University of Sheffield

ScHARR

School of Health and Related Research

Colorectal cancer screening options appraisal

Cost-effectiveness, cost-utility and resource impact of alternative screening options for colorectal cancer

Report to the English Bowel Cancer Screening Working Group

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Paul Tappenden
Simon Eggington
Richard Nixon
Jim Chilcott
Hannah Sakai
Jon Karnon

Executive summary

1. Aims and objectives

The aim of this study was to conduct a detailed assessment of research evidence and to develop a mathematical model to estimate the costs, benefits and capacity implications of alternative screening options for colorectal cancer in England. The effectiveness and cost-effectiveness of eight screening options using faecal occult blood testing (Haemoccult guaiac test), flexible sigmoidoscopy, or a combination of the two modalities are compared to a policy of 'no screening.'

2. Evidence on the effectiveness of screening for colorectal cancer

To date, four randomised controlled trials of FOBT have been published, all of which have reported a reduction in colorectal cancer-specific mortality for the screened group versus controls; a recent meta-analysis of these trials reported a 16% reduction in colorectal cancer-specific mortality in favour of the screened group (95% C.I. 0.07, 0.23). Three randomised controlled trials assessing the effectiveness of flexible sigmoidoscopy in reducing colorectal cancer incidence and mortality are currently in progress. It is anticipated that the UK flexible sigmoidoscopy trial will publish early results in 2005.

3. Review of existing economic studies

We undertook a systematic search to identify existing model-based evaluations of colorectal cancer screening programmes to inform the structure, parameter sources and assumptions for use in the model developed within this study. Fourteen economic evaluations were retrieved for inclusion in the review. The studies included in the review employed a variety of alternative modelling methodologies, including Markov processes, semi-Markov processes and discrete event simulation. Each methodology has different implications for the modelling of the natural history of colorectal cancer, and the availability of evidence for use in populating the model. The key limitation of existing studies is the lack of good quality direct evidence for use in estimating model parameters. There exists an important trade-off between the degree of complexity in the definition of the natural history of the disease, and extent to which model parameters must be calibrated to observed data. In general, those models which incorporate more complex representations of natural history require a greater number of parameters to be fitted. Each of the studies included in the review were subject to one or more of a number of important limitations:

- Oversimplification of the underlying disease process;

- Use of constant dwell-times for polyp-cancer transitions, and between cancer stages, that fail to allow for fast-progressing polyps or cancers (and are thus likely to bias results in favour of infrequent screening programmes);
- Failure to incorporate higher recurrence rates for the development of new adenomas following polypectomy;
- Poor reporting (or absence) of methods for calibrating model outputs against published data to fit unobservable model input parameters;
- Assumptions of perfect compliance which overestimate the effectiveness of the screening programme;
- Omission of quality of life effects associated with diagnosed cancer and subsequent treatment.

Some of these problems may be avoided through the use of more appropriate structural model assumptions, and through the identification of better quality evidence. Unfortunately, current evidence does not enable the resolution of the uncertainties surrounding the natural history of the underlying disease.

4. Strategies assessed by the ScHARR colorectal cancer screening model

The model developed within this study evaluates the incremental cost-effectiveness and cost-utility of five core screening strategies:

(1) FOBT for individuals aged 50-69 (biennial screening)

(2) FOBT for individuals aged 60-69 (biennial screening)

(3) 'Once-only' flexible sigmoidoscopy for individuals aged 55

(4) 'Once-only' flexible sigmoidoscopy for individuals aged 60

(5) 'Once-only' flexible sigmoidoscopy for individuals aged 60, followed by FOBT for individuals aged 61-70 (biennial screening)

The cost-effectiveness and cost-utility of an additional three 'extension' screening options are also evaluated:

(6) FOBT for individuals aged 60-67 (biennial screening)

(7) FOBT for individuals aged 60-71 (biennial screening)

(8) FOBT for individuals aged 60-73 (biennial screening)

5. Data sources

A full assessment of the literature was undertaken in order to identify studies which could be used to estimate parameters to populate the model. Whereby evidence is weak or inconsistent, plausible parameter ranges were derived from the current literature and subsequently calibrated against published outcome data.

Crude age and sex-specific incidence rates of adenomas within the average-risk population were estimated from a series of 6 autopsy studies; only one of these studies was undertaken in an English population. The transition rate between low and high risk polyps was estimated from a study of individuals with small adenomas left in situ and followed up after 2 years. The rate at which colorectal adenomas develop into malignant cancer were estimated from a study of large polyps left in situ (whereby radiological surveillance was opted for over surgical resection). Transition rates through the pre-clinical cancer states, and the probability that an individual with cancer presents symptomatically cannot be estimated from empirical evidence; estimates for these parameters were calibrated against published estimates of colorectal cancer incidence and mortality. Polyp recurrence rates following excision of the initial polyp were estimated from a randomised trial which evaluated the effectiveness two alternative colonoscopy surveillance intervals.

The true sensitivities of flexible sigmoidoscopy, colonoscopy and FOBT in detecting colorectal adenomas and cancers are not known. Miss rates for endoscopy were derived from prospective colonoscopy studies. The sensitivities of FOBT in detecting polyps and cancers were estimated from a meta-analysis of two large population-based studies. Probabilities of harm caused by screening and follow-up (perforation of the bowel and post-endoscopy bleeds) were derived from the experience of the UK FOBT and flexible sigmoidoscopy trials. Rates of compliance with FOBT were estimated from the UK FOBT trial and the UK demonstration pilot study. Participation rates for follow-up colonoscopy following a positive screen-test were estimated from the UK demonstration pilot.

The quality of life impact associated with the diagnosis and treatment of various stages of colorectal cancer were derived from a standard gamble utility study undertaken in the US.

The cost of flexible sigmoidoscopy for screening was estimated from a costing study. The cost of each FOB test, and the costs of pathology for adenomas and cancers were obtained from expert opinion. All remaining cost estimates were obtained from the NHS Reference lists and updated to current prices using Health Inflation Indices.

The annual sex- and age-specific probability of dying from causes other than colorectal cancer were estimated from current UK life expectancy tables. The probability of dying from colorectal cancer was estimated from analysis of an audit study undertaken in the Wessex Region by the South West Cancer Information Service.

6. Model structure

The ScHARR model uses the state transition (Markov) methodology to provide a macro-simulation of the life experience from normal colonic epithelium to adenomatous polyp to malignant carcinoma in the general population of England. The model is centred around three sub-models:

(1) A Markov model which simulates the natural history of colorectal cancer;
(2) A model of the screening intervention (and subsequent adenoma surveillance intervention for high risk individuals) which is directly superimposed upon the natural history model
(3) A mortality model which is used to reflect age-specific 'other-cause' mortality, mortality due to colorectal cancer and mortality resulting from perforation due to endoscopic procedures.

The model evaluates the costs and benefits associated with each of the alternative screening options over the lifetime of the cohort using an annual cycle length. Health states within the model are defined according to the index lesion , that is, the presence or absence of the largest/most pathologically advanced adenoma, or the most advanced cancer. The distal and proximal colon are modelled separately to take account of the reach of flexible sigmoidoscopy.

7. Limitations of the health economic model

The model developed here covers a broader scope than existing UK models. To date, the model presented here is the only UK model to incorporate flexible sigmoidoscopy screening options as well as combinations strategies of FOBT and flexible sigmoidoscopy. The model also incorporates up-to-date stage-specific utility data for individuals with diagnosed cancer. Further, none of the existing studies have used appropriate methods to explore second-order uncertainty in the true mean values of model inputs. The base case model results presented here should be approached with caution; there remain considerable uncertainties in terms of the natural history of colorectal cancer, together with uncertainties concerning the true single-test sensitivities of FOBT and flexible sigmoidoscopy. The model is subject to several limitations:

- The paucity of direct evidence on the rate at which adenomas develop within the general English population, the rate at which adenomas develop into invasive cancer, and the rate at which early local cancer progresses to late-stage metastatic disease, means that several of the model parameters had to be fitted to published data. In short, there may be several potentially valid solutions which appear fit the data, yet may not be optimal.
- Transition probabilities estimated within the model are assumed to be constant (with the exception of age-specific adenoma incidence and mortality rates); in reality however, this assumption is unlikely to be accurate. The absence of direct evidence however means that this assumption is unavoidable.
- Data from the prevalence screening round from the Nottingham FOBT trial are used as a means of model validation; ideally however, these data would be used to inform natural history and sensitivity parameters.
- Despite indirect evidence to suggest that a proportion of colorectal cancers may arise *de novo*, the current model assumes that all cancers derive from pre-existing adenomas. This assumption is likely to favour all screening options versus no screening. In particular, this assumption means that flexible sigmoidoscopy screening strategies, which have a high sensitivity in detecting adenomas, will be favoured by the model.
- The model assumes that a proportion of proximal cancers are associated with large ‘sentinel’ adenomas located in the distal colon, which would subsequently lead to examination of the entire colon. This proportion however, should be an output of the model rather than an input parameter. Further, the probabilities of cancer progression are assumed to be equivalent in both the distal and proximal colon, which in reality is unlikely to be accurate. In order to address this issue, discrete lesions would need to be modelled, requiring a more complex representation of the natural history of the disease for which data do not exist.
- The central uncertainty concerning the natural history of colorectal cancer concerns the prevalence of pre-clinical cancer within the general population. There exists limited empirical evidence with which to estimate this; the only potential data sources are the Nottingham FOBT trial (uncertainty in the prevalence is coupled with uncertainty in the true prevalence of pre-clinical cancer) and the only UK autopsy study (in which only 365 specimens were examined).

8. Conclusions on the results of the economic model

The deterministic and stochastic results generated from the health economic model suggest that each of the screening options considered for colorectal cancer is likely have a cost-effectiveness and cost-utility compared to no screening that is better than many health interventions currently funded by the NHS. The stochastic uncertainty analysis suggests that the effectiveness and cost impact of each screening option overlap with at least one alternative screening option; as a result, the question of *"which screening option is most cost-effective?"* is difficult to ascertain with any certainty.

Each of the screening options considered have differing impacts on resource requirements, and specifically on requirements for flexible sigmoidoscopy, colonoscopy and cancer surgery services. Due to parametric uncertainty in the cost-effectiveness estimates, and the fact that all of the options appear to be economically attractive in comparison to a policy of no screening, the key issue concerns the viability of each option within the constraints of current and future NHS staff and capital resource capacity. The projected economic and resource impact of each screening option summarised is the table below.

Summary of economic outcomes for core screening options

Criteria	FOBT 50-69	FOBT 60-69	FSIG 55	FSIG 60	FSIG 60, FOBT 61-70
Cost-effectiveness rank-ordering	5	4	cost-saving	cost-saving	cost-saving
Probability of being optimal at £30,000 per QALY threshold	0.39%	0%	57%	0%	43%
Total 1st year cost	£128,486,326	£75,501,096	£27,273,502	£27,040,449	£82,826,186
Quality adjusted life days saved per person invited to screening	8.29	3.80	9.86	8.07	10.29
Additional number of flexible sigmoidoscopies *	0	0	344,605	274,969	274,969
Additional number of colonoscopies *	83,373	39,176	7,093	8,638	47,967
Additional number of WTE nurse-trained endoscopists *	0	0	110	88	88
Additional number of WTE gastrointestinal consultants *	53	25	4-5	5-6	31

* = additional requirements when compared to a policy of no screening

9. Conclusions on the results of the cost effectiveness and resource impact analysis

The incremental cost-effectiveness acceptability curves suggest that for willingness to pay thresholds of less than £50,000 per QALY (i.e. the amount society is willing to pay to save one quality adjusted life year) once only flexible sigmoidoscopy at age 55 has the greatest probability of providing the greatest expected net benefit.

It should be noted that when compared with a policy of no screening, all five core screening options are expected to produce health gains at a cost considered acceptable to the NHS.

The feasibility of the options in terms of endoscopist requirements is an important consideration in assessing these options. The two once-only flexible sigmoidoscopy options have similar impacts on quality adjusted life days saved and costs compared to no screening. These options also minimise the requirement for consultant gastroenterologists, though relying on a greater number of nurse endoscopists. If the availability of nurse endoscopists is constrained then offering flexible sigmoidoscopy to individuals aged 60 would be the preferable option.

The cost and resource analysis suggests that the most costly option in terms of screening and cancer management costs in the first year of the screening programme would be for the FOBT 50-69 strategy, owing to the high number of people who would be screened each year. The higher number of cancers detected under the FOBT age 50-69 option would have significant cost implications, particularly in terms of the increase in surgery volume of around 5,500 in the first year.

If total endoscopy services are constrained then the favoured option is likely to be the programme of biennial FOB testing between the ages of 60 and 69, however this option is estimated to be the least effective in terms of quality adjusted life days saved and is estimated to have a total first year cost in the middle of the estimated range.

10. Recommendations for further research

The uncertainties within this modelling work are a direct result of the paucity of direct evidence concerning the natural history of colorectal cancer and the operating characteristics of the screening tests available. The central uncertainty within the evidence concerns the true prevalence of undiagnosed asymptomatic colorectal cancer within the English population; inevitably, this is highly influential in determining the effectiveness and cost effectiveness of any screening programme.

Whilst the natural history of the disease (i.e. the adenomas incidence rate, the rate at which adenomas develop to cancer, and the rate at which cancer progresses from early local stages to advanced or metastatic disease) cannot be observed using standard study designs, there are three potential designs that could provide information.

- Direct observation of natural history from colonoscopy screening of the general population. This however is ethically infeasible.
- Further valuable evidence could potentially be obtained through undertaking a large autopsy series in England, or more broadly, the UK. Given a sufficiently large sample size, such a study could be used to obtain better age and sex-specific estimates of adenoma incidence rates, and also to determine the underlying prevalence of pre-clinical colorectal cancer.
- Analysis of existing UK and international screening trials. The problem with the screening trials, and conventional methods of analysis, is that the results confound the natural history and the characteristics of the screening test. Analytical methods which synthesise data from other sources (for example ONS incidence and mortality, and stage distribution at diagnosis, and survival estimates from audit studies) allow information concerning natural history and test characteristics contained within the trial data to be drawn out. Bayesian synthesis analysis of existing trial data, based upon an underlying model of disease natural history and incorporating data from a range of available sources, should be undertaken.

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Acknowledgements

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1. Aims and objectives

The aim of this study was to conduct a detailed assessment of research evidence and to produce a mathematical model to estimate the costs, benefits and capacity implications of alternative screening options for colorectal cancer in England. The specific objectives of this work include the detailed assessment and modelling of:

(1) Participation rates at prevalence and incidence rounds;
(2) Activity generated by screening, further diagnostic procedures and additional treatments required, requirements for additional surveillance of screen-detected polyps and earlier detection of cancers, as well as reductions in activity resulting from reduced presentations with advanced disease;
(3) Benefits resulting from screening programmes in terms of life years gained, quality adjusted life years gained, and cancers prevented;
(4) Impact of screening programmes upon resources (requirements and potential savings), including workforce, facilities and costs;
(5) Cost-effectiveness (measured in terms of life years gained) and cost-utility (measured in terms of quality-adjusted life years gained).

2. Background

2.1 Colorectal cancer

Cancer of the large bowel (colorectal cancer) is the third most common form of cancer after lung cancer in the United Kingdom. Around 30,000 new cases of colorectal cancer are diagnosed in England and Wales each year.[1] Colorectal cancer is registered as the underlying cause of approximately 15,000 deaths in England and Wales each year, and accounts for over ten percent of all cancer deaths.[2] Around two thirds of tumours develop in the colon and the remainder in the rectum. Colon cancer is equally common in men and women, although rectal cancer is more common in men. Incidence and mortality estimates for colorectal cancer in England and Wales are shown in Tables 1 and 2.

Table 1 Colorectal cancer registrations in England and Wales by age and sex (2000)[1]

	All ages	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	>80
Men	15795	1	4	24	166	529	2009	4158	5827	3077
Women	13774	0	9	34	146	530	1429	2738	4467	4421
Men and women	29569	1	13	58	312	1059	3438	6896	10294	7498

Table 2 Deaths due to colorectal cancer in England and Wales by age and sex (2000)[2]

	All ages	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	>80
Men	7533	0	0	7	54	197	791	1694	2598	2192
Women	6742	0	1	2	44	146	468	989	2053	3039
Men and women	14275	0	1	9	98	343	1259	2683	4651	5231

Hereditary and environmental factors are important in the aetiology of colorectal cancer. Diets low in fibre and vegetables but high in red meat and animal fat predispose to the condition. A high intake of animal fat in the diet is linked with an increase in faecal bile acids and neutral steroids, which are degraded by certain anaerobic bacteria to produce carcinogens. The two main inherited colorectal cancer syndromes are familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer. FAP accounts for less than 1% of all colorectal cancers. It is caused by a mutation in the adenomatous polyposis coli (APC) gene. Patients develop multiple adenomatous polyps in the bowel between the ages of 10 to 30 years. These polyps are histologically identical to those in sporadic colorectal cancer, however, the large numbers of polyps found in the large bowel amount to almost 100% chance of developing colorectal cancer by the age of 40.

Hereditary non-polyposis colorectal cancer (HNPCC) accounts for 5-10% of all colorectal cancers, and is caused by a dominantly inherited alteration in the DNA mismatch repair genes. Tumours tend to occur in the proximal colon and patients with HNPCC are also associated with both synchronous and metachronous tumours. The diagnosis of HNPCC is set out by the 'Amsterdam' criteria (patients must have at least three family members with colorectal cancer, must have at least two generations affected, one person must have been under 50 years of age at the time of diagnosis, and FAP has been excluded). In general, the risk of developing colorectal cancer is greater for people with a family history of the disease, even when no specific genetic syndrome is found.

Sporadic cancers account for around 90% of all colorectal cancer. Unless at high risk of having an inherited colorectal cancer syndrome, the likelihood of developing colorectal cancer at a young age is typically very low. Among individuals aged 45 to 55, the incidence of colorectal cancer is about 25 per 100,000 per year. However, among those aged 75 and above, the incidence rate is over 300 per 100,000 per year. It is now a commonly accepted concept that most colorectal cancers develop from pre-existing adenomatous polyps located in the bowel wall.[3;4] Adenomas are particularly common in older age groups, and around one third of people will develop at least one adenoma by the age of 60. Most adenomatous polyps are asymptomatic and remain undiagnosed, and most do not develop into cancer. Indirect evidence suggests that the adenoma-carcinoma sequence is typically slow; adenomas may be present for 10 years or more before malignancy develops.[5] The size, histological type, presence of epithelial dysplasia, and the number of adenomas can affect the risk associated with the development to carcinoma. Converse to the slow progression of adenomatous polyps to invasive cancer, small flat adenomas which develop in the muscosa are thought to progress more rapidly.

2.2 Clinical features of colorectal cancer

Bowel cancer typically progresses slowly, although approximately 20% of patients arrive through Accident and Emergency departments.[6] Most presenting patients have had symptoms for weeks, and often months, before admission. The clinical symptoms and signs of colorectal cancer or large polyps depend on the site of the tumour. Proximal (right-sided) lesions often present with a history of anaemia (as a result of occult gastrointestinal bleeding) and weight loss. Distal (left-sided) lesions tend to present with rectal bleeding, persisting changes in bowel habit, and lower abdominal pain. These symptoms are however common amongst the general population and can have a variety of alternative causes. Early symptoms may be mild and are often ignored; furthermore some patients do not become symptomatic until their cancer is far advanced. Table 3 shows the distribution of stage of colorectal cancer at diagnosis and 5-year survival estimates based on an audit study undertaken in the Wessex region during the 1990s. In England and Wales, approximately 55% of patients present with advanced colorectal cancer which has spread to the lymph nodes, metastased to other organs, or is so locally invasive that that surgery to remove the primary tumour alone is unlikely to be sufficient for cure (Dukes' C or Stage D).[6]

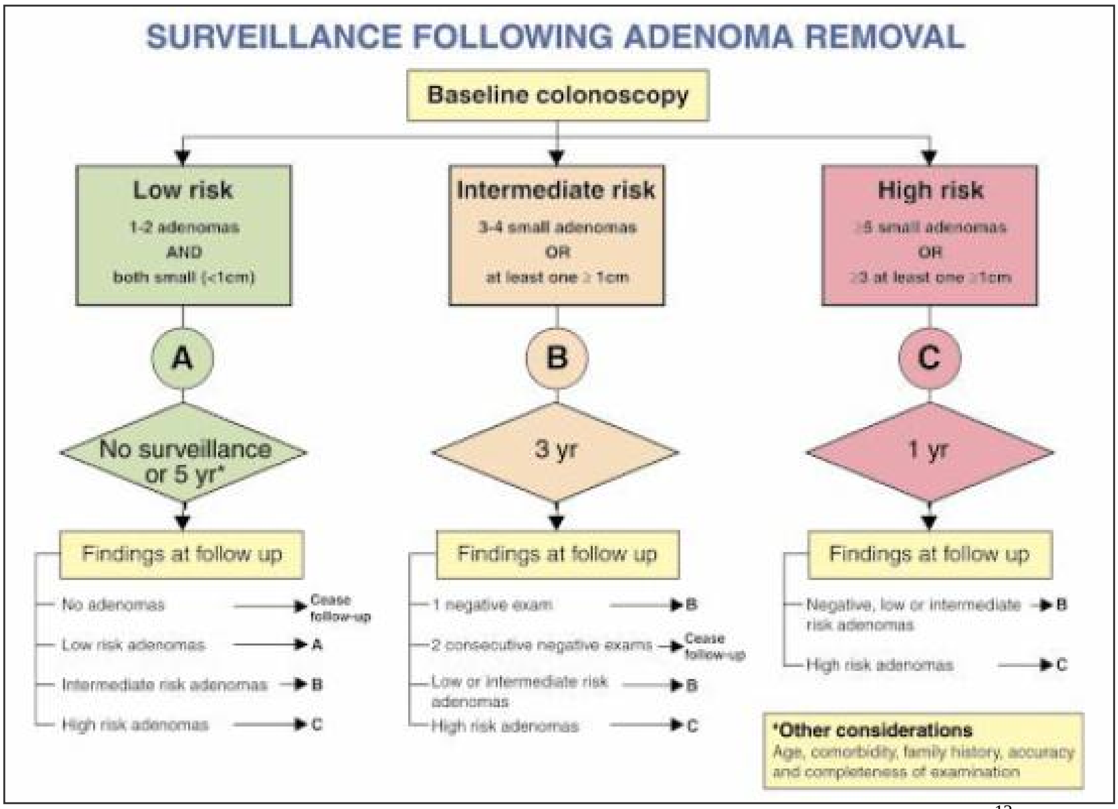
Table 3 Distribution of stage at diagnosis and 5 year survival estimates by stage of colorectal cancer[7]

Dukes' Stage (modified) [8;9]	Definition	Approximate frequency at diagnosis	5-year survival
A	Cancer localised within the bowel wall	11%	75%
B	Cancer penetrating the bowel wall	32%	57%
C	Cancer in lymph nodes	26%	35%
D	Distant metastases (most often in the liver)	23%	12%

2.3 Surveillance guidelines following the removal of adenomatous polyps

Repeated colonoscopic surveillance is currently recommended for individuals with colorectal adenomas.[10] Although no direct evidence exists to demonstrate the effectiveness of endoscopic polypectomy in reducing colorectal cancer mortality, The National Polyp Study[11] observed a 70-90% lower than expected incidence of colorectal cancer in patients undergoing colonoscopic surveillance compared with the reference population. Guidelines for the colonoscopic surveillance of individuals following removal of adenomatous polyps have recently been published.[12] Alternative surveillance strategies for individuals with adenomatous polyps are determined by patients' risk status at baseline colonoscopy, as shown in Figure 1. The reader should note that within a screening context, individuals in whom low risk adenomas are found would not receive 5-year follow-up (*Personal communication: Dr Wendy Atkin, Deputy Director, Colorectal Cancer Unit, St. Mark's Hospital, Harrow)*.

Figure 1 Guidelines for surveillance following the removal of adenomatous polyps



Atkin and Saunders(2002) [12]

2.4 Current treatment for colorectal cancer

2.4.1 Surgery

The mainstay of treatment for colorectal cancer is surgical excision; it has been estimated that four out of five patients with colorectal cancer require some form of surgery.[13] The type of surgery depends on the location, stage and size of the cancer. The main types of surgery for colorectal cancer are:

- Local resection
- Resection of the bowel (with or without temporary colostomy)
- Resection of the bowel with permanent colostomy
- Resection of the rectum with permanent colostomy

2.4.2 Adjuvant radiotherapy

Despite apparently curative surgery for colorectal cancer, a proportion of patients develop recurrent disease. Radiotherapy given either pre- or post-operatively reduces local recurrence rates and thus may increase survival.[13]

2.4.3 Chemotherapy

Current guidelines from the National Institute for Health and Clinical Excellence (NICE) recommend the use of 5-fluorouracil plus folinic acid as adjuvant chemotherapy in CRC given intraveneously over a period of 6 months.[14] NICE is currently appraising the use of irinotecan, oxaliplatin and capecitabine for the adjuvant treatment of Dukes' C colon cancer. Patients with advanced colorectal cancer may receive chemotherapy for downstaging, or as palliative treatment. Currently NICE recommends the use of oxaliplatin in combination with 5-FU/FA for downstaging,[14] and 5-FU/FA followed on progression by irinotecan for palliative chemotherapy.[14] The use of chemotherapy to treat colorectal cancer is likely to change considerably in the near future. The MRC-sponsored FOCUS trial (Fluorouracil, Oxaliplatin and Irinotecan: Use and Sequencing[15]), which aims to assess the role of irinotecan and oxaliplatin in the management of advanced colorectal cancer is expected to release preliminary results in November 2004. NICE has provisionally recommended the use of irinotecan and oxaliplatin for the treatment of advanced colorectal cancer. NICE is also currently appraising two monoclonal antibodies, bevacizumab and cetuximab for the treatment of advanced colorectal cancer.

2.4.5 Follow-up following surgical resection

Recent guidelines for the follow-up of patients with colorectal cancer following surgical resection have been published.[16] Scholefield and Steele[16] suggest offering liver imaging to asymptomatic patients under the age of 70 for the detection of operable liver metastases once during the first two years after resection, and colonoscopy five years after surgery and thereafter at five yearly intervals to detect treatable recurrent tumours up to the age of 70 years.

2.5 The case for colorectal cancer screening

At present there is no national screening programme in place in the UK. However, recent evidence from several randomised controlled trials[17-20] suggests that population-based screening for colorectal cancer is feasible and can significantly reduce mortality. Further randomised controlled evidence of the effectiveness of screening in reducing colorectal cancer mortality is expected to reach publication in 2005.[21] The typically slow transformation from adenomatous polyp to invasive colorectal carcinoma, the relatively long sojourn time prior to the development of symptoms, and the strong relationship between stage at diagnosis and survival,[7] suggest that timely screening within the general population may potentially have a substantial impact upon morbidity and mortality. Furthermore, whilst the introduction of a national colorectal screening programme would inevitably entail substantial immediate costs, such expenditure may be offset by the avoidance of costs incurred later as a result less individuals presenting symptomatically with advanced cancer.

Several alternative tests, and combinations of tests, may be used to screen for colorectal cancer. These are:

- Faecal occult blood testing (FOBT)
- Flexible sigmoidoscopy
- Colonoscopy
- Double-contrast barium enema (DCBE)

2.5.1 Faecal occult blood testing (FOBT)

Both cancers and large polyps (adenomas) may bleed, however the quantity of blood in the stool may not be visible; more sensitive tests for faecal occult blood (FOB) may be required; this is the rationale for FOBT screening. Individuals whose FOBT result is positive are typically followed-up using colonoscopy, or in some cases barium enema. The most common protocol for guiuac-based tests, such as Haemoccult II, requires the participant to take 2 separate samples from 3 consecutive stools (a total of six samples). Dietary restriction is recommended prior to undertaking the test, as peroxidase activity may be found in fresh fruits, vegetables, bacteria as well as animal haemoglobin and myoglobin. Repeat testing may be required for weakly positive test results.

Cancers detected through FOBT screening are typically less advanced than cancers found in individuals who present symptomatically. However, not all colon cancers bleed, and alternative screening methods may have a greater sensitivity in detecting adenomatous polyps. Many studies have attempted to determine the single-test sensitivity of FOBT in detecting colorectal polyps and cancers with little agreement. True positive and false positive rates are affected by adherence to dietary restrictions prior to undertaking the test, and rehydration of the stool specimen prior to analysis. The effect of rehydration has been shown to increase both the true-positive and false-positive rate, which results in a decrease in the positive predictive value of the test.

2.5.2 Flexible sigmoidoscopy

Most colorectal cancers result from malignant changes in polyps which can be detected and removed during endoscopic examination of the colonic lumen. Flexible sigmoidoscopy, which is a quicker and generally less difficult procedure than colonoscopy, can be used to detect and remove approximately 70% of adenomas; this procedure may be more appropriate for people who are not at especially high risk of colorectal cancer. Prior to examination using flexible sigmoidoscopy, the contents of the bowel must be evacuated. During the procedure, the patient lies on their left side whilst the physician inserts a short flexible tube into the rectum and is slowly guided into the colon to allow examination of the bowel wall. In most cases, polypectomy may be undertaken during the procedure using snare diathermy. Baseline findings from a multicentre MRC trial of screening using flexible sigmoidoscopy in people aged 55-64, followed by colonoscopy for high risk patients have recently been published.[21] Baseline results from this trial suggest that detection rates for cancer (0.3%) and adenomas (12%) using flexible sigmoidoscopy compare favourably with FOBT. However, endoscopic screening carries a risk of harm to the participant; there is a risk that the bowel may be perforated, which in some cases is fatal. Sigmoidoscopy may also lead in abdominal pain and bleeding, particularly following polypectomy. Evidence suggests however, that perforation rates associated with sigmoidoscopy are low.[21-23]

2.5.3 Colonoscopy

Colonoscopy is widely held as the 'gold standard' method for examining the bowel, as the procedure enables the visualisation of the entire bowel to the caecum. Colonoscopy is however, the most expensive method and requires full bowel preparation and sedation. As with flexible sigmoidoscopy, polypectomy may also be performed during the procedure using snare diathermy. The risk of perforation of the bowel during colonoscopy is considerably higher than the risk of perforation using flexible sigmoidoscopy. Due to the high cost and risk associated with colonoscopy, it is generally considered unsuitable for population-based screening. Most commonly, colonoscopy is reserved for individuals who are considered to be at a high risk of developing colorectal cancer.

2.5.4 Double-Contrast Barium Enema (DCBE)

As with colonoscopy, DCBE enables the examination of the whole bowel. The procedure is a cheaper alternative to colonoscopy and has fewer complications. As DCBE is an invasive procedure, bowel preparation is required. DCBE does not allow for the removal or biopsy of a lesion if found, and the sensitivity and specificity of the test is lower than that for colonoscopy; there may be increased false-positive results as small faeces may be mistaken for lesions.

Only flexible sigmoidoscopy and FOBT, or a screening programme which incorporates the two, are considered within this option appraisal. Both the effectiveness and cost-effectiveness of alternative screening options are central to addressing the question *"which screening option is worth doing?"*, however, a further and equally important consideration is whether given current resources, alternative screening options are feasible on a national level. Thus, estimates of projected resource use for each screening option are presented using intermediate outcomes from the cost-effectiveness model.

2.6 Structure of the report

Chapter 3 presents a summary of current evidence from randomised controlled trials concerning the effectiveness of screening in reducing colorectal cancer mortality.

Chapter 4 reports a detailed review of existing health economic evaluations of colorectal screening programmes. The review was used to inform the representation of the natural history of colorectal cancer, the structural assumptions and the data sources used within the colorectal cancer screening model. Issues concerning the level of complexity of the model structure, and directly related to this, the methods of parameterisation of unknown model inputs and model calibration are also discussed.

Chapter 5 reports an assessment of evidence used to estimate parameter values for use in the health economic model. The design of those studies used to inform parameter values are detailed together with a description of the methods and assumptions used to estimate parameter values, both to ensure clarity of approach, and to highlight weaknesses in the current evidence base.

Chapter 6 reports the data sources and assumptions used to estimate lifetime costs for individuals with diagnosed colorectal cancer by stage and mode of detection.

Chapter 7 describes the scope, structure and assumptions of the colorectal cancer screening model. Methods for exploring parametric uncertainty within the model are also detailed.

Chapter 8 reports the methods of model calibration against published incidence, mortality and other observed outcome data.

Chapter 9 reports the estimated costs and health outcomes from the model. Multivariate uncertainty analysis is reported to assess the relative impact of alternative natural history and test sensitivity parameter estimates. Additional one-way sensitivity analysis is presented to demonstrate the impact of alternative cost and compliance assumptions on the cost-effectiveness of the alternative screening options.

Chapter 10 reports estimates of resource use and cost impacts associated with the alternative screening options using intermediate outcomes generated from the model.

Chapter 11 presents a discussion of the results of the cost-effectiveness analysis and resource impact analysis. This chapter also provides a general discussion of the limitations of the health economic model developed within this study and weaknesses in the current evidence base. Recommendations for future research are also presented.

3.0 Effectiveness of screening for colorectal cancer

3.1 Introduction

Considerable evidence exists on the effectiveness of screening in reducing mortality resulting from colorectal cancer. The majority of the evidence concerns the effectiveness of FOBT, as demonstrated by randomised controlled trials.[17-20] Three randomised controlled trials to evaluate the effectiveness of flexible sigmoidoscopy are currently in progress.[21;24;25]

The key determinants of the effectiveness of any colorectal cancer screening programme are reductions in colorectal cancer incidence and mortality. To date, four randomised controlled trials[17-20] have demonstrated that screening average-risk individuals using FOBT can reduce colorectal cancer mortality. The effectiveness of colorectal cancer screening remains the subject of ongoing research; the results of the UK FOBT demonstration pilot has recently reported results from the prevalence round.[26;27] Evidence on the long-term impact of screening on colorectal cancer incidence and mortality from this study is not yet available. Baseline results from the UK flexible sigmoidoscopy screening trial have recently been published.[21]

3.2 Evidence on the effectiveness of FOBT

3.2.1 Randomised controlled trial of faecal-occult-blood screening for colorectal cancer - Hardcastle et al[17]

Hardcastle and colleagues[17] undertook a randomised controlled trial to evaluate the effectiveness of Haemoccult in reducing colorectal cancer incidence and mortality. 152,850 individuals aged 45-74 were recruited to the study between February 1985 and June 1991. Households were randomly allocated to receive screening or no screening. Individuals within the screening group who accepted the test took 2 samples from each of 3 consecutive stools, and returned the completed FOB cards to their general practice. Individuals who tested positive were invited for a follow-up examination. Those individuals who were found to have adenomas or colorectal cancer at follow-up were treated and transferred to endoscopic follow-up programmes. Individuals who tested negative with FOBT, and those who tested positive with FOBT but were found to be negative at colonoscopy, were invited to take part in subsequent FOBT screening at 2 yearly intervals. All individuals were offered between 3 and 6 FOB tests. Individuals allocated to the control group were not told about the study, and received no intervention.

