



Bowel Cancer Services: Costs and Benefits

Final Report to the Department of Health

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APRIL 2007



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Executive Summary

Background: The Burden of Bowel Cancer

Bowel cancer is a leading cause of mortality and morbidity in England. It accounts for 12% of all cancers in England. In 2003, there were approximately 27,800 new cases registered in England, making it the third most common cancer after breast and lung cancer. The number of deaths resulting from bowel cancer in 2003 in the UK was 7,488 for men and 6,466 for women, resulting in an estimated 154,182 premature life years lost.

Historically, survival rates in England are lower than those in many European and North American countries. Five year survival rates for patients in England and Wales with bowel cancer are 42% for men and 40% for women (for those diagnosed between 1991-93). This compares with a five year survival rate for Europe of around 50% for women and between 45 - 49% for men. The recent Eurocare study indicated that compared to Europe, patients in the United Kingdom present at a more advanced stage in the disease and that a lower percentage of patients are resected.

Background to the Research

The Policy Research Programme of the Department of Health commissioned this research to identify the costs, activity and outcomes of current bowel cancer treatments and consider options for service re-configuration.

The study has been undertaken by a research team from the York Health Economics Consortium at the University of York and the School of Health and Related Research at the University of Sheffield. They have been supported by an Advisory Group established by the Department of Health, and external advisers.

Outputs

Two reports have been produced from this research study. This report quantifies the activities, costs and outcomes, associated with the current treatment of bowel cancer and predicts the costs and outcomes of options for re-configuration of bowel cancer services. An accompanying report summarises the literature reviewed as part of this the study.

Methodology

Phase one of the study comprised developing and populating the treatment pathway for bowel cancer to reflect current practice. The pathway is based on evidence derived from published literature supplemented by expert opinion. The pathway was populated with data synthesised from a number of sources including published literature, expert opinion and audits. Phase two comprised developing a model to predict the impact of changes in the delivery of bowel cancer services on costs and outcomes, with a view to prioritising options for service improvement.

The Treatment Pathway

The treatment pathway considers the following aspects of care:

- Pathway A Access to bowel cancer services;
- Pathway B Treatment of colon cancer;
- Pathway C Treatment of rectal cancer;
- Pathway D Follow-up;
- Pathway E Surveillance of individuals with adenomatous polyps;
- Pathway F Management of increased-risk groups.

Assessment of Current Costs, Activity and Outcomes of Bowel Cancer Diagnosis & Treatment

The research estimates the total diagnosis and treatment costs of bowel cancer based on current service provision. Total annual diagnosis and treatment costs in England are estimated to be approximately £1.1billion.

The largest component of the total cost is the cost of diagnosis which makes up 26.4%. The next most substantial cost is the follow-up cost of patients with bowel cancer which accounts for 24.7% of the total cost of illness.

The mean cost per patient for rectal cancer treatment was estimated at £12,037 in comparison with the mean cost of colon cancer treatment of £8,808.

The additional cost of screening by Faecal Occult Blood Testing for those aged 60 to 69 biennially was estimated to be £112.8m in the first full year, although these are predicted to fall in subsequent years.

A summary of the cost of the main care components, aggregated for both colon and rectal cancers, is presented in the table below.

Care component	Total Cost (£)
Screening Cost (additional year 1 cost.)	£112,828,886
Non-cancer patients (i.e. diagnosis costs to exclude cancer)	£270,129,193
Diagnosis costs for confirmed cancer patients	£20,595,291
Primary Treatment (surgery, CT/RT)	£200,628,632
Follow-up (surveillance)	£24,402,914
Recurrence	£246,653,295
Stoma	£52,076,567
Palliative	£118,552,980
(of which End of life care costs)	(£21,408,066)
High-risk patients - surveillance	£53,758,184
Total Cost of Illness	£1,099,625,942

Options Assessment

Options considered in the model are summarised below:

- **1.** Improving GP referral criteria for suspected colorectal pathology;
- 2. Raised bowel cancer awareness in the general population of England;
- 3. Management of emergency presentation and delivery of care;
- 4. Increasing the use of colonoscopy from 70 per cent to 90 per cent;
- 5. Improving colonoscopy completion rates via national training;
- 6. The use of laparoscopic versus open surgery for colon cancer patients;
- **7.** Assessment of the impact of surgical expertise for outcomes and/or developing specialist pathology services;
- 8. Pre-operative versus post-operative radiotherapy for rectal cancer patients;
- **9.** The use of alternative chemotherapy sequencing:
 - a. The use of alternative adjuvant chemotherapies;
 - **b.** The use of alternative palliative sequences for chemotherapy.
- **10.** The use of the Enhanced Recovery Programme (ERP) following surgery;
- **11.** Intensive versus relaxed follow-up;
- **12.** Increasing liver/lung resections for metastatic disease;
- **13.** Increasing palliative surgery (e.g. palliative bypass) and stenting.

The options model has been used to obtain base-case cost-effectiveness results from which to estimate the incremental cost per LYG and the incremental cost per QALY gained associated with options for change. The options are intended to provide an indication of the potential cost effectiveness of each of the interventions described above. Prior to implementing any of the interventions, further research on their cost effectiveness, particularly taking into account a more detailed assessment of their costs, is recommended.

The model suggests that increasing the use of colonoscopy from 70% to 90% is cost saving and would improve health outcomes. Future research concerning the natural history of the disease and the probability of polyps being detected through flexible sigmoidoscopy in patients with distal colon cancer would be valuable. The introduction of an Enhanced Recovery Programme is also cost saving with initial indications of a low associated risk of detrimental clinical outcomes. This option is again relatively robust and at an advanced stage of development for implementation.

The model suggests that the most costly options would be the further development of GP referral criteria guidelines, although this is also associated with a reasonable improvement in life years gained. However, this option is highly uncertain due to the lack of evidence surrounding disease progression and the cost of implementation. It would also require substantial further research in order to identify referral criteria that will affect improve sensitivity without detrimental impact upon specificity. Greater knowledge is required regarding the relationship between symptomology and disease progression.

Increasing the use of emergency stenting is expected to be very effective for a small number of patients consuming colorectal cancer resources, but is associated with a relatively high cost. The options to improve surgical expertise and/or pathology are associated with improvements in health outcomes and may be potentially cost saving. Similarly, the options to improve adjuvant or palliative chemotherapies are expected to improve health outcomes, although cost impact is more uncertain. The remainder of the options which were assessed had smaller effects on both costs and health outcomes.

Many of the options assessed within the model display huge variability due to the large amount of uncertainty associated with both the base case model and the options. There is very little evidence regarding health utility scores for bowel cancer services, which makes it difficult to differentiate between the effectiveness of many of the options. This is a clear area in which further research would be merited.

Summary

This study is believed to represent the most robust attempt to capture the full costs of treating bowel cancer in England. The research estimates that bowel cancer costs almost \pounds 1.1bn per annum to manage. The options appraisal exercise suggests that outcomes could be improved and in some cases costs reduced, through changes to the current treatment pathways.

Acknowledgements

This project was commissioned by the Policy Research Programme at the Department of Health.

The authors would like to acknowledge the detailed clinical input of Professor David Sebag-Montefiore, Cookridge Hospital, Leeds; Professor Matt Seymour, Cookridge Hospital, Leeds; Dr Rob Glynne-Jones, Mount Vernon Hospital, Middlesex; Dr Graeme Poston, Royal Liverpool University Hospital, Liverpool; Dr Greg Wilson and Dr Mark Saunders, The Christie Hospital, Manchester; Professor David Radstone, Weston Park Hospital, Sheffield, Professor Peter Franks, Dr William Hamilton, Professor Bill Heald, Basingstoke, Dr Robin Kennedy, Mrs Jackie Mann, Basingstoke Dr Eva Morris, NYCRIS and Dr Merv Rees, Basingstoke.

The authors are also grateful to the advisory group which the Department of Health set up to provide expert advice on the study. This was chaired by Professor Mike Richards (National Cancer Director) and the independent members were Tim Elliott, Professor Alastair Gray, Lynn Faulds Wood, Professor David Forman, Dr Rob Glynne-Jones, Marion Kerr, Dr Sue Moss, Professor John Northover, Professor Matt Seymour, Professor Bob Steele, Dr Ursula Wells and Dr Andrew Veitch.

Abbreviations

5FU/5FA	5-fluorouracil
ACGBI	Association of Coloproctology of Great Britain and Ireland
APC	Argon Plasma Coagulation
APER	Abdominoperineal resection
AR	Anterior resection
BCAG	Bowel Cancer Action Group
BE	Barium enema
CEA	Carcinoembryonic antigen
COL	Colonoscopy
CRC	Colorectal cancer (Bowel cancer)
CRM	Circumferential resection margin
CT	Computerised tomography
CXR	Chest X-ray
DALM	Dysplasia Associated Lesion or Mass
DES	Discrete Event Simulation
DVT	Deep vein thrombosis
EORTC	European Organisation for Research and Treatment of Cancer
ERP	Enhanced Recovery Programme
EUA	Examination under anaesthetic
FA	Folinic acid
FAP	Familial Adenomatous Polyposis
FOBT	Faecal Occult Blood Test
FSIG	Flexible sigmoidoscopy
GP	General Practitioner
HES	Health Episode Statistics
HNPCC	Hereditary Non-Polyposis Colorectal Cancer
HTA	Health Technology Assessment
IAP	lleoanal pouch
IOCC	Improving Outcomes in Colorectal Cancer
IRA	lleorectal anastomosis
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
NBOCAP	National Bowel Cancer Audit Project
NCP	Negative Cancer Patient
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NYCRIS	Northern and Yorkshire Cancer Registrations Information Service
OGD	Oesophagogastroduodenoscopy
ONS	Office for National Statistics (UK)
OPCS	Office of Population Censuses and Surveys (UK)
PC	Personal Communication
PET	Positron Emission Tomography
PR	Per-rectal
QALY	Quality Adjusted Life Years
ScHARR	School of Health and Related Research
ТМЕ	Total mesorectal excision
UC	Ulcerative Colitis
US	Ultrasound
YHEC	York Health Economics Consortium

1.1 INTRODUCTION

1.1.1 Rationale for the Research

Bowel cancer, also known as colorectal cancer, causes a substantial number of deaths in England each year. Historically, survival rates for patients with bowel cancer in England are lower than those in many countries of Europe and North America.

Against the backdrop of the desire by the Government to improve cancer services, as laid out in The National Health Service (NHS) Cancer Plan of September 2000¹, the Policy Research Programme of the Department of Health has initiated a study to estimate the costs and benefits of bowel cancer services in England. In particular, the Department of Health wishes to examine how to allocate future investment in bowel cancer services to deliver optimal benefit to patients at an acceptable economic cost.

This research study has been undertaken in response to the Department of Health objectives and aims to identify expenditure at a national level in England on bowel cancer services as a whole, as well as expenditure on the different elements of service provision. The study also seeks to quantify the likely costs and benefits of different options for the development of bowel cancer services, including the likely time scale for the costs and benefits to take effect.

1.1.2 Scope of the Research Study

The Department of Health identified two distinct phases of research (See Appendix D):

- The first phase was to investigate the overall activity and expenditure on bowel cancer within the NHS (including affiliated organisations, such as hospices) as well as the patient outcomes that result from this activity;
- The second phase was to investigate what improvements in outcomes might be achievable at what cost and within what timescale.

The Department of Health has also specified a number of areas that should be addressed by the research including:

- Earlier presentation and improved assessment in primary care;
- Optimising diagnostic services;
- Optimising potentially curative treatments;
- Optimising palliative treatment and care.

Department of Health September (2000) 'The NHS Cancer Plan: A plan for investment, a plan for reform.'

The outputs of this study are intended to assist ministers and policy makers in the optimal allocation of health care resources. The research is intended to help identify areas in which current expenditure levels are inconsistent with the clinical and cost-effectiveness evidence base. The research is also intended to inform decisions about the re-allocation of resources to optimise the outputs of bowel cancer treatment. Finally, it is hoped that the methodology might provide a template to facilitate comparisons of expenditure at a network level and internationally.

This research study has been undertaken through a collaboration between York Health Economics Consortium (YHEC) at the University of York, and the Health Economics and Decision Science Group from the School of Health and Related Research (ScHARR) at the University of Sheffield.

1.2 STRUCTURE OF THE REPORT

This report comprises 6 sections:

- Section 1 provides an introduction to the research study, some background information about bowel cancer and its impact, and an overview of the methodology adopted for the research study;
- Section 2 describes the pathways for the diagnosis, treatment and follow-up of individuals with bowel cancer (including those pathways followed by individuals without bowel cancer who consume bowel cancer service resources);
- Section 3 describes the detail of the methodology and calculation of the costs, activity and outcomes for the current management of patients with bowel cancer in England;
- Section 4 describes the methodology used to simulate the expected costs and health outcomes resulting from an identified set of potential options for service reconfiguration;
- Section 5 describes the expected health outcomes and costs associated with each of the options for change;
- Section 6 summarises the research results including discussion and recommendations for further research.

The report also includes the following appendices.

- Appendix A: Parameters and outcomes;
- Appendix B: Elicitation methods and calibration;
- Appendix C: Options model;
- Appendix D: Research brief.

There is also an accompanying report of the literature review which provides an overview and summary of the literature used to derive the evidence for the development and population of the pathways and models.

1.3 BACKGROUND TO BOWEL CANCER IN ENGLAND

Bowel cancer includes cancerous growths in the colon, rectum and appendix (cancer of the appendix has not been considered within the current study). The cancer cells may spread to nearby lymph nodes (local recurrences) and also to more remote lymph nodes and other parts of the body (metastatic recurrences). The liver and the lungs are common sites for metastatic spread. The most common symptoms on presentation are blood on or mixed with stools; change in bowel habit; anaemia; weight loss, nausea and anorexia; and abdominal pain. However, these symptoms are not exclusively associated with bowel cancer and are associated with a variety of benign conditions which are prevalent in the general population. Importantly, some symptoms may not become apparent until the cancer is at an advanced stage, by which time the prognosis is poor. Patients are likely to develop a variety of physical and psychological symptoms during the life of the disease Seymour *et al.* (1997).

1.3.1 Guidance on Service Provision

Guidance was initially issued in 1997, and subsequently updated in 2000, on *Improving Outcomes in Colorectal Cancer* (IOCC 2004). The IOCC guidance document summarised the evidence to date on the management of those with bowel cancer and provided recommendations for best clinical practice. The evidence focuses on diagnosis, treatment and follow-up of patients. Options for the management of patients after diagnosis include combinations of surgery, radiotherapy and chemotherapy and palliative care for those patients who have a poor prognosis.

The manual was not designed to provide a set of mandatory instructions or clinical practice guidelines. However, as stated in the manual:

"By focusing on components of provision which are most relevant to patient outcomes, considering the resource implications of change, and by giving information on anticipated health benefits of implementing the recommendations, the manual will help commissioners concentrate on areas most likely to make a difference" (NICE IOCC, 2004).

The National Institute for Health and Clinical Excellence (NICE) has issued guidance on:

- Referral of patients by GPs for all cancers, which includes bowel cancer;
- The use of laparoscopic and open surgery for bowel cancer;
- The use of adjuvant chemotherapy for colon cancer;
- The use of chemotherapy for patients with advanced and metastatic bowel cancer.

The care and treatment of patients with bowel cancer has been estimated to account for approximately 2% of all bed days and for between 10 - 20% of all palliative care provision in the UK Mountney *et al.* (1994).

1.3.2 Epidemiology of Bowel Cancer

Bowel cancer is the third most common cancer in England after breast cancer and lung cancer, accounting for around 12% of all cancers in England. In 2003, approximately 27,800 new cases were registered in England (See Table 1.1).

ICD-10	Site description	Number of registrations	% of total malignancies
Males			
C61	Prostate	26,798	23.8
C34	Lung	17,525	15.5
C18-20	Bowel	15,213	13.5
	Other malignancies	53,196	47.0
	Total all malignancies	112,732	100%
Females			
C50	Breast	36,509	31.8
C18-20	Bowel	12,587	11.0
C34	Lung	12,226	10.7
	Other malignancies	53,418	47.0
	Total all malignancies	114,740	100%
Total	Bowel	27,800	12.2%
	All malignancies	227.472	100%

Table 1.1:The three most common cancers in England* (2003)

* excluding non-melanoma skin cancer.

Source: Office for National Statistics (2005).

Around 71% of bowel cancers develop in the colon, with the remaining 29% developing in the rectum (ONS 2003). Rectal cancer is more common in men than women, as shown in Table 1.2.

ICD		Male		Female		Total	
-10	Site description	No reg	%	No reg	%	No reg	%
	Malignant neoplasm of						
c18	the colon	8,949	58.8%	8,536	67.8%	17,485	62.9%
	Malignant neoplasm of						
	the rectosigmoid						
c19	junction	1,293	8.5%	927	7.4%	2,220	8.0%
	Malignant neoplasm of						
c20	the rectum	4,971	32.7%	3,124	24.8%	8,095	29.1%
	Total	15,213	100%	12,587	100%	27,800	100%

Source: Office for National Statistics (2005).

In 2003, the rates of newly diagnosed cases of bowel cancer for England were 62.3 for men and 49.5 for women per 100,000 population. The probability of developing bowel cancer increases sharply with age. In individuals below the age of 40 years, the risk is very low, with an incidence rate of 4.9 per 100,000 population in men and 4.0 per 100,000 population for women. However, between the ages of 40-49 years, the incidence rate rises to 20.9 per 100,000 population in men and 16.5 per 100,000 population in women. This increases further to over 396.5 per 100,000 population in men and 236.3 per 100,000 population in

women aged 75 years and above, ONS (2005). The median age of patients at diagnosis is 72 NBOCAP (2005).

There is not only age- and sex-specific incidence, but also a regional specific incidence, which shows a range per 100,000 from 41.4 in London to 77.6 in the North East for men and from 36.4 in London to 61.1 in the South West for women. These differences reflect not just lifestyle and environmental factors, but also the underlying demography, with London having a younger population.

1.3.3 Survival

Prognosis is strongly related to the stage of cancer at diagnosis; late-stage cancers are associated with poorer survival, more intensive and disfiguring treatments, and increased morbidity. Furthermore, patients diagnosed at an earlier stage are more likely to undergo successful resection and may be cured. Importantly, the treatment of patients with bowel cancer focuses not just on improving survival, but also on morbidity. Whilst surgery and subsequent adjuvant therapies are often associated with favourable outcomes, many patients will eventually develop advanced disease and distant metastases, which typically present within two years of the initial treatment. In around 15% of cases, patients will present with advanced disease, and 50% of these patients will present with liver metastases.

