Colorectal cancer: colonoscopic surveillance for prevention of colorectal cancer in patients with ulcerative colitis, Crohn's disease and polyps

APPENDICES
Part 2

Appendix 7 – Health economic evaluation – inflammatory bowel disease

Appendix 8 – Health economic evaluation – polyps

Appendix 7 – Health economic evaluation

Cost-effectiveness analysis for inflammatory bowel disease

1 Introduction

NICE has been asked by the Department of Health to produce a short clinical guideline on colonoscopic surveillance for patients with ulcerative colitis, Crohn's disease and polyps to prevent colorectal cancer. What follows is the cost-effectiveness analysis developed to support the Guideline Development Group (GDG) in making recommendations for adults with inflammatory bowel disease considered to be at 'high risk'.

This analysis has been conducted according to NICE methods outlined in the Guide to the methods of technology appraisal 2008 and the Guidelines Manual 2009. Therefore, it follows the NICE reference case (the framework NICE requests all cost-effectiveness analysis to follow) in the methods used.

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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Contents

4 Decision problem

Table 1 outlines the decision problem that will be 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' with flat dysplastic lesions (low grade or high grade), age 30 to 85.
Interventions	Conventional colonoscopy	Annual colonoscopy
Comparators	Surveillance	No surveillance, surveillance
Outcome(s)	Costs, quality-adjusted life years (QALYs) and cost per QALY	Cost per QALY

4.1 Population

Ulcerative colitis and Crohn's disease are collectively termed as inflammatory bowel disease (IBD). Both conditions share the same risk of developing colorectal cancer given a similar extent and duration of disease. Therefore, when conducting the economic evaluation both conditions were grouped together.

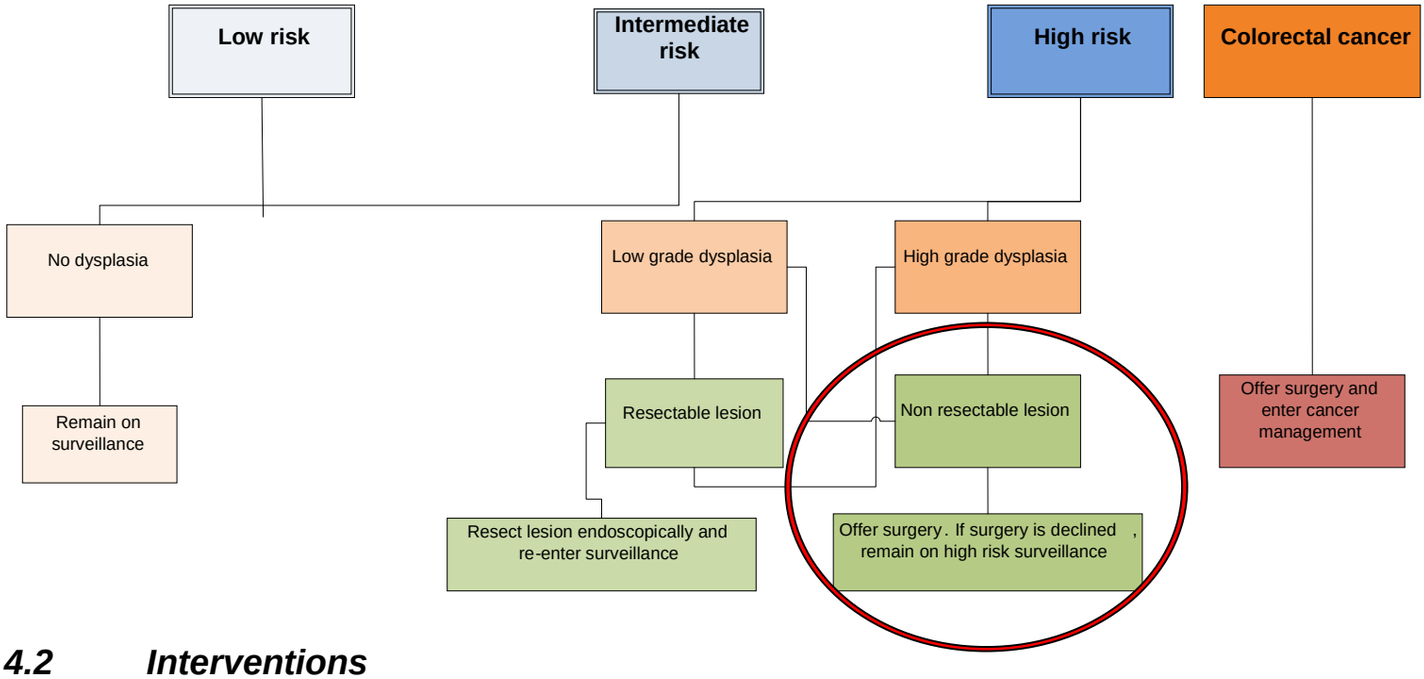
Based on the data available at the time of guideline development, the model was initially constructed with the idea that the surveillance intervals would depend on the degree of dysplasia (since dysplasia is a premalignant marker for colorectal cancer). However, in the final GDG, it was determined that the surveillance interval should depend on a person's personal risk factors. So, the IBD surveillance schedule was stratified according to the risk of developing colorectal cancer. The GDG identified three risk groups: low risk, intermediate risk and high risk.

Because of the tight timelines between the final GDG and the consultation date, the original model that was created based on dysplasia allowed the cost effectiveness to be determined only for the high-risk group because people at high risk (as defined by the GDG), were people with a previous history of primary sclerosing cholangitis, ongoing inflammation, dysplasia or colonic strictures. More specifically, the model simulated men and women aged 30 to 85 years who had flat dysplastic lesions (that is, non-resectable low or high-

grade dysplasia) and declined surgery; please refer to the circled area in figure 1.

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

Figure 1: Management of dysplasia



4.2 Interventions

In order to demonstrate that surveillance is beneficial for people with IBD, there needs to be a reduction in mortality caused by colorectal cancer. Colonoscopic surveillance was found to be clinically effective for people with IBD. Therefore the intervention used in the model was colonoscopy. It will be assumed, as is recommended in the updated British Society of Gastroenterology (2010) guidelines for IBD, that surveillance colonoscopy should be performed when colonic disease is in remission.

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) during the course of their disease depending on their degree of dysplasia. However, surgery will not be considered in this model. For simplicity, it was assumed that all those who enter the model have confirmed dysplasia (either low or high grade) and have declined surgery. The surveillance schedule proposed in this guideline is based on existing guidelines (British Society of Gastroenterology 2010) and GDG opinion, as follows:

- 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 will be used to analyse the cost effectiveness of colonoscopic surveillance for people with non-resectable dysplastic lesions who are considered to be 'high risk' and require annual surveillance. This will require 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 directly relevant papers that specifically examined colonoscopic surveillance for prevention of colorectal cancer in people with IBD. However, during the search, three studies were identified (Nguyen et al. 2009, Provenzale et al. 1995 and Delco et al. 2000) which 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 were used to explore approaches to modelling strategies and, where applicable, to inform the model structure. The views of a health economist and the GDG plus clinical data were also used to inform the model. Given the absence of

any appropriate analysis that addressed the decision problem directly, a new cost-effectiveness model was constructed.

5.2 Potential modelling approach

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

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

The modelling started at age 30. It was assumed that the person had colitis symptoms for at least 10 years (that is, symptoms began at age 20), had a screening colonoscopy which identified dysplasia, and consequently entered a surveillance programme. The cycle length of a quarter of a year (that is, 3 months) seemed most appropriate, because surveillance for the high-risk group occurs annually and this cycle length allowed asymptomatic and symptomatic cancer to potentially develop between colonoscopies.

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

5.3 Natural history review

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

needed to be able to calculate unobserved transitions. Further details are provided in the transition probability section (section 6.2).

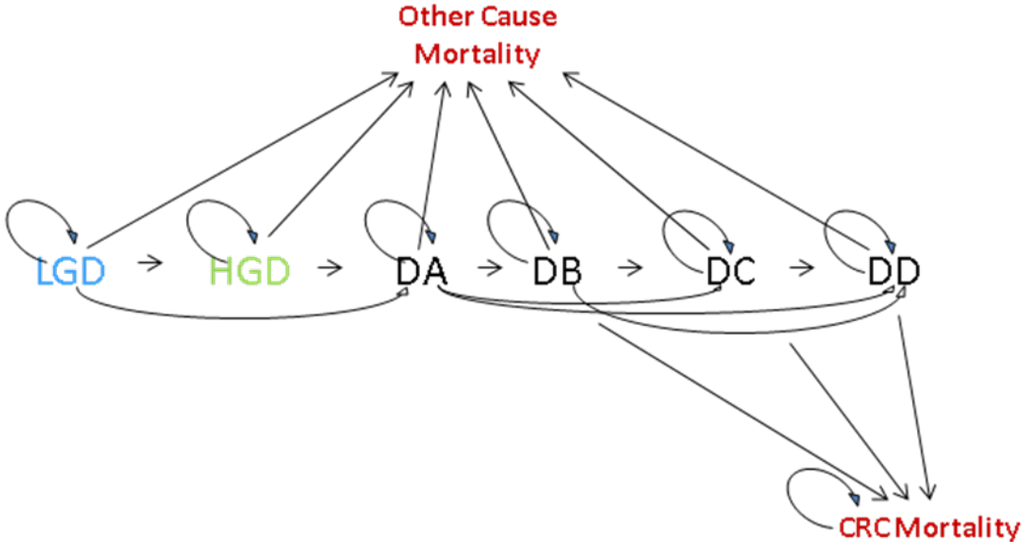
The natural history of colorectal cancer was obtained from a published cost-effectiveness study by Tappenden et al. (2004) that systematically reviewed cost-effectiveness studies for colorectal cancer screening in the UK. Therefore, colorectal cancer transition probabilities (that is, progression to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

6 Model

6.1 Model Structure

Figure 2 shows the basic outline of the surveillance model for the high-risk group.

Figure 2 Markov state diagram for the high-risk group in the IBD colonoscopic surveillance programme



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

Each section will now be discussed in detail.

6.1.1 Surveillance/natural history

Colonoscopic surveillance is recommended on an annual basis (every fourth cycle in the model) and it was assumed that colonoscopy was completed at the beginning of the cycle. The development of colorectal cancer could be sequential, that is, progression from low-grade dysplasia to high-grade dysplasia to colorectal cancer; or from low-grade dysplasia directly to colorectal cancer, because not all people with low-grade dysplasia 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. Likewise, progress 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 Cancer

Cancer states were stratified by tumour stage at diagnosis using Dukes' staging. If a person developed Dukes' A, 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' stage B, C and D and therefore was applied to each of these states. Once cancer is diagnosed, the person was assumed to enter a cancer management programme; that is, people receive chemotherapy, surgery and/or radiotherapy. All the cancer states were allocated both costs and utility values.

6.1.3 Adverse events

The model assumed no complications from colonoscopy. Although perforation and bleeding are serious risks of colonoscopy they occur infrequently. Therefore to simplify the model it was assumed that no complications occurred during the 55 years of surveillance.

Likewise, the cost-effectiveness study by Nguyen et al. (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 seems reasonable, because people are more likely to adhere to a programme when they are informed that they are at the highest risk of developing colorectal cancer among those with IBD. Similarly, the study by Rutter et al. reported a long-term compliance rate of 94.3%.

6.2 Transition probabilities

There are two sets of transitions included in the model; the natural history of dysplasia and of colorectal cancer. The details of the chosen values are outlined in the following sections.