The median follow-up period for the study was 7.8 years. Of those individuals allocated to the screening intervention group, 28,720 (38.2%) completed all FOB tests they were offered. 16,118 (21.4%) individuals completed at least one but not all the tests they were offered, and

31,415 (40.4%) did not complete any FOB tests. A total of 236 cancers were detected by screening, 249 interval cancers presented, 400 cases of colorectal cancer were diagnosed in non-responders and 856 were diagnosed in the control group. The number of deaths with an underlying cause of colorectal cancer was lower in the screening group; Hardcastle et al[17] reported a highly significant survival advantage for the screened group over the control group (360 cancers versus 420); a reduction in verified CRC mortality of 15% (odds ratio = 0.85, 95% C.I. 0.74-0.98, p=0.026).

<u>3.2.2 Randomised study of screening for colorectal cancer with faecal-occult-blood test - Kronborg et al[18]</u>

Kronborg and colleagues[18] report the results of a randomised controlled trial of screening for colorectal cancer using FOBT undertaken in Fünen, Denmark. This study used a protocol similar to the Nottingham RCT.[17] 61,933 people aged 45-75 were enrolled into the study in 1985. 30,967 individuals were randomised to the screening group and 30,966 individuals were randomised to the control group. The control group were not told about the study. The screening group were invited to undergo biennial screening using the Hemoccult-II test. Test slides were not rehydrated. Dietary restriction was recommended prior to undertaking the test. Individuals were asked to provide two samples from each of three consecutive stools. Individuals who tested positive were invited for follow-up colonoscopy. Only individuals who agreed to participate in the first screening round were invited for further screening in subsequent rounds. Analyses were undertaken according to the intention to treat principle.

After 10 years of follow-up, a total of 481 (1.57%) individuals in the screening group were found to have colorectal cancer, compared with 483 (1.55%) in the control group. 413 individuals in the screening group (1.35%) were diagnosed with adenomas ≥1cm; 174 adenomas ≥1cm (0.56%) were diagnosed in the control group. Mortality due to all causes did not differ significantly between the screening and control group. The colorectal cancer-specific mortality rate for screening versus controls (including deaths due to cancer treatment) was 0.80 (95% C.I. 0.61-1.02) in men, and 0.84 (95% C.I. 0.68-1.05) in women. The overall survival in patients with colorectal cancer was significantly higher in the screening group than in the control group (p<0.01). Notably, no statistically significant difference in survival within individual stages of cancer were observed (p>0.05), although individuals with Dukes' A cancer detected through screening tended to have improved survival compared to the control group (p=0.13).

3.2.3 Reducing Mortality from Colorectal Cancer by Screening for Fecal Occult Blood - Mandel et al[19]

Mandel and colleagues[19] undertook a randomised controlled trial to evaluate the effectiveness of FOBT in the US. 46,551 participants aged 50-80 years were randomly assigned to receive screening using the Hemoccult test annually, biennially, or no screening. Participants were asked to return two smears from each of three consecutive stools; dietary restrictions were recommended 24 hours prior to the collection of the samples. The majority of slides (82.5%) were rehydrated. Individuals with one or more slides testing positive were urged to return for evaluation at the hospital. The annually screened group completed 75.2% of the screening offered, and the biennially screened group completed 78.4% of screening tests offered.[19] Approximately 90% of the 2 screening groups completed at least one FOB test.

12,246 colonoscopies were undertaken, resulting in 4 perforations and 11 cases of serious bleeding. At 13 years of follow-up, cumulative incidence rates were almost identical, although a survival advantage was reported in the two screening groups versus the no screening group (annually screened group 5.88 per 1,000, biennially screened group 8.33 per 1,000, control group 8.83 per 1,000). The rate ratio for mortality due to colorectal cancer was reported to be 0.67 in the annual screening group (95% C.I. 0.50, 0.87), and 0.94 in the group receiving screening biennially (05% C.I. 0.68, 1.31).

3.2.4 Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. Results for 68,308 subjects. - Kewenter et al[20]

Kewenter et al[20] undertook a randomised controlled trial of FOBT in 68,308 subjects in Goteborg, Sweden. Subjects in the test group were invited undergo screening using the Hemoccult II FOB test. Tests were undertaken on 3 consecutive days; individuals were invited to repeat the test after 16-24 months.

21,347 people completed and returned the test during the prevalence screening round (63.0%), and 19,991 (60.0%) completed the re-screen test. 942 (4.4%) individuals tested positive in the prevalence round. Of these, 47 individuals were found to have cancer, and 129 individuals were diagnosed with colorectal adenomas greater than or equal to 1cm. In the repeat screening round, 5.1% individuals had a positive test; 34 cancers and 122 large adenomas were diagnosed. Between the screening rounds, colorectal cancer was diagnosed in an additional 19 subjects in the screening group, and 15 were diagnosed in the non-responders. 4 cancers were diagnosed in the control group during the same period. The study reported a relative risk of mortality due to colorectal cancer in the screening group versus the control group of 0.88 (95% C.I. 0.68, 1.12).

3.2.5 Results of the first round of a demonstration pilot of screening for colorectal cancer in the United Kingdom - Steele et al[26;27]

Steele et al(335} and Weller et al[27] report the results of the first round of a demonstration pilot study to assess the feasibility of introducing NHS colorectal cancer screening using FOBT. 478,250 individuals aged 50-69 were invited to take part in the study. The study population covered 2 English Health Authorities and 3 Scottish Health Boards. Screening began on 29 March 2000. Individuals were offered the Hema-screen (Immunostics, USA) guaiac test, which has identical characteristics to the Haemoccult test used in the Danish and English FOBT trials.[17;18] Two samples from each of three stools were assessed from each participant. Repeat tests were undertaken for weakly positive results. People testing positive were invited to endoscopic follow-up.

The prevalence round had an overall uptake of 56.8%, with 271,646 individuals completing the test. This is comparable to the Nottingham RCT.[17] 5,050 individuals were invited for colonoscopy, of which 4,116 attended (81.5%). Ten patients (0.24%) were admitted for bleeding or abdominal pain, and there were two perforations (0.05%) at follow-up colonoscopy.

552 cancers were found through screening: of these, 22% were polyp cancers, 26% were true stage A, 25% were Dukes' stage B, 26% were Dukes' stage C, and 1% were stage D. Steele and colleagues report a positive predictive value of 10.9% for invasive cancer, and 35.0% for adenoma. Estimates of reductions in colorectal cancer incidence and mortality are not yet available.

3.3. Evidence on the effectiveness of flexible sigmoidoscopy screening

Evidence on the effectiveness of flexible sigmoidoscopy in reducing colorectal cancer incidence and mortality is less developed than FOBT. There are currently three trials in progress to evaluate the effectiveness of flexible sigmoidoscopy.[21;24;25]

3.3.1 Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial - Atkin et al[21]

A randomised controlled trial is currently underway in the UK to test the hypothesis that once-only screening using flexible sigmoidoscopy at age 60 can lower the incidence and mortality of colorectal cancer. Study participants aged 55-64 were recruited to the study across 14 geographical centres in the UK. All individuals had previously expressed an interest in screening. The main randomised phase of the study began in 1996. Control subjects were not contacted about the study. All flexible sigmoidoscopy was undertaken using a 60cm Olympus video-endoscope, and all procedures were videotaped. Sample size calculations were based on the ability of the study to detect a 40% difference in colorectal cancer incidence at 10 years and a 40% difference in mortality due to colorectal cancer at 15 years with 90% power. 57,254 individuals were randomised to the screening group, and 113,178 individuals were randomised to the control group.

Endoscopists were advised to remove all small polyps during the flexible sigmoidoscopy procedure, with the exception of smaller polyps thought to be hyperplastic which were ignored at the discretion of the endoscopist. Patients with high-risk characteristics (adenomas greater than or equal to 1cm in diameter, greater than or equal to 3 adenomas, adenomas with tubulovillous or villous histology, severe dysplasia or malignancy, or greater than or equal to 20 hyperplastic polyps above the distal rectum) were referred for colonoscopy to examine the entire colon. Individuals with low-risk characteristics or a negative test result at screening were discharged and offered no further follow-up. 1,380 individuals were identified to be high risk. 2,131 individuals were referred on for follow-up colonoscopy. It is anticipated that early results of the trial will be reported in 2005.

<u>3.4 Summary of existing randomised controlled trials of colorectal cancer screening</u>

Current evidence from randomised controlled trials suggests that screening using FOBT can reduce colorectal cancer mortality. The considerably higher mortality reduction reported by Mandel et al[19] is likely to be due to the rehydration of the FOB slides, which subsequently led to a considerably higher colonoscopy rate than the other three FOBT trials. A meta-analysis of the four randomised controlled trials of FOBT estimated the relative risk reduction for mortality due to colorectal cancer to be 0.16 (95% C.I. 0.07, 0.023) in favour of the screening group. The effectiveness of flexible sigmoidoscopy screening in reducing colorectal cancer mortality has not yet been proven in a randomised controlled setting.

4.0 Review of existing colorectal cancer screening models

4.1 Introduction

This section presents a review of the methodological approaches employed by existing health economic models of colorectal cancer screening programmes. This review was undertaken to identify alternative modelling methodologies, structural assumptions and data sources used within existing health economic evaluations of colorectal cancer screening programmes, and to appraise their validity for use in the development the health economic screening model reported within this study. Given the numerous important weaknesses in evidence concerning the natural history of colorectal cancer, the modelling methodology, structural assumptions, and methods of model calibration should be considered central to the reliability and robustness of the results.

4.2 Search strategy

Systematic searches were conducted using a number of electronic databases including MEDLINE, EMBASE, and NHS EED. Additional model-based evaluations were identified through handsearching the retrieved studies. The searches included keywords and MeSH headings such as ‘colorectal neoplasms’, ‘mass screening’, ‘economics’, ‘quality of life’ and ‘cost and cost analysis.’ The search strategies are available from the authors. Over 200 potentially relevant economic studies were identified; fourteen model-based studies were included in the review.

4.3 Studies identified for inclusion within the review

The studies identified here used a variety of alternative modelling approaches, including the Markov methodology,[27-35] the semi-Markov methodology,[36-40] discrete event simulation (DES),[41-43] and Maximum Likelihood Estimation (MLE).[44;45] Each methodology has different implications with respect to the flexibility with which the natural history of colorectal cancer may be modelled. Simpler methodologies, such as the Markov approach may enable the retention of more explicit, intuitive and ‘understandable’ model structures, but may be subject to certain restrictions concerning the explicit modelling of the presence of multiple polyps and cancers. More complex techniques on the other hand, such as DES, may allow for the incorporation of more detailed representations of the natural history of the disease, although direct evidence to inform such models is severely limited.

Directly related to the level of complexity with which the natural history of colorectal cancer is represented by the model are issues surrounding the parameterisation of unobservable events. Three alternative approaches to parameterisation have been defined: (1) fully fitted models whereby all parameters fitted simultaneously to a combined data source, (2) partially fitted models whereby a set of parameters is fitted simultaneously with the remaining parameters are estimated individually, and finally, (3) individually estimated models in which all parameters are estimated individually using separate data sources. The literature provides no consensus regarding the relative superiority of these three approaches. There exists a trade-off between the level of complexity with which the natural history of the disease is represented, and the number of parameters that require calibration against observed outcome data (i.e. cancer incidence and mortality data etc.).

4.4 Colorectal cancer model structures and assumptions

There is considerable variation in the representation of the natural history of colorectal cancer within the identified modelling studies. It should be noted that the reporting of methods within the majority of these studies is generally unclear, and many of the model assumptions used are not fully justified within the text. The following review and critique of existing analyses begins with brief discussions concerning the more simple structures and subsequently moves up to the most complex representations of the underlying disease process. The process of reviewing and appraising existing evaluations, together with additional advice from clinical experts, was central to the development of the model structure used in this analysis.

4.5 Review and discussion of existing model structures

Neilson et al[27] report a cohort-based Markov model developed to evaluate the health economics of FOBT screening within the UK colorectal cancer screening demonstration pilot. It is unclear why Neilson used a different model structure here to the semi-Markov model used to evaluate the Nottingham FOBT trial.[38-40] The model evaluates two screening options: FOBT offered to individuals aged 50-69 and FOBT offered to individuals aged 60-69. Separate analyses for men and women were undertaken. The outcome for the analysis is the cost per QALY gained. The structure of the model is based primarily on the work of Frazier et al.[30] The simulation begins with a cohort aged 50 years; the model uses an annual cycle length.

During any model cycle, individuals exist within one of six primary health states in the model: normal, low-risk polyp, high-risk polyp, Dukes' A&B, Dukes' C&D or dead. As the model was developed to evaluate FOBT screening only, the health states are not subdivided to represent the distal and proximal colon separately. During each model cycle, individuals within the model cohort progress through the health states, as described by annual transition probabilities. During any model cycle individuals may present symptomatically, die from colorectal cancer or die from other causes.

The reporting of this model is limited, hence it is unclear whether parameter values such as the incidence and prevalence of adenomas have been estimated from direct evidence, calibrated against observed outcomes, or simply assumed by the authors. A 'utility adjustment for quality of life' is modelled, although it is unclear how, or to whom it is applied. Furthermore, comparisons with the economic model reported by Frazier et al[30] clearly indicates that many of the unobservable parameter values used to populate the model, including probabilities of progressing between health states and probabilities of symptomatic presentation, were taken directly from Frazier et al,[30] and have not been calibrated against UK data.

Sonnenberg and colleagues[28;29] describe a simple Markov model used to assess the cost-effectiveness of 3 screening options: annual FOBT, flexible sigmoidoscopy every 3 years, and colonoscopy every 10 years. The model included five main states: non-compliance with screening, status after screening, status after colonoscopy, status after polypectomy, and colorectal cancer. Patients remain in the 'status after…' states until the next screening-related intervention unless they develop cancer in the interim period. If the next screening intervention is refused, the patient enters the non-compliance arm and is subject to a risk of cancer equal to the age-specific incidence. A rate of preventive efficacy is seemingly applied to all persons with polyps who undergo polypectomy, whilst the cases that progress to cancer following polypectomy are assumed to be detected earlier, leading to improved survival.

No relationship between adenomas and cancer is specified, for example, it is not clear which cancer incidence rates are applied to persons with a negative screen result, a group that includes true negative and false negative test results. Overall, the methodology adopted by Sonnenberg and colleagues,[28;29] which *"tried to reduce the complex natural history of colorectal cancer to few essential states and avoid transition assumptions for which little or no published data existed"*, resulted in a model that is appears to fail to capture the events relevant to an assessment of colorectal cancer screening.

Frazier et al[30] use a Markov model to evaluate the incremental cost per life year saved resulting from 22 potential screening options, including colonoscopy, FOBT, flexible sigmoidoscopy, barium enema and combination strategies. Separate analyses were undertaken according to sex and ethnicity. The model uses an annual cycle length and a lifetime time horizon. The model structure describes the progressions between low- and high-risk polyps (≥1cm or containing villous histology), and three stages of cancer (local, regional, and distant). The two sides of the colon (the distal or proximal colon) are modelled separately to explicitly account for the reach of flexible sigmoidoscopy. Whilst multiple polyps are not explicitly modelled, correlations between neoplasia arising in the distal and proximal colon are dealt with by assuming a proportion of proximal cancers are accompanied by 'sentinel' polyps located in the distal colon. The text suggests that identical transition probabilities were applied to polyps originating in either side of the colon. Due to the use of a transition matrix to describe the adenoma-carcinoma sequence, the model does not explicitly assume the proportion of polyps progressing to cancer, although the model structure implies that all cancers originate from prior adenomatous polyps.

Frazier et al[30] also incorporates separate sensitivity rates for low-risk polyps, high-risk polyps and cancer, as well as differential recurrence rates for low-risk polyps following the detection and removal of low- and high-risk polyps. Model input parameters were based on a comprehensive review of current evidence. The authors also report extensive 1-way sensitivity analysis varying key model parameters for the most cost-effective screening strategy identified within the base case analysis. The authors report several limitations of the model: firstly, the model assumes that all cancers arise from adenomas; *de novo* cancers are not included in the model. Further, the development of polyps in the distal and proximal colon are modelled as independent events, whilst it is likely that they are correlated. The study undertaken by Frazier et al[30] is one of the most transparent modelling evaluations identified within this review. Despite the limitations described above, the structural assumptions employed within the model and extensive review of evidence suggest that the model is one of the most robust evaluations identified within this review.

Vijan et al[46] reports the use of a Markov model to evaluate the cost per life year saved resulting from four screening options: annual FOBT, flexible sigmoidoscopy every 5 years, annual FOBT plus flexible sigmoidoscopy every 5 years, and colonoscopy at age 50 and 60. Within the model, persons with a normal colonic epithelium may develop polyps, or may progress directly to the local cancer state. Polyps are assumed to remain as polyps, enter a pre-malignant dwelling state, or progress to local cancer without passing through the pre-malignant state. The model explicitly assumes a polyp dwell-time of 10-years based upon indirect evidence and consensus opinion. Patients either remain in the pre-malignant state, or progress to local cancer. Separate states are used to represent local, regional and disseminated cancer. Vijan et al[46] assume constant durations within different cancer states through the use of separate year 1 and year 2 local states to represent 2-year duration, and a single regional state to represent 1-year duration, i.e. all persons remain in each state for one annual cycle on their way to the disseminated state. The validity of constant durations for polyp dwell-time and cancer dwell-time is questionable, as it does not allow for differential progression rates between fast and slow-growing polyps and cancers. The authors do not report any assumptions concerning stage-dependent probabilities of symptomatic presentation with cancer.

Alternative polyp locations are not modelled, although the estimated sensitivity of flexible sigmoidoscopy was adjusted to account for the proportion of polyps and cancers that could be reached by the procedure. Alternative incidence rates and follow-up strategies are described for adenomatous and hyperplastic polyps. Subsequent recurrence rates are described for the development of new adenomas polyps following removal of detected adenomas, but not for hyperplastic polyps. Presumably, all hyperplastic polyps remain in the initial polyp state until death or detection. In addition to defining separate incidence rates for adenomatous polyps and hyperplastic polyps, Vijan et al[46] also define the proportion of multiple polyps and those larger than 1cm, which are used to define surveillance schedules following the detection of polyps. One-way and three-way sensitivity analyses were undertaken to explore the impact of different parameter values on cost-effectiveness results. The authors report that model predictions closely match expected incidence reported from the Surveillance, Epidemiology and End Results (SEER) registry; the text suggests that stage-specific mortality rates were varied by stage of cancer based on SEER data. Given the model assumptions concerning dwell times in each health state, this does not however guarantee that the model is representative of the true natural history of colorectal cancer in the US.

Shimbo et al[34] developed a Markov model to determine the cost-effectiveness of seven colorectal cancer screening strategies in Japan. The screening options modelled include FOBT, and flexible sigmoidoscopy. The model projects the histories of 100,000 asymptomatic 40-year old Japanese men and women until the age of 75. It is likely however, that stopping the simulation before the entire cohort is dead may underestimate the lifetime impact of screening on incidence and mortality. The model simulates the progression of persons who are ‘polyp-free and cancer-free’ to one of three states: hyperplastic polyp, adenomatous polyp, or cancer. Cancer is modelled as three separate stages: A, B, and C. The model assumes that 97% of all polyps remain benign in order to match prevalence estimates. The model does not explicitly describe polyp location, though the estimated sensitivity of flexible sigmoidoscopy was adjusted to account for the proportion of polyps and cancers that could be reached. Persons with detected polyps are assumed to rejoin the normal state and are not subject to alternative recurrence rates; however direct evidence[11;47-49] clearly suggests that this assumption is flawed. Alternative recurrence rates were however tested in the sensitivity analysis. Both the exposition of the model structure and the parameter estimates used to populate the model are unclear.

Ladabaum and colleagues[50] reported the use of a Markov model to evaluate the use of aspirin as an adjunct to colorectal cancer screening in the general US population. The model is evaluated over 30 annual Markov cycles, from age 50 to age 80. The screening options include FOBT, flexible sigmoidoscopy and colonoscopy. The model structure is slightly simpler than the above models, describing only an adenomatous polyp state, and a probability of progressing from polyp to cancer. Ninety percent of cancers are assumed to originate from polyps, with the remaining ten percent arising ***de novo***. Cancer is divided into local, regional, and distant. As with the model reported by Vijan et al,[46] constant durations are assumed for each cancer state: (2 years in local, 2 years in regional). Transition probabilities from normal to polyp to cancer states were estimated to match SEER incidence data.

Separate sensitivity rates for polyps and cancers were estimated for FOBT and flexible sigmoidoscopy, with the sensitivity of sigmoidoscopy accounting for the proportion of cancers within reach. Patients with detected adenomas undergo a more intensive surveillance programme, though it is not stated whether alternative recurrence rates are applied. Multivariate sensitivity analysis was undertaken to explore second-order uncertainty in model input parameters. However, parameters describing the natural history of the underlying disease were held constant during the simulation. As the true mean values of the natural history parameters are not just uncertain, but in fact unknown, the results of the Monte Carlo analysis considerably underestimate the uncertainty in the decision model.

Khandker et al[35] reports the use of a 'dynamic' state transition model used to evaluate the cost-effectiveness of recent guidelines for colorectal cancer screening published by the American Gastroenterological Association. The model estimates the cost per life year saved resulting from screening using flexible sigmoidoscopy, FOBT plus flexible sigmoidoscopy, barium enema or colonoscopy. The model uses a 35-year time horizon, evaluating the cost-effectiveness of the various screening options from the age of 50 to 85.

The basic model describes the incidence of hyperplastic and adenomatous polyps. The model assumes that all cancers develop from pre-existing adenomas. Undetected adenomatous polyps progress to undetected cancer, which subsequently may progress to a treatment stage either through screen-detection or clinical diagnosis. The authors indicate that more detail is included within this basic structure; the complete model contains over 60 states incorporating polyp histology (size and stage of development), location (distal or proximal colon), age (5-year intervals), and cancer stage (local, regional, and distant, and number of years in each stage). Tunnel states are used to apply time-in-state dependent transition probabilities from the polyp state (modelled as 10 states of 2-year duration), which allow the probability of progression to increase as a function of dwell time in the colon. Persons with detected adenomas are transferred to a surveillance state from which increased rates of polyp incidence are applied. Tunnel states are also used to describe the progression of patients with undiagnosed cancer, which allows the use of alternative probabilities of detection or disease progression as a function of time with cancer. The probability of progressing from polyp to cancer was based on an equation derived from Whynes et al,[51] which was in turn, based on data reported by Stryker et al.[5]

Decision trees are appended to each of the basic model states to incorporate extra detail, for example, at the end of each cycle a decision tree is solved for all patients in the adenomatous polyp state to describe the proportion of patients progressing to alternative states within the model as a function of the interactions between the screening tests and the characteristics of the adenomatous polyps (e.g. histology and location). An appraisal of parameter estimates used to populate the model is not possible, as the reporting of these is not transparent within the text. Full compliance is assumed within the base case, which is unlikely in the context of a national screening programme. Lower compliance rates are explored in the sensitivity analysis. The authors acknowledge that a clearer understanding of the rate at which polyps progress to cancer, and the dwell time in various stages of cancer are central to evaluating the effectiveness of screening.

Wagner and colleagues[37] report a health economic model to assess the cost-effectiveness of a periodic programme of colorectal cancer screening in the elderly US population. Wagner et al[37] do not explicitly describe the model structure employed, although the text suggests a constant dwell time of 6 years for a 5mm adenoma to progress to colorectal cancer. Whilst it appears that polyps are not modelled by size or risk of malignant transformation, it is apparent that polyps are defined as either those that will progress to cancer or those that will not (i.e. adenomatous and hyperplastic respectively). The model assumes that 57% of cancers originate from polyps, and a proportion of cancers are lifetime latent. Cancers are defined as either early- or late-stage (corresponding to Dukes' stages A & B, and C & D, respectively), with lifetime latent cancers remaining never progressing to late stage cancer.

The model uses very pessimistic assumptions concerning the rapid rate of polyp and cancer progression which bias the results in favour of more frequent screening options. The model assumes that early cancers take 1-year to progress to late-stage cancer, and 1-year is required for late-stage cancer to be detected. The text does not describe the probability that early cancers may present symptomatically, although it is likely that this event is not included in the model. Interestingly, Wagner et al[37] undertook a one-way sensitivity analysis in which the authors increased the speed of the polyp-cancer sequence (polyp-cancer in three years rather than six); this substantially decreased the cost-effectiveness of all screening options evaluated. It is unclear why the authors did not explore the impact of reducing the speed of the polyp-cancer sequence in the model, given the pessimistic assumptions used in the base case analysis. The text does not state whether the model has been calibrated against colorectal cancer incidence or mortality estimates.

The US Office of Technology Assessment (OTA)[36] model is based on the work of Wagner et al.[37] The model evaluates the cost-effectiveness of 6 alternative screening options including annual FOBT, flexible sigmoidoscopy repeated at regular intervals, colonoscopy repeated at regular intervals, as well as combination strategies for FOBT plus flexible sigmoidoscopy, and DCBE plus FOBT. The natural history model traces health status and health care costs incurred due to colorectal cancer in a population between the ages of 50 and 85. The main difference is that the OTA model does not explicitly describe the proportion of lifetime latent cancers, but does present age-specific survival rates for early-stage colorectal cancer as well as for late-stage. This implies a difference from the Wagner model as the OTA model states a fixed dwelling time in the early stages, and a fixed duration in the late-stages prior to clinical detection for all cancers, whilst Wagner et al[37] specify a proportion of early-stage cancers that remain latent in the early stages over the lifetime of the individual. The model assumes that all persons with detected polyps die of other causes.

Neilson & Whynes[38-40] use a semi-Markov process, evaluated at the level of the individual patient, to evaluate the cost-effectiveness of FOBT screening in the UK. The model is based on aggregated data from the Nottingham colorectal cancer screening trial.[17] This model also builds on the model structure developed by Wagner.[37] The general model structure describes progression from healthy to adenoma to early asymptomatic cancer to late asymptomatic cancer. A proportion of cancers are assumed to progress directly from the healthy state without passing through the polyp health states. The authors make reference to the existence of ‘true non-progressive polyps’, which implies that separate adenomatous and hyperplastic polyp states were defined. The prevalence and incidence of lifetime latent cancers are specified as input parameters, indicating that this aspect of the model follows Wagner et al[37] more closely than the OTA model,[36] as this implies that life years gained are also estimated on the basis of the prevention of late-stage cancers (i.e. treated early-stage cancers are assumed to be cured).

The primary difference between the Neilson & Whynes model[38-40] and the Wagner model[37] appears to be the use of a semi-Markovian sampling strategy to describe the transition of persons through the model. Instead of assuming uniform durations in different states within the model, Neilson & Whynes[38-40] sample the next state to which each person will move, then, given the state to which the person will progress, a holding time in the current state is sampled from the relevant probability distribution. Utility estimates for invasive cancer were derived from an earlier study undertaken by Whynes et al.[52] Whilst the use of semi-Markovian ‘holding time’ may enable a more valid representation of the natural history of the disease, very limited information is reported on the methods, data sources and assumptions used to populate the unknown parameters within the model.

Two further patient-level simulation models were identified;[41-43] both the MISCAN[41;42] and the Ness et al[43] models describe lifetime profiles for a large set of individual and then apply alternative screening schedules to each life history that may alter the course of each person’s lifetime events.

Loeve et al[41;42] report the development of a microsimulation model used to evaluate the net costs and life-years gained resulting from 5-yearly flexible sigmoidoscopy screening. The model is based on available evidence; where such evidence was unavailable estimates were obtained from clinical experts. The model simulates the progression of separate lesions within individuals. Each individual is assigned a risk index that describes their relative risk of developing polyps, or the population can be split into strata that represent, for example, alternative risk categories based on population characteristics. Each polyp is assigned an anatomical site defined in terms its location within the bowel, and a percentage that indicates the localisation within this part. Polyps are modelled according to their size (<5mm, 6-9mm, >10mm), and an individual may progress from either of the two larger polyp states to pre-clinical cancer. The expert panel agreed on an estimate of average sojourn time (the duration between onset of a progressive polyp and clinical diagnosis of colorectal cancer) of 20 years. A proportion of non-progressive adenomas (purposefully not defined as hyperplastic polyps, which have separate consequences) remain in the middle polyp stage, the remaining non-progressive polyps eventually progress to the largest polyp stage. The base case model assumes that all cancers originate from polyps, although this assumption is tested in the sensitivity analysis.

Pre-clinical cancers are modelled according to Stages I to IV, and may be clinically diagnosed at any stage, from which point a stage-specific survival time is sampled. The average duration of pre-clinical cancer is reported to be 2 years, 1 year, 1.5 years, and 0.8 years in stages I-IV respectively. The characteristics of the screening tests incorporate a random element to false test results, and a systemic factor, such that not all false results are treated as independent. Time of death due to causes other than colorectal cancer is sampled for each individual, and this time is applied unless any of the lesions occurring in an individual lead to colorectal cancer death prior to the point of death from other causes. Pathways between states can depend on age and the anatomical site. For each possible transition between two stages a probability distribution of the dwelling time in the current state is defined. It is also possible to correlate dwelling times in successive states. The authors suggest that model results should be considered preliminary due to current uncertainties in the natural history of colorectal cancer, and suggest that the results of forthcoming flexible sigmoidoscopy trials may allow for greater certainty in the representation of the natural history of the disease.

Ness et al[43] use the discrete event simulation (DES) methodology to evaluate the cost per QALY saved resulting from screening using once-only colonoscopy. The underlying model structure reported is similar to that developed by Loeve et al;[41;42] the model follows the progression of separate adenomas within individuals. An individually assigned genetic risk value is used to adjust the age-dependent polyp incidence rate for each individual. Each polyp is described in terms of its size (<5mm, 6-9mm, >10mm) and location (left, right, sigmoid, high-rectum, low-rectum). Incident polyps are assigned to either a 'fast growing' or 'slow growing' group. All polyps are assumed to have the potential to progress to cancer, but many are assumed not to do so within the natural lifetime of the individual. Polyps may progress to cancer from any of the three polyp states. Cancer is modelled as local, regional and distant, and progression directly from local to distant cancer is permitted. Transition probabilities from polyps to cancer, and through the cancer states are not fixed, but are instead sampled probabilistically from distributions.

Of particular interest within the study reported by Ness et al,[43] are the use and fairly detailed reporting of extensive model calibration methods: the model was calibrated against SEER incidence and mortality statistics, adenoma prevalence estimates from various autopsy studies, as well as colonoscopic detection rates from the National Polyp Study. A further commendation of the study reported by Ness and colleagues[43] is the incorporation of stage-specific quality of life impacts associated with various states of diagnosed cancer and treatment.[53]

Eddy[31-33] reports the use of a nine-state Markov process model to evaluate the clinical and economic outcomes resulting from eleven alternative screening strategies. Health states describe persons who have no diagnosis of cancer, who have cancer diagnosed in various stages (Dukes' stage A, B, C, and D), persons who have died from cancer, and those who have died from other causes. For each year of a person's life, the model calculates 5 main probabilities:

1. that a person who has no diagnosis of cancer has an asymptomatic but potentially detectable cancer or precancerous lesion;
2. that a screening test if applied would detect an existing cancer or precancerous lesions in such a person;
3. for persons with detected cancers or precancerous lesions, the stage of the cancer when detected;
4. for persons with cancer diagnosed in various stages, the probability of dying from cancer in the coming year;
5. the probability that a person will die from other causes in the coming year.

A set of differential equations, solved using numerical integration, is used to estimate each of the above probabilities, for example, the first probability above is based on age- and sex-specific cancer incidence rates, risk factors, the pre-clinical detectable period and the history of previous screening tests. The second probability is a function of the lesion's stage of development, the random false-negative rate of the screening test(s), the location of the lesion, and the region of the bowel reached by the screening test. The stage at detection is determined by the lesions rate of development, the history of previous screening tests and the random false-negative rate of the screening test. Stage-specific survival rates inform the probability of dying from cancer. Eddy[31-33] assumes that 93% of cancers emanate from polyps, and that 5% of adenomas that reach 5mm develop into invasive cancer.

Gyrd-Hansen et al[44;45] present an evaluation of FOBT based on data from the Funen trial.[18] The authors use Maximum Likelihood Estimation to combine estimates of test sensitivity and average sojourn time with age-specific incidence rates in a simulation process to estimate the number of cancers detected at each screening round. The simulation process is used to evaluate 60 screening options comprising alternative combinations of eligible ages and screening intervals. The authors assume that 30% of screen-detected cancer patients survive due to early detection; this percentage is assumed to be constant across different screening intervals. The life years gained from the early detection of cancer are estimated as the sum of the age-specific life expectancies for surviving individuals after adjusting for mean lead-time.

The impact of non-invasive polyps is based on the cumulative risk of large polyps progressing to cancer, which is applied to the observed difference in the number of polyps detected to estimate the number of cancers avoided due to the detection of polyps. The relative risk of colorectal cancer for persons in whom a polyp is detected and followed-up is applied to age-specific incidence rates, and these cancers are assumed to have the same mortality risk as screen-detected cancers.

4.6 Summary of existing economic evaluations

The review of existing screening models demonstrates a number of alternative approaches to modelling the natural history of colorectal cancer. Given the limitations of the evidence base, the issue of model parameterisation is central to the structure of the model. Whilst more sophisticated structures may provide a more realistic clinical representation of the underlying natural history of colorectal cancer, the greater the level of detail included, the greater the number of assumptions are required. This is particularly problematic in the evaluation of any screening programme, as several parameters such as annual probabilities of progressing between pre-clinical cancer states cannot be estimated empirically. Thus more complex models, such as those described by Loeve et al[41;42] and Ness et al[43] typically involve a greater number of input parameters which must be fitted simultaneously to observed outcome data. This issue is highlighted by Church who raises questions concerning the accuracy of the MISCAN-PROSTATE cancer model on account of its 37 fitted input parameters.[54] If the number of parameters in the model exceeds the number of outputs available to calibrate the parameter values, the parameters themselves will be under-determined, hence many different sets of input values may yield the same outputs. The uncertainty in the process is analogous to *"fitting a straight line through a single data point."*[54] Simpler representations of the natural history of the disease may require lesser assumptions concerning the underlying disease may enable greater certainty, or at least a smaller number of potential solutions concerning the underlying natural history, albeit at the cost of bias due to oversimplification.