Based on published sources, the overall five-year survival rate for patients with colon cancer is reported to be 47.6% for men and 47.4% for women. The overall five-year survival rate for patients with rectal cancer is estimated to be 48.7% for men and 51.35% for women² based on data for people diagnosed between 1996 and 1999 Coleman 2004. However, mortality rates vary according to both age and stage of disease at presentation. Mortality rates are higher for men than women, as shown in Table 1.3.

Table 1.3:Mortality rates for England by sex

Gender	Number of deaths	Age-standardised mortality rate per 100,000 population
Male	7,488	23.5
Female	6,466	14.2
		· · · · · · · · · · · · · · · · · · ·

Source: Office for National Statistics (UK) ONS, Statistics for England and Wales (2004).

The mortality rate increases significantly with age, as shown in Table 1.4 overleaf, which also shows the total life years lost for each age group as a result of premature death due to bowel cancer.

² This study considered cancer 5-year survival for some of the most recent cohorts of patients with bowel cancer that were split by colon and rectal cancer.

	Age (years)								
	20-44	45-54	55-64	65-74	75-84	85+	Total		
Number of deaths Male	123	349	1,150	2,223	2,638	1,005	7,488		
Rate per 100,000 Male	1.4	10.4	40.8	109.1	207.4	340.9	23.5		
Total life years lost Male	4,625	9,227	21,601	26,718	20,205	5,329	87,705		
Number of deaths Female	110	225	694	1,408	2,351	1,658	6,466		
Rate per 100,000 Female	1.0	8.5	24.5	57.7	131.8	241.3	14.2		
Total life years lost female	4,196	5,978	13,099	16,735	17,677	8,792	66,477		

Table 1.4: Mortality by age

Sources: ONS Update to Cancer Trends and Cancer Statistics for England and Wales (2004)

As noted above, there are considerable differences in survival according to the stage of the disease at the point of diagnosis; in general, the more advanced the stage of the cancer at diagnosis, the lower the likelihood of long-term survival. Table 1.5 shows the approximate frequencies of bowel cancer stage at diagnosis and associated 5-year survival rates. This indicates that the 5-year survival rate for metastatic bowel cancer is very low. Median survival after diagnosis for patients with metastatic disease is consistently reported to be around 12 months.

Table 1.5: Survival according to stage of cancer at presentation

Dukes' Stage (modified)	Definition of stage	Approximate frequency at diagnosis (%)	5-year survival (%)
A	Cancer localised within bowel wall	13.7	83
В	Cancer which penetrates the bowel wall	36.6	64
С	Cancer spread to the lymph nodes	34	38
D	Cancer with distant metastases	14.6	3

Source: Tekkis NBOCAP (2005) for years 2000-2003 (Frequency at diagnosis).

There is also evidence of marked variations in survival rates across countries, as demonstrated in Table 1.6 overleaf.

Country Registry 3-year				Dukes' stage (%)			
	Reference (pt numbers)	relative survival rate (%)	A	В	С	D	(%)
USA	11,191	69	24	30	23	18	92
Europe	2,492	57	14	34	21	21	85
Italy	Varese (445)	56	19	31	17	27	82
-	Modena (306)	67	9	39	24	17	88
France	Calvados (262)	63	10	35	20	24	85
	Somme (228)	58	14	29	19	21	84
	Cote d'Or (237)	60	21	36	25	14	93
Netherlands	Rotterdam (202)	57	19	39	20	15	86
	Eindhoven (256)	62	15	40	19	21	92
Spain	Granada (173)	51	7	34	23	19	77
UK	Mersey (207)	52	11	29	23	23	82
	Thames (176)	44	12	30	24	23	80

Table 1.6: Comparative 3-year relative survival (%), stratified by Dukes' stage

Source: Ciccolallo et al. (2005).

These data indicate that the UK has a lower 3-year relative survival rate, than the US and the European countries included in the study. The data also appear to indicate that at diagnosis, patients from the UK are less likely to have Dukes' A cancer, and that a lower percentage of patients are resected. However, it should also be noted that:

- Although the study was published in 2004, the data refer to 1990/91; since the Cancer Registries in the UK have been reviewed through the Gillis report, quality processes have been implemented to improve the quality of the data;
- The number of patients for all registries and in particular from the UK are relatively low;
- Staging information was not available for more than 10% of UK patients in the study.

Nonetheless, the results of this study have been supported by the results from the EUROCARE studies. The EUROCARE 3 study followed up patients who were diagnosed in 1990-94 until the end of 1999. The European average 5-year survival rate for rectal and colon cancers was around 50% with slightly lower rates for rectal than colon, as shown in Table 1.7 overleaf. The poorer survival rate for the UK reported in the EUROCARE study has been attributed to late presentation and delay in the treatment of patients. Monnet (1999) considered the influence of stage at diagnosis on the survival of rectal cancer patients in European countries and found that stage at diagnosis was the only main factor that explained survival inequalities.

Table 1.7: European 5-year survival rate for bowel cancer

Site of	Woi	nen	Men		
malignancy	No of patients	5-year survival	No of patients	5-year survival	
Rectum	40,463	49.6%	52,504	45.1%	
Colon	78,258	51.0%	72,234	49.2%	

1.3.4 Aetiology

The incidence of bowel cancer is three to four times greater in developed than in developing countries Quinn *et al.* (2001). Risk factors for bowel cancer are thought to include diets high in fats and animal proteins and low in fruit, vegetables and fibre as well as the lack of physical exercise and a family history of bowel cancer Ward *et al.* (2003). Most of the tumours are thought to develop from adenomatous polyps, which may be present in the bowel for many years before a malignancy develops. The risk of developing bowel cancer is raised for patients with familial adenomatous polyposis (FAP) and other hereditary conditions. In these individuals, many polyps are present in the bowel, which results in a notably greater predisposition to cause malignancy. Table 1.8 shows the impact of risk factors.

Table 1.8: Risk factors associated with new cases of bowel cancer

Risk factor	Definition	Percentage of patients
Average risk	Those aged 50 years and more with no special risk factors	Approx. 75%
Family history	Those with a positive family history	15-20%
HNPCC	Hereditary non-polyposis colorectal cancer	Approx. 5%
FAP	Familial adenomatous polyposis	Approx. 1%
IBD	Inflammatory bowel disease	Approx. 5%

Source: NICE IOCC (2004).

1.4 METHODOLOGY

1.4.1 Overview

The research team has adopted an approach underpinned by the design and population of a treatment pathway model for the management of patients with bowel cancer. The research has also been supported by a Project Advisory Group established by the Department of Health, and by the use of a large number of external advisers, contacted independently by the research teams.

The study has been undertaken within three phases:

- The set up phase. This has included the design of the generic pathway, using literature, previous work and expert opinion. The generic pathway has also been discussed at the Bowel Cancer Action Group (BCAG) meeting of November 2005 and the first Project Advisory Group Meeting in February 2006;
- Phase One. Refining and populating the pathway, to reflect current practice, activity and expenditure;
- Phase Two. Identifying potential options for service reconfiguration, and developing and populating a complex simulation model to allow for the assessment of the impact of these options on the expected costs accrued and benefits generated by the bowel cancer service.

The set up phase was undertaken by both teams, although the generic pathway used as its basis was based on previous research undertaken by ScHARR for the bowel cancer screening option appraisal, Tappenden *et al.* (2007). Work on phases one and two has, as of necessity, overlapped considerably. Most of the data collected and utilised is common across the two models, and the models themselves have been validated against external data sources, and the two models have been calibrated against one another. Details of the calibration exercise can be found in appendix A. Where the evidence base is weak or where data does not exist, a process of elicitation has been undertaken using clinical experts in the field. The elicitation was supported by Bayesian Elicitation of Expert Probabilities (BEEP) collaborative research team (<u>http://www.shef.ac.uk/beep/index.html</u>). Novel methods of elicitation were used focussing on determining probabilistic judgements for key parameters in the model in the presence of important covariate structures.

Additionally, the research team have completed a literature review as part of the research in order to populate the baseline and options models. A report of the findings of the literature review has been made available as an accompanying report.

1.4.2 The Patient Pathway

An overview of the patient pathway and the approach adopted is presented in this section. A description of the patient pathway is presented in Section 2, and the details of the baseline costs and activities can be found in Section 3.

The approach adopted follows the options for presentation, diagnosis, and treatment for patients with bowel cancer, including palliative care. Figure 1.1 provides an example of a high-level illustrative pathway for a patient at normal risk. During the research study, the pathway was expanded and developed in detail for each of the phases described. Separate pathways were developed for colon and rectal cancer patients, and those who are at an increased risk of developing bowel cancer, i.e. those with FAP, Hereditary Non-Polyposis (HNPPC), pre-identified adenomatous polyps ulcerative colitis and Crohn's disease.



Figure 1.1: High level illustrative pathway for patients with bowel cancer

1.4.3 Populating the Pathway

The baseline pathway has been developed in the form of a treatment pathway model. Each node in the pathway has been populated with current evidence relating to:

- Activity, including number or percentage of patients following a particular treatment option in the model;
- Costs, applied to the activities in the pathway;
- Outcomes, as a result of the activities in the pathway.

1.5 LITERATURE SEARCH METHODOLOGY

The searches were undertaken by the Centre for Reviews and Dissemination at the University of York, as well as YHEC. A more detailed discussion of the search methodology can be found in the report of the literature review.

1.5.1 Guidelines Searches

Searches were undertaken to identify guidelines and systematic reviews of interventions for bowel cancer. A summary is given as Appendix A.

1.5.2 Economic Searches

Searches to identify resource, cost and cost-effectiveness studies of interventions for bowel cancer were also undertaken. The literature searches were conducted using a combination of subject headings and text words for 'colorectal cancer'. The searches were restricted as required by using a methodological search filter to help identify 'economic/cost' studies only. The searches were further restricted by date range: 1996-2005.

The databases searched were:

- MEDLINE and PreMEDLINE (1996-2005);
- EMBASE (1996-2005);
- NHS Economic Evaluation Database (NHS EED) (1996-2005);
- Health Economic Evaluation Database (HEED) (1996-2005).

The search strategies used in MEDLINE were translated and adapted as appropriate for each database searched.

The search results are provided in an Appendix to the Literature Report.

1.5.3 Additional Searches

A series of additional searches were undertaken, which targeted explicit aspects of the patient pathway. To minimise the size and scope of the results the search strategies were very precise. Limited text words were used and occasionally only the title field was searched, in some cases only subject index terms were used and these were often focussed. A limited number of databases were searched, and many strategies were limited by date range to 2000-2006 to include the most recent literature.

This approach enabled the calculation of the activity and costs associated with each phase of the pathway, such as the annual cost of diagnosing all cases of bowel cancer. Our overall outcome measure is quality adjusted life years (QALY) saved, although we have provided information on intermediate outcomes where possible.

1.6 USE OF EXPERT ELICITATION TO POPULATE AREAS WHERE CURRENT EVIDENCE IS INSUFFICIENT

Owing to a lack of empirical evidence in a number of areas, several of the model parameters were elicited from experts using dedicated software where possible. This elicitation process was supported by a team of statisticians from the Open University with a specific research interest and expertise in the elicitation of expert judgement. The elicitation focussed on determining probabilistic judgements for key parameters in the model in the presence of important covariate structures.

1.6.1 Using the Pathway to Generate Options

The treatment pathway structure was used as a basis for modelling the expected costs and outcomes associated with each of the options. The options model was produced using discrete event simulation methods using the software package SIMUL8. The simulation operates on an individual patient-level basis with each individual being assigned a set of characteristics. The data collected for the baseline activity model were used within the simulation model.

1.6.2 Calibration of the Baseline Activity Model and the Options Model

The respective purposes of the baseline activity and cost model and the options simulation model are different. The former is intended to provide estimates of the costs of the current bowel cancer service in England, whilst the latter simulates the expected costs and outcomes of various service reconfigurations for a hypothetical cohort of individuals. Consequently, the two models have used differing methodologies in order to achieve these two different objectives.

The two models have been calibrated to ensure that their outputs are consistent. This process will involve comparing certain key results or outcomes. The calibration process involved comparing the cost results at key points within the models, comparison of life years lost and the numbers of patients at different points within the model to check for consistency. Where unacceptable differences were identified the causes of these were investigated and resolved. Details of the calibration can be found in Appendix B.

Section 2 Summary: Pathways

This section provides both a description of the pathway's which are used within the two models and the schematics of these pathways. These have been developed using literature, NICE Technology Appraisal Guidance reports, national guidelines for bowel cancer patients within the UK and advice from clinical experts.

The pathways are presented by their individual interlinked parts of the pathway and are as follows:

- **1.** Pathway A Access to bowel cancer services. This sub-section includes:
 - Discussion of the entry routes for diagnosis of those patients with bowel cancer either by clinical presentation to their GP, presentation at an Accident and Emergency (A&E) department and referral elsewhere in secondary care.
- **2.** Pathway B Treatment of colon cancer. This sub-section includes:
 - This first part of this sub-section describes those patients that are operable with pre-operative curative intent, those patients that are potentially operable with metastatic disease and treatment of patients that are inoperable;
 - The last part of this section describes the management of those patients following relapse.
- **3.** Pathway C Treatment of rectal cancer. This sub-section includes:
 - The management of patients that are operable with pre-operative curative intent, the management of patients with potentially operable rectal cancer;
 - There is also a discussion about the management of emergency treatment for rectal cancer and the management of those patients following relapse.
- **4.** Treatment Pathway D Follow-up. This sub-section includes:
 - This includes an outline of follow-up schedules.
- **5.** Treatment Pathway E Surveillance of individuals with adenomatous polyps. This sub-section includes:
 - This section describes the portion of the pathway with respect to surveillance of patients with adenomatous polyps.

- 6. Treatment Pathway F Management increased-risk groups. This sub-section includes:
 - A description of the pathway with respect to Familial Adenomatous Polyposis (FAP) patients;
 - A description of Hereditary Non-Polyposis Colorectal Cancer (HNPCC);
 - A description of the pathway for those patients with Ulcerative Colitis/Crohn's disease.

2.1 INTRODUCTION

This section presents a patient flow diagram and textual description that captures the range of pathways experienced by people using bowel cancer services in England. These have been developed using advice from clinical experts, relevant literature, National Institute for Health and Clinical Excellence (NICE) Technology Appraisal Guidance and recent national guidelines on the diagnosis, treatment and follow-up of bowel cancer in the UK. These pathways form the structural assumptions employed within the health economic models.

This section describes six interlinked portions of the pathway; schematics are presented at the end of this section:

- Pathway A Access to bowel cancer services;
- Pathway B Treatment of colon cancer;
- Pathway C Treatment of rectal cancer;
- Pathway D Follow-up;
- Pathway E Surveillance of individuals with adenomatous polyps;
- Pathway F Management of increased-risk groups.

2.2 TREATMENT PATHWAY A - ACCESS TO BOWEL CANCER SERVICES

Patients with significant colon or rectal pathology may present in a variety of ways. The most common entry routes for diagnosis are:

- 1. Clinical presentation to GP;
- 2. Presentation at an Accident and Emergency (A&E) department;
- **3.** Referral from elsewhere in secondary care.

In addition, certain groups of patients are known to have an increased risk of developing bowel cancer, these include:

- Individuals who are identified with Familial Adenomatous Polyposis (FAP);
- Individuals who are identified with Hereditary Non-Polyposis Colorectal Cancer (HNPCC);
- Patients who are identified as having pre-identified adenomatous polyps;
- Individuals with long-standing conditions such as Crohn's disease and ulcerative colitis (UC) who are identified through ongoing surveillance.

The three main bowel cancer diagnosis routes are discussed in this section. The diagnosis and management of increased-risk and high-risk groups are discussed in Pathways E and F.

It should be noted that screening is not included within the current diagnostic pathways for bowel cancer.

2.2.1 Diagnosis Route (1) Patients Who Present Symptomatically To Their GP

Patients visit their GP and are either referred or not (appropriately or missed), based upon Department of Health guidelines for the referral of patients with suspected bowel cancer. There are three broad options for referral:

- Standard referral not "2 week wait";
- Fast-track referral "2 week wait";
- Emergency admission if the patient has acute symptoms, for example, obstructive symptoms such as obstipation, abdominal pain (although abdominal pain may be present without obstruction) and vomiting, or non-obstructive symptoms such as profound rectal bleeding, they may be referred directly to A&E.

Patients who are referred either as "2 week wait" or as a standard referral are invited to attend a normal clinic which may be led by either a nurse or a consultant. At the clinic:

- All patients would undergo a general patient consultation (patient history and general examination e.g. abdominal examination);
- All patients would have a pre-rectal (PR) examination to determine whether the patient has a palpable mass in their rectum or anal canal;
- All patients would undergo either a rigid or flexible sigmoidoscopy to look for the presence of rectal cancer. Flexible sigmoidoscopy is currently less common at this stage although may sometimes be used as "straight to investigation" on the basis of symptoms described in the referral letter from the GP, perhaps via a specialist nurse-led clinic;
- Most patients would have a haemoglobin check (this would be undertaken by a phlebotomist);
- If there is evidence of rectal bleeding, the patient would also have a proctoscopy which allows for the visualisation of the anal canal (usually looking for haemorrhoids, visualising around 8 cm of the anal canal and rectum).

From the clinic, the patient would either attend an endoscopy suite or a radiology suite. If the patient attends the endoscopy suite, investigative options would include:

- A flexible sigmoidoscopy (FSIG);
- A colonoscopy (COL);
- A FSIG followed by a COL (if the FSIG suggests the presence of cancer or adenomatous polyps);
- A COL followed by a barium enema (BE) in the radiology suite (if a complete COL to the caecum was not possible).

If the patient attends the radiology suite directly following the clinic visit, they will undergo one of three investigations:

- If there is a palpable mass found during the abdominal examination in the clinic (see above), the patient may have an abdominal ultrasound (US), and would have a computerised tomography (CT) scan of their abdomen and pelvis (they would receive a chest CT later);
- A BE which is performed by a radiographer / supervising radiologist and reported by a radiologist;
- If the patient is frail, they may receive a CT pneumocolon (colonography). Again this is performed by a radiographer / supervising radiologist and reported by radiologist.

If a tumour is found at endoscopy, the patient will undergo staging of the chest, abdomen and pelvis via a CT scan or abdominal US and chest X-ray (CXR). If a tumour is found at radiology, the patient will attend the endoscopy suite for direct visualisation/ biopsy (this is done via COL or FSIG) and histological confirmation and undergo a CT scan of their chest (if they have not already had one). Right-sided or transverse colon tumours are not necessarily visualised and biopsied, although two criteria of malignancy should be fulfilled before resection such as a positive barium enema and anaemia, a positive CT scan, or presence of a palpable mass.

If the neoplasia is rectal or rectosigmoid, the majority of patients would undergo a Magnetic Resonance Imaging (MRI) scan and CT scan, with the remainder receiving a CT scan alone.

