Colonoscopic surveillance for prevention of colorectal cancer in patients with ulcerative colitis, Crohn's disease or adenomas

APPENDICES
Part 2

Appendix 7 – Health economic evaluation – inflammatory bowel disease

Appendix 8 – Health economic evaluation – adenomas

Appendix 7 – Health economic evaluation

Cost-effectiveness analysis for inflammatory bowel disease

1 Introduction

The Department of Health asked NICE to produce a short clinical guideline on colonoscopic surveillance for the prevention of colorectal cancer in patients with ulcerative colitis, Crohn's disease and polyps.

A cost-effectiveness analysis has been carried out to support the Guideline Development Group (GDG) in making recommendations for adults with inflammatory bowel disease considered to be at high risk of developing colorectal cancer. This analysis has been conducted according to the methods outlined in the NICE Guide to the methods of technology appraisal 2008 and the Guidelines Manual 2009. The methods used follow the NICE reference case, which is the framework NICE request all cost-effectiveness analyses to follow.

Given the quality of the data available this analysis should be considered an exploration of the cost effectiveness of colonoscopic surveillance for inflammatory bowel disease.

2 Acknowledgements

On behalf of the GDG and the NICE technical team, we would like to acknowledge and thank Paul Tappenden and Hazel Pilgrim for their support in the development of this guideline by providing the uplifted cost data for stage-specific colorectal cancer.

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4 Decision problem

Table 1 outlines the decision problem that is addressed in this guideline and is based on the final scope.

Table 1 Decision problem

	Scope	**Approach taken**
Population	People with inflammatory bowel disease (IBD: ulcerative colitis or Crohn's disease)	People considered to be at high risk of colorectal cancer with flat dysplastic lesions (low grade or high grade), age 30 to 85 years
Interventions	Colonoscopic surveillance using colonoscopy, chromoscopy, computerised tomography colonoscopy, narrow band imaging, double-barium contrast enema	Colonoscopic surveillance using colonoscopy
Comparators	No colonoscopic surveillance	No colonoscopic surveillance
Outcome(s)	Costs, quality-adjusted life years (QALYs) and cost per QALY gained	Cost per QALY gained

4.1 Population

Ulcerative colitis and Crohn’s disease are collectively termed inflammatory bowel disease (IBD). People with these conditions share the same risk of developing colorectal cancer given a similar extent and duration of disease. For the economic evaluation both conditions have therefore been grouped together.

Based on the data available at the time of guideline development, a model was developed assuming that surveillance intervals would depend on the degree of dysplasia (because dysplasia is a precancerous marker for colorectal cancer). The model simulated men and women aged 30–85 years with flat dysplastic lesions (that is, non-resectable low- or high-grade dysplasia) who had declined surgery. However, at the final meeting of the GDG, it was decided that the surveillance intervals should depend on a person’s risk of developing colorectal cancer and the IBD surveillance schedule was stratified accordingly. The GDG identified three groups for surveillance: people at low risk, intermediate risk and high risk of developing colorectal cancer

Because of the tight timelines between the final GDG meeting and consultation, the cost effectiveness of surveillance based on the dysplasia model was determined only for the high-risk group. People at high risk (as defined by the GDG), include people with a previous history of primary sclerosing cholangitis, ongoing moderate or severe active inflammation, dysplasia or colonic strictures, or a family history of colorectal cancer in a first-degree relative aged under 50 years. For more details please see the main guideline.

The choice of 30 years as the starting age in the model was based on the British Society of Gastroenterology (BSG) guidelines for IBD (British Society of Gastroenterology 2004), which reported that both ulcerative colitis and Crohn's disease affect young people and have a peak incidence between the ages of 10 and 40 years in the UK. The GDG members agreed with this.

4.2 Interventions

To demonstrate that surveillance is beneficial for people with IBD, a reduction in mortality caused by colorectal cancer in people with IBD having surveillance would have to be shown in clinical studies. Because colonoscopic surveillance was found to reduce mortality from colorectal cancer for people with IBD, the intervention used in the model was colonoscopy. It was assumed that surveillance colonoscopy should be performed when colonic disease is in remission (as recommended in the updated BSG 2010 guidelines for IBD).

4.3 Comparators

Surveillance is not consistently offered across the NHS. Therefore 'no surveillance' was considered as the comparator for surveillance. The GDG pointed out that some people are offered surgery (colectomy) depending on their degree of dysplasia. Although managing dysplasia with surgery was not considered in this model because no evidence was reviewed, surgery upon, colorectal cancer detection has been factored into the mean lifetime cost of colorectal cancer treatment (section 8.1.1.2). For simplicity, it was assumed that all people who enter the model have confirmed dysplasia (either low or high grade) at baseline colonoscopy and have declined surgery. The surveillance schedule proposed by the GDG is consistent with the BSG 2010 guidelines:

- Low risk – surveillance every 5 years
- Intermediate risk – surveillance every 3 years
- High risk – surveillance every year.

4.4 Outcomes

In line with the NICE reference case a cost–utility analysis was used to analyse the cost effectiveness of colonoscopic surveillance for people with non-resectable dysplastic lesions who are considered to be at high risk of developing colorectal cancer and require surveillance every year. This required the calculation of resource use and quality-adjusted life years (QALYs) to assess effectiveness.

5 Review of existing cost-effectiveness analyses

5.1 Search for cost-effectiveness analyses

A search for cost-effectiveness studies did not identify any relevant papers that examined colonoscopic surveillance for the prevention of colorectal cancer in people with IBD. However, during the search, three studies were identified (Nguyen et al. 2009; Provenzale et al. 1995; Delco et al. 2000) that examined colorectal cancer surveillance using colonoscopy for people with ulcerative colitis. Two of the studies (Nguyen et al. and Provenzale et al.) compared surveillance with surgery. All three studies explored approaches to modelling strategies such as decision tree versus Markov models, and when applicable, informed the model structure. Given the absence of any appropriate analysis that addressed the decision problem directly, a new cost-effectiveness model was developed based on the views of the GDG and clinical data available at the time of guideline development.

5.2 Modelling approach

IBD is a chronic condition; a Markov model appeared to be most appropriate to answer the decision problem.

The Markov model split the single state of dysplasia into two mutually exclusive states of low-grade and high-grade dysplasia. Similarly, the single colorectal cancer state was broken down into four mutually exclusive states of Dukes' A, Dukes' B, Dukes' C and Dukes' D colorectal cancer.

The model started at age 30. It was assumed that the person had symptoms of colitis for at least 10 years (that is, symptoms began on average at age 20), had a screening colonoscopy that identified dysplasia, and subsequently entered a surveillance programme. A cycle length of 3 months seemed most appropriate, because surveillance for the high-risk group occurs every year and this cycle length was long enough to allow the possible development of asymptomatic and symptomatic cancer between colonoscopies.

The analysis was run over a 55-year time horizon, until age 85, and examined the use of colonoscopy for surveillance compared with no surveillance for people at high risk of developing colorectal cancer (section 4.1).

5.3 Natural history review

A major component of the IBD model is the natural history of dysplasia, because dysplasia is used as a precancerous marker of colorectal cancer risk. Because of the lack of resources and time, a full systematic review of the data on the natural history of dysplasia to calculate transition probabilities was not possible. Therefore, a clinical study that reported the 30-year follow-up of a UK colonoscopic surveillance programme for neoplasia in ulcerative colitis (Rutter et al. 2006) was used to calculate the progression of low- and high-grade dysplasia to colorectal cancer using a Bayesian dirichlet method. The Bayesian approach was needed to calculate unobserved transitions. Further details are provided in the transition probability section (section 6.2).

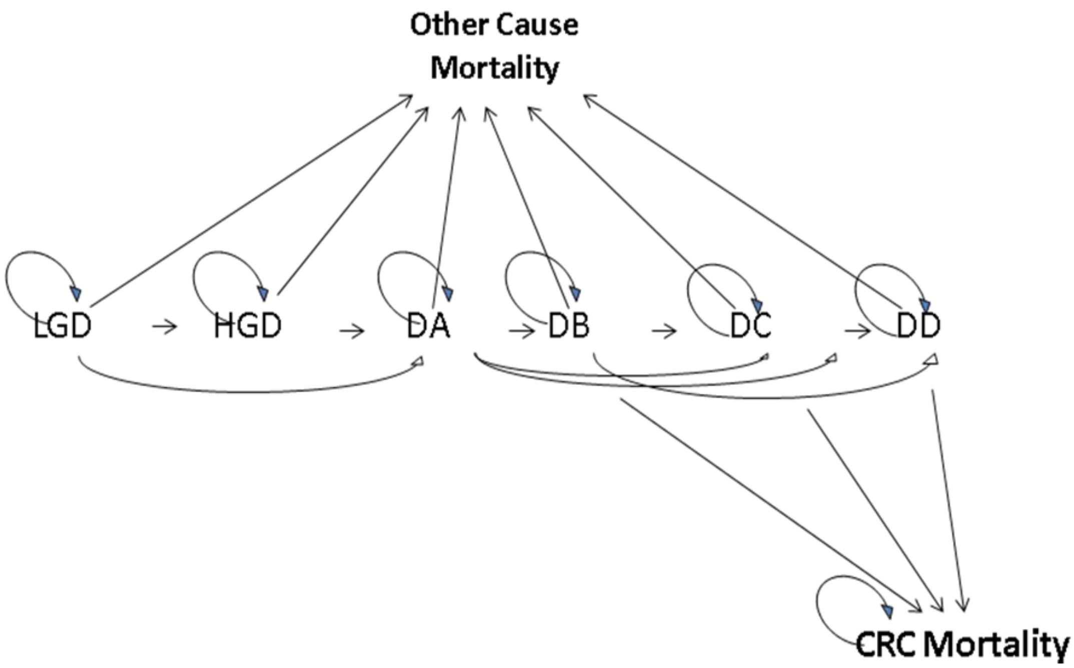
Data on the natural history of colorectal cancer were also obtained from a published cost-effectiveness study by Tappenden et al. (2004) that systematically reviewed cost-effectiveness studies for colorectal cancer screening in the UK. Colorectal cancer transition probabilities (that is, progression to symptomatic and/or asymptomatic colorectal cancer and cancer-related mortality) were obtained from this study and followed the Bayesian approach.

6 Model

6.1 Model structure

Figure 1 shows the basic outline of the surveillance model for the high-risk group.

Figure 1 Colonoscopic surveillance model for people with IBD in the high-risk group



LGD: low-grade dysplasia; HGD: high-grade dysplasia; DA: Dukes' A; DB: Dukes' B; DC: Dukes' C; DD: Dukes' D; CRC: colorectal cancer

6.1.1 Surveillance and natural history

Colonoscopic surveillance is recommended every year in the high-risk group (every fourth cycle in the model) and it was assumed that colonoscopy was carried out at the beginning of the scheduled cycle. In the model, the development of colorectal cancer could be sequential, that is, progress from low-grade to high-grade dysplasia to cancer; or from low-grade dysplasia directly to colorectal cancer because some people do not progress through a detectable phase of high-grade dysplasia. People with high-grade dysplasia could also progress directly to colorectal cancer and were assumed not to regress to low-grade dysplasia. Progression to colorectal cancer could occur either asymptomatically or symptomatically between the scheduled surveillance colonoscopies. Over time, if people had no evidence of progression they would remain in the same state. Any other cause of mortality was also considered in all states in the model.

6.1.2 Colorectal cancer

Cancer states were stratified by tumour stage at diagnosis using Dukes' staging. If a person developed Dukes' A colorectal cancer, they could either continue to progress to a higher Dukes' stage or stay in the same state. According to the literature, colorectal cancer mortality occurs only at Dukes' stages B, C and D, so it was applied only to each of these states in the model. After cancer was diagnosed, the person was assumed to enter a cancer management programme; that is, the person receives chemotherapy, surgery and/or radiotherapy. All the cancer states were allocated both costs and utility values.

6.1.3 Complications

The model assumed there were no complications from colonoscopy during the 55 years of surveillance. Although perforation and bleeding are serious risks of colonoscopy, they occur infrequently and were assumed to be negligible.

Likewise, the cost-effectiveness study by Nguyen et al. (2009) that included colectomy as a comparator to enhanced surveillance assumed that acute complications from colonoscopy and colectomy were negligible.

6.1.4 Compliance

It was assumed that everyone participating in the surveillance programme adhered to the colonoscopic surveillance protocol. This seemed reasonable, because people are more likely to adhere to a programme when they are informed that they have a high risk of developing colorectal cancer. The study by Rutter et al. (2006) reported a long-term compliance rate for surveillance of 94.3%.

6.2 Transition probabilities

Two sets of transition probabilities were included in the model, for the natural history of dysplasia and for colorectal cancer.

The probabilities derived from the observational study by Rutter et al. (2006) were chosen because the study followed a UK population for 30 years of colonoscopic surveillance. The study reported the first and maximal neoplasia as required by the cost-effectiveness model. The cancer outcomes were also reported as Dukes' staging and the study was included in the clinical-effectiveness data for this guideline. Therefore, it was considered appropriate to use this study as the basis to calculate transition probabilities for the natural history of dysplasia. It was assumed that having a colonoscopy does not alter the risk of colorectal cancer because for people with non-resectable dysplastic lesions, colonoscopy would be used as a diagnostic tool rather than as an interventional procedure.

The transition probabilities for the natural history of colorectal cancer were taken from Tappenden et al. (2004) and were used in conjunction with the transition probabilities for neoplasia calculated by Rutter et al. (2006) using a Bayesian dirichlet method. This method permits the probabilities to be calculated for unobserved transitions.

Age-related mortality rates were assumed for low- and high-grade dysplasia and the asymptomatic cancer states. It seemed reasonable to assume that people in the asymptomatic cancer states have the same probability of dying as people in the general population at the same age because they are unlikely to have an increased risk of death until their cancer progresses. Annual colorectal cancer-related mortality was taken from Tappenden et al. (2004) and was used for all symptomatic cancer states. Age-related mortality was applied in addition to colorectal cancer mortality for all symptomatic cancer states.

Data from published interim life tables for the UK (Office of National Statistics, 2009) were used to produce age-related mortality probabilities. Because these probabilities vary with time they were subtracted from the probabilities of staying in the same health state. This ensured that all probabilities summed to one.

To convert the 30-year observational data from Rutter et al. (2006) into a yearly cycle length, the following formula was used where p is the yearly probability (Briggs et al. 2003):

$$yearly\ probability = 1 - e^{((\ln 1-P)*(1/30))}$$

The transition matrix for natural history is presented in table 2.