This review has identified important weaknesses with several of the published colorectal cancer screening models; some of these are unavoidable due to the paucity of direct evidence, whilst others may be resolved through the use of more appropriate assumptions and the use of better quality up-to-date evidence. Of the health economic models included within the review, all are subject to one or more of the following problems:

- Oversimplification of the underlying disease process;

- Use of constant duration dwell-times for polyp-cancer transitions, and between cancer stages, that fail to allow for fast-progressing polyps or cancers (and are thus likely to bias results in favour of infrequent screening programmes);
- Failure to incorporate alternative recurrence rates for the development of new polyps following polypectomy;
- Poor reporting (or absence) of methods for calibrating model outputs against published data to fit unobservable model input parameters;
- Assumptions of perfect compliance which overestimate the effectiveness of the screening programme;
- Omission of quality of life effects associated with diagnosed cancer and subsequent treatment.

5.0 Assessment of research evidence

5.1 Introduction

This section describes the data sources, methods and assumptions used to derive parameter estimates for use in the health economic model detailed in Chapter 7; these are reported in detail to ensure that all methods and assumptions are explicit. The reader should note the substantial uncertainties in the evidence base, which consequently lead to important uncertainties within the model and cost-effectiveness results. Primarily, these concern the natural history of colorectal cancer, and are largely a result of problems in measuring unobservable events such as the rate of progression from adenomatous polyp to cancer, and the rate at which individuals progress from pre-clinical local cancer to metastatic disease.

In instances whereby evidence was available but was either limited or inconsistent, for example incidence of adenomas within the English population, parameter estimates were firstly derived from the literature and subsequently calibrated against published estimates of colorectal cancer incidence and mortality. Whereby evidence was not available, for example, the rate at which local cancer develops into metastatic disease, clinically plausible ranges were assumed from the literature and parameter estimates were calibrated against published outcome data. Each area of evidence is reviewed, its strengths and weaknesses discussed, followed by a description how the evidence is applied within the model.

5.2 Incidence of adenomatous polyps

The true incidence of colorectal adenomas cannot be directly measured within an unselected population. Whilst several studies of individuals undergoing surveillance colonoscopy have been published, such studies are likely to overestimate of the prevalence of colorectal adenomas, as study subjects are typically at a higher risk of developing colorectal cancer than the general population. Autopsy studies present an alternative and potentially more accurate source of evidence from which age-specific incidence rates of adenomatous polyps may be estimated. The key benefit of this study design is that the subjects are more likely to be unselected, and are likely to represent the average risk population. Furthermore, as the entire large bowel is removed prior to examination, the identification of adenomas is not dependent on the sensitivity of endoscopy. Autopsy studies typically report information on the prevalence of hyperplastic and adenomatous polyps for different age groups from which crude polyp incidence rates may be estimated. We identified six autopsy studies examining the prevalence of polyps in the large bowel.[55-60] Three of these studies were undertaken in the US,[55-57] two in Norway,[58;59] and one was undertaken in England.[60]

Estimates of prevalence within different age groups varied considerably between the studies; much of this variation is likely to be due to the limited sample sizes, particularly the small number of individuals within each age group, and geographical factors. Several of the studies are also quite dated, and may not reflect the prevalence of adenomas within the current general population. Furthermore, as the prevalence of adenomas within each age group is not related to those estimated for other age groups within the same study, estimates are likely to be subject to other historical factors such as general changes in health and lifestyle which may bias these estimates in older study subjects.

Williams and colleagues[60] report the results of a prospective necropsy study of the large bowel in 365 cases. Whilst the period during which the study was undertaken is not reported, the results were published in 1982. 134 of the 365 specimens came from cases dying in hospital, whilst the remaining 231 specimens were from necropsies ordered by a coroner where death had occurred outside of hospital. In each specimen, the entire large bowel was removed, washed out and examined. The size, site and configuration of any mucosal polyp or cancer was recorded. Polyps were categorised by major histological group: hyperplastic/metaplastic polyp and neoplastic adenoma. Adenomas were classified as tubular, villous and tubulovillous types. The prevalence of adenomas was reported to be higher in men than women (36.87% vs. 28.74%).

Vatn[58] reports the results of 445 consecutive autopsies examined for the presence of colorectal lesions under an illuminating magnifying lens. 100 autopsies for groups of individuals aged 50-59, 60-69, 70-79, 80 or older years were undertaken, together with an additional 45 autopsies in subjects under 50 years of age. The study was undertaken during the period 1972-1973. Each examination was undertaken by removing the entire large bowel, washing the intestines with tap water, and studying the specimen under an illuminating magnifying lens. All polyps were classified according to size, location and histology. Vatn[58] reports an overall prevalence of adenomas of 33.26%; the prevalence in men was 34.47% and 31.49% in women.

Eide and colleagues[59] undertook unselected autopsies on 171 males and 109 females over the age of 20 years in Tromso, Northern Norway. The study was undertaken during the period 1974-1976. The large intestine was removed and its contents washed out with cold water. Specimens were subsequently examined 2 days later using an illuminating magnifying lens. Polyps were classified by size, location and histology. The prevalence in men was reported to be 39.77%, whereas a lower prevalence of 33.03% was found in women.

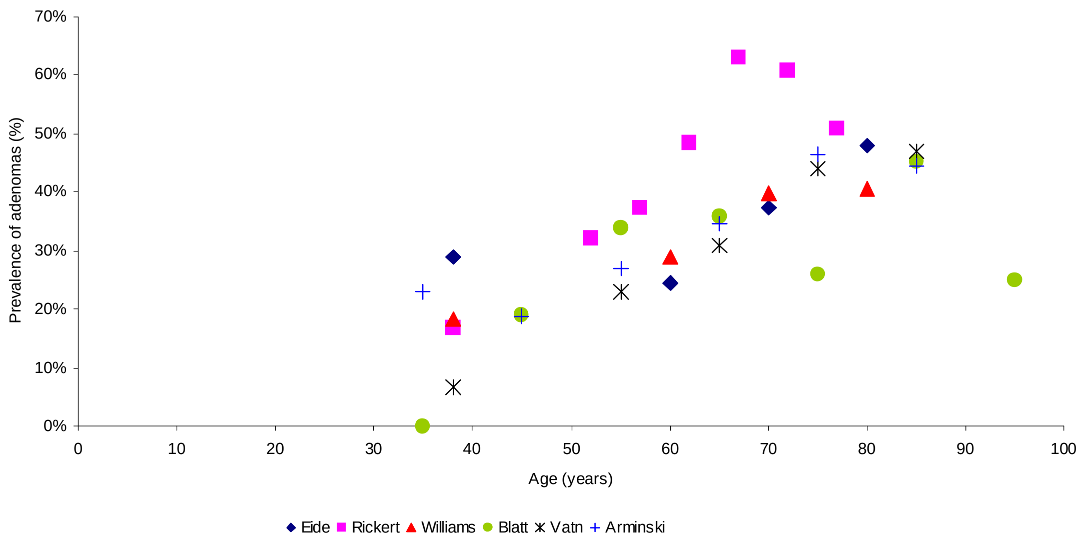
Blatt[57] reports the results of 446 consecutive autopsies in the US. A wide distribution of age groups was included in the study, with the lowest age range 30-39, and the highest, 100 years of age. Limited information is provided on the setting for the study, or the period during which the study was undertaken. The bibliographic details suggest that the study was undertaken in New York, and the study was published in 1961. Following the removal of the colon, specimens were opened and washed, fixed in formalin, photographed and sectioned. Non-adenomatous polyps were excluded from the study. All identified adenomas were categorised according to their size, location within the colon. In contrast to the other autopsy studies, a higher prevalence was reported in women than men (36.87% vs. 27.82%).

Arminski and McLean[56] undertook 1,000 autopsy examinations in Detroit, Michigan. Whilst the exact date during which the study was undertaken is not reported, the manuscript was accepted for publication in 1964. Little information is reported concerning the methods used to identify polyps during each examination. The authors report an overall prevalence of 34.43% in men, and 31.29% in women.

Rickert and colleagues[55] report the results of an autopsy survey undertaken in 518 subjects. The study was undertaken in Livingston, New Jersey, and published in 1979. Subjects with previously diagnosed colorectal cancer were excluded from the study. Intestines were removed, washed, stored and photographed for examination. The overall prevalence is reported to be higher in men (52.77%) than women (38.39%),

The results of the six autopsy studies identified are shown in Figure 2. Due to the limited reporting of the distributions of subjects within each age group, inferences have been made concerning the age at which these prevalence estimates apply, for example, the prevalence within each age group is assumed to occur at the class mid-point.

Figure 2 *Estimated prevalence in autopsy studies*



The comparison of results from autopsy studies shows considerable differences in adenoma prevalence by age between the studies. It is unclear whether these inconsistencies are a result of geographical factors, limited sample sizes, or other historical factors. Interestingly, many of the studies suggest a reduction in the incidence of polyps within the older age groups, suggesting that the incidence of adenomas begins to plateau around the age of 65-75 years of age.

Existing modelling studies have assumed a prevalence of adenomas within the model cohort at age 50 (the age of the model cohort at the introduction of screening). Given the limited information reported within the autopsy studies and the inconsistencies in the results, it is extremely difficult to estimate the number of pre-clinical cancers from this source. Thus, rather than estimating the prevalence of adenomas at the earliest age at screening would be introduced (in this case, 50 years of age), the ScHARR simulation model begins at age 30, assuming that no individuals have either cancer or polyps. Whilst this may not be entirely true, this assumption allows the model to 'build up' the prevalence of adenomas and pre-clinical cancers at the point at which a screening programme may be introduced. In estimating the incidence of adenomas, greatest weight was given to the study reported by Williams et al[60] as this is the only study which related to the English population. The model assumes an annual incidence rate of 1.5%, although this estimate was varied within the calibration process. From the age of 60 onwards, the model assumes a proportionate reduction in the polyp incidence rate of 1.5% per year to reflect a general plateau trend apparent in Figure 2.

The autopsy studies provided only limited information concerning the location of adenomas within each of the age groups. Given the assumption that all cancers arise from pre-existing adenomas, together with the assumption that progression rates in the proximal and distal colon are equivalent (again due to a paucity of direct evidence), the proportion of adenomas located in the distal and proximal colon was estimated by calibrating the model against published location-specific colorectal cancer incidence data.[1]

5.3 Growth of unresected colorectal adenomas

Very few studies have evaluated growth rates of polyps left in situ. Three studies which attempted to examine growth rates in unresected polyps were identified,[61-63] however very limited information was available from the published papers. Two of the studies of unresected polyps[4;62] did not report useful estimates of polyp growth rates. Knoerschild[63] reports the results of a study of 257 patients identified to have asymptomatic benign polyps whilst undergoing routine sigmoidoscopy. During the procedure, a permanent tattoo mark was placed in the mucosa near the identified polyp. Sigmoidoscopy was repeated at between 3 and 5 years. Of the 213 patients remaining in the study at follow-up, 4% of polyps demonstrated at significant increase in size. Assuming a mean follow-up of 4 years and constant risk, this suggests that approximately 1% of small low-risk polyps progress to high-risk polyps each year. As with the estimates of polyp incidence, this estimate was allowed to vary within the model calibration process.

5.4 Malignant transformation from adenoma to carcinoma

The rate at which colorectal adenomas develop into invasive cancer remains uncertain. Only one study which attempted to examine this relationship was identified.[5] Stryker and colleagues undertook a retrospective review of Mayo Clinic records over a 6-year period in 226 patients wih diagnosed colonic polyps greater than or equal to 10mm in diameter, in whom periodic radiographic colonic examination was elected over surgical excision. In most cases the polyp was left in situ due to poor medical condition which precluded resection. The mean follow-up duration of patients was 108 months (range 24-225 months). During the earlier years of the study, examinations were repeated at 12-month intervals, however stable polyps were examined less often. During the surveillance period, polyp growth was detected in 83 (37%) of the polyps. At 5 years, 2.5% of the cohort were identified to have developed invasive cancer. At 10 years, approximately 8% of the cohort had developed cancer, and at 20 years, 24% of the remaining study cohort had developed invasive colorectal cancer. It should be noted however, that the number of patients remaining under evaluation declined considerably over the course of the study, with only 103/226 patients remaining in the study at 10 years, and just 14/226 patients undergoing follow-up at 20 years. The text notes that the large proportion of subjects lost to follow-up was primarily attributable to the subsequent excision of non-malignant polyps due to growth.

The cumulative risk of diagnosis of invasive cancer at the site of the index polyp was used to generate a survival curve describing the ‘survival’ of patients without invasive cancer. Exponential and Weibull survival curves were fitted to the published data points using the least-squares approach in order to extrapolate the risk of developing cancer beyond the follow-up period, as shown in Figure 3.

Figure 3 Fitted survival curve to estimate risk of invasive cancer

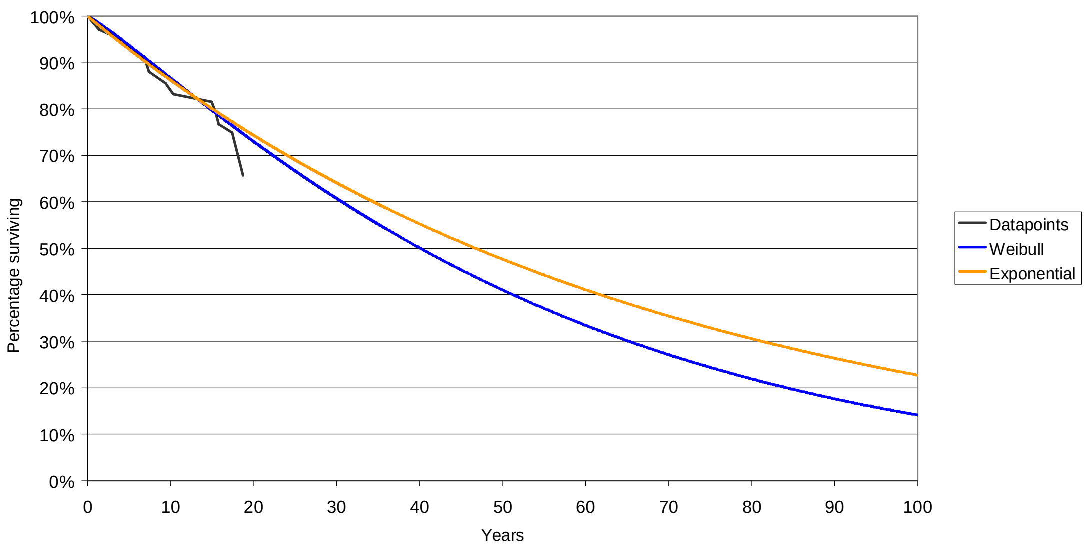


Figure 3 shows that the weibull and exponential survival curves are similar, suggesting a constant risk of invasive cancer of roughly 1.5% per year. However, this estimate should be approached with caution, as the Stryker study[5] followed up patients with colonic polyps once they had been detected. Hence, some of the individuals may have had large adenomas for a long period of time, whilst others may have developed adenomas within period immediate to the beginning of the study. Unfortunately, the rate at which large adenomas become malignant cannot be accurately estimated from these data, as one would require unobservable information concerning the point at which the polyp became ‘incident.’ At best, Stryker demonstrate that the adenoma-carcinoma sequence is generally slow, and may take 10 years or longer. The transition from high-risk adenoma to colorectal cancer was estimated within the model calibration process.

5.5 Progression through undiagnosed cancer states and symptomatic presentation

There exists no empirical evidence from which to estimate the rate at which patients progress through pre-clinical cancer states prior to diagnosis, or the probability that an individual with pre-clinical disease will present symptomatically within a given time period. Information on the former set of parameters is entirely unobservable; these were uninformed parameters which had to be fitted during the model calibration process. With respect to the latter set of probabilities, it is reasonable to suggest that the probability that an individual with pre-clinical Dukes' C or D is more likely to present symptomatically than an individual with Dukes' stage A or B cancer. Clinically plausible ranges describing the probability of symptomatic presentation with colorectal cancer were derived from an existing screening modelling study,[30] and were allowed to vary stochastically within wide uniform distributions during the model calibration process (See Table 25).

5.6 Correlations between the distal and proximal colon

Recent evidence suggests that in a proportion of cases of proximal cancer, the tumour is accompanied by a 'sentinel' polyp located in the distal colon.[64;65] Dinning and colleagues[64] undertook a retrospective study of 634 colorectal adenomacarcinomas treated at a tertiary referral centre and Veteran Affairs hospital during the period 1979-1982. The authors reviewed the records of patients with cancers proximal to the splenic flexure for the presence, location, size and histopathology of synchronous neoplastic lesions found at colonoscopy. In 72% of cases of proximal cancer, there was no presence of 'sentinel' neoplasia in the distal colon. [64] Within the health economic model, it is assumed that in 28% of patients with proximal cancer, the tumour is accompanied by a sentinel polyp in the distal colon which, upon detection, would lead to further investigation and workup following flexible sigmoidoscopy.

5.7 Recurrence rates of adenomas following polypectomy

Empirical evidence strongly suggests that individuals with a history of adenomatous polyps are more likely to develop subsequent polyps than individuals without polyps.[11;23;47;49] Winawer and colleagues[47] undertook a comparative study of the effectiveness of colonoscopy performed three years after colonoscopic removal of adenomatous polyps and colonoscopy performed both one and three years after colonoscopic removal of adenomatous polyps. 2,632 patients were included in the study. All patients had one or more adenomas, no previous polypectomy prior to study entry, a complete colonoscopy and all subjects had apparently had all their polyps removed.

Endoscopic examinations were performed by the study investigators. All removed polyps were classified as small (less than or equal to 5mm), medium (6 to 10mm) or large (greater than 10mm). Polyps were also classified according to the degree of dysplasia present. The baseline characteristics of the two surveillance groups are shown in Table 4.

Table 4 Baseline characteristics of study cohort

Size of largest adenoma at baseline*	Two-examinations group		One-examination group	
	N (699)	%	N (719)	%
Small (≤5mm)	186	27.6	186	26.7
Medium (6-10mm)	236	35.0	269	38.6
Large (>10mm)	252	37.4	242	34.7

****These data exclude 44 patients with polyps that were classified as non-adenomatous upon review. 24 of these were in the two-examination group and 20 were in the one-examination group)***

Table 4 shows that the numbers of small, medium and large adenomas detected within the two examination groups were similar at baseline. At the first follow-up examination, the recurrence of adenomas was similar between the two groups, despite the fact that the first follow-up in the one-examination group was undertaken 2 years after the first follow-up examination in the two-examinations group. It is possible that some of the 'new' polyps were adenomas missed at the baseline examination. However, the similarity of results at the first follow-up examination for both groups strongly suggest that a large proportion of new adenomas which recur do so shortly after the removal of the initial adenoma.

Table 5 Findings in study groups at first and second follow-up examinations

Finding at follow-up examination	1st follow-up examination				2nd follow-up examination	
	Two-examinations group (follow-up at 1 year)		One-examination group (follow-up at 3 years)		2 examinations group (follow-up at 3 years)	
	N (545)	%	N (428)	%	N (338)	%
Small (≤5mm)	92	16.9%	87	20.3%	55	16.3%
Medium (6-10mm)	46	8.4%	38	8.9%	15	4.4%
Large (>10mm)	12	2.2%	12	2.8%	3	0.9%

Table 5 shows the number of new adenomas found at first follow-up (median follow-up approximately 2 years) in the two study groups combined, based on the size of the largest adenoma found at baseline.

Table 6 Adenoma recurrence at first follow-up in the two study groups by presence of adenoma at baseline

% with adenomas at enrolment	Number with adenoma (without advanced pathological features)	Number with adenoma (with advanced pathological features)	Number examined
Small (≤5mm)	44	3	228
Medium (6-10mm)	101	8	354
Large (>10mm)	107	17	356

As shown in Table 6, the majority of recurrent polyps were found to be predominantly small, with only low-grade dysplasia. Only a small number of polyps detected at follow-up had advanced pathological features (>1.0cm, high grade dysplasia or invasive cancer).

Estimates of recurrence rates for individuals with low-risk and high-risk adenomas following polypectomy were derived from the results reported by Winawer and colleagues.[47] We assumed that those adenomas classified as larger than 10mm would be classified as high-risk, and those with small or medium sized polyps would be classified as low-risk. We also assumed a higher rate of adenoma recurrence in individuals with a history of high-risk polyps than in individuals with a history of low-risk polyps. Tunnel states were used to model a higher probability of recurrence in the first year after polypectomy compared to subsequent years. We estimated that the risk of developing a new low-risk adenoma given a history of prior low-risk adenomas was 18% in the first year following excision, and 5% each year thereafter. For individuals with previously excised high-risk polyps, we assumed that the risk of developing a new low-risk polyp was 25% in the first year after excision, and 6% per year thereafter. Replication of polyp recurrence following polypectomy using these estimates gives similar results to those reported by Winawer et al.[47]

5.8 Test characteristics

The true sensitivity and specificity of the screening and diagnostic tests are difficult to estimate to a high degree of accuracy. In particular, the literature contains a considerable amount of evidence concerning the operating characteristics of FOBT; however many of these studies are likely to overestimate the true sensitivity of the test. Ideally, the sensitivity of FOBT would be estimated by testing a large group of average-risk individuals using FOBT, and subsequently re-testing the same population using a ‘gold-standard’ test such as colonoscopy. However, colonoscopy itself is not 100% sensitive or specific, and such a study design would be difficult to undertake within an average risk population. We undertook systematic searches using MEDLINE in order to identify studies attempting to measure the sensitivity and specificity of FOBT. Studies evaluating miss rates for colonoscopy were identified through searching MEDLINE and from advice from experts.

5.8.1 Faecal occult blood testing

The systematic searches identified eleven studies relating to the test sensitivity of unrehydrated Hema-screen and Haemoccult guaiac-based FOBT in detecting colorectal neoplasia in average risk patients. It should be noted that the estimates of sensitivity and specificity reported by these studies are unlikely to be accurate, particularly with regards to the sensitivity of the test in detecting adenomas. Sensitivity estimates reported in existing modelling studies are typically around 30-40% for cancer, and around 10-15% for adenomas. Of the eleven studies identified, the two studies reported by Allison and colleagues[66;67] included the largest number of study subjects and used reasonable assumptions within their analysis.

The first study reported by Allison et al[66] attempted to estimate the sensitivity of the Hemoccult II guaiac test using a comparative analysis of mutually exclusive groups of patients:

(1) A prospective study of a large group of patients screened with Hemoccult for up to 4 years;
(2) A retrospective study of patients in the Kaiser Permanente pathology database with known colorectal cancer who had undergone Hemoccult tests prior to clinical diagnosis.

The prospective study (group 1) included 15,188 patients aged 45 and over who underwent Hemoccult II testing during health evaluations from April 1979-December 1980. 44% of the study population were men and 56% were women. The mean age of the study population was 60. Dietary restrictions were recommended 2 days prior to and during the completion of the test. Three separate stool samples were tested per patient (with 2 stool specimens) from separate parts of each stool sample. Slides were not rehydrated and slides returned after the day of the patient appointment were not accepted.

Medical records of all patients with a positive test were reviewed to determine whether colorectal neoplasia (cancer or polyps or both) were diagnosed after the screening test. The histopathology of each lesion discovered in patients with positive tests obtained between May 1979 and April 1980 was examined by the same pathologist. Neoplasms discovered thereafter were classified by reviewing each patient’s pathology report. Patients with a negative test who were subsequently found to have colorectal neoplasms were identified through searching the Kaiser Permanente computerised database pathology files. The authors assumed that all colorectal neoplasms found within 2 years of a positive Hemoccult test were the probable cause of the positive test. Similarly, if a colorectal neoplasm was present at the time of a negative test result, it was assumed that it would manifest itself within 4 years at subsequent screens or symptomatically.

The retrospective study included 426 patients. Patients were aged 45 and over and had been diagnosed with a colorectal neoplasm between the years 1979 and 1984. All patients who had undertaken a Haemoccult II test within the 2 years prior to diagnosis were included in the study. Sensitivity was estimated as the percentage of patients who had tested positive for colorectal cancer or adenoma within 1, 2 or 4 years prior to diagnosis. Specificity was estimated as the percentage of patients who had a negative Hemoccult test and did not develop colorectal cancer within 1, 2 or 4 years of follow-up. Table 7 shows the results of the analysis at the three durations of follow-up for the prospective study group.

Table 7 Estimates of sensitivity and specificity of Hemoccult II in the prospective study group

	Number of true positives	Number of true negatives	Number of false positives	Number of false negatives	Estimated sensitivity	Estimated specificity
(1) Prospective study group (n=15,188)						
1 year (n=14,542)						
Colorectal cancer	16	14,526	183	16	50% (33%, 67%)	98.8% (98.6%, 98.9%)
Colorectal adenoma	36	14,478	163	64	36% (27%, 45%)	98.9% (98.7%, 99.1%)
2 Years (n=14,080)						
Colorectal cancer	19	14,055	177	25	43% (29%, 58%)	98.8% (98.6%, 98.9%)
Colorectal Adenoma	38	13,982	158	98	28% (20%, 35%)	98.9% (98.7%, 99.1%)
4 Years (13,276)						
Colorectal cancer	21	13,212	168	64	25% (16%, 34%)	98.7% (98.6%, 98.9%)
Colorectal Adenoma	43	13,071	146	203	17% (13%, 22%)	98.9% (98.7%, 99.1%)

Of the 426 patients included in the retrospective group, a diagnosis of colorectal cancer was made within 1-year of the test in 118 of the Hemoccult-positive and 61 of the Hemoccult-negative patients, thus suggesting a sensitivity of 66% (95% C.I. 59%, 73%). A diagnosis of colorectal cancer was made within 2-years of the test in 119 of the Hemoccult-positive and 75 of the Hemoccult-negative patients, suggesting a lower sensitivity of 61% (95% C.I. 54%, 68%). The sensitivity of Hemoccult in detecting colorectal adenomas within 1 and 2 years was estimated to be 53% (95% C.I. 46%, 59%), and 48% (95% C.I. 42%, 54%) respectively.

The later study reported by Allison and colleagues[67] presents a comparative analysis of 3 faecal occult blood tests: (1) Hemoccult II, (2) Hemoccult II Sensa, and (3) HemeSelect.

10,702 persons aged 50 years or older scheduled for health appraisals at the Kaiser Permanente Medical Centre in Oakland, California were included in the study. Sensitivity and specificity were evaluated using 2-year follow-up data.

75.7% of the eligible patients (8,104) had at least one interpretable test. Patients were advised to restrict their diet one week prior to the health appraisal. Completed cards were not rehydrated. It was assumed within the analysis that neoplasms becoming clinically diagnosed within 2 years of screening were the cause of positive test results. It was also assumed that all polyps or cancers present at the time of a negative test became clinically apparent within 2 years through subsequent screening or the presentation of symptoms. Table 8 shows the estimates of sensitivity and specificity for the Haemoccult II test only.

Table 8 Sensitivity and specificity estimates for Hemoccult II

Hemoccult II (n= 8,104)	Number of true positives	Number of true negatives	Number of false positives	Number of false negatives	Estimated sensitivity	Estimated specificity
Polyp (>1cm)	33	7771	152	74	30.8% (21.6%, 37.1%)	98.1%, (97.7, 98.4%)
Carcinoma	13	7845	185	22	37.1% (19.7%, 54.6%)	97.7% (97.3%, 98.0%)

Allison et al[67] estimates the sensitivity of Hemoccult to be 30.8% (95% C.I. 21.6%, 40.1%) in detecting colorectal adenomas and 37.1% (95% C.I. 19.7%, 54.6%) in detecting colorectal cancer. Specificity was reported to be 97.7% (95% C.I. 97.3%, 98.0%) for cancer and 98.1 (95% C.I. 97.7%, 98.4%) for adenomas. As polyps do not commonly present symptomatically, the estimates of sensitivity and specificity for polyps are likely to be overestimates.

<u>Meta-analysis of FOBT sensitivity and specificity studies</u>

As the study methodology and populations were broadly homogeneous, we undertook a simple meta-analysis of these two studies[66;67] using 2-year follow-up results. Within the combined study population, a total of 23,292 individuals were screened using Hemoccult II. It should be noted that the sensitivity of polyps estimated here is likely to be weak, as the earlier study reported by Allison[66] categorised adenomas by size, whereas the later study[67] evaluated the sensitivity of the test in detecting all adenomas. Table 9 shows the results of the meta-analysis.

Table 9 Results of meta-analysis of FOBT sensitivity

	Number of true positives	Number of true negatives	Number of false positives	Number of false negatives	Sensitivity	Specificity
Adenoma	71	21753	310	172	29.22%	98.59%
Colorectal cancer	32	21900	362	47	40.51%	98.37%

The combined results suggest that the sensitivity of FOBT in detecting colorectal cancer is approximately 40.51%; this estimate is used in the health economic model. The combined sensitivity for adenomas is estimated to be approximately 29.2%. However, as very few polyps present symptomatically, this is likely to be a considerable overestimate. In the absence of robust methods for evaluating the true sensitivity of the test, the ScHARR model assumed a lower sensitivity in detecting adenomas of 5% (ranging from 0-10% within the uncertainty analysis).

5.8.2 Miss rates for endoscopy

Colonoscopy is broadly accepted as the 'gold standard' diagnostic technique for colorectal adenomas and cancer. However, colonoscopy is not 100% sensitive; this is particularly true for small diminutive adenomas. The true sensitivity of colonoscopy and flexible sigmoidoscopy in usual clinical practice is unknown; recent evidence suggests that detection rates may vary considerably between different centres.[68] The sensitivity of endoscopy is operator-dependent; miss rates at colonoscopy and flexible sigmoidoscopy are dependent on the adequacy of the bowel preparation and the competence and experience of the endoscopist. Three studies were used to estimate estimates of the sensitivity of colonoscopy and flexible sigmoidoscopy.[69-71]

Rex and colleagues[71] undertook a study to assess colonoscopic miss rates of adenomas using back-to-back colonoscopies undertaken on the same day. Consecutive colonoscopies were undertaken in 183 patients by endoscopists who had performed at least 500 colonoscopies during training and practice. The first endoscopist undertook the first colonoscopy with the instruction to remove all polyps with the exception of numerous small hyperplastic polyps. The second endoscopist was blinded to the results of the first colonoscopy. All polyps identified during the second colonoscopy were classified as 'missed polyps.' A total of 89 adenomas were identified at the second colonoscopy in addition to the 289 adenomas identified at the first colonoscopy, thus implying an overall miss rate of 24%. However, the miss rate was considerably higher for small polyps <10mm in size. A total of 259 adenomas <10mm were identified at the first colonoscopy, with an additional 87 adenomas identified by the second endoscopist. This suggests a miss rate of 25.1% for smaller polyps. 30 adenomas

≥10mm were identified at the first colonoscopy. Only 2 further adenomas ≥10mm were detected at the second colonoscopy, thus suggesting a much lower miss rate for large polyps (6.3%). It is possible that these are overestimates of the true miss rate, as a small number of adenomas may have been missed by both the first and second endoscopist.

Hixson et al[69] undertook a prospective blinded trial of the colonoscopic miss-rate for large colorectal polyps. The study included 90 patients scheduled to undergo routine outpatient colonoscopy for clinical indications. All patients underwent bowel preparation and full colonoscopy to the caecum. All identified polyps or masses were removed or a biopsy was taken. A second colonoscopy was subsequently undertaken; as with Rex et al,[71] the second endoscopist was blinded to the results of the first examination. All polyps detected at the second examination were classed as ‘missed polyps.’ A total of 163 neoplastic polyps ≤9mm were identified in 61 patients. 20 (14.7%) of these polyps were missed at the first colonoscopy. Neither examiner missed any polyps >8mm in size.

Bressler and colleagues[70] undertook a retrospective analysis of colonoscopic miss rates using electronic data obtained from the Canadian Institute for Health Information and the Ontario Health Insurance Program. Individuals included in the analysis were at least 18 years of age, and all study subjects had a new diagnosis of colorectal cancer. The cohort was separated into 3 groups depending on whether the cancer was located in the right side of the colon, the transverse colon, or the rectal or sigmoid colon. Each group was classified as either ‘detected cancer’ (patients who had undergone colonoscopy/flexible sigmoidoscopy within 6 months prior to diagnosis of cancer in whom it was assumed the endoscopic procedure had identified the cancer) or ‘missed cancer’ (patients who had received colonoscopy/flexible sigmoidoscopy 6-36 months prior to diagnosis in whom it was assumed the endoscopic procedure had missed the cancer). The study cohort used in the analysis consisted of 10,187 patients. 2,580 patients had right-sided cancer, 702 patients had cancer located in the transverse colon, and 6,905 patients had cancer located in the rectum or sigmoid colon. Of these, 157 patients (6.1%) with right-sided cancer were missed, 29 patients (4.1%) with transverse cancer were missed, and 207 patients (3.0%) with cancer in the rectum or sigmoid colon were missed. This study suggests that the miss rate may be dependent on the location of the adenoma or cancer, with slightly higher miss rates in the proximal colon.

Within the health economic model, a higher miss rate was assumed for smaller adenomas (24.0%) compared to those for larger adenomas and cancer. Based on the work of Bressler et al,[70] it was also assumed that the miss rate was higher for large polyps and cancers located in the proximal colon (94.0% sensitivity) compared to those located in the distal colon (97.0%

sensitivity). Due to limited evidence on the sensitivity and specificity of flexible sigmoidoscopy in usual clinical practice, with current evidence restricted only to case-control studies,[72] we assumed that miss rates for flexible sigmoidoscopy were identical to those for colonoscopy within the distal colon.

5.9 Inadequate rates for endoscopy

In a small number of cases endoscopic examination may need to be repeated due to inadequate bowel preparation. The UK flexible sigmoidoscopy trial[21] reported that approximately 5% of tests had to be repeated due to inadequate bowel preparation. In cases whereby colonoscopy is incomplete due to inadequate bowel preparation, it is likely that barium enema would be used instead (*Personal communication: Dr Wendy Atkin, Deputy Director, Colorectal Cancer Unit, St. Mark's Hospital, Harrow).* Recent guidance on the use of endoscopy in England and Wales[73] estimated that approximately 10% of colonoscopies are not completed due to inadequate bowel preparation.

5.10 Harm caused by screening

A reasonable body of evidence exists concerning the risk of bowel perforation and bleeding resulting from endoscopy. Consistently, the literature suggests that the risk of perforation is higher for colonoscopy than flexible sigmoidoscopy. The baseline findings of the UK flexible sigmoidoscopy trial[21] reported only one perforation in 40,764 people screened using flexible sigmoidoscopy, which gives a probability of perforation of 0.002%; this estimate is used within the health economic model. It is assumed within the model that this risk is the same for flexible sigmoidoscopy with and without polypectomy. This perforation rate is similar to that reported by Levin and colleagues,[22] who found only 2 serious perforations in 107,704 individuals who underwent flexible sigmoidoscopy screening in members of the Northern California Kaiser Permanente Medical Care Program. Atkin et al[21] reported 4 perforations in 2,377 colonoscopies (with polypectomy). The model assumes that the risk of perforation associated with colonoscopy with polypectomy is 0.168%. The probability of perforation for colonoscopy without polypectomy is assumed to be half of the risk of colonoscopy with polypectomy, which results in a probability of perforation of 0.084%.

Estimates of gastrointestinal bleeding rates following endoscopy were derived from the experience of the UK flexible sigmoidoscopy screening trial.[21] Of the 40,674 subjects who attended screening, twelve were admitted to hospital for bleeding following flexible sigmoidoscopy screening;[21] an probability of bleeding following flexible sigmoidoscopy of 0.0295% is used in the model. Of the 2,051subjects undergoing colonoscopy with polypectomy, nine patients were admitted to hospital with bleeding;[21] a probability of bleeding following colonoscopy of 0.439% is used within the model.

5.11 Mortality

The model incorporates three causes of mortality: death due to other causes (not colorectal cancer), death due to colorectal cancer, and death due to perforation of the bowel.

5.11.1 Other cause mortality

The annual probability of dying from causes other than colorectal cancer was estimated using standard life expectancy tables obtained from the Government Actuaries Department.[74] These tables describe the probability of dying from any cause during a given year depending on age and sex. These life tables were adjusted to avoid double-counting of colorectal cancer deaths by subtracting the age and sex-specific risk of death due to colorectal cancer using mortality estimates obtained from the ONS.[2]

5.11.2 Colorectal cancer-specific mortality

We derived crude estimates of mortality specifically attributable to colorectal cancer from patient-level data collected as part of an audit study undertaken in the Wessex Region in order to validate the mortality estimates used in the model.[7] These data were collected from the Wessex Colorectal Cancer Audit during the period 1991-1995, and comprised of 5-year follow-up of 5,173 patients with a diagnosis of colorectal cancer. The data included the patient's date of diagnosis, stage at diagnosis, age, and date and cause of death. The data were however somewhat incomplete; for example in a substantial number of cases, the date of death was not always accompanied by a corresponding cause of death, and vice-versa. Two diagnosis dates were given for each patient in the data set: histological diagnosis and clinical diagnosis. In many cases, only one of these dates was given; in the case of both dates being recorded, the most recent of the two was used within the analysis. In instances whereby neither a date nor a cause of death were recorded, subjects were assumed to be alive at the end of the 5-year period.

Survival analysis was performed using data from patients with sufficient information (n=4,872); probabilities of mortality within one year of diagnosis were derived. Analysis of variance (ANOVA) showed that age was not a significant predictor of mortality due to colorectal cancer. Estimates of mortality (averaged across all age groups) are given in Table 10. These annual mortality rates were allowed to vary within tight ranges within the model calibration process.

Table 10 Annual mortality estimates by stage and cause

Cancer Stage	Probability of death due to colorectal cancer	Probability of death due to any other cause	Probability of death due to colorectal cancer or other causes within 1 year of diagnosis
Dukes A	1.25%	3.76%	5.02%
Dukes B	5.04%	3.42%	8.46%
Dukes C	13.25%	4.21%	17.5%
Dukes D	40.74%	4.63%	45.37%

5.11.3 Death due to bowel perforation

Probabilities of death due to perforation of the large bowel were derived from a study undertaken by Gatto et al.[23] The study used a population-based cohort consisting of a random 5% of Medicare beneficiaries living in regions of the US covered by the SEER Programme registries in order to estimate rates of perforation within 14 days of a colonoscopy or sigmoidoscopy procedure. All individuals included within the analysis were aged 65 or older. The study results are shown in Table 11.

Table 11 Number of deaths after perforation within 14 days of colonoscopy or sigmoidoscopy procedure[23]

Procedure	No. of perforations	No. of deaths	Odds ratio (adjusted for patient characteristics)
Colonoscopy	77	4	9.0 (95% C.I. 3.0, 27.3)
Sigmoidoscopy	31	2	8.8 (95% C.I. 1.6, 48.5)

Of the 77 perforations due to colonoscopy, 4 patients died within 14 days (5.19%). Of the 31 perforations following flexible sigmoidoscopy, 2 patients died within 14 days (6.45%). Due to the limited number of subjects included in the analysis, a probability of dying following bowel perforation of 5.82% was assumed within the model, regardless of the type of endoscopy causing the perforation.

5.12 Participation rates for screening and follow-up

Participation rates associated with different screening tests inevitably have a significant impact upon both the effectiveness and cost-effectiveness of any screening programme. Whilst lower compliance rates may reduce the effectiveness of a screening programme, lower compliance will also reduce the costs of the programme. Many existing health economic evaluations assume an independent probability of participating in FOBT screening, typically around 60%,[27;30] regardless of whether the individual completed/attended the previous screen. Participation rates for FOBT screening and flexible sigmoidoscopy screening are not entirely clear. The FOBT demonstration pilot reported a compliance rate of 59.2% at the prevalence screen in England. The Nottingham RCT[17] reported that 59.6% of individuals returned at least one test kit offered; of those individuals who complied with at least one screening test, the mean number of tests returned was approximately 1.8 per person (*personal communication: Derek Coleman, Colorectal Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton)*. However, an important issue concerns compliance rates between screening rounds; assuming an independent compliance rate between screening rounds of around 60% means that after 3-4 tests offered, almost all individuals offered screening would have returned at least one test kit; this is unlikely to be true in reality. The Nottingham trial[17] reported that 40.4% of individuals did not return any test kits offered. Whilst it is unlikely that all of these individuals would never participate in screening (as some individuals would have been offered less FOBT kits than others), it is likely that some proportion of individuals would never participate in screening.

To address the impact of this issue, the model assumes two groups of individuals within the model; (1) individuals who comply with at least one screening round, and (2) individuals offered screening who never comply with a test. For the sake of simplicity, the latter probability is assumed to be independent of compliance with previous screening rounds, thus a random proportion of individuals are assumed to comply with each screening test offered, regardless of previous compliance. Within the base case analysis, the model assumes that a random 60% of all individuals comply with FOBT screening. The proportion of individuals who never participate with screening was varied within the sensitivity analysis.

As noted in Chapter 3, the UK flexible sigmoidoscopy trial[21] included only those individuals who had expressed a prior interest in screening, hence compliance rates observed within the trial are unlikely to reflect compliance rates for a national screening programme. The model assumes that 60% of individuals offered screening using flexible sigmoidoscopy would attend the screening session.

A further complication concerns those individuals who may be willing to participate in FOBT screening, but may be averse to screening using flexible sigmoidoscopy, or vice versa. Within the model these two probabilities were assumed to be independent. Again, the proportion of individuals who would never comply with FOBT screening was varied within the sensitivity analysis.

Estimates of attendance rates for colonoscopy were derived from the UK demonstration pilot.[27] The pilot study evaluation reports the uptake of colonoscopy within the English Pilot to be 77.5%, although the accompanying text suggests this rate to be low due to artefacts in the analysis of the routine data from the study;[27] this compliance is similar to that reported by Lund et al.[75] A higher compliance rate of 80.0% is assumed within the model for both colonoscopy following a positive screening test as well as for the surveillance of individuals in whom high risk adenomas are detected.

5.13 Health-related quality of life

Evidence on the quality of life associated with colorectal cancer is scant and conflicting. Whilst there exist several cost-utility studies of screening options for colorectal cancer, most have modelled only the quality of life impact of screening without taking full account of the impact of quality of life resulting from the diagnosis and treatment of cancer. As the underlying principle of colorectal screening is to detect adenomas before they become malignant, and to detect cancers before they progress to more severe disease, quality of life is inevitably an important consideration.

Only 3 studies which attempted to evaluate health-related quality of life associated with colorectal cancer were identified.[52;53;76] Dominitz and colleagues[76] measured utilities for a single, global description of colorectal cancer in individuals with and without colorectal cancer using the time-trade off method. This global description did not include the impact of cancer stage on health outcomes. Whynes et al[52] evaluated population-based utility scores for outcome states of colorectal cancer, but found little difference between cancer stage. Whynes' valuations of different CRC health states were extremely close to valuations for perfect health (i.e. a valuation of 1.0).

One study[53] was identified which assessed utilities associated with stage of cancer and treatment. The study recruited 90 individuals who had previously undergone removal of a colorectal adenoma. Individuals were interviewed and were asked to assess utilities for stage-dependent outcome states using the standard gamble technique. Seven health states for colorectal cancer were presented to the study participants, although only five scenarios were presented during each interview. The scenarios described specific areas of morbidity associated with colorectal cancer and treatment such as tiredness and weakness, changes in bowel habits, sexual problems, pain, cognitive problems, social problems, and emotional problems. The results of the analysis for each of the individual CRC-specific health states are shown in Table 12.

Table 12 Utility scores used to describe health-related quality of life[43;53]

CRC-specific health state scenario	Utility score
No known adenomas	0.91[43]
Stage I rectal or stage I/II colon cancer treated with resection only	0.74 (0.69-0.78)
Stage III colon cancer treated with resection and chemotherapy without significant side effects	0.70 (0.63-0.77)
Stage III colon cancer treated with resection/chemotherapy with significant side effects	0.63 (0.56-0.70)
Stage II/III rectal cancer treated with resection/chemotherapy/radiation therapy	0.59 (0.54-0.64)
Stage II/III rectal cancer treated with resection/chemotherapy/radiation therapy/permanent ostomy	0.50 (0.44-0.56)
Stage IV metastatic/unresectable disease without ostomy	0.24 (0.16-0.32)
Stage IV metastatic/unresectable disease with ostomy	0.27 (0.18-0.36)

Within the health economic model, the utility associated with all cancer-free and polyp free states was assumed to be equivalent to the 'no known adenomas' health state (utility score = 0.91). Due to their unknown presence, this utility score was also assumed for individuals with undiagnosed cancer. Utility scores of 0.74 for Dukes' A cancer and a value of 0.27 for stage D cancer are assumed. As utility scores for stage II cancers were not evaluated separately, utility values of 0.7 for Dukes' B cancer (high score), and 0.5 for Dukes' C cancer (low score) were assumed. Utility estimates were not adjusted to account for the impact of comorbidities associated with age.

Ideally, additional health-related quality of life evidence would be used within the health economic model; it is likely that the experience of undergoing screening, follow-up and polyp surveillance, or the experience of receiving a positive test result has a transient yet important impact on an individuals' wellbeing. However, no studies were identified which clearly attributed a quality of life decrement associated with these experiences.

5.14 Summary of parameter inputs used in the base case screening model

Table 13 presents a summary of all parameter inputs used in the modelling.

Table 13 Summary of model input parameters

Model parameter	Parameter estimate
FOBT Sensitivity for polyps	5.00%
FOBT Sensitivity for CRC	40.58%
FOBT Specificity	98.50%
FSIG Sensitivity for low risk distal polyps	76.00%
FSIG Sensitivity for high risk distal polyps	97.00%
FSIG Sensitivity for distal CRC	97.00%
FSIG Specificity	100.00%
COL Sensitivity for low risk distal polyps	76.00%
COL Sensitivity for low risk proximal polyps	76.00%
COL Sensitivity for high risk distal polyps	97.00%
COL Sensitivity for high risk proximal polyps	94.00%
COL Sensitivity for distal CRC	97.00%
COL Sensitivity for proximal CRC	94.00%
COL Specificity	100.00%
Probability of distal polyp given proximal cancer	28.00%
Normal epithelium to low risk polyp (men and women) †	1.60%
First polyp growth at age	38
Low risk polyp to high risk polyp†	2.12%
High risk polyp to Dukes A†	3.26%
Dukes A to Dukes B†	58.29%
Dukes B to Dukes' C†	65.55%
Dukes C to Dukes D†	86.48%
Probability of developing low-risk adenoma given history low risk polyp (yr1)	18.00%
Probability of developing low-risk adenoma given history low risk polyp (yr2+)	5.00%
Probability of developing low-risk adenoma given history high risk polyp (yr1)	25.00%
Probability of developing low-risk adenoma given history high risk polyp (yr2+)	6.00%
Probability of presenting symptomatically with Dukes A†	7.00%
Probability of presenting symptomatically with Dukes B†	32.00%
Probability of presenting symptomatically with Dukes C†	49.00%
Probability of presenting symptomatically with stage D†	85.40%
Colonoscopy probability of perforation (without polypectomy)	0.08%
Colonoscopy Probability of perforation (with polypectomy)	0.17%
Colonoscopy Probability of death following perforation	5.82%
Flexible sigmoidoscopy probability of perforation (without polypectomy)	0.0025%
Flexible sigmoidoscopy probability of perforation - (with polypectomy)	0.0025%
Flexible sigmoidoscopy probability of death following perforation	5.82%
Probability of bleeding following flexible sigmoidscopy	0.0295%
Probability of bleeding following colonoscopy	0.439%
FOBT participation for each screening round	60.00%
Follow-up compliance	80.00%
Probability comply with at least one FOBT test	100.00%
Flexible sigmoidoscopy compliance	60.00%
Surveillance colonoscopy compliance	80.00%
Utility cancer free	0.91
Utility Dukes A	0.74
Utility Dukes B	0.70
Utility Dukes C	0.50
Utility Stage D	0.25

Probability of inadequate bowel preparation (FSIG)	5.26%
Probability of inadequate bowel preparation (COL)	10.00%
Annual CRC-specific mortality rate (Dukes A) †	0.00%
Annual CRC-specific mortality rate (Dukes B) †	1.00%
Annual CRC-specific mortality rate (Dukes C) †	6.02%
Annual CRC-specific mortality rate (Stage D) †	38.67%
Survival gain attributable to screening	0.00%
Cost of FSIG (without polypectomy)	£51.60
Cost of FSIG (with polypectomy)	£51.60
Cost of FOBT (2 tests)	£11.74
Cost of COL Diagnostic	£188.40
Cost of COL Therapeutic	£188.40
Cost of treating bowel perforation (major surgery)	£5,407.74
Cost of admittance for bleeding (overnight stay on medical ward)	£250.21
Pathology cost for adenoma	£30.00
Pathology cost for cancer	£250.00
Lifetime cost - screen-detected Dukes' A	£7,250.84
Lifetime cost - screen-detected Dukes' B	£12,441.41
Lifetime cost - screen-detected Dukes' C	£19,076.90
Lifetime cost - screen-detected Dukes' D	£11,945.78
Lifetime cost - symptomatic Dukes' A	£8,299.24
Lifetime cost - symptomatic Dukes' B	£12,441.41
Lifetime cost - symptomatic Dukes' C	£19,076.90
Lifetime cost - symptomatic Dukes' D	£11,945.78

† *All transition probabilities are for a 1-year model cycle. These probabilities were obtained through calibrating the model against published incidence and mortality data (See Chapter 8)*

6.0 Resources and costs associated with the diagnosis and treatment of colorectal cancer in England and Wales

6.1 Introduction

This chapter sets out the resource use and associated cost assumptions for use in the colorectal cancer (CRC) screening options appraisal model. These resource use estimates have been drawn from assumptions detailed within the FOBT Colorectal Cancer Pilot Evaluation Report,[77] a Health Needs Assessment report on the management of colorectal cancer,[13] recent NICE technology assessments,[78;79] NICE guidelines on the treatment of colorectal cancer,[14] evidence from current chemotherapy and radiotherapy trials, input from members of the English Bowel Cancer Advisory Group, expert advice from UK-based oncologists, and related literature. Evidence on the current use of chemotherapy, radiotherapy and surgery in the UK is scant, hence many of the assumptions concerning resource use reported here have been drawn from expert opinion.

Cost estimates used within the analysis have been derived from 2004 NHS Reference Costs,[80] Unit Costs of Health and Social Care,[81] cost estimates from recent NICE assessments,[54;79] and other relevant literature. The cost analysis includes costs directly incurred by the NHS only; indirect costs such as out-of-pocket expenses incurred by patients and lost productivity are excluded from the cost analysis. This evidence on resource consumption and costs of colorectal cancer services have been drawn together to estimate the lifetime costs for patients diagnosed with colorectal cancer according to their stage at diagnosis.

6.2 Diagnosis of colorectal cancer

6.2.1 Stage distribution at diagnosis

According to current registry data, an estimated 29,472 individuals in England and Wales are diagnosed with colorectal cancer each year.[82;83] The estimated proportions of patients diagnosed with each stage of cancer are shown in Table 14. Around 13% of patient records within the Wessex audit study did not include information on stage at diagnosis; it was thus assumed that 50% of unspecified cancers would be Dukes' stage C, and the remaining 50% of unspecified cancers would be stage D.

Table 14 Estimated number of patients with colorectal cancer by stage

Dukes stage	Percentage of patients[7†]	Estimated annual number of patients diagnosed by stage of colorectal cancer
A	11%	3,242
B	32%	9,431
C	26%	7,663
D	30%	8,842
Total	100%	29,472

† Assuming that unstaged patients have stage C or stage D CRC

6.2.2 Elective presentation with symptoms (Dukes' stage A and B cancer)

Evidence on how patients present with colorectal cancer, and how they are diagnosed with colorectal cancer is severely limited; it is anticipated that the forthcoming results of the GRAF study[84] will provide important information on the proportions of patients who present with symptomatic colorectal cancer electively or as emergency cases. In the absence of more robust estimates, the analysis assumes that patients diagnosed with Dukes' stage A & B CRC would present electively (43% of all cases, 12,673 patients). Assumptions concerning the resources consumed in the diagnosis of these patients are shown in Table 15. It should be noted there exists variation in the resources used to diagnose CRC cancer throughout England, hence these assumptions may not be typical of all cancer centres.

Table 15 Resources and unit costs associated with elective symptomatic presentation

Resource component	Unit cost
1 GP consultation	£20.00[81]
New attendance outpatient clinic	£75.89[80]
2 follow-up attendances at outpatient clinic	£127.31[80]
Colonoscopy/flexible sigmoidoscopy	£188.40[80]
Ultrasound for abdomen & pelvis	£114.36[80]
Pathology	£250.00 (*Personal communication, Prof N. Shepherd, Royal Gloucestershire Hospital*)
CT scan	£175.82 [80]
MRI scan (rectal patients)	£264.01 [80]

6.2.3 Emergency symptomatic presentation (Dukes' C and stage D cancer)

The analysis assumes that patients diagnosed with Dukes' stage C and stage D CRC present as emergency cases (56% of all CRC cases, 16,504 patients each year). Of these, 50% (8,252 patients) are assumed to present as Accident and Emergency cases (e.g. due to bowel obstruction).[77] The remaining 50% (8,252 patients) are assumed to be admitted directly to a general surgical ward prior to surgery or other treatment; this assumption was taken from a costing analysis undertaken as part of the Colorectal Cancer Screening Pilot Evaluation

Report.[77] All patients are assumed to undergo a CT scan post-operatively if they have not had one previously. Patients with rectal cancer are assumed to undergo an MRI scan.

6.2.4 Costs associated with emergency symptomatic presentation

Table 16 outlines the assumed resources required for emergency symptomatic presentation and their associated unit costs.

Table 16 Resources and costs associated with emergency symptomatic presentation

Resource component	Cost
A&E attendance (50% cases)	£48.62 [80]
7 days on general surgical ward (50% cases)	£799.48 [80]
Pathology	£250 (*Personal communication, Professor N Shepherd, Consultant Pathologist, The Royal Gloucestershire Hospital, Gloucester*)
CT scan	£175.82 [80]
MRI scan (rectal patients)	£264.01 [80]

6.2.5 Screen-detected polyp-cancers (Dukes' A only)

A proportion of early colorectal cancers known as 'polyp cancers' may be detected endoscopically and removed at the point of detection; consequently, these patients will use less resources such as surgery and chemotherapy. During the prevalence round of the UK Faecal Occult Blood Test (FOBT) screening pilot, an estimated 23% of detected cancers were polyp-cancers.[26] The analysis thus assumes that 23% of Dukes' A cancers (746 patients) are excised endoscopically. The analysis assumes that these patients require a CT scan to exclude metastases and subsequently undergo routine follow-up (See Section 6.7) (*Personal communication, Professor T. Maughan, Clinical Consultant Oncologist, Velindre Hospital, Cardiff*).

6.3 Surgical resection

6.3.1 Resection of primary tumour

In the absence of screening, all patients with Dukes' stage A-C cancer are assumed to undergo surgery following diagnosis (20,336 patients). The costs of palliative stenting was excluded from the analysis as the proportion of patients that currently undergo stenting is thought to be small (around 2%).

6.3.2 Hepatic resection

Recent trials suggest that around 80% of patients with advanced cancer have liver metastases with or without metastases elsewhere,[78] and around 50% of patients have metastases confined to the liver (7,895 patients each year).[85] Of these 10-20% will be resectable.[86] The analysis assumes that a lower estimate of 10% of patients (790 patients) will be resectable. Approximately 14% of patients with advanced cancer (963 patients) with initially unresectable liver metastases may be successfully downstaged using chemotherapy, resulting in an estimated 1,752 patients (790 + 963) undergoing hepatic resection.

6.3.3 Hepatic re-resection

Of the estimated 1,752 patients undergoing hepatic resection each year, around 60% (1,051 patients) will subsequently relapse, of whom 20% (210 patients) will undergo re-resection (*Personal communication, Dr G. Poston, Consultant, Royal Liverpool University Hospital, Liverpool*).

6.3.4 Non-hepatic resection

Of the 50% of advanced cancer patients with metastases which is not confined solely to the liver (7,895 patients), around 4% of these (316 patients) may still be resectable (*Personal communication, Dr G. Poston, Consultant, Royal Liverpool University Hospital, Liverpool*). Following resection, around two-thirds of these patients will relapse (211 patients) (*Personal communication, Dr G. Poston, Consultant, Royal Liverpool University Hospital, Liverpool*). It should be noted that there is no current evidence to support these estimates.

6.3.5 Costs of surgery

There currently exist no reliable cost estimates for alternative surgical procedures. Surgery costs for both screen-detected and symptomatic cancers are based on NHS Reference Costs, by taking a weighted average of all categories of colorectal surgery (weighted by the number of operations of each type).[80] The individual costs of each type of procedure are presented in Table 17. The resulting weighted cost of surgery is estimated to be £4,558.25 per procedure. This cost is assumed to apply to all surgery, regardless of the stage of cancer.

Table 17 Weighted cost of surgery for colorectal cancer [80]

Cost component	Number of procedures	Weight (%)	Unit cost	Weighted mean cost	Source
Elective large intestine – Complex procedures	7,278	19%	£5,273.16	£986.61	NHS Reference Costs 2004 (TELIP F31) [80]
Elective large intestine - Very major procedures	11,641	30%	£4,587.09	£1,372.74	NHS Reference Costs 2004 (TELIP F32) [80]
Elective large intestine - Major procedures w cc	1,590	4%	£3,718.96	£152.01	NHS Reference Costs 2004 (TELIP F33) [80]
Elective large intestine - Major procedures w/o cc	4,102	11%	£2,920.01	£307.92	NHS Reference Costs 2004 (TELIP F34) [80]
Non-elective large intestine - Complex procedures	2,067	5%	£5,407.74	£287.35	NHS Reference Costs 2004 (TNELIP F31) [80]
Non-elective large intestine - Very major procedures	9,035	23%	£4,876.74	£1,132.71	NHS Reference Costs 2004 (TNELIP F32) [80]
Non-elective large intestine - Major procedures w cc	1,661	4%	£4,418.82	£188.69	NHS Reference Costs 2004 (TNELIP F33) [80]
Non-elective large intestine - Major procedures w/o cc	1,525	4%	£3,321.51	£130.22	NHS Reference Costs 2004 (TNELIP F34) [80]
Weighted mean cost of surgery				£4,558.25	

6.4 Adjuvant chemotherapy

6.4.1 Adjuvant chemotherapy

Current NICE guidelines recommend the use of 5-fluorouracil plus folinic acid as adjuvant chemotherapy in CRC given intraveneously over a period of 6 months.[14] The Mayo (bolus) regimen is most commonly used in adjuvant chemotherapy in the UK (*Personal communication, Prof. J Cassidy, Honorary Consultant Oncologist, University of Glasgow, Glasgow*). An increasing proportion of patients with stage B colorectal cancer receive adjuvant chemotherapy; this is supported by the QUASAR1 trial.[87] Selection criteria for adjuvant chemotherapy varies by cancer centre, although most now offer adjuvant chemotherapy to patients with Dukes' stage B cancer based on:

- extramural vascular invasion;
- serosal involvement;
- perforation or obstruction;
- younger age;
- patient choice.

In some centres one of these characteristics may be sufficient to trigger adjuvant chemotherapy (>60% patients), whilst in other centres, two or more characteristics may be required (around 33%) (*Personal communication, Dr M. Seymour, Cancer Research UK Clinical Centre, Cookridge Hospital, Leeds*). The resource use analysis assumes that a lower estimate of 33% of patients with Dukes' stage B cancer (3,112 patients) receive adjuvant chemotherapy. Around 20-25% of these patients will suffer a relapse (*Personal communication, Dr M. Seymour, Cancer Research UK Clinical Centre, Cookridge Hospital, Leeds*); the analysis assumes that 22.5% of stage B patients will relapse (2,122 patients).

It is estimated that over 85% of patients with stage C cancer (6,513 patients per year) receive adjuvant chemotherapy (*Personal communication, Dr M. Seymour, Cancer Research UK Clinical Centre, Cookridge Hospital, Leeds*). Based on the results of the recent X-ACT trial, it is estimated that 52% (3,985 patients) will relapse.[88] Using the results of a pooled multicentre RCT of adjuvant 5-FU/FA compared to follow-up alone, the analysis assumes that adjuvant chemotherapy provides a 29% relative risk reduction compared to follow-up alone.[89] Thus, 73% of those patients who do not receive adjuvant chemotherapy are assumed to relapse (842 patients).

6.4.2 Resources and associated costs of adjuvant chemotherapy for CRC

The costs of adjuvant chemotherapy using the currently recommended 5-FU/FA regimen were estimated using the 5-FU/FA arm of the X-ACT trial, as shown in Table 18.[88]

Table 18 Costs and resources associated with adjuvant chemotherapy

Resource component	Cost
5-FU/FA cost per month	£96.37 [90]
Medical oncology outpatient costs per month	£591.71 [80]
Pharmacy costs per month	£49.94 (*Personal communication, M. Rowe, Chief Technician – Clinical Services, The Christie Hospital Trust, Manchester*)
Drug costs per month	£9.78 [91]
Consultation costs per month	£79.81 [91]
Test per month	£64.55 [91]
Primary care per month	£10.42 [91]
Total of 6 month course of adjuvant 5-FU/FA	£5,415.50

6.5 Chemotherapy for advanced CRC

Around 15,800 patients in England and Wales per year develop advanced colorectal cancer.[78]

6.5.1 Chemotherapy for downstaging

NICE currently recommends the use of oxaliplatin in combination with 5-FU/FA for downstaging.[14] An estimated 963 patients with initially unresectable tumours may be successfully downstaged each year (See Section 6.3.2). The cost analysis assumes that patients receive downstaging chemotherapy for 2 months (*Personal communication, Dr Rob*

Glynne-Jones, Consultant Clinical Oncologist, Mount Vernon Hospital and Watford and Barnet Hospital, London).

6.5.2 Palliative chemotherapy

NICE currently recommends first-line 5-FU/FA followed on progression by second-line single agent irinotecan.[78] The Institute does not currently recommended a specific third-line therapy. An estimated 14,900 patients per year have "uncured" colorectal cancer and may be eligible to receive palliative chemotherapy; it should be noted that this includes patients previously treated with adjuvant chemotherapy who subsequently relapse. Of these, it is estimated that 85-90% of these will receive first-line chemotherapy, although this may vary by network (*Personal communication, Dr M. Seymour, Cancer Research UK Clinical Centre, Cookridge Hospital, Leeds*). This equates to an estimated 12,665–13,410 patients who receive first-line palliative chemotherapy each year. Preliminary data from the MRC-sponsored FOCUS trial of alternative chemotherapy sequences[92] suggests that around 56% of these patients (7,092 patients) receive second-line chemotherapy. The analysis assumes that a further 5% of patients who receive second-line therapy (317 patients) will subsequently receive third-line chemotherapy.

6.5.3 Costs of chemotherapy for advanced CRC

The costs associated with alternative irinotecan and oxaliplatin-containing sequences of chemotherapy have been estimated as part of the recent update to previous NICE guidance on the use of chemotherapy for individuals with advanced cancer;[78] the estimated lifetime cost per patient receiving 5-FU/FA followed on progression by irinotecan monotherapy was estimated to be around £11,500.[78]

6.6 Radiotherapy for CRC

6.6.1 Pre-operative and post-operative radiotherapy

Pre-operative and post-operative radiotherapy are currently indicated only for patients with carcinoma of the rectum. Current NICE guidelines recommend the use of short-course pre-operative radiotherapy. Longer course pre-operative radiotherapy is recommended for selected patients with invasive tumours, where shrinking would facilitate curative resection. Post-operative radiotherapy is recommended for patients who are at a high risk of recurrence following surgery.[14]

Evidence on the use of radiotherapy for patients with rectal cancer is scarce; the majority of the estimates presented here have been drawn from the current MRC-sponsored CR07 trial, and from expert clinical opinion. The number of patients with rectal cancer as a proportion of all patients with CRC is shown in Table 19.[13]

Table 19 Proportion of cancers located in rectum[13]

Stage	Rectum	Colon	% rectum
A	5.3	6.1	46.49%
B	8.5	24.4	25.84%
C	6.3	13.1	32.47%
D	5.7	17.6	24.46%

The analysis assumes that MRI-staged T2 cancers and minimal T3 cancers are not irradiated (*Personal communication, Professor T. Maughan, Clinical Consultant Oncologist, Velindre Hospital, Cardiff*); the corresponding assumption is that roughly 50% of Dukes' stage B and 100% of Dukes' stage C cancers undergo radiation therapy. The decision whether to offer rectal cancer patients radiotherapy or chemoradiation is based largely on an MRI scan predicts a safe and complete resection of the tumour (R0 resection).

Based upon current ONS colorectal cancer incidence rates,[82] together with the estimated proportions of cancers located in the rectum,[13] around 1,218 patients present with Dukes' stage B rectal cancer and 2,488 patients present with Dukes' stage C rectal cancer and may be offered radiation therapy. Of these, an MRI scan would predict an R0 resection in around 65-80% of cases (*Personal communication, Professor D. Sebag-Montefiore, Consultant Clinical Oncologist, Leeds Cancer Centre, Leeds*). The resource use analysis assumes an R0 resection is predicted in 72.5% of all cases (883 Dukes' B and 1,804 Dukes' C patients). The analysis assumes that an abdominoperineal resection (APER) is planned in 22.5% of cases (199 Dukes' B and 406 Dukes' C patients). An estimated 85% of these patients will receive pre-operative radiotherapy or chemoradiation (169 Dukes' B and 345 Dukes' C patients).

Of the estimated 15% patients who do not receive pre-operative radiation therapy (30 Dukes' B and 61 Dukes' C patients), around 25% (7 Dukes' B and 15 Dukes' C patients) will have CRM involvement and hence receive post-operative radiotherapy or chemoradiation (*Personal communication, Professor D. Sebag-Montefiore, Consultant Clinical Oncologist, Leeds Cancer Centre, Leeds*). Of the 78% of patients with rectal cancer for whom an R0 resection is predicted and anterior resection is planned (685 Dukes' B and 1,398 Dukes' C patients), it is assumed that 20% (137 Dukes' B and 280 Dukes' C patients) will undergo pre-operative radiotherapy or chemoradiation (*Personal communication, Professor D. Sebag-Montefiore, Consultant Clinical Oncologist, Leeds Cancer Centre, Leeds*). Of the patients who do not receive pre-operative radiotherapy or chemoradiation, around 15% (82 Dukes' B and 168 Duke' C patients) will have CRM involvement and hence receive post-operative radiotherapy or chemoradiation (*Personal communication, Professor D. Sebag-Montefiore, Consultant Clinical Oncologist, Leeds Cancer Centre, Leeds*). These estimates assume that around 40% of patients with rectal cancer do not receive radiation therapy.

6.6.2 Radiotherapy for relapse

If patients develop local recurrence and have not previously received radiotherapy (an estimated 110 stage B patients and 254 stage C patients) it is likely that radiotherapy will be delivered as palliative treatment. An estimated 38% of these patients (41 stage B patients and 95 stage C patients) are assumed to receive palliative radiotherapy, with the remaining 63% (69 stage B patients and 159 stage C patients) receiving long-course chemoradiation (*Personal communication, Professor D. Sebag-Montefiore, Consultant Clinical Oncologist, Leeds Cancer Centre, Leeds*).

6.6.3 Radiotherapy for synchronous metastases at presentation

An estimated 1,081 patients have synchronous metastases at presentation. An estimated 30% of these (324 patients) will receive short course palliative radiotherapy, with the remaining 70% (757 patients) receiving long-course radiotherapy (*Personal communication, Professor D. Sebag-Montefiore, Consultant Clinical Oncologist, Leeds Cancer Centre, Leeds*).

6.6.4 Costs of radiotherapy

Costs associated with alternative radiotherapy regimens are available from NHS Reference Costs,[80] as shown in Table 20.

Table 20 Radiotherapy unit costs

Resource	Cost
Short-course radiotherapy (complex teletherapy with imaging, >3 <13 fractions)	£1,066 (TRDTHY W14) [80]
Long-course radiotherapy (complex teletherapy with imaging, >23 fractions)	£2,046 (TRDTHY W16) [80]

6.7 Follow-up

Follow-up policies for CRC patients vary considerably across England. The analysis assumes that patients receive 3-monthly outpatient attendances each year for the first two years, followed by annual clinic visits. It is assumed that patients would receive a colonoscopy every five years following diagnosis of CRC. It is also assumed that patients would also receive 2 ultrasound scans for the first two years following diagnosis to detect the development of liver metastases. Table 21 shows the estimated lifetime costs of follow-up for patients with stage A-D CRC.

Table 21 Lifetime costs of follow-up

		Average resource use assumed			Unit costs			
Cancer stage	Mean survival (years)	OP visits	Colonoscopy	Ultrasound	OP visits[80]	Colonoscopy[80]	Ultrasound[80]	Total follow-up cost
A	11 years[93]	17	2	4	£1,853	£ 376.00	£501.12	£ 2,730
B	11 years[93]	17	2	4	£1,853	£ 376.00	£501.12	£ 2,730
C	8.7 years[88‡]	14	1	4	£1,526	£ 188.00	£501.12	£ 2,215
D	1.4 years[92]	5	0	2	£545	£ -	£250.56	£ 796

‡Estimated by extrapolating overall survival curve using Weibull regression analysis

6.8 Cost summary

Table 22 and 23 shows the estimated mean per patient cost of diagnosis and treatment of colorectal cancer for patients diagnosed with Dukes' stages A-D CRC.