All patients with a positive diagnosis of colorectal cancer (CRC) have a baseline carcinoembryonic antigen (CEA) test and appropriate treatment options or palliation are discussed at a Multi Disciplinary Team (MDT) meeting. A full blood count (FBC) and Electrolytes, Urea and Creatinine examination (EUC) are also carried out.

If the patient does not have CRC but is considered to be at intermediate or high risk due to the presence of adenomatous polyps, they will have their polyps removed via polypectomy and will subsequently be offered endoscopic surveillance using either COL, or FSIG if the colon has been removed previously (See Pathway E). In a small number of cases it will not be possible to remove adenomas via polypectomy and surgery may be required. Other non-neoplastic diagnoses (such as hyperplastic minimal risk polyps) are treated by leaving 'in situ' or by polypectomy with snare diathermy, usually without follow-up surveillance.

2.2.2 Diagnosis Route (2) Presentation at Accident and Emergency

Patients following this route present either at an A&E department directly, or are referred to A&E as an emergency admission after seeing their GP or following a visit from an emergency care practitioner (nurses or paramedics). The patient would see a triage nurse to establish how quickly they need to be seen. The patient would be seen by an A&E doctor who would take their history and undertake a general examination (with or without a PR examination) and may arrange simple investigations as deemed appropriate i.e. blood tests

and plain abdominal X-ray (this is likely to be on the basis of a number of factors, such as belly ache). Obstructed patients might be referred directly to surgery on the basis of their patient history and general examination only (need for admission depends on symptoms at presentation). Only rarely do patients present via A&E with haemorrhage sufficient to warrant emergency admission. A proportion of individuals presenting at A&E would be referred elsewhere in the system if their diagnosis is considered to be non-surgical (for example, patients presenting with symptoms of gastroenteritis such as abdominal pain and diarrhoea may be referred to a medical team. A more common route of referral is with iron deficiency anaemia, presenting to the physicians/A&E with cardiac failure, angina, myocardial infarction, or shortness of breath.). Furthermore, a proportion of individuals presenting at A&E directly will be sent home if diagnostic investigations do not suggest the presence of significant pathology.

If the patient is thought to be obstructed due to the presence of a tumour in either the colon or rectum, the patient would receive a CEA test (*note* - although this is sometimes forgotten at baseline due to the emergency context of care) and a CT of their abdomen and pelvis. This may or may not be accompanied by a water soluble contrast enema to assess whether the patient is suffering from complete obstruction or pseudo-obstruction. In a small proportion of cases, the patient will go straight to theatre without undergoing further imaging based on their clinical findings (i.e. the patient's history and examination) and plain X-rays. These patients would not undergo a CT of their abdomen and pelvis, contrast enema or MRI if the cancer is rectal. Rectal cancers which are palpable on PR examination under anaesthetic rarely obstruct as the rectal lumen is wide. Obstruction is a problem with non-palpable upper rectal cancer involving the rectosigmoid junction, where the lumen is narrower.

If complete obstruction is confirmed, the patient may either:

- Receive no active intervention if they are severely compromised by co-morbidity. These patients would subsequently receive best supportive care, but may perforate and die of Faecal peritonitis imminently or succumb to the effects of obstruction;
- 2. Go straight to surgery without CT, unless the diagnosis has been wrong. These patients would subsequently have a CT scan of their chest (plus a CT of their abdomen and pelvis if they have not already had this). The patient would then be discussed at an MDT meeting to determine further appropriate treatment;
- **3.** Undergo stenting. This would be done by a (consultant) radiologist or endoscopist with a subsequent CT scan of their chest (again, the patient would receive a CT scan of their abdomen and pelvis if not previously done). The patient would then be discussed at an MDT meeting to determine subsequent appropriate treatment.

Stenting may be done for two reasons: either (1) to "buy time" to allow for surgery commonly referred to as a bridge to elective surgery (i.e. to make the patient nutritionally and medically fit for surgery with a view to reducing mortality, reported as 16% after emergency resection to <5% after elective resection); or (2) to relieve the obstruction in an unfit patient or one with extensive metastatic disease so that they do not suffer subsequent perforation or have unnecessary emergency surgery when cure is impossible.

If the intention is to buy time to optimise the patient for subsequent surgery, and the stenting is successful, the patient may later undergo surgery (if they consent). If the stenting is unsuccessful in these patients or if they have a stent complication of perforation, the patient will go on to have emergency surgery at that point if they are sufficiently fit. These patients would subsequently have a CT of their chest (and a CT of their abdomen and pelvis if not previously done) and would be discussed at an MDT meeting.

If the intention is to use stenting to relieve the obstruction in an unfit patient or one with widespread incurable metastatic disease so that they do not suffer subsequent perforation, and the stenting is successful, the patient will receive palliative/supportive care. If the stenting is unsuccessful and the patient is unfit for further treatment, they will die of faecal peritonitis imminently. These patients would not receive further imaging.

If the patient is not obstructed, they will have a haemoglobin check and diagnostic tests as described in the GP route (See Diagnosis Route 1 above).

2.2.3 Diagnosis Route (3) Referral from Elsewhere in Secondary Care

These patients may have had diagnostic investigations undertaken by another medical team (these will usually be either CT or COL which are suggestive of probable cancer), hence these patients get referred directly to the MDT. If the patient has symptoms but has not undergone diagnostic investigations, they may go directly to clinic first as described above.

2.3 TREATMENT PATHWAY B – TREATMENT OF COLON CANCER

This section describes the likely treatment pathways for patients who have a positive diagnosis of colon cancer within Pathway A.

2.3.1 Treatment of Patients Who Are Operable With Pre-Operative Curative Intent

If the patient is operable and if there is no evidence of advanced disseminated disease (and if the patient gives consent), they would undergo surgical resection of the primary tumour (with or without prior stenting to optimise the patient, as described in Pathway A). It should be noted that a proportion of those patients who undergo stenting to optimise surgery may not actually undergo subsequent surgery. For those patients who do undergo surgery, some surgeons require the patient to undergo mechanical bowel preparation (i.e. enemas or purgatives such as Picolax, given in the morning and afternoon prior to the operation unless the patient is obstructed). In addition, patients may receive thromboembolism prophylaxis to avoid deep vein thrombosis (DVT) and pulmonary embolism (either using low-molecular weight heparin, graduated compression stockings, intravenous dextran and intermittent pneumatic calf compression) and all patients should receive antibiotic prophylaxis to avoid post-operative sepsis. The patient would also undergo bladder catheterisation. Surgical excision is most likely to be a right-, extended right, subtotal, left-hemicolectomy, or high anterior resection but may include other techniques such as Hartmann's procedure if the

patient is obstructed. It should be noted that some metastases may be missed by diagnostic tests and may be later found at surgery.

Following surgical resection and recovery, patients with Dukes' stage C colon cancer who are sufficiently fit will be offered adjuvant chemotherapy. It is recommended that this treatment commences within 6 weeks of surgery if possible. NICE currently recommends 5-fluorouracil (5-FU) in combination with folinic acid (FA), oxaliplatin (in combination with 5-FU/FA) and capecitabine as adjuvant chemotherapy options for Dukes' C colon cancer. These chemotherapies would be given for a period of 6-months (although patients may discontinue treatment due to recurrence or unacceptable treatment-related toxicities). Patients with Dukes' stage B colon cancer may also be offered adjuvant chemotherapy using 5-FU/FA based regimens. Whilst neither oxaliplatin nor capecitabine are licensed within this indication, these therapies are still used in some centres. The decision to offer patients chemotherapy is likely to be based on:

- Extramural vascular invasion;
- Serosal involvement;
- Perforation or obstruction;
- Younger age;
- Patient choice.

In some centres just one of these features may be enough to trigger the decision to offer adjuvant chemotherapy. Following surgical resection, patients would be followed up routinely according to local protocols (see Pathway D).

2.3.2 Management of Patients with Potentially Operable Metastatic Disease

A proportion of patients will present with distant metastases. Some proportion of these patients will have primary tumours which are resectable at presentation, whilst the remainder will not be resectable. Patients who are not resectable may be offered palliative stenting, a defunctioning stoma, a palliative bypass, palliative/supportive care or palliative chemotherapy. If the primary tumour is resectable and the patient is sufficiently fit, the primary tumour will be surgically removed (as described above). A proportion of those patients with distant metastases will be resectable; these are most likely to be where the patient has metastases which are confined to the liver, or in a smaller proportion of cases, the lungs. The primary tumour is resected some weeks before the liver metastases. If the metastases are not initially resectable, it may be possible to downstage a small proportion of tumours using chemotherapy. If successful, patients would undergo surgical resection. If the downstaging is unsuccessful, then patients may be offered palliative stenting, palliative bypass, palliative/supportive care or palliative.

2.3.3 Treatment of Patients Who Are Inoperable

Patients who are considered inoperable (see Pathway A, "Presentation at Accident and Emergency") may undergo palliative stenting, receive a defunctioning stoma or palliative bypass (without surgical resection of the tumour), receive palliative chemotherapy, or may receive supportive/palliative care.

2.3.4 Management of Patients Presenting with Colon Cancer

Hartmann's resection is often used for emergency colon cancer cases. In these patients, the cancer will be found using CT with or without flexible sigmoidoscopy with or without water soluble contrast enema if the clinical signs suggest localised tenderness, unless laparotomy is performed for generalised peritonitis with no pre-operative investigations.

2.3.5 Management of Patients Following Relapse

Relapse in patients undergoing routine follow-up may be identified in two ways: either through abnormalities identified via standard CT, MRI liver scans, ultrasound, rises in CEA etc., or through symptomatic presentation during the interval between follow-up tests (these patients may re-present either via their GP or as emergency cases as described in Pathway A). Recurrence may be either local or distant.

Patients who relapse may still be amenable to further surgical resection. Local recurrence is rare (compared with metastatic disease) and usually occurs at the suture line; if distant metastases are not evident, the patient would be offered re-resection, stent or palliative bypass if re-resection is not possible. If the recurrence is distant, treatment options are as described above (see Pathway B "Management of patients with synchronous metastases upon presentation"). Re-resection of the liver may be possible in some patients who have previously undergone hepatic resection but have subsequently relapsed.

For those patients who will not benefit from further surgery, treatment options are essentially palliative, offering symptom control, and enhanced health-related quality of life. Survival benefits are possible only through the use of chemotherapy, although these are typically modest. If the patient is sufficiently fit, they may be offered a chemotherapy using a variety of alternative regimens. Currently NICE recommends infusional 5-FU/FA, alone or in combination with irinotecan or oxaliplatin as first-line treatment options for the management of advanced CRC. Most commonly 5-FU/FA for advanced CRC is given according to the modified De Gramont regimen in England. This involves an initial bolus and subsequent infusional components which allow the majority of chemotherapy to be administered as an outpatient using a 2-weekly cycle length. As there is some evidence that giving all three cytotoxic drugs is better than two, the optimal treatment sequence would be 5-FU/FA plus irinotecan followed on progression by 5-FU/FA plus oxaliplatin, although treatment options are guided by patient preferences, tolerability of side effects and fitness. Following disease progression on second-line chemotherapy, although there is currently no firm guidance on

which therapy should be used. The use of monoclonal antibodies such as bevacizumab (Avastin, Roche) and cetuximab (Erbitux, Merck) is not currently recommended by NICE.

2.4 TREATMENT PATHWAY C – TREATMENT OF RECTAL CANCER

This section describes the likely treatment pathways for patients who have a positive diagnosis of rectal cancer within Pathway A. The adjuvant treatment of rectal cancer differs from that for colon cancer, mainly due to the potential benefits of chemoradiation therapy or radiation alone, although adjuvant chemotherapy may be used within similar indications to those for colon cancer. Unless presenting as an emergency, most patients with rectal cancer undergo an MRI scan as well as a CT scan, with the remainder undergoing a CT scan alone (see Pathway A). The results of the MRI scan are central in determining subsequent appropriate elective treatment.

2.4.1 Management of Patients Who Are Operable with Pre-Operative Curative Intent MRI predicts R0 resection (all margins histologically free of tumour)

There are two main surgical procedures used in the excision of rectal tumours: abdominoperineal resection (APER) and anterior resection (AR), although other procedures have been used. Both APER and AR can be undertaken alongside total mesorectal excision (TME). The choice of resection technique is guided primarily by the location of the tumour within the rectum. If the tumour is in the lower third of the rectum and the rectal MRI scan suggests that a R0 resection is possible, it is likely that the surgeon will plan to undertake an APER. Conversely, if the tumour is in the upper two thirds of the rectum, it is likely that the surgeon will plan to undertake an AR. Some lower third rectal cancers are amenable to low anterior resection, provided that 1cm distal clearance can be obtained and the MRI predicts R0 resection. Downsizing after chemoradiation may permit a restorative AR.

Radiation therapy and/or chemotherapy may be used either pre-operatively or postoperatively in the adjuvant treatment of rectal cancer. Long-course pre-operative radiotherapy (with or without concurrent 5-FU based chemotherapy), given as 25-28 fractions at 45Gy-54Gy, is used for three purposes:

- Macroscopic tumour shrinkage to facilitate successful resection;
- Reduction of local recurrence risk;
- To increase the probability of sphincter preservation.

Patients who receive long-course radiation therapy undergo a laparoscopic or trephine defunctioning stoma to stop the bowel motion passing the irradiated field, which results in complications and discomfort for the patient.

Alternatively short-course pre-operative radiotherapy, given as five fractions of 25Gy over 5 days, may be used to reduce the risk of local recurrence by 50% even if the tumour is fully mobile and easily resectable, as confirmed in the CR07 trial.

If the tumour is in the lower third of the rectum and is operable, or is rendered operable by long course chemo-radiotherapy, and the patient fit enough to undergo surgery, an APER is usually performed, if an R0 resection or preservation of the anal sphincter cannot be achieved by low anterior resection. This may be preceded by either:

- Long-course radiotherapy (with or without chemotherapy);
- Short-course radiotherapy (this is less usual);
- No pre-operative radiation therapy (this is unusual unless the patient is elderly).

An MRI scan of their rectum precedes chemoradiotherapy to reassess the stage and operability of the tumour. If the results of the MRI scan are equivocal for operability, the patient may have an examination under anaesthetic (EUA). Assessment for operability takes place two months after completion of 5 weeks' chemoradiotherapy. If a tumour remains inoperable, a further period of two months is advisable before assessing again for operability with or without EUA. If the patient is sufficiently fit, they would undergo APER; if the patient is not sufficiently fit they would receive palliative care. Surgical preparation (bowel preparation unless defunctioned by loop ileostomy prior to long course CRT, thromboembolism prophylaxis, antibiotic prophylaxis) is required as described in Pathway B.

If the patient does not receive pre-operative radiotherapy, and there is post-operative pathology evidence of circumferential resection margin (CRM) involvement, the patient may be offered post-operative radiation therapy (with or without chemotherapy). This would be given at 45-54Gy given in 25-30 fractions, sometimes alongside concurrent 5-FU based chemotherapy. This would usually be after anterior resection as most surgeons now give pre-operative radiotherapy (with or without chemotherapy) for APER. The decision to offer post-operative chemotherapy is typically based on:

- Lymph node involvement (stage III disease);
- CRM involvement;
- Extramural vascular invasion;
- pT4;
- Acute presentation with obstruction;
- Tumour perforation.

Patients may also be offered adjuvant chemotherapy following complete resection of the tumour, as described in Pathway B. The patient would then be followed up according to local protocols (see Pathway D).

If an anterior resection is planned, patients may be offered short-course pre-operative radiotherapy or long course chemoradiotherapy. Short course pre-operative adjuvant treatment is often used except for T1 and some T2 tumours. Long course chemoradiation is often used for MRI-predicted CRM involvement or for bulky, node positive predicted T3 tumours.

Similar to APER, if there is pathological evidence of CRM involvement following the resection and the patient has not received pre-operative treatment, the patient may be

offered post-operative radiotherapy (with or without chemotherapy). The patient would then be followed up according to local protocols (see Pathway D).

As with colon cancer, if the patient presents with synchronous metastases, it may be possible to subsequently resect part of the liver and/or the lungs.

2.4.2 Management of Patients with Potentially Operable Rectal Cancer

If the MRI predicts an R1/R2 resection, the patient would be offered long-course preoperative radiotherapy (with or without chemotherapy, dependent on whether the patient is able to tolerate treatment-related toxicities) in order to downstage the tumour. This would be given at 45-50Gy given in 25-28 treatments over 5 weeks with concurrent 5-FU based chemotherapy. A pre-treatment loop ileostomy would usually be fashioned. If the tumour is successfully downstaged, the patient would undergo surgery; if the downstaging is unsuccessful, the patient would receive palliative/supportive care.

2.4.3 Emergency Treatment of Rectal Cancer

Hartmann's procedure may be used for low sigmoid or upper rectal tumours if perforated. Hartmann's procedure is usually done as an emergency procedure for patients who are obstructed if stenting facilities are unavailable. Within this subset of patients, the cancer will be found using CT with or without flexible sigmoidoscopy with or without water soluble contrast enema if the clinical signs suggest localised tenderness, unless laparotomy is performed for generalised peritonitis with no pre-operative investigations.

2.4.4 Management of Patients Who Are Inoperable/Following Relapse

The palliative treatment of rectal cancer is typically similar to that for colon cancer in terms of the chemotherapy options available (see Pathway B). If the patient has not previously received radiotherapy, they may also be offered dose-limited palliative radiotherapy for metastatic disease.

2.5 TREATMENT PATHWAY D – FOLLOW-UP

Follow-up of patients following curative resection varies considerably across England. Usually this comprises of regular clinical reviews, CEA tests, CT (with or without PET)/ultrasound scans and colonoscopy. However, the timing and frequency at which each investigation is undertaken varies by centre. Commonly, patients undergo a clinical review and CEA test at 3-month intervals for the first 2 years, then at 6-month intervals for the subsequent 3 years. Patients will also undergo a routine COL at five years (COL can be done through stomas, hence all patients receive this). Patients for whom a complete COL was not achieved preoperatively, (for example, obstructing cancer) will also undergo COL within 6-months of diagnosis. Depending on centre, patients may receive up to 6 CT scans over the first three years of follow-up. If the patient's CEA rises, two further CEA tests are given monthly. If these suggest continuing increases in CEA, the patient may be given a CT

of their chest, abdomen and pelvis to attempt to identify the site of possible recurrence. If CEA rises but then drops, follow-up would continue as described above. If the CT or MRI liver/pelvis suggests recurrence, the patient may be offered further resection, or downstaging/ palliative chemotherapy. A metachronous cancer or suture line recurrence needs to be excluded by COL. A rising CEA and negative scans is an indication for CT-PET. The reader should note that there currently exists no common standard effective follow-up regimen.