Table 2 Natural history transition matrix (yearly)

	LGD	**HGD**	**DA**	**DB**	**DC**	**DD**	**mCRC**	**mOther**
LGD	#	0.0095	0.0050	0.0000	0.0000	0.0000	0.0000	Age
HGD	0.0000	#	0.0037	0.0000	0.0000	0.0000	0.0000	Age
DA	0.0000	0.0000	#	0.5830	0.0228	0.0029	0.0000	Age
DB	0.0000	0.0000	0.0000	#	0.6560	0.0000	0.0100	Age
DC	0.0000	0.0000	0.0000	0.0000	#	0.8650	0.0600	Age
DD	0.0000	0.0000	0.0000	0.0000	0.0000	#	0.3870	Age

1 minus other states; LGD: low-grade dysplasia; HGD: high-grade dysplasia; DA: Dukes' A; DB: Dukes' B; DC: Dukes' C; DD: Dukes' D; mCRC: colorectal cancer mortality; mOther: other cause mortality

The grey shaded areas represent annual transitions, available from Tappenden et al. (2004)

The method used to calculate unobserved events is also the preferred method of incorporating uncertainty into a Markov model with several states, using the dirichlet distribution in a Bayesian framework.

The dirichlet distribution is a multinomial equivalent of the beta distribution (a probability distribution that is bounded by 0 and 1). This allows distributions to be placed on a parameter while maintaining the axiom of probabilities (summing to one).

The Bayesian approach allows calculation of a probability based on understanding the probability distribution of an event and on any prior information. These two parts are called the posterior and the prior.

In this case prior beliefs can be included for transitions for which there are no observed data but which can occur. Therefore, for transitions where a transition probability was needed, uninformative priors were used, which allowed these transitions to be calculated. For more details on the method please see Briggs et al. (2003).

The chosen priors are presented in table 3.

Table 3 Priors for the natural history transition matrix

	LGD	**HGD**	**DA**	**DB**	**DC**	**DD**	**mCRC**	**mOther**
LGD	0.12	0.12	0.12	0	0	0	0	Age
HGD	0	0.12	0.12	0	0	0	0	Age
DA	0	0	0.12	0.12	0.12	0.12	0	Age
DB	0	0	0	0.12	0.12	0.12	0.12	Age
DC	0	0	0	0	0.12	0.12	0.12	Age
DD	0	0	0	0	0	0.12	0.12	Age

LGD: low-grade dysplasia; HGD: high-grade dysplasia; DA: Dukes' A; DB: Dukes' B; DC: Dukes' C; DD: Dukes' D; mCRC: colorectal cancer mortality; mOther: other cause mortality

A value of 0.12 was chosen for the uninformative priors because of a calculating error in Excel (the small numbers involved resulted in num! errors) which meant smaller priors were not possible. This was resolved by increasing the size of the observed data by multiplying them by 1000 to maintain the relative difference between the priors and the observed data. All the transitions that were expected to occur within the model were given the same prior value (0.12) so that each data set (Rutter et al. 2006 and Tappenden et al 2004) contributed equally to the model.

Calculating the probabilities from Rutter et al. (2006) and the dirichlet framework, the following transition matrices for natural history (table 4) were used. These represent the 3-monthly (or quarter of a year) transitions used in the model.

Table 4 Final natural history transition matrix (every 3 months)

	LGD	HGD	DA	DB	DC	DD	mCRC	mOther
LGD	0.99466	0.00354	0.00180	0.00000	0.00000	0.00000	0.00000	Age
HGD	0.00000	0.99759	0.00241	0.00000	0.00000	0.00000	0.00000	Age
DA	0.00000	0.00000	0.85793	0.13559	0.00572	0.00075	0.00000	Age
DB	0.00000	0.00000	0.00000	0.84623	0.15122	0.00003	0.00253	Age
DC	0.00000	0.00000	0.00000	0.00000	0.79066	0.19443	0.01491	Age
DD	0.00000	0.00000	0.00000	0.00000	0.00000	0.90778	0.09222	Age

LGD: low-grade dysplasia; HGD: high-grade dysplasia; DA: Dukes' A; DB: Dukes' B; DC: Dukes' C; DD: Dukes' D; mCRC: colorectal cancer mortality; mOther: other cause mortality

7 Quality of life

NICE recommends that changes in HRQoL as a result of an intervention or treatment should be directly reported by patients. These changes should be based on preferences determined using a choice-based method in a representative sample of the UK general public. Ideally a full systematic review would be carried out to identify health-related quality of life (HRQoL) studies and appropriate values to include in a health economic model. However, because of the lack of resources and time a search was carried out for quality of life studies. The cost-effectiveness studies that were used to explore approaches to modelling strategies were also searched for QALY data.

7.1 Literature search

The search identified one paper, a study by Gregor et al. (1997) that examined quality of life in patients with Crohn's disease. The study reported utility values by disease severity calculated using the time-trade-off method. Several studies reported values obtained from a disease-specific questionnaire (the Inflammatory Bowel Disease Questionnaire). However, these values could not be used for calculating QALYs because they did not report the values on a 0–1 scale, which is the format for generic questionnaires.

7.2 People's health states

NICE recommends the use of the EuroQol 5 dimensions (EQ-5D) or another generic tool that enables patients to describe their health state and how the public values their health state. Although Gregor et al. (1997) reported utility values using a generic tool; the study was not in complete accordance with NICE methods. The values obtained in the study were collected from people with Crohn's disease who were asked to value health states that described their disease severity, specifically mild, moderate and severe Crohn's disease.

7.3 Low- and high-grade dysplasia

The GDG agreed that the values obtained from Gregor et al. (1997) could be used to represent the utility values for people with low- and high-grade dysplasia. The utility value for mild Crohn's disease was used as a proxy for low-grade dysplasia and the utility value for moderate Crohn's disease was used as a proxy for high-grade dysplasia. This approach seemed acceptable because the patient experts on the GDG felt that a person with low-grade dysplasia has a lower quality of life than a person in the general population and a person with high-grade dysplasia has a lower quality of life than a person with low-grade dysplasia.

7.4 Cancer

Stage-specific utility values for symptomatic colorectal cancer were obtained from Ness et al. (1999) and were applied to each symptomatic Dukes' state. Asymptomatic cancers were assigned the same utility value as their diagnostic state because if cancer is asymptomatic it is unlikely to affect the quality of life of the person until it is detected (that is, until it becomes symptomatic).

7.5 Age-related quality of life

For all the health states in the model the specific health state utility values were multiplied by the age-related utility values. Age-related utility values for the UK population were available from Kinder et al. (1999). This approach was taken because it was assumed that as a person ages their quality of life steadily decreases and if the same person has a condition that affects their life, this multiplies the effect.

7.6 Final quality of life values

Table 5 Final health-related quality of life estimates

Health state	Mean value	Standard error	Reference
All health states	Age dependent	N/A	Kinder et al. (1999)
LGD (mild Crohn's disease)	0.95	0.008014	Gregor et al. (1997)
HGD (moderate Crohn's disease)	0.88	0.014416	Gregor et al. (1997)
Dukes' A	0.74	0.031276	Ness et al. (1999)
Dukes' B	0.7	0.051192	Ness et al. (1999)
Dukes' C	0.5	0.061521	Ness et al. (1999)
Dukes' D	0.25	0.206870	Ness et al. (1999)
LGD: low-grade dysplasia; HGD: high-grade dysplasia			

Uncertainty about utility values that were not time dependent was captured using a lognormal distribution.

8 Resource use

8.1 Literature search

The initial search identified three studies (Hanauer et al. 1998; Stark et al. 2006; Bodger et al. 2002) that examined resource use for people with IBD. The study by Hanauer et al. was excluded because it reported the cost of Crohn's disease from a US perspective. The study by Stark et al. was excluded because it reported the cost of IBD from a German perspective. Bodger et al. was the only UK study looking at the cost of Crohn's disease in one hospital. However, the study did not include a breakdown of the costs, which were reported in US dollars, as required by the model.

Only one study provided information on the lifetime costs of colorectal cancer in the UK by Dukes' staging (Tappenden et al. 2004).

8.1.1 Specific costs for the model

The main cost inputs that required consideration included:

- colonoscopy (procedure and biopsy specimens)
- cancer (diagnosis, treatment and follow-up).

8.1.1.1 Colonoscopy

The cost of colonoscopy was obtained from a GDG member and was validated using NHS reference costs 2008/09.

8.1.1.2 Cancer

The estimated mean lifetime costs associated with the diagnosis, treatment (chemotherapy, radiotherapy, surgery) and follow-up of colorectal cancer were reported in the study by Tappenden et al. (2004). The 2004 costs were updated to 2010 costs by the lead author of the study and are listed in table 6. These were only applied to people transitioning into the colorectal cancer health state.

8.1.1.3 Distributions of estimates

Briggs et al. (2003) recommends that the gamma distribution is the most appropriate probability distribution for costs. To fit a gamma distribution the standard error is required for each value. Costs taken from NHS reference costs 2008/09 and published papers, which have a stated standard error, were used in the model. For the cancer pathology costs, standard errors were calculated because only the mean values were available.

Table 6 Mean costs and standard errors used in the probabilistic sensitivity analysis

Parameter	Mean cost (£)	Standard error (£)
Symptomatic Dukes' A	11,965.78	6,490.90
Symptomatic Dukes' B	16,224.50	3811.55
Symptomatic Dukes' C	21,033.60	2368.03
Symptomatic Dukes' D	24,096.80	3050.62
Cancer pathology	250.00	277.98
Histology/histopathology	25.72	21.10
Colonoscopy	516.78	178.92

9 Assumptions

9.1 Cycle length

A cycle length of 3 months was assumed to be the most appropriate, because surveillance for the high-risk group occurs every year and a 3-month cycle allowed possible development of asymptomatic and symptomatic cancer between colonoscopies.

9.2 Histopathology

The GDG recommended a median of eight biopsy specimens per colonoscopy, with a lower limit of five and an upper limit of ten. Uncertainty was captured using a simple uniform distribution with the minimum and maximum because no information on the distribution was available.

9.3 Age dependency

The age-dependent variables used in the model were other cause mortality and age-related utilities. All other variables were independent of time. Other cause mortality was age dependent because it was assumed that people with IBD have the same mortality as the rest of the UK population.

9.4 Misdiagnosis

It was assumed that no misdiagnoses were made during colonoscopy. This follows the assumption that there may have been some degree of misdiagnosis in the study by Rutter et al. (2006). Therefore, to include it would double count the number of misdiagnoses.

9.5 Complications

It was assumed that people on surveillance have no complications caused by colonoscopy, such as perforations or bleeding.

9.6 Compliance

It was assumed that everyone participating in the surveillance programme adhered to the colonoscopic surveillance protocol.

9.7 Diagnosis and treatment of cancer

It was assumed that cancer is detected once it becomes symptomatic and asymptomatic cancer is only detected by surveillance colonoscopy.

Cancer costs and benefits have been separated, with costs applied only when a person enters the colorectal cancer health state and benefits applied for each time period in that state. This was assumed in the cost-effectiveness study by Tappenden et al. (2004) and was a limitation of that study. This limitation could potentially lead to conflicting conclusions about the effect of colorectal cancer. However, because modelling the entire colorectal cancer pathway is not possible in this guideline, this was considered an acceptable simplification.

10 Results

The overall deterministic results are presented in table 7. Uncertainty about the results follows in section 11.1.

Table 7 Deterministic analysis over a 55-year period

	QALYs	Cost (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
No surveillance	16.42	2320.44			
Surveillance – high-risk group only	17.19	15,785.13	0.77	13,464.69	17,557.32
QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio					

The analysis suggested that surveillance for the high-risk group is cost effective.

11 Sensitivity analysis

Two approaches to testing the robustness of the model results were taken: a series of one-way deterministic sensitivity analyses and a probabilistic sensitivity analysis.

11.1 Deterministic sensitivity analyses

A one-way sensitivity analysis describes the process of changing one parameter in the model and analysing the results of the model to see if this parameter influences any of the overall results.

Sources of uncertainty were the number of biopsy specimens per colonoscopy, the utility values and the costs. These were investigated using a one-way sensitivity analysis. For each of the variables either the lower or the upper point estimate was used, keeping all other variables constant. The resulting incremental cost-effectiveness ratios (ICERs) are reported for each variable in table 8.

Table 8 Varying the point estimate showing different ICERs

Parameter	Base case	Range values		Distribution	Deterministic ICER (£)	
		Lower	**Upper**		**Lower**	**Upper**
Biopsy specimen per colonoscopy	8	5	10	Uniform	15,654.07	18,826.15
Utility values						
LGD	0.95	0.94	0.97	Gamma	17,511.19	17,650.29
HGD	0.88	0.86	0.91	Gamma	17,452.29	17,717.24
Dukes’ A	0.74	0.69	0.78	Gamma	19,911.93	16,039.92
Dukes’ B	0.7	0.63	0.77	Gamma	17,299.27	17,823.18
Dukes’ C	0.5	0.44	0.56	Gamma	17,392.96	17,724.80
Dukes’ D	0.25	0.16	0.36	Gamma	17,511.85	17,613.21
Cost parameters						
Histopathology	£25.72	£7.33	£35.80	Beta	13,928.47	19,546.67
Colonoscopy	£516.78	£392.91	£634.27	Beta	14,501.94	20,455.62
Dukes’ A	£11,965.78	£10,387.24	£19,143.46	Beta	17,303.59	18,711.88
Dukes’ B	£16,224.50	£14,009.49	£19,151.27	Beta	17,609.59	17,488.60
Dukes’ C	£21,033.60	£19,445.98	£22,640.46	Beta	17,640.86	17,473.07
Dukes’ D	£24,096.80	£22,032.30	£26,147.59	Beta	17,617.74	17,497.60
ICER: incremental cost-effectiveness ratio; LGD: low-grade dysplasia; HDG: high-grade dysplasia						

The results from table 8 suggest that the variables with the greatest impact on the ICER are the number of biopsy specimens per colonoscopy, the utility value allocated to stage Dukes' A, and the costs of histopathology and colonoscopy.

11.2 Probabilistic sensitivity analysis

The major limitation of a one-way sensitivity analysis is that there is often uncertainty about many parameters at the same time. The joint impact of altering all parameters simultaneously was therefore estimated using probabilistic sensitivity analysis. The analysis was run 1000 times and for each simulation, different values were picked from the various distributions for each variable in the model.

The overall analysis is presented in table 9.

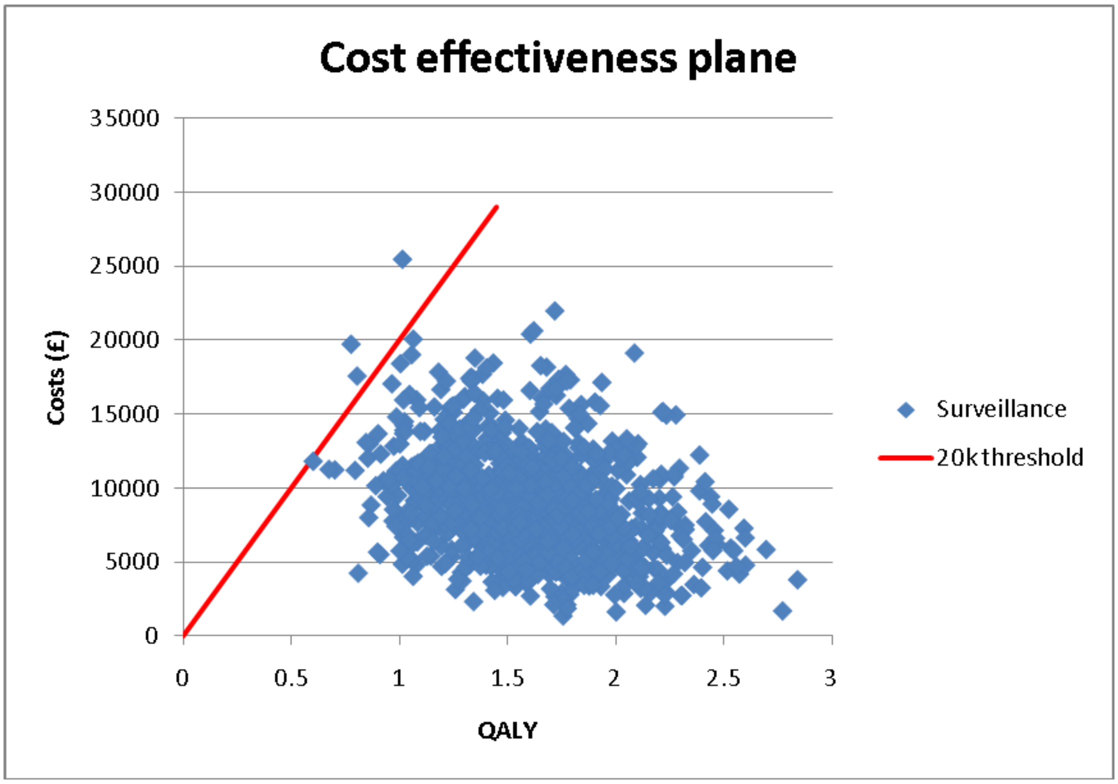
Table 9 Probabilistic sensitivity analysis over a 55-year period

	QALYs	Costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)	Probability of being cost effective at £20,000 per QALY gained
No surveillance	13.04	7368.92	–	–	–	–
Surveillance – high-risk group only	14.64	16,316.82	1.61	8947.90	5571.44	99%
QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio						

The incremental cost-effectiveness ratio (ICER) from the probabilistic sensitivity analysis was lower than the ICER from the deterministic sensitivity analysis. This suggests that there may be a high degree of uncertainty associated with some model parameters, which resulted in a large change in the ICER. However, in spite of the uncertainty the probabilistic sensitivity analysis suggests that there is a 99% probability that colonoscopic surveillance for the high-risk group (among the three risk groups) with IBD is cost effective at the usual threshold of £20,000 per QALY gained.

Figure 2 shows the results of the 1000 simulations of the probabilistic sensitivity analysis represented on the cost-effectiveness plane.

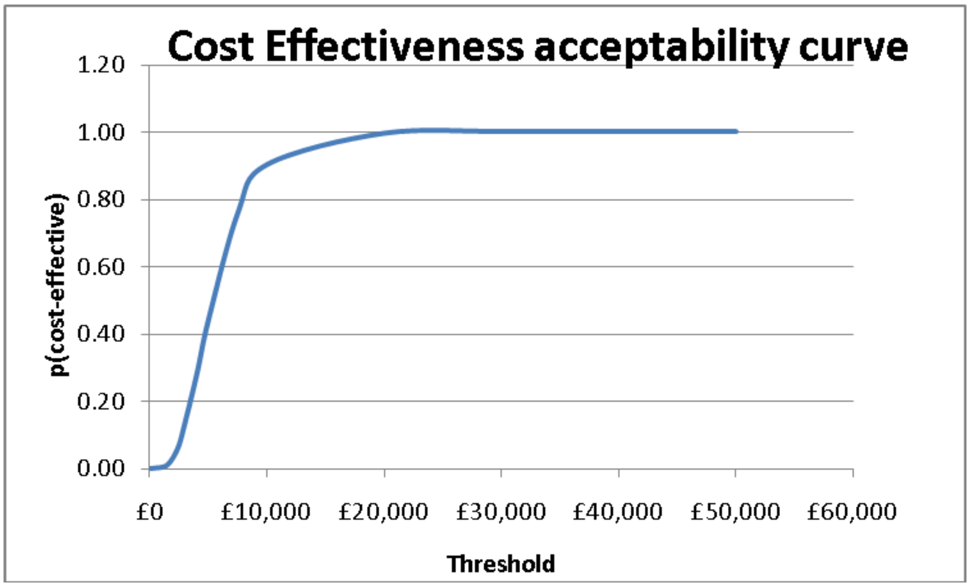
Figure 2 Cost-effectiveness plane for the high-risk group (IBD)



11.2.1 Cost-effectiveness acceptability curves

Figure 3 shows the cost-effectiveness acceptability curve for the high-risk surveillance strategy. At a threshold of £20,000 per QALY gained and higher, it shows the probability of being cost effective as nearly 100% for the high-risk group compared with a no surveillance strategy.

Figure 3 The cost-effectiveness acceptability curve for the high-risk surveillance strategy



12 Discussion

12.1 Strengths of the model

This model is similar to models used in previously published cost-effectiveness studies on ulcerative colitis. One advantage this model has over the others is that cancer has been divided into mutually exclusive states representing Dukes' staging. Therefore, it more accurately considers the different outcomes according to the stage of cancer. This allows better identification of whether annual colonoscopies detect early-stage cancer, which reduces cancer-related mortality.

A probabilistic sensitivity analysis was conducted to explore uncertainties in the data.

12.2 Limitations of the model

12.2.1 Transition probabilities

The clinical data used to derive the transition probabilities were from an observational study of low quality (Rutter et al. 2006). No randomised controlled trial data were available because of the ethical issues of denying people surveillance if they have an increased risk of cancer.

12.2.2 Management of dysplasia: high-risk group

It is recognised that people diagnosed with dysplasia may opt for surgery (such as colectomy) depending on their personal preference and their clinician's judgement. However, to simplify the model structure the cohort was made up of people that decline surgery. This may have overestimated the number of people that stay in surveillance.

12.2.3 Misdiagnosis

It was assumed that colonoscopy was associated with 100% sensitivity and 100% specificity. The GDG discussed the current sensitivity and specificity of colonoscopy to be around 95%. In addition, clinical data were mainly obtained from observational studies in which misdiagnosis was accounted for in the published literature. However, further work could incorporate the sensitivity and specificity of the chosen surveillance method where appropriate.

12.2.4 Complications

The potential complications of colonoscopy were not considered because of a lack of time and resources. The inclusion of this factor could increase the ICERs and make surveillance less cost effective.

12.2.5 Quality of life data

Uncertainty remains about the appropriate method to account for quality of life associated with dysplasia because it is asymptomatic, whereas other risk factors such as inflammation are symptomatic. The patient experts and clinical specialists in the GDG considered that the psychological burden of being diagnosed with dysplasia and the grade of dysplasia could be very high. The approach taken to address the uncertainty was to conduct both a one-way sensitivity analysis and a probabilistic sensitivity analysis, varying the utility values.

12.2.6 Treatment pathway

A large proportion of people may opt for surgery during the course of their surveillance. The number of people requiring annual surveillance based on their dysplasia may therefore have been overestimated. In either case it is likely that colonoscopic surveillance will remain cost effective.

12.2.7 Chromoscopy

Chromoscopy was recommended for use in routine surveillance for people with IBD. According to the NHS reference costs 2008/09, chromoscopy costs the same as conventional colonoscopy. The GDG felt that although the procedure may cost the same, the time needed to train healthcare professionals to use chromoscopy is longer than training them to use colonoscopy. Unfortunately, staff training time is usually already incorporated into the reference costs therefore this cost-effectiveness model was unable to compare conventional colonoscopy with chromoscopy. The GDG also stated that chromoscopy takes longer to perform than colonoscopy. However, the difference was not found to be statistically significant. Finally, for a true comparison, sensitivity and specificity would need to be incorporated to differentiate between the two types of colonoscopy.

12.2.8 Costing

Costs based on NHS reference costs may not be representative of the true costs of the procedure. However, these are published costs and they represent the average NHS costs across the country.

13 Conclusions

The analysis indicates that colonoscopic surveillance is a cost-effective programme for people considered at high risk of developing colorectal cancer among the three risk groups for IBD surveillance, with an ICER below £20,000 per QALY gained when deterministic and probabilistic analyses are considered.

14 Future work

Because of the lack of time between the final meeting of the GDG when the surveillance schedule was created and consultation for the guideline, it was not possible to construct a new cost-effectiveness model to assess surveillance for all three risk groups because transition probabilities would depend on several factors in any given risk group. There is the possibility that surveillance may not be cost effective for all three groups simultaneously. For the future it will be important to evaluate whether surveillance for all three risk groups, including those with resectable lesions, will be cost effective for people with IBD.

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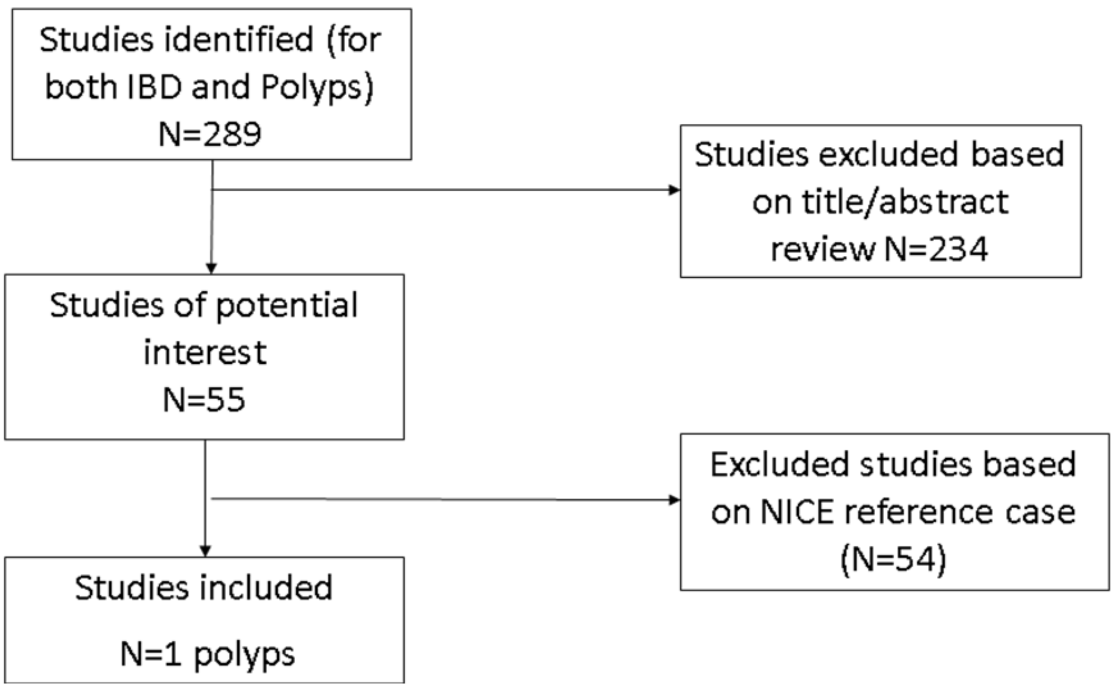
16 Appendices

16.1 Inclusion and exclusion criteria

Figure 4 Flowchart of the number of cost-effectiveness studies included and excluded



16.2 Quality checklist for de novo cost effectiveness

IBD high-risk group

Guideline topic: Colonoscopic surveillance for IBD by Y Rajput 2010		**Question no:**
Check list completed by K Jeong		
Section 1: Applicability	**Yes/ partly/ no/unclear/ NA**	**Comments**
1.1 Is the study population appropriate for the guideline?	Partly	30-year-old men and women who have had colitis symptoms for 10 years and are considered to be at high risk of developing colorectal cancer. Low- and intermediate-risk groups were not modelled.
1.2 Are the interventions appropriate for the guideline?	Partly	The main clinically effective interventions/strategies (conventional colonoscopy) were included in the scope. Chromoscopy was recommended for IBD and was not assessed in the model.
1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	
1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5 Are all direct health effects on individuals included?	Partly	QALY data from the USA using standard gamble technique used.
1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	Yes	
1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	
1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Yes	
1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	IBD QALY data were taken from a Crohn's disease study using time trade off.

		Colorectal cancer QALY data from the USA using standard gamble technique used.
1.10 Overall judgement: directly applicable/partially applicable/not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'. Partially applicable		
Other comments		
Section 2: Study limitations (the level of methodological quality) *This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline*	**Yes/ partly/ no/ unclear/ NA Comments**	**Comments**
2.1 Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	Use of a younger population than other chronic conditions
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	55 years
2.3 Are all important and relevant health outcomes included?	Yes	
2.4 Are the estimates of baseline health outcomes from the best available source?	Yes	Observational study in the UK setting
2.5 Are the estimates of relative treatment effects from the best available source?	Yes	Best quality studies identified from clinical review
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	NHS specific
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Is there no potential conflict of interest?	No	
2.12 **Overall assessment**: minor limitations/potentially serious limitations/very serious limitations Potentially serious limitation, only one subgroup in the high-risk group was evaluated. However the ICER for the high-risk group was robust (as demonstrated in the probabilistic sensitivity analysis).		
IBD: inflammatory bowel disease; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year		

Appendix 8 – Health economic evaluation

Cost-effectiveness analysis of colonoscopic surveillance: adenomas

1 Introduction

The Department of Health asked NICE to produce a short clinical guideline on colonoscopic surveillance for the prevention of colorectal cancer in patients with ulcerative colitis, Crohn's disease and polyps.

A cost-effectiveness analysis has been carried out to support the Guideline Development Group (GDG) in making recommendations for adults with adenomas considered to be at high risk of developing colorectal cancer. This analysis has been conducted according to the methods outlined in the NICE Guide to the methods of technology appraisal 2008 and the Guidelines Manual 2009. The methods used follow the NICE reference case, which is the framework NICE requests all cost-effectiveness analyses to follow. In the model, it is assumed that people at the endpoint of colonoscopic surveillance would return to the UK population norm then enter the NHS Bowel Cancer Screening Programme according to the current criteria.

Given the quality of the data available this analysis should be considered an exploration of the cost effectiveness of colonoscopic surveillance for adenomas.

2 Acknowledgements

On behalf of the GDG and NICE technical team, we would like to acknowledge and thank Paul Tappenden and Hazel Pilgrim for their support and help in the development of this guideline by providing the uplifted costing data for stage-specific colorectal cancer.

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4 Decision problem

Table 1 outlines the decision problem that is addressed in this guideline and is based on the final scope.

Table 1 Decision problem

	Scope	**Approach taken**
Population	People with polyps including adenomas in the colon and rectum	People aged 50 years who have adenomas removed in the colon and rectum at baseline colonoscopy
Interventions	Colonoscopic surveillance using colonoscopy, chromoscopy, computerised tomography colonoscopy, narrow band imaging, double-barium contrast enema	Colonoscopic surveillance using colonoscopy
Comparator	No colonoscopic surveillance	No colonoscopic surveillance
Outcome(s)	Costs, quality-adjusted life years (QALYs) and cost per QALY gained	Cost per QALY gained

4.1 Population

The estimated prevalence of colonic adenomas is 30–40% at age 60 years (Williams et al. 1982) and the lifetime cumulative incidence of colorectal cancer is 5.5% (Lieberman et al. 2000). Adenomas are diagnosed on average 10 years before colorectal cancer (Olsen et al. 1988). Therefore, the model simulated men and women aged 50 years in order to identify precancerous polyps. People entering the model had adenomas and were at high risk of developing colorectal cancer. Any detected adenomas were removed at baseline colonoscopy and during subsequent surveillance.

4.2 Interventions

From the clinical review there was no direct evidence for or against routine colonoscopic surveillance for the prevention and early detection of colorectal cancer after removal of adenomas. Currently there is no national guidance based on the clinical and cost effectiveness of surveillance in the NHS. The model assessed the cost effectiveness of current practice in the NHS, which broadly follows the British Society of Gastroenterology (BSG) guidelines – people are offered colonoscopic surveillance after removal of adenomas (Atkin and Saunders 2002).

4.3 Comparators

Colonoscopy is the gold standard for surveillance and screening for colorectal cancer in the NHS. Therefore, colonoscopic surveillance using colonoscopy is the main comparator in the surveillance model compared with no surveillance. Colonoscopic surveillance after adenoma removal is consistent with the BSG guidelines (Atkin and Saunders 2002; Cairns et al. 2010). The person's risk state is determined after the baseline colonoscopy and is based on the number and size of adenomas removed at the baseline colonoscopy. In the model, surveillance in low-, intermediate- and high-risk groups is referred to as surveillance in all risk groups. The BSG guidelines are not definitive for surveillance of people at low risk of developing colorectal cancer, therefore surveillance in the intermediate- and high-risk groups only is also considered. An outline of the surveillance strategies considered in the model is given in table 2.

Table 2 Surveillance schedule after adenoma removal in the model

Risk status	**Schedule**
Low risk :one or two adenomas smaller than 10 mm	No surveillance is recommended. However surveillance at 5 years, then no surveillance if subsequent colonoscopy results are negative can be considered and will be explored in the analysis.
Intermediate risk: three or four adenomas smaller than 10 mm **or** one or two adenomas if one is 10 mm or larger	Surveillance is offered every 3 years until there are two consecutive negative colonoscopies, then surveillance is stopped.
High risk: five or more adenomas smaller than 10 mm **or** three or more adenomas if one is 10 mm or larger	A colonoscopy is offered at or within 1 year to detect missed lesions: • if high-risk adenomas are detected, the person remains high risk • if results are negative, or low- or intermediate-risk adenomas are detected, the surveillance programme for people at intermediate risk is followed.

4.4 Outcomes

In line with the NICE reference case, a cost–utility analysis was used to assess the cost effectiveness of colonoscopic surveillance using conventional colonoscopy. Given the absence of an appropriate analysis, a Markov model was developed to fit the decision problem. This required the calculation of resource use and quality-adjusted life years (QALYs) to assess effectiveness.

5 Review of existing cost-effectiveness analyses

5.1 Search for cost-effectiveness analyses

A search for cost-effectiveness, quality of life and resource papers was carried out. These papers were then subject to a systematic search. Papers were initially excluded, for example, on the basis of the title, subject, intervention or condition. Of the remaining papers, abstracts were then searched to see if they contained relevant information. These papers were then categorised into: cost effectiveness – colonoscopic surveillance, cost effectiveness – natural history, quality of life and resource use.

5.2 Review of cost-effectiveness studies – colonoscopic surveillance

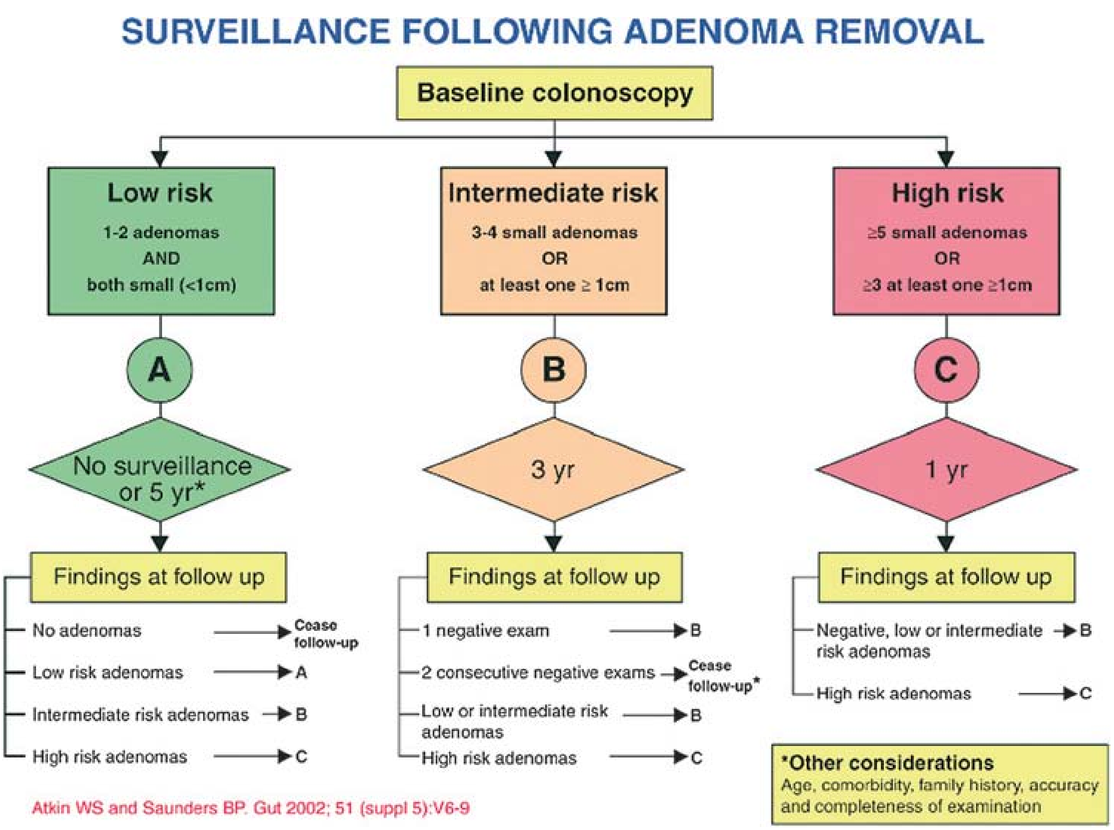
Of 289 studies identified for both polyps and inflammatory bowel disease, 234 were excluded based on the title and an abstract review. The applicability of 55 studies was assessed using a checklist. Of 55 studies of potential interest, 54 were excluded based on NICE methods and the NICE reference case using modified GRADE methods. Only one analysis was relevant to surveillance for adenomas (Tappenden et al. 2004). A modified GRADE table that summarises this analysis is presented in section 16.5.

The study by Tappenden et al. (2004) was considered of high quality and provided valuable information on the modelling approach. However, the study had limited applicability because the population and comparators were different to the decision problem and so a new Markov model was developed.

5.3 Modelling approach

Colonic polyps and recurrent adenomas are chronic conditions that require lifetime surveillance to prevent colorectal cancer (Atkin and Saunders 2002). The transformation of adenomas to invasive colorectal cancer is slow and can take 10–15 years (South West Cancer Intelligence Service 1995). Therefore, a Markov model was developed over a lifetime horizon (50 years). This was associated with risks of developing colorectal cancer over time and the importance of detecting the transformation of adenoma to cancer. The three diagnostic states in the model, low, intermediate and high risk, differ only in terms of the surveillance offered. Movement between diagnostic states is only possible through surveillance or symptomatic presentation of colorectal cancer. The health states represented the progression of the condition from adenoma free after adenoma removal, to new non-advanced adenomas after adenoma removal, to asymptomatic and symptomatic colorectal cancer (using Dukes' A, B, C and D classification; Dukes 1932) to death. The GDG acknowledged that the future risk of developing colorectal cancer or advanced adenomas after removal of adenomas depends on the number and size of adenomas removed at baseline colonoscopy, as indicated in the BSG guidelines (Atkin and Saunders 2002; Cairns et al. 2010) (see figure 1).

Figure 1 Surveillance after adenoma removal (Atkin and Saunders 2002)



For simplicity, people in the surveillance programme were assumed to adhere to the schedule, but in reality this is unlikely. For the purpose of the guideline, when comparing a surveillance programme with no surveillance, the sensitivity and specificity of colonoscopy were assumed to be 100% in adenoma detection. This was agreed with the GDG. In reality, the actual rates would be lower; however, the clinical data may take this into account in the estimates of progression. It was also assumed that each colonoscopy is complete, which increases uncertainty in the results.

5.4 Natural history

It is widely accepted that most colorectal cancers arise from pre-existing adenomas, based on epidemiological, clinical, post-mortem, and molecular biology evidence. The size of adenomas is correlated with malignant potential (Muto et al. 1975). It is unlikely for a small adenoma (≤5 mm) to progress to invasive cancer in less than 5 years (Eide 1986). Winawer et al. (1993b) reported that people with a history of adenoma removal are more likely to develop subsequent adenomas. The majority of recurrent adenomas are found to be predominantly small (≤5 mm) at follow-up (Winawer et al. 1993b).

Outcomes of clinical treatment can be determined by using the natural history of adenomas leading to colorectal cancer. The clinical results of treatment can be extrapolated to a lifetime horizon to account for the long-term benefits of treatment. Because of a lack of resources and time a full systematic review of the natural history data to calculate transition probabilities was not possible. Therefore, all cost-effectiveness studies were reviewed to estimate the progression of polyps to colorectal cancer. One analysis was found that reported the cost effectiveness and cost–utility of colorectal cancer screening options in England (Tappenden et al. 2004). Tappenden et al. obtained estimates from two sources: the National Polyp Study (Winewar et al. 1993a) and calibrating their model against 60,000 random iterations, of which around 400 potential solutions were identified that appeared to fit the published incidence and mortality data. These data on the natural history of undetected colorectal cancer, polyp incidence and growth rates, the rate at which high-risk adenomas develop into cancer, and stage-specific colorectal cancer-related mortality represented the best available source and were used in the model.

6 Model

6.1 Model structure

The structure of the colonoscopic surveillance model for people with adenomas is given in figure 2.

Figure 2 Colonoscopic surveillance model for people with adenomas

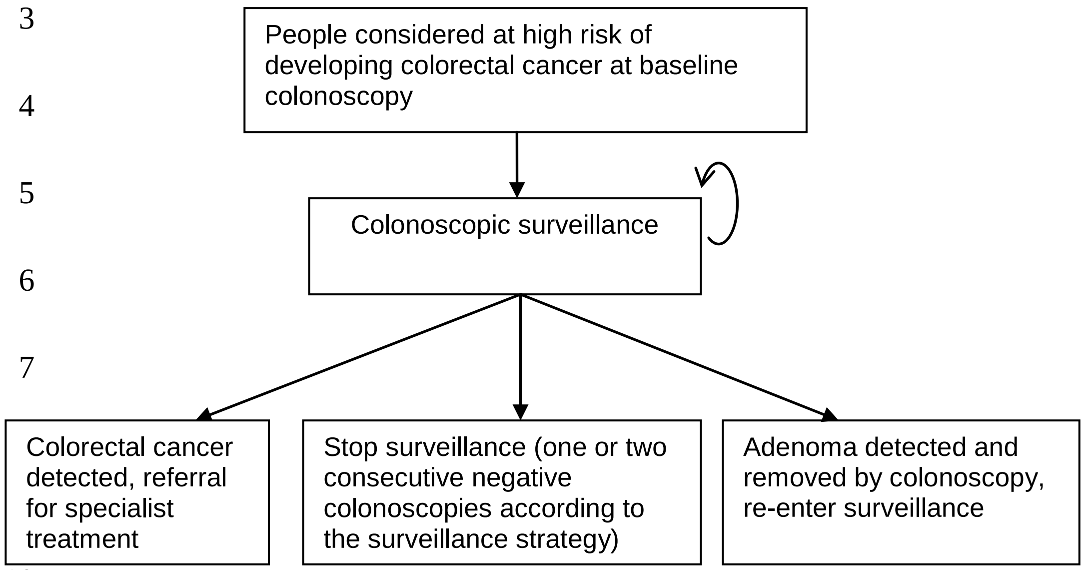
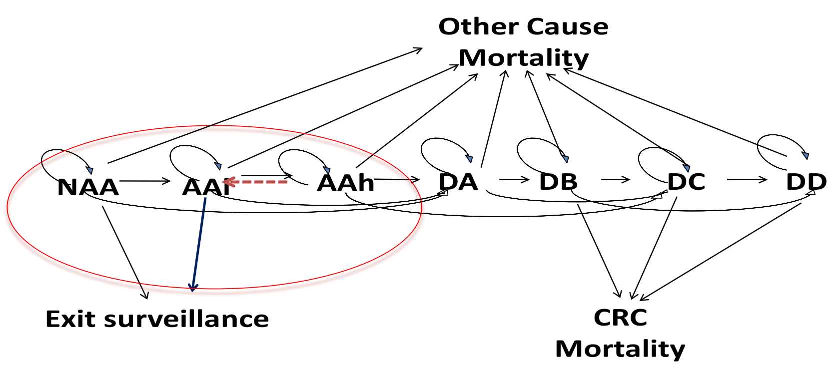


Figure 3 Outline of model



NAA: non-advanced adenoma; AAi: advanced adenoma, intermediate risk; AAh: advanced adenoma, high risk; DA: Dukes' A; DB: Dukes' B; DC: Dukes' C; DD: Dukes' D; CRC: colorectal cancer.

Limited evidence exists about the actual risk of developing advanced adenomas and colorectal cancer after removal of adenomas. Figure 3 gives an outline of the natural history model. Given the slow transformation of adenomas to colorectal cancer and the fact that most recurrent adenomas are small (≤5 mm) (Winawer et al.1993b), the risk state at baseline colonoscopy is inversely correlated with the size of the group in the initial starting cohort. For example, the higher the risk of developing colorectal cancer, the smaller the group in the initial starting cohort. The proportions chosen were based on Lieberman et al. (2008) with 64% of the cohort starting in the low-risk, 20% in the intermediate-risk and 16% in the high-risk group. This reflects the fact that small adenomas are most commonly found during colonoscopy. The main components of the model were the surveillance and natural history strategies.

6.1.1 Surveillance and natural history

The effectiveness of colonoscopic surveillance was modelled as an intervention under near-perfect conditions to determine whether colonoscopic surveillance using colonoscopy for the early detection of adenomas and colorectal cancer was clinically and cost effective compared with no surveillance. Health states included being polyp free and having recurrent adenomas to incorporate the natural history of recurring adenomas after adenoma removal. The strategies analysed were surveillance of all risk groups and surveillance of the intermediate- and high-risk groups only.

Movement between the three diagnostic states was only possible through surveillance or symptomatic presentation of colorectal cancer. According to surveillance criteria, people could drop out of surveillance and be assumed to return to UK population norms.

6.1.2 Colorectal cancer

Symptomatic and asymptomatic colorectal cancers were included in the surveillance model. It was assumed that colorectal cancer is diagnosed by symptomatic presentation or surveillance. People who stop surveillance were assumed to have the same mortality risk as the general population. The GDG agreed with this assumption. The cost of treating colorectal cancer was not varied according to the method of diagnosis, that is, by surveillance or symptoms. Costs were varied by stage of cancer – Dukes' A, B, C or D. Therefore, if cancers are detected early, the average cost is reduced.

6.1.3 Complications

No complications or adverse events were assumed in the model. This assumption was agreed with the GDG.

6.1.4 After removal of adenomas (tunnel states)

In the model, tunnel states were used to represent two health states after removal of adenomas, depending on whether the person had previous adenomas, to determine the surveillance strategy:

- adenoma free after removal of non-advanced adenoma at year 1 and year 2 onwards
- adenoma free after removal of advanced adenoma at year 1 and year 2 onwards.

It was assumed that all adenomas are removed endoscopically during surveillance. It was also agreed with the GDG to assume that all colorectal cancers arise from pre-existing adenomas.

The main consideration in this model is that the long-term outcomes from repeated colonoscopic surveillance depend on two factors: timing of adenoma removal (prevention of colorectal cancer) and timing of cancer detection (detection of early colorectal cancer). This affects the proportion of people who can be treated with surgery only (Dukes' A colorectal cancer) and subsequent long-term survival. Therefore, the treatment benefit distinguishes between cancer that is detected early and is asymptomatic, and symptomatic cancer, which is reflected in the costs and health benefits (QALYs). It was assumed that people diagnosed with colorectal cancer (asymptomatic or symptomatic) received identical stage-specific treatments. This allowed a comparison of colonoscopic surveillance with no surveillance under identical conditions. It was also assumed that people could progress to death from all health states.

6.2 Transition probabilities

The transition probabilities were taken from Tappenden et al. (2004). Although these data were from the best available source, transferring them to another model was not ideal and there was potential uncertainty. In addition, there were no data for people at intermediate risk of developing colorectal cancer. Therefore, the data for the high-risk group were extrapolated to this group. To reflect the fact that the probability of the intermediate-risk group progressing from adenoma free is likely to be less than for the high-risk group, a variable factor was added to reduce the rate of progression. A base-case value of 0.85 was chosen at random, but it was varied in the probabilistic sensitivity analysis.

Data from published interim life tables for the UK (Office of National Statistics 2009) were used to calculate age-related mortality probabilities. It was assumed that for people in the asymptomatic colorectal cancer health states the probability of dying is the same as the age-related probability of dying. This appears to be reasonable because people without symptoms are unlikely to have an increased risk of death until their cancer progresses. This ensured that all probabilities added up to one (table 3).

Table 3 Natural history yearly transition matrix

	AF	NAA	AA	DA	DB	DC	DD	mCRC	mOthers
AF(NAAR) year 1	#	0.18	0	0	0	0	0	0	Age
AF (NAAR) year 2+	#	0.05	0	0	0	0	0	0	Age
AF (AAR) year 1	#	0.25	0	0	0	0	0	0	Age
AF (AAR) year 2+	#	0.06	0	0	0	0	0	0	Age
NAA	0	#	0.021	0	0	0	0	0	Age
AA	0	0	#	0.0326	0	0	0	0	Age
DA	0	0	0	#	0.5829	0	0	0.0	Age
DB	0	0	0	0	#	0.6555	0	0.010	Age
DC	0	0	0	0	0	#	0.8648	0.0602	Age
DD	0	0	0	0	0	0	#	0.3867	Age
mCRC	0	0	0	0	0	0	0	1	0
mOthers	0	0	0	0	0	0	0	0	1

AF: adenoma free; NAAR: non-advanced adenoma removed; AAR: advanced adenoma removed; NAA: non-advanced adenoma; AA: advanced adenoma; DA: Dukes' A colorectal cancer (CRC); DB: Dukes' B CRC; DC: Dukes' C CRC; DD: Dukes' D CRC; mCRC: death caused by CRC; mOthers: death from other causes, # 1 minus other states; Age: age dependent.

7 Quality of life

NICE recommends that changes in HRQoL as a result of an intervention or treatment should be directly reported by patients. These changes should be based on preferences determined using a choice-based method in a representative sample of the UK general public. Ideally a full systematic review would be carried out to identify HRQoL studies and appropriate values to include in a health economic model. However, because of the lack of resources and time, a search was carried out for quality of life studies. The quality of life data included in the cost-effectiveness analyses identified in section 5 are reviewed.

7.1 Literature search

A literature search found studies relating to quality of life in people with polyps or adenomas. Quality of life evidence for people with colorectal cancer was limited.

7.1.1 Review of the literature

The main study identified was Ness et al. (1999), which assessed utility values associated with the stage of cancer and treatment. It is crucial to capture utility values that include pre-cancerous stages and any possible positive and/or negative impact of the test results on the person's wellbeing. However, there was no evidence identified from the search demonstrating a decrease in utility values associated with colonoscopic surveillance.

7.2 People's health states

NICE recommends the use of the EuroQol 5 dimensions (EQ-5D) or another generic tool that enables patients to describe their health states and how the public values their health states. In addition, no one set of values can be used for the entire model. There are also potential issues when different values are used from different sources, which may lead to inconsistencies. For example, time trade off and standard gamble techniques have a tendency to produce different estimates for the same health states. To minimise potential inconsistency, studies were chosen that follow the NICE methods and also share similar populations and methods of determining and valuing health states.

Ness et al. (1999) assessed utility values associated with the stage of cancer and treatment in the USA. People were asked to assess utility values for stage-dependent outcome states using the standard gamble technique. These states were not valued by the UK public. The GDG considered the very limited evidence on the colorectal cancer stage-specific utilities, and agreed that the use of utility values from Ness et al. was appropriate in the model.

7.3 Cancer-free and adenoma-free health states

Utility values associated with the cancer-free and the adenoma-free health states were assumed to be the same as the 'no known adenomas' heath state with a utility value of 0.91 (Ness et al. 2000; Tappenden et al. 2004). This was considered to be a reasonable assumption because adenomas are likely to be asymptomatic.

7.4 Cancer

Evidence about people's quality of life, especially in stage-specific colorectal cancer, was very limited. No published studies were found that considered the quality of life impact of colonoscopic surveillance, diagnosis and subsequent treatment of colorectal cancer. Ness et al. (1999) interviewed 90 people who had previously had colorectal adenomas removed to assess utility values associated with stage-specific colorectal cancer using a standard gamble technique.

Asymptomatic cancer and undiagnosed cancer were assigned the same utility value as their diagnostic state (0.91) because if cancer is asymptomatic it is unlikely to affect the quality of life of the person until it is detected (that is, until it becomes symptomatic).

7.5 Colonoscopy

The patient experts in the GDG felt that the utility value for the cancer-free health state would be less than 0.91 because of the significant temporary disability caused by intensive bowel preparation and the recovery period after the procedure. Therefore discomfort associated with the procedure was explored in the sensitivity analysis using a disutility value of 0.0025 (Saini et al. 2010; Syngal et al. 1998).

7.6 Final quality of life values

Table 4 Final health-related quality of life estimates

Health state	Mean value	Standard error	Reference
Cancer-free state	0.91	0.015306	Ness et al. (2000)
Asymptomatic cancer	0.91	0.051020	Ness et al. (2000)
Dukes' A CRC	0.74	0.022959	Ness et al. (1999)
Dukes' B CRC	0.70	0.035714	Ness et al. (1999)
Dukes' C CRC	0.50	0.030612	Ness et al. (1999)
Dukes' D CRC	0.25	0.030612	Ness et al. (1999)
CRC: colorectal cancer			

8 Resource use

8.1 Literature search

From the initial search, only one study was identified that examined resource use in the NHS (Tappenden et al. 2004) that was applicable to the model. Stage-specific colorectal cancer treatment costs were uplifted to incorporate the relevant NICE guidance published since 2004 (personal communication with Paul Tappenden and Hazel Pilgrim, 8 April 2010).

8.1.1 Specific costs for the model

The main cost inputs that required consideration include:

- colonoscopy and pathology
- lifetime treatment costs for stage-specific colorectal cancer.

8.1.1.1 Endoscopy (colonoscopy)

The cost of endoscopy was obtained from NHS reference costs 2008/09 (£517; NHS cost code FZ26A – endoscopic or intermediate large intestine procedures 19 years and over).

8.1.1.2 Pathology for adenomas

The cost of pathology for adenomas was obtained from NHS reference costs 2008/09 (NHS cost code DAP824 – histology or histopathology.

8.1.1.3 Stage-specific treatment costs for colorectal cancer

Recently uplifted stage-specific treatment costs for colorectal cancer were based on Tappenden et al. (2004) (personal communication with Paul Tappenden and Hazel Pilgrim, 8 April 2010). These broadly include chemotherapy, surgery or radiotherapy (if appropriate), follow-up, and palliative care.

8.1.1.4 Distributions of estimates

The gamma distribution is recommended as the appropriate probability distribution for costs (Briggs et al. 2003). To fit a gamma distribution the standard error is required for each value. The standard errors for the costs obtained from Tappenden and Pilgrim were calculated using the mean costs, 97.5% and 2.5% credibility intervals (Tappenden and Pilgrim 2010). There is no agreed method on how to calculate standard errors for reference costs. Only the mean and quartile values (except the median) are available. Therefore the method used was the solver function in Excel to find the variables for the gamma function that produce the relevant estimates of the upper and lower quartiles.

9 Assumptions

The GDG agreed that the model would only examine factors relating to colorectal cancer development; other epidemiological factors would be considered only when a risk of developing colorectal cancer can be demonstrated.

9.1 Age of cohort and cycle length

The GDG agreed on a cohort age of 50 years and a cycle length of 3 months, which allows transition to other states in between surveillance visits. The GDG agreed that no further surveillance would be carried out after 85 years because of the slow transformation of adenomas to colorectal cancer over 10–15 years (Winawer 1993a), and the potential risks and benefits of colonoscopic surveillance. Therefore the model was run over 50 years with a surveillance duration of 35 years.

9.2 Age dependency

Apart from other cause mortality all other variables were independent of time. This was because of a lack of information on the relationship between time and a number of important variables such as the rate of cancer progression. Other cause mortality was age dependent because it was assumed that people with adenomas have the same mortality as the rest of the UK population. This seemed appropriate because there is no other reported difference in life expectancy other than increased rate of recurrent adenomas and increased colorectal cancer rate in people with adenomas.

9.3 Misdiagnosis

The GDG acknowledged that the underlying data from observational studies already included a degree of misdiagnosis. Therefore it was assumed in the model that there was no misdiagnosis.

9.4 Complications

For simplicity, no complications relating to colonoscopy or adenoma removal were assumed in the model. The GDG discussed potential risks associated with colonoscopy and adenoma removal, including bowel perforation and bleeding. The GDG noted that the number of colonoscopy-related complications reported was small but these events could be fatal.

9.5 Compliance

In the model, the cohort was assumed to adhere to the colonoscopy schedule. The GDG discussed the higher compliance rate in people who were informed of an increased risk of developing colorectal cancer and this assumption was considered to be reasonable.

9.6 Stopping surveillance

The GDG agreed that the low-risk group would not have further surveillance after one negative colonoscopy. The intermediate-risk group would have a follow-up at 3 years, then would stop surveillance after two consecutive negative results. The high-risk group would have a follow-up colonoscopy at 1 year, which would determine the surveillance strategy: if the colonoscopy is negative, or low- or intermediate adenomas are found, they would follow the frequency of surveillance for the intermediate-risk group; if high-risk adenomas are found, they would have colonoscopic surveillance at 1 year. This surveillance schedule follows the current BSG guidelines (Atkin and Saunders 2002; Cairns et al. 2010). Health benefits (QALY gains) of people who meet the criteria for stopping surveillance were accounted for in the surveillance models.

9.7 Diagnosis and treatment of cancer

Colonoscopy, removal of adenomas and pathology were included for the surveillance and treatment of adenomas detected during surveillance. Surgery, chemotherapy and radiotherapy were included for the treatment for colorectal cancer. Appropriate NICE guidance for the treatment of colorectal cancer was also taken into account. Therefore, the impact of colonoscopic surveillance on the cost effectiveness is the relative benefit of prevention or early detection of colorectal cancer. Costs incurred at each stage of colorectal cancer and detrimental to quality of life were also included.

Cancer costs and benefits were separated, with costs applied only when a person entered the colorectal cancer health state and benefits applied for each time period in the state. This was assumed in Tappenden et al. (2004)

and was a limitation of that study. This limitation could lead to conflicting conclusions over the effect of colorectal cancer. However, because modelling the entire colorectal cancer pathway was not possible, this was considered an acceptable simplification.

9.8 Adenoma recurrence rate during surveillance

in the model it was assumed that he probability of people in the high-risk group who have had adenomas removed developing further adenomas is higher than for people with no previous history of adenomas. In the surveillance model two tunnel states represent post-adenoma removal (see section 6.1.4). Tappenden et al. (2004) gave the key uncertainties in their analysis, including the probability of progressing through undiagnosed cancer states, the probability of clinical presentation by cancer stage, polyp incidence and growth rates, the rate at which high-risk adenomas develop into cancer, and stage-specific colorectal cancer mortality rate.

9.9 Transition probabilities

Estimated transition probabilities were assumed to be constant with the exception of age-specific adenoma incidence (Tappenden et al. 2004) and age-specific mortality rates, which were taken from government sources. Because of limited evidence the GDG agreed that all transitions from one health state to the next in the model are progressive.

9.10 Utility values for cancer-free health states

Because a person with adenomas who is cancer free is likely to be asymptomatic, the utility value estimate for this health state was assumed to be the same as that for the general population (Ness et al. 2000; Tappenden et al. 2004). The GDG considered this was necessary because most people with adenomas are asymptomatic.

9.11 Colorectal cancer

Probabilities of cancer progression were assumed to be equivalent in both the distal and proximal colon. This appears to be a reasonable assumption because the population included in the model have no familial or previous history of colorectal cancer.

9.12 Final costs

Stage-specific colorectal cancer treatment costs, obtained from NHS reference costs, were uplifted (personal communication with Tappenden and Pilgrim, 8 April 2010). The final values and a breakdown are presented in table 5.

Table 5 Mean costs and standard errors used in the base-case analysis and probabilistic sensitivity analysis

Costs	Mean (£)	Standard error (£)	Reference
Diagnostic/therapeutic colonoscopy	517.00	178.92	NHS reference costs 2008/09 (2010)
Pathology for adenoma	26.00	21.50	NHS reference costs 2008/09 (2010)
Pathology for cancer	250.00	277.98	Tappenden et al. (2004)
Lifetime cost			
Dukes' A	11,965.78	6490.90	Tappenden and Pilgrim (2010)
Dukes' B	16,224.50	3811.55	Tappenden and Pilgrim (2010)
Dukes' C	21,033.60	2368.03	Tappenden and Pilgrim, (2010)
Dukes' D	24,096.80	2050.62	Tappenden and Pilgrim (2010)

10 Sensitivity analysis

10.1 Deterministic sensitivity analysis

Deterministic sensitivity analysis was carried out on a range of variables, including all costs and utility values. The key areas of uncertainty (see section 9.8) were explored by examining two sets of transition matrices: higher values from the literature and another set of lower values. The full matrices are given in table 6. Costs were reduced and increased by 50% to examine this effect. A person's quality of life was explored in relation to the potential (dis)utility associated with full bowel preparation and the recovery period (Sandi et al. 2010).

Table 6 Transition probabilities through model calibration (Tappenden et al. 2004)

Annual transition probability		Parameter estimate used in base-case analysis	Uniform distribution used in calibration	
State from	State to		Minimum	Maximum
LR	HR	0.02	0.005	0.0400
HR	DA	0.033	0.0100	0.0600
DA	DB	0.5830	0.3000	0.9000
DB	DC	0.6560	0.3000	0.9000
DC	DD	0.8650	0.3000	0.9000
PSDA	–	0.0700	0.0200	0.1500
PSDB	–	0.3200	0.1000	0.3500
PSDC	–	0.4900	0.5000	0.9000
PSDD	–	0.8540	0.5000	0.9000
DA	mCRC	0.000	0.000	0.0050
DB	mCRC	0.0100	0.0050	0.0300
DC	mCRC	0.0600	0.0200	0.1500
DD	mCRC	0.3870	0.3500	0.4500
LR: low risk; HR: high risk; DA: Dukes' A colorectal cancer (CRC); DB: Dukes' B CRC; DC: Dukes' C CRC; DD: Dukes' D CRC; mCRC: death caused by CRC; mOthers: death from other causes; PSDA: probability of presenting with symptomatic Dukes' A CRC; PSDB: probability of presenting with symptomatic Dukes' B CRC; PSDC: probability of presenting with symptomatic Dukes' C CRC; PSDD: probability of presenting with symptomatic Dukes' D CRC				

10.2 Structural sensitivity analysis

The following structural assumptions and variables were explored.

10.2.1 Age of the cohort

The base case assumes an average age of 50 years for the cohort because most published cost-effectiveness analyses use 45 years based on limited prevalence data. Average cohort ages of 35, 40 and 45 (varying the duration of surveillance) were explored.

10.2.2 Stopping surveillance at different ages

The cutoff age for stopping surveillance was altered from 85 to 65, 70 and 75, because remaining life expectancy is likely to be less than the average time required for adenomas to develop into colorectal cancer.

10.3 Probabilistic sensitivity analysis

All transition probabilities in the natural history were varied using beta distributions. Because no standard errors were available, a sample size of 100 was assumed. This value and the mean were used to calculate the relevant factors.

10.3.1 Utility values

Beta distributions of the differences between the estimates were used to ensure that the results remained consistent. Table 7 outlines the utility values varied according to their difference.

Table 7 Probabilistic sensitivity analysis calculations for quality of life

State	**Mean**	**Standard error**	**Distribution**
Cancer free	0.91	0.02	Beta
Undiagnosed asymptomatic colorectal cancer	0.91	0.02	Beta
Dukes' A	0.74	0.02	Beta
Dukes' B	0.70	0.04	Beta
Dukes' C	0.50	0.03	Beta
Dukes' D	0.25	0.05	Beta

10.3.2 Costs

Table 8 outlines the costs and standard errors that were modelled using a gamma distribution.

Table 8 Probabilistic sensitivity analysis: gamma or normal distribution of costs

Costs	Mean (£)	Standard error (£)
Colonoscopy	517.00	178.92
Pathology for adenoma	26.00	21.50
Pathology for cancer	250.00	277.98
Lifetime treatment cost		
Dukes' A	11,965.78	6490.90
Dukes' B	16,224.50	3811.55
Dukes' C	21,033.60	2368.03
Dukes' D	24,096.80	3050.62

11 Results

11.1 Deterministic results

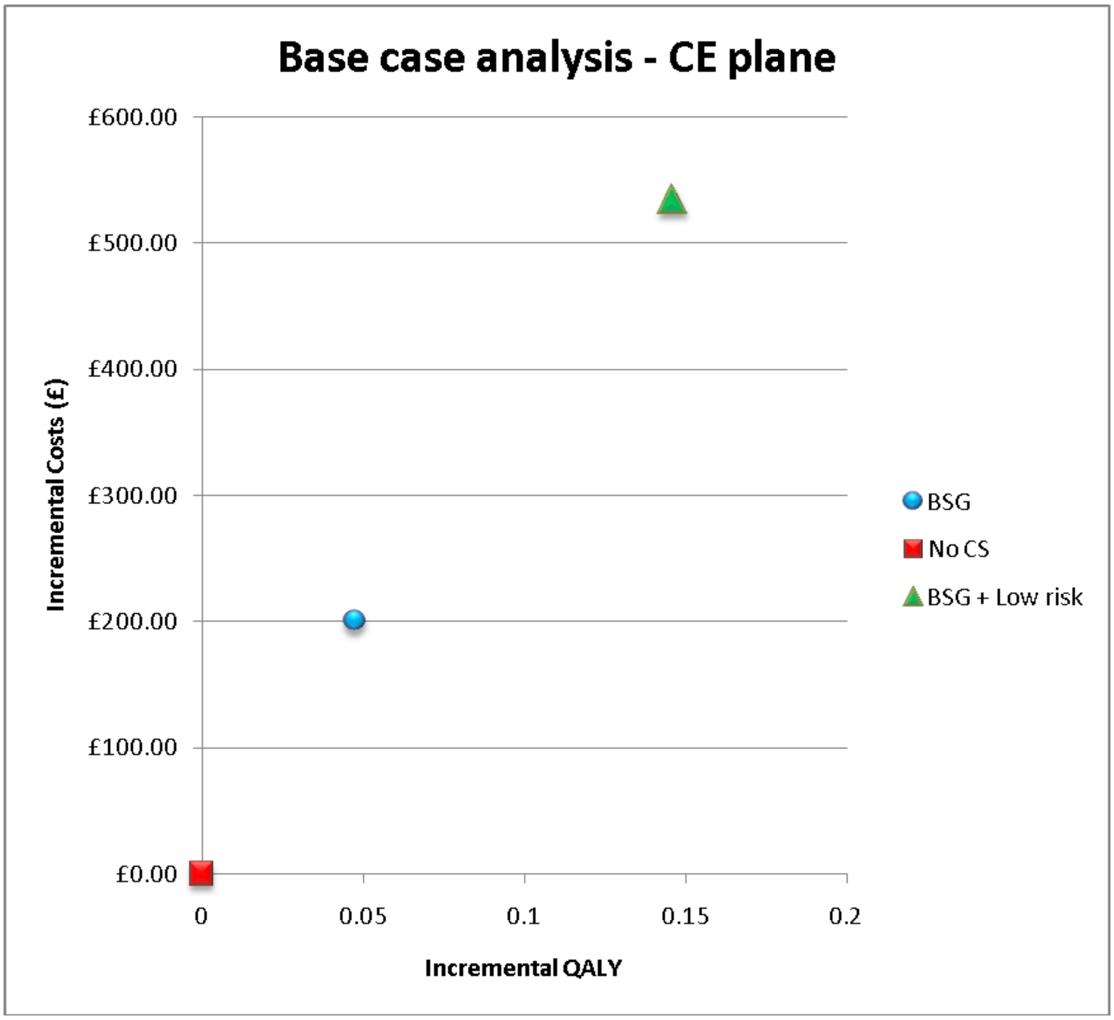
Table 9 presents results of the deterministic base case. Colonoscopic surveillance following the BSG guidelines and the inclusion of the low-risk group are both associated with ICERs below £20,000 per QALY gained compared with no surveillance. These results appear to have face validity because the total cost of surveillance according to the BSG guidelines 2010 was estimated to be £1100, which is consistent with the value given in table 9.

Table 9 Deterministic analysis over a 50-year period

	QALYs (utilities)	Costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
No surveillance	16.11	641.06	–	–	–
Colonoscopic surveillance in intermediate- and high-risk groups	16.16	841.54	0.05	200.49	4235.75
Colonoscopic surveillance in all risk groups	16.26	1177.03	0.15	535.970	3669.70
QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio					

The cost-effectiveness plane for the base-case analysis is shown in figure 4.

Figure 4 Cost-effectiveness plane



These results indicate that surveillance of the intermediate- and high-risk groups (denoted as BSG in Figure 4) is extendly dominated by suveillance of all risk groups. This is because surveillance of all risk groups is associated with a lower ICER. These results suggest that surveillance of all risk groups (denoted as BSG + Low risk in Figure 4) is the most cost-effective strategy.

11.1.1 Transition matrices

Table 10 presents the results if the upper estimates for transition probabilities are used.

Table 10 Deterministic results with upper estimates for transition probabilities

50-year time horizon	QALYs (utilities)	Costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
No surveillance	15.74	1532.85			
Intermediate- and high-risk groups	15.90	1468.76	0.16	–64.09	–388.66
All risk groups	16.24	1229.93	0.50	–302.92	Extended dominance
QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio.					

Table 11 presents the results if the lower estimates for transition probabilities are used.

Table 11 Deterministic results with lower estimates for transition probabilities

50-year time horizon	QALYs (utilities)	Costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
No surveillance	16.259	38.91			
Intermediate- and high-risk groups	16.261	420.20	0.002	381.28	191,602
All risk groups	16.265	1151.88	0.006	1112.97	181,288.36
QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio.					

The natural history transitions have a significant impact on the estimates of cost effectiveness. However, the deterministic results of cost effectiveness were consistent when colonoscopic surveillance in intermediate- and high-risk groups was a cost-effective strategy compared with no surveillance.

11.1.2 Potential disutility associated with colonoscopy

The GDG agreed that potential discomfort and recovery from sedation associated with colonoscopy would have an effect on the QALYs gained. A potential disutility of 0.0025 was used in the base-case analysis to explore the impact of disutility on the ICERs (see table 12).

Table 12 Disutility of 0.0025 associated with colonoscopy

Strategy	QALYs (utilities)	Costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
No surveillance	16.07	641.06	–	–	
Intermediate- and high-risk groups	16.12	841.54	0.05	200.49	4242.84
All risk groups	16.22	1177.03	0.15	535.97	3675.82
QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio.					

The GDG discussed the potential psychological and physical impacts of colonoscopy, including anxiety and discomfort. It was agreed that despite the inconvenience related to full bowel preparation and the recovery time after each procedure, the long-term benefit of colonoscopic surveillance outweighs the short-term discomfort. The estimated ICERs for each strategy showed little variation. Therefore surveillance following the BSG guidelines and including the low-risk group remained more cost effective.

11.2 Structural sensitivity analysis

11.2.1 Age of the cohort

The age of the cohort was varied from 50 to 35, 40 and 45 years and surveillance was stopped at 85 years for each strategy. The model was run for 50 years to see the costs and health benefits of surveillance over a lifetime for each strategy. Table 13 outlines the results. The overall trends of ICER estimates show that colonoscopic surveillance in all risk groups is a cost-effective strategy compared with no surveillance at £20,000 and £30,000 per QALY gained. The results indicate that the younger the cohort, the more cost-effectiveness the strategy. This is an important consideration when examining other published cost-effectiveness analyses because most examine a cohort age of 50 years. However, the transitions from adenomas to colorectal cancer were assumed to be constant. Therefore there is some uncertainty about the results for cohorts younger than the base case.

Table 13 ICER estimates when varying age of cohort

Age of cohort (years)	Strategy	QALYs	Costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
35	No surveillance	19.41	1095.10			
	Intermediate- and high-risk groups	19.51	1172.34	0.10	77.24	772.44
	All risk group	20.71	1229.36	0.32	134.26	419.44
40	No surveillance	18.54	943.39			
	Intermediate- and high-risk groups	18.63	1061.51	0.08	118.11	1416.22
	All risk group	18.81	1218.69	0.26	275.30	1040.05
45	No surveillance	17.43	791.33			
	Intermediate- and high-risk groups	17.50	951.16	0.06	159.83	2458.97
	All risk group	17.63	1202.24	0.20	410.91	2016.25

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio.

11.2.2 Stopping surveillance at different ages

Table 14 outlines the results of stopping surveillance at different ages over a lifetime horizon (50 years).

Table 14 Stopping surveillance at different ages

Stopping age (years)	Strategy	QALYs	Costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
65	No surveillance	16.11	641.06			
	Intermediate - and high-risk groups	16.16	841.54	0.047	200.49	4235.38
	All risk groups	16.25	1127.48	0.142	486.42	3414.14
70	No surveillance	16.11	641.06			
	Intermediate - and high-risk groups	16.16	841.54	0.047	200.49	4235.75
	All risk groups	16.26	1155.91	0.145	514.85	3543.54
75	No surveillance	16.11	641.06			
	Intermediate - and high-risk groups	16.16	841.54	0.052	200.49	4235.45
	All risk groups	16.26	1169.41	0.1506	528.36	3620.90
80	No surveillance	16.11	641.06			
	Intermediate - and high-risk groups	16.16	841.54	0.05	200.49	4235.75
	All risk groups	16.26	1175.22	0.15	534.17	3657.73
	QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio.					

The results show that stopping surveillance at 60, 65 or 75 years has little impact on ICERs and the results are consistent with the base-case results. Surveillance in all risk groups is therefore a cost-effective strategy.

11.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis enables the uncertainty associated with parameters to be reflected in the results of the model. In non-linear decision models, probabilistic sensitivity analysis provides the best estimates of mean costs and health consequences in terms of QALYs gained. Table 15 outlines the results. The costs are slightly higher and given the low incremental QALYs do cause the ICERs to increase compared with the deterministic results, but not significantly.

Table 15 Probabilistic sensitivity analysis over a 50-year period

	QALYs	Costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)	Probability of being cost effective at £20,000 per QALY gained (%)
No surveillance	16.12	562.91	–	–	–	–
Intermediate- and high-risk groups	16.17	786.25	0.04	223.33	5298.03	78
All risk groups	16.25	1167.77	0.13	604.85	4626.57	81
QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio.						

11.3.1 Cost-effectiveness plane

Figures 5 and 6 show the results of the probabilistic sensitivity analysis plotted on a graph of incremental costs and QALYs. It appears that effectiveness and cost are negatively correlated. That is, the more progressive the condition, the more people develop colorectal cancer, and therefore, the greater the potential savings from reduced surveillance. It is also apparent that surveillance in all risk groups is associated with greater variation in values, but also potentially greater gains.

Figure 5 Cost-effectiveness (CE) plane – intermediate-risk (IR) and high-risk (HR) group surveillance

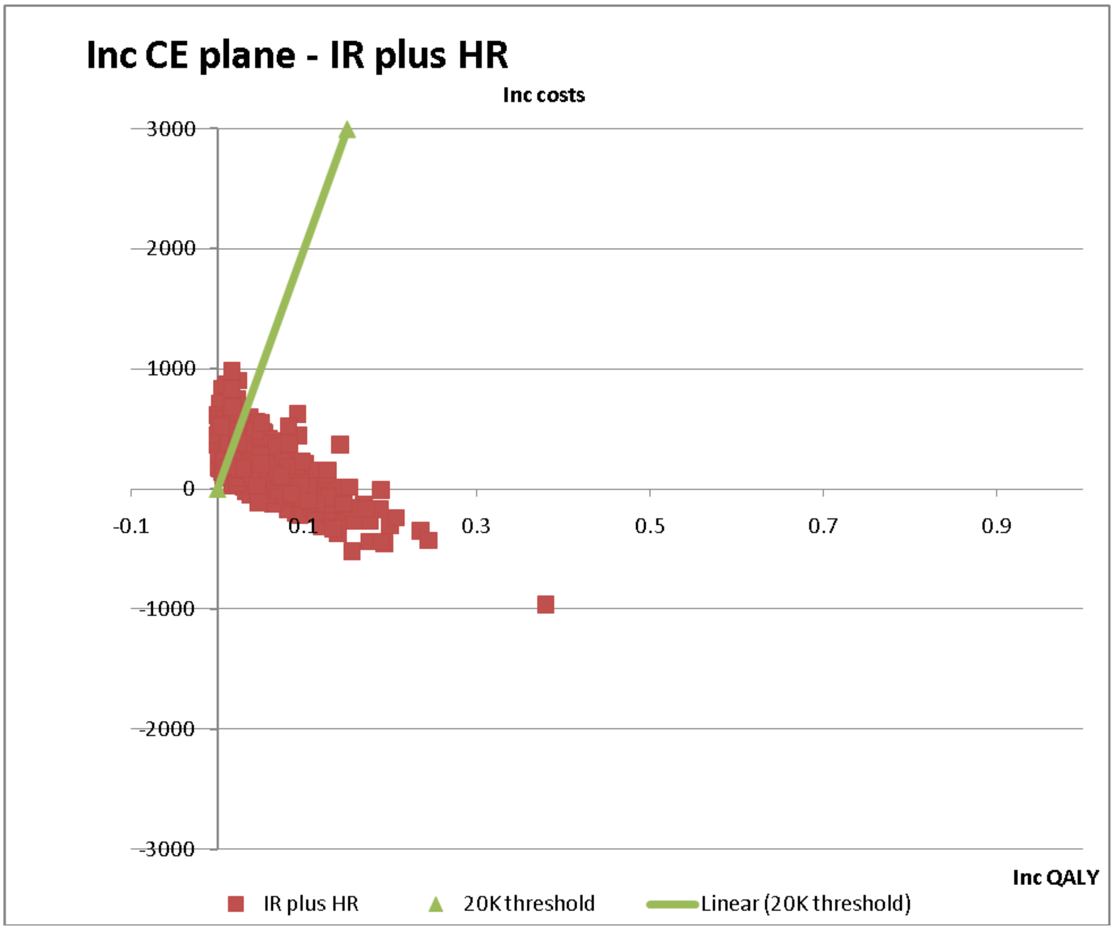
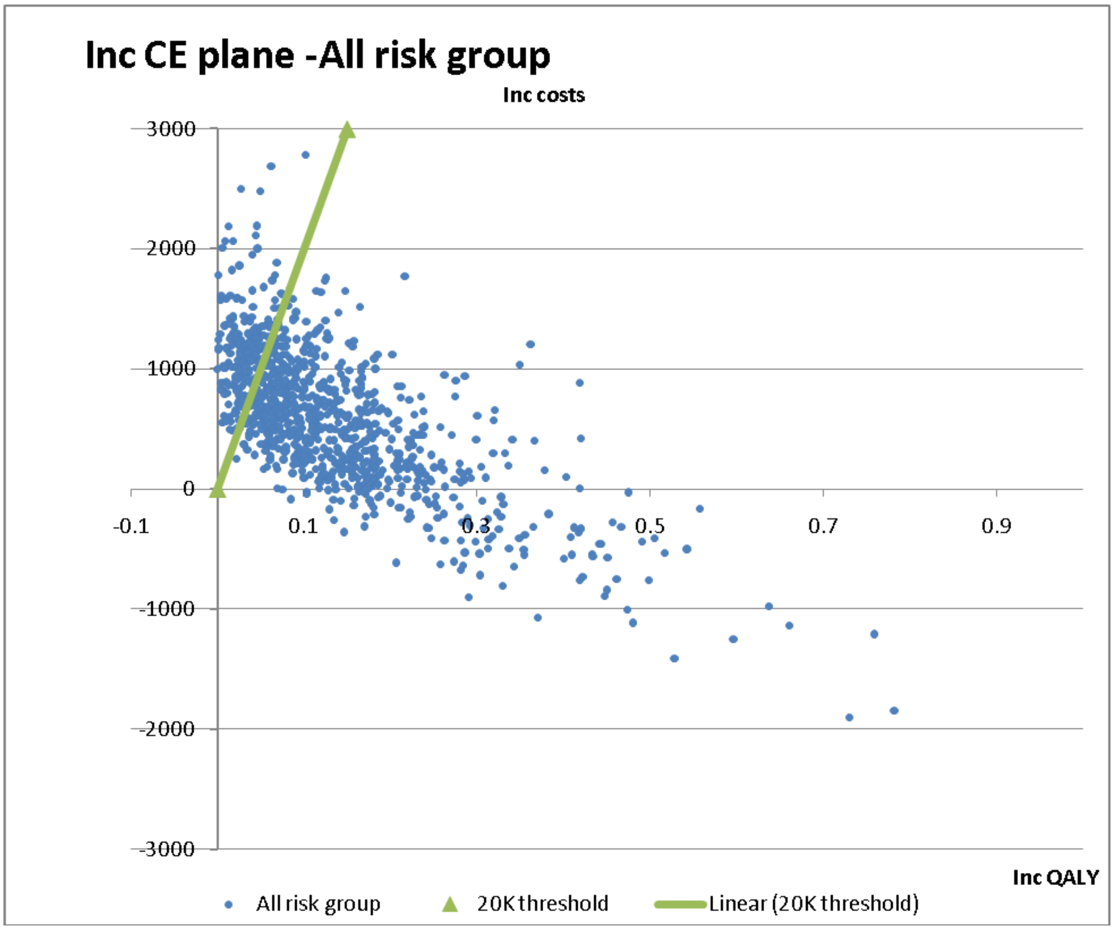


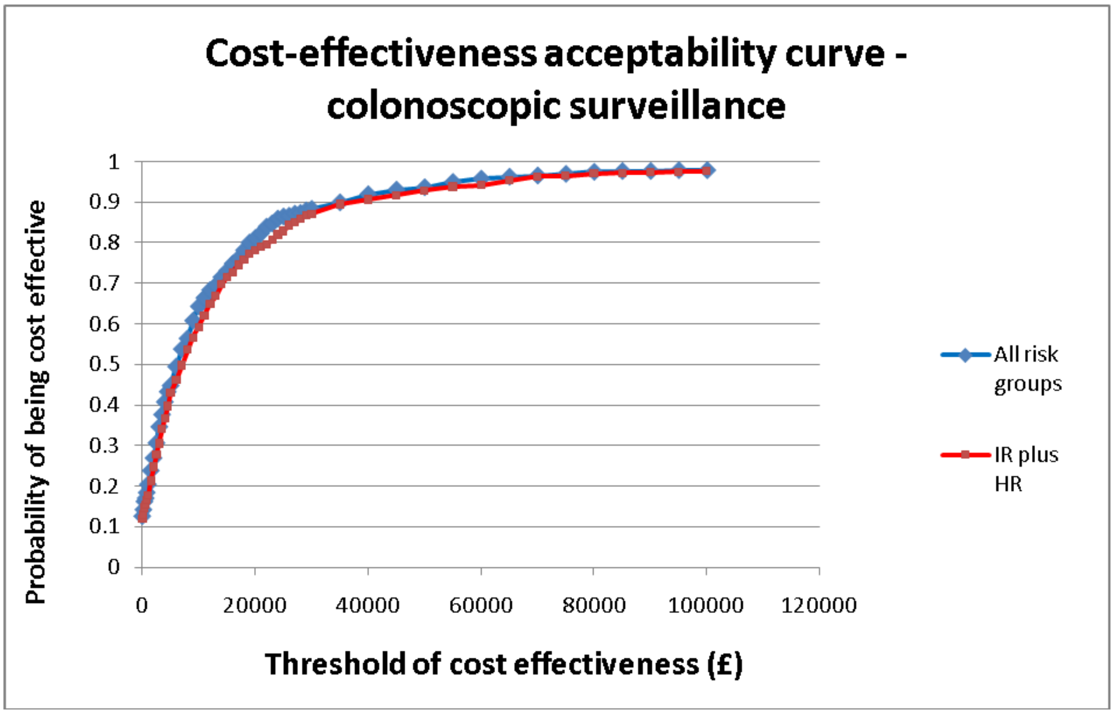
Figure 6 Cost-effectiveness (CE) plane – all risk groups



11.3.2 Cost-effectiveness acceptability curves

Figure 7 presents the cost-effectiveness acceptability curves for the different surveillance strategies. At a threshold of £20,000 per QALY gained, colonoscopic surveillance in the intermediate- and high-risk groups is associated with a probability of being cost effective of over 78% compared with no surveillance. In all risk groups the probability of being cost effective is 81%. At £30,000 per QALY gained these figures increase to 87% and 88% respectively.

Figure 7 The cost-effectiveness acceptability curve for different surveillance strategies

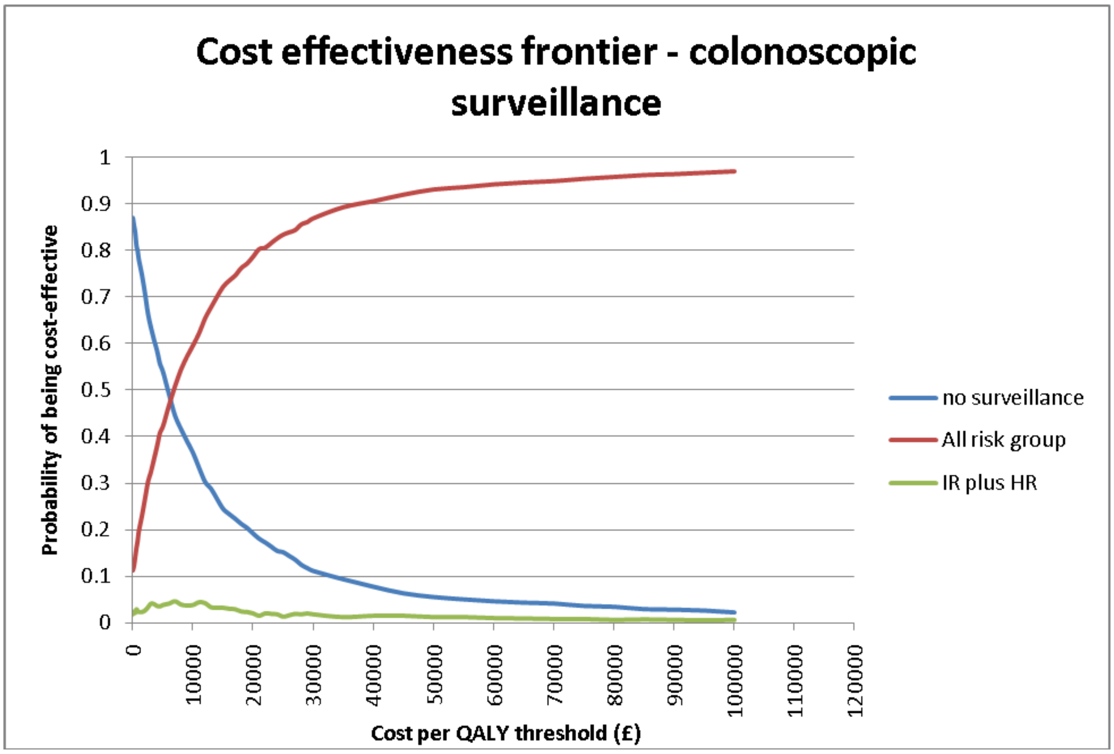


The results support findings from the base-case analysis that surveillance of all risk groups is the preferred option because it is associated with the lowest ICERs and the least uncertainty.

11.3.3 Cost-effectiveness acceptability frontiers

Figure 8 presents the cost-effectiveness acceptability frontiers for the different surveillance strategies.

Figure 8 Cost-effectiveness acceptability frontiers for different surveillance strategies



These results indicate that at £20,000 per QALY gained and £30,000 per QALY gained the optimum strategy is the all risk groups surveillance strategy.

12 Discussion

12.1 Strengths of the model

The main strength of the model is its comprehensiveness, using the most up-to-date evidence available in the public domain. Extensive sensitivity analyses were performed to explore any uncertainty in the data and the model. The model included projected health benefits and related resource use following the BSG guidelines, taking into account different recurrence rates of adenomas in the NHS.

12.2 Limitations of the model

12.2.1 Natural history data

Because of a lack of time, a systematic review was not carried out examining the natural history of the progression of adenomas into colorectal cancer. However, the GDG agreed to use assumptions consistent with a published analysis by Tappenden et al. (2004). Although the analysis by Tappenden et al. would not have taken into account newly published evidence, it was confirmed in the recently updated BSG guidelines (Cairns et al. 2010) that there is no new evidence associated with polyps and adenoma surveillance.

The model focused on colonoscopic surveillance and so different treatment options and chemoprevention for stage-specific colorectal cancer were not distinguished in the model because of a lack of time and resources. Ideally these options would have been included in the model to show different health benefits and subsequent resource use.

12.2.2 Clinical data

Limitations include the lack of directly observed progression and regression data for the development of adenomas. The transition probabilities in the model were obtained from Tappenden et al. (2004). Transferring these data to another model was not ideal and there was potential uncertainty.

In the model it was assumed that all colorectal cancers arise from pre-existing adenomas. However, direct evidence suggests that new colorectal cancers can also arise. This assumption led to bias in favour of surveillance compared with no surveillance.

12.2.3 Misdiagnosis

For adenoma detection, 100% sensitivity and specificity were assumed. The GDG discussed the current sensitivity and specificity of colonoscopy to be around 95%. In addition, clinical data were mainly obtained from observational studies in which misdiagnosis was accounted for in the published literature.

Further work could incorporate the sensitivity and specificity of the chosen surveillance method where appropriate.

12.2.4 Complications

The probabilities of perforation during colonoscopy with and without adenoma removal were reported to be 0.17% and 0.08% respectively (Tappenden et al. 2004). Because of a lack of time and resources these complications were not considered in the model.

12.2.5 Quality of life data

Uncertainty remains about the appropriate method to account for quality of life for people with polyps and colorectal cancer. The patient experts and clinical specialists in the GDG considered that the psychological burden of being diagnosed with adenomas at high risk of progressing to colorectal cancer could be very high. The GDG also highlighted the discomfort and inconvenience associated with full bowel preparation before colonoscopy and the recovery period after each procedure. However, the GDG acknowledged that referral for colonoscopic surveillance was broadly reassuring and not associated with adverse psychological consequences in the long term (Miles et al. 2009). More work will be required on the short- and long-term benefits of colonoscopic surveillance in preventing colorectal cancer.

12.2.6 Surveillance using colonoscopy

The updated BSG guidelines (Cairns et al. 2010) highlighted the user-dependency of colonoscopy and the importance of careful and thorough colonoscopy in preventing colorectal cancer with a ‘fail-safe system’ in place for recall of patients at high risk.

12.2.7 Costing

NHS reference costs are published costs and represent the average NHS costs across the country. However, the GDG highlighted that these costs could potentially underestimate the true cost of the procedure. This was explored by increasing the costs in the deterministic sensitivity analysis. It should be noted that the incremental costs are the most important figures, not the absolute costs. A true micro-costing exercise in a UK setting would have been the preferred option.

12.2.8 Systematic reviews

Ideally systematic reviews would have been carried out for all model inputs so that the most robust evidence was selected. However, the GDG agreed that the approach was acceptable given the limited time and resources for guideline development.

12.2.9 Full care pathway modelling

The current analysis simplifies the actual treatment by modelling identical treatment pathways for stage-specific colorectal cancer. It was necessary to explore the cost effectiveness of colonoscopic surveillance for the detection and prevention of colorectal cancer in the given timeframe. The model does not take into account the possibility of a person progressing between treatments, loss to follow-up or colorectal cancer arising from other causes. If improved clinical-effectiveness data were to be collected, these should be included in a more comprehensive model in the future to allow a more detailed comparison to be made.

13 Conclusions

This analysis indicates that colonoscopic surveillance in all risk groups is the most cost-effective strategy for people with adenomas at high risk of developing colorectal cancer. ICER estimates below £20,000 and £30,000 per QALY gained are apparent when deterministic and probabilistic analyses are considered. However, the GDG acknowledged that there was uncertainty about the clinical benefits of colonoscopic surveillance in the low-risk group. The GDG discussed the potential risks of perforation and bleeding associated with colonoscopy and adenoma removal in the low-risk group, which could outweigh potential benefits (Ransohoff et al. 1991). In the absence of evidence for increased detection of adenomas and colorectal cancer leading to reduced mortality in the low-risk group, the GDG agreed that colonoscopic surveillance in this group would not be recommended as routine practice in the NHS. The GDG highlighted, however, that clinical judgement should be used for people with small adenomas (≤5 mm): their age, co-morbidities, potential risks of bleeding and perforation should be considered.

14 Future work

A better understanding of the natural history of colonic polyps and the progression of adenomas to colorectal cancer is a priority so that the full course of the disease, from diagnosis to the stage-specific treatments for colorectal cancer, can be modelled in the future. Therefore, the potential for discrete event simulation should be considered to make modelling less time consuming.

Carrying out audits of current surveillance for people with adenomas will provide valuable data for identifying gaps in the evidence, training and development needs in clinical practice, as well as the provision of patient information. Audit should include colonoscopy adherence, complications associated with colonoscopy, a breakdown of possible causes of complications, and the outcomes and additional techniques used when the results of colonoscopy are inconclusive and/or incomplete. Audit will also provide information about areas for training needs.

Ongoing research on the long-term safety of a no surveillance strategy for people at low risk of developing colorectal cancer is expected to report outcomes in the next 2 years (Cairns et al. 2010). This will provide invaluable evidence for future guidance development.

The NHS Bowel Cancer Screening Programme was fully rolled out in 2009 and so reports and outcomes will be available soon. Careful consideration and further study of the relationship between the population eligible for the screening programme and the colonoscopic surveillance population are needed. This will ensure that the most appropriate and timely interventions are in place for reducing mortality associated with colorectal cancer and improving relevant health benefits in the NHS.

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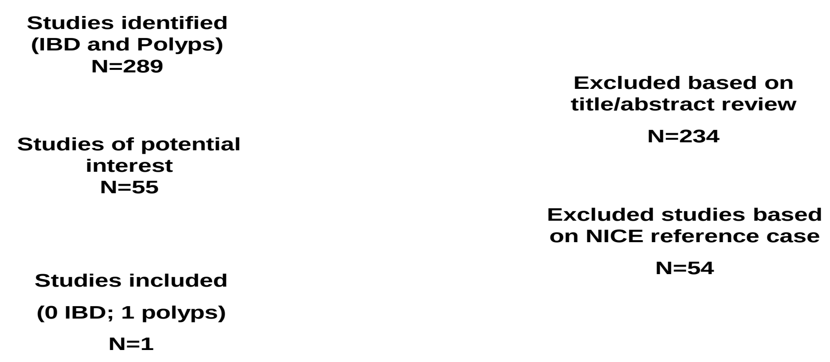
16 Appendices

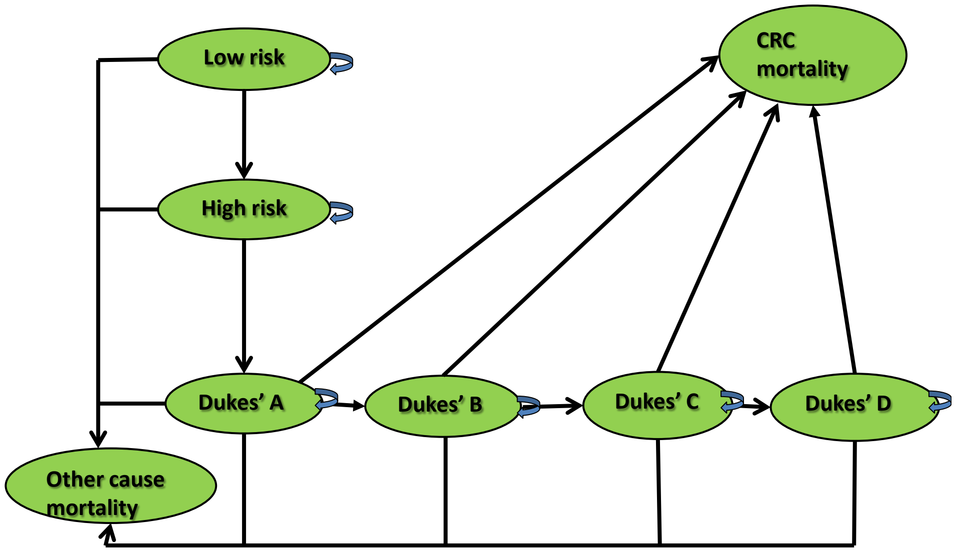
16.1 Inclusion and exclusion criteria



16.2 Review of Tappenden et al. (2004)

The objective of the report 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. As part of the report, the authors considered subsequent colonoscopic surveillance in people with high-risk polyps at index colonoscopy, which broadly follows the current BSG guidelines.

Figure 9 Model structure from Tappenden et al. (2004)



In this model people are allocated to a risk state based on a baseline colonoscopy: low risk, intermediate risk or high risk. People can then progress or regress in each diagnostic state and will stay there until surveillance re-classifies them or until they develop cancer. If there is no surveillance then colorectal cancer is only diagnosed when the person becomes symptomatic. Asymptomatic cancer can be detected by surveillance. Death from other causes is based on age-related mortality. This model does not include misdiagnosis from surveillance, but allows an initial misdiagnosis at baseline colonoscopy, because the natural history data take misdiagnosis into account.

The overall quality of the report was very high and all assumptions and variables were justified. The possible limitations of the report are that the surveillance strategies examined include faecal occult blood testing, flexible sigmoidoscolonoscopy, and colonoscopy in a general population. The population for this analysis was people with polyps who are at high risk of developing colorectal cancer.

16.3 *Quality checklist for Tappenden et al. (2004) study*

Study name	**Colorectal cancer screening options appraisal: cost effectiveness, cost–utility and resource impact of alternative options for colorectal concer (2004)** **Tappenden P, Eggington S, Nixon R et al.**	
Study question	**Grade (yes/ no/ not clear/ N/A)**	**Comments**
	Study design	
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
	Data collection	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	From systematic review and additional published studies
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Because of a lack of RCT evidence no meta-analysis was conducted, but the means of obtaining probabilities were stated.

11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	In the absence of utility values in stage-specific colorectal cancer using EQ-5D as the preferred method in line with the NICE reference case, utility estimates were used from published sources that used standard gamble
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	Use of NHS reference costs implies that there is no requirement to separately calculate unit costs as all costs are included in estimates.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	NHS reference cost codes quoted where possible. Uplifted treatment cost data for stage-specific colorectal cancer were obtained from personal communications.
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	

24. Was the choice of rate justified?	Yes	All costs and health outcomes are discounted at 3.5% per year as recommended by NICE.
25. Was an explanation given if costs or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as an aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond and Jefferson (1996). Cited in Centre for Reviews and Dissemination (2008).		

16.4 Quality checklist for new cost-effectiveness analysis

Guideline topic: colonoscopic surveillance in polyps by Y Rajput		
Cost-effectiveness modelling for colonoscopic surveillance in people with adenomas by K Jeong 2010		
Section 1: Applicability	**Yes/ partly/ no/unclear/ NA**	**Comments**
1.1 Is the study population appropriate for the guideline?	Yes	50-year old men and women who have adenomas removed at baseline colonoscopy with a high risk of developing colorectal cancer
1.2 Are the interventions appropriate for the guideline?	Yes	All clinically effective interventions/strategies included within the scope
1.3 Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	
1.4 Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	
1.5 Are all direct health effects on individuals included?	Partly	QALY data from USA using standard gamble technique, there is very limited evidence available on the colorectal cancer stage-specific utility data
1.6 Are both costs and health effects discounted at an annual rate of 3.5%?	Yes	
1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	
1.8 Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	Yes	
1.9 Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	No	QALY data from USA using standard gamble technique used
1.10 **Overall judgement:** Directly applicable/partially applicable/not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable' Directly applicable		
Other comments		
Section 2: Study limitations (the level of methodological quality) *This checklist should be used once it has*	**Yes/partly/ no/unclear/ NA**	**Comments**

been decided that the study is sufficiently applicable to the context of the clinical guideline	**Comments**	
2.1 Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	45-year time horizon, uncertainty verified using different starting age of cohort (50, 55, 60, 65 years)
2.3 Are all important and relevant health outcomes included?	Yes	
2.4 Are the estimates of baseline health outcomes from the best available source?	Yes	
2.5 Are the estimates of relative treatment effects from the best available source?	Yes	Best quality studies identified from clinical review
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	NHS specific
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Is there no potential conflict of interest?	No	
2.12 **Overall assessment**: Minor limitations/potentially serious limitations/very serious limitations Minor limitations		

16.5 Modified GRADE for health economic literature

	Ref ID	Country	Population	Comparators	Outcome measure	Study design	Cost-effectiveness results (base case)	Applicability
Tappenden et al. (2004)	Identified through lateral search	UK	Cohort at age 30	Biennial FOBT 50–69 years; biennial FOBT 60–69 years; FSIG once at 55 years; FSIG once at 60 years; FSIG once at 60 years, followed by biennial FOBT 61–70 years	QALY	DES	Screening using FOBT and/or FSIG is potentially a cost-saving strategy for the early detection of colorectal cancer. However, the practical feasibility of alternative screening programmes is inevitably limited by current pressures on endoscopy services.	Applicable
CRC: colorectal cancer; DES: discrete event simulation; FOBT: faecal occult blood test; FSIG: flexible sigmoidoscopy; QALY: quality-adjusted life year.								