6.2.1 Natural history and cancer

The probabilities derived from the observational study by Rutter et al. were chosen because the study followed a UK population for 30 years of colonoscopic surveillance. The study reported the first and maximal neoplasia as needed by the cost-effectiveness model. The cancer outcomes were also reported in Dukes' staging and the study was included in the clinical-effectiveness data for this guideline. Therefore, it was deemed appropriate to use this study as the basis for the calculation of 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 an interventional procedure, as it is for resectable dysplastic lesions.

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

Mortality for low-grade dysplasia, high-grade dysplasia and asymptomatic cancer states were assumed to be age dependent (that is, age-related

mortality). It was assumed that people in the asymptomatic cancer states have the same probability of dying as people in the general population at that same age. This appears to be reasonable because asymptomatic people are unlikely to have an increased risk of death until their cancer progresses. Annual colorectal cancer-related mortality was taken from Tappenden et al. 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 state. This ensured that all probabilities summed to one.

To convert the 30-year observational data from Rutter et al. 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 yearly transition matrix

	LG	HG	DA	DB	DC	DD	mCRC	mOther
LG	#	0.0095	0.0050	0.0000	0.0000	0.0000	0.0000	Age
HG	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

1minus 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.

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 is intuitively simple. It allows calculation of a probability based not only on understanding the probability distribution of an event but also on any prior information there is. These two parts are technically called the posterior and the prior.

In this case prior beliefs can be included for the transitions for which there are no observed data but it is known they can occur. For more details on the method please see Briggs et al.

Therefore, for transitions where a transition probability is needed, uninformative priors will be used, thereby allowing these transitions to be calculated.

The chosen priors are presented in table 3.

Table 3 Priors for natural history transition matrix

	LG	HG	DA	DB	DC	DD	mCRC	mOther
LG	0.12	0.12	0.12	0	0	0	0	Age
HG	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 used for transitions where no data are available but transitions are expected to occur. 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 observed data.

So, calculating the probabilities from Rutter et al and the dirichlet framework, the following transition matrices for the natural history (table 4) will be used. These represent the tri-monthly (or quarter of a year) transitions used in the model.

Table 4 Final transition matrix - natural history (quarter of a year)

	LG	HG	DA	DB	DC	DD	mCRC	mOther
LG	0.99466	0.00354	0.00180	0.00000	0.00000	0.00000	0.00000	Age
HG	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								

6.2.2 Histopathology

The GDG recommended the median of 8 biopsy specimens per colonoscopy, with a lower limit of 5 and an upper limit of 8. Uncertainty was captured using a simple uniform distribution with the minimum and maximum because no information on the distribution was available.

7 Quality of life section

Ideally a full systematic review would be carried out to identify health-related quality of life (HRQoL) studies and appropriate values for inclusion in a health economic model. However, because of the constraints of resources and time this was not possible. Therefore 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 explored for quality-adjusted life year (QALY) data.

7.1 Literature search

The search that was carried out identified one potential paper. The study by Gregor et al. (1997) 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 (TTO). 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 to 1 scale as provided by generic questionnaires.

7.2 Quality of life

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

7.3 Natural history/surveillance

The GDG agreed that the values obtained from Gregor et al. could be used as a proxy for 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 seems 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 subsequently 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 Duke's state. Asymptomatic cancers were assigned the same utility value as their

diagnostic state because if the cancer is still 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

All the health states in the model had their specific health state utility value multiplied by their age-related utility value. 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, it multiplies the effect.

7.6 Final quality of life values

Table 5 Final health-related quality of life estimates

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

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

8 Resource use

8.1 Literature search

From the initial search 3 studies (Hanauer et al. 1998, Stark et al. 2006, Bodger et al. 2002) were identified that examined resource use in IBD. The study by Hanauer et al. was excluded because it reported the cost of illness of Crohn's disease from a US perspective. The study by Stark et al. was

excluded because it reported the cost of illness of inflammatory bowel disease from a German perspective. Bodger et al. was the only study from a UK perspective on the cost of illness of Crohn's disease from one hospital. However, the costs were reported in US dollars and did not have a breakdown of the costs as needed in the model.

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

8.1.1 Specific costs for the model

The main cost inputs that required consideration include:

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

Each of these costs will now be considered in detail below.

8.1.1.1 Colonoscopy

The cost of colonoscopy was obtained from a GDG member and was validated with the publically listed price in NHS reference costs 2008/09.

8.1.1.2 Cancer

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

8.1.1.3 Distributions of estimates

It is recommended (Briggs et al. 2003) 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. For the values derived from the NHS and other published papers which have a stated standard error, these will be

utilised in the model. For the cancer pathology costs standard errors were calculated because only the mean value was available.

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

Mean cost	Mean	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 a quarter of a year was assumed to be most appropriate, because surveillance for the high-risk group occurs annually and it allowed asymptomatic and symptomatic cancer to potentially develop between colonoscopies.

9.2 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.

9.3 Sensitivity/specificity

We assumed no misdiagnosis for colonoscopy. This follows the assumption that there may have been some degree of misdiagnosis in the study by Rutter et al. Therefore, to include it would double count the number of misdiagnoses.

9.4 Adverse events

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

9.5 Compliance

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

9.6 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 state and benefits applied for each time period in the state. This was assumed in the cost-effectiveness study by Tappenden et al. and was a limitation identified in that study. This limitation could potentially lead to conflicting conclusions over the effect of colorectal cancer. However, because modelling the entire colorectal cancer pathway is not possible within this guideline this is an acceptable simplification.

10 Results

The overall deterministic results are presented in table 7 and uncertainty regarding the results will follow.

Table 7 Base-case results over a 55-year period

	Base case				
	QALY	**Costs**	**Incremental QALY**	**Incremental costs**	**ICER**
No CS	16.42	£2320.44			
CS -Higher risk only	17.19	£15,785.13	0.77	£13,464.69	£17,557.32

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; CS: colonoscopic surveillance

The analysis suggested that surveillance for the high-risk group does appear to be 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 analysis

'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.

A few 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 these variables either the lower or the upper point estimate was used while keeping all other variables constant and the resulting ICER is reported for each 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 the table above 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 both the 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. So the joint impact of altering all of these simultaneously needs to be estimated. The method used to do this is known as probabilistic sensitivity analysis (PSA). The PSA 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 PSA is presented in table 9.

Table 9 Probabilistic sensitivity analysis

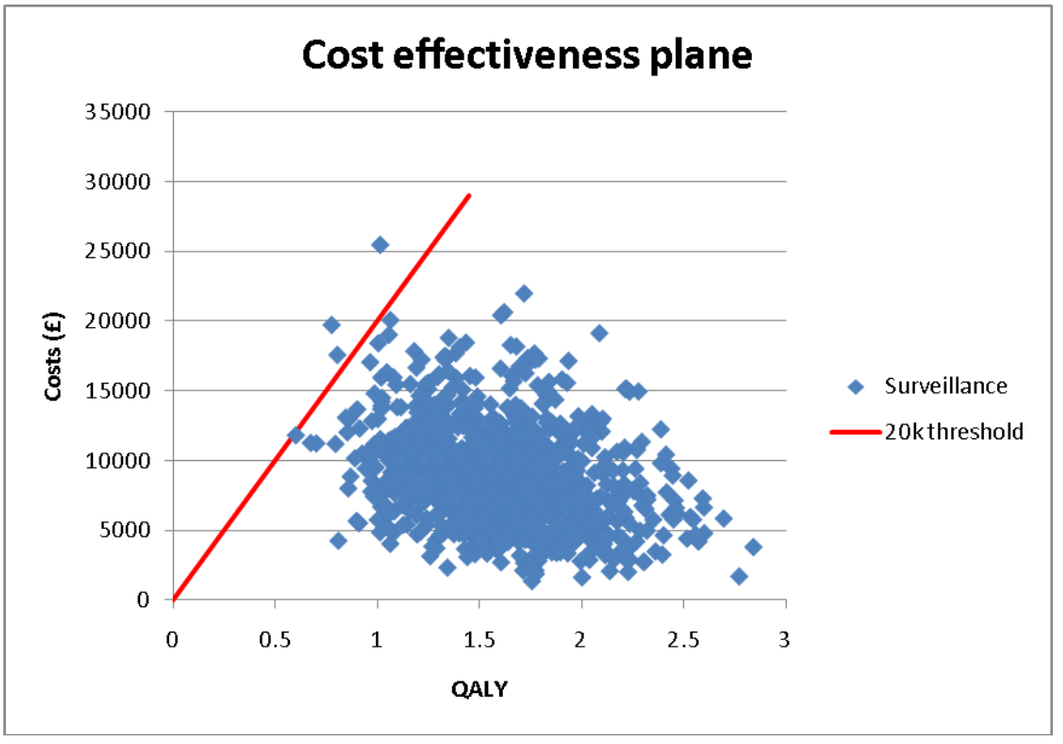
	PSA				
	QALY	**costs**	**Inc QALY**	**Inc costs**	**ICER**
No CS	13.04	£7,368.92			
CS _high-risk only	14.64	£16,316.82	1.61	£8,947.90	£5,571.44

PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; CS: colonoscopic surveillance

The PSA shows that colonoscopic surveillance for the high-risk population is an optimal strategy compared with a no surveillance strategy. The PSA ICER was lower than the deterministic ICER; this suggests that there may be a high degree of uncertainty associated with some model parameters (as discussed in section 11.1) resulting in a large change in the ICER. However, in spite of the uncertainty the results are still cost effective and remain under £20,000 per QALY gained. Among the 1000 simulations, surveillance was found to be cost effective in 100% of the cases.

The figure below shows the results of the 1000 simulations of the PSA represented on the cost-effectiveness plane.

Figure 3: Cost-effectiveness plane for high-risk group (IBD)



12 Discussion and conclusions

12.1 Strengths

This model is similar to 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 depending on the stage of cancer detection. This allows better identification of whether annual colonoscopies detect early stage cancer, which reduces cancer-related mortality.

The analyses attempt to consider the uncertainty in the data and therefore probabilistic sensitivity analyses have been conducted to explore it.

12.2 Limitations

12.2.1 Natural history of dysplasia

The clinical data used to derive the transition probabilities were from an observational study of low quality. 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

The high-risk group is composed of two subgroups: people with non-resectable dysplastic lesions who have declined surgery and people with resectable dysplastic lesions which have been removed endoscopically. Both these subgroups require annual surveillance using colonoscopy. It seems unlikely that both groups would progress to colorectal cancer at the same rate; and because of the time constraints, this model only assessed the former group.

12.2.3 Quality of life data

There remains uncertainty over 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. From the patient experts and clinical specialists on the GDG the psychological burden of being diagnosed with dysplasia and its grade can be very high. The approach taken to address the uncertainly was to conduct both a one-way sensitivity analysis and a probabilistic sensitivity analysis by varying the utility values.

12.2.4 Treatment pathway

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

12.2.5 Chromoscopy

Chromoscopy was recommended for use in routine surveillance for people with IBD. According to the NHS reference costs 2008/09, chromoscopy has the same tariff as conventional colonoscopy (that is, it costs the same). The GDG felt that although the procedure may cost the same, the time needed to train healthcare professionals on how to use chromoscopy took 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 and chromoscopy. The GDG also stated that chromoscopy took longer to perform than colonoscopy. However, the difference was not found to be statistically significant. Finally, for a true comparison the incorporation, of sensitivity and specificity would be required to differentiate between the two modes of colonoscopy.

12.2.6 Costs based on reference costs

These costs may not be representative of the true costs of the procedure. However, these are published NHS costs and therefore, represent the average NHS costs across the country.