2.6 TREATMENT PATHWAY E – SURVEILLANCE OF INDIVIDUALS WITH ADENOMATOUS POLYPS

Surveillance of patients with adenomatous non-malignant polyps

Patients who are considered to be high risk due to the presence of adenomatous polyps would be invited to receive 3-yearly surveillance COL, based upon the British Society for Gastroenterology guidelines. Patients, who are considered to be high-risk or intermediate-risk, would continue to undergo annual or 3-yearly COL until they have 2 clear results or until they do not attend surveillance.

2.7 TREATMENT PATHWAY F – MANAGEMENT OF INCREASED-RISK GROUPS

2.7.1 Familial Adenomatous Polyposis (FAP)

FAP carriers are identified either through linkage analysis (family history) and/or genetic testing (direct mutation analysis) once they reach the age of around 12, or based on COL investigations undertaken due to symptomatic presentation. FAP patients in whom malignant bowel tumours are not found are offered ongoing annual surveillance using FSIG between the ages of 13-15. It is recommended that at the age of about 20 years, COL surveillance should be started, alternating between FSIG and COL thereafter.

If cancer is found via surveillance endoscopy, the patient would undergo a CT scan of their chest, abdomen and pelvis or an abdominal ultrasound with a normal CXR. If the neoplasia is in the rectum the patient will undergo an MRI scan. Upon a confirmed diagnosis of cancer, the patient will have a haemoglobin test, a CEA test and treatment options will be discussed at an MDT meeting. Following a confirmed diagnosis of CRC, or when the patient reaches the age of 25 without a diagnosis of cancer, FAP patients are offered:

- Surgical removal of their bowel and rectum via proctocolectomy (plus ileoanal pouch [IAP]) followed by duodenal surveillance via oesophagogastroduodenoscopy (OGD) (6-monthly to 3-yearly depending on severity of duodenal polyposis);
- 2. Surgical removal of bowel via colectomy plus ileorectal anastomosis (IRA) followed by surveillance of the rectum using FSIG and duodenal surveillance via oesophagogastroduodenoscopy (OGD) (6-monthly to 3-yearly depending on severity of duodenal polyposis).

The choice of surgery is driven by:

- Patient preference (saving bowel and related functioning);
- Location of polyps e.g. relative rectal sparing and lower risk of rectal cancer before 50 and higher risk of infertility with rectal excision and pouch vs. colectomy and IRA;
- Location of the cancer if present.

After colectomy and IRA, polyp surveillance continues 6-12 monthly and while polyps are controllable with argon plasma coagulation (APC) or snare polypectomy or fulguration by diathermy, can defer rectal excision and pouch. A high polyp load not amenable to polypectomy or presence of rectal cancer is an indication for proctocolectomy and pouch. If further polyps or dysplasia are found after the primary surgery, the patient will have their rectum surgically removed and will have an IAP as above. Treatment of those patients in whom cancer is identified is essentially the same as for sporadic bowel cancers.

If duodenal cancer is detected (via OGD surveillance) and the patient is sufficiently fit, the patient may be considered for Whipple's procedure, which involves resecting the head of the pancreas, the duodenum and the bile duct (this is quite rare). If the patient is not sufficiently fit to undergo further surgery, they may be offered palliative/supportive care omit as these people are young and generally fit. Abdominal surgery may be prevented by the development of desmoid disease which usually presents as intestinal obstruction or a palpable abdominal mass. Chemotherapy may be useful.

2.7.2 Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

As with FAP, patients are identified either through family history or through symptom-driven COL. Clinical genetics input is essential. Patients begin surveillance via COL every 2 years at the age of 25 or at 5 years younger than the youngest HNPCC affected relative (whichever is earlier). This surveillance continues until either: the patient reaches the age of 75, or until the causative mutation in that family has been excluded. Patients with probable cancer undergo a CT scan of their chest, abdomen and pelvis or an abdominal ultrasound with a normal CXR. If the neoplasia is in the rectum the patient will undergo an MRI scan. Upon a confirmed diagnosis of cancer, the patient will also have a CEA test and treatment options will be discussed within an MDT setting. Following a confirmed diagnosis of CRC, or prophylactically, patients with HNPCC are offered:

- **1.** Surgical removal of their bowel and rectum via proctocolectomy (plus ileoanal pouch);
- 2. Surgical removal of bowel via colectomy plus ileorectal anastomosis followed by surveillance of the rectum using FSIG at 1-3 yearly intervals (this option is more usual than proctocolectomy).
As with FAP, the choice of surgery is driven by patient preferences and the location of the tumour. If further polyps or dysplasia are found in patients who have a colectomy and ileorectal anastomosis, the patient will have their rectum excised and will have an ileoanal pouch or permanent ileostomy as described above.

2.7.3 Long-Standing Ulcerative Colitis/Crohn's Disease Surveillance Groups

Patients with long-standing ulcerative colitis (UC) or Crohn's disease have a higher predisposition to develop CRC. These patients are managed via their GP and gastroenterologists (seen for diagnosis of UC/Crohn's). Patients are offered regular COL surveillance at intervals of 1-3 years depending on their risk status.

- Annual COL for patients who have had UC/Crohn's between 30/40 years;
- 2 yearly COL for patients who have had UC/Crohn's between 20/30 years;
- 3 yearly COL for patients who have had UC/Crohn's between 10/20 years.

The finding of bowel cancer, severe dysplasia or dysplasia associated lesion or mass (DALM) is an indication for proctocolectomy and ileoanal pouch or permanent ileostomy. Pouch patients will need ongoing pouchoscopy and biopsy long-term on an annual basis.

2.8 **TREATMENT PATHWAY DIAGRAMS**

Pathway A – Diagnosis of Bowel cancer and other Related Pathology 2.8.1

Diagnosis (Colon and rectum)







2.8.3 Pathway C – Treatment of Rectal Cancer



Follow-up following resection of the primary tumour (rectal and colon)

Time (0)	Surgical resection	
3m	CEA	
6m	CEA, (plus a follow-up COL if not completed during dia	gnostic work-up)
9m	▼ CEA, CT chest, abdomen and pelvis	
12m	CEA	
15m	CEA	
18m	CEA	
21m		Local recurrence may be shown by COL
24m	CEA, CT chest, abdomen and pelvis	Symptomatic presentation would return to diagnostic pathway (GP & A&E routes)
30m	CEA	
36m	CEA	
42m	CEA	
48m	CEA	
54m	♥ CEA	
60m	♥ CEA, COL	

2.8.5 Pathway E – Surveillance of Non-Malignant Neoplasia



2.8.6 Pathway F - Management of Increased-Risk Groups

Management of high risk groups



HIGH RISK GROUP 3: LONG-STANDING ULCERATIVE COLITIS/CROHN'S DISEASE PATIENTS

Section 3: Summary: Current Baseline Costs, Activity and Outcomes

		Colon Mean Cost (£)	Rectal Mean Cost (£)	Total Mean Cost (£)		
Col	Row	1	2	3		
Α	Diagnosis	£14,622,657	£5,972,634	(£20,595,291)		
В	Primary Treatment	£128,759,653	£71,868,979	(£200,628,632)		
С	- Surgery	(£67,477,601)	(£35,704,009)			
D	- CT/RT	(£61,282,052)	(£36,164,970)			
E	Follow-up (surveillance)	£17,562,685	£6,840,229	(£24,402,914)		
F	Recurrence	£185,533,600	£61,119,695	(£246,653,295)		
G	- Chemotherapy	(£175,848,853)	(£56,898,483)			
Н	- Surgery	(£9,684,747)	(£4,221,212)			
I	Stoma	£24,328,903	£27,747,664	(£52,076,567)		
J	Palliative	£80,399,658	£38,153,322	(£118,552,980)		
K	- Interventions	(£66,733,715)	(£30,410,599)			
L	- End of Life care	(£13,665,943)	(£7,742,723)			
Μ	Prevalence Cost	£451,207,156	£211,702,523	£662,909,679		
Ν	Non-cancer patients	£270,129,193				
0	Screening Cost (additional year 1 cost.)£112,828					
Р	High-risk patients	£53,758,184				
Q	Total Cost of Illness (M3+N3+O3+P3) £1,099,625,942					

Table 3.i: Summary Costs of Bowel Cancer Services in England

Table 3.i summarises the estimated costs of bowel cancer services in England. Throughout the discussion of the model results, the cells within this table have been referenced by column and row. For example, the total cost of illness can be found in cell (Q3).

Activity data were mainly derived from 2003-4 national data (e.g. Hospital Episode Statistics), supplemented with data from national audits, literature and expert opinion. Costs are reported at 2004-5 price levels and were mainly derived from NHS reference costs, published literature and NICE Technology Assessment Reports. The costs and activities have been calculated separately for rectal and colon cancer, as well as general cancer patients and increased-risk patient groups, including patients with FAP, HNPCC and

Ulcerative Colitis and Crohn's disease. The costs associated with the management of patients diagnosed within a year (i.e. the incidence costs) and those who have been diagnosed in previous years, but who are still alive and are being managed in the year of consideration (i.e. the prevalence costs) are presented in separate analyses. A separate calculation has been made for the costs of patients who were referred with suspected cancer but were subsequently found not to have cancer. Finally, the costs for each year after the introduction of screening have been estimated for 5 years.

The costs have been broken down by:

- Diagnosis;
- Rectal cancer primary treatment;
- Colon cancer primary treatment;
- Follow-up;
- Stoma care;
- Palliative care;
- Screening Cost;
- Increased-risk patients.

The prevalent cost includes all of the above costs for those patients within a year that are currently being treated for bowel cancer. The incidence cost includes those patients who are newly diagnosed within a year and their total and average treatment costs over a one-year period.

The total annual cost of illness is estimated to be £1.1bn (M3+N3+O3+P3). The total cost consists of the prevalent cost (£662.9m), non-cancer patients (£270.1m), (those suspected of bowel cancer but who are subsequently diagnosed negative), screening cost (£112.8m) and the cost of increased-risk patients (£53.8m). The incidence cost was estimated to be £419.6m which represents the treatment cost of all newly diagnosed patients over a one-year period.

The breakdown of the costs by their respective point in the treatment pathway has been summarised in Table 3.i. The largest cost as a proportion of the total cost of illness is the cost of diagnosis (A3+N3) which makes up 26.4% of the overall cost. The next most significant cost is that of the prevalent patients follow-up cost (E3+F3), estimated to account for 24.7% of the total cost of illness.

A large proportion of the diagnosis cost is due to the cost of those patients in whom bowel cancer is suspected that subsequently receive a negative diagnosis (described herein as non-cancer patients). The cost of the non-cancer patients going through diagnosis and returning as negative bowel cancer patients was £270.1m (N3). Those patients diagnosed with bowel cancer were estimated in the model to cost £20.6m in diagnosis costs (A3).

The mean cost per patient for rectal cancer treatment is estimated to be £12,037 in comparison with the mean cost per patient with colon cancer treatment which is estimated to be £8,808. (Table 3.6, page 43). There are three main factors that explain why the rectal

cancer surgery cost per patients was estimated to be greater than the colon cancer per patient cost:

- Firstly, there are a higher proportion of rectal cancer patients who undergo stomas and stoma reversal;
- Secondly, a proportion of rectal cancer patients undergo pre and post-operative chemoradiation;
- Thirdly, higher numbers of rectal cancer patients undergo adjuvant chemotherapy.

The total cost of rectal cancer follow-up is \pounds 67.9m (E2+F2) and is made up of the surveillance costs of \pounds 6.8m and recurrence treatment costs of \pounds 61.1m. The total cost of colon cancer follow-up of \pounds 203m (E1+F1) comprises surveillance costs of \pounds 17.5m and recurrence treatment costs of \pounds 185.5m.

The stoma care cost has been estimated to reflect an annual cost of all prevalent permanent stoma costs related to bowel cancer. The total cost of stoma care is estimated to be approximately £52m (I3). This consisted of a stoma care cost of £27.7m for patients who have previously undergone rectal surgery and £24.3m for those patients who have previously undergone colon surgery. The mean cost per year was calculated as £1,279 per patient.

The total palliative care costs can be broken down by the palliative intervention costs and the end of life costs in the treatment of bowel cancer. The estimated total palliative care cost for bowel cancer in England was £118.6m (J3).

The total screening cost is estimated at £112.8m (O3). This cost includes the cost of the screening programme for those aged 60 to 69 and the additional treatment cost in the first year for those patients who are diagnosed.

Increased-risk patients account for a smaller proportion of the cost at 5.5% of the total cost of illness, estimated to be £53.8m (P3). However, there is a high degree of uncertainty surrounding this as data sources to populate this aspect of the treatment pathway were limited.

Section 3: Current Baseline Costs, Activity and Outcomes

3.1 OVERVIEW

This section presents the methodology and results of the baseline pathway for bowel cancer services. This is intended to provide an estimate of the total annual costs, activities and outcomes of treating bowel cancer. These estimates are based on a modelling exercise, which represents a separate but inter-linked process from the development of the options model. Whilst the models are consistent, their objectives and outputs are quite distinct, with the baseline model providing an estimate of the total costs of current services for bowel cancer and the options model simulating the expected costs of outcomes of various service reconfigurations for a hypothetical cohort of patients with bowel cancer. Both models are based to a large extent on the literature review which accompanies this report. A process of validation of the models has been completed to ensure that the models are consistent, in terms of the predicted outcomes and costs produced by each.

The activity and costs associated with each element of the pathway have been estimated along with the key intermediate outcomes. For each node of the pathway, details have been provided on how the values were derived. This detail has been provided in Appendix A of the report and the pathways are presented at the end of this section. Summaries of all literature from which evidence was extracted can be found in the literature review report which accompanies this report.

The model estimates rely upon the structure of the pathway and the data used to populate the pathway. This section discusses in detail the derivation of the cost and activity data. The resulting estimates were taken from the Bowel Cancer Model 3.52 as of 12th March 2007. Any data that could not be found from literature or other data sources has been derived through elicitation processes undertaken with a selection of clinicians. Highlighted, throughout the results are problems with data availability. In these circumstances, assumptions based on clinical opinion have been used.

There are eleven separate sub-sections in Section 3 of the report:

Section 3.1:	Overview;
	,

- Section 3.2: Methodology;
- Section 3.3: Summary of Activity and Costs with Outcomes;
- Section 3.4: Presentation and Diagnosis;
- Section 3.5: Primary Treatment of Rectal Cancer;
- Section 3.6: Primary Treatment of Colon Cancer;
- Section 3.7: Stoma Care Costs;
- Section 3.8: Follow-up Activity;
- Section 3.9: Palliative Care Activity and Costs;

Section 3.10: Bowel Cancer Screening; Section 3.11: Increased-risk Patients.

3.2 METHODOLOGY

3.2.1 The Structure of the Baseline Pathway and Model

The baseline pathway follows the pathway developed within section two of this report, where previously the pathway algorithms have been discussed in detail. The pathway adopted in this exercise is intended to mirror that used in the options model however, some differences do occur in a number of places for the purpose of more detailed cost calculations. These include:

- In the following sections additional detail has been included:
 - In primary surgery, the costs of different procedures have been considered in detail;
 - The addition of activity and costs associated with stoma care;
 - The inclusion of palliative and end of life care activity and costs.
- The pathways for increased-risk patients, i.e. FAP, HNPPC and ulcerative colitis have been developed, populated and estimation of the costs were performed separately;
- The activity and costs for the baseline reflect annual costs, whereas the options model reflects lifetime costs and outcomes;
- The baseline activities and cost model calculates incidence costs (i.e. the costs associated with the new cases presenting in a year) and prevalence costs (i.e. the costs associated with those patients being managed with or as a result of bowel cancer diagnosed in previous years).

The populated pathways are given at the end of this section and the sources for parameters and costs can be found in Appendix A. The pathways are shown separately for the management of rectal cancer, colon cancer, and for increased-risk patients, i.e. FAP, HNPPC and ulcerative colitis. The pathway follows the elements of the patient journey, namely:

- Presentation and diagnosis;
- Rectal cancer treatment:
 - Primary rectal surgery;
 - o Stoma care;
 - Chemotherapy and radiotherapy.
- Colon cancer treatment:
 - Primary colon surgery;
 - o Stoma care;
 - o Chemotherapy.
- Stoma care;
- Follow-up;

Palliative care:

- Interventional palliative care;
- End of life palliative care.

3.2.2 Derivation of Data

3.2.2.1 Derivation of activity data

Activity data were derived from the following sources:

- National published data such as Hospital Episode Statistics (HES) and Office of National Statistics;
- Nationally published audits such as the NBOCAP Audit;
- Locally published data, such as Northern and Yorkshire Cancer Registry (NYCRIS), and data analysed for the research study by staff at NYCRIS;
- Locally collected data, analysed for or provided to the research study, for example, audits and trials;
- Published literature;
- Expert opinion;
- Elicitation of expert judgement. The methodology is provided in the appendices of this report.

The data have been imputed where it has not been possible to find published sources of data and where it could not be obtained through expert opinion or local sources. It was anticipated that further data might be made available on a number of aspects of the treatment pathway including radiotherapy activity and aspects of the treatment pathway for increased-risk patients. Unfortunately, this information was not made available in time for inclusion in this report.

3.2.2.2 Derivation of cost data

Cost data have been derived from:

- NHS Reference Costs published by the Department of Health;
- Standard costs collected and published annually by Curtis and Netten (2005) from the Personal Social Services Research Unit (PSSRU) at the University of Kent;
- Published literature;
- Local sources and expert opinion.

NHS Reference Costs are available for 2004/05 and all other cost data have been uplifted to 2004/5 price levels using the Hospital & Community Health Services (HCHS) inflation indices, published by Curtis and Netten (2005).

3.2.2.3 Derivation of outcome data

Outcomes data have been derived from the following sources:

- National published data such as Hospital Episode Statistics (HES), and Office of National Statistics, for the production of mortality statistics;
- Nationally published audits such as the NBOCAP Audit;
- Locally published data, such as Northern and Yorkshire Cancer Registry (NYCRIS), and data analysed for the research study by staff at NYCRIS;
- Locally collected data, analysed for or provided to the research study, for example, audits and trials;
- Published literature;
- Expert opinion.

3.2.2.4 Elicitation of data unavailable from literature and data sources

In those areas where empirical evidence was insufficient, evidence to inform parameters has been elicited by using clinical experts. The methodology for elicitation can be found in the appendices of this report. The main areas where parameters have been elicited are in:

- Presentation and diagnosis;
- The use of stenting;
- The use of chemotherapy in the treatment of colon and rectal cancer;
- The use of radiotherapy in the treatment of rectal cancer;
- The use of liver resection for metastatic disease.