Table 22 Estimated mean cost of diagnosis, treatment and follow-up of colorectal cancer (no screening)

Resource Component	Dukes' Stage A	Dukes' Stage B	Dukes' Stage C	Stage D
Diagnosis	£1,010.86	£956.33	£993.30	£931.12
Chemotherapy	£0.00	£3,890.21	£10,490.99	£9,347.08
Surgery	£4,558.25	£4,706.24	£4,972.56	£657.72
Radiotherapy	£0.00	£158.51	£404.94	£214.30
Follow-up	£2,730.12	£2,730.12	£2,215.12	£795.56
Number of patients	3,241.92	9,431.04	7,662.72	8,841.60
Mean cost per patient	£8,299.24	£12,441.41	£19,076.90	£11,945.78

Table 23 Estimated mean cost of diagnosis, treatment and follow-up of colorectal cancer (with screening)

Resource Component	Dukes' Stage A	Dukes' Stage B	Dukes' Stage C	Stage D
Diagnosis	£1,010.86	£956.33	£993.30	£931.12
Chemotherapy	£0.00	£3,890.21	£10,490.99	£9,347.08
Surgery	£3,509.85	£4,706.24	£4,972.56	£657.72
Radiotherapy	£0.00	£158.51	£404.94	£214.30
Follow-up	£2,730.12	£2,730.12	£2,215.12	£795.56
Number of patients	3,241.92	9,431.04	7,662.72	8,841.60
Mean cost per patient	£7,250.84	£12,441.41	£19,076.90	£11,945.78

7.0 The ScHARR colorectal cancer screening model

7.1 Introduction

The question to be addressed by the model is *"what is the likely impact of introducing various alternative colorectal cancer screening programmes in terms of incidence of cancer and mortality resulting from cancer, and in terms of costs and cost-effectiveness, for the typical population of England?"* Resource, capacity and staffing requirements are estimated from intermediate model outcomes, but are calculated separately; these are reported in Chapter 10.

7.2 Screening options evaluated

The model evaluates the impact of five core screening options against a policy of no screening:

(1) FOBT for individuals aged 50-69 (biennial screening)
(2) FOBT for individuals aged 60-69 (biennial screening)
(3) Once-only flexible sigmoidoscopy for individuals aged 55
(4) Once-only flexible sigmoidoscopy for individuals aged 60
(5) Once-only flexible sigmoidoscopy for individuals aged 60, followed by FOBT for individuals aged 61-70 (biennial screening)

The cost-effectiveness and cost-utility of the following three additional extension screening options are assessed within the sensitivity analysis:

(6) FOBT for individuals aged 60-67 (biennial screening)
(7) FOBT for individuals aged 60-71 (biennial screening)
(8) FOBT for individuals aged 60-73 (biennial screening)

The results of the extension strategies are not central to the economic analysis, and are thus reported in Appendix 1.

7.3 Modelling methodology and structure

The health economic model uses the state transition (Markov process) methodology to provide a macro-simulation of the life experience from normal colonic epithelium to adenomatous polyp to malignant carcinoma in the general population of England. The Markov methodology is particularly useful for modelling diseases or conditions whereby risk is ongoing over time, where events may occur more than once, and where the timing of events is important. Although this modelling approach is generally more simplistic than some other methodologies described in the review of colorectal cancer screening models, the Markov methodology is sufficiently flexible to capture all important events surrounding colorectal cancer screening, whilst remaining both explicit and intuitive to the user.

Central to the Markov modelling methodology is the division of the disease process into a finite number of mutually exclusive health states. At any given point in time, all patients within the model exist within one of these health states. The distribution of patients across each of the model's health states during each cycle is governed by a time-variant transition matrix which describes the probability of transiting from the current health state to an alternative health state. The model calculates the number of patients residing in each health state using iterative matrix multiplication and an annual cycle length.

Due to difficulties in defining the true prevalence of adenomas and pre-clinical cancers at the time of the first screening round (in this case age 50), the cohort enters the simulation at age 30, whereby it is assumed that the prevalence of pre-clinical polyps and cancers is zero. The prevalence of polyps at the time of the first screen (age 50-60 depending on the screening strategy under evaluation) is thus built up over the pre-screening period. Costs and health outcomes accrued beyond the age of 50 years are estimated and the simulation is continued for 50 years (until the cohort is aged 100), thus practically all of the original cohort have been absorbed into the 'death' health state.

The health economic model is centred around three sub-models:

(1) A state transition (Markov) model which simulates the natural history of colorectal cancer;
(2) A model of the screening intervention (and subsequent adenoma surveillance for high risk individuals) which interacts directly with the natural history model; and
(3) A model of mortality, which is used to reflect age-specific 'other-cause' mortality, mortality due to colorectal cancer and mortality resulting from perforation due to endoscopic procedures.

The health states used in the model are shown in Box 1.

Box 1: Health states used in colorectal cancer screening model

1. Normal colonic epithelium
2. Hyperplastic polyp (distal colon)
3. Hyperplastic polyp (proximal colon)
4. Low-risk polyp (distal colon)
5. Low-risk polyp (proximal colon)
6. High-risk polyp (distal colon)
7. High-risk polyp (proximal colon)
8. Pre-clinical Dukes' A CRC (distal colon)
9. Pre-clinical Dukes' A CRC (proximal colon)
10. Pre-clinical Dukes' B CRC (distal colon)
11. Pre-clinical Dukes' B CRC (proximal colon)
12. Pre-clinical Dukes' C CRC (distal colon)
13. Pre-clinical Dukes' C CRC (proximal colon)
14. Pre-clinical Stage D CRC (distal colon)
15. Pre-clinical Stage D CRC (proximal colon)
16. Clinical management Dukes' A CRC
17. Clinical management Dukes' B CRC
18. Clinical management Dukes' C CRC
19. Clinical management Stage D CRC
20. Screen-detected Dukes' A CRC
21. Screen-detected Dukes' B CRC
22. Screen-detected Dukes' C CRC
23. Screen-detected Stage D CRC
24. Status post-polypectomy (history of low-risk polyp)
25. Status post-polypectomy (history of high-risk polyp)
26. Dead

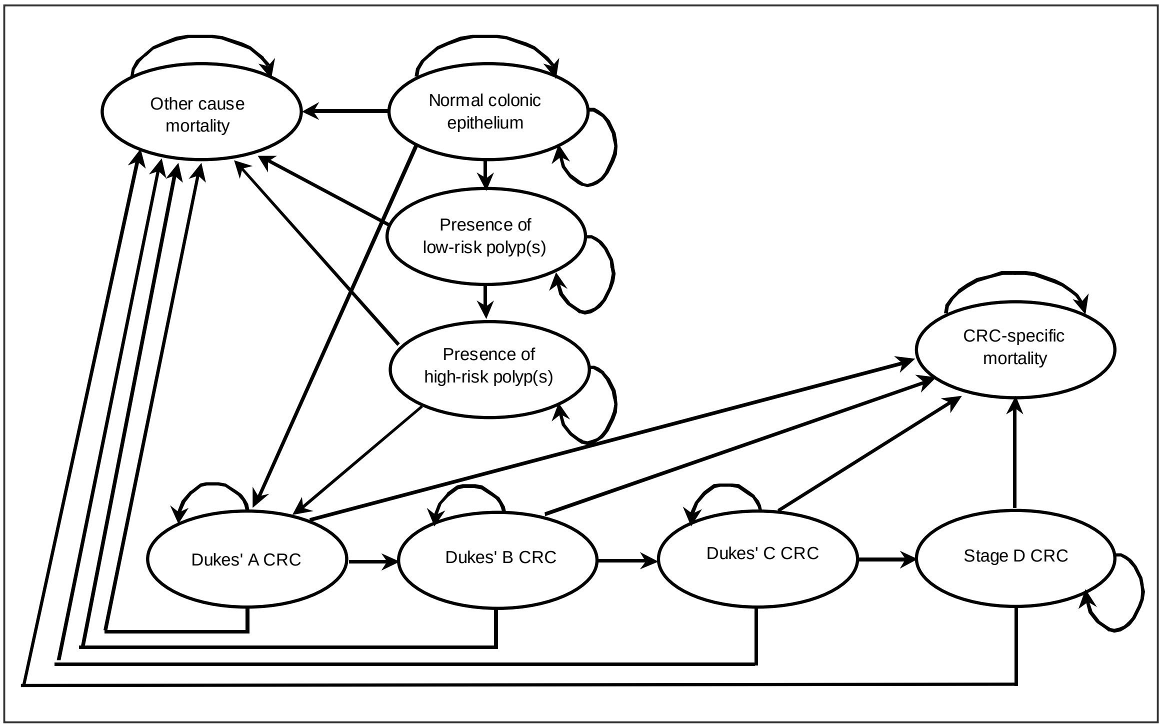
7.4 Natural history model

The natural history model simulates the progression from normal epithelium to adenomatous polyp to colorectal cancer and eventually, death. As the Markov methodology requires mutually exclusive states, health states describing the presence of adenomas and pre-clinical cancers are defined in terms of the 'index' lesion; that is, the greatest malignant potential of the adenoma present, or the most advanced cancer present. Individuals with adenomas are classified as either low-risk or high-risk. Discrete cancer states are modelled individually according to the Turnbull modification[8] of Dukes' staging[9] in which metastatic disease is classified as Stage D. The presence of adenomatous polyps and cancers located in the distal and proximal colon are considered separately in order to account for the reach of flexible sigmoidoscopy (although some correlation between the two is implicitly modelled).

Due to weaknesses in evidence concerning the incidence of adenomas, time-homogeneous transition probabilities are used to describe adenoma growth, progressions to pre-clinical cancer, and the rate at which pre-clinical cancers progress from early local cancer to regional disease and subsequently, metastatic disease. Time-variant probabilities are used to reflect different incidence rates for adenomas arising in the distal and proximal colon, and age-specific probabilities of other cause mortality.

It is generally accepted that most colorectal cancers follow the adenoma-carcinoma sequence,[3] however there also exists evidence that a lesser number of colorectal cancers may arise without prior adenoma. Due to the lack of direct evidence concerning the rate at which apparently *de novo* cancers develop, the model presented here assumes that all cancers arise from pre-existing adenomas. All transitions in the model are progressive; 'backwards' transitions are not allowed for within the model. Figure 4 describes the possible transitions allowed during each annual Markov cycle.

Figure 4 Progression diagram for underlying colorectal cancer natural history model

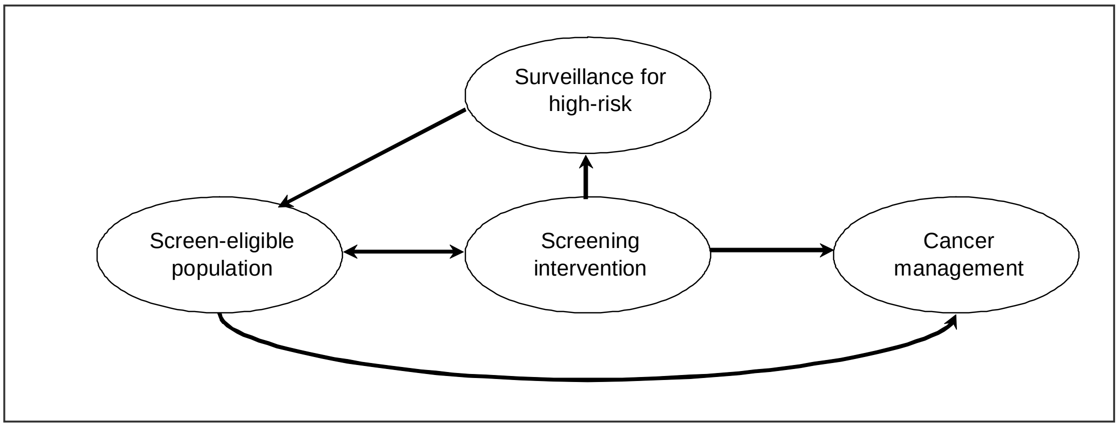


The probability that an individual with colorectal cancer seeks medical attention due to symptoms is assumed to vary according to the stage of cancer; this probability is assumed to be higher for more advanced stages of cancer as symptoms are likely to be more apparent. Individuals with cancer who present symptomatically transit to one of four clinically diagnosed cancer health states, depending on the stage of the cancer. The stage of the cancer at diagnosis determines the annual probability of dying from colorectal cancer, the subsequent treatment and follow-up strategies, and the utility associated with the health state.

7.5 Screening intervention model

Superimposed upon the colorectal cancer natural history model is a screening intervention model which allows for the detection and removal of polyps through endoscopy and the detection and treatment of colorectal cancer. A simplified schematic of the screening model is shown in Figure 5.

Figure 5 Colorectal cancer screening model schematic



The test characteristics of FOBT, flexible sigmoidoscopy, and colonoscopy are defined in terms of the probability of achieving positive or negative test results given an individual's true underlying histological state: that is the true sensitivity and specificity of the test. The impact of the different screening tests, follow-up colonoscopy and treatment of polyps and cancers are modelled by re-distributing the model cohort across the health states at the point of screening. For example, an individual in whom a low-risk adenoma is detected by flexible sigmoidoscopy is assumed to undergo polypectomy and is subsequently moved to the 'low-risk post-polypectomy' health state.

The effectiveness of each screening modality is thus modelled as a function of an individual's true histological state, the probability of participation with the screening test, the characteristics of the screening test, a probability of death due to screening, the probability that the individual attends any subsequent follow-up, the characteristics of the follow-up test, and the probability of death due to follow-up. For example, an individual with Dukes' A CRC who is offered FOBT has a probability of completing and returning the test kit, a probability of testing positive with FOBT, a probability of attending the follow-up colonoscopy, a probability of testing positive for CRC with colonoscopy, and a probability of dying due to endoscopic perforation of the bowel.

7.6 Treatment of screen-detected adenomas

It is assumed that for FOBT screening options, all individuals testing positive are assumed to be followed-up using colonoscopy (barium enema is not considered within the model). In practice, most adenomas are removed via polypectomy, however for larger adenomas this may not always possible, and in some cases surgery may be required. For the sake of simplicity, the model assumes that all identified polyps are removed at the point of detection, i.e. polypectomy during colonoscopy following a positive FOB test, or during the flexible sigmoidoscopy screen, regardless of risk status of the individual.

Evidence suggests that following the detection and removal of adenomatous polyps, the probability of developing new polyps is greater than in individuals with no prior history of adenoma.[11;47] In addition to the primary disease states, a further two health states are used to model the subsequent risk of developing new polyps following polypectomy: 'low-risk post-polypectomy' and 'high-risk post-polypectomy.' The probability of developing a new adenoma in these states is higher in these patients than in patients with no prior history of adenomas.

7.7 Surveillance strategies for high-risk individuals

The screening model developed within this study broadly follows recent guidelines for the surveillance of polyps using colonoscopy.[12] Within the model, individuals identified with high-risk adenomas are assumed to undergo polypectomy and are subsequently offered colonoscopy at three-yearly intervals. During this surveillance period, it is assumed that all polyps detected by colonoscopy are removed by polypectomy. If no further high-risk adenomas are detected after two consecutive colonoscopies (i.e. at a minimum of six years following baseline colonoscopy), individuals are assumed to leave the surveillance model and re-enter the screening model. Individuals in whom new high-risk polyps are found continue to be offered colonoscopy every three years until no further high-risk polyps are found at two consecutive colonoscopies. Individuals who do not attend two surveillance colonoscopies re-enter the screening model in their underlying health state. Individuals identified to be low-risk at baseline (follow-up) colonoscopy re-enter the screening population and receive no further follow-up or surveillance.

Individuals who would be classified as intermediate risk according to the BSG guidelines (multiple small adenomas) are not included in the model. This is a necessary simplification, owing to limitations in the evidence base in terms of the rate at which individuals progress from low-risk to intermediate-risk, and the subsequent rate at which these individuals develop cancer; further research in this area is indicated.

Individuals in whom colorectal cancer is detected by flexible sigmoidoscopy, follow-up colonoscopy, or surveillance colonoscopy, enter into one of four 'screen-detected clinical management' health states depending on the stage of the disease at the point of detection. The model assumes no further surveillance of adenomas is undertaken beyond 80 years of age.

7.8 Mortality

The model incorporates three elements of mortality: death due to other causes, death due to colorectal cancer, and death due to endoscopic perforation of the bowel. The probability of dying from other causes is modelled as a time-variant probability depending on the age of the model cohort at the beginning of each Markov cycle. Differential probabilities are applied depending on the sex of the cohort. An age-independent probability of dying due to colorectal cancer is applied to all cancer states: that is, pre-clinical cancer, clinically diagnosed cancer and screen-detected cancer states. This risk of dying due to colorectal cancer is obviously higher for more advanced disease. The probability that an individual with colorectal cancer will die during any Markov cycle is calculated as the age and sex-specific probability of dying from other causes plus a stage dependent probability of dying from colorectal cancer.

The risk of death due to endoscopic bowel perforation is applied at three separate points within the screening and surveillance process. For FOBT screening options, the probability of death due to perforation of the bowel is applied at the point of follow-up only, whereas for flexible sigmoidoscopy screening options, this risk is applied both at the point of screening, as well as at follow-up colonoscopy for those individuals found to have high-risk or malignant neoplasia. The risk of perforation due to surveillance colonoscopy is modelled in the same way for the first and subsequent colonoscopies.

7.9 Compliance

Within the base case analysis, a participation rate of 60% is assumed for both flexible sigmoidoscopy and FOBT screening. For individuals found to have cancer at flexible sigmoidoscopy a participation rate of 100% is assumed. A participation rate of 80% is assumed for colonoscopy for all other positive screen test, and for the surveillance of individuals identified to have high-risk adenomas.

7.10 Costs

The cost of FOBT screening is calculated as the number of people alive within the model at the beginning of each model cycle multiplied by the unit cost of an FOB test kit. The model assumes that two test kits are sent to each individual during each screening round. The cost of flexible sigmoidoscopy screening is calculated as the number of people attending flexible sigmoidoscopy screening multiplied by its unit cost. Costs of follow-up and surveillance colonoscopy are calculated as the number of individuals who attend the colonoscopy multiplied by the unit cost of colonoscopy. Pathology costs are applied to all adenomas and cancers detected through screening, and to individuals who present symptomatically. The cost of perforation is assumed to be equal to the cost of a major surgical procedure.[80] The lifetime cost of cancer (screen-detected or diagnosed) is applied as a one-off lifetime cost for all new cancers diagnosed (See Chapter 6). The cost of treating gastrointestinal bleeding is taken to be the cost of an overnight admittance to a medical ward.

7.11 Health outcomes

The model estimates cost-effectiveness in terms of natural units (life years gained) and quality adjusted life years (QALYs). Life years gained are calculated as the sum of the number of people alive at the beginning of each of the 50 model cycles (i.e. age 50 to 100). The model incorporates adjustments for the health-related quality of life associated with different states of health by applying different utility weights to each year spent in the 26 model health states. A constant utility score is applied to all non-cancers states (no known adenomas or cancer). The model uses stage-specific utility weights for clinically diagnosed cancer states to reflect severity of the disease and the invasiveness of treatment.

7.12 Discounting

Discounting of costs and health outcomes is standard practice within health economic evaluation. Costs and benefits that accrue in the future are given less weight to those which occur in the present.[94] In line with current recommendations from the UK Treasury Department and recent methodological guidance published by the National Institute for Clinical Excellence,[95] all costs and health outcomes are discounted at 3.5% per year.

7.13 Uncertainty analysis

Most existing colorectal screening modelling studies report the extensive use of one-way, or occasionally three-way sensitivity analysis to explore the impact of changing up to three parameter estimates on the base case results. The problem with this approach is the likely under-representation of the true parametric uncertainty within the model; for example, lowering the assumed sensitivity of FOBT is unlikely to have a significant impact on the model. Conversely, lowering the sensitivity of FOBT in addition to increasing the rate at which high-risk adenomas progress to cancer and increasing the rate of progression through cancer states is likely to have a marked impact on the effectiveness and cost-effectiveness of each intervention. Multivariate sensitivity analysis was undertaken using a set of around 400 potentially valid sets of natural history parameters estimated during the model calibration process (See Chapter 8). Due to uncertainty in the true sensitivity of FOBT and the true miss rate associated with endoscopy in usual clinical practice, uncertain distributions were assigned all test characteristics, as shown in Table 24.

Table 24 Uncertain distributions for screening and follow-up test characteristics used in multivariate sensitivity analysis

Parameter	Central estimate used in base case model	Lower bound	Upper bound
FOBT Sensitivity for polyps	5.00%	0.00%	10.00%
FOBT Sensitivity for CRC	40.58%	30.00%	50.00%
FOBT Specificity	98.50%	97.00%	99.00%
FSIG Sensitivity for low risk distal polyps	76.00%	65.00%	85.00%
FSIG Sensitivity for high risk distal polyps	97.00%	95.00%	99.00%
FSIG Sensitivity for distal CRC	97.00%	95.00%	99.00%
COL Sensitivity for low risk distal polyps	76.00%	65.00%	85.00%
COL Sensitivity for low risk proximal polyps	76.00%	65.00%	85.00%
COL Sensitivity for high risk distal polyps	97.00%	95.00%	99.00%
COL Sensitivity for high risk proximal polyps	94.00%	92.00%	96.00%
COL Sensitivity for distal CRC	97.00%	95.00%	99.00%
COL Sensitivity for proximal CRC	94.00%	92.00%	96.00%

For each of the 400 potential sets of natural history parameters, 5 random samples of test characteristics based on the distributions above were generated. Thus, the model was run a total of 2,000 times to generate ranges for all costs and health outcomes associated with each screening option. During this process, the cost of flexible sigmoidoscopy was also varied to allow for potentially lower unit costs associated with the procedure.

Further one-way sensitivity analysis was also undertaken to explore the impact of changing the baseline cost and compliance assumptions used in the base case analysis.

7.14 Limitations of the model

The model presented here covers a broader scope than existing UK models[27;38] as it also estimates costs and health outcomes resulting from flexible sigmoidoscopy and combination FOBT/flexible sigmoidoscopy screening strategies. Further, a more accurate surveillance model is presented, and up-to-date cancer stage-specific utility data are used. However, the results presented here should be approached with caution; there remain considerable uncertainties in terms of the natural history of colorectal cancer, together with uncertainties concerning the true single-test sensitivities of FOBT and flexible sigmoidoscopy. The model is subject to several limitations:

- The absence of direct evidence on the rate at which adenomas develop within the general English population, the rate at which adenomas develop into invasive cancer, and the rate at which early local cancer progresses to late-stage metastatic disease, means that several of the model parameters had to be fitted to published data. However, there are several potentially valid solutions which fit the data.
- The transition probabilities estimated within the model are assumed to be constant (with the exception of age-specific adenoma incidence and mortality rates); in reality however, this is unlikely to be accurate.
- Despite some indirect evidence that a proportion of colorectal cancers arise *de novo*, the model assumes that all cancers derive from pre-existing adenomas. This assumption favours all screening options versus no screening. In particular, the impact of this assumption is that those screening strategies which have a high sensitivity for detecting adenomas (i.e. flexible sigmoidoscopy) will be favoured by the model.
- The model assumes that a proportion of proximal cancers are associated with distal ‘sentinel’ polyps which would subsequently lead to colonoscopic examination of the entire colon. This proportion however, should be an output of the model, as opposed to a parameter input. Further, probabilities of cancer progression are assumed to be equivalent in both the distal and proximal colon, which in reality is unlikely to be accurate. Ideally, the model would operate at the level of the individual lesion; however, such a complex representation of the natural history of the disease would require a greater number of parameters to be fitted, for which data do not exist.

8.0 Model calibration and validation

8.1 Introduction

There currently exists no best practice with respect to the simultaneous fitting of several model inputs against published data in the absence of empirical evidence. Given the requirement for some simplification of the underlying disease and the synthesis of evidence from distinct and separate sources, one would not expect any model to provide a perfect fit to published data, thus a degree of prediction error is inevitable. The calibration methods used within existing colorectal cancer models identified in the literature vary in terms of the number of data sources against which models are validated. Generally speaking, more complex model structures tend to require a greater number of unknown parameters to be fitted, which in turn, may lead to a greater number of potential sets of solutions which appear to fit published incidence and mortality estimates. One of the key benefits of retaining a simpler model structure is the minimisation of unknown parameters that require calibration, which may result in increased confidence that the chosen set of parameter values is valid. Similarly, as outcomes such as cancer incidence, cancer stage at diagnosis and mortality, are highly correlated, the greater the number of data sources against which a model can be calibrated to match simultaneously, the more the likely it is that the predicted set of parameters is optimal.

One disquieting feature of several of the published screening evaluations is the limited reporting of the calibration methods used. Most published analyses report that the authors attempted to fit unknown parameter values to national incidence rates and detection rates from RCTs of screening programmes. Many of these studies appear to imply that parameter values were adjusted manually until the model 'fitted' the data. However, there may exist numerous potential model solutions which 'fit' the data, thus raising important doubts over the validity of the results of these analyses. Of the modelling studies identified by the review, only Frazier[30] and Ness[43] provide a detailed description of (potentially) robust model calibration methods. The approach employed here are an extension of these existing methods.

8.2 Calibration methods

The key unknown parameters within the model relate to the natural history of undetected colorectal cancer; these are the probabilities of progressing through undiagnosed cancer states, and probabilities of clinical presenting by cancer stage. Other parameter estimates derived from weaker sources of evidence were also adjusted within the calibration process; these include polyp incidence and growth rates, the rate at which high-risk adenomas develop into cancer, and stage-specific colorectal cancer-specific mortality rates.

We identified several observed data sources that provided a useful means of model validation:

(1) English colorectal cancer age and site-specific incidence rates[1]
(2) English colorectal cancer age-specific mortality rates[2]
(3) Adenoma prevalence by age[55-60]
(4) Stage distribution of symptomatic colorectal cancer at diagnosis (in the absence of screening) [7]
(5) Annual colorectal cancer-specific mortality rates by stage[7]

Unpublished data from the Nottingham FOBT trial[17] and the UK flexible sigmoidoscopy screening trial[21] were kindly made available for this modelling; these data were also used to check estimates of the single test sensitivities of FOBT and flexible sigmoidoscopy in detecting adenomas and cancers.

Where possible, clinically plausible ranges for uncertain parameters were derived from the literature.[30] Each model parameter was then assigned a wide uniform distribution, and all distributions were randomly sampled from over 60,000 iterations. Mean squared errors between the model predictions and published incidence, mortality, stage distribution data and prevalence data were recorded. A strict threshold for the degree of 'acceptable' error between the model and each separate data source was defined, and potentially valid sets of parameters were recorded.

<u>8.3 Results of the calibration process</u>

Of the 60,000 random iterations, around 400 potential solutions were identified which appeared to fit the published incidence and mortality data. The set of natural history parameters used within the base case analysis (see Table 25) is just one of these potential sets, and is thus subject to considerable uncertainty.

Table 25 Transition probabilities estimated through model calibration

Transition probability (annual)	Parameter estimate used in base case analysis	Uniform distribution used in calibration	
		Minimum	Maximum
Normal epithelium to low risk polyp (men and women)	1.6%	0.5%	2.0%
Low risk polyp to high risk polyp	2.1%	0.5%	4.0%
High risk polyp to Dukes A	3.3%	1.0%	6.0%
Dukes A to Dukes B	58.3%	30.0%	90.0%
Dukes B to Dukes' C	65.6%	30.0%	90.0%
Dukes C to Dukes D	86.5%	30.0%	90.0%
Probability of symptomatic presentation (Dukes' A)	7.0%	2.0%	15.0%
Probability of symptomatic presentation (Dukes' B)	32.0%	10.0%	35.0%
Probability of symptomatic presentation (Dukes' C)	49.0%	50.0%	90.0%
Probability of symptomatic presentation (Stage D)	85.4%	50.0%	90.0%
Annual CRC-specific mortality rate (Dukes A)	0.0%	0.0%	0.5%
Annual CRC-specific mortality rate (Dukes B)	1.0%	0.5%	3.0%
Annual CRC-specific mortality rate (Dukes C)	6.0%	2.0%	15.0%
Annual CRC-specific mortality rate (Stage D)	38.7%	35.0%	45.0%

Figure 6 shows a comparison of colorectal cancer incidence rates per 100,000 population reported by the ONS, and equivalent cancer incidence rates predicted by the screening model. The chart clearly shows a very close approximation in cancer incidence over all age ranges.

Figure 6 ONS and model predicted age-specific colorectal cancer incidence

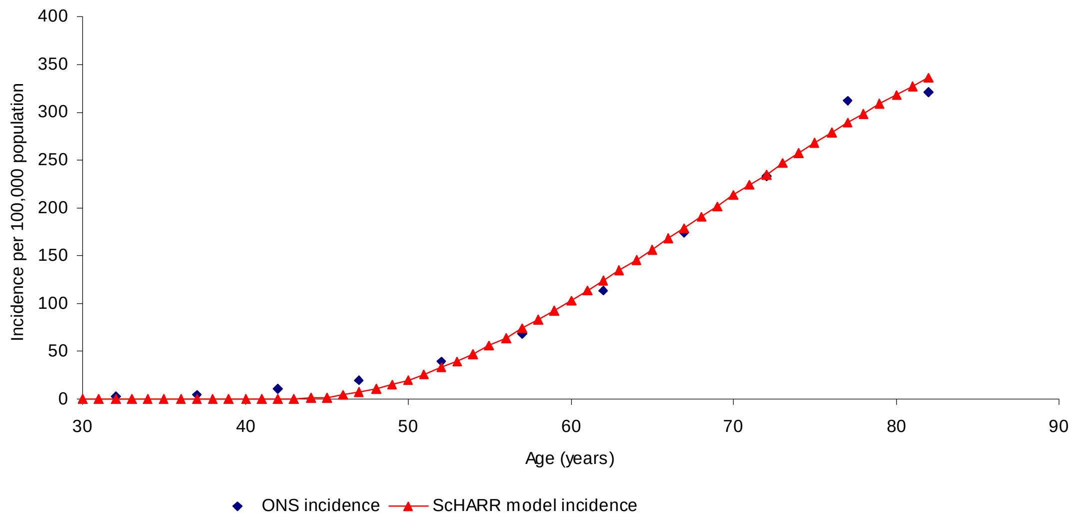


Figure 7 shows a comparison of model-predicted colorectal cancer mortality rates per 100,000 population compared with equivalent ONS published estimates. The chart indicates that the model gives a fairly close prediction of annual mortality rates due to colorectal cancer, with some overestimation between 60 and 80 years of age.

Figure 7 ONS and model predicted age-specific colorectal cancer mortality

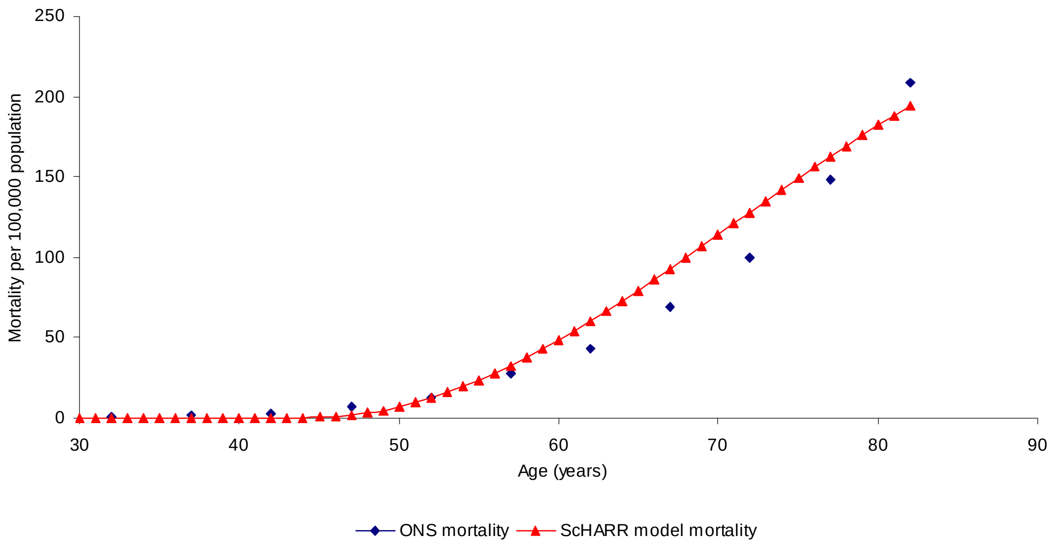


Figure 8a and 8b show a colorectal cancer incidence rates per 100,000 population for the cancers arising in the distal and proximal colon respectively. Again, the model provides a good fit to the data; there however the model appears underestimate proximal cancer incidence beyond the age of 70 years.

Figure 8a ONS and model-predicted colorectal cancer incidence (distal colon)

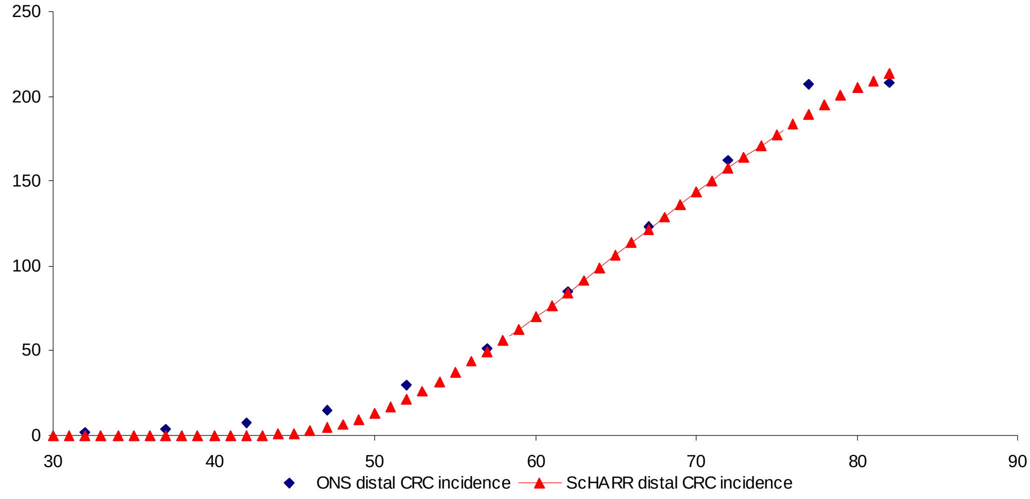


Figure 8b ONS and model predicted colorectal cancer incidence (proximal colon)

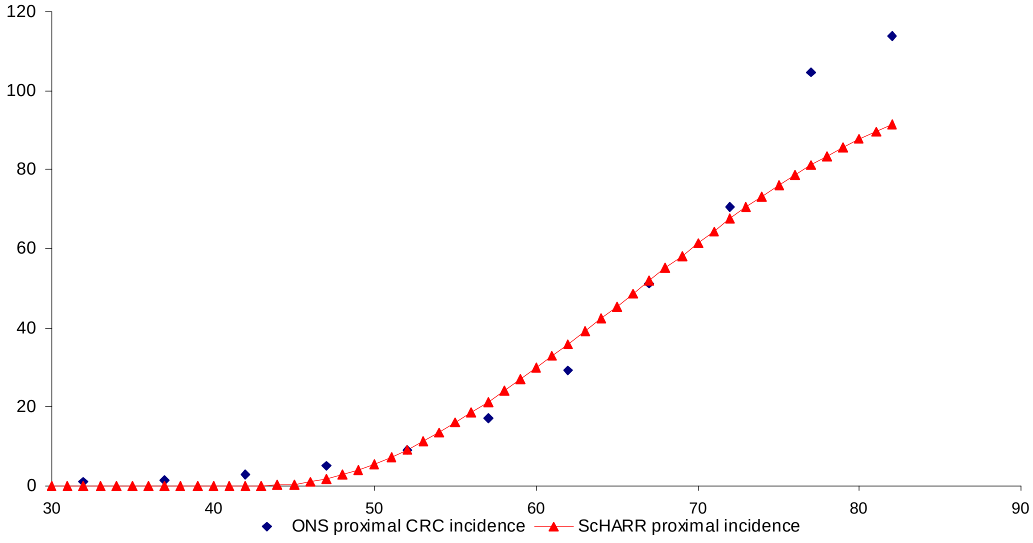


Figure 9 shows a comparison of data on stage distribution of colorectal cancer at diagnosis obtained from the Wessex audit study, [7] compared with the predicted stage distribution at diagnosis estimated by the colorectal cancer screening model. The chart demonstrates that the model provides an excellent fit for all four stages of cancer.

Figure 9 Predicted versus observed stage distribution at diagnosis

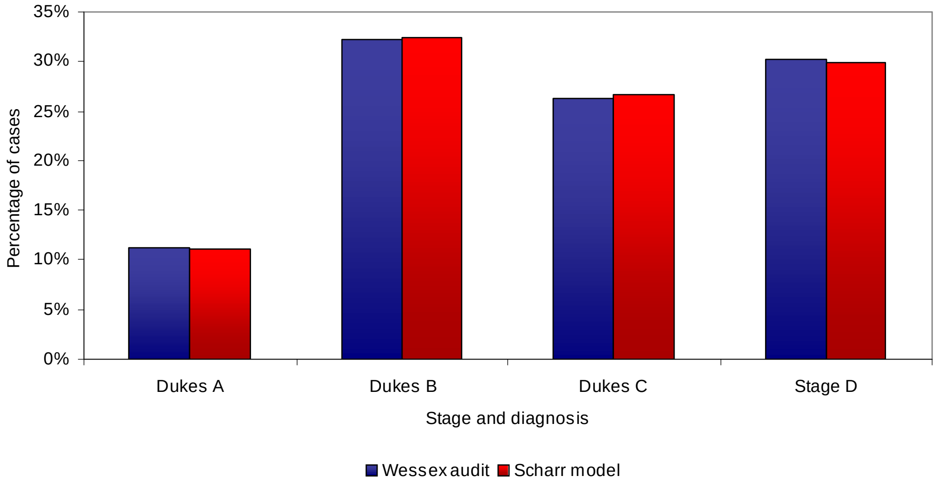
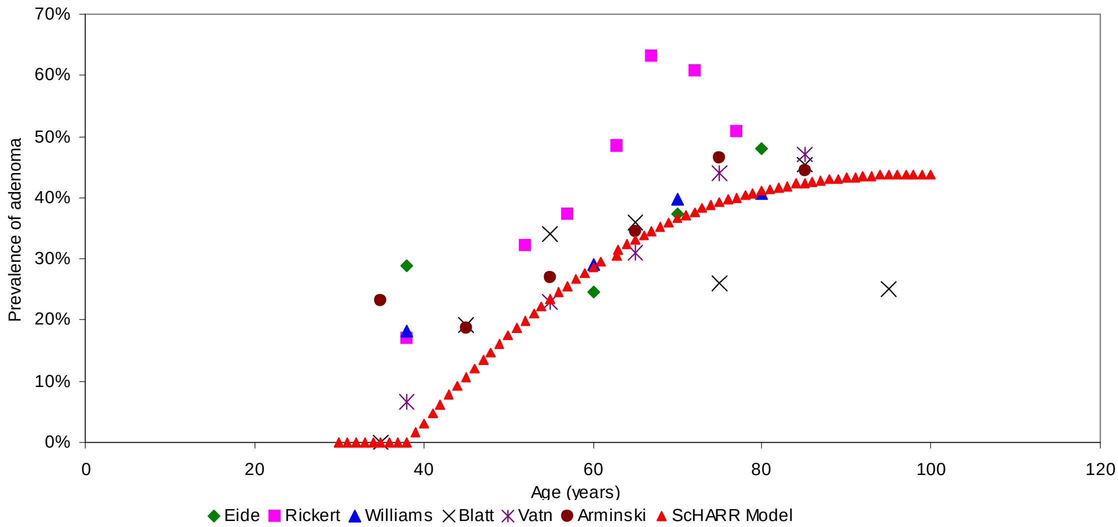


Figure 10 shows the prevalence of adenoma by age compared with estimates reported from the autopsy studies. Due to inconsistencies in the autopsy evidence, it is difficult to determine whether the model provides a good approximation to the true underlying prevalence of adenomatous within the general population. However, the baseline adenoma incidence assumed by the model, together with the assumption of a decline in adenoma incidence rate beyond 60 years of age appears to roughly follow the autopsy results reported by Williams et al.[60]

Figure 10 Published versus model-predicted adenomas prevalence by age

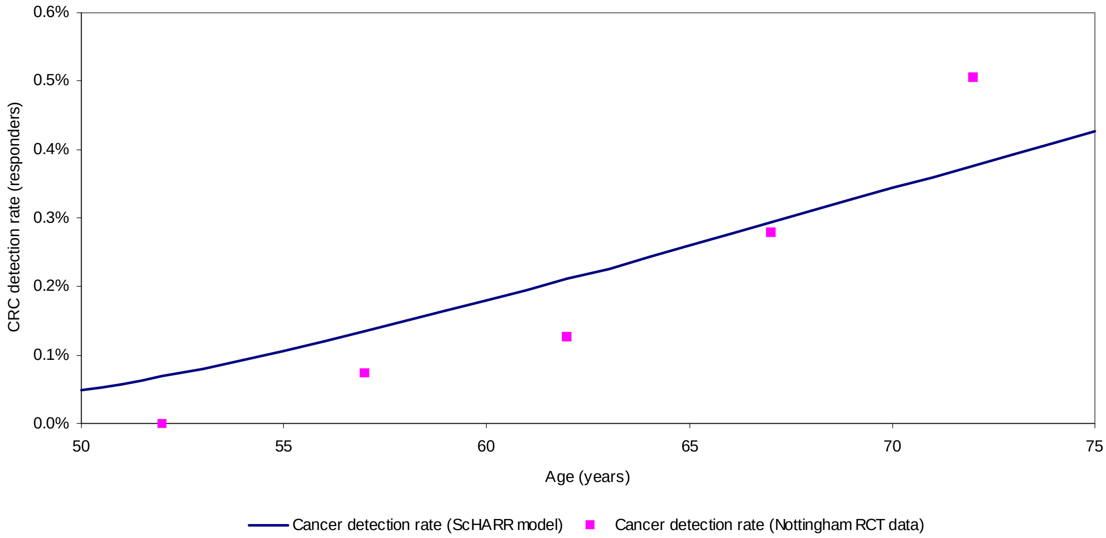


It is further reassuring that in calibrating the model for men and women separately (by adjusting the annual adenoma incidence rate), once the model gave a good visual fit of adenoma incidence against results from the Williams study,[60] incidence and mortality rates predicted by the model were similar to published ONS data.[1;2]

Whilst the underlying natural history model appears to provide a close approximation against published evidence, the model should also be able to provide a reasonable approximation against detection rates reported with existing colorectal cancer screening trials. This is however particularly problematic due to considerable uncertainties surrounding the true test sensitivity of FOBT in detecting colorectal adenomas and cancer, and variable miss rates for flexible sigmoidoscopy. Results from the prevalence round of the Nottingham RCT[17] and the baseline findings of the flexible sigmoidoscopy trial[21] were used to validate the detection rates estimated by the screening model.

Figure 11 shows the proportion of individuals with colorectal cancer who tested positive using Haemoccult II during the prevalence round of the Nottingham RCT for age ranges 50-54, 55-59, 60-64, 65-69 and 70-74. Unsurprisingly due to weaknesses in evidence on the natural history of the disease used to inform parameters within the model, the model gives only a reasonable fit to the data. Whilst other artefacts may be present within the Nottingham data, such as variations in colonoscopy attendance, the model appears to slightly overestimate the sensitivity of FOBT in detecting cancers in younger age groups, whilst it seems to slightly underestimate the sensitivity in older age groups.

Figure 11 True positives predicted by the model versus true positives from the Nottingham RCT prevalence round



An additional check of model validity was undertaken, comparing cancer detection rates from the UK flexible sigmoidoscopy trial to predicted detection rates simulated by the model. The UK flexible sigmoidoscopy screening trial[21] reported an overall detection rate for colorectal cancer located in the distal colon of 0.30% of all individuals aged 55-64 who attended screening. The model predicted that the number of individuals aged 60 who would test positive for distal cancer using flexible sigmoidoscopy was 0.39%; this suggests only a slight prediction error within the model. However, unpublished data from the flexible sigmoidoscopy trial for individuals aged 55 and 60 suggested slightly lower cancer detection rates; it is unclear whether this was due to the limited sample size at these ages (less than 6000 individuals screened), or whether the difference is due to higher detection rates in older individuals.

9.0 Health economic results

9.1 Introduction

This section presents the results of the health economic model for a hypothetical 50-year old English cohort of 100,000 people. Owing to a high level of uncertainty in the cost-effectiveness results and issues surrounding the feasibility of implementing alternative screening options, an incremental analysis is not reported. Instead, marginal results for each screening policy options are presented versus the ‘no screening’ policy option. For this reason, the uncertainty analysis (cost-effectiveness ranges and incremental cost-effectiveness acceptability curves) is presented as the headline results of the economic analysis (Section 9.2); central estimates of costs and effectiveness are presented subsequently (Section 9.3). It is crucial to acknowledge the high degree of uncertainty surrounding the costs and effects estimated by the model; the baseline results presented in Section 9.3 relate only to a single set of calibrated natural history parameters.

The multivariate sensitivity analysis (Section 9.2) demonstrates that alternative potentially valid sets of natural history parameters yield considerably different costs and effects. Equivalent analyses for the three extension FOBT screening options are presented in Appendix 1. Additional one-way sensitivity analysis is presented in Section 9.4 to explore the impact of alternative screening compliance assumptions.

9.2 Headline health outcomes and cost-effectiveness results

The multivariate sensitivity analysis presented within this section explores the impact of alternative 2,000 potentially valid sets of natural history and test sensitivity parameters on the costs and effects of each screening option. Each alternative parameter set was run through the model in order to generate likely ranges for costs and effects resulting from each screening option.

9.2.1 Multivariate uncertainty analysis for core screening options

Table 26 shows the uncertain ranges for key health outcomes for the five core screening options. It should be noted that all health outcomes relate to a population of 100,000 persons invited to screening in England. The table suggests a substantial amount of uncertainty in the effectiveness of all five core screening options. Whilst the central estimates presented within the base case analysis (Section 9.3) suggest a clear rank ordering of the core screening options in terms of marginal effectiveness versus no screening, Table 26 demonstrates that when uncertainty concerning the natural history and test characteristics is propagated through the model, these rank orderings may change, hence the most effective screening option becomes less clear.

Table 26 Uncertainty analysis results: key health outcome ranges for core screening options

Strategy	Screen-detected cancers	CRC detected at surveillance colonoscopy	Clinical cancers	Deaths due to CRC	Cases of CRC avoided	CRC deaths avoided	% reduction in CRC incidence	% reduction in CRC mortality
FOBT at 50-69yrs (biennial)	488-1209	0-2	2631-4182	1188-2547	-96-857	217-912	-2% - 18%	9% - 35%
FOBT at 60-69yrs (biennial)	375-876	0-1	3190-4406	1380-2643	-86-444	133-559	-2% - 9%	6% - 22%
FSIG once at 55yrs	135-218	0-2	3147-3864	1251-2302	758-1041	357-687	17% - 22%	19% - 26%
FSIG once at 60yrs	211-352	1-3	3033-3722	1252-2275	788-1048	378-699	18% - 22%	20% - 26%
FSIG once at 60yrs and FOBT at 61-69yrs (biennial)	463-897	1-3	2413-3410	1071-2093	755-1320	475-1011	17% - 28%	26% - 39%
No screening	0-0	0-0	4101-4955	1650-2912				

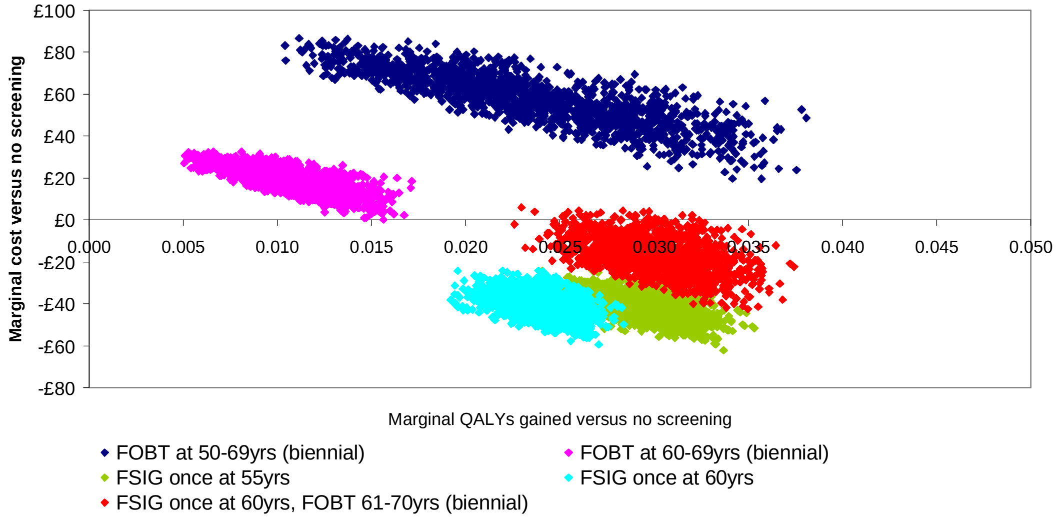
Table 27 shows ranges for the marginal costs and benefits of each of the core screening strategies versus no screening for a population of 100,000 people in England. As with the health outcomes, the introduction of parametric uncertainty leads to considerable uncertainty in the expected costs and benefits for each screening option. Notably, even at the upper range of cost-effectiveness, all five core screening options have a cost-effectiveness profile that is better than other health interventions currently funded by the NHS. The uncertainty analysis suggests that the once-only flexible sigmoidoscopy options are always expected to be cost-saving compared to a policy of no screening.

Table 27 Uncertainty analysis results: cost-effectiveness ranges for core screening options

Strategy	Marginal cost	Marginal life years saved	Marginal QALYs saved	Cost per life year saved	Cost per QALY saved
FOBT at 50-69yrs (biennial)	£19.68-£86.61	0.012 - 0.044	0.01 - 0.038	£613 - £6,249	£551 - £7,992
FOBT at 60-69yrs (biennial)	£0.24-£32.59	0.006 - 0.021	0.005 - 0.017	17 - 4536	£15 - £6,111
FSIG once at 55yrs	£-62.1-£-24	0.017 - 0.032	0.023 - 0.036	£-2,736 - £-926	£-1,894 - £-874
FSIG once at 60yrs	£-59.37-£-24.02	0.014 - 0.026	0.019 - 0.029	£-3,225 - £-1,039	£-2,256 - £-1,007
FSIG once at 60yrs and FOBT at 61-69yrs (biennial)	£-44.22-£6.05	0.017 - 0.037	0.022 - 0.038	£-1,815 - £267	£-1,317 - £263

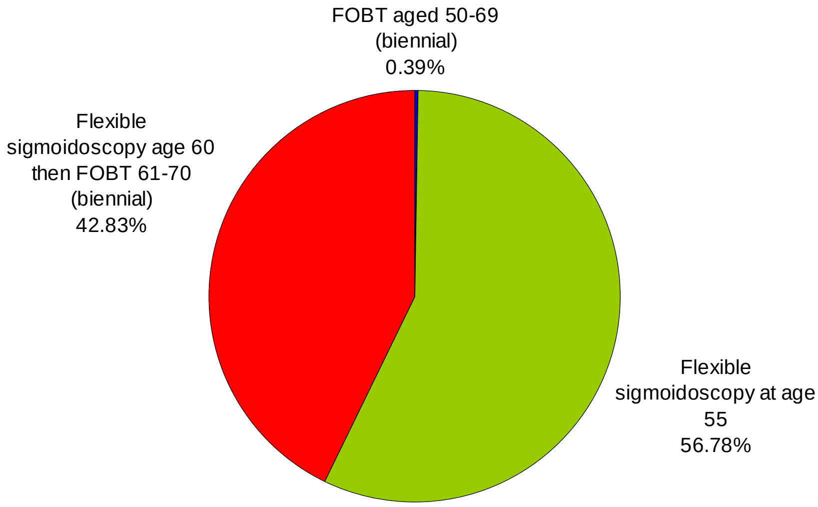
Figure 12 presents the results of the uncertainty analysis using a cost-effectiveness plane. The uncertainty analysis clearly demonstrates a fairly wide variability in marginal costs and effects for all five screening options, in particular the policy of offering FOBT biennially to all individuals aged 50-69. Whilst the chart suggests a high degree of clustering of costs and effects, there some overlap between the once-only flexible sigmoidoscopy options. It is noteworthy that despite the uncertainty surrounding the natural history of the disease and the true sensitivity of the screening tests, all of the screening options appear to be economically attractive compared to a policy of no screening. In particular, flexible sigmoidoscopy offered to individuals aged 55 or aged 60 is always expected to be cost-saving in comparison to no screening. However, offering FOBT to individuals aged 50-69 is potentially the most effective option in terms of life years saved (although offering the combined option is equally effective in terms of quality-adjusted life years saved). The chart clearly suggests that the FOBT 60-69 policy is always dominated (more expensive and less effective) by the once-only flexible sigmoidoscopy options.

Figure 12 Cost-effectiveness planes for core screening options



In order to identify the most economically attractive screening option, the expected net benefit for each screening option (the benefits of the programme measured in monetary terms less any cost consequences) was estimated for each model iteration. Figure 13 shows the proportion of times each screening option is expected to result in the greatest absolute net benefit (i.e. is the optimal screening option), assuming a cost-effectiveness threshold of £30,000 per QALY gained.

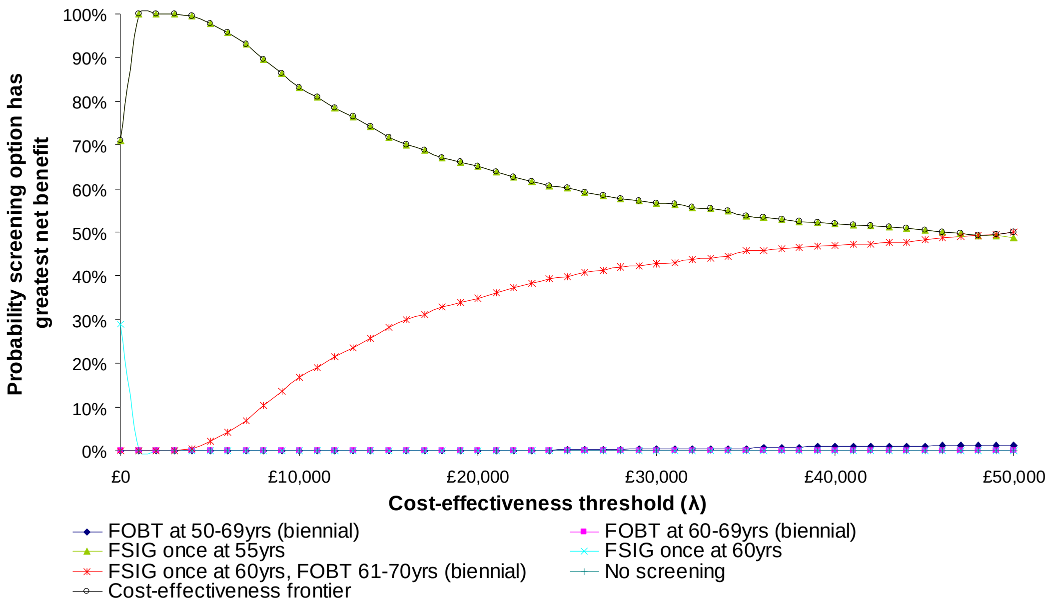
Figure 13 Probability each screening option produces the greatest expected net benefit



Assuming a willingness to pay threshold (λ) of £30,000 per QALY

The pie chart indicates that offering FOBT to individuals aged 60-69, flexible sigmoidoscopy at age 60 and the policy of no screening are never optimal in terms of maximum expected net benefit (assuming a willingness to pay threshold of £30,000 per QALY). The combined flexible sigmoidoscopy and FOBT option has a 43% probability of being optimal, whilst offering flexible sigmoidoscopy to individuals aged 55 has a 57% probability of being optimal. The probability that offering FOBT biennially to individuals aged 50-69 is optimal is below 1%. Figure 14 presents cost-effectiveness acceptability curves (CEACs) for each of the five core screening options and no screening. The CEACs show the probability that each option results in the greatest expected net benefit over a range of willingness to pay thresholds (λ).

Figure 14 *Cost effectiveness acceptability curves with cost-effectiveness frontier for core screening options and no screening*



The incremental CEACs and cost-effectiveness frontier demonstrate that offering once-only flexible sigmoidoscopy to individuals aged 55 is most likely to be the optimal screening option over reasonable societal willingness-to-pay thresholds. Importantly, the CEACs suggest that the FOBT option for individuals aged 50-69, 60-69, offering flexible sigmoidoscopy to individuals aged 60, and the no screening options are not expected to be optimal irrespective of the cost-effectiveness threshold assumed.

9.3 Base case model results for core screening options

This section reports the central estimates of effectiveness and cost-effectiveness according to the base case assumptions. As demonstrated within the uncertainty analysis presented in Section 9.3, these central estimates of effectiveness and cost-effectiveness are highly uncertain and should be interpreted with caution.

9.3.1 Base case results: Key health outcomes for core screening options

Table 28 shows the marginal health outcomes for the five core screening options versus the ‘no screening’ policy option. The base case results indicate that a policy offering FOBT screening to individuals aged 50-69 would result in the greatest number of screen-detected cancers. However, the model suggests that offering flexible sigmoidoscopy at age 60 followed by biennial FOBT at age 61-70 would result in the greatest reduction in both colorectal cancer incidence (23%) and mortality (33%).

Table 28 Key health outcomes for core screening options under base case assumptions

Strategy	Screen-detected cancers	CRC detected at surveillance colonoscopy	Symptomatic cancers	Deaths due to CRC	Cases of CRC avoided	CRC deaths avoided	% reduction in CRC incidence	% reduction in CRC mortality
FOBT at 50-69yrs (biennial)	715.88	0.43	3029.68	1655.00	354.70	506.05	8.65%	23.42%
FOBT at 60-69yrs (biennial)	531.73	0.27	3407.88	1852.79	160.80	308.26	3.92%	14.26%
FSIG once at 55yrs	150.83	0.71	3146.55	1662.04	802.61	499.01	19.57%	23.09%
FSIG once at 60yrs	240.22	0.97	3032.97	1636.60	826.54	524.45	20.16%	24.27%
FSIG once at 60yrs and FOBT at 61-70yrs (biennial)	581.96	1.15	2586.75	1439.60	930.85	721.45	22.70%	33.38%
No screening	0.00	0.00	4100.70	2161.05				

Figure 15 shows the predicted colorectal cancer incidence rate per 100,000 persons under the base case model assumptions. The chart shows considerable peaks in incidence during screening years (individuals who would either present with symptomatic cancer later or never present clinically), followed by subsequent troughs in incidence due to reductions in symptomatic cancers following screening. Figure 15 indicates that all five core screening options lead to an overall reduction in lifetime colorectal cancer incidence compared to the no screening policy. The model suggests that offering individuals flexible sigmoidoscopy at age 60 followed by biennial FOBT screening between the ages 61-70 provides the greatest long-term reduction in cancer incidence (23% reduction over no screening).

Figure 15 Predicted impact of core screening options on colorectal cancer incidence

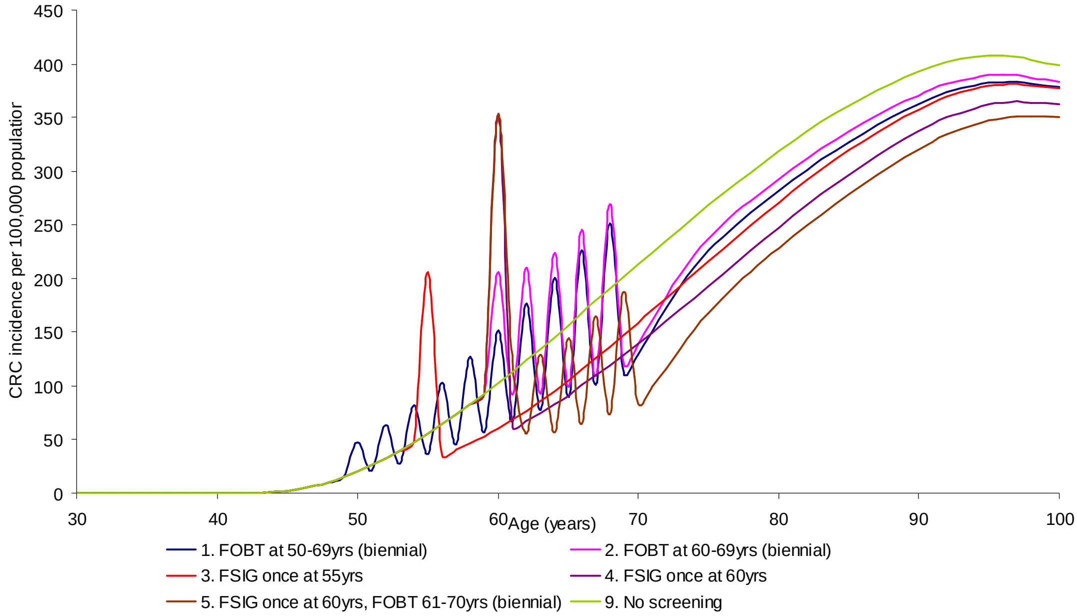
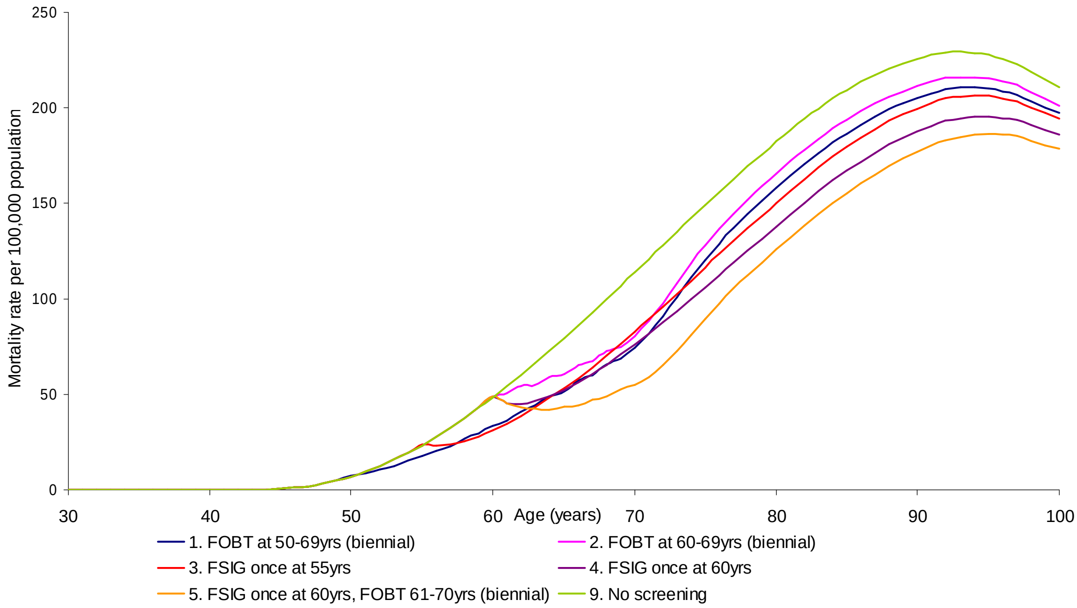


Figure 16 shows the predicted impact of the five core screening options on mortality due to colorectal cancer. The chart indicates that all five core screening options result in a lifetime reduction in cancer-specific mortality. Under the base case assumptions, the model suggests that offering individuals flexible sigmoidoscopy at age 60 followed by biennial FOBT screening between the ages 61-70 provides the greatest reduction in lifetime mortality compared with the no screening policy (33% reduction over no screening).

Figure 16 Predicted impact of core screening options on colorectal cancer mortality



9.3.2 Base case results: cost-effectiveness and cost-utility for core screening options

Table 29 presents the marginal cost-effectiveness and cost-utility results for the five core screening options versus the 'no screening' policy.

Table 29 Base case results: Marginal cost-effectiveness and cost-utility for core screening options

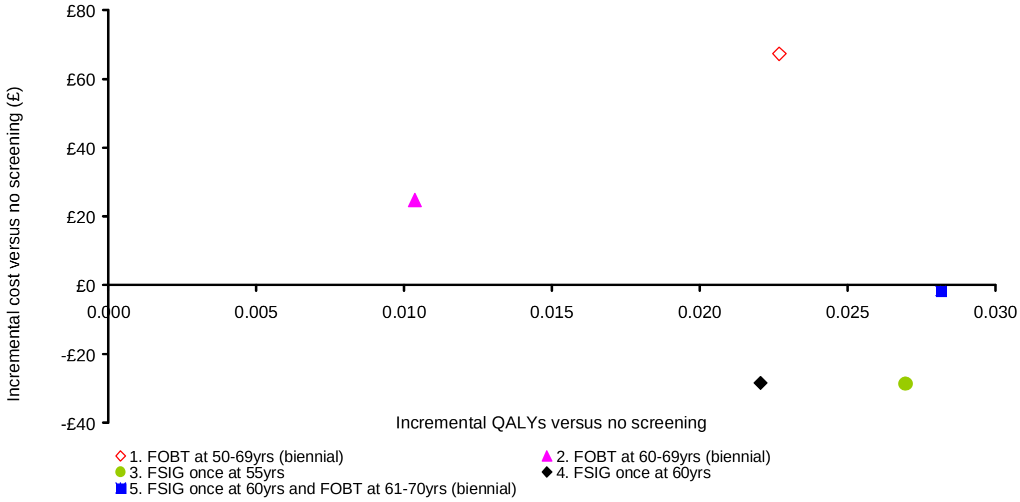
Strategy	Marginal cost	Marginal life years saved	Marginal QALYs saved	Cost per life year saved	Cost per QALY saved
FOBT at 50-69yrs (biennial)	£66.95	0.0260	0.0227	£2,576.72	£2,949.64
FOBT at 60-69yrs (biennial)	£24.53	0.0126	0.0104	£1,950.29	£2,364.99
FSIG once at 55yrs	-£28.77	0.0237	0.0270	-£1,212.66	-£1,066.75
FSIG once at 60yrs	-£28.51	0.0197	0.0221	-£1,443.66	-£1,292.19
FSIG once at 60yrs and FOBT at 61-70yrs (biennial)	-£1.92	0.0271	0.0282	-£70.70	-£68.05

Whilst the expected health gains for each person offered screening are small, ranging from 4.59 to 9.89 days of life saved, the average cost per person invited to screening is also low. Offering FSIG once to individuals aged 60 followed by FOBT screening from age 61-70 is predicted to have the greatest impact on both survival and quality-adjusted survival (9.89 and 10.28 days respectively), although this is not the least expensive strategy. Offering FOBT to individuals aged 60-69 is expected to offer the smallest survival and quality-adjusted survival gain over no screening (4.59 days and 3.79 days respectively). Offering flexible sigmoidoscopy screening to all individuals aged 55 or aged 60 appear to be the most cost-effective options; under the base case scenario these options are both cost-saving compared to no screening.

Table 28 suggests a greater reduction in colorectal cancer deaths associated with the combined flexible sigmoidoscopy and FOBT screening option. It is interesting to note that the health economic model suggests that the inclusion of quality of life effects for cancers avoided has a relatively minor impact on the cost-effectiveness of each screening option.

Figure 17 shows a cost-effectiveness plane, which describes the central estimates of additional QALYs saved and additional costs of the five core screening options compared to a policy of 'no screening.'

Figure 17 Base case results: Cost-effectiveness plane for core screening options



9.3.3 Base case results: Lifetime endoscopy resource use for core screening options

Table 30 shows the expected lifetime resource usage for the five core screening options for a cohort of 100,000 50-year old individuals invited to screening. The model suggests that offering FOBT to individuals aged 50-69 results in the greatest number of follow-up colonoscopies over the lifetime of the cohort. Clearly, the flexible sigmoidoscopy screening options result in the greatest overall impact on endoscopy. The reader is advised to note that as with the other results presented here, resource use estimates relate to the entire population offered screening (i.e. per 100,000 individuals), not just those who attend.

Table 30 Base case results: Lifetime endoscopy resource use for core screening strategies

Strategy	Number of flexible sigmoidoscopies undertaken	Number of follow-up colonoscopies undertaken	Number of polypectomies
FOBT at 50-69yrs (biennial)	-	13,720.47	4,750.04
FOBT at 60-69yrs (biennial)	-	7,340.12	2,750.20
FSIG once at 55yrs	61,079.25	3,479.52	8,011.23
FSIG once at 60yrs	57,842.49	4,930.68	9,495.78
FSIG once at 60yrs and FOBT at 61-70yrs (biennial)	57,842.49	11,142.78	11,645.55

9.2.4 Base case results: Lifetime complications for core screening options

Table 31 presents the estimated number of gastrointestinal bleeds, bowel perforations and deaths due to perforation over the lifetime of a cohort of 100,000 people invited to screening. As expected, offering FOBT to all individuals aged 50-69 is predicted to result in the greatest number of perforations and subsequent deaths due to perforation (0.84 deaths over the lifetime of 100,000 people invited to screening); this is due to the higher perforation rate associated with colonoscopy. A lesser number of perforations and subsequent deaths are predicted to result from the once only flexible sigmoidoscopy options (5.39-6.95 perforations over the lifetime of 100,000 people invited to screening).

Table 31 Base case results: Lifetime complications for core screening options

Strategy	Number of bleeds	Number of perforations	Number of deaths due to perforation
FOBT at 50-69yrs (biennial)	60.21	14.49	0.84
FOBT at 60-69yrs (biennial)	32.21	7.93	0.46
FSIG once at 55yrs	33.29	5.39	0.31
FSIG once at 60yrs	38.70	6.95	0.40
FSIG once at 60yrs and FOBT at 61-70yrs (biennial)	65.96	13.51	0.79

9.3.5 Base case results: Adenomas detected at screening/follow-up for core screening options

Table 32 shows the predicted number of people with adenomas detected through screening over the lifetime of 100,000 individuals screened. As expected, the combination FOBT/flexible sigmoidoscopy screening option is predicted to result in the greatest number of adenomas detected through screening and surveillance.

Table 32 Base case results: Adenomas detected at screening/follow-up for core screening strategies

Strategy	Adenomas detected at screening/follow-up		Adenomas detected during surveillance colonoscopy	
	Low-risk adenomas	High-risk adenomas	Low-risk adenomas	High-risk adenomas
FOBT at 50-69yrs (biennial)	3,580.87	867.84	286.21	15.11
FOBT at 60-69yrs (biennial)	1,966.86	590.79	182.90	9.64
FSIG once at 55yrs	6,234.97	1,281.49	469.92	24.84
FSIG once at 60yrs	6,986.41	1,841.77	633.96	33.65
FSIG once at 60yrs and FOBT at 61-70yrs (biennial)	8,608.82	2,242.66	754.10	39.97

9.3.6 Base case results: Cancers diagnosed by stage and means of detection for core screening options

Table 33 shows the cancers diagnosed by stage and means of detection for the five core screening options, as predicted by the model. The model suggests that offering FOBT to all individuals aged 50-69 will result in the greatest number of cancers detected, although the duration of this screening programme is longer than all other options. The model suggests that offering flexible sigmoidoscopy once at age 60 and subsequently offering FOBT biennially between the ages 61-70 leads to a high yield of cancers detected through screening, but also results in the greatest reduction in symptomatic cancers.

Table 33 Base case results: Cancers identified by stage and means of detection for core screening strategies

Strategy	Cancers detected at screen				Cancers detected during surveillance colonoscopy				Symptomatic cancers			
	Dukes' A	Dukes' B	Dukes' C	Stage D	Dukes' A	Dukes' B	Dukes' C	Stage D	Dukes' A	Dukes' B	Dukes' C	Stage D
FOBT at 50-69yrs (biennial)	338.24	230.57	106.97	40.10	0.33	0.08	0.02	0.00	224.44	958.50	862.15	984.59
FOBT at 60-69yrs (biennial)	239.66	172.38	85.57	34.12	0.21	0.05	0.01	0.00	242.50	1,061.47	973.48	1,130.43
FSIG once at 55yrs	68.11	48.80	24.49	9.43	0.55	0.13	0.03	0.00	214.16	962.55	902.48	1,067.35
FSIG once at 60yrs	103.16	78.32	41.72	17.02	0.74	0.18	0.04	0.01	208.13	931.18	869.14	1,024.52
FSIG once at 60yrs and FOBT at 61-70yrs (biennial)	260.82	188.20	95.03	37.91	0.88	0.21	0.05	0.01	190.06	817.14	736.89	842.66

9.4 One-way sensitivity analysis

Further one-way sensitivity analysis was undertaken to explore the impact of alternative parametric assumptions on the cost-effectiveness and cost-utility of each of the five core screening options.

9.4.1 One-way sensitivity analysis - 20% individuals offered FOBT never comply

The likely rates of compliance with FOBT between screening rounds in population screening are unclear; Table 34 presents the cost-effectiveness results under the assumption that 40% of individuals offered screening never participate, whilst an independent 60% of participants comply with each screening round.

Table 34 One-way sensitivity analysis: 40% individuals offered FOBT never comply

Strategy	Marginal cost	Marginal life years saved	Marginal QALYs saved	Cost per life year saved	Cost per QALY saved
FOBT at 50-69yrs (biennial)	£40.37	0.0156	0.0136	£2,589.75	£2,964.56
FOBT at 60-69yrs (biennial)	£14.86	0.0075	0.0062	£1,969.02	£2,387.70
FSIG once at 55yrs	-£28.67	0.0237	0.0270	-£1,208.81	-£1,063.36
FSIG once at 60yrs	-£28.38	0.0197	0.0221	-£1,437.19	-£1,286.40
FSIG once at 60yrs and FOBT at 61-70yrs (biennial)	-£12.25	0.0242	0.0257	-£507.05	-£476.35

Table 34 shows that altering the base case assumptions concerning the nature of FOBT compliance has only a minor impact on the cost-effectiveness of the FOBT screening options. As fewer individuals comply with FOB tests, fewer adenomas and cancers would be found. Although non-compliers are assumed to continue to accrue the costs of sending FOB tests kits, the total cost of the programme is slightly offset by the reduction in colonoscopy costs.

<u>9.5.2 One-way sensitivity analysis: 60% compliance with follow-up colonoscopy</u>

Table 35 shows the impact on cost-effectiveness results when a lower compliance rate is assumed for follow-up colonoscopy.

Table 35 One-way sensitivity analysis: 60% compliance rate for follow-up colonoscopy

Strategy	Marginal cost	Marginal life years saved	Marginal QALYs saved	Cost per life year saved	Cost per QALY saved
FOBT at 50-69yrs (biennial)	£70.63	0.0202	0.0175	£3,501.71	£4,031.09
FOBT at 60-69yrs (biennial)	£26.39	0.0097	0.0079	£2,730.46	£3,325.14
FSIG once at 55yrs	-£29.14	0.0237	0.0270	-£1,228.44	-£1,080.66
FSIG once at 60yrs	-£28.95	0.0197	0.0221	-£1,465.72	-£1,311.98
FSIG once at 60yrs and FOBT at 61-70yrs (biennial)	-£1.61	0.0254	0.0267	-£63.50	-£60.35

As demonstrated by Table 35, altering the compliance rate for follow-up colonoscopy has only a very small impact on the cost-effectiveness of the screening strategies.

<u>9.6 Summary of health economic results</u>

The results of the health economic analysis suggest that screening for colorectal cancer is likely have a cost-effectiveness and cost-utility that is better than many health interventions currently funded by the NHS. The central estimates of cost-effectiveness suggest that offering flexible sigmoidoscopy to individuals aged 60 followed by biennial FOBT for individuals aged 61-70 is the most effective option in terms of both survival and quality adjusted survival; this is not however the most cost-effective option. According to the deterministic analysis, the most cost-effective options would be a policy whereby individuals aged 55 or 60 are offered once-only flexible sigmoidoscopy alone; these policies are suggested to be cost-saving. However, the multivariate sensitivity analysis presented in Section 9.2 demonstrates that modelling the uncertainty surrounding the natural history of colorectal cancer and the true sensitivities and specificities of FOBT and endoscopy has a considerable impact on cost-effectiveness of each screening option. Due to the overlap in costs and effects demonstrated by the uncertainty analysis, the question of *"which screening option is most cost-effective?"* becomes somewhat unclear. The incremental cost-effectiveness acceptability curves suggest that for cost-effectiveness thresholds less than £50,000 per QALY, offering once-only flexible sigmoidoscopy to individuals aged 55 has the greatest probability of being optimal, that is, this options is most likely to result in the greatest incremental net benefit. However, the economic analysis consistently suggests that all five screening options are expected to produce health gains at a marginal cost that is currently considered acceptable to the NHS.

It is important to note that both the deterministic base case analysis and the stochastic uncertainty analysis suggests that a policy offering FOBT screening biennially to individuals aged 60-69 is dominated by the flexible sigmoidoscopy screening options; on the grounds of incremental cost-effectiveness this screening policy should not be considered as a viable option. However, due to the uncertainty in the estimates of cost-effectiveness, and the fact that all of the options appear to be economically attractive in comparison to a policy of no screening, the real issue concerns the viability of each option within the constraints of current NHS capacity. Analysis of immediate costs and resource of the five core screening options and issues surrounding the feasibility of each option are addressed in Chapter 10.

10. Predicted resource impacts

10.1 Introduction

This chapter presents estimates of likely resource impacts resulting from the introduction of alternative colorectal cancer screening programmes; this analysis includes only the five core screening options.

10.2 Approach to estimating immediate costs and resource use for core screening options

The impact of the different screening options on resource use has been estimated for the first five years of each strategy, in which it assumed that patients undergo all subsequent treatment in the year of their initial diagnosis. This medium-term analysis horizon ensures that costs associated with patients who relapse with advanced disease are incorporated (e.g. costs of further surgery for liver metastases and palliative chemotherapy). Data from the X-ACT study of chemotherapies for the adjuvant treatment of colorectal cancer were used to inform the assumptions regarding timing of relapses up to five years.

The resource use is broken down into the costs associated with diagnosis and treatment (cancer management costs are discussed in detail in Chapter 6). The expected number of cancers and adenomas in the relevant population were estimated for each screening option directly from the model, and in combination with the compliance rates for FOBT and flexible sigmoidoscopy, these give the total number of colonoscopies, flexible sigmoidoscopies and FOB tests performed in reaching a diagnosis, and all subsequent costs associated with cancer management. It is important to note that all results presented within this chapter are presented as the additional resource use requirements associated with each strategy, when compared to a "no screening" strategy and are not the absolute resource use and cost estimates.

The total number of additional colonoscopies and flexible sigmoidoscopies required for each screening option have been used to estimate the additional number of endoscopy units which would be required in the first year of the screening programme. A typical clinic session within an endoscopy unit is assumed to last 3 hours, during which it is assumed that 10 flexible sigmoidoscopies or 5 colonoscopies could be carried out. Each unit is assumed to operate for 45 weeks per year.

A number of simplifying assumptions were made in the analysis of the impact on resource use; many of these relate to treatment regimens for patients with different stages of colorectal cancers and are discussed in Chapter 6. In additional to these, it has been assumed that compliance rates are 60% for FOBT (with 80% compliance for any subsequent colonoscopy), and 60% for flexible sigmoidoscopy (with 100% compliance for any subsequent colonoscopy).

Under each scenario, cancers detected through screening in the first year are added to those presenting symptomatically (from the same age population) and compared to the number of symptomatic cases detected in the absence of screening. For example, under a screening programme of once-only flexible sigmoidoscopy at age 60, the number of cancers in the first year relates only to those patients aged 60, whether they are detected through screening or present symptomatically, as compared to the number of symptomatic cancers which would occur in 60-year-olds in the absence of screening. In the second year of the programme, the number of cancers detected via screening would be the same (using a similar population of previously unscreened 60-year-olds); however, the number of symptomatic cancers in the second year is calculated as those aged 60 (who do not attend screening), and any 61-year-olds who present with cancer the year after the first screening round. The number of symptomatic cancers in each year therefore includes the current screen-eligible cohort and those from previously screen-eligible cohorts.

10.3 Results of cost and resource use analysis

The resource use and cost implications have been assessed separately for each of the five core screening strategies, for the first five years of the screening programme. The results provide estimates of the direct screening costs and the impact on services required by patients with colorectal cancer such as radiotherapy and chemotherapy services. Also presented are estimates of the impact of each screening strategy on endoscopy unit capacity in terms of additional future staff and equipment requirements and associated costs, including training of nurse endoscopists.

10.3.1 Resource use for individual strategies

Table 36 shows the ***additional*** resource use implications of biennial FOBT age screening for people aged 50-69 in the first five years of the screening programme, when compared with the equivalent implications for the relevant population under a “no screening” policy.

Table 36 Additional Resource Use for biennial FOBT ages 50-69

Unit	Number in Year 1	Number in Year 2	Number in Year 3	Number in Year 4	Number in Year 5
Number of FOBT kits	5,309,723	5,309,723	5,309,723	5,309,723	5,309,723
Number of positive test results (FOBT)	83,796	83,796	83,796	83,796	83,796
Number of colonoscopies with polypectomy (FOBT)	42,492	42,492	41,928	41,928	41,509
Number of colonoscopies without polypectomy (FOBT)	40,880	40,717	39,486	39,486	38,688
Total number of additional cancers detected	6,282	6,119	3,638	3,638	2,156
Number of patients entering polyp surveillance	7,130	7,130	6,982	6,982	6,860
Total number of polyp pathology examinations	7,130	7,130	6,982	6,982	6,860
Total number of cancer pathology examinations	6,282	6,119	3,638	3,638	2,156
Number of CT scans	6,672	6,613	5,284	5,284	4,762
Number of GP appointments	6,008	5,949	4,651	4,651	4,143
Number of initial outpatient appointments	6,008	5,949	4,651	4,651	4,143
Number of further outpatient appointments	12,017	11,899	9,302	9,302	8,286
Number of ultrasounds	6,008	5,949	4,651	4,651	4,143
Number of A&E attendances	-195	-247	-823	-823	-1,303
Number of stays on general medical ward	-195	-247	-823	-823	-1,303
Number of patients receiving short-course RT	584	579	411	417	345
Number of patients receiving chemotherapy for downstaging	36	54	8	12	23
Number of patients receiving chemoRT	1,055	1,047	776	786	657
Number of patients receiving primary RT	24	16	-69	-69	-146
Number of patients undergoing surgery (including relapse)	5,509	5,447	3,597	3,608	2,695
Number of patients undergoing adjuvant chemotherapy	1,607	1,551	637	637	146
Number of patients undergoing chemotherapy for advanced disease	554	768	-136	-76	-801
Number of follow-up appointments (OP)	25,128	49,603	45,309	41,505	38,551
Number of follow-up appointments (colonoscopy)	0	0	0	0	6,282
Number of follow-up appointments (ultrasound)	12,564	24,802	19,514	14,552	11,588
Number of follow-up appointments (CT)	6,282	12,401	9,757	7,276	5,794

The number of FOBT kits used is the same in all five years, given the assumption of a constant screen-eligible population aged 50-69. The most notable result is the decline in the additional number of cancers detected through screening - this is due to a joint decline in the number of screen-detected cancers and symptomatic cancers. In both cases, the numbers will decline because repeat screening will detect and treat patients with polyps, preventing the onset of colorectal cancer. As time goes on, the total number of cancers detected is reduced because people who may have developed cancer in the absence of screening have been screened biennially, reducing the likelihood of these patients developing cancer.

The number of attendances at Accident and Emergency units and the number of inpatients stays on general medical wards are seen to be lower than under a “no screening” policy, as indicated by the negative values in the table. This is also attributable to the expected reduction in symptomatic cases following the introduction of FOB testing. The costs associated with these changes in resource use are shown in Table 37.

Table 37 Additional costs for biennial FOBT ages 50-69

Unit	Cost in Year 1	Cost in Year 2	Cost in Year 3	Cost in Year 4	Cost in Year 5
Number of FOBT kits	£62,336,146	£62,336,146	£62,336,146	£62,336,146	£62,336,146
Number of colonoscopies with polypectomy (FOBT)	£8,005,534	£8,005,534	£7,899,329	£7,899,329	£7,820,245
Number of colonoscopies without polypectomy (FOBT)	£7,701,858	£7,671,103	£7,439,070	£7,439,070	£7,288,814
Total number of polyp pathology examinations	£213,899	£213,899	£209,474	£209,474	£205,787
Total number of cancer pathology examinations	£1,570,513	£1,529,703	£909,495	£909,495	£538,986
Number of CT scans	£1,173,005	£1,162,648	£928,964	£928,964	£837,217
Number of GP appointments	£120,166	£118,987	£93,016	£93,016	£82,858
Number of initial outpatient appointments	£455,950	£451,480	£352,935	£352,935	£314,393
Number of further outpatient appointments	£1,529,888	£1,514,889	£1,184,232	£1,184,232	£1,054,908
Number of ultrasounds	£687,096	£680,360	£531,857	£531,857	£473,775
Number of A&E attendances	-£9,470	-£12,007	-£40,008	-£40,008	-£63,353
Number of stays on general medical ward	-£155,713	-£197,419	-£657,808	-£657,808	-£1,041,646
Number of patients receiving short-course RT	£622,651	£617,347	£437,758	£444,648	£367,334
Number of patients receiving chemotherapy for downstaging	£92,053	£138,534	£19,943	£31,683	-£58,069
Number of patients receiving chemoRT	£2,157,656	£2,141,179	£1,586,851	£1,608,890	£1,343,784
Number of patients receiving primary RT	£41,189	£28,867	-£121,244	-£121,244	-£256,135
Number of patients undergoing surgery (including relapse)	£25,111,426	£24,828,593	£16,395,672	£16,445,097	£12,282,605
Number of patients undergoing adjuvant chemotherapy	£8,700,456	£8,398,219	£3,450,400	£3,450,400	£789,518
Number of patients undergoing chemotherapy for advanced disease	£3,991,101	£5,535,735	-£985,006	-£550,645	-£5,788,119
Number of follow-up appointments (OP)	£1,599,598	£3,157,631	£2,884,271	£2,642,086	£2,454,075
Number of follow-up appointments (colonoscopy)	£0	£0	£0	£0	£1,183,538
Number of follow-up appointments (ultrasound)	£1,436,809	£2,836,281	£2,231,539	£1,664,133	£1,325,166
Number of follow-up appointments (CT)	£1,104,516	£2,180,331	£1,715,448	£1,279,267	£1,018,693
Total Costs	**£128,486,326**	**£133,338,040**	**£108,802,333**	**£108,081,015**	**£94,510,520**

The *additional* costs associated with biennial FOBT screening for people aged 50-69 in the first year of the screening programme are expected to be around £128m, approximately half of which is attributable to the costs of FOB test kits. By the fifth year of the programme, the costs are expected to be reduced to around £94m, reflecting the lower treatment costs associated with the reduction in the number of cancers detected (when compared to a no screening policy). The other main cost implications arise from the number of patients undergoing surgery (including surgery for patients who relapse with advanced disease) and the costs of colonoscopies for patients who test positive at screening (of which a large proportion will be found to be false positives).

Table 38 shows the 5-year resource use implications (compared to no screening) for biennial FOBT screening for ages 60-69.

Table 38 Additional Resource Use for biennial FOBT ages 60-69

Unit	Number in Year 1	Number in Year 2	Number in Year 3	Number in Year 4	Number in Year 5
Number of FOBT kits	3,011,173	3,011,173	3,011,173	3,011,173	3,011,173
Number of positive test results (FOBT)	39,464	39,464	39,464	39,464	39,464
Number of colonoscopies with polypectomy (FOBT)	21,809	21,809	21,542	21,542	21,393
Number of colonoscopies without polypectomy (FOBT)	17,366	17,203	16,340	16,340	15,727
Total number of additional cancers detected	4,044	3,881	2,353	2,353	1,452
Number of patients entering polyp surveillance	4,323	4,323	4,244	4,244	4,198
Total number of polyp pathology examinations	4,323	4,323	4,244	4,244	4,198
Total number of cancer pathology examinations	4,044	3,881	2,353	2,353	1,452
Number of CT scans	4,310	4,251	3,462	3,462	3,148
Number of GP appointments	3,894	3,835	3,063	3,063	2,756
Number of initial outpatient appointments	3,894	3,835	3,063	3,063	2,756
Number of further outpatient appointments	7,789	7,671	6,126	6,126	5,513
Number of ultrasounds	3,894	3,835	3,063	3,063	2,756
Number of A&E attendances	-133	-185	-554	-554	-848
Number of stays on general medical ward	-133	-185	-554	-554	-848
Number of patients receiving short-course RT	380	375	276	282	239
Number of patients receiving chemotherapy for downstaging	24	35	5	9	-11
Number of patients receiving chemoRT	683	675	515	526	450
Number of patients receiving primary RT	16	9	-46	-46	-92
Number of patients undergoing surgery (including relapse)	3,551	3,470	2,346	2,354	1,792
Number of patients undergoing adjuvant chemotherapy	1,062	1,006	444	444	146
Number of patients undergoing chemotherapy for advanced disease	372	486	-87	-44	-466
Number of follow-up appointments (OP)	16,176	31,698	28,977	26,746	25,079
Number of follow-up appointments (colonoscopy)	-	-	-	-	4,044
Number of follow-up appointments (ultrasound)	8,088	15,849	12,467	9,411	7,609
Number of follow-up appointments (CT)	4,044	7,925	6,233	4,705	3,804

As would be expected from population estimates, the predicted resource implications are approximately half of those for the 50-69 screening programme. As with the 50-69 age group, the additional number of cancers detected declines over time due to the removal of polyps at screening, which prevents the onset of cancer. It is of note that although the population covered by this strategy is less than half of that in the 50-69 group, the number of cancers does not reflect this, owing to the higher incidence of colorectal cancer in the more elderly age group. Table 39 shows the corresponding costs associated with this screening strategy.

Table 39 Additional costs for biennial FOBT ages 60-69

Additional Unit	Cost in Year 1	Cost in Year 2	Cost in Year 3	Cost in Year 4	Cost in Year 5
FOBT kits	£35,351,168	£35,351,168	£35,351,168	£35,351,168	£35,351,168
Colonoscopies with polypectomy (FOBT)	£4,108,906	£4,108,906	£4,058,523	£4,058,523	£4,030,483
Colonoscopies without polypectomy (FOBT)	£3,271,836	£3,241,081	£3,078,412	£3,078,412	£2,962,902
Polyp pathology examinations	£129,695	£129,695	£127,314	£127,314	£125,938
Cancer pathology examinations	£1,010,979	£970,169	£588,158	£588,158	£362,961
CT scans	£757,852	£747,495	£608,620	£608,620	£553,443
GP appointments	£77,888	£76,710	£61,256	£61,256	£55,129
Initial outpatient appointments	£295,534	£291,064	£232,427	£232,427	£209,180
Further outpatient appointments	£991,631	£976,631	£779,880	£779,880	£701,879
Ultrasounds	£445,357	£438,620	£350,256	£350,256	£315,225
A&E attendances	-£6,478	-£9,014	-£26,961	-£26,961	-£41,231
Stays on general medical ward	-£106,509	-£148,215	-£443,294	-£443,294	-£677,924
Short-course RT	£404,832	£399,855	£293,792	£300,682	£254,801
Chemotherapy for downstaging	£61,589	£88,496	£13,773	£22,189	-£29,359
Number of patients receiving chemoRT	£1,396,752	£1,381,321	£1,053,670	£1,075,709	£921,075
Number of patients receiving primary RT	£28,390	£16,068	-£80,289	-£80,289	-£160,366
Number of patients undergoing surgery (including relapse)	£16,184,502	£15,819,265	£10,694,596	£10,730,028	£8,167,101
Number of patients undergoing adjuvant chemotherapy	£5,749,440	£5,447,203	£2,406,126	£2,406,126	£791,032
Number of patients undergoing chemotherapy for advanced disease	£2,682,116	£3,502,566	-£631,332	-£319,945	-£3,365,040
Number of follow-up appointments (OP)	£1,029,702	£2,017,839	£1,844,612	£1,702,560	£1,596,476
Number of follow-up appointments (colonoscopy)	£0	£0	£0	£0	£761,874
Number of follow-up appointments (ultrasound)	£924,910	£1,812,485	£1,425,660	£1,076,171	£870,146
Number of follow-up appointments (CT)	£711,005	£1,393,309	£1,095,946	£827,283	£668,906
Total Costs	**£75,501,096**	**£78,052,717**	**£62,882,312**	**£62,506,272**	**£54,425,797**

As with the 50-69 strategy, approximately 50% of the costs in the first year of the programme are attttributable to the cost of FOB test kits, though this proportion increases over time due to the reduced incidence of cancer following the introduction of the screening programme. Costs of surgery again make up a significant proportion of the total cost.

Table 40 shows the 5-year resource use implications (compared to no screening) for once-only flexible sigmoidoscopy at age 55.

Table 40 Additional Resource Use for flexible sigmoidoscopy at age 55

Unit	Number in Year 1	Number in Year 2	Number in Year 3	Number in Year 4	Number in Year 5
Number of positive test results (at FSIG)	45,364	45,364	45,364	45,364	45,364
Number of FSIGs with polypectomy	44,563	44,563	44,563	44,563	44,563
Number of FSIGs without polypectomy	300,042	300,042	300,042	300,042	300,042
Number of colonoscopies	7,093	6,919	6,728	6,527	6,334
Number of additional cancers detected	861	687	496	295	101
Number of patients entering polyp surveillance	7,598	7,598	7,598	7,598	7,598
Number of polyp pathology examinations	7,598	7,598	7,598	7,598	7,598
Number of cancer pathology examinations	861	687	496	295	101
Number of CT scans	891	822	748	673	602
Number of GP appointments	798	729	655	580	509
Number of initial outpatient appointments	798	729	655	580	509
Number of further outpatient appointments	1,597	1,458	1,310	1,160	1,018
Number of ultrasounds	798	729	655	580	509
Number of A&E attendances	-15	-68	-126	-189	-250
Number of stays on general medical ward	-15	-68	-126	-189	-250
Number of patients undergoing short-course RT	71	62	52	43	33
Number of patients undergoing chemotherapy for downstaging	5	4	0	-4	-7
Number of patients undergoing chemoRT	131	116	100	84	69
Number of patients undergoing primary RT	4	-3	-10	-19	-27
Number of patients undergoing surgery (including surgery for relapse)	746	625	489	347	214
Number of patients undergoing adjuvant chemotherapy	210	150	85	15	-51
Number of patients undergoing chemotherapy for advanced disease	84	42	-31	-114	-189
Number of follow-up appointments (OP)	3,444	6,190	5,591	4,710	3,534
Number of follow-up appointments (colonoscopy)	0	0	0	0	861
Number of follow-up appointments (ultrasound)	1,722	3,095	2,365	1,581	792
Number of follow-up appointments (CT)	861	1,548	1,183	791	396

The number of positive results from screening with flexible sigmoidoscopy is assumed to be constant over time (due to the assumption of a constant screen-eligible patient population). The number of cancers detected through screening is therefore the same each year (with a new cohort of patients aged 55), and the decrease in the number of additional cancers seen in the table is due to the reduction in symptomatic cancers in subsequent years in patients who were screened at age 55. The costs of these resource implications are shown in Table 41.

Table 41 Additional costs for flexible sigmoidoscopy at age 55

Unit	Cost in Year 1	Cost in Year 2	Cost in Year 3	Cost in Year 4	Cost in Year 5
Flexible sigmoidoscopies with polypectomy	£2,299,438	£2,299,438	£2,299,438	£2,299,438	£2,299,438
Flexible sigmoidoscopies without polypectomy	£15,482,158	£15,482,158	£15,482,158	£15,482,158	£15,482,158
Colonoscopies	£1,336,404	£1,303,570	£1,267,637	£1,229,742	£1,193,261
Polyp pathology examinations	£227,927	£227,927	£227,927	£227,927	£227,927
Cancer pathology examinations	£215,234	£171,665	£123,983	£73,697	£25,288
CT scans	£156,709	£144,538	£131,511	£118,276	£105,823
GP appointments	£15,969	£14,584	£13,102	£11,597	£10,180
Initial outpatient appointments	£60,590	£55,337	£49,714	£44,002	£38,627
Further outpatient appointments	£203,304	£185,676	£166,811	£147,643	£129,609
Ultrasounds	£91,307	£83,390	£74,917	£66,309	£58,209
A&E attendances	-£738	-£3,292	-£6,128	-£9,188	-£12,174
Stays on general medical ward	-£12,138	-£54,130	-£100,755	-£151,069	-£200,160
Short-course RT	£76,088	£66,334	£55,939	£45,334	£35,444
Chemotherapy for downstaging	£13,501	£9,906	£855	-£9,731	-£18,845
Chemo-RT	£267,710	£237,458	£205,328	£172,218	£141,251
Primary RT	£7,349	-£4,677	-£18,096	-£32,686	-£47,112
Surgery (including relapse)	£3,399,465	£2,849,130	£2,230,878	£1,583,908	£973,841
Adjuvant chemotherapy	£1,139,891	£814,834	£457,749	£81,376	-£278,118
Chemotherapy for advanced disease	£1,725,834	£2,644,656	£3,373,434	£4,121,757	£4,960,414
Follow-up appointments (OP)	£219,220	£394,064	£355,928	£299,857	£224,992
Follow-up appointments (colonoscopy)	£0	£0	£0	£0	£162,200
Follow-up appointments (ultrasound)	£196,910	£353,960	£270,478	£180,850	£90,558
Follow-up appointments (CT)	£151,371	£272,100	£207,924	£139,025	£69,614
Total costs	**£27,273,502**	**£27,548,625**	**£26,870,733**	**£26,122,438**	**£25,672,424**

A large proportion of the costs for this screening strategy are the direct costs of flexible sigmoidoscopy. Since the number of patients screened each year is assumed to be constant, the total costs of the screening programme remain relatively stable over the first five years following the introduction of the programme. The increase in the costs of chemotherapy for advanced disease are related to the relapse of patients detected and treated at screening. Since this cohort of patients (i.e. those previously treated and at risk of relapse) increases each year, so too do the costs of treating such relapses. The total costs are considerably lower than for either of the FOBT screening strategies, due to the smaller screen-eligible population. The smaller number of cancers detected through flexible sigmoidoscopy screening are reflected in the lower costs of cancer management seen in the above table.

Table 42 shows the additional 5-year resource use implications (compared to no screening) for once-only flexible sigmoidoscopy at age 60.

Table 42 Additional Resource Use for flexible sigmoidoscopy at age 60

Unit	Number in Year 1	Number in Year 2	Number in Year 3	Number in Year 4	Number in Year 5
Number of positive test results (at FSIG)	45,073	45,073	45,073	45,073	45,073
Number of FSIGs with polypectomy	43,994	43,994	43,994	43,994	43,994
Number of FSIGs without polypectomy	230,975	230,975	230,975	230,975	230,975
Number of colonoscopies	8,638	8,386	8,115	7,829	7,537
Number of additional cancers detected	1,148	896	625	339	47
Number of patients entering polyp surveillance	9,178	9,178	9,178	9,178	9,178
Number of polyp pathology examinations	9,178	9,178	9,178	9,178	9,178
Number of cancer pathology examinations	1,148	896	625	339	47
Number of CT scans	1,193	1,098	998	895	792
Number of GP appointments	1,075	980	879	777	673
Number of initial outpatient appointments	1,075	980	879	777	673
Number of further outpatient appointments	2,150	1,960	1,759	1,553	1,347
Number of ultrasounds	1,075	980	879	777	673
Number of A&E attendances	-23	-101	-186	-278	-372
Number of stays on general medical ward	-23	-101	-186	-278	-372
Number of patients undergoing short-course RT	96	83	70	56	42
Number of patients undergoing chemotherapy for downstaging	8	5	0	-6	-12
Number of patients undergoing chemoRT	174	154	132	110	87
Number of patients undergoing primary RT	6	-4	-15	-28	-41
Number of patients undergoing surgery (including surgery for relapse)	995	824	635	436	236
Number of patients undergoing adjuvant chemotherapy	294	207	114	16	-84
Number of patients undergoing chemotherapy for advanced disease	122	54	-55	-178	-297
Number of follow-up appointments (OP)	4,591	8,176	7,233	5,901	4,096
Number of follow-up appointments (colonoscopy)	0	0	0	0	1,148
Number of follow-up appointments (ultrasound)	2,296	4,088	3,043	1,928	772
Number of follow-up appointments (CT)	1,148	2,044	1,521	964	386

Given the differences in the populations covered, it is more meaningful to compare the two flexible sigmoidoscopy strategies with each other than with any of the other strategies. Although the cohort of screen-eligible patients is smaller for this strategy than for the flexible sigmoidoscopy at age 55 strategy, this is offset by the higher incidence at age 60, and this is reflected in the similar results seen for the two strategies. As before, the reduction in the additional number of cancers detected is due to the associated reduction in symptomatic cancers in patients following screening, and does not represent a fall in the number of cancers detected directly through screening patients at age 60 (which remains constant, with a new cohort of 60-year-olds each year). The cost estimates associated with this resource use breakdown are given in Table 43.

Table 43 Additional costs for flexible sigmoidoscopy at age 60

Unit	Cost in Year 1	Cost in Year 2	Cost in Year 3	Cost in Year 4	Cost in Year 5
Flexible sigmoidoscopies with polypectomy	£2,270,073	£2,270,073	£2,270,073	£2,270,073	£2,270,073
Flexible sigmoidoscopies without polypectomy	£11,918,331	£11,918,331	£11,918,331	£11,918,331	£11,918,331
Colonoscopies	£1,627,415	£1,579,995	£1,528,937	£1,475,032	£1,420,038
Polyp pathology examinations	£275,344	£275,344	£275,344	£275,344	£275,344
Cancer pathology examinations	£286,966	£224,041	£156,290	£84,759	£11,783
CT scans	£209,784	£193,094	£175,408	£157,317	£139,180
GP appointments	£21,499	£19,600	£17,588	£15,530	£13,467
Initial outpatient appointments	£81,573	£74,370	£66,736	£58,928	£51,099
Further outpatient appointments	£273,710	£249,539	£223,925	£197,725	£171,458
Ultrasounds	£122,927	£112,072	£100,568	£88,802	£77,005
A&E attendances	-£1,101	-£4,913	-£9,056	-£13,511	-£18,099
Stays on general medical ward	-£18,110	-£80,778	-£148,899	-£222,142	-£297,591
Short-course RT	£102,103	£88,592	£74,350	£59,735	£45,226
Chemotherapy for downstaging	£19,434	£13,198	-£357	-£16,040	-£30,700
Chemo-RT	£356,596	£314,412	£270,109	£224,216	£178,539
Primary RT	£11,144	-£7,141	-£27,063	-£48,591	-£71,012
Surgery (including relapse)	£4,534,922	£3,755,471	£2,892,488	£1,986,257	£1,077,212
Adjuvant chemotherapy	£1,589,990	£1,122,790	£617,803	£84,810	-£454,881
Chemotherapy for advanced disease	£2,601,218	£3,952,975	£5,027,910	£6,128,171	£7,399,955
Follow-up appointments (OP)	£292,280	£520,471	£460,445	£375,631	£260,718
Follow-up appointments (colonoscopy)	£0	£0	£0	£0	£216,257
Follow-up appointments (ultrasound)	£262,535	£467,503	£347,952	£220,527	£88,324
Follow-up appointments (CT)	£201,818	£359,383	£267,481	£169,526	£67,897
Total costs	**£27,040,449**	**£27,418,423**	**£26,506,360**	**£25,490,431**	**£24,809,622**

The costs are seen to be similar to those associated with flexible sigmoidoscopy at age 55. Although the direct screening costs in the age 60 group are lower (because of the smaller screen-eligible cohort), the cancer management costs are higher because of the higher incidence of colorectal cancer at this age.

Table 44 shows the additional resource use implications of the combined screening strategy of flexible sigmoidoscopy at age 60, followed by biennial FOB testing for ages 61-70.

Table 44 Additional Resource Use for flexible sigmoidoscopy at age 60 and biennial FOBT for ages 61-70

Unit	Number in Year 1	Number in Year 2	Number in Year 3	Number in Year 4	Number in Year 5
Number of positive test results (at FSIG)	45,191	45,191	45,191	45,191	45,191
Number of FSIGs with polypectomy	43,994	43,994	43,994	43,994	43,994
Number of FSIGs without polypectomy	230,975	230,975	230,975	230,975	230,975
Number of FOBT kits	1,330,277	1,330,277	1,330,277	1,330,277	1,330,277
Number of positive tests (at FOBT)	39,634	39,009	30,258	36,140	29,480
Number of therapeutic colonoscopies	22,081	21,482	16,783	19,607	16,091
Number of diagnostic colonoscopies	25,886	25,619	19,650	20,561	17,481
Number of additional cancers detected	5,397	4,993	1,892	-484	-495
Number of patients entering polyp surveillance	13,678	13,525	12,620	12,980	12,396
Number of polyp pathology examinations	13,678	13,525	12,620	12,980	12,396
Number of cancer pathology examinations	5,397	4,993	1,892	-484	-495
Number of CT scans	5,725	5,467	3,590	2,712	2,666
Number of GP appointments	5,172	4,929	3,146	2,262	2,246
Number of initial outpatient appointments	5,172	4,929	3,146	2,262	2,246
Number of further outpatient appointments	10,343	9,858	6,293	4,523	4,493
Number of ultrasounds	5,172	4,929	3,146	2,262	2,246
Number of A&E attendances	-164	-237	-849	-1,598	-1,581
Number of stays on general medical ward	-164	-237	-849	-1,598	-1,581
Number of patients undergoing short-course RT	495	472	259	118	129
Number of patients undergoing chemotherapy for downstaging	33	45	-9	-73	-65
Number of patients undergoing chemoRT	892	852	494	263	271
Number of patients undergoing primary RT	24	13	-81	-190	-189
Number of patients undergoing surgery (including surgery for relapse)	4,726	4,458	2,099	466	494
Number of patients undergoing adjuvant chemotherapy	1,414	1,287	251	-607	-541
Number of patients undergoing chemotherapy for advanced disease	515	639	-390	-1,614	-1,502
Number of follow-up appointments (OP)	21,588	41,559	32,936	16,020	7,824
Number of follow-up appointments (colonoscopy)	-	-	-	-	5,397
Number of follow-up appointments (ultrasound)	10,794	20,779	13,769	2,815	-1,960
Number of follow-up appointments (CT)	5,397	10,390	6,885	1,408	-980

This screening programme is the second most intensive in terms of resources used, primarily because of the increased number of cancers detected through screening. It is because of the repeated screening of patients over a short period of time that the additional number of cancers detected (compared to no screening) decreases so dramatically. Since polyps detected at earlier screening rounds are removed, a large number of subsequent cancers are prevented, meaning that the number of cancers detected (including those presenting symptomatically) becomes *less* than the number which would be seen if the equivalent population were not screened at all. The costs of these resources are shown in Table 45.

Table 45 *Additional costs for flexible sigmoidoscopy at age 60 and biennial FOBT for ages 61-70*

Unit	Cost in Year 1	Cost in Year 2	Cost in Year 3	Cost in Year 4	Cost in Year 5
FSIGs with polypectomy	£2,270,073	£2,270,073	£2,270,073	£2,270,073	£2,270,073
FSIGs without polypectomy	£11,918,331	£11,918,331	£11,918,331	£11,918,331	£11,918,331
FOBT kits	£15,617,458	£15,617,458	£15,617,458	£15,617,458	£15,617,458
Therapeutic colonoscopies	£4,160,006	£4,047,233	£3,161,933	£3,693,939	£3,031,630
Diagnostic colonoscopies	£4,876,934	£4,826,549	£3,702,014	£3,873,676	£3,293,348
Polyp pathology examinations	£410,347	£405,745	£378,612	£389,411	£371,891
Cancer pathology examinations	£1,349,270	£1,248,140	£473,012	-£121,122	-£123,855
CT scans	£1,006,580	£961,263	£631,129	£476,860	£468,760
GP appointments	£103,431	£98,584	£62,930	£45,234	£44,926
Initial outpatient appointments	£392,452	£374,064	£238,778	£171,635	£170,464
Further outpatient appointments	£1,316,828	£1,255,128	£801,191	£575,902	£571,972
Ultrasounds	£591,408	£563,697	£359,827	£258,646	£256,882
A&E attendances	-£7,973	-£11,541	-£41,271	-£77,718	-£76,863
Stays on general medical ward	-£131,093	-£189,764	-£678,582	-£1,277,835	-£1,263,788
Short-course RT	£528,158	£503,213	£275,807	£125,808	£137,229
Chemotherapy for downstaging	£84,543	£116,005	-£21,792	-£186,962	-£166,026
ChemoRT	£1,825,600	£1,743,388	£1,010,850	£538,875	£553,488
Primary RT	£41,295	£21,967	-£141,741	-£332,780	-£330,380
Surgery (including surgery for relapse)	£21,544,158	£20,319,660	£9,567,860	£2,123,741	£2,250,004
Adjuvant chemotherapy	£7,656,042	£6,969,018	£1,357,754	-£3,286,307	-£2,930,012
Chemotherapy for advanced disease	£3,714,756	£4,604,163	-£2,820,405	£11,646,093	-£10,837,391
Follow-up appointments (OP)	£1,374,259	£2,645,514	£2,096,592	£1,019,786	£498,057
Follow-up appointments (CT)	£948,920	£1,826,717	£1,210,458	£247,479	-£172,288
Follow-up appointments (colonoscopy)	£0	£0	£0	£0	£1,016,810
Follow-up appointments (ultrasound)	£1,234,402	£2,376,282	£1,574,623	£321,932	-£224,121
Total Costs	**£82,826,186**	**£84,510,886**	**£53,005,439**	**£26,739,970**	**£26,346,599**

These cost estimates indicate that this screening strategy is the second most costly of the five core strategies considered within this analysis. There is a sharp decline in the costs seen after the second year of the programme, reflecting the lower number of cancers detected at the second round of screening (the majority of whom have already been screened in the first year). Significant cost savings are seen through the reduction in both screen-detected and symptomatic cancers over time, particularly with respect to costs of chemotherapy for advanced disease and in the adjuvant setting.

Tables 46-50 provide a condensed summary of the resource use results to allow a direct comparison between the five core screening strategies, across the first five years of the screening programme. The figures again represent additional resources required when compared to a policy of no screening.

Table 46 Comparison of additional resource use for all screening strategies in year 1

Unit	FOBT 50-69	FOBT 60-69	Flexible sigmoidoscopy at 55	Flexible sigmoidoscopy at 60	Flexible sigmoidoscopy at 60, FOBT 61-70
Number of FOB test kits sent	5,309,723	3,011,173	0	0	1,330,277
Number of flexible sigmoidoscopies	0	0	344,065	274,969	274,969
Number of colonoscopies	83,372	39,175	7,093	8,638	47,967
Additional number of cancers detected	6,282	4,044	861	1,148	5,397
Number undergoing surgery	5,509	3,551	746	995	4,726

Table 47 Comparison of additional resource use for all screening strategies in year 2

Unit	FOBT 50-69	FOBT 60-69	Flexible sigmoidoscopy at 55	Flexible sigmoidoscopy at 60	Flexible sigmoidoscopy at 60, FOBT 61-70
Number of FOB test kits sent	5,309,723	3,011,173	0	0	1,330,277
Number of flexible sigmoidoscopies	0	0	344,605	274,969	274,969
Number of colonoscopies	83,209	39,012	6,919	8,386	47,101
Additional number of cancers detected	6,119	3,881	687	896	4,993
Number undergoing surgery	5,447	3,470	625	824	4,458

Table 48 Comparison of additional resource use for all screening strategies in year 3

Unit	FOBT 50-69	FOBT 60-69	Flexible sigmoidoscopy at 55	Flexible sigmoidoscopy at 60	Flexible sigmoidoscopy at 60, FOBT 61-70
Number of FOB test kits sent	5,309,723	3,011,173	0	0	1,330,277
Number of flexible sigmoidoscopies	0	0	344,065	274,969	274,969
Number of colonoscopies	81,414	37,882	6,728	8,115	36,433
Additional number of cancers detected	3,638	2,353	496	625	1,892
Number undergoing surgery	3,597	2,346	489	635	2,099

Table 49 Comparison of additional resource use for all screening strategies in year 4

Unit	FOBT 50-69	FOBT 60-69	Flexible sigmoidoscopy at 55	Flexible sigmoidoscopy at 60	Flexible sigmoidoscopy at 60, FOBT 61-70
Number of FOB test kits sent	5,309,723	3,011,173	0	0	1,330,277
Number of flexible sigmoidoscopies	0	0	344,065	274,969	274,969
Number of colonoscopies	81,414	37,882	6,527	7,829	40,168
Additional number of cancers detected	3,638	2,353	295	339	-484
Number undergoing surgery	3,608	2,354	347	436	466

Table 50 Comparison of additional resource use for all screening strategies in year 5

Unit	FOBT 50-69	FOBT 60-69	Flexible sigmoidoscopy at 55	Flexible sigmoidoscopy at 60	Flexible sigmoidoscopy at 60, FOBT 61-70
Number of FOB test kits sent	5,309,723	3,011,173	0	0	1,330,277
Number of flexible sigmoidoscopies	0	0	344,065	274,969	274,969
Number of colonoscopies	80,197	37,120	6,334	7,537	33,572
Additional number of cancers detected	2,156	1,452	101	47	-495
Number undergoing surgery	2,695	1,792	214	236	494

These figures give an indication of the scale of the impact of each strategy in the first year. It can be seen that the FOBT strategies incur the highest resource impact, owing primarily to the wider population base covered by these policies. The higher number of cancers detected at screening by the FOBT strategies has a knock-on effect on the cancer management implications, with the number of patients undergoing surgery being most affected. By contrast, the flexible sigmoidoscopy strategies screen a smaller number of patients, detect fewer cancers, and are thus less costly, both in terms of direct screening costs, and subsequent cancer management costs.

5.3.2 Impact on endoscopy services

The costs presented so far do not assess capacity issues associated with each screening strategy. The primary issue is likely to be the necessary expansion of existing endoscopy services to meet the needs of a colorectal screening programme. A recent audit [96] of endoscopy services reported that half of all endoscopy units would require capital expenditure to provide the physical space for additional endoscopy requirements. The study also highlighted the existing lack of endoscopists and endoscopy-trained nurses as a major constraint in the expansion of capacity.

Endoscopy unit requirements vary considerably across the different screening strategies; the additional number of flexible sigmoidoscopies and colonoscopies required in the first year of each programme are given in Table 51, and have been used to derive estimates of the additional number of endoscopy units required, and their associated costs. First year estimates only are presented, since the resultrs suggest that the majority of the impact on endoscopy services will be seen within the first 12 months of any of the core screening programmes. Each endoscopy unit is assumed to require 4 trained nurse endoscopists and 1.4 WTE gastrointestinal consultants.

Table 51 Additional endoscopy unit requirements

Strategy	Number of flexible sigmoidoscopies	Number of colonoscopies	Additional number of endoscopy units *
FOBT at 50-69yrs (biennial)	0	83,373	20
FOBT at 60-69yrs (biennial)	0	39,176	9
FSIG once at 55yrs	344,605	7,093	40
FSIG once at 60yrs	274,969	8,638	33
FSIG once at 60yrs and FOBT at 61-70yrs (biennial)	274,969	47,967	38

* These figures refer to the number of 2-room units required – the estimates are only for endoscopy services relating to the screening programme.

It must be stressed that these estimates relate only to the endoscopy capacity arising directly from a colorectal screening programme (i.e. screen-detected cancers and polyps), and do not include the additional resources required for endoscopy for work unrelated to colorectal cancer. There are an estimated 240 hospital-based endoscopy units in England, at which approximately one third of all activity is concerned with colorectal cancer. It is assumed that 80% of these units have two endoscopy rooms, with the remainder having either one room or more than two rooms (*Personal Communication with Dr Roland Valori, Consultant Gastroenterologist, Gloucester Royal Hospital*). The figures outlined in Table 51 suggest significant investment would be required to meet the requirements of the implementation of any of the screening strategies on a nationwide basis.

This high number of endoscopy units will naturally mean an increased demand for trained endoscopists. The NHS Cancer Plan launched a 3-year project costing £2.5 million, with the aim of training 600 professionals in gastrointestinal endoscopy between 2001 and 2004. This equates to around £4,170 per person trained, and these costs should be borne in mind given the increased demand for endoscopy services under any of the above screening strategies.

5.3.3 Limitations of the resource use analysis

The primary limitation of the resource use analysis is that the estimates of the number of people attending screening, testing positive for polyps/cancer and presenting symptomatically are taken directly out of the screening model, and so are subject to the same levels of uncertainty as all other results presented in this report. The estimates of resource use are presented the first five year of each screening strategy, and given the patterns seen in the results over this time period, it is likely that the impact would continue to decrease beyond this period as the number of screen-detected and symptomatic cancers decreases.

The estimates of the number of patients receiving each treatment regimen are based on the assumptions in Chapter 6, but since policy on diagnostic procedures and treatment regimens is likely to vary between health authorities depending on existing capacity and cost issues, the resource use implications should be interpreted as broad approximations.

The analysis of the additional number of units and associated staffing requirements makes the assumption that all existing endoscopy units are already operating at full capacity and so would be unable to deal with any additional cancer patients – this may not apply to all units, and there is likely to be considerable difference across England in how units could accommodate patients arriving through the screening programme. It may be feasible in some units to expand the size of the endoscopy suite (i.e. the addition of another endoscopy room), or for referrals from screening to be dealt with at community-based units, which currently do very little colorectal cancer work.

11. Conclusions and discussion

11.1 Introduction

The usefulness of any health economic model is determined by its ability to synthesise the available evidence and to capture all important events within a policy decision. Consequently, the model presented here is subject to important weaknesses in the evidence base; the model is only as good as the data that is used to populate it. Whilst the calibration of the natural history model appears to provide a good 'fit' to published incidence, mortality and adenomas prevalence data, as well as detection rates from UK screening trials, the set of parameter used in the base case analysis represents just one of a range of potential solutions. Thus, the central estimates of effectiveness and cost-effectiveness should be approached with considerable caution as alternative natural history parameter sets may offer substantially different results. The uncertainty analysis presented in Section 9.2 is potentially a more useful resource for policymaking than the deterministic model. Particular reference should be made to the incremental cost-effectiveness acceptability curves, which provide information on the probability that each screening option is likely to result in the greatest net benefit over a range of cost-effectiveness thresholds.

11.2 Limitations and caveats of the health economic model

The model developed here covers a broader scope than existing UK models. To date, the model presented here is the only UK evaluation to incorporate flexible sigmoidoscopy screening options as well as combinations strategies of FOBT and flexible sigmoidoscopy. The model also incorporates up-to-date stage-specific utility data for individuals with cancer. Further, none of the existing studies have used appropriate methods to explore second-order uncertainty in the true mean values of model inputs. The base case model results presented here should be approached with caution; there remain considerable uncertainties in terms of the natural history of colorectal cancer, together with uncertainties concerning the true single-test sensitivities of FOBT and flexible sigmoidoscopy. The model is subject to several limitations:

- The paucity of direct evidence on the rate at which adenomas develop within the general English population, the rate at which adenomas develop into invasive cancer, and the rate at which early local cancer progresses to late-stage metastatic disease, means that several of the model parameters had to be fitted to published data. In short, there may be several potentially valid solutions which appear fit the data, yet may not be optimal.
- Transition probabilities estimated within the model are assumed to be constant (with the exception of age-specific adenoma incidence and mortality rates); in reality however, this

assumption is unlikely to be accurate. The absence of direct evidence however means that this assumption is unavoidable.

- Data from the prevalence screening round from the Nottingham FOBT trial are used as an means of model validation; ideally however, these data would be used to inform natural history and sensitivity parameters.
- Despite indirect evidence to suggest that a proportion of colorectal cancers may arise *de novo*, the current model assumes that all cancers derive from pre-existing adenomas. This assumption is likely to favour all screening options versus no screening. In particular, this assumption means that flexible sigmoidoscopy screening strategies, which have a high sensitivity in detecting adenomas, will be favoured by the model.
- The model assumes that a proportion of proximal cancers are associated with large 'sentinel' adenomas located in the distal colon, which would subsequently lead to examination of the entire colon. This proportion however, should be an output of the model rather than an input. Further, the probabilities of cancer progression are assumed to be equivalent in both the distal and proximal colon, which in reality is unlikely to be accurate. In order to address this issue, discrete lesions would need to be modelled, requiring a more complex representation of the natural history of the disease for which data do not exist.
- The central uncertainty concerning the natural history of colorectal cancer concerns the prevalence of pre-clinical cancer within the general population. There exists limited empirical evidence with which to estimate this; the only potential data sources are the Nottingham FOBT trial (uncertainty in the prevalence is coupled with uncertainty in the true prevalence of pre-clinical cancer) and the only UK autopsy study (in which only 365 specimens were examined).

11.3 Conclusions on the results of the economic model

The deterministic and stochastic results generated from the health economic model suggest that each of the screening options considered for colorectal cancer is likely have a cost-effectiveness and cost-utility compared to no screening that is better than many health interventions currently funded by the NHS. The two once-only flexible sigmoidoscopy options and the combined FOBT and flexible sigmoidoscopy option all appear to be cost-saving within the base case analysis.

Each of the screening options considered have differing impacts on resource requirements, and specifically on requirements for flexible sigmoidoscopy, colonoscopy and cancer surgery services. Due to parametric uncertainty in the cost-effectiveness estimates, and the fact that all of the options appear to be economically attractive in comparison to a policy of no screening, the key issue concerns the viability of each option within the constraints of current and future NHS staff and capital resource capacity. The projected economic and resource impact of each screening option is discussed below and summarised in Table 52.

11.3.1 FOBT 50-69

In the base case, offering FOBT to individuals aged 50-69 results in the third greatest survival and the fourth greatest quality-adjusted survival. This option ranks fifth in terms of cost-effectiveness and cost-utility according to the deterministic model results. The uncertainty analysis suggests that assuming a cost-effectiveness threshold of £30,000 per QALY saved, there is a 0.39% probability that this screening option is optimal, that is the option has the greatest expected net benefit.

The model suggests that an additional 5,500 people will undergo surgery for colorectal cancer in the first year. However this option has the highest expected first-year screening and cancer management costs, estimated at around £128 million. In the first year an estimated 83,000 additional colonoscopies will be required; assuming 5 colonoscopies per session and 1.4 consultants per session, this suggests that around 53 additional wte gastrointestinal consultant staff would be required. It is estimated that around 20 additional 2-room colonoscopy equipped endoscopy units would be required.

11.3.2 FOBT 60-69

Under the base case assumptions, offering FOBT to individuals aged 60-69 is the least effective of the five core screening options in terms of both survival and quality adjusted survival. This policy ranks fourth in terms of cost-effectiveness and cost-utility. When incremental net benefit is considered, the strategy is never optimal regardless of the cost-effectiveness threshold chosen. However, the reduced screening population leads to smaller resource implications, with the strategy being expected to detect approximately 4,044 additional cancers in the first year, at a total cost of around £75 million. The associated impact on the number of additional colonoscopies, an estimated 39,000 procedures, is expected to lead to the need for an estimated 25 wte gastrointestinal consultants estimated on the same basis as FOBT 50-69 above. An estimated 9 additional 2-room colonoscopy endoscopy units would be required.

11.3.3 Once-only flexible sigmoidoscopy at age 55

The deterministic model suggests that a policy of offering flexible sigmoidoscopy to individuals aged 55 is cost-saving compared to a policy of no screening. This policy ranks second in terms of survival and first in terms of quality-adjusted survival. Whilst this option is expected to cost-saving in comparison to no screening, the uncertainty analysis suggests that at a cost-effectiveness threshold of £30,000 per QALY saved, there is a 57% probability that this option will result in the greatest net benefit.

This policy screens a considerably lower population than the FOBT options, and hence the additional number of cancers detected is much lower at approximately 861 compared to no screening (in the first year). Total screening and cancer management costs in the first year are estimated at around £27 million. The impact on endoscopy services is higher than for FOBT strategies with an estimated 345,000 additional flexible sigmoidoscopies and 7,100 additional colonoscopies in the first year. It is estimated that approximately 110 wte trained endoscopy nurses and 4-5 wte gastrointestinal consultants would be required with approximately 40 additional 2 room endoscopy units equipped for both flexible sigmoidoscopy and colonoscopy.

11.3.4 Once-only flexible sigmoidoscopy at age 60

The deterministic model results suggests that a policy of offering flexible sigmoidoscopy to individuals aged 60 results in cost savings compared to a policy of no screening. However, this option ranks fourth in terms of survival and third in terms of quality-adjusted survival compared with no screening. The incremental cost-effectiveness acceptability curve indicates that this screening option is unlikely to result in the greatest net benefit at any cost-effectiveness threshold.

The costs associated with this option are similar to those for the flexible sigmoidoscopy screening at age 60, with the analysis suggesting total first year costs of around £27 million, associated with an additional 1,148 detected cancers in the first year. Endoscopy requirements would be slightly lower than offering flexible sigmoidoscopy to individuals aged 55 due to the smaller screen-eligible population, with approximately estimated 275,000 additional flexible sigmoidoscopies and 8,600 additional colonoscopies required in the first year. This corresponds to the requirement of an estimated 88 wte trained endoscopy nurses and 5-6 wte gastrointestinal consultants. It is estimated that 33 additional 2 room endoscopy units equipped for both flexible sigmoidoscopy and colonoscopy would be required.

11.3.5 Flexible sigmoidoscopy at age 60 followed by FOBT at age 61-70

The results of the deterministic model suggest that a policy of offering flexible sigmoidoscopy to individuals aged 60 followed by biennial screening from 61-70 years is cost-saving in comparison to no screening. This options ranks first in terms of overall survival and second in terms of quality adjusted survival. The uncertainty analysis suggests that this screening option has a 43% probability of providing the greatest net benefit at £30,000 per QALY gained.

This strategy has first year costs in the region of £83 million covering screening and cancer management costs, associated with an additional 5,400 cancers being detected. Endoscopy service costs would also be high, with an estimated 275,000 additional flexible sigmoidoscopies and 48,000 additional colonoscopies being required. This strategy is estimated to require an additional 88 wte trained endoscopy nurses and 31 wte gastrointestinal consultants, together with roughly 38 additional endoscopy units equipped for both flexible sigmoidoscopy and colonoscopy.

Table 52 Summary of economic outcomes for core screening options

Criteria	FOBT 50-69	FOBT 60-69	FSIG 55	FSIG 60	FSIG 60, FOBT 61-70
Cost-effectiveness rank-ordering	5	4	cost-saving	cost-saving	cost-saving
Probability of being optimal at £30,000 per QALY threshold	0.39%	0%	57%	0%	43%
Total 1st year cost	£128,486,326	£75,501,096	£27,273,502	£27,040,449	£82,826,186
Quality adjusted life days saved per person invited to screening	8.29	3.80	9.86	8.07	10.29
Additional number of flexible sigmoidoscopies *	0	0	344,605	274,969	274,969
Additional number of colonoscopies *	83,373	39,176	7,093	8,638	47,967
Additional number of WTE nurse-trained endoscopists *	0	0	110	88	88
Additional number of WTE gastrointestinal consultants *	53	25	4-5	5-6	31

* = additional requirements when compared to a policy of no screening

11.4 Conclusions on the results of the cost-effectiveness analysis and resource impact analysis

The incremental cost-effectiveness acceptability curves suggest that for willingness to pay thresholds of less than £50,000 per QALY (i.e. the amount society is willing to pay to save one quality adjusted life year) once only flexible sigmoidoscopy at age 55 has the greatest probability of providing the greatest expected net benefit.

It should be noted that when compared with a policy of no screening, all five core screening options are expected to produce health gains at a cost considered acceptable to the NHS.

The feasibility of the options in terms of endoscopist requirements is an important consideration in assessing these options. The two once-only flexible sigmoidoscopy options have similar impacts on quality adjusted life days saved and costs compared to no screening. These options also minimise the requirement for consultant gastroenterologists, though relying on a greater number of nurse endoscopists. If the availability of nurse endoscopists is constrained then offering flexible sigmoidoscopy to individuals aged 60 would be the preferable option.

The cost and resource analysis suggests that the most costly option in terms of screening and cancer management costs in the first year of the screening programme would be for the FOBT 50-69 strategy, owing to the high number of people who would be screened each year. The higher number of cancers detected under the FOBT age 50-69 option would have significant cost implications, particularly in terms of the increase in surgery volume of around 5,500 in the first year.

If total endoscopy services are constrained then the favoured option is likely to be the programme of biennial FOB testing between the ages of 60 and 69, however this option is estimated to be the least effective in terms of quality adjusted life days saved and is estimated to have a total first year cost in the middle of the estimated range.

11.5 Recommendations for further research

The uncertainties within this modelling work are a direct result of the paucity of direct evidence concerning the natural history of colorectal cancer and the operating characteristics of the screening tests available. The central uncertainty within the evidence concerns the true prevalence of undiagnosed asymptomatic colorectal cancer within the English population; inevitably, this is highly influential in determining the effectiveness and cost effectiveness of any screening programme.

Whilst the natural history of the disease (i.e. the adenomas incidence rate, the rate at which adenomas develop to cancer, and the rate at which cancer progresses from early local stages to advanced or metastatic disease) cannot be observed using standard study designs, there are three potential designs that could provide information.

- Direct observation of natural history from colonoscopy screening of the general population. This however is ethically infeasible.
- Further valuable evidence could potentially be obtained through undertaking a large autopsy series in England, or more broadly, the UK. Given a sufficiently large sample size, such a study could be used to obtain better age and sex-specific estimates of adenoma incidence rates, and also to determine the underlying prevalence of pre-clinical colorectal cancer.
- Analysis of existing UK and international screening trials. The problem with the screening trials, and conventional methods of analysis, is that the results confound the natural history and the characteristics of the screening test. Analytical methods which synthesise data from other sources (for example ONS incidence and mortality, and stage distribution at diagnosis, and survival estimates from audit studies) allow information concerning natural history and test characteristics contained within the trial data to be drawn out. Bayesian synthesis analysis of existing trial data, based upon an underlying model of disease natural history and incorporating data from a range of available sources, should be undertaken.

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Appendix 1: Base case model results for extension FOBT screening options

A1.1 Introduction

This appendix presents the central estimates of the health outcomes and cost-effectiveness results for the three extension FOBT screening options under the base case assumptions.

A1.2 Key health outcomes for extension screening strategies

As one would expect, the greater the number of FOBT screening rounds offered, the greater effectiveness provided by the screening programme, as shown in Table A1. Offering FOBT biennially to individuals aged 60-73 is predicted to result in approximately 350 more cancers being detected compared to a policy offering FOBT screening biennially to individuals aged 60-67. For every additional screening round, there is an additional benefit in terms of the number of cases of symptomatic cancer avoided and the number of deaths due to colorectal cancer avoided.

Table A1 Key health outcomes for extension screening strategies

Strategy	Number of screen-detected cancers	Number of CRC cases detected at surveillance COL	Number of cases of clinical CRC	Number of deaths due to CRC	Number of cases of CRC avoided	CRC deaths avoided	% reduction in CRC incidence	% reduction in CRC mortality
FOBT Age 60-67 (biennial)	416.10	0.22	3542.81	1909.94	141.56	251.11	3.5%	11.6%
FOBT Age 60-71 (biennial)	649.06	0.32	3279.62	1800.21	171.69	360.84	4.2%	16.7%
FOBT Age 60-73 (biennial)	765.18	0.36	3161.09	1753.28	174.07	407.77	4.2%	18.9%
No screening	0.00	0.00	4,100.70	2,161.05				

A1.3 Marginal cost effectiveness for extension screening strategies versus no screening

Table A2 shows the marginal cost-effectiveness of the three extension options versus a policy of no screening. As with the core screening options, whilst the marginal health benefits offered by the extension FOBT options are small (3.95 to 5.51 unadjusted days of life), so too are the marginal costs of offering screening (£20.47 to £32.72).

Table A2 Marginal cost effectiveness for extension screening strategies versus no screening

Strategy	Marginal cost	Marginal life years saved	Marginal QALYs saved	Cost per life year saved	Cost per QALY saved
FOBT Age 60-67 (biennial)	£ 20.47	0.011	0.009	£ 1,892.18	£ 2,278.19
FOBT Age 60-71 (biennial)	£ 28.85	0.014	0.011	£ 2,062.35	£ 2,519.46
FOBT Age 60-73 (biennial)	£ 32.72	0.015	0.012	£ 2,169.26	£ 2,669.56

A1.4 Lifetime endoscopy resource use for extension screening options

Table A3 presents the endoscopy resource use implications over the lifetime of 100,000 individuals offered screening. A comparison of these estimates with those reported in Table 35 suggests that each additional screening round is likely to result in roughly 1,300 additional individuals who test positive with FOBT and subsequently attend follow-up colonoscopy.

Table A3 Lifetime endoscopy resource use for extension screening strategies under base case assumptions

Strategy	Number of flexible sigmoidoscopies undertaken	Number of colonoscopies undertaken	Number of polypectomies
FOBT Age 60-67 (biennial)	-	5,927.25	2,207.60
FOBT Age 60-71 (biennial)	-	8,688.41	3,271.79
FOBT Age 60-73 (biennial)	-	9,948.55	3,762.64

A1.5 Lifetime complications for extension screening strategies

Table A4 shows the expected number of bleeds, perforations and deaths due to perforation over the lifetime of 100,000 individuals invited to participate in colorectal cancer screening. Whilst the model estimates that screening will result in between 26 and 44 bleeding episodes following endoscopy, the number of perforations and deaths due to perforation is low.

Table A4 Lifetime complications for extension screening strategies

Strategy	Number of bleeds	Number of perforations	Number of deaths due to perforation
FOBT Age 60-67 (biennial)	26.01	6.39	0.37
FOBT Age 60-71 (biennial)	38.13	9.40	0.55
FOBT Age 60-73 (biennial)	43.66	10.78	0.63

A1.6 Adenomas detected at screening/follow-up for extension screening strategies

Table A5 shows the predicted number of adenomas detected through screening for the three extension screening options.

Table A5 Adenomas detected at screening/follow-up for extension screening strategies

Strategy	Adenomas detected at screening/follow-up		Adenomas detected during surveillance colonoscopy	
	Low-risk adenomas	High-risk adenomas	Low-risk adenomas	High-risk adenomas
FOBT Age 60-67 (biennial)	1,589.62	462.62	147.56	7.80
FOBT Age 60-71 (biennial)	2,325.46	719.23	215.74	11.35
FOBT Age 60-73 (biennial)	2,659.69	844.96	245.11	12.87

A1.7 Cancers detected by stage and means of detection for extension screening strategies

Table A6 shows the number of cancers detected by stage and detection for the three extension screening options. The table suggests that offering additional screening rounds beyond the age of 69 is likely to result in a greater number of cancers detected across each stage.

Table A6 Cancers diagnosed by stage and means of detection for extension screening options

Strategy	Cancers detected at screen				Cancers detected during follow-up colonoscopy				Cancers presenting symptomatically			
	Dukes' A	Dukes' B	Dukes' C	Stage D	Dukes' A	Dukes' B	Dukes' C	Stage D	Dukes' A	Dukes' B	Dukes' C	Stage D
FOBT Age 60-67 (biennial)	187.06	134.76	67.29	26.99	0.17	0.04	0.01	0.00	247.69	1,095.57	1,013.65	1,185.90
FOBT Age 60-71 (biennial)	292.75	210.61	104.26	41.44	0.25	0.06	0.01	0.00	237.64	1,029.08	935.21	1,077.69
FOBT Age 60-73 (biennial)	345.03	248.49	122.89	48.77	0.28	0.07	0.01	0.00	233.19	999.12	899.75	1,029.02

A1.8 Impact of uncertainty on key health outcomes and cost-effectiveness estimates for extension FOBT screening options

Tables A7 and A8 demonstrate the impact of introducing uncertainty concerning the natural history parameters and test characteristics on health outcomes and cost-effectiveness.

Table A7 Uncertainty analysis results: key health outcome ranges for extension screening options

Strategy	Number of screen-detected cancers	Number of CRC cases detected at surveillance colonoscopy	Number of cases of clinical CRC	Number of deaths due to CRC	Number of cases of CRC avoided	CRC deaths avoided	% reduction in CRC incidence	% reduction in CRC mortality
FOBT Age 60-67 (biennial)	295-685	0-1	3381-4507	1427-2685	-58-375	107-462	-1% - 8%	5% - 18%
FOBT Age 60-71 (biennial)	454-1073	0-1	3020-4305	1334-2609	-121-494	158-642	-3% - 10%	7% - 25%
FOBT Age 60-73 (biennial)	530-1269	0-1	2855-4208	1296-2577	-164-537	180-720	-4% - 11%	8% - 28%
No screening	0-0	0-0	4101-4955	1650-2912				

Table A8 Uncertainty analysis results: cost-effectiveness ranges for core screening options

Strategy	Marginal cost	Marginal life years saved	Marginal QALYs saved	Cost per life year saved	Cost per QALY saved
FOBT Age 60-67 (biennial)	£-0.66-£27.18	0.005 - 0.019	0.004 - 0.015	£-52 - £4,518	£-48 - £5,997
FOBT Age 60-71 (biennial)	£1.59-£37.56	0.006 - 0.023	0.005 - 0.019	£100 – £4,586	£93 – £6,276
FOBT Age 60-73 (biennial)	£3.51-£42.13	0.007 - 0.025	0.006 - 0.02	£208 - £4,681	£194 - £6,472