13 Conclusions

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

14 Future work

Unfortunately because of time constraints between the final GDG where the surveillance schedule was created and the consultation date for the guideline, it was not possible to construct a new cost-effectiveness model which assessed surveillance for all three risk groups because transition probabilities

would be dependent on several factors in any given risk group. There is the possibility that surveillance may not be cost effective for all three groups simultaneously.Therefore, it would be important for future work in IBD to evaluate whether the entire surveillance programme, (for all three risk groups including those with resectable lesions), would prove to be cost effective.

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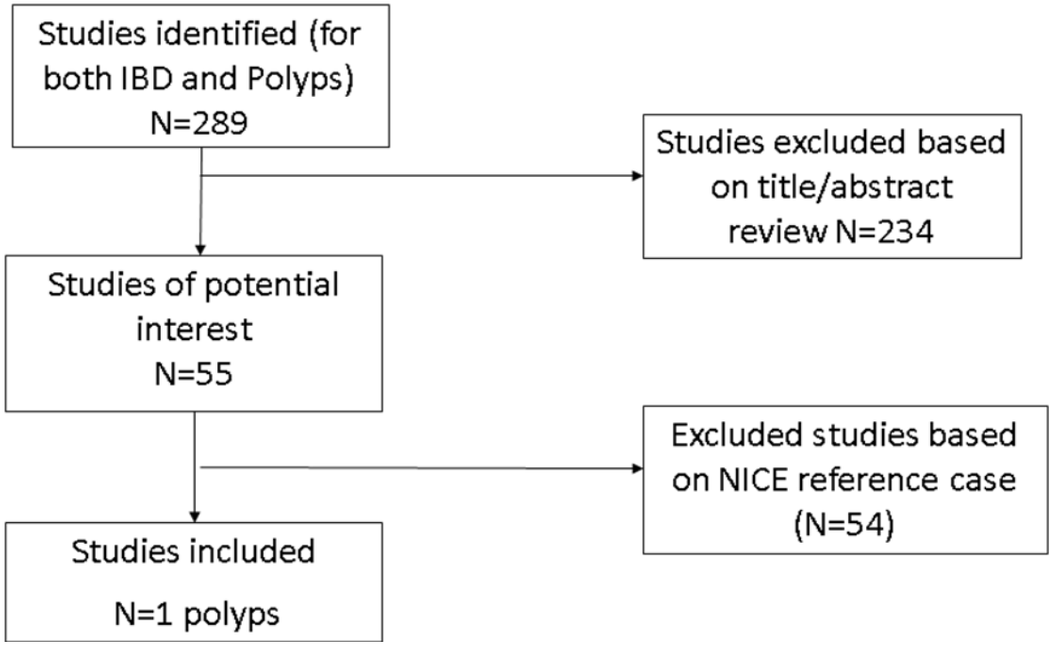
16 Appendices

16.1 Inclusion/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 US 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 was taken from a Crohn's disease study using

		time trade off. CRC QALY data from US 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 higher risk group was evaluated. Robust ICER for the higher risk group nonetheless (as demonstrated in the PSA).		

Appendix 8 – Health economic evaluation

Cost-effectiveness analysis of colonoscopic surveillance: adenomas

1 Introduction

NICE has been asked by the Department of Health to produce a short clinical guideline on colonoscopic surveillance for patients with ulcerative colitis, Crohn's disease and polyps to prevent colorectal cancer. What follows is the cost-effectiveness analysis for colonoscopic surveillance for polyps developed to support the Guideline Development Group (GDG) in making recommendations.

This analysis has been conducted according to NICE methods outlined in the Guide to the methods of technology appraisal 2008 and the Guidelines Manual 2009. Therefore, it follows the NICE reference case (the framework NICE requests all cost-effectiveness analysis to follow) in the methods used.

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.

3 Contents

4 Decision problem

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

Table 2 Decision problem

	Scope	Approach taken
Population	Adults with polyps including adenomas in the colon and rectum	Men and women at the age of 50 years who have polyps removed at baseline colonoscopy
Interventions	No surveillance	No surveillance Surveillance using colonoscopy
Comparators	Surveillance using conventional colonoscopy, chromoscopy, computerised tomography colonoscopy, narrow band imaging, double-barium contrast enema	Surveillance using conventional colonoscopy
Outcome(s)	Costs, quality-adjusted life years (QALYs)and cost per QALY	Cost per QALY

*QALY – quality-adjusted life years

4.1 Population

Evidence suggests that the prevalence of polyps is 30–40% at age 60 years (Williams et al. 1982) and adenomas are diagnosed on average 10 years

earlier than colorectal cancers (Olsen et al. 1988). Therefore, the age of the cohort in the model is 50 years in order to capture premalignant polyps. People who have adenomas with advanced pathology entering the surveillance model would have any detected polyps removed at baseline colonoscopy. All polyps and adenomas identified during surveillance would be removed at the point of detection. People in the model would be at high risk of developing colorectal cancer and have adenomas with advanced pathology.

4.2 Interventions

From the clinical review there was no evidence for or against routine colonoscopic surveillance for the prevention and early detection of colorectal cancer after removal of adenomas. Colonoscopic surveillance is recommended for people with polyps after removal of adenomatous polyps in preventing colorectal cancer (Atkin and Saunders 2002). Currently there is no national guidance based on the clinical and cost effectiveness of surveillance in the NHS. A new model will assess the cost effectiveness of current practice in the NHS, which broadly follows the British Society of Gastroenterology guidelines (Atkin and Saunders 2002).

4.3 Comparators

The British Society of Gastroenterology recommended surveillance after removal of adenomatous polyps (Atkin and Saunders 2002). The guidelines have recently been updated with no change in the recommendations because there was no further evidence published (Cairns et al. 2010). These recommendations included the frequency of surveillance using colonoscopy depending on the size and number of adenomas removed at the baseline colonoscopy. In the NHS bowel cancer screening programme has been fully rolled out at the end of 2009. There is a gap identified where an evidence-based national guideline on colonoscopic surveillance is required in order to reduce variations in clinical practice and colorectal cancer-related mortality in the NHS. Colonoscopy has been used as the gold standard for surveillance and screening for colorectal cancer in the NHS. Therefore, colonoscopic surveillance using colonoscopy will be the main comparator in the surveillance

model compared with no surveillance. From the baseline colonoscopy a person's risk status is defined in terms of the index lesion, which is the greatest malignant potential of the adenoma present or the most advanced cancer present. Alternative surveillance strategies for people after removal of adenoma(s) were determined by the person's risk status at baseline colonoscopy. The surveillance model broadly follows the British Society of Gastroenterology guideline in terms of size and number of adenomas detected at baseline colonoscopy (Atkin and Saunders, 2002). In the model surveillance in low, intermediate and high-risk groups will be referred to as following the British Society of Gastroenterology guidelines for simplicity. The outline of the surveillance strategies considered in the new model is shown in table 2.

Table 3 Surveillance schedule following adenoma removal in the new model

Risk status	Schedule
Low risk :1-2 adenomas AND both small (<1cm)	Follow up at 5 years, then exit surveillance if negative outcome
Intermediate risk: (3-4 adenomas OR at least one ≥ 1cml	Every three years till 2 consecutive negative outcomes
High risk: ≥ 5 small adenomas OR ≥ 3 at least one ≥1cm	Follow-up at 12 months; • If high risk adenomas detected follow-up yearly • If negative, low risk or intermediate risk adenomas detected step-down to intermediate risk

4.4 Outcomes

In line with the NICE reference case a cost–utility analysis will be used to assess the cost effectiveness of colonoscopic surveillance using conventional colonoscopy. If possible an existing analysis will be used if it fits the decision problem; if not then a new analysis will be constructed. This will require 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 (see appendices 13.1). 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 data. The remaining 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 (IBD), 234 studies were excluded based on title and abstract review. The applicability of 55 studies was assessed using a checklist. Of 55 studies of potential interest, 54 studies were excluded based on NICE methods and the NICE reference case using modified GRADE methods. Only one study was relevant to surveillance for polyps (Tappenden et al. 2007), which was an extension of an original study (Tappenden et al. 2004). A GRADE table which summarises the studies is presented in appendices 14.5.

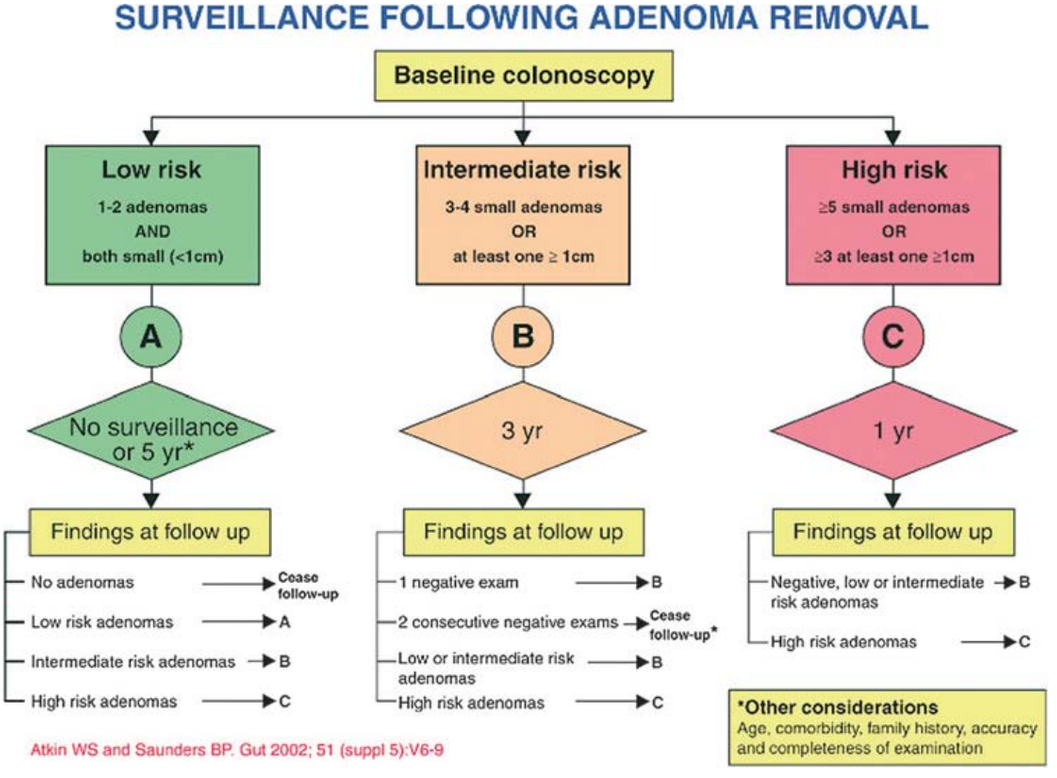
After review one identified study was considered of high quality and provided valuable information on the modelling approach. However, the study has limited applicability because of the different population and comparators for the decision problem. Therefore, a new model will be required to address this question.

5.3 Potential modelling approach

Colonic polyps and recurrent adenomas are chronic conditions that require lifetime surveillance in preventing colorectal cancer (Atkin and Saunders, 2002). The transformation of adenomatous polyps to invasive colorectal

cancer is slow and can take 10–15 years before becoming symptomatic cancer (South West Cancer Intelligence Service 1995). Therefore, a lifetime horizon will be considered in a Markov model. This is associated with constant and/or increased risk over time and the importance of timing detection in the transformation of adenoma to cancer. The states will represent the progression of the condition over time from adenoma-free post-polypectomy to new non-advanced adenomas post-polypectomy to asymptomatic and symptomatic colorectal cancer (using modified Turnbull stages/classification Dukes' A to Dukes' D) (Dukes 1932) to death. A person's risk status as defined by the British Society of Gastroenterologists guideline is used according to the outcome of the index lesion at baseline colonoscopy in figure 1 (Atkin and Saunders, 2002).

Figure 1 Surveillance following adenoma removal (Atkin and Saunders, 2002)



The GDG acknowledged that the future risk of developing colorectal cancer or advanced adenoma after removal of adenomas depends on the number and

size of adenomas removed at baseline colonoscopy as indicated in the British Society of Gastroenterology guidelines (Cairns et al. 2010). The ultimate goal of colonoscopic surveillance lies in the prevention of subsequent colorectal cancer rather than the detection and removal of adenomas, most of which will not become malignant.

In the new model, risk status was decided by the size and number of adenomas detected in the baseline colonoscopy and subsequent colonoscopic surveillance. All newly detected adenomas are assumed to be endoscopically removed at the point of detection in the surveillance model. People in the surveillance programme are assumed to adhere to the colonoscopy schedule. For the purpose of the guideline in comparing a surveillance programme with no surveillance, the sensitivity and specificity of colonoscopy were assumed to be 100%. This was agreed with the GDG.

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. Colorectal cancers are diagnosed average 10 years after initial diagnosis of adenomas (Olsen et al. 1988). The estimated prevalence of colonic adenomas is 30–40% at age 60 years with the lifetime cumulative incidence of colorectal cancer at 5.5% (Lieberman et al. 2000). The size of adenomas correlated positively with malignant potential (Muto et al. 1975). It is likely for small adenomas to progress to invasive cancer in more than 5 years (Eide 1986).

Outcomes of clinical treatment can be extracted through using natural history of adenoma/polyps 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 constraints 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 provide estimates for the progression of polyps to colorectal cancer. One study was identified which originally reported the cost

effectiveness and cost–utility of colorectal cancer screening options in England (Tappenden et al. 2004). In the report, surveillance for colorectal cancer was modelled after a systematic review of literature. These studies were examined for suitable transition probabilities for a new Markov model. However, the GDG fully appreciated the limited evidence in the natural history of the adenoma to cancer sequence in colorectal cancer.

One study was selected (Tappenden et al. 2004) which included a systematic review of the literature. The key unknown parameters related to the natural history of undetected colorectal cancer and polyp incidence and growth rates, the rate at which high-risk adenomas develop into cancer, and stage-specific colorectal cancer-specific mortality were derived through 60,000 random iterations, of which around 400 potential solutions were identified that appeared to fit the published incidence and mortality data (Tappenden et al. 2004). Therefore the input parameters for the model were chosen in a systematic way according to the NICE methods, which recommend that parameters should be chosen in a systematic way and ideally based on a systematic review.

The data available on the natural history of colorectal cancer developing from adenomatous polyps is limited. The National Polyp Study (Winawer et al. 1993) has been frequently used in several identified studies. Data about the natural history of colorectal polyps and colorectal cancer were taken from Tappenden et al. (2004) which used 60,000 calibrations against published incidence and mortality data based on a systematic review of the literature.

6 Model

6.1 Model structure

The overall structure of the colonoscopic surveillance model in given in figure 2.

Figure 2 Model structure

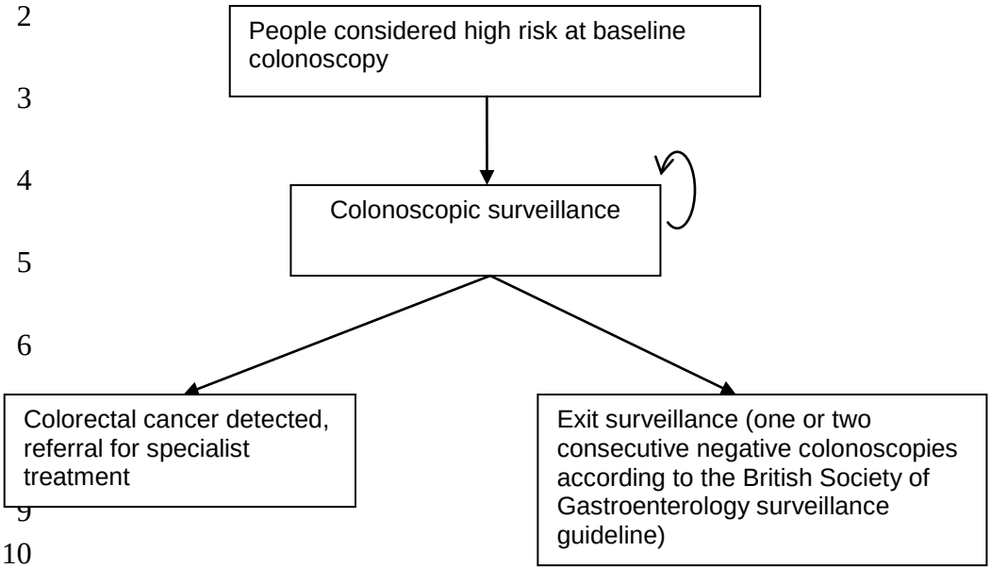
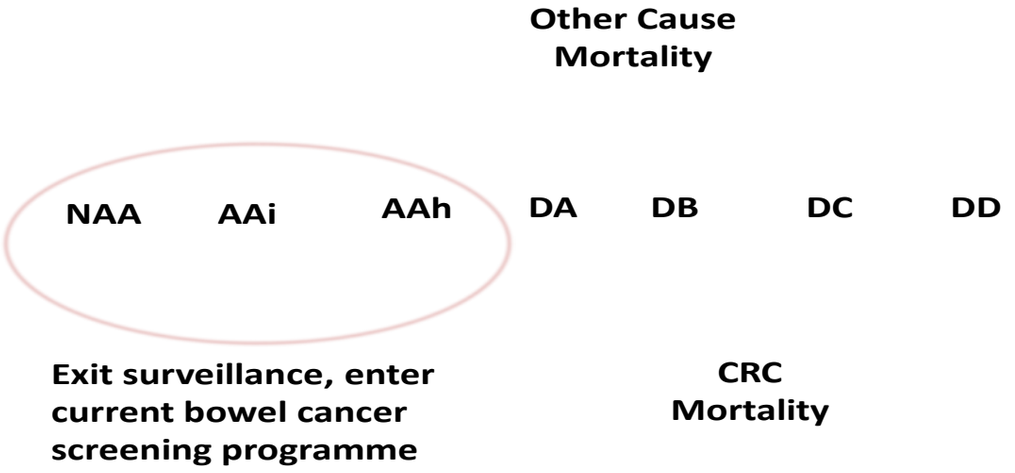


Figure 3 Outline of surveillance model



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.

The outline of the model with the main features highlighted is presented in figure 3. The main components are the natural history and surveillance strategy. Each section will now be discussed in detail.

6.1.1 Surveillance

In the surveillance model a Markov state is used to represent repeated colonoscopic surveillance. 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. The effectiveness of colonoscopic surveillance in removing adenomas for prevention of colorectal cancer was measured from QALY gains in people who exit the surveillance programme according to the surveillance strategies. The state includes the polyp-free states and recurrent adenomas to incorporate the natural history of recurring adenomas following adenoma removal. The strategy for colonoscopic surveillance using colonoscopy will depend on the person's risk status defined at the index colonoscopy as outlined in the British Society of Gastroenterology guidelines (Atkin and Saunders, 2002). The current British Society of Gastroenterology guideline recommends either no surveillance or follow-up at 5 years in the low-risk group. In this analysis, the current British Society of Gastroenterology guideline refers to surveillance for people in the low, intermediate, and high-risk groups. The probability of developing a new adenoma in people at high risk of developing colorectal cancer was assumed to be higher than in people with no prior history of adenomas (Winawer et al. 1993).

6.1.2 Colorectal cancer

Symptomatic and asymptomatic colorectal cancers will be modelled in the surveillance model. Colorectal cancers incur the same costs assigned to health states in both the natural history and surveillance model because the effectiveness of the surveillance strategy will affect detection rates of premalignant and early cancer. This will only affect the average costs. It was

assumed the detection and/or diagnosis of colorectal cancer will be made by symptomatic presentation or surveillance in the model.

6.1.3 Adverse events

In the surveillance model no complications or adverse events were assumed. This was agreed with the GDG for the purpose of assessing the cost effectiveness of providing colonoscopic surveillance for preventing colorectal cancer compared with no surveillance in the NHS. Therefore, each strategy is treated as an intervention.

6.1.4 Post states (tunnel states)

In the surveillance model two states represent post-removal of adenomas depending on previous adenomas to determine surveillance strategy:

- Adenoma-free (AF) post-removal of non-advanced adenoma (NAA) at year 1 and year 2 onwards
- AF post-removal of advanced adenoma (AA) at year 1 and year 2 onwards

It was assumed that all adenomas are removed endoscopically at the point of detection during surveillance. It was also agreed with the GDG that all colorectal cancers arise from pre-existing adenomas, therefore all colorectal cancers will be detected by surveillance unless people become symptomatic. The main consideration is that in this model 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 that can be treated with surgery only (in Dukes' A colorectal cancer) and subsequent long-term survival. Therefore, the model is designed to distinguish between those who have had treatments for an asymptomatic cancer detected through surveillance and those who have had cancer detected when they became symptomatic. In the model the treatment benefit will distinguish between early detected cancer and asymptomatic and symptomatic cancer

reflected in the costs and health benefits (QALYs). People who are diagnosed with colorectal cancer (asymptomatic or symptomatic) will receive identical stage-specific treatments. This was assumed in order to compare the magnitude of colonoscopic surveillance in detecting adenomas and preventing colorectal cancers compared with no surveillance under identical conditions. People can transit to death from all states.

6.2 Transition probabilities

The yearly transition probabilities were taken from Tappenden et al. (2004). They were obtained by calibrating the model against the published incidence and mortality data that were systematically reviewed in their report. Data from published interim life tables for the UK (Office of National Statistics 2009) was used to produce age-related mortality probabilities. It will be assumed that people in the asymptomatic colorectal cancer states have the same probability of dying as their age-related probability. This appears to be reasonable because asymptomatic patients are unlikely to have an increased risk of death until their cancer progresses. This ensured that all probabilities sum to one.

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 – other states, Age: age-dependent

7 Quality of life section

The QALY is a measure of a person's length of life weighted by a valuation of their health-related quality of life (HRQoL) over that period. The HRQoL 'weighting' includes the description of changes in HRQoL itself and a valuation of that described HRQoL. NICE recommends the information on changes in HRQoL as a result of intervention/treatment should be directly reported by patients. The valuation of changes in HRQoL reported by patients 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 for inclusion in a health economic model. However, because of constraints of

resources and time this was not possible. Therefore a search will be carried out for quality of life studies and the quality of life data included in the cost-effectiveness analyses identified in section 4 will be reviewed.

7.1 Literature search

A literature search retrieved literature relating to quality of life in people with polyps or adenomas. Evidence about quality of life for people with colorectal cancers was also limited.

7.1.1 Review of literature

Utility values (health benefits) associated with all cancer-free states and polyp-free states were assumed to be equivalent to 'no known history of adenomas' (utility value 0.91) (Tappenden et al. 2004). The main study referenced was Ness et al. (1999). Ness et al. (1999) assessed utility values associated with the stage of cancer and treatment in 90 people who previously had colorectal adenomas removed. 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.

7.1.2 Quality of life – model

NICE recommends the use of the EuroQol 5 dimensions (EQ-5D) or another generic tool which enables patients to describe their health states and how the public values their health states. In addition, there is no one set of values that can be used for the entire model. There are also potential issues with using different values from different sources, which may lead to inconsistency. For example time trade off and standard gamble techniques have a tendency to produce different estimates for the same health states. To minimise potential issues studies will be 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. (1999) was appropriate in the model.

7.1.3 Cancer-free state and quality of life

Utility values associated with the cancer-free health state and the adenoma-free health state were assumed to be 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. The utility value associated with asymptomatic cancer and undiagnosed cancer was assumed to be 0.91. Utility value estimates were age-independent in the model.

7.1.4 Stage-specific colorectal cancer and QALYs

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

7.1.5 Quality of life – colonoscopy

Because of the lack of demonstrated decreases in utility values associated with discomfort from intensive bowel preparation and the recovery period, these were not considered in cancer-free health state. However, 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, the assumption of disutility associated with colonoscopy (Syngal et al. 1998) will be considered in sensitivity analyses.

7.1.6 Final QALY scores

Table 4 Final health-related quality of life estimates

State	Mean value	Standard error	Reference
Cancer-free state	0.91	0.836	Ness et al. (2000)
Dukes' A CRC	0.74	0.784	Ness et al. (1999)
Dukes' B CRC	0.70	0.770	Ness et al. (1999)
Dukes' C CRC	0.50	0.701	Ness et al. (1999)
Dukes' D CRC	0.25	0.569	Ness et al. (1999)
Asymptomatic cancer	0.91	0.836	Ness et al. (2000)
CRC: colorectal cancer			

8 Resource use

8.1 Literature search

From the initial search 2 studies were identified that examined resource use in the NHS. These studies were 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 Colonoscopy and natural history – cost-effectiveness studies

For the UK the reference costs are the main publically collected resource sets. A potential limitation associated with NHS reference costs is acknowledged and concerns whether they accurately represent the underlying costs involved.

8.1.2 Specific costs for the model

The input parameters for costs considered in the model broadly include:

- Colonoscopy and pathology
- Lifetime treatment costs for stage-specific diagnosed and symptomatic colorectal cancer.

Each of these costs will now be considered in detail below.

8.1.2.1 Endoscopy

The cost of endoscopy is provided by the NHS cost code FZ26A – endoscopic or intermediate large intestine procedures 19 years and over with a corresponding cost of £517 (NHS reference costs 2008/09).

8.1.2.2 Pathology for adenoma and cancer

The cost of pathology for adenomas is provided by the NHS cost code DAP824 – histology or histopathology (NHS reference costs 2008/09).

8.1.2.3 Stage-specific treatment costs for colorectal cancer

Recently uplifted stage-specific treatment costs for colorectal cancer were obtained through personal communication and based on a study published in 2004 by Tappenden et al. (personal communication with Paul Tappenden and Hazel Pilgrim, 8 April 2010). These broadly include chemotherapy, surgery/radiotherapy (where appropriate), follow-up, and palliative care.

8.1.2.4 Distributions of estimates

It is recommended (Briggs et al. 2003) that the gamma distribution is the appropriate probability distribution for costs. To fit a gamma distribution the standard error is required for each value. For the values obtained from personal communication with Tappenden and Pilgrim the standard errors were calculated using the mean costs, 97.5% and 2.5% credibility intervals (Tappenden and Pilgrim, 2010). For the reference costs standard errors were calculated because only the mean and quartile values (except the median) were available. There is no agreed method on the appropriate methodology for the calculation of standard errors from the reference costs. The method utilised was to use the solver function in Excel to find the variables for the gamma function that produces the relevant estimates of the upper and lower quartile.

9 Assumptions

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

9.1.1 Cycle length and age of cohort

The GDG agreed the cohort age to be 50 because of the slow transformation of adenoma to cancer from the published literature. It was considered that a yearly cycle length was appropriate because of the slow transformation of adenomas to colorectal cancer over 10–15 years (Winawer 1993). Therefore, a yearly cycle allows transitions to other states in between surveillance.

9.1.2 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, this assumption was therefore considered to be reasonable.

9.1.3 Drop out from surveillance

The GDG agreed that the low-risk group will not have further surveillance when one negative surveillance colonoscopy is obtained. The high-risk group will have a follow-up colonoscopy at 12 months. This decides the surveillance strategy; either to follow the frequency of surveillance for the intermediate-risk group or have subsequent colonoscopy at yearly intervals. People in the intermediate-risk group will have a 3 yearly follow-up, then exit surveillance if two consecutive negative results are obtained. People who do not need further surveillance will be sent to the current bowel cancer screening programme in the NHS. This surveillance schedule broadly follows the current British Society of Gastroenterology surveillance guideline (Atkin and Saunders, 2002). Health benefits (QALY gains) of people who meet the criteria for exiting the surveillance schedule are accounted for in the surveillance models.

9.1.4 Age dependency

Apart from age-dependent variables all others are 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. Death rate is age dependent. This is assuming that people with polyps have the same mortality as the rest of the UK population. This seems appropriate because there is no other reported difference in life expectancy than increased cancer rate and increased rate of recurrent adenomas in people with polyps.

9.1.5 Diagnosis and treatment of cancer

Colonoscopy, subsequent polypectomy and pathology are included for the surveillance and treatment of adenomas detected during surveillance. Surgery, chemotherapy and radiotherapy are included as the treatment for colorectal cancer. This includes appropriate NICE guidance for the treatment of colorectal cancer. Therefore, the impact of this on the cost effectiveness is the relative benefit of prevention or early detection of colorectal cancer. Costs incurred in each stage of colorectal cancer and detrimental to quality of life will be captured in the analysis.

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

9.1.6 Adenoma recurrence rate during surveillance

The probability of people in the high-risk group who have had adenomas removed developing further adenomas is higher than for people with no prior history of adenomas. All identified adenomas are removed at the point of detection. In the surveillance model two states represent post-adenoma

removal and depend on previous adenomas to determine the surveillance strategy. Tappenden et al. (2004) acknowledged the key uncertainties in their analysis, including the probabilities of progressing through undiagnosed cancer states, the probabilities of clinical presentation by cancer stage, polyp incidence and growth rates, the rate at which high-risk adenomas develop into cancer, and stage-specific CRC mortality rate.

9.1.7 Transitions in the model

Transition probabilities estimated in the model are assumed to be constant with the exception of age-specific adenoma incidence and mortality rate. Because of limited evidence the GDG agreed that all transitions from one health state to the next in the model are progressive, backward transitions are not allowed in the model.

9.1.8 Misdiagnosis

It was assumed that there was no misdiagnosis for colonoscopy in the model. The GDG acknowledged that the underlying data from observational studies included a degree of misdiagnosis and to include misdiagnosis would result in double counting the number of misdiagnoses. Therefore this assumption was reasonable to be made in the model.

9.1.9 Complications

For simplicity, in order to answer key clinical question 1, no colonoscopy-related or polypectomy-related complications were assumed in the model. The GDG discussed potential risks associated with colonoscopy and polypectomy, including bowel perforation and bleeding. The numbers reported were very small but these events could be fatal.

9.1.10 Utility values for cancer-free states

A person with adenomas, that is cancer-free, is likely to be asymptomatic. Therefore the utility value estimate in the cancer-free state is assumed to be the same as for the general population (Ness et al. 2000; Tappenden et al. 2004). The GDG considered this necessary for the model because most adenomas are asymptomatic.

9.1.11 Discomfort and disutility associated with colonoscopy

Colonoscopy requires full bowel preparation before the procedure and recovery from sedation after the procedure. This potentially results in short-term disutility. Discomfort associated with bowel preparation and recovery after the procedure will be explored using a disutility value of 0.0025 (Saini et al. 2010; Syngal et al. 1998).

9.1.12 Time horizon

It was agreed by the GDG that no further surveillance would be undertaken after 80 years of age, considering a slow transformation of adenoma to cancer over a decade. Therefore the model will be run over 30 years. A different time horizon may be considered in the sensitivity analyses.

9.1.13 Colorectal cancer

All colorectal cancers arise from pre-existing adenomas. A hypothetical cohort of men and women aged 50 with confirmed adenomas at the baseline colonoscopy will enter the surveillance programme. Probabilities of cancer progression are assumed to be equivalent in both the distal and proximal colon. Cancer is detected once it becomes symptomatic, asymptomatic cancer is only detected by colonoscopic surveillance. This appears to be a reasonable assumption because the population have no familial or previous history of colorectal cancer.

9.1.14 Final costs

Costs in the model were obtained from published NHS costs that represent the average NHS costs across the country. These costs are applied to people transitioning into the state. Stage-specific colorectal cancer treatment costs were uplifted from existing literature (personal communication with Tappenden and Pilgrim, 8 April 2010). The final values and breakdown are presented in table 5.

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

Costs	Mean	Standard error	Reference

Colonoscopy diagnostic/therapeutic	£517	172.78	NHS Reference costs 08/09
Pathology for adenoma	£26	20.79	NHS Reference costs 08/09
Pathology for cancer	£250	268.85	Tappenden et al. (2004)
Lifetime cost – Dukes' A	£11,965.78	6277.76	Tappenden & Pilgrim, 2010
Lifetime cost – Dukes' B	£16,224.50	3686.39	Tappenden & Pilgrim, 2010
Lifetime cost – Dukes' C	£21,033.60	2290.27	Tappenden & Pilgrim, 2010
Lifetime cost – Dukes' D	£24,096.80	2950.45	Tappenden & Pilgrim, 2010

10 Analysis

The incremental cost effectiveness ratio (ICER) is used as the measure of cost effectiveness because it is easier to interpret and also allows more sophisticated analyses. The threshold values that will be chosen are £20,000 and £30,000 per QALY gained. An ICER has been calculated for each treatment option in comparison with no surveillance.

10.1 Deterministic sensitivity analysis

Deterministic sensitivity analysis will be carried out on a range of variables including all costs and utility values. As discussed in section 8.1.6, the key uncertain areas in transition probability caused by lack of direct clinical data will be explored by examining two sets of transition matrices; one of the upper values from the literature and another set of lower values. The full matrices are in table 6. Costs will be explored by reducing them by 50% and increasing them by 50% to examine this effect. For quality of life, a person's quality of life will be explored in relation to the potential (dis)utility associated with intensive bowel preparation and the recovery period (Sandi et al. 2010 *in press*).

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	
			Minimum	Maximum
State from	state to			
LR	HR	0.02	0.005	0.0200
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 symptomatic Dukes' A CRC; PSDB: probability of presenting symptomatic Dukes' B CRC; PSDC: probability of presenting symptomatic Dukes' C CRC; PSDD: probability of presenting symptomatic Dukes' D CRC

10.2 Probabilistic sensitivity analysis

The following sections outline the variables and distributions subject to PSA. The cost-effectiveness plane, cost-effectiveness acceptability curves and cost-effectiveness acceptability frontiers will be presented from this analysis.

All transition probabilities in the natural history were varied using the probabilistic dirichlet distributions. These include natural history and stage-specific colorectal cancer mortality.

10.2.1 Utility values

Beta distributions of the differences between the estimates will be used to ensure that the probabilistic results remain consistent. Table 7 outlines the utility values that are varied according to their difference.

Table 7 Probabilistic sensitivity analysis calculations for quality of life

State	Mean	Standard error	Distribution
Cancer-free	0.91	0.8977	Log normal
Undiagnosed asymptomatic colorectal cancer	0.91	0.9090	Log normal
Dukes' A	0.74	0.7390	Log normal
Dukes' B	0.70	0.6733	Log normal
Dukes' C	0.50	0.4887	Log normal
Dukes' D	0.25	0.2321	Log normal

10.2.2 Costs

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

Table 8 PSA Gamma or normal distribution of costs

	Mean	Standard error
Colonoscopy	517.00	172.784
Lifetime treatment cost – Dukes' A	11965.78	6277.76
Lifetime treatment cost – Dukes' B	16224.50	3686.39
Lifetime treatment cost – Dukes' C	21033.60	2290.27
Lifetime treatment cost – Dukes' D	24096.80	22032.30

10.3 Structural sensitivity analysis

The following structural assumptions and variables will be explored in sensitivity analysis.

10.3.1 Time horizon

The time horizon will be varied from 35 to 40 and 45 years.

10.3.2 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 will be explored.

10.3.3 Stopping surveillance

The cut off age for stopping surveillance will be altered from 85 to 65 and 75, because remaining life expectancy is likely to be less than the average time required for adenoma to develop in to cancer.

11 Results

11.1 Deterministic results and sensitivity analysis

11.1.1 Deterministic results

Table 9 presents the deterministic base-case results from the analysis. From this analysis colonoscopic surveillance in the intermediate and high-risk groups is considered cost effective, with ICERs below £20,000 per QALY gained.

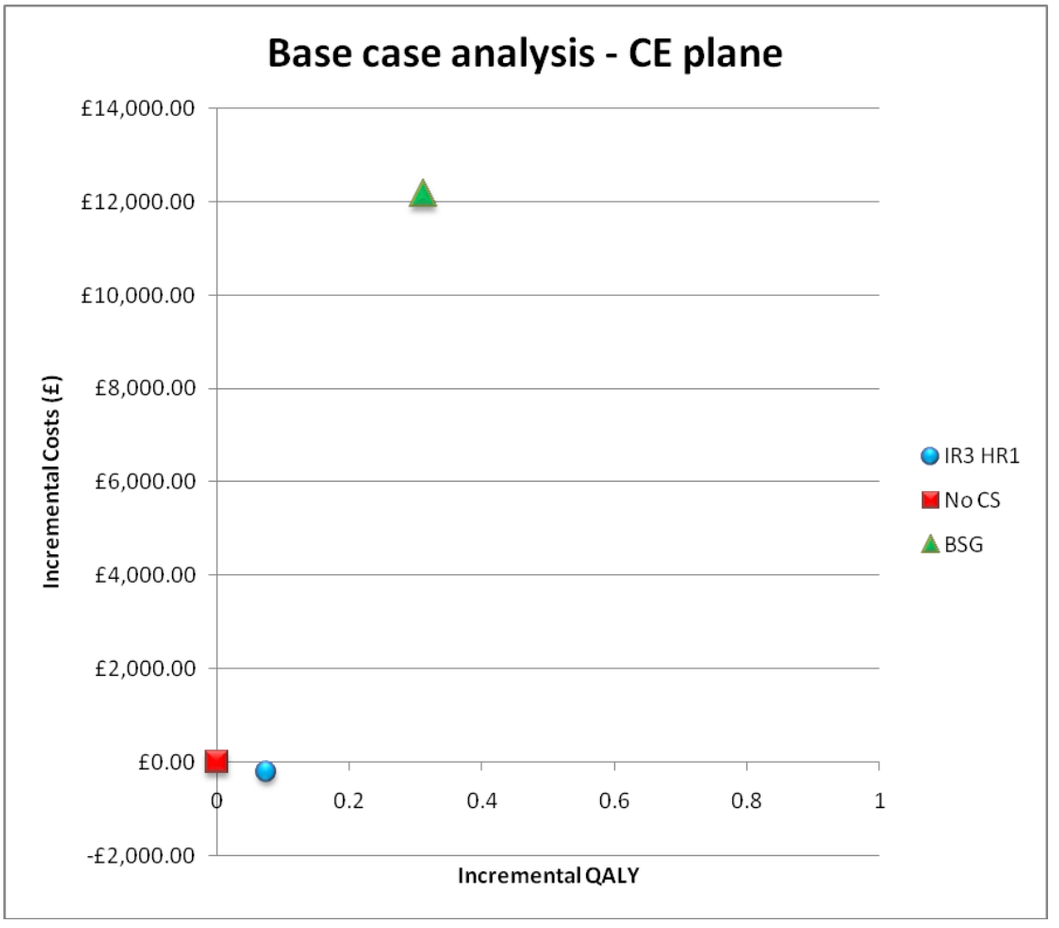
Table 9 Deterministic results

45 year time horizon	QALYs	Costs (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
No surveillance	15.48	£664.72	-	-	-
BSG surveillance guideline	15.79	£12,831.72	0.152	£12,166.30	£39,032.10
IR and HR	15.55	£458.78	0.074	-£205.93	Dominating

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; BSG: British Society of Gastroenterology; IR: intermediate-risk group; HR: high-risk group.

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

Figure 4 Cost-effectiveness plane



11.1.2 Transition matrices

Table 10 below presents the results if the upper estimates are used.

Table 10 Deterministic results with upper estimates for transitions

45 year time horizon	QALYs (utilities)	Costs (£)	Incremental utility values	Incremental costs (£)	ICER (£)
No surveillance	15.36	1,040.95	-	-	-
BSG surveillance guideline	15.63	12,826.63	0.269	11,785.67	43,733.23
IR and HR	15.49	655.80	0.132	-385.15	Dominating

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; BSG: British Society of Gastroenterology; IR: intermediate-risk group; HR: high-risk group.

Table 11 below presents the results when the lower estimates are used.

Table 11 Deterministic results with lower estimates for transitions

45 year time horizon	QALYs (utilities)	Costs (£)	Incremental utility values	Incremental costs (£)	ICER (£)
No surveillance	15.62	40.22	-	-	-
BSG surveillance guideline	15.63	12,848.57	0.0076	12,808.35	1,671,724.02
IR and HR	15.49	46.57	0.0038	6.34	1,661.72

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; BSG: British Society of Gastroenterology; IR: intermediate-risk group; HR: high-risk group.

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

11.1.3 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. A potential disutility of 0.0025 was used in the base case to explore the impact of disutility on the ICERs (see table 12).

Table 12 Disutility of 0.0025 associated with colonoscopy

Strategy	QALYs	Costs (£)	Incremental QALY	Incremental costs (£)	ICER (£)
No surveillance	15.44	646.71	-	-	-
BSG surveillance guideline	15.75	12,890.57	0.30	12,225.86	39,527.52
IR and HR	15.66	475.96	0.22	-188.74	Dominating

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; BSG: British Society of Gastroenterology; IR: intermediate-risk group; HR: high-risk group.

The GDG discussed the potential psychological impacts of colonoscopy. It was agreed that despite the inconvenience related to the bowel preparation

and the required recovery time following each procedure, the long-term benefit of colonoscopic surveillance outweighs the short-term discomfort. The estimated ICERs for each strategy showed little changes and surveillance in intermediate and high-risk groups remained dominant.

11.1.4 Stopping surveillance at different ages

Table 13 below shows the results of stopping surveillance at different ages over a lifetime horizon (from 50 years to 95 years of cohort age).

Table 13 Stopping surveillance at different ages

Stopping age	Strategy	QALYs	Costs (£)	Incremental QALY	Incremental Costs (£)	ICER (£)
65 years	No surveillance	15.47	646.77	-	-	-
	BSG surveillance guideline	15.62	9,939.15	0.15	9292.38	61,949.20
	IR and HR	15.55	458.78	0.08	-187.99	Dominating
75 years	No surveillance	15.47	647.77	-	-	-
	BSG surveillance guideline	15.63	12,342.52	0.16	11,695.75	73,098.44
	IR and HR	15.55	458.78	0.08	-187.99	Dominating
	QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; BSG: British Society of Gastroenterology; IR: intermediate-risk group; HR: high-risk group.					

The results showed that stopping surveillance at 65 or 75 years for intermediate and high-risk groups is a cost-effective strategy. The GDG highlighted that careful consideration should be given to the potential risks and benefits of the procedure each time. These include comorbidities, age, accuracy and completeness of the examination (Atkin and Saunders, 2002; Cairns et al. 2010).

11.2 Probabilistic sensitivity analysis

11.2.1 Table of results

Table 14 below presents the results of the PSA. It showed marginal QALY gain at a cost of £92,984 in the British Society of Gastroenterology

surveillance guideline compared with no surveillance. On the other hand, a marginal QALY gain in favour of surveillance for the intermediate and high-risk groups showed that surveillance was a cost effective and cost saving strategy compared with no surveillance.

Table 14 Probabilistic base-case results

45 year time horizon	QALY	Costs (£)	Incremental QALY	Incremental costs (£)	ICER (£)
No surveillance	14.83	£925.29	-	-	-
BSG surveillance guideline	14.96	£12,890.58	0.128	£11,905.72	£92,984.20
IR and HR	14.93	£648.30	0.097	-£2,846.73	Dominating

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; BSG: British Society of Gastroenterology; IR: intermediate-risk group; HR: high-risk group.

Overall trends in the PSA support the base-case results, with significantly increasing costs with very marginal QALY gains for the British Society of Gastroenterology surveillance guideline. PSA results reinforce the base-case results that surveillance in intermediate and high-risk groups is a dominant and cost-effective strategy.

11.2.2 Cost-effectiveness plane

Figures 5 and 6 below show the output of the probabilistic sensitivity analysis plotted on a graph of incremental costs and QALYs. From the graphs it appears that surveillance strategies are associated with considerable uncertainties in that the simulations are widespread across the cost-effective and cost-ineffective quadrants. The simulations of intermediate and high-risk group surveillance are spread across the cost-effective and cost-ineffective quadrants, however the simulations very close to the X-axis in figure 6 incur less incremental costs per QALY gained compared with the British Society of Gastroenterology surveillance guideline in figure 5. The costs of surveillance and stage-specific colorectal cancer treatments are equally assigned in each surveillance strategy. The health benefits of surveillance are captured in the early detection of colorectal cancer and removal of recurring adenomas through surveillance leading to reduced mortality associated with colorectal

cancer. Similar trends in PSA were presented in the surveillance model in Barrett's oesophagus in a recent health technology assessment report (Garside et al. 2006). This is potentially a limitation of using cohort modelling where the same number of people was allocated to each strategy in the model while the risk status of people after colorectal adenoma removal is not always proportionate in clinical practice.

Figure 5 Cost-effectiveness plane – British Society of Gastroenterology surveillance guideline

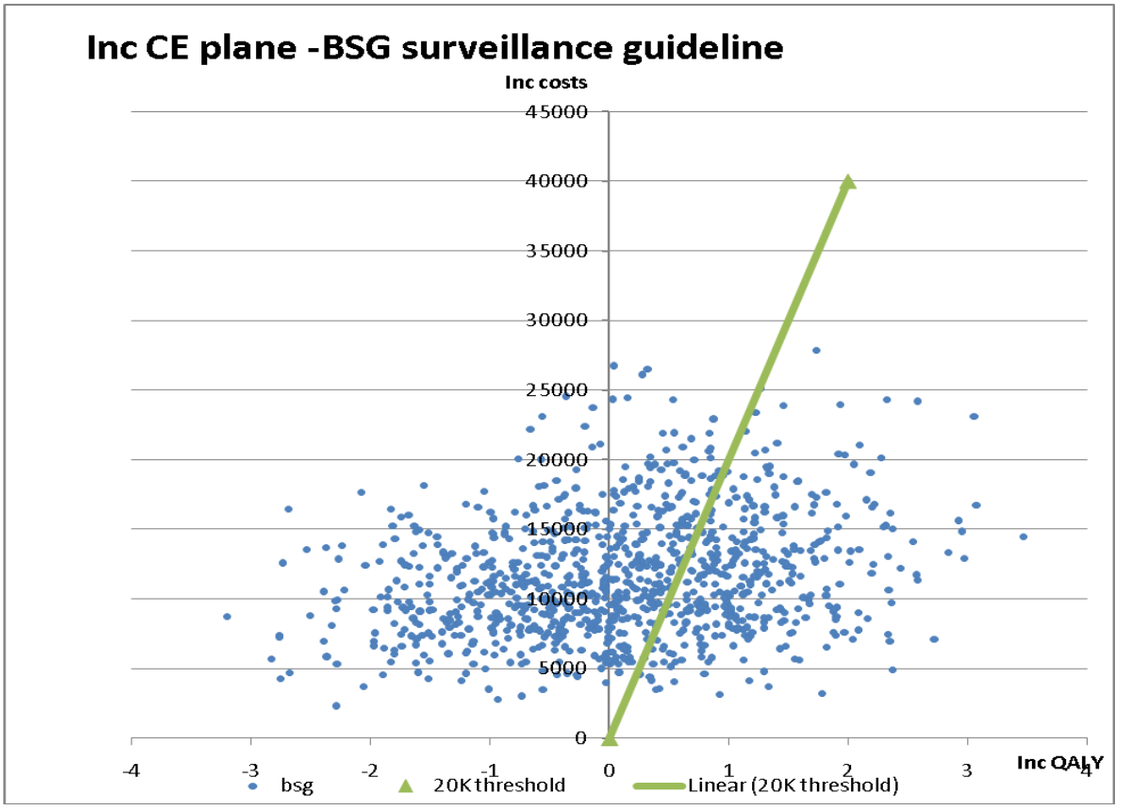
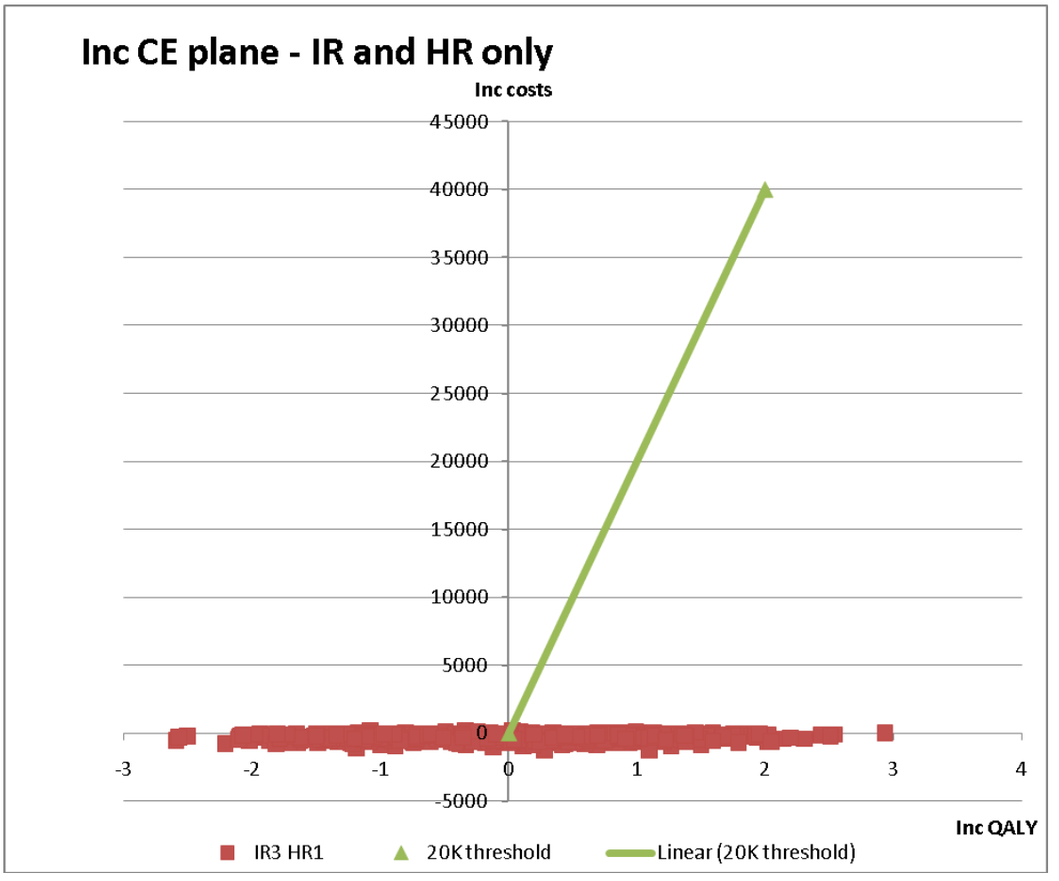


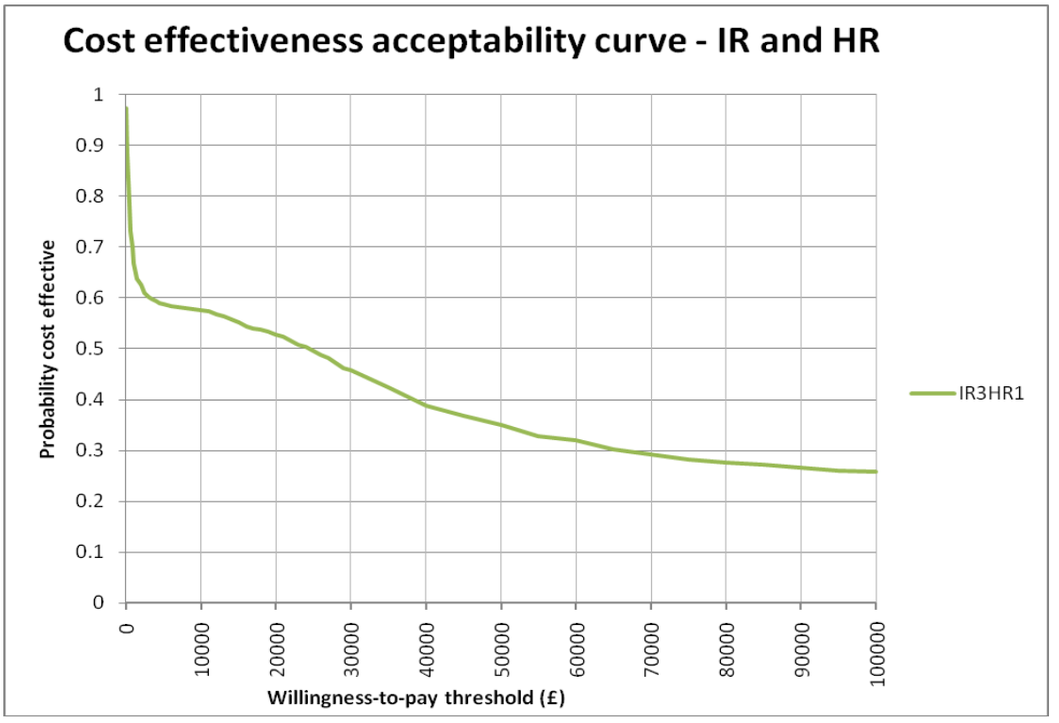
Figure 6 Cost-effectiveness plane – intermediate and high-risk group surveillance



11.2.3 Cost-effectiveness acceptability curves

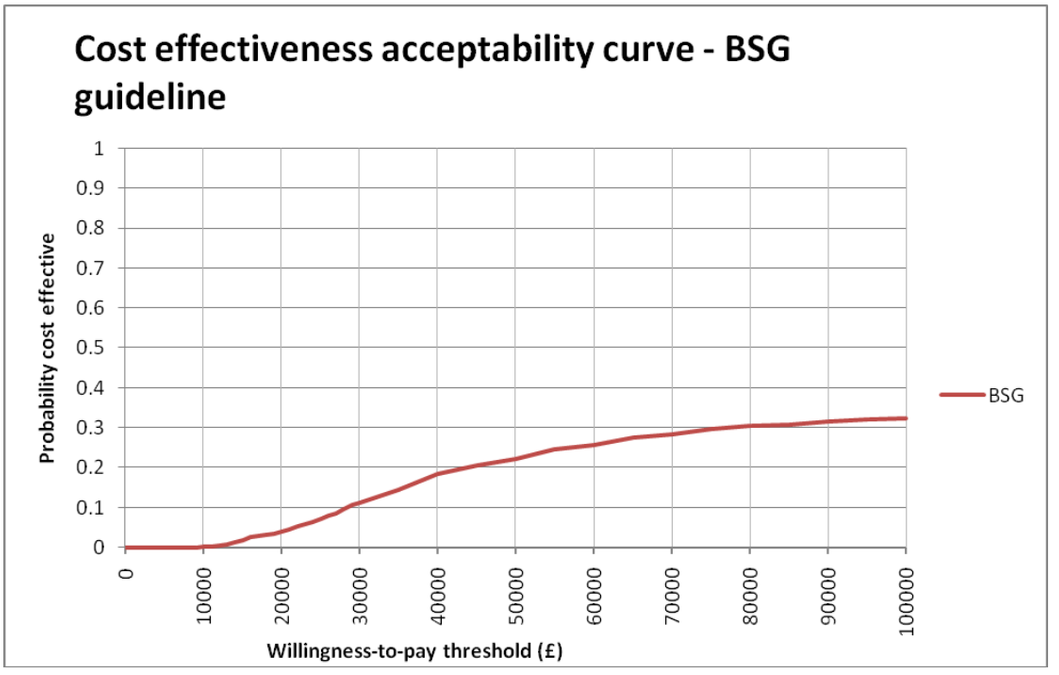
Figure 7 below presents the cost-effectiveness acceptability curves for surveillance in the intermediate and high-risk groups. At the threshold of £20,000 per QALY gained it shows the probability of being cost effective of over 50% in colonoscopic surveillance in intermediate and high-risk groups compared with no surveillance strategy in figure 8.

Figure 7 The cost-effectiveness acceptability curve for surveillance in intermediate and high-risk groups



Colonoscopic surveillance of low-risk groups (following the current British Society for Gastroenterology guideline) is not cost effective at different willingness-to-pay thresholds, indicating this strategy is not cost effective. The cost-effectiveness acceptability curve for the British Society for Gastroenterology guideline is presented in figure 8.

Figure 8 Cost-effectiveness acceptability curve for British Society for Gastroenterology surveillance guideline



PSA results support findings from the base case that at £20,000 per QALY gained, surveillance in intermediate and high-risk groups has the highest probability of being cost effective. Following the current British Society for Gastroenterology surveillance guideline, including low-risk groups has a less than 50% chance of being cost effective. At a £30,000 per QALY gained threshold, surveillance in intermediate and high-risk groups is marginally cost effective compared with no surveillance. When including low-risk groups in surveillance the current British Society for Gastroenterology surveillance guideline remains the least cost-effective strategy at both £20,000 and £30,000 per QALY gained.

11.3 Structural sensitivity analysis

These results indicate that age-dependent utility values result in the ICERs increasing. This is probably caused by the potential benefit from treatment being reduced as demonstrated by the reduced QALY from no surveillance. However, this is unlikely to be a valid analysis because various quality of life

data are being mixed together. Adding additional data when is the findings are already inconsistent is not advised.

11.3.1 Age of the cohort

In the model the age of cohort was varied from 50 to 35, 40 and 45 years with stopping surveillance at 85 years for each strategy. The model was run for a lifetime horizon (until 95 years) in order to see the costs and health benefits of surveillance over a lifetime for each strategy. Table 15 below shows the deterministic results with different ages of the cohort.

Table 15 ICER estimates when varying age of cohort

Age of cohort	Strategy	QALYs	Costs (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
35 years	No surveillance	18.54	£1,003.25	-	-	-
	BSG surveillance guideline	20.97	£13,528.64	2.43	£12,525.39	1,671,724.02
	IR and HR	15.95	£504.95	0.14	-£2355.79	Dominating
40 years	No surveillance	17.79	£916.39	-	-	-
	BSG surveillance guideline	19.35	£13,392.05	1.56	12,221.20	£7,997.22
	IR and HR	17.91	£598.95	0.12	-£317.44	Dominating
45 years	No surveillance	16.76	£801.09	-	-	-
	BSG surveillance guideline	17.54	£13,171.00	0.78	12,369.91	£15,852.76
	IR and HR	16.86	£534.65	0.09	-£266.44	Dominating

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; BSG: British Society of Gastroenterology; IR: intermediate-risk group; HR: high-risk group.

The ICER estimates varied at different ages of the cohort in the model. Overall trends showed that colonoscopic surveillance in intermediate and high-risk groups was a cost-effective strategy. Table 15 presents the mean deterministic ICER for each of the strategies for the various average ages for the cohort.

These results indicate that the younger the cohort the better the cost-effectiveness results. This is an important consideration when examining other published cost-effectiveness analyses because the majority examine a cohort of 50 years.

12 Discussion and conclusions

12.1 Discussion

The aim of colonoscopic surveillance is to identify asymptomatic colorectal cancer by testing an identified high-risk group of people who have not yet developed clinical symptoms. Efficacious surveillance rests on the premise

that the detection of early asymptomatic colorectal cancer and subsequent effective treatment will alter the natural course of the disease, leading to improved patient outcome.

12.1.1 Strengths

The main strength of the analysis is its comprehensiveness, using the most up-to-date evidence available in the public domain. Extensive sensitivity analyses were performed to explore the uncertainty in the data and the model. It has addressed the projected health benefits and related resource use following the current British Society of Gastroenterology surveillance guideline with the inclusion of different recurrence rates of adenomas in the NHS.

12.1.2 Limitations

12.1.2.1 Clinical data

A number of input parameters for transition needed to be fitted to published incidence data because of the lack of direct evidence about the rate at which adenomas develop in the general population in the UK, the rate at which adenomas develop into invasive cancer, and the rate at which early local cancer progresses to metastatic cancer. Most transition probabilities estimated in the model were assumed to be constant; however this is not the case in practice.

In the model it was assumed that all colorectal cancers arise from pre-existing adenomas. However, direct evidence suggested new colorectal cancers also arise. This assumption naturally led to biased outcome in favour of surveillance over no surveillance.

12.1.2.2 Misdiagnosis

For adenoma detection, 100 % sensitivity and 100% specificity in the cohort assumed to be adhering to surveillance reinforced the outcome of the model in favour of surveillance. The GDG discussed the current sensitivity and specificity of colonoscopy to be around 95%. In addition, clinical data were mainly obtained from observational studies where misdiagnosis was

accounted for in the published literature. However, further work could have the sensitivity and specificity of the chosen surveillance method incorporated where appropriate.

12.1.2.3 Complications

The probabilities of perforation for colonoscopy with polypectomy and without polypectomy were 0.17% and 0.08%, respectively (Tappenden et al. 2004). Because of time and resource constraints these were not considered in the model.

12.1.2.4 Natural history data

Because of the time constraints a systematic review of the natural history of the development of adenoma into cancer in colorectal cancer was not carried out. However, the GDG accepted a published analysis by Tappenden et al. (2004), so similar assumptions from Tappenden et al. (2004) were adopted in the model. Newly published evidence might therefore not have been taken into consideration. However, it was confirmed that there was no new evidence associated with polyps and adenoma surveillance in the recently updated British Society of Gastroenterology guideline (Cairns et al. 2010).

The analysis was focused on colonoscopic surveillance. Therefore, different treatment options and chemoprevention in stage-specific colorectal cancer were not distinguished in the model because of time and resource constraints. Ideally those states would have represented different health benefits and subsequent resource use in the model.

12.1.2.5 Systematic reviews

Ideally systematic reviews would have been carried out for all inputs into the model for the most robust evidence to be selected. However, the pragmatic approach adopted had the advantage that no data were likely to have been excluded and therefore represents a reasonable compromise. The GDG agreed that the approach was acceptable given the limited time and resources for guideline development.

12.1.2.6 Costing

The GDG highlighted that the NHS reference costs could potentially underestimate the true cost of the procedures. This was explored by increasing the costs in the deterministic sensitivity analysis. It should be noted that the incremental costs are the most important issue, not the absolute costs. A true micro costing exercise in a UK setting would have been the preferred option.

12.1.2.7 Quality of life data

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

12.1.2.8 Surveillance using colonoscopy

The updated British Society of Gastroenterology guideline (Cairns et al. 2010) highlighted the importance of careful and through colonoscopy in preventing colorectal cancer with a ‘fail-safe system’ in place for recall of higher risk patients.

12.1.2.9 Audit trails and trainings

Further audits of current surveillance for people with adenomas will provide valuable data for identifying gaps in evidence and skills and for training development in clinical practice as well as for patient information. It should

include colonoscopy adherence, complications associated with colonoscopy, breakdown of possible causes of complications and outcomes and additional techniques used when the results of colonoscopy are inconclusive and/or incomplete.

12.1.2.10 Potential impact of the NHS bowel cancer screening programme

The NHS bowel cancer screening programme has started recently, and reports and outcomes will be made available. Careful consideration and further study of the inter-relationship between the current population eligible for the screening programme for bowel cancer and the colonoscopic surveillance population is needed. This will identify all people who require either screening or surveillance, with the aim of providing the most appropriate and timely interventions in reducing mortality associated with colorectal cancer and improving relevant health benefits in the NHS.

12.1.2.11 Full care pathway modelling

The current analysis simplifies the actual treatment by modelling identical treatment pathways in stage-specific colorectal cancer. It was necessary to explore the cost effectiveness of colonoscopic surveillance in detecting early cancer and preventing colorectal cancer in the analysis in the given timeframe. It does not take into account the possibility of a person progressing between treatments, loss to follow-up or colorectal cancer arising from other causes. It is possible that this could further differentiate between the treatments and that if improved clinical-effectiveness data are collected, this should be modelled in more detail in future to allow a true comparison to be made.

12.1.3 Conclusions

This analysis indicates that colonoscopic surveillance in intermediate and high-risk groups is the most cost-effective strategy for people with adenomas with an increased high risk of developing colorectal cancer. An ICER below £20,000 per QALY gained was apparent when deterministic and probabilistic

analyses were considered. The GDG acknowledged the limitations of the model, with uncertainties from assumptions of near-perfect conditions including no complications or misdiagnosis associated with colonoscopy and a colonoscopy-adherent cohort in the model.

12.1.4 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 a true understanding of the course of the disease can be modelled.

Future models should attempt to consider the full course of the disease from diagnosis to the stage-specific treatments for colorectal cancer, to fully consider all the issues discussed in this report. Therefore, the potential for discrete event simulation should be considered to make the modelling less time consuming.

Audit of current surveillance for people with adenomas will provide valuable data for further research. It should include compliance, complications, additional techniques used if the results of colonoscopy are inconclusive and/or incomplete. It will also provide information about areas for further 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 would give valuable evidence on future guidance development in relevant areas.

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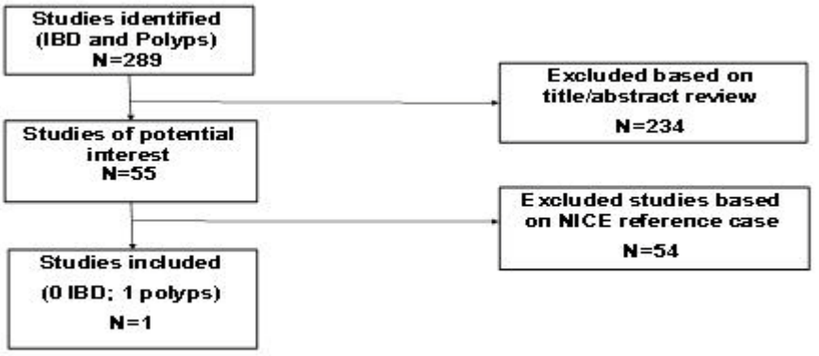
14 Appendices

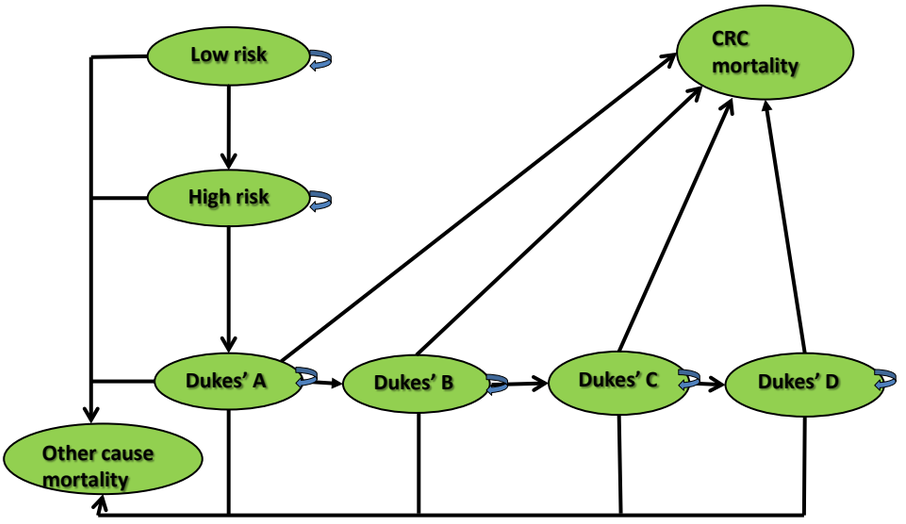
14.1 Inclusion/exclusion criteria



14.2 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 British Society of Gastroenterology surveillance guideline.

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



In this model people are allocated to a state based on a baseline colonoscopy into low-risk, intermediate-risk, or high-risk groups. People can then progress or regress in each diagnostic state and will stay there until surveillance re-classifies them into a different group or until they develop cancer. If there is no surveillance then cancer is only picked up when the person becomes symptomatic. Asymptomatic cancer can be picked up 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 contains artefacts of misdiagnosis.

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

14.3 Quality checklist – 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, Chilcott J, Sakai H, Karnon J.**	
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 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 cost 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 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 MF, Jefferson TO (1996). Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.		

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14.4 Quality checklist for new cost effectiveness analysis

Cost effectiveness modelling for colonoscopic surveillance in people with polyps by K Jeong 2010		
Guideline topic: colonoscopic surveillance in polyps	Question no:	
Check list completed by Yamina Rajput		
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 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	
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		

14.5 Modified GRADE for health economic literature

	Ref ID	Country	Population	Comparators	Outcome measure	Study design	Cost-effectiveness results (base case)	Applicability
Tappenden (2007) CRC screening in England	109	UK	Cohort at age 50	Biennial FOBT 50-69y; biennial FOBT 60-69 yrs; FSIG once at 55 yr; FSIG once at 60; FSIG once at 60, followed by biennial FOBT 61-70	QALY	Discrete event simulation (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
Tappenden (2004) Original study of Tappenden (2007)	identified through lateral search	UK	Cohort at age 30	Biennial FOBT 50-69y; biennial FOBT 60-69 yrs; FSIG once at 55 yr; FSIG once at 60; FSIG once at 60, followed by biennial FOBT 61-70	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; FOBT: faecal occult blood test; FSIG: flexible sigmoidoscopy; QALY: quality-adjusted life year