3.2.2.5 Modelled Overall survival Curves

The options model was used to estimate overall survival curves for colon cancer patients and rectal cancer patients for use in the baseline activity and cost model. These are modelled overall survival curves and are best estimates of current survival given the current baseline. These were based on data derived from a number of sources (CRO7 2006, Mawdsley 2005, FOCUS 2004, MOSAIC 2004, X-ACT 2005, COST 2004 and ONS 2003) and details of the methods used can be found in Section 4. The one-, three- and five-year overall survival³ rates for rectal cancer are 84%, 66% and 51%, respectively. The one-, three- and five-year survival rates for colon cancer are 86%, 72% and 59%, respectively.

³ These are the estimated survival curves from the model.

	Within ye	Cumulative		
Year	Death rectal cancer	Survive	Other causes death	Overall survival
Year 0	0.00%	100.00%	0.00%	100%
Year 1	15.51%	84.27%	0.23%	84%
Year 2	6.45%	89.19%	4.36%	75%
Year 3	8.08%	87.82%	4.09%	66%
Year 4	7.61%	88.11%	4.28%	58%
Year 5	7.83%	87.56%	4.60%	51%
Year 6	11.48%	83.76%	4.76%	43%
Year 7	5.97%	89.63%	4.40%	38%
Year 8	4.74%	89.90%	5.37%	34%
Year 9	3.18%	90.62%	6.20%	31%
Year 10	2.27%	91.83%	5.90%	29%
Year 11	1.35%	92.18%	6.47%	26%
Year 12	0.10%	93.89%	6.01%	25%
Year 13	0.16%	92.52%	7.32%	23%
Year 14	0.12%	92.90%	6.98%	21%
Year 15	0.06%	91.80%	8.14%	20%
Year 16	0.07%	90.59%	9.35%	17%

Table 3.1: Rectal cancer survival and mortality

Source: Model Survival curves.

Table 3.2: Colon cancer survival and mortality

	Within year survival and mortality			Cumulative
Year	Death colon cancer	Survive	Other causes death	Overall survival
Year 0	0.00%	100.00%	0.00%	100%
Year 1	13.09%	86.40%	0.51%	86%
Year 2	3.57%	91.81%	4.62%	79%
Year 3	4.30%	91.00%	4.70%	72%
Year 4	4.49%	90.89%	4.62%	65%
Year 5	5.32%	90.00%	4.69%	59%
Year 6	6.16%	88.95%	4.89%	52%
Year 7	3.59%	91.03%	5.38%	47%
Year 8	3.27%	91.13%	5.60%	43%
Year 9	2.30%	92.31%	5.39%	40%
Year 10	1.27%	92.70%	6.03%	37%
Year 11	1.07%	92.76%	6.17%	34%
Year 12	0.25%	92.95%	6.80%	32%
Year 13	0.00%	92.65%	7.35%	29%
Year 14	0.00%	91.73%	8.27%	27%
Year 15	0.00%	92.59%	7.41%	25%
Year 16	0.00%	92.09%	7.91%	23%

Source: Model Survival curves.

Graph 3.1: Overall survival for colon and rectal cancer patients



Overall survival for Colon and Rectal Cancer Patients

3.2.2.6 Verification of number of patients in the pathway

The number of cancer registrations reported in England in 2003/4 was approximately 27,800. It has been assumed that of these 29% are cases of rectal cancer and 71% colon cancer ONS (2003). The figure was based on this and other events in the treatment pathway which have been determined by applying probabilities derived from the data sources listed above (e.g. probability of undergoing surgery, chemotherapy etc). However, it should be acknowledged that there may be some uncertainty in the accuracy of the number of cancer registrations, due to inaccurate reporting.

3.2.2.7 Parameter values

The value and source of each data item used has been documented for each node of the pathway, as described in Appendix A. Below is an example of the description of the cost and activity data, and two examples of the outcome data for the colonoscopy node. The literature review provides a more comprehensive discussion of the parameters that were taken from the literature.

Table 3.3: Examples of parameters and outcomes

Cost and Activity: Nor	mal clinic-colonoscopy: Node number 16
Activity Parameter:	41%
Activity Reference:	Elicitation and Ward et al. (2004)
Activity Comments:	Elicitation was used to define the percentage endoscopy compared to
	double contrast barium enema and Ward et al. 2004 for colonoscopy and
	flexible sigmoidoscopy.
Activity Distribution	Beta distribution defined by assumptions
Cost Parameter:	£352
Reference:	Reference Costs, Department of Health (2005)
Cost Comments:	None
Cost Distribution:	Normal distribution based on reference costs
Outcomes: Colonosco	py: Node number 16
Bowles CJA (2004)	The overall completion rates for Colonoscopy were 76.9%, which included
	surveillance and therapeutic colonoscopy. The completion rate for a
	general district hospital was 74.5%. This compared to 76.6% for a teaching
	hospital. Perforation rates were reported at 0.13%, bleeding in 0.07% of
	patients. The reported mortality rate was 0.07%.
De Zwart (2001)	The completion rates ranged from 54% to 98%. The perforation rate was
	0.08%.

3.2.2.8 Prevalence model data source

The prevalence estimate extracted from the literature was an ONS estimate provided by Forman (2003). The ONS prevalence estimate for colon cancer was 137 per 100,000 population and for rectal cancer was 104 per 100,000 population. A table of the prevalence figures based on the population of England of 49,855,700 is as follows:

Table 3.4: Prevalence estimates for England

Gender	Male	Female
Colon	33,449	44,012
Rectal	25,392	22,897
Total	58,841	66,909
England prevalence:	125,750	

Source: Forman (2003).

The estimated prevalence from this source for bowel cancer in England is 125,750. The baseline model 5-year prevalence estimate was 118,433 patients.

3.2.3 Model Uncertainty

In order to estimate the uncertainty around the parameters each activity and cost parameter was described by a unique probability distribution. The distributions were defined by assessment of the magnitude and nature of the uncertainty surrounding the mean parameter estimates obtained from the literature and other data sources that produced the characteristics of the distributions surrounding the parameters. Covariance was assumed in the estimation of the activity parameters for those patients who were treated with chemotherapy.

The joint uncertainty surrounding all of the model parameters was analysed using Monte Carlo sampling techniques. This technique involves randomly sampling from all model parameters simultaneously in order to produce probability distributions for the model outputs. For the most part, beta distributions were used to describe the probability parameters, whilst normal distributions were used to describe uncertainty surrounding most of the other model parameters. A description of each probability can be found in Appendix A.

The model was run over 10,000 random iterations to take account of uncertainty and the results have been reported in the following sections. The results are reported with their respective 95% confidence intervals around the mean per patient costs or total costs. The distribution of the total cost of illness is also presented visually in the form of a probability density function.

3.3 SUMMARY OF ACTIVITY AND COSTS WITH OUTCOMES

3.3.1 Summary Costs

The final costs have been reported in five different forms:

- Incidence model costs;
- Prevalence model costs;
- Negative cancer patient costs (non-cancer patients);
- Screening cost;

- Increased-risk patient cost;
- Total cost of Illness.

3.3.1.1 Incidence model cost

The incidence model estimates the annual treatment cost associated with patients who are newly diagnosed within a one year period. A total cost figure as well as a cost per patient figure has been calculated. This does not include new patients who undergo presentation and diagnosis but are diagnosed as negative in a particular year.

3.3.1.2 Prevalence model cost

The prevalence costs are made up of the total cost of a single cohort of patients followed over the course of their lifetime. For example, cohort 1 represents those patients who were diagnosed in the current year; cohort 2 the patients who were diagnosed in the previous year and so on. This assumes that a single cohort is followed until all patients have died either of bowel cancer or other causes are the same as a snapshot of all cohorts in a single year of costs.

3.3.1.3 Cost of negative cancer patients

Patients who are suspected of having bowel cancer but are subsequently diagnosed negative (negative cancer patients) have been separated in terms of the estimate of cost. The total cost of presenting and diagnosis has been produced for these patients and then a cost per negative cancer patient has been provided.

3.3.1.4 Screening cost

The NHS Bowel Cancer Screening programme was initially rolled out in June 2007, with the plan to establish all centres nationally by March 2007. The aim of the screening programme is to detect bowel cancer at an earlier stage when the disease is still asymptomatic.

The screening programme will offer screening every two years to all men and women that are aged 60 to 69 using the Hemoccult Faecal Fecal Occult Blood Test (FOBT). Those patients over 70 years of age can also request a screening kit from their pilot centre. The FOB test identifies blood which can sometimes be produced from cancers and large polyps, which may not be visibly obvious in the stool. Individuals in whom the FOBT test is positive are typically followed-up using colonoscopy or in some cases barium enema.

The baseline model was developed to fulfil a specific objective which was to model the current activities and costs of bowel cancer in England. The evaluation of the impact of screening is not viable in this specific framework because of the following reasons:

• The cost will change each year as more cancers will be detected in the first year in comparison to future years. This would mean that presenting an annual cost would be difficult to interpret and would also present less information than the original screening option appraisal model Tappenden *et al.* (2007). The phenomena of the

prevalence and incidence screening rounds would also render a single estimate meaningless;

- The baseline model does not specifically include stage at every node of the pathway. It would be inappropriate to feed this into the baseline, as the additional number of screen-detected cancers would be insensitive to the true impact of the FOBT screening;
- The baseline model includes current pathways and is populated with the present non-screened population. The re-distribution of resource requirements following the roll-out of a national screening programme are unknown and require a large number of assumptions.

In light of this, the original ScHARR bowel cancer screening model (Tappenden *et al.* (2007)) was used to estimate the cost impact of screening upon the baseline. The approach uses activity data from the ScHARR screening model and updated costs taken from the baseline bowel cancer activity and cost model. The model assumes a FOBT test for individuals between the ages of 60 - 69 biennially. An estimate of the total additional annual costs has been presented for the 5 years following the roll-out of screening, together with a projection of any potential cost saving. The analysis necessarily assumes that screening will take immediate effect in the relevant population across England.

The cost of screening was estimated using the original ScHARR bowel cancer screening model. This model was updated using the costs from the baseline bowel cancer costs and activity model. The model assumes that individuals aged between 60 to 69 are invited to attend FOBT screening biennially. The total additional annual cost of screening has been presented for the 5-years following the roll-out of screening. Total cost of Illness for the current year includes the additional costs of the first year of screening.

3.3.1.5 Cost of bowel cancer services for high-risk patients

The costs have been provided for each of the three increased-risk groups. These costs include the prevalent total cost and the cost of negative cancer patients. The cost for a year of bowel cancer services per increased-risk patient has then been calculated.

3.3.1.6 Total cost of illness for bowel cancer patients

The final cost provided is the total cost of bowel cancer services for the current year. This cost includes the prevalent total cost, the cost of negative cancer patients, screening cost (year 1) and the cost of increased-risk patients.

3.3.2 Summary Results

Table 3.5 overleaf provides a summary of the total pathway costs for both incident and prevalent patients. These are discussed in more detail in the subsequent sections.

Patients	Mean total cost (£) 95% Cl Lower bound (£)		95% CI Upper bound (£)	Mean cost per patient (£)
Total cost of incident patients (A)	£419,562,097	£269,788,375	£633,194,142	£16,099
Prevalent patients treatment (B)	£662,909,679	£420,076,480	£989,138,078	£6,257
Non-cancer patients (C)	£270,129,193	£239,373,004	£295,267,010	£365
Screening cost (D)	£112,828,886	£112,828,886	£112,828,866	-
High-risk patients (E)	£53,758,184	£53,758,184	£53,758,184	£1,978
Total cost of prevalent patients (B+C+D+E)	£1,099,625,942	£845,469,893	£1,426,199,227	£1,384

Table 3.5: Summary total costs for bowel cancer services

Graph 3.1: Total cost of illness distribution



The total cost of illness is estimated to be £1.1bn. This total cost consists of the prevalent patients, non-cancer patients, screening cost and increased-risk patients. These results are shown in Table 3.5. The total cost of managing incident patients is estimated to be £419.6m which is the treatment cost of all newly diagnosed patients within a one-year period. Graph 3.1 presents the distribution around the mean point estimate for the total cost of illness.

The breakdown of the costs by their respective point in the clinical pathway is summarised in Table 3.6. The cost of diagnosis is the largest component cost of illness, accounting for 26.4% of the total cost. The second largest component cost is the prevalent patients follow-up cost estimated to be 26.7% of the total cost of illness. Screening in the first year of the programme, accounts for approximately 10% of the estimated total cost of illness.

A significant proportion of the diagnosis cost is for those patients in whom bowel cancer is suspected but is subsequently diagnosed negative (non-cancer patients). The cost of the non-cancer patients going through diagnosis and returning as negative bowel cancer

patients is estimated to be £270.1m. Those patients who were diagnosed as having bowel cancer are estimated to cost £20.6m.

The mean cost per patient for rectal cancer treatment was estimated to be £12,037 in comparison with the mean cost of colon cancer treatment which was estimated to be £8,808. Rectal cancer treatment was estimated to cost more than colon cancer treatment. There are three main reasons which may explain the higher cost of rectal cancer surgery (Table 3.6). Firstly, there are a higher proportion of rectal cancer patients who undergo stomas and stoma reversal. Secondly, a proportion of rectal cancer patients undergo pre- and post-operative chemoradiotherapy. Thirdly, higher numbers of rectal cancer patients undergo adjuvant chemotherapy.

Increased-risk patients account for a smaller proportion of the total cost of illness, accounting for 5.5% of this cost. There is a high degree of uncertainty surrounding this cost as data sources for the estimation for both activity and costs for increased-risk patients was very limited. The prevalence breakdown of the estimated prevalence costs are provided in Table 3.6.

Patients	Mean total cost (£)	95% CI Lower bound (£)	95% CI Upper bound (£)	Proportion of total cost of illness per year (%)	Mean cost per patient (£)
Diagnosis	£290,724,484	£257,336,709	£317,789,656	26.44%	£379
Rectal cancer treatment	£71,868,979	£44,596,515	£109,026,293	6.54%	£12,037
Colon cancer treatment	£128,759,653	£79,550,757	£195,119,329	11.71%	£8,808
Stoma cost (prevalence)	£52,076,567	£31,694,913	£81,281,478	4.74%	£1,279
Palliative care cost (prevalence)	£118,552,980	£68,529,235	£193,207,422	10.78%	£7,360
Follow-up (prevalence)	£271,056,209	£164,332,652	£405,834,474	24.65%	£11,183
High-risk	£53,758,184	£53,758,184	£53,758,184	4.89%	£1,978
Screening Cost (Year 1)	£112,828,886	-	-	10.26%	-
Total cost of illness	£1,099,625,942	-	-	100%	-

Table 3.6: Summary of cost breakdown

3.4 PRESENTATION AND DIAGNOSIS

3.4.1 Overview

	Mean total cost (£)	Mean cost per patient (£)	95% Cl Lower bound (£)	95% Cl Upper bound (£)
Total diagnosis cost All patients	£290,724,484	£379	£335	£413
Diagnosis cost Bowel cancer patients	£20,595,291	£790	£623	£962
Diagnosis cost Non bowel cancer patients, who undergo diagnostic testing	£232,592,637	£487	£391	£550
Diagnosis cost Non bowel cancer patients, who do not undergo diagnostic testing	£37,536,556	£143	£95	£220

Table 3.7: Presentation and diagnosis cost table

The total diagnosis cost in Table 3.7 above comprises the cost of referral and diagnosis of all those who present via a GP, Accident and Emergency (A&E) or from elsewhere in secondary care. The 95% confidence intervals are presented to indicate the degree of uncertainty around the mean cost estimates based on the methods that were described in Section 3.2.3.

This cost is broken down into three component parts:

- The referral and diagnosis costs of those patients who are diagnosed with bowel cancer;
- The referral and diagnosis costs of those patients who are not diagnosed with bowel cancer but undergo diagnostic testing such as colonoscopy, flexible sigmoidoscopy or double contrast barium enema;
- The referral and diagnosis costs of those patients who are either sent home or referred elsewhere before undergoing diagnostic tests such as colonoscopy, flexible sigmoidoscopy or double contrast barium enema.

A detailed description of the derivation of these cost estimates is presented in the following section.

3.4.2 Access Routes

There are six ways in which patients may access bowel cancer services in England and are as follows:

- **1.** Symptomatic presentation to GP;
- 2. Presentation at an Accident and Emergency (A&E) department;
- 3. Referral from elsewhere in secondary care;
- 4. Identification of Familial Adenomatous Polyposis (FAP);
- 5. Identification of Hereditary Non Polyposis Colorectal Cancer (HNPCC);
- **6.** Surveillance for patients with long-standing conditions such as Crohn's disease and ulcerative colitis (UC).

Separate pathways for routes 4, 5 and 6 are termed 'increased-risk patients'. These are discussed in a separate section.

3.4.3 Referral

Approximately 3.5% of individuals presenting with symptoms of bowel cancer are diagnosed with confirmed bowel cancer Vellacott (2002). Therefore, it was estimated that 767,108 patients will present with symptoms which results in 26,185 positive diagnoses of bowel cancer (excluding those that are considered to be at an increased-risk). Of these, it has been assumed that 71% present via their GP, 7% through A&E and 22% elsewhere in secondary care and based on data from the Department of Health (Personal Communication: Department of Health Working Times Database 2006). Of those presenting to their GP, it was estimated that 55% are referred and 45% are managed in primary care. Of those referred, 37.5% have a standard referral, 49.5% have a fast track referral and 13% become an emergency (Personal Communication: Department of Health).

Those patients who enter the pathway through A&E (either having been sent by their GP or self presenting) are assumed to undergo preliminary tests in the A&E department. The model assumes that 50% of these will have either been referred to another department or sent home. Since these percentages were not known a 50-50 split was assumed. However, it should be noted that this assumption does not have an effect on overall costs. The other 50% of patients are either referred to the normal clinic or straight to surgery by an MDT if an obstruction is identified. Law (2002), states that between 15% and 20% of bowel cancer cases present with an obstruction so 7.5% of patients are sent directly to MDT and 42.5% are referred for further diagnostic testing.

Those patients who enter through other secondary care referrals are assumed either to have had some form of previous diagnostic tests which has identified bowel cancer or the patient is sent for diagnostic testing. Only 1.5% of patients are assumed to have had some form of previous diagnostic test that identified bowel cancer and these patients are considered by an MDT. However, the majority of these patients, 98.5%, have not had any previous diagnostic tests and are subsequently referred for diagnostic testing.

3.4.4 Normal Diagnostic Clinic

Patients can be referred to the normal clinic through standard or fast-track GP referrals. These patients are assumed to undergo an initial review comprising of a haemoglobin test and a rigid sigmoidoscopy, Phillips (2002). Following this, an assumption was made that 10% of patients are sent home and that 90% are sent for further diagnostic tests.

3.4.5 The Overall Costs of Presentation and Diagnosis

The overall cost of diagnosis shown in Table 3.7 is estimated to be £290.7m; this includes the cost of referral and diagnosis of all patients who present via a GP, A&E or from elsewhere in secondary care.

The 26,062 patients diagnosed with bowel cancer are estimated at £20.6m which is 7% of the total presentation and diagnosis cost. However, when compared to the cost of non-cancer patients who undergo diagnostic testing and non-cancer patients who do not undergo diagnostic testing the costs in per patient terms are higher for those diagnosed with bowel cancer. The costs for these three groups of patients are £487 per patient, £143 per patient and £790 per patient, respectively.

Those patients who are ultimately not diagnosed with bowel cancer but undergo diagnostic testing cost a total of £232.6m which accounts for 80% of the total cost of diagnosis. These patients undergo the same diagnostic procedures as those patients who are diagnosed with bowel cancer. However, the per patient costs are smaller because these patients do not progress to MDT, treatment and follow-up and as such do not incur these costs.

The final group includes those patients who do not undergo diagnostic testing. These patients are either not referred by their GP, sent home or sent to another department if they present at A&E. These patients cost £37.5m, which is 13% of the total cost of illness and this group of patients has the lowest cost per patient of the three groups of patients at £143.

The overall costs are particularly sensitive to two parameters, mainly because of the large number of patients involved:

- The percentage of cancers diagnosed as positive. The mean value used for this parameter was taken from the mid-point of the literature values for a positive diagnosis. This model is highly sensitive at the diagnostic stages to changes in the value of this parameter. For example, if the upper estimate of 7%, from the literature were to be used, then notably fewer individuals would present to achieve the 26,253 positive cancers and vice versa for lower estimates;
- The percentage that GPs refer to secondary care.

The 95% confidence intervals provide an indication of the degree of uncertainty surrounding the mean cost estimates. A considerable proportion of this uncertainty is attributable to the factors mentioned above.

3.4.6 The Cost of Diagnostic Testing For All Patients

Diagnostic procedure/complication	Total cost
Colonoscopy	£67,074,992
Flexible sigmoidoscopy	£44,242,103
Double contrast barium enema	£26,184,585
Multiple tests	£17,875,218
Perforation	£1,409,505
Death	£285,995
Total cost of diagnostic tests	£157,072,398

Table 3.8: The Cost of diagnostic testing for all patients

Patients can be sent for further diagnostic tests by three different routes; from the normal clinic, through A&E or elsewhere in secondary care. This results in 465,504 patients being sent for further diagnostic tests. These patients are then examined by either a colonoscopy, (41%), flexible sigmoidoscopy (34%) or, double contrast barium enema (25%), according to Ward *et al.* (2004) and the elicitation exercise. Unit cost estimates for each procedure were obtained from the NHS Reference Costs (2005) and were:

- £352 for colonoscopy;
- £279 for flexible sigmoidoscopy;
- £225 for double contrast barium enema.

This results in total colonoscopy costs of \pounds 67.1m, total flexible sigmoidoscopy costs of \pounds 44.2m and total double contrast barium enema costs of \pounds 26.2m (Table 3.8).

In cases where the initial diagnostic test is incomplete or inconclusive a second diagnostic test is required for a definitive diagnosis. In the model, it was assumed that 13% of patients undergoing an initial diagnostic test subsequently require further tests, based on the findings of a study by Smith and O'Dwyer (2001). This results in 60,515 extra diagnostic tests at a cost of £17.9m. The activity and costs associated with multiple testing were calculated using weighted averages of initial diagnostic procedures which resulted in a cost of £295 for multiple diagnostic tests.

All diagnostic tests are associated with a risk of complications such as perforation. The model estimates that 208 perforations would occur each year. The annual cost of managing these complications is estimated to be £1.4m. Perforation rates for colonoscopy and flexible sigmoidoscopy were estimated to be 1/769, which were derived from Bowles *et al.* (2004) and 1/40,674 Atkin *et al.* (2002), respectively. Double barium enema was assumed to be associated with a perforation rate of 1/100,000 based on De Zwart *et al.* (2001). Perforation rates for multiple tests were calculated using a weighted average of initial diagnostic tests. Perforations were assumed to be treated with laparoscopic surgery in 90% of cases and treated conservatively in 10% of cases. These assumptions yielded a weighted mean cost of £5,038.

There is also a small risk of mortality associated with diagnostic tests which is most commonly due to perforation. The model estimates that 137 patients die as a result of diagnostic testing at a cost of £285,995. The mortality rates for colonoscopy and double contrast barium enema were taken from Bowles *et al.* (2004) and De Zwart *et al.* (2001), respectively.

3.4.7 Outcomes of the Further Diagnostic Tests

As noted above, Vellacott *et al.* (2002) estimates that 3.5% of those patients who undergo the diagnostic tests are diagnosed with bowel cancer. The remaining 96.5% of patients who present are therefore assumed to have a negative diagnosis of bowel cancer although a proportion of these patients will be diagnosed with polyps and other pathologies. Patients who are diagnosed with bowel cancer are subsequently referred to a MDT.

3.4.8 Outcomes Associated with Referral and Diagnosis

The quality of diagnostic testing is important. Two key metrics are used to measure quality; sensitivity rates and completion rates. This section gives an indication of the different completion and sensitivity rates for the different diagnostic tests that are seen in the literature.

Higher completion rates mean that the diagnosis is more likely to be accurate and there is less likelihood of false negatives or the need for multiple tests. However, studies by Bowles et al. (2004), De Zwart (2001) indicate that completion rates vary from 54% to 98%, the variability due in part to the quality of preparation of the bowel. Quality is also measured by problems such as levels of pain or rate of perforation of the bowel according to Bretthauer (2002). The consensus in the literature is that colonoscopy is the gold standard, although recent trials have indicated that flexible sigmoidoscopy is more sensitive Atkin (2002). Flexible sigmoidoscopy appears to have lower levels of adverse events Atkin (2002) and Blom (2004). Verma (2001) demonstrated that open access flexible sigmoidoscopy had shorter waiting times and higher diagnostic yield compared to hospital indicated flexible sigmoidoscopy. Double contrast barium enemas are still used, but the mean overall sensitivity rate of barium enema for the detection of bowel cancer is reported to be 85.9% by Tawn (2005), compared to a mean overall sensitivity rate of colonoscopy of 95% Rex (1997) with a miss rate of between 7 to 24% according to Leslie (2002). Consultants have lower miss rates compared to trainees Halligan (2003). Rex (1997) reports that the sensitivity rate of colonoscopy was higher when performed by a gastroenterologist (97.3%) compared to a non-gastroenterologist (87.0%).

3.5 PRIMARY TREATMENT OF RECTAL CANCER

	Total mean cost (£)	Mean cost per patient (£)	95% Cl Lower bound (£)	95% Cl Upper bound (£)
Total rectal primary treatment	£71,868,979	£12,037	£11,110	£12,940
Primary rectal surgery	£35,704,009	£5,980	£5,675	£6,199
Chemotherapy and radiotherapy	£36,164,970	£7,726	£4,937	£11,271

Table 3.9: Summary of primary treatment of rectal cancer costs

In Table 3.9 the total rectal cancer primary treatment cost includes costs after diagnosis and prior to follow-up, which include the rectal surgery costs and chemotherapy and radiotherapy costs. The total rectal primary treatment cost is estimated to be £71.9m. Those patients who undergo primary rectal cancer treatment are estimated on average, to cost £12,037.

The primary rectal surgery cost includes MRI and pathology costs, stoma costs, stoma closure costs, complication costs and stenting costs. The primary rectal surgery total cost is estimated to be £35.7m. The average cost for those undergoing primary potentially curative surgery is £5,980 per patient.

The chemotherapy and radiotherapy costs include the cost of pre-operative chemoradiation, post-operative chemoradiation and the cost of adjuvant chemotherapy. The total cost of chemotherapy and radiotherapy is estimated to be £36.2m. The mean cost for those undergoing chemotherapy and radiotherapy is estimated to be £7,726 per patient.

3.5.1 Primary Rectal Surgery

Table 3.10: Breakdown of primary rectal surgery costs

Procedure	Cost (£)
MRI Cost	£1,609,096
Surgery for primary tumour cost (includes stenting)	£32,765,542
Stoma reversal cost	£1,329,371
Total Cost of primary rectal surgery	£35,704,009

The following section describes the activity and cost assumptions with regards to primary rectal surgery. This includes the MRI costs, pathology costs, stenting costs, stoma reversal costs and complication costs.

Based on 2003/04 cancer registrations (excluding increased-risk patients) the model estimates that 7,558 patients based on 2003/2004 cancer registrations (excluding increased-risk patients) who undergo treatment for rectal cancer. It was assumed from an audit of the Trent region and Wales that 79% of patients may undergo curative treatment for their primary tumour Mella *et al.* (1997).

3.5.2 Initially Curable Patients

Based on data from Mella *et al.* (1997), the model estimates that 5,971 patients undergo curative treatment. These patients either present as emergency cases or elective cases.

3.5.3 Emergency Cases

The model estimates that there are 830 emergency cases. Patients can either undergo stenting as a bridge to surgery or go directly to surgery. Evidence from the literature was limited on the proportions undergoing stenting. Expert elicitation was therefore used to derive this proportion. The elicitation process estimated that 2% of patients who were emergency admissions undergo stenting as a bridge to surgery. This figure was applied to both colon and rectal cancer patients.

Presently, stenting is carried out infrequently so this figure should be regarded as an upper estimate. According to $IOCC^4$ (2004) "About 30 hospitals in the UK use stenting regularly. Most offer stenting only for palliation of intestinal obstruction."

The average cost of stenting was \pounds 1,879.79 which was taken from Osman *et al.* (2000). The total cost of stenting as a bridge to surgery was estimated to be \pounds 31,202.

3.5.4 Elective Cases

The majority of elective patients who are diagnosed with rectal cancer will undergo a Magnetic Resonance Imaging (MRI) scan. The results of the MRI scan are crucial in determining the appropriate elective treatment. The MRI will either predict the patient as R0 (all margins are histologically free of tumour) or it will predict R1/R2 (microscopic/gross residual disease.)

3.5.5 Elective Patients MRI Predicts R0 Resection

The model assumes that 82% of patients are predicted R0, which was taken from a study by Chau (2003). These patients are assumed to have pre- or post-operative chemoradiotherapy or no chemotherapy alongside surgery. The proportion of R0 patients who are assumed to have pre-operative chemoradiotherapy could not be identified from the literature or other data sources and was therefore elicited. As a result of the elicitation the model assumes that 60% of those predicted R0 will undergo pre-operative chemoradiotherapy. Of those patients who did not have pre-operative radiotherapy, 11% are assumed to have post-operative chemoradiotherapy (CR07 trial 2006).

⁴ Improving Outcomes in Colorectal Cancer IOCC (2004) Manual Update page 76.

3.5.6 Elective Patients MRI Predicts R1/R2 Resection

The model assumes 18% of patients are predicted R1/R2 (microscopic/gross residual disease.) These patients will receive long course chemoradiotherapy, of which a proportion will be downstaged and undergo curative surgery.

The total cost of MRI scans for both groups of patients is estimated to be £1.6m.

3.5.7 Costs of Surgery for Primary Rectal Tumour

3.5.7.1 Surgical procedures assumptions

- Of all surgical procedures for rectal cancer, 14% are emergency cases and 86% are elective cases. HES (2004);
- The percentage breakdown for the major surgical procedures have been grouped as follows:
 - 46% undergo a Anterior Resection procedure (AR);
 - o 21% undergo a Abdominoperineal Resection (APER);
 - o 6% undergo a Hartmann's procedure;
 - 27% undergo another procedure related to a diagnosis of rectal cancer as their primary procedure.

The proportion of patients having primary treatment for rectal cancer was taken from two sources:

- Hospital Episode Statistics HES (2004) which indicated a large proportion of patients having a variety of procedure which were mainly of ARs or APERs;
- The Northern and Yorkshire Cancer Registry Information Services NYCRIS (2004) showed that 54% of patients have an AR, 26% have an APER and 14% have a different procedure. The differences in percentages may be due to the NYCRIS data extractors assigning procedures as written in case notes to AR and APER rather than adhering to the OPCS-4 codes as given.

The model assumes an average of these two data sources.

The individual unit costs for operations were taken from NHS Reference Costs (2005) using a mapping of Healthcare Resource Groups (HRG) to provide an average cost for each individual procedure. The costs estimated for each procedure are as follows:

Table 3.11: The unit cost of rectal primary tumour procedures

Procedure	Unit cost (£)
AR	£5,729.00
APER	£5,969.00
Hartmanns	£5,249.00
Other procedure	£5,164.60

Source: These were based on Reference Costs (2005) and HRG's for the different OPCS code procedures.

The model used the unit costs in Table 3.11 to estimate the mean total costs and mean per patient costs based on the patient activity. The mean cost of an emergency procedure with stenting is estimated to be \pounds 7,477 per patient compared to an elective procedure of \pounds 5,598.21 per patient. The estimated total staging cost is \pounds 85,439 for rectal cancer patients undergoing primary treatment. (Table 3.12).

Surgery type	Total cost (£)	Per patient cost (£)
Emergency procedure with stenting	£124,126	£7,477.96
Emergency procedure without stenting	£4,553,283	£5,598.21
Elective procedure	£28,002,694	£5,598.21
Staging cost	£85,439	£14.65
Total cost for primary tumour surgery	£32,765,542	£5,618.21

Table 3.12: Breakdown of primary tumour surgery costs

3.5.7.2 Stoma activity and cost assumptions

There are two components of the cost of stoma care which are the primary fitting costs and reversal and the lifetime permanent stoma care costs for patients. In the primary rectal treatment cost, the cost of fitting and reversal are taken into account. The lifetime stoma care costs can be found in the life time stoma care costs section.

The data from HES (2004) suggests that 67% of patients who have undergone primary surgery for rectal cancer have a stoma which may be either temporary or permanent. The proportion of patients having a temporary stoma was 40% which was taken from Kairaluoma (2002). This study also reported data on stoma closure, based on which we assume that 67% of those stomas that are temporary are closed.

The cost of stoma closure is estimated to be £1.33m for those rectal cancer patients who had undergone primary treatment (Table 3.10). The cost of fitting the stoma was assumed to be within the reference costs for the main procedure.

3.5.8 Summary of Chemotherapy Costs for Rectal Cancer Patients

Table 3.13:Summary of chemotherapy costs

Chemotherapy treatment	Total cost (£)
Pre/Postoperative chemoradiotherapy	£8,444,270
Adjuvant chemotherapy	£27,720,700
Total cost of chemotherapy/radiotherapy	£36,164,970

The total cost of chemotherapy and radiotherapy for rectal cancer patients is estimated to be \pounds 36.2m. The components of this cost included pre/postoperative chemoradiation at a cost of \pounds 8.4m and adjuvant chemotherapy at a cost of \pounds 27.7m.

3.5.8.1 Adjuvant chemotherapy activity assumptions

The pathway assumes that a proportion of patients who undergo surgery, consisting of those patients who receive pre-operative chemoradiation followed by surgery, those who receive post-operative chemoradiation followed by surgery and those with surgery alone, receive adjuvant chemotherapy. Tekkis NBOCAP (2005) provided the data for this group of patients so that they could be represented by Dukes' stage:

Table 3.14: Dukes' staging of surgical patients

Dukes' Stage	Percentage of rectal surgery patients
Dukes' A	16%
Dukes' B	44%
Dukes' C	40%

Patients with Dukes' A are assumed not to receive any adjuvant chemotherapy. A proportion of those patients with Dukes' B and Dukes' C will receive adjuvant chemotherapy if they are deemed sufficiently fit. Owing to limitations of the current evidence base, assumptions concerning the proportion of these patients receiving adjuvant chemotherapy were elicited from expert opinion. The results of the elicitation process suggest that 28% of Dukes' B cancer and 75% of patients with Dukes' C cancer would receive adjuvant chemotherapy following complete resection of their primary tumour.

3.5.8.2 Adjuvant chemotherapy costs

The total cost of adjuvant chemotherapy for rectal cancer patients is estimated to be £27.7m. The cost of adjuvant chemotherapy is estimated to be £11,209 per patient. This was calculated as a mean cost under the assumptions that 50% of adjuvant patients would receive capecitabine and the remaining 50% would receive oxaliplatin plus 5-FU/LV (FOLFOX).

Table 3.15: Adjuvant chemotherapy cost breakdown

Chemotherapy Regime	Proportion	Cost of regime
Capecitabine	0.5*	£3,250
FOLFOX	0.5	£19,168
Mean regime cost	1	£11,209

*Note: 0.5 taken from the elicitation process.

3.5.9 Patients Treated with Curative Intent

The model estimates that 1,587 patients have incurable disease, based on the findings of the audit by Mella *et al.* (1997). These patients may receive palliative interventional care. These costs are not included in the total rectal cancer treatment cost as they are captured in the palliative treatment costs. There was little evidence from the literature on the proportions of patients being managed according to different regimens at this point in the pathway.

Based upon the results of the elicitation exercise, the model estimates that 1,323 (83%) of the 1,587 patients will undergo palliative chemotherapy for metastatic disease. The remaining 13% are assumed to undergo palliative stenting, palliative stoma, palliative bypass or radiotherapy. Further detail on these patients is given in the palliative care costs section.

3.6 PRIMARY TREATMENT OF COLON CANCER

	Mean total cost (£)	Mean cost per patient (£)	95% Cl Lower bound (£)	95% Cl Upper bound (£)
Total colon cancer primary treatment	£128,759,653	£8,808	£8,309	£9,314
Primary colon surgery	£67,477,601	£4,616	£4,503	£4,722
Chemotherapy	£61,282,052	£11,209	£10,105	£12,311

Table 3.16: Summary of primary treatment of colon cancer costs

In Table 3.16 the total colon cancer primary treatment cost includes costs after diagnosis and prior to follow-up which include the colon surgery costs and chemotherapy costs. The total colon cancer primary treatment cost is estimated to be approximately £128.8m. Those patients who undergo primary colon cancer treatment are estimated, on average, to cost £8,808 per patient.

The primary colon surgery costs include pathology costs, stoma costs, stoma closure costs, complication costs and stenting costs. The primary colon cancer surgery total cost is estimated to be £67.5m. The mean cost for patients undergoing primary potentially curative surgery is £4,616 per patient.

The total cost of adjuvant chemotherapy is estimated to be \pounds 61.3m. The average cost for patients undergoing adjuvant chemotherapy for colon cancer treatment is estimated to be \pounds 11,209 per patient.

3.6.1 Primary Colon Surgery

Table 3.17: Breakdown of primary colon surgery costs

Procedure	Cost (£)
Surgery for primary tumour cost (includes stenting.)	£66,756,469
Stoma reversal cost	£721,132
Total Cost primary colon surgery	£67,477,601

The following section describes the activity and cost assumptions with regards to primary colon cancer surgery. This includes the pathology costs, stenting costs, stoma reversal costs and complication costs.

Based on 2003/4 cancer registrations (excluding increased-risk patients who undergo treatment for colon cancer) the model estimates that 18,504 patients undergo treatment for colon cancer. Based on an audit of the Trent region and Wales, it has been assumed that 79% of patients are initially curable and 21% of patients are incurable Mella *et al.* (1997).

3.6.2 Patients Treated with Curative Intent

The model uses data from the Mella *et al* (1997) audit that estimated that 14,618 patients are initially treated with curative intent. The initially curable patients either present as emergency cases or elective cases.

3.6.3 Emergency Cases

The model assumes 4,835 emergency cases present which can either then undergo stenting as a bridge to surgery or go straight to surgery. Evidence from the literature was limited on the proportions undergoing stenting and as a result of this we used expert elicitation to derive the proportion. Expert elicitation was therefore used to derive this proportion. The elicitation process estimated that 2% of patients who were emergency admissions undergo stenting as a bridge to surgery. This figure was applied to both colon and rectal cancer patients.

The average cost of stenting was \pounds 1,879.79 which was taken from Osman *et al.* (2000). The total cost of stenting as a bridge to surgery is estimated to be \pounds 164,872.

3.6.4 Elective Cases

Those patients who are elective are assumed to proceed to surgery with a proportion undergoing laparoscopic surgery and a proportion having open surgery for colon cancer. The current proportion undergoing laparoscopic surgery was assumed to be 2.4% (NICE 2006).

3.6.5 Costs of Surgery for Primary Colon Tumour

3.6.5.1 Surgical procedures assumptions

- The model assumes that 30% are emergency primary procedures and 70% are elective surgical primary procedures Davies (2004);
- The percentage breakdown for the major surgical procedures have been grouped as follows:
 - 13% have left hemicolectomy;
 - 41% undergo a right hemicolectomy;
 - 5% undergo a Hartmann's procedure;
 - 41% have another procedure.

An average of the proportion of patients having primary treatment for colon cancer was taken from two sources: HES (2004) and NYCRIS (2004).

The individual unit costs for operations were taken from the NHS Reference Costs (2005) using a mapping of HRG's to provide a mean cost estimate for each individual procedure. The costs were calculated for each of the procedures for open surgery and then for laparoscopic surgery. See Tables 3.18 and 3.19 below.

Table 3.18: Open surgical procedure unit cost breakdown

Procedure	Unit Cost (£)
Left hemicolectomy	£5,249.00
Right hemicolectomy	£5,249.00
Hartmanns	£5,249.00
Other procedure	£3,516.00

Source: These were based on Reference Costs (2005) and HRG's for the different OPCS code procedures.

Table 3.19: Laparoscopic surgical procedure unit cost breakdown

Procedure	Unit Cost (£)
Left hemicolectomy	£5,477.00
Right hemicolectomy	£5,477.00
Hartmanns	£5,477.00
Other procedure	£3,516.00

Source: These were based on Reference Costs (2005) and HRG's for the different OPCS code procedures.

The model uses these unit costs and the assumed proportions of patients within each branch of the pathway to estimate the total costs and mean per patient costs which are displayed in Table 3.20. The mean cost of an emergency procedure with stenting is estimated to be £6,418.22 per patient in comparison to an elective procedure of £4,541.70 per patient. The estimated total staging cost is £214,157 for rectal cancer patients undergoing primary treatment.

Table 3.20: Breakdown of primary tumour surgery costs

Surgery type	Total cost (£)	Per patient cost (£)
Emergency procedure with stenting	£562,938	£6,418.22
Emergency procedure without stenting	£19,505,255	£4,538.47
Elective procedure	£46,474,119	£4,541.70
Staging cost	£214,157	£14.65
Total cost for primary tumour surgery	£66,756,469	

3.6.5.2 Stoma activity and cost assumptions

There are two components of the cost of stoma care, the primary fitting costs and reversal and the lifetime permanent stoma care costs for patients. In the primary colon treatment cost the cost of fitting and reversal are taken into account. The lifetime stoma care costs can be found in the stoma care costs section.

HES data (2004) suggests that 67% of patients who have undergone primary surgery for rectal cancer have a stoma which may be temporary or permanent. The proportion of patients having a temporary stoma was 40% and was taken from Kairaluoma (2002). This study also reported data on stoma closure, based on which it was assumed that 67% of those stomas that are temporary are closed.

The cost of stoma closure is estimated to be £721,132 for those colon cancer patients who had undergone primary treatment (Table 3.17). The cost of fitting the stoma is assumed to be included within the NHS Reference Costs for the main procedure.

3.6.6 Summary of Chemotherapy Costs for Colon Cancer Patients

Table 3.21: Summary of adjuvant chemotherapy costs for colon patients

Chemotherapy treatment	Total cost (£)
Total adjuvant chemotherapy cost	£61,282,052

The total cost of adjuvant chemotherapy for colon cancer patients is estimated to be £61.3m.

3.6.7 Adjuvant Chemotherapy Activity Assumptions

The pathway assumes that a proportion of those that have surgery will receive adjuvant chemotherapy. In this group of patients it is assumed that the patients are of the following Dukes' staging which was taken from an audit by NYCRIS (2004).

Table 3.22: Dukes' staging for colon surgery patients

Dukes' stage	Percentage of colon surgery patients
Dukes' A	12%
Dukes' B	32%
Dukes' C	28%
Dukes' D	28%

Patients with Dukes' A cancer are assumed not to receive adjuvant chemotherapy. A proportion of patients with Dukes' B and Dukes' C colon cancer are assumed to receive adjuvant chemotherapy if they are deemed sufficiently fit. The assumptions made on the proportion of these patients were taken from the elicitation process. The elicitation data showed that for Dukes' B 39% and for Dukes' C 89% of patients following surgery would receive adjuvant chemotherapy.

3.6.8 Adjuvant Chemotherapy Costs

The total cost of adjuvant chemotherapy for colon cancer patients is estimated to be \pounds 61.3m. The cost of adjuvant chemotherapy is estimated to be \pounds 11,209 per patient. This was calculated as a mean cost under the assumptions that 50% of adjuvant patients would receive capecitabine and 50 % would receive FOLFOX.
Table 3.23: The breakdown of adjuvant chemotherapy cost

Chemotherapy regime	Proportion	Cost of regime
Capecitabine	0.5*	£3,250
FOLFOX	0.5	£19,168
Mean regime cost	1	£11,209

*Note: 0.5 taken from the elicitation process.

3.6.9 Incurable Patients

The model assumes that 3,886 patients with colon cancer will have incurable disease. These patients will receive palliative interventional care. These costs are not included in the total colon treatment cost and are captured in the palliative treatment costs. There was little evidence from the literature and data sources on the proportion of patients managed on the different regimens at this point in the pathway. The majority of patients, 3,238 (83%) of the 3,886 are assumed to undergo palliative chemotherapy. The remaining 13% are assumed to undergo palliative stoma, palliative bypass or radiotherapy.

3.7 STOMA CARE COSTS

Table 3.24: Total stoma care costs

Stoma cost	Mean total cost (£)	Mean cost per patient (£)	95% Cl Lower bound (£)	95% Cl Upper bound (£)
Rectal stoma care costs	£27,747,664	£1,279	£1,043	£1,513
Colon stoma care Costs	£24,328,903	£1,279	£1,038	£1,522
Total Stoma Care costs	£52,076,567	£1,279	£1,113	£1,447

In Table 3.24, the stoma care cost has been estimated to be an annual cost of all prevalent permanent stoma costs related to bowel cancer. The total cost of stoma care is estimated to be \pounds 52.1m. This consisted of a stoma care cost of \pounds 27.7m for those patients who had previously undergone rectal cancer surgery and \pounds 24.3m for those patients who had previously undergone colon cancer surgery. The mean cost per year is estimated to be \pounds 1,279 per patient.

3.7.1 The Activity Assumptions

The number of patients undergoing stoma care was calculated for all cohorts. This means that those patients previously diagnosed with bowel cancer are included in the total number of patients with stomas. The following assumptions underpinned the calculation of these estimates:

• The number of permanent stomas remaining after primary treatment was used as a method of calculating all the stoma cost of the current cohort and all previous cohorts;

• The survival of patients with stomas that were fitted at primary treatment had the same survival as those that did not have any stoma appliance fitted. There was insufficient reliable evidence to determine the difference in survival between these two groups.

3.7.2 The Cost Assumptions

In the absence of an agreed figure from the literature, the cost was estimated by the Derby Stoma care unit. The mean cost calculated is £1,279. The costs involved in different appliances for stoma care are summarised in Table 3.25.

Table 3.25:	Types of stoma	appliance
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Stoma type	Туре	Cost (£)
Colostomist	One Piece Appliance	
Cost per month	2.5 bags a day	£155 per month
Cost per annum		£1,860 per annum
Colostomist	Two Piece appliance	
	Flange 2 per week	£26.00
	Pouch 2/3 per day	£96.00
Cost per month		£119 per month
Cost per annum		£1,428 per annum
Illeostomist	One piece	£80 per month
Cost per annum	One piece	£960 per annum
Illeostomist	Two piece	£103 per month
Cost per annum	Two piece	£1,236 per annum

These costs were then weighted according to the assumption that 67% of patients will have an ileostomy and the remainder a colostomy. This is then weighted by whether the patient has a one-piece appliance or a two-piece appliance in equal proportion.

Table 3.26: Breakdown calculation of national average stoma cost

Stoma type	Proportion of colostomy versus ileostomy	Average appliance cost (£)	Weighted appliance cost (£)
Colostomy	33%	£1,644	£547
lleostomy	67%	£1,098	£732
		Average stoma cost	£1,279

This means stoma cost of £1,279 per year was assumed for all those patients who have permanent stomas.

3.8 FOLLOW–UP ACTIVITY

This section analyses the results for follow-up by colon cancer and rectal cancer.

3.8.1 Rectal Cancer Follow-up Overview

	Mean total cost (£)	Mean cost per patient (£)	95% Cl Lower bound (£)	95% Cl Upper bound (£)
Rectal follow-up total costs	£67,959,925	£9,669	£7,656	£11,025
Rectal surveillance costs	£6,840,229	£973	£901	£1,047
Rectal recurrence costs	£61,119,695	£9,279	£7,136	£10,722

Table 3.27: Rectal cancer follow-up costs

Table 3.27 shows the total estimated cost of rectal cancer follow-up of £68m, which comprises surveillance costs of £6.8m and recurrence treatment costs of £61.1m.

The 95% confidence intervals for this cost estimate are wider than for most other cost estimates. This is due to the high level of uncertainty surrounding follow-up schedules.

3.8.2 Rectal Cancer Surveillance Costs

The total surveillance costs are £6.8m which is approximately 10% of the total rectal followup costs. It was assumed that patients undergo surveillance for 5-years following their primary treatment. Surveillance schedules vary considerably between centres. The average regime was calculated from a sample of approximately 30 regimes that were collected through an *ad hoc* survey of participating centres within the Royal College of Radiologists. This survey confirmed the presence of considerable variation in follow-up schedules between centres. From this data, assumptions concerning a representative follow-up schedule were produced. Although it should be noted that this may not reflect current practice in many centres across England. Table 3.28 identifies the tests undertaken during each year of follow-up and the total cost of surveillance for that year.

Table 3.28:	Surveillance regimes and costs for each year	ar

Year	CEA test	CT scan	Colonoscopy	Clinical consultation	Cost
Year 1	4	1	0	1	£268.1
Year 2	2	1	0	1	£247
Year 3	2	1	0	1	£247
Year 4	0	0	0	1	£65.9
Year 5	0	0	1	1	£417.9

The overall surveillance costs were calculated using a cohort analysis which enabled us to present a snapshot of the total cost of rectal cancer of follow-up for a given year. Each

cohort of patients represents a group of patients who were diagnosed and underwent primary treatment in a particular year. Cohort 1 represents the patients who were diagnosed in this current year, cohort 2 represents those who were diagnosed in the previous year and so on. It was assumed that those patients who had metastatic recurrence but were successfully treated re-started surveillance. This meant that for a single cohort of patients there would be patients who were in different years of surveillance. The number of patients from each cohort and year of surveillance has been shown in Table 3.29, as are the total costs for each year of surveillance.

	Surveillance regime year				
	Year 1	Year 2	Year 3	Year 4	Year 5
Cohort 1	7,029				
Cohort 2	1,799	4,570			
Cohort 3	1,4427	1,720	2,533		
Cohort 4	658	1,365	1,650	1,316	
Cohort 5	307	629	1,309	1,579	571
Cost	£3,008,135	£2,046,308	£1,356,465	£190,795	£238,526

Table 3.29: Surveillance regimes by cohort

3.8.3 Rectal Cancer Recurrence Treatment Costs

The follow-up recurrence treatment costs are estimated to be £61.1m which constitutes 90% of the overall rectal cancer follow-up cost (Table 3.27). The overall recurrence treatment costs are comprised of two components, the costs associated with metastatic recurrence which are £59.3m and local recurrence which are £1.8m.

3.8.4 Metastatic Recurrence Costs

Metastatic recurrence is assumed to take place in the first 5 years after primary treatment. This assumption is based on findings from the CR07 trial which showed that the majority of patients who underwent metastatic recurrence happen within 5 years. A modelling simplification was agreed with the clinicians that those patients who would recur after 5 years are assumed to relapse in year 5.

Patients who develop metastatic disease may undergo downstaging chemotherapy with or without subsequent liver resection, some may undergo liver resection without prior chemotherapy (if initially respectable), some may receive palliative chemotherapy and some may receive best supportive care alone.

Table 3.30: Metastatic recurrence treatment costs

Treatment	Costs	
Chemotherapy	£56,898,483	
Liver resection	£2,376,234	
No interventional care	£0	
Total Metastatic recurrence treatment cost	£59,274,717	

3.8.4.1 Liver resections

An assumption was made regarding activity for metastatic relapse. Liver resections were assumed to take place in 8% of cases with metastatic recurrence in the first year. This was then assumed to decline linearly for each year after diagnosis. This was based on three sources; HES (2004) data on liver resections, an audit of a single centre liver resection (Basingstoke) for a single year and expert elicitation. These are described below:

- The HES (2004) data suggested that 531 liver resections were performed in the period 2003/2004 specifically for bowel cancer. However, this should be taken with caution as it may be an underestimate of the current figures due to problems with coding;
- The Basingstoke data suggested that for the same period in 2003/2004, they undertook 110 liver resections for bowel cancer. The mean age of patients was 63 years old with 58% undergoing resections for colon cancer and 42% for rectal cancer. The mean duration of the procedure was 249 minutes and the mean hospital stay was 8 days;
- The elicitation process generated a point estimate of 8% of patients with metastatic recurrence. The uncertainty around this estimate was taken into account in the assumptions that surrounded the distribution upon this parameter.

Based on these figures, the model estimated a total of 329 liver resections for rectal surgery patients. The costs associated with liver resections were taken from NHS Reference Costs (2005).

3.8.4.2 Chemotherapy and no interventional care

The remaining patients were assumed to be split 50:50 between chemotherapy and no interventional care. The cost of chemotherapy was obtained through the elicitation process and was assumed to be the same as palliative chemotherapy.

The cost for no interventional care was assumed to be nothing as these patients receive no care at this stage but are costed as they progress to end of life care.

3.8.5 Local Recurrence Costs

Local recurrence rates for patients receiving pre-operative and post-operative radiotherapy were taken from the CR07 trial (2006). Local recurrence was assumed to be treated with a re-resection in 50% of cases and no interventional care was given in the other 50% of cases. The total cost of re-resections following local recurrence is £1.8m.

3.8.6 Uncertainty Surrounding Follow-Up

For metastatic and local recurrence treatment many of the activity parameters are assumed or based on clinical opinion. As such, these estimates are associated with a greater level of uncertainty.

3.8.7 Overview Colon Cancer Follow-Up

	Mean total cost (£)	Mean cost per patient (£)	95% Cl Lower bound (£)	95% Cl Upper bound (£)
Colon follow-up total costs	£203,096,285	£11,802	£9,886	£13,449
Colon surveillance costs	£17,562,685	£1,021	£946	£1,094
Colon recurrence costs	£185,533,600	£9,554	£7,868	£11,027

Table 3.31: Colon cancer follow-up costs

Table 3.31 shows the total cost of colon cancer follow-up of £203.1m, which comprises surveillance costs of £17.6m and recurrence treatment costs of £185.5m

The 95% confidence intervals for follow-up are wider than for many other sections of the treatment pathway and this is because of the greater level of uncertainty surrounding follow-up regimes.

3.8.8 Colon Cancer Surveillance Costs

The total surveillance costs are estimated to be £17.6m which is approximately 8.5% of the total colon cancer follow-up costs. It was assumed that patients undergo surveillance for 5-years following primary treatment. As noted earlier, follow-up schedules vary significantly across centres. As with rectal cancer, assumptions concerning follow-up were based on survey data from the Royal College of Radiologists. Table 3.32 identifies the tests undertaken during each year of follow-up and the total cost of surveillance for that year.

Table 3.32:	Surveillance schedules and costs for each year	

Year	CEA test	CT scan	Colonoscopy	Clinical consultation	Cost
Year 1	4	1	0	1	£268.1
Year 2	2	1	0	1	£247
Year 3	2	1	0	1	£247
Year 4	0	0	0	1	£65.9
Year 5	0	0	1	1	£417.9

The overall surveillance costs were calculated using a cohort analysis which enabled us to present a snapshot of the total cost colon cancer of follow-up for a given year. Each cohort of patients represents a group of patients who were diagnosed and underwent primary treatment in a particular year. Cohort 1 represents the patients who were diagnosed in this current year, cohort 2 represents those who were diagnosed in the previous year and so on. It was assumed that those patients who had metastatic recurrence but were successfully treated re-started surveillance. This meant that for a single cohort of patients there would be patients in different years of surveillance. The number of patients from each cohort that are

in each year of surveillance is given in Table 3.33, as the total costs for each year of surveillance.

	Surveillance schedule year				
	Year 1	Year 2	Year 3	Year 4	Year 5
Cohort 1	17,209				
Cohort 2	4,846	11,142			
Cohort 3	3,048	4,622	7,008		
Cohort 4	1,689	2,907	4,405	4,356	
Cohort 5	1,225	1,611	2,771	4,201	2,337
Cost	£9,357,431	£6,346,123	£4,438,048	£1,127,848	£1,128,391

Table 3.33: Surveillance schedules by cohort

3.8.9 Colon Cancer Recurrence Treatment Costs

Table 3.34 shows that the follow-up recurrence treatment costs are £185.5m which represents 91.4% of the overall colon cancer follow-up cost.

3.8.10 Metastatic Recurrence Costs

Metastatic recurrence is assumed to take place in the first 5 years after primary treatment. This assumption is based on findings from Phillips (2002) which showed that the majority of patients who underwent metastatic recurrence happen within 5 years. A modelling simplification was agreed with the clinicians that those patients who would recur after 5 years were assumed to relapse in year 5.

In those patients who have metastatic recurrence some will undergo chemotherapy, some will receive a liver resection and some will not receive any interventional care.

Table 3.34: Metastatic recurrence treatment costs

Treatment	Costs
Chemotherapy	£175,848,853
Liver Resection	£9,684,747
No Interventional Care	£0
Total metastatic recurrence treatment costs	£185,533,600

3.8.10.1 Liver resections

An assumption was made regarding activity for metastatic relapse. Liver resections were assumed to take place in 8% of cases with metastatic recurrence in the first year. This was then was assumed to decline linearly for each year after diagnosis. This was guided by three sources; HES (2004) data on liver resections, an audit of a single centre liver resection (Basingstoke) for a single year and expert elicitation. The three sources were previously explained in section 3.8.4.1.

Based on these figures, the model estimated a figure of 1,453 liver resections for colon cancer patients. The costs associated with liver resections were taken from NHS Reference Costs (2005).

3.8.11 Local Recurrence Costs

There was assumed to be no local recurrence for colon cancer patients on the basis of the evidence provided in Phillips (2002) which suggested a very low level of local recurrence amongst colon cancer patients. There was also agreement from clinicians that this assumption was appropriate given the evidence currently available.

3.8.12 Uncertainty Surrounding Follow-up

The parameters for those patients who undergo treatment for metastatic recurrence were derived from clinical opinion. This has resulted in a marked degree of uncertainty surrounding the associated costs for this group of patients.

3.9 PALLIATIVE CARE ACTIVITY AND COSTS

The palliative care activity and costs are reported for colon and rectal cancer patients. They comprise the palliative intervention costs and the end of life costs for the treatment of bowel cancer. A description of what each of these costs entails for both colon cancer and rectal cancer is described in this section. The estimated total palliative care cost for bowel cancer in England was £118.6m (Table 3.6).

3.9.1 Rectal Cancer Palliative Care Overview

	Mean total cost (£)	Mean cost per patient (£)	95% Cl Lower bound (£)	95% Cl Upper bound (£)
Total rectal cancer palliative care costs	£38,153,323	£7,016	£5,647	£8,417
Rectal cancer palliative intervention costs	£30,410,599	£17,173	£14,628	£20,393
Rectal cancer end of life care costs	£7,742,723	£2,086	£1,936	£2,237

Table 3.35 shows the total palliative care cost for rectal cancer is estimated to be £38.2m which equates to a cost per patient of £7,016. This cost consists of two components, palliative intervention costs of £30.4m and end of life care costs of £7.7m.

Palliative intervention	Cost (£)
Palliative chemotherapy	£29,701,981
Palliative stenting	£119,340
Palliative bypass	£351,851
Palliative stoma	£85,734
Palliative radiotherapy	£151,693
Total rectal palliative interventions	£30,410,599

Interventional palliative care costs are estimated to be £30.4m, which is almost 80% of the total palliative care cost for rectal cancer (Table 3.36). Interventional palliative care involves procedures that are intended to prolong and improve quality of life in patients with incurable disease.

The most common and most costly palliative intervention is palliative chemotherapy. This costs £29.7m which is 97.7% of the total palliative intervention costs. In the model 1,461 patients are estimated to receive palliative chemotherapy. 83.3% of patients received palliative chemotherapy and that 26.7% of these patients chemotherapy in the form of 5FU followed by 5FU and irinotecan at a cost of £12,542.50 and 73.3% receive a regime of FOLFIRI/FOLFOX at a cost of £22,864.46 from this a weighted mean cost of £20,324.30 was estimated.

The level of palliative stenting was also calculated through the elicitation process and the total cost of palliative stenting was estimated to be £119,340. The elicitation process estimated the proportion split for 88% of the palliative intervention procedures. This corresponded to 97% of the cost. However, for the remaining palliative care procedures an assumption was required. This was that each procedure was equally likely to be used and hence the percentage of patients either, undergoing a palliative bypass, a palliative stoma fitting or a palliative radiotherapy was assumed to be 3.8%. Costs are estimated to be £351,851 for palliative bypass, £85,734 for palliative stoma and £151,693 for palliative radiotherapy. In total, these patients cost £589,278 which is less than 3% of the total rectal cancer palliative intervention costs.

3.9.1.1 Rectal cancer end of life care costs

The other component of the total palliative care costs are the end of life care costs. The end of life care costs for rectal cancer is \pounds 7.7m which accounts for just over 20% of the total palliative care costs. These costs are for non-interventional procedures that focus mainly on pain and symptom management but also include hospital or hospice days where relevant. It was not possible to find the percentage of rectal cancer sufferers whom die at home, in hospital or in a hospice. It was therefore assumed that there was one single cost of end of life care for the three different places. This was taken from Guest *et al.* (2006) and was \pounds 2,086 which represents an average cost of end of life care.

3.9.2 Colon Cancer Palliative Care Overview

	Mean total cost (£)	Mean cost per patient (£)	95% Cl Lower bound (£)	95% Cl Upper bound (£)
Total colon cancer palliative care costs	£80,399,658	£7,703	£6,244	£9,263
Colon cancer palliative intervention costs	£66,733,715	£17,173	£14,290	£20,081
Colon cancer end of life care costs	£13,665,943	£2,086	£1,943	£2,231

Table 3.37: Colon cancer palliative care cost table

Table 3.37 shows the total palliative care cost for colon cancer is estimated to be of \pounds 7,703 per patient. This cost is made up of two components; palliative intervention costs of \pounds 66.7m and end of life care costs of \pounds 13.7m.

3.9.2.1 Colon cancer palliative intervention costs

Table 3.38: Colon cancer palliative intervention costs

Palliative intervention	Cost (£)
Palliative chemotherapy	£65,811,836
Palliative stenting	£292,178
Palliative stoma	£629,701
Total colon palliative interventions	£66,733,715

Interventional palliative care costs are estimated to be £66.7m, which represents 83% of the total palliative care cost for colon cancer (Table 3.38). Interventional palliative care involves procedures that are intended to prolong and improve quality of life of patients who are unable to be cured.

The most common and most costly palliative intervention is palliative chemotherapy. This is estimated to cost £65.8m, which represents 98.6% of the total palliative intervention costs. In the model 3,138 patients are predicted to receive palliative chemotherapy. The model assumes that 83.3% of patients receive palliative chemotherapy. 26.7% of these patients received chemotherapy in the form of 5FU followed by 5FU and irinotecan at a cost of £12,542.50 and 73.3% receive a regime of FOLFIRI/FOLFOX at a cost of £22,864.46. From this a weighted mean cost of £20,324.30 was estimated.

The number of patients who received palliative stenting was estimated through the elicitation process and the total cost of palliative stenting is $\pounds 292,178$. Patients requiring a palliative stoma are estimated to cost $\pounds 629,701$, which is just less than 3% of the total colon cancer palliative intervention costs.

3.9.2.2 Colon cancer end of life care costs

The other component of the total palliative care costs are the end of life care costs. The end of life care cost for colon cancer is estimated to be £13.7m which accounts for 17% of the total palliative care costs. These costs are for non-interventional procedures that focus mainly on pain and symptom management but also include hospital or hospice days where relevant. It was not possible to find what percentage of colon cancer sufferers die at home, in hospital or in a hospice, as such a single for cost end of life care is used. This was taken from Guest *et al.* (2006) and is £2,086 which represents a mean cost of end of life care.

3.10 BOWEL CANCER SCREENING

The model assumes that FOBT test is offered to individuals aged between 60 and 69 biennially. An estimate of the total additional annual costs has been presented for the 5 years following the roll-out of screening, together with a projection of any potential cost saving. The analysis necessarily assumes that screening will take immediate effect in the relevant population across England.

Table 3.39 presents the total cost of screening bowel cancer in England over the 5 years from which the screening programme commenced.

	Year 1	Year 2	Year 3	Year 4	Year 5
FOBT Kits	£36,482,405	£36,482,405	£36,482,405	£36,482,405	£36,482,405
Diagnostics	£13,789,600	£13,732,224	£13,334,464	£13,334,464	£13,066,240
Pathology	£1,399,612	£1,348,593	£867,883	£867,883	£584,446
CT scans	£689,600	£680,160	£553,920	£553,920	£503,680
Appointments	£1,445,174	£1,423,280	£1,136,663	£1,136,663	£1,022,868
Ultrasound	£459,608	£452,645	£361,526	£361,526	£325,290
A&E attendances	-£6,685	-£9,299	-£27,847	-£27,847	-£42,625
Ward stay	-£109,917	-£152,892	-£457,851	-£457,851	-£700,826
CRT	£22,089,035	£23,815,722	£4,928,999	£5,871,665	-£6,573,449
Surgery for relapse	£33,926,254	£33,152,380	£22,413,684	£22,490,116	£17,120,768
Follow-up	£2,664,200	£5,220,765	£4,372,166	£3,620,470	£4,577,624
Total Cost	£112,828,886	£116,145,982	£83,966,012	£84,233,414	£66,366,422

Table 3.39: The total cost of screening bowel cancer in England over 5 years

The results show an additional cost of screening in year 1 of £112.8m. The additional cost of screening falls in year 3 to £84m and again in year 5 to £66.4m. These reductions in the cost of screening between years 3 and 5 can be explained by two main changes to patient activity. The first explanation is because screening identifies patients earlier and consequently reduces the number that present at A&E. This appears as a negative cost in Table 3.39 because these represent cost savings in terms of the baseline cost. The second explanation is due to the reduction in chemotherapy and relapse surgery costs.

reductions in costs are caused by a shift in stage through earlier diagnosis of screened patients. This results in fewer patients requiring complex and costly treatments.

3.11 INCREASED-RISK PATIENTS

3.11.1 Overview

In some areas of the pathway data from published literature was scarce. In the majority of these cases assumptions were required to complete the analysis. In addition to this, there are very high levels of uncertainty regarding these pathways and parameters, the high-risk groups were excluded from the Monte Carlo sensitivity analysis as the interpretation of the confidence intervals would be problematic.

3.11.1.1 Familial adenomatous polyposis (FAP)

The incidence rate of FAP incidence is 1/13,528 Dunlop (2002), giving 3,703 cases in 2003/04. It was calculated that 833 are positive cases, as it had been assumed that 2% of new cases of cancer are due to FAP (IOCC 2004). All positive cases receive an annual follow-up with an MDT review at which they undergo a flexible sigmoidoscopy. The model assumes that 20% will receive no further interventional care of whom 70% will die and 30% will be managed in the following year. The model also assumes that 50% of all negative cases and 40% of the positive cases receiving interventional care will undergo a proctocolectomy. It is further assumed in the model that the remaining 50% of all negative cases and 40% of the positive cases receiving interventional care will undergo a colectomy. These patients will also undergo surveillance of the rectum, of whom it was assumed that 40% will have no polyps and 60% will have polyps. All of those with polyps and those who have undergone a proctocolectomy will then undergo further duodenal surveillance. The model assumes that 70% are assumed to be negative and 30% positive. 50% of the positive cases will undergo a Whipple's procedure, and 50% will receive no further interventional care, of which 50% will die in the year and 50% will be managed in the following year.

The total cost for the management of patients with FAP is estimated to be £32.7m at a cost of £12,071 per patient.

3.11.1.2 Hereditary non polyposis colorectal cancer (HNPCC)

The rate of HNPCC incidence is 1/3139 Dunlop (2002), giving 15,960 cases in 2003/04. All cases receive a biennial colonoscopy, of which 559 cases are assumed to be positive. This is derived from the assumption that 3% of new cases of cancer are due to HNPCC (IOCC 2004), and the rest are negative. Of those diagnosed as positive, all undergo 'normal clinic' tests, followed by an MDT review. It has been assumed that 20% receive non-interventional care, of which 80% will die in the year. Of those diagnosed negative, we assume that 20% receive a surgical intervention. Of those who are negative and received a surgical intervention, and those who are positive and receiving further care, 50% will receive a proctocolectomy and 50% a colectomy. Of those with a colectomy, all receive a follow-up

sigmoidoscopy and subsequent surveillance of the rectum, following which we assume that 40% have polyps, and an excision of the rectum.

The total cost of managing patients with HNPCC is estimated to be £17.2m at £1,075 per patient.

3.11.1.3 Ulcerative colitis and crohns

Cancer has been reported to be present in 10 - 25% of cases of long-term ulcerative colitis (UC) (i.e. over 20 years of duration), Phillips (2002). The model estimates there to be 7,515 cases at risk, of which 225 will be positive cancers. Diagnosis is via colonoscopy assumed to be performed on all high-risk cases. Those with a positive diagnosis undergo normal clinic tests and assessment by the MDT Team. It has been assumed that 80% undergo surgery and 20% receive non-interventional care, of which 50% will die in the year of diagnosis.

The total cost of managing increased-risk patients with UC is estimated to be £3.9m at an average of £520 per patient.

Please note Figures 3.1 - 3.10 need to be printed on A3 paper.

Figure 3.1: Referral Diagnostics pathway



Perforation-25 280 307 E1409,505 E16,83.04 No Perforation-26 465,087 470,622 E0 E0 Die-27 137 2 E285,995 E5,427	Positive Cancer - 28 16,288 18,690 Negative Cancer - 29 449,079 452,237	Negative Cancer -Polyps 30 112,270 94,752	MDT - 32 26,062 E7,911,150 37,882 E11,526,503 31

Figure 3.2: Rectal surgery pathway





Year 1 £25,165,626 £34,646,932









		Die Other Causes-343				
		95	116			
		Die-	344			
		1,127	1,374			
		£2,350,378	£2,795,969			
		Alive-345				
		15 097	10/05			
		10,001	10,100			







eillance o	of Rectum N	lo Polyps-428
	579	

veillance of RectumPolyps-429			E	Excision rectum-430	
	386			386	
				£2,027,332	



Section 4 Summary: Options Model

This section describes the fourteen options (including Option 9 as two Options, 9a and 9b) which will be used to evaluate ways in which the treatment for bowel cancer can be improved. The second part of this section details the option model methodology.

The options that were assessed are as follows:

- 1. Improving GP referral criteria for suspected colorectal pathology;
- 2. Raised bowel cancer awareness in the general population of England;
- **3.** Management of emergency presentation and delivery of care;
- **4.** Increasing the use of colonoscopy (instead of using flexible sigmoidoscopy) from 70 per cent to 90 per cent;
- **5.** Improving colonoscopy completion rates via national training;
- 6. The use of laparoscopic versus open surgery for colon cancer patients;
- **7.** Assessment of the impact of surgical expertise for outcomes and/or developing specialist pathology services;
- 8. Pre-operative versus post-operative radiotherapy for rectal cancer patients;
- **9.** The use of alternative chemotherapy sequencing:
 - **a.** The use of alternative adjuvant chemotherapies;
 - **b.** The use of alternative sequences of palliative chemotherapy.
- **10.** The use of an Enhanced Recovery Programme (ERP) following surgery;
- **11.** 'Intensive' versus 'relaxed' follow-up;
- **12.** Increasing liver/lung resections for metastatic disease;
- **13.** Increasing palliative surgery (e.g. palliative bypass) and stenting.

The options included for assessment were agreed within the advisory group meetings for this project based upon a detailed examination of the minutes of previous meetings of the English Bowel Cancer Advisory Group. These options were assessed using the bowel cancer options model which was produced in SIMUL8. The second half of this section presents the options assumptions and the methods used for estimating health utilities associated with events and states of health associated with bowel cancer.

4.1 INTRODUCTION

The second objective of the project was to evaluate ways in which the existing bowel cancer service cancer could be improved. This section presents the options under consideration and the way in which they have been modelled. There are numerous areas whereby further research is required in order to verify or improve upon this analysis; its aim is to present an idea of the types of options for change which may improve the bowel cancer service in England in order to guide further research.

4.2 OPTIONS FOR ASSESSMENT

We have identified a number of potential options for evaluation based on discussions and subsequent correspondence with the Project Advisory Group (9th February 2006) and the English Bowel Cancer Advisory Group (23rd November 2005, plus previous meetings' minutes). The options are broadly categorised into three sections:

- 1. Access to services;
- **2.** Treatments;
- **3.** Palliative care.

The following section outlines the rationale for evaluating each option and describes how these options are modelled.

4.2.1 Options Concerning Access to Services

1. Improving GP referral criteria for suspected colorectal pathology

The Department of Health has published guidelines for the referral of suspected bowel cancer for the use of GPs. Increasing the sensitivity of the GP referral criteria is expected to reduce the proportion of advanced cancers at diagnosis and reduce the workload at A&E. Increasing the specificity of the referral criteria may reduce unnecessary referrals and diagnostic work-up. In addition, as there are long waiting times for standard referrals, many patients are unnecessarily referred urgently, thus resulting in resource wastage (Personal communication, Dr Rob Glynne-Jones, Mount Vernon Hospital, Middlesex).

In order to simulate the impact of improvements to the existing GP referral criteria, the sensitivity of GP referral was improved in order to estimate the likely impact of this on health outcomes, costs and resource implications. The results of this option are dependent upon the underlying rate of disease progression which has been calibrated using the ScHARR screening model. The level of evidence which may be used to inform effectiveness and cost parameters associated with this set of options is weak.

2. Raised bowel cancer awareness in the general population of England

By raising public awareness (e.g. via media campaigns) it is possible that more people would present to their GP at an earlier stage. However, this will also increase GP workloads and is likely to increase the number of false positives referred for investigation and hence producing further pressures on diagnostic services.

The number and case mix of presenting patients was varied in the model within potentially plausible ranges to represent the expected impact of such a programme. The model incorporates the additional costs and effects of such a programme, although given the lack of prior public awareness campaigns for bowel cancer, these values are based on assumptions. Evidence concerning the effectiveness of such a programme on elective GP presentation is very limited.

3. Management of emergency presentations and delivery of care (including guidelines and training of specialist GI surgical expertise, and stenting)

Currently, a sizeable proportion of patients present as emergency cases due to obstruction; typically, these patients would undergo emergency surgery. It may be possible to improve outcomes in these patients by enhancing surgical expertise via national training programmes. In particular, the increased use of stenting to optimise the patient prior to surgery, or to alleviate obstruction in patients who are unfit for surgical resection, may offer improvements in health outcomes. In addition, the conversion of emergency procedures to elective procedures may decrease the use of stomas required, whilst using stenting for inoperable patients may improve palliation and quality of life.

The effect upon costs and benefits was modelled by altering the percentage of patients following the stenting pathway. The additional cost estimates include those associated with training, implementation and guideline development.

4. Increasing the use of colonoscopy from 70% to 90% rather than using flexible sigmoidoscopