐	☐	☐	☐	☐	☐	☐	Not claustrophobic
Staff did not make me feel at ease	☐	☐	☐	☐	☐	☐	☐	Staff made me feel at ease
Bloated afterwards	☐	☐	☐	☐	☐	☐	☐	Not bloated afterwards
Undesirable side effects	☐	☐	☐	☐	☐	☐	☐	No undesirable side effects
I was not pleased with how it went	☐	☐	☐	☐	☐	☐	☐	I was pleased with how it went

Please turn to the next page...

AFTER THE TEST

How did you feel in the hours immediately after the test?

.....

.....

.....

How satisfied were you with the instructions on what to do after the bowel test?

Very dissatisfied	Dissatisfied	Satisfied	Very satisfied
☐	☐	☐	☐

Did you receive information about the results of your test after you left the examination room (before you left the hospital)? Yes ☐ No ☐

Did you have any follow up investigation immediately after the test? Yes ☐ No ☐

Were you given something to drink after your bowel test? Yes ☐ No ☐

Were you given something to eat after your bowel test? Yes ☐ No ☐

If **not**, would you like to have been given some food and/or drink after the test?

Food	Drink	Both	Neither
☐	☐	☐	☐

Did you experience any of the following symptoms after the test?

	None	Mild	Moderate	Severe
Abdominal pain/cramps	☐	☐	☐	☐
Nausea/vomiting	☐	☐	☐	☐
Faint feeling or dizziness	☐	☐	☐	☐
Wind	☐	☐	☐	☐
Bottom soreness	☐	☐	☐	☐
Soiling	☐	☐	☐	☐
Sleep difficulties	☐	☐	☐	☐
Anxiety	☐	☐	☐	☐

Please indicate below how long you felt it took before you had fully recovered from the test?

Immediately	Up to 1 hour	Up to 3 hours	Up to 6 hours	Up to 12 hours	More than 12 hours	Still recovering
☐	☐	☐	☐	☐	☐	☐

Please turn to the next page...

Which of the following was the LEAST acceptable aspect of the test?

Bowel Preparation (Laxative)	Bowel test	Other
☐	☐	☐

If other please specify:

.....

.....

.....

Would you recommend this test as part of a screening programme? In other words, to be used on healthy people with NO particular bowel problems to test for illnesses such as bowel cancer?

Yes	No	Don't know
☐	☐	☐

Please fill in TODAY'S DATE: D D / M M / Y Y Y Y

Please check you have answered **all** the questions. Your answers are very important to us so we might contact you about any missing information.

☐ I do not wish to be contacted about any missing information.

THANK YOU VERY MUCH FOR TAKING THE TIME TO COMPLETE THIS QUESTIONNAIRE

If you lose the Freepost envelope, please post to:
St Marks Hospital, SIGGAR1, FREEPOST LON 2069,
CR-UK Colorectal Unit, St Marks Hospital,
Northwick Park HARROW. HA1 3BR
(no stamp is needed)

Study Number:	
Initials:	
Diagnostic pathway before randomisation:	Colonoscopy ☐ Barium enema ☐
Date randomised:	

AFTER THE TEST II

Dear Patient,

By filling in the questionnaire you are helping us to fully understand what it is like to have a bowel test including the experiences following the examination.

All of your responses will be used to compare your experiences with those of other patients and ultimately enable us to improve services in the future.

Your answers will be treated in strict confidence and are very important for our research into improving patient care.

Please fill in this questionnaire and return it in the enclosed freepost envelope. No stamp is required.

For any questions, please contact the study co-ordinator.

Study Co-ordinator
Reshma Kanani
Tel: 020 8235 4253, Fax: 020 8864 2693

SIG-PT2-1-906

Please turn to the next page...

HOW ARE YOU FEELING RIGHT NOW?

Below is a list of words that describe different feelings you might be experiencing right now. We are interested in your GENERAL mood at the moment. Please read EACH word and tick (✓) the box that best indicates the extent to which you feel this way right now. Have a look at the EXAMPLE below:

EXAMPLE: Consider the word 'sleepy'.

If you are **NOT** feeling sleepy right now you should tick (✓) 'very slightly or not at all'

	Very slightly or not at all	A little	Moderately	Quite a bit	Extremely
Sleepy	☑	☐	☐	☐	☐

Or if you feel **MODERATELY** 'sleepy', you should tick (✓) 'moderately '

	Very slightly or not at all	A little	Moderately	Quite a bit	Extremely
Sleepy	☐	☐	☑	☐	☐

Now please read **EACH** word carefully. If a word does not apply or make sense to you, please tick 'very slightly not at all'. It is important that you tick (✓) a box for **EVERY** word.

	Very slightly or not at all	A little	Moderately	Quite a bit	Extremely
Active	☐	☐	☐	☐	☐
Distressed	☐	☐	☐	☐	☐
Excited	☐	☐	☐	☐	☐
Upset	☐	☐	☐	☐	☐
Strong	☐	☐	☐	☐	☐
Guilty	☐	☐	☐	☐	☐
Scared	☐	☐	☐	☐	☐
Hostile	☐	☐	☐	☐	☐
Enthusiastic	☐	☐	☐	☐	☐
Proud	☐	☐	☐	☐	☐
Irritable	☐	☐	☐	☐	☐
Alert	☐	☐	☐	☐	☐
Ashamed	☐	☐	☐	☐	☐
Inspired	☐	☐	☐	☐	☐
Nervous	☐	☐	☐	☐	☐
Determined	☐	☐	☐	☐	☐
Attentive	☐	☐	☐	☐	☐
Jittery (on edge)	☐	☐	☐	☐	☐
Interested	☐	☐	☐	☐	☐
Afraid	☐	☐	☐	☐	☐

Please turn to the next page...

RECEIVING THE RESULTS

Can you remember which of the following bowel tests you had? If you had MORE than one, can you remember which of these was your FIRST bowel test?

Barium Enema ☐ CT colonography (scan) ☐ Colonoscopy ☐ Don't know ☐

How did you feel when you received the results from this test?

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.....

When did you receive the results of this test?

During the test ☐ Immediately after the test ☐ The same day ☐ The next day ☐ 2-3 days after ☐

4-5 days after ☐ A week after the test ☐ 2-4 weeks after the test ☐ More than 4 weeks ☐ I have not had the results yet ☐

How did you receive the results of the test?

Face to face ☐ On the phone ☐ In a letter ☐ Can't remember ☐

Who gave you the results?

The hospital ☐ My GP ☐ Can't remember ☐

Did you have any questions after you received the results? Yes ☐ No ☐

If you ticked **YES**, can you remember what they were?

.....

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.....

Did you receive answers to these questions?

Yes ☐ No ☐ Did not have any questions ☐

Please turn to the next page...

Overall, how satisfied were you with the way the results of this test were explained to you?

Very Satisfied ☐ Satisfied ☐ Dissatisfied ☐ Very Dissatisfied ☐

Please indicate how long you felt it took before you fully recovered from the test?

Immediately ☐ Up to 30 minutes ☐ Up to 2 hours ☐ Up to 4 hours ☐ Up to 6 hours ☐ up to 1 day ☐

Up to 2 days ☐ Up to 3 days ☐ A week ☐ A fortnight ☐ One month or more ☐ Still recovering ☐

Overall, which of the following was the LEAST accepable aspect of the test?

Bowel Preparation (Laxative) ☐ Bowel test ☐ Other ☐

If other, please specify:

.....

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Would you agree to having the same test again in future if necessary? Yes ☐ No ☐

Would you recommend this test as part of a screening programme? In other words, to be used on healthy people with NO particular bowel problems to test for illnesses such as bowel cancer?

Yes ☐ No ☐ Don't know ☐

Please turn to the next page...

FOLLOW-UP TESTS

Did you have a follow-up bowel test?

Yes ☐ No ☐

If **YES**, please answer the questions below

If **NO**, skip to **PAGE 6**

PLEASE READ AND RESPOND TO THE QUESTIONS BELOW IF YOU HAD A FOLLOW-UP BOWEL TEST

Which of these was your **SECOND** bowel test?

Barium Enema ☐ CT colonography (scan) ☐ Colonoscopy ☐ Flexible Sigmoidoscopy ☐ Don't know ☐

How did you feel when you received the results?

.....

.....

.....

When did you receive the results of this test?

During the test ☐ Immediately after the test ☐ The same day ☐ The next day ☐ 2-3 days after ☐

4-5 days after ☐ A week after the test ☐ 2-4 weeks after the test ☐ More than 4 weeks ☐ I have not had the results yet ☐

How did you receive the results of this test?

Face to face ☐ On the phone ☐ In a letter ☐ Can't remember ☐

Who gave you the results of this test?

The hospital ☐ My GP ☐ Can't remember ☐

Did you have any questions after you received the results for this test? Yes ☐ No ☐

If you ticked **YES**, what questions did you have?

.....

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.....

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Did you receive answers to these questions?

Yes ☐ No ☐ Did not have any questions ☐

Please turn to the next page...

Overall, how satisfied were you with the way the results of this test were explained to you?

Very Satisfied ☐ Satisfied ☐ Dissatisfied ☐ Very Dissatisfied ☐

Please indicate below how long you felt it took before you fully recovered from the follow-up test?

Immediately ☐ Up to 30 minutes ☐ Up to 2 hours ☐ Up to 4 hours ☐ Up to 6 hours ☐ up to 1 day ☐

Up to 2 days ☐ Up to 3 days ☐ A week ☐ A fortnight ☐ One month or more ☐ Still recovering ☐

Did you mind having the follow-up test?

Not at all ☐ Somewhat ☐ Moderately ☐ Very much ☐

Overall, which of the following was the LEAST acceptable aspect of the follow-up test?

Bowel preparation (Laxative) ☐ Bowel test ☐ Other ☐

If other, please specify:

.....

.....

.....

.....

Would you agree to having the same test again in future if necessary? Yes ☐ No ☐

Would you recommend this test as part of a screening programme? In other words, to be used on healthy people with NO particular bowel problems to test for illnesses such as bowel cancer?

Yes ☐ No ☐ Don't know ☐

If you had to have JUST ONE of the tests again which one would you prefer?

Test 1 ☐ Test 2 ☐

Please comment, *your answer will be treated with strict confidence.*

.....

.....

.....

Please turn to the next page...

PAGE 6 – YOUR OVERALL EXPERIENCE

DO YOU THINK THAT YOUR OVERALL EXPERIENCE OF THE BOWEL TEST(S) HAS

Given you a sense of reassurance that you do not have bowel cancer?

Not at all ☐ | A little bit ☐ | Quite a bit ☐ | A great deal ☐

Made you feel more able to do the things that you normally do?

Not at all ☐ | A little bit ☐ | Quite a bit ☐ | A great deal ☐

Made you more hopeful about the future?

Not at all ☐ | A little bit ☐ | Quite a bit ☐ | A great deal ☐

Made you get on better with those around you?

Not at all ☐ | A little bit ☐ | Quite a bit ☐ | A great deal ☐

Given you a greater sense of well-being?

Not at all ☐ | A little bit ☐ | Quite a bit ☐ | A great deal ☐

Made you feel LESS anxious about bowel cancer?

Not at all ☐ | A little bit ☐ | Quite a bit ☐ | A great deal ☐ | Did not feel anxious ☐

Please turn to the next page...

YOUR CURRENT HEALTH

About how many times have you been to see your GP in the last 3 months?

Haven't been	Once	Twice	Three or more times
☐	☐	☐	☐

Would you say that for someone of your age your own health is:

Excellent	Good	Fair	Poor
☐	☐	☐	☐

Would you say that since the bowel test your bowel-related problems have:

Got better	Stayed the same	Got worse	Never had any problems
☐	☐	☐	☐

Please fill in TODAY'S DATE: D D / M M / Y Y Y Y

Please check you have answered **all** the questions. Your answers are very important to us so we might contact you about any missing information.

☐ I do not wish to be contacted about any missing information.

THANK YOU VERY MUCH FOR TAKING THE TIME TO COMPLETE THIS QUESTIONNAIRE

If you lose the Freepost envelope, please post to:
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CR-UK Colorectal Unit, St Marks Hospital,
Northwick Park HARROW. HA1 3BR
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Appendix 4 Economics tables

Data accessed at the UK Government websites[76,77] which contain public sector information licensed under the Open Government Licence v3.0 URL: www.nationalarchives.gov.uk/doc/open-government-licence/version/3.

TABLE 41 Unit costs of other diagnostic procedures and surgical interventions related to colonic lesions: costs shown were NHS reference costs 2010/11 unless otherwise specified

Other diagnostic procedures					
Procedure	Value (£)	Low range (£)	High range (£)	Procedure codes used to identify unit costs	Description; other sources of cost information (if not from NHS reference cost 2010/11)
CT abdomen	95	73	106	RA08Z	CT scan, one area, no contrast
CT abdomen and pelvis	151	116	177	RA13Z	CT scan, three areas with contrast
CT chest and abdomen	151	116	177	RA13Z	CT scan, three areas with contrast
CT chest, abdomen and pelvis	151	116	177	RA13Z	CT scan, three areas with contrast
Contrast enema	135	91	162	RA17Z	Contrast fluoroscopy procedures 20–40 minutes
MRI pelvis	165	108	188	RA01Z	MRI scan, one area, no contrast
Outpatient	106			104	Outpatient: colorectal surgery
Rigid sigmoidoscopy	180	132	212	FZ57Z	Diagnostic or therapeutic rigid sigmoidoscopy for patients ≥ 19 years
Surgical procedures					
Abdominoperineal resection	6411	4892	7255	FZ08B	Complex large intestine procedures without major CC
Abdominoperineal resection	6411	4892	7255	FZ08B	Complex large intestine procedures without major CC
Altemeier operation	3723	3003	4387	FZ11B	Large intestine – major procedures without major CC
Anterior resection	5954	4802	6902	FZ10B	Distal colon procedures without major CC
Anterior resection and loop ileostomy	5954	4802	6902	FZ10B	Distal colon procedures without major CC
Anterior resection and loop ileostomy and splenectomy	9969	7831	11,542	FZ10B and GA07B	Distal colon procedures without major CC and hepatobiliary procedures category three without CC
Anterior resection/ sigmoid colectomy	5954	4802	6902	FZ10B	Distal colon procedures without major CC
Colonoscopy polypect (general anaesthetic)	1424	1008	1777	FZ50Z	Intermediate large intestine procedures ≥ 19 years
End ileostomy/mucous fistula	3695	2869	4337	FZ67B	Major small intestine procedures without CC
Evacuation	1424	1008	1777	FZ50Z	Evacuation
Extended right hemicolectomy	5260	4359	5942	FZ09B	Proximal colon procedures without major CC

continued

TABLE 41 Unit costs of other diagnostic procedures and surgical interventions related to colonic lesions: costs shown were NHS reference costs 2010/11 unless otherwise specified (*continued*)

Other diagnostic procedures					
Procedure	Value (£)	Low range (£)	High range (£)	Procedure codes used to identify unit costs	Description; other sources of cost information (if not from NHS reference cost 2010/11)
Hartmann's procedure	5954	4802	6902	FZ10B	Distal colon procedures without major CC
High anterior resection	5954	4802	6902	FZ10B	Distal colon procedures without major CC
High anterior resection/ sigmoid colectomy	5954	4802	6902	FZ10B	Distal colon procedures without major CC
Ileotransverse bypass	3723	3003	4387	FZ11B	Large intestine – major procedures without major CC
Lap subtotal colectomy and ileostomy	6411	4892	7255	FZ08B	Complex large intestine procedures without major CC
Laparoscopic-assisted low anterior resection with loop ileostomy	6265	5042	7247	FZ10B; cost adjusted	Distal colon procedures without major CC; reference cost adjusted by a factor of 1.05 (inflated 5%) for laparoscopic procedure based on Murray *et al.*[108]
Laparoscopic-assisted right hemicolectomy	5523	4577	6239	FZ09B; cost adjusted	Proximal colon procedures without major CC; reference cost adjusted by a factor of 1.05 (inflated 5%) for laparoscopic procedure based on Murray *et al.*[108]
Laparoscopic-assisted anterior resection	6265	5042	7247	FZ10B; cost adjusted	Distal colon procedures without major CC; reference cost adjusted by a factor of 1.05 (inflated 5%) for laparoscopic procedure based on Murray *et al.*[108]
Laparoscopic sigmoid colectomy	6265	5042	7247	FZ10B; cost adjusted	Distal colon procedures without major CC; reference cost adjusted by a factor of 1.05 (inflated 5%) for laparoscopic procedure based on Murray *et al.*[108]
Laparoscopy and repair of umbilical hernia	1969	1548	2346	FZ18C; cost adjusted	Inguinal umbilical or femoral hernia repairs ≥ 19 years without CC; reference cost adjusted by a factor of 1.05 (inflated 5%) for laparoscopic procedure based on Murray *et al.*[108]
Laparotomy and right oophorectomy	4066	3295	4628	MA06Z	Open major upper and lower genital tract procedures
Laparotomy only	3177	2217	3968	FZ12F	General abdominal – very major or major procedures without CC
Left hemicolectomy	5954	4802	6902	FZ10B	Distal colon procedures without major CC
Left hemicolectomy and high anterior resection	5954	4802	6902	FZ10B	Distal colon procedures without major CC
Left hemicolectomy and low anterior resection and loop ileostomy	5954	4802	6902	FZ10B	Distal colon procedures without major CC
Left hemicolectomy/left oophorectomy and small bowel resection	6411	4892	7255	FZ08B	Complex large intestine procedures without major CC
Local excision other sites	3723	3003	4387	FZ11B	Large intestine – major procedures without major CC
Low anterior resection	5954	4802	6902	FZ10B	Distal colon procedures without major CC

TABLE 41 Unit costs of other diagnostic procedures and surgical interventions related to colonic lesions: costs shown were NHS reference costs 2010/11 unless otherwise specified (*continued*)

Other diagnostic procedures					
Procedure	Value (£)	Low range (£)	High range (£)	Procedure codes used to identify unit costs	Description; other sources of cost information (if not from NHS reference cost 2010/11)
Pelvic clearance	5510	2952	6986	FZ12B	General abdominal – very major or major procedures without CC/with major or intermediate CC
Perianal excision	1498	1186	1715	FZ22A	Intermediate anal procedures in patients ≥ 19 years
Right hemicolectomy	5260	4359	5942	FZ09B	Proximal colon procedures with/without major CC
Right hemicolectomy and anterior resection	6411	4892	7255	FZ08B	Complex large intestine procedures without major CC
Sigmoid colectomy	5954	4802	6902	FZ10B	Distal colon procedures with/without major CC
Sigmoid colectomy and appendectomy	6411	4892	7255	FZ08B	Complex large intestine procedures without major CC
Sigmoid colectomy and small bowel resection	6411	4892	7255	FZ08B	Complex large intestine procedures without major CC
Sigmoid colectomy with en bloc right hemicolectomy	6411	4892	7255	FZ08B	Complex large intestine procedures without major CC
Spare	3723	3003	4387	FZ11B	Large intestine – major procedures without major CC
Subtotal colectomy	6411	4892	7255	FZ08B	Complex large intestine procedures with/without major CC
	5260	4359	5942	FZ09B	Proximal colon procedures without major CC
Transverse colectomy	2078	1417	2396	FZ21Z	Major anal procedures
Transanal endoscopic microsurgery	2078	1417	2396	FZ21Z	Major anal procedures
Transanal procedure	6411	4892	7255	FZ08B	Complex large intestine procedures without major CC

CC, complications and comorbidities; MRI, magnetic resonance imaging.

TABLE 42 Unit costs of surgical interventions and other diagnostic procedures related to extracolonic findings after CTC – costs shown were NHS reference costs 2010/11 unless otherwise specified

Procedure	Value (£)	Low range (£)	High range (£)	Procedure codes used to identify unit costs	Description; other sources of cost information (if not from NHS reference cost 20010/11)
Surgical procedures					
Adrenalectomy	5033	3432	6366	KA04Z	Adrenal procedure
Bilateral oophorectomy	2561	2067	2896	MA08Z	Upper genital tract laparoscopic/ endoscopic major procedures
Bilateral salpingo-oophorectomy	2561	2067	2896	MA08Z	Upper genital tract laparoscopic/ endoscopic major procedures
Unilateral salpingo-oophorectomy	2561	2067	2896	MA08Z	Upper genital tract laparoscopic/ endoscopic major procedures
Hysterectomy and bilateral salpingo-oophorectomy	3175	2632	3688	MA07D	Upper genital tract major procedures without major CC
Endovascular aneurysm repair	6940	4499	8375	QZ01B; cost adjusted	Aortic or abdominal surgery without CC; reference cost was adjusted by a factor of 1.05 (inflated 5%) based on estimates in [a]NICE guideline 2010[109]
Open-tube graft repair	6609	4285	7976	QZ01B	Aortic or abdominal surgery without CC
Laparotomy	3177	2217	3968	FZ12F	General abdominal – very major or major procedures ≥ 19 years without CC
Laparoscopic cholecystectomy	2326	1821	2653	GA10D	Laparoscopic cholecystectomy with length of stay ≥ 1 day without CC
Inguinal hernia repair	1875	1475	2234	FZ18C	Inguinal umbilical or femoral hernia repairs ≥ 19 years without CC
Partial nephrectomy	5175	4009	6040	LB02C	Kidney major open procedure ≥ 19 years without CC
Radical nephrectomy	5175	4009	6040	LB02C	Kidney major open procedure ≥ 19 years without CC
Right upper lobectomy	6043	4515	7051	DZ02C	Complex thoracic procedures without CC
Splenectomy	4015	3029	4640	GA07B	Hepatobiliary procedures category three without CC
Whipple procedure	8424	5704	10493	GA03B	Hepatobiliary procedures category seven
Other diagnostic procedures					
Bronchoscopy	1081	377	1198	DZ07A	Fibre optic bronchoscopy ≥ 19 years
Flexible cystoscopy	1107	865	1287	LB14E	Bladder intermediate endoscopic procedure ≥ 19 years
Hysteroscopy	206	157	248	MA21Z	Diagnostic hysteroscopy
ERCP	1091	722	1335	GB06D	ERCP category two with length of stay ≤ 2 days
Bone scan	181	131	214	RA36Z	Nuclear medicine – category two
Dimercaptosuccinic acid scan	181	131	214	RA36Z	Nuclear medicine – category two
Endoscopic ultrasonography	168	72	155	GB03B	Endoscopic/radiology category two without CC

TABLE 42 Unit costs of surgical interventions and other diagnostic procedures related to extracolonic findings after CTC – costs shown were NHS reference costs 2010/11 unless otherwise specified (*continued*)

Procedure	Value (£)	Low range (£)	High range (£)	Procedure codes used to identify unit costs	Description; other sources of cost information (if not from NHS reference cost 20010/11)
Positron emission tomography scan lung	354	118	478	RA39Z	Nuclear medicine – category five
Renal ultrasonography	53	39	61	RA23Z	Ultrasonography scan < 20 minutes
Barium meal	92	47	120	RA16Z	Contrast fluoroscopy procedures < 20 minutes
Lymph node biopsy	211	137	292	WA24Z	Procedures on the lymphatic system
Prostate biopsy	200	147	212	LB27Z	Prostate or bladder neck minor endoscopic procedure – male
Renal biopsy	191	155	199	LB04B	Kidney major endoscopic procedure without CC
Blood test	99	31	149	WA21Y	Other procedures and health-care problems without CC
Extracorporeal shock wave lithotripsy	140	140	142	LB36Z	Extracorporeal lithotripsy
Fluid aspiration and culture	1162	777	1300	MA19A	Vacuum aspiration with cannula – < 14 weeks' gestation
Intravenous urography	87	40	103	RA26Z	Ultrasonography mobile scan/ intraoperative procedures 20–40 minutes
Oesophagogastroduodenoscopy	747	391	881	FZ60Z	Diagnostic endoscopic procedures on the upper GI tract 19 years and over
Prostate-specific antigen test	200	147	212	LB27Z	Prostate or bladder neck minor endoscopic procedure – male
Stent insertion	281	101	381	QZ15C	Therapeutic endovascular procedures without CC
Surveillance	99	31	149	WA21Y	Other procedures and health-care problems without CC
Urine test	99	31	149	WA21Y	Other procedures and health-care problems without CC
Video-assisted thoracic surgery	3576	2349	4684	DZ04B	Intermediate thoracic procedures without CC
CT endovascular aortic repair protocol	6940	4499	8375	QZ01B; cost adjusted	Aortic or abdominal surgery without CC; reference cost was adjusted by a factor of 1.05 (inflated 5%) based on estimates in [a]NICE guideline 2010[109]
CT abdomen	95	73	106	RA08Z	CT scan, one area, no contrast
CT abdomen and pelvis	112	90	124	RA11Z	CT scan, two areas without contrast
CT aorta	95	73	106	RA08Z	CT scan, one area, no contrast
CT chest	95	73	106	RA08Z	CT scan, one area, no contrast
CT chest and abdomen	112	90	124	RA11Z	CT scan, two areas without contrast
CT chest abdomen and pelvis	151	116	177	RA13Z	CT scan, three areas with contrast
CTC	160	89	186	RA14Z	CT scan, more than three areas

continued

TABLE 42 Unit costs of surgical interventions and other diagnostic procedures related to extracolonic findings after CTC – costs shown were NHS reference costs 2010/11 unless otherwise specified (*continued*)

Procedure	Value (£)	Low range (£)	High range (£)	Procedure codes used to identify unit costs	Description; other sources of cost information (if not from NHS reference cost 20010/11)
CT pancreas	95	73	106	RA08Z	CT scan, one area, no contrast
CT renal	95	73	106	RA08Z	CT scan, one area, no contrast
CT surveillance	95	73	106	RA08Z	CT scan, one area, no contrast
CT-guided biopsy	95	73	106	RA08Z	CT scan, one area, no contrast
MRI liver	165	108	188	RA01Z	MRI scan, one area, no contrast
MRI abdomen	165	108	188	RA01Z	MRI scan, one area, no contrast
MRI abdomen and pelvis	211	131	258	RA04Z	MRI scan, two–three areas, no contrast
MRI adrenal glands	165	108	188	RA01Z	MRI scan, one area, no contrast
MRI liver	165	108	188	RA01Z	MRI scan, one area, no contrast
MRI pancreas	165	108	188	RA01Z	MRI scan, one area, no contrast
MRI pelvis	165	108	188	RA01Z	MRI scan, one area, no contrast
MRI spine	165	108	188	RA01Z	MRI scan, one area, no contrast
MRI thoracic spine	165	108	188	RA01Z	MRI scan one area, no contrast
Ultrasonography abdomen	53	39	61	RA23Z	Ultrasonography scan < 20 minutes
Ultrasonography abdomen and pelvis	66	50	73	RA24Z	Ultrasonography scan > 20 minutes
Ultrasonography aorta	53	39	61	RA23Z	Ultrasonography scan < 20 minutes
Ultrasonography biliary	53	39	61	RA23Z	Ultrasonography scan < 20 minutes
Ultrasonography jejunal mesentery	53	39	61	RA23Z	Ultrasonography scan < 20 minutes
Ultrasonography liver	53	39	61	RA23Z	Ultrasonography scan < 20 minutes
Ultrasonography pelvis	53	39	61	RA23Z	Ultrasonography scan < 20 minutes
Ultrasonography renal	53	39	61	RA23Z	Ultrasonography scan < 20 minutes
Ultrasonography surveillance	53	39	61	RA23Z	Ultrasonography scan < 20 minutes
Ultrasonography transvaginal	53	39	61	RA23Z	Ultrasonography scan < 20 minutes
Ultrasound-guided biopsy	53	39	61	RA23Z	Ultrasonography scan < 20 minutes
Ultrasound-guided drainage	53	39	61	RA23Z	Ultrasonography scan < 20 minutes
Ultrasound-guided fine-needle aspiration	53	39	61	RA23Z	Ultrasonography scan < 20 minutes
Radiography chest	95	73	106	RA08Z	CT scan, one area, no contrast
Radiography humerus	21			RA08-RA11	CT scan; Tariff 2010/11
Radiography pelvis	21			RA08-RA11	CT scan; Tariff 2010/11
Radiography skeleton	21			RA08-RA11	CT scan; Tariff 2010/11
Radiography surveillance	21			RA08-RA11	CT scan; Tariff 2010/11

CC, complications and comorbidities; ERCP, endoscopic retrograde cholangiopancreatography; MRI, magnetic resonance imaging; NICE, National Institute for Health and Care Excellence.
a 2010 document used, but 2013 referenced as that link is active at the time of writing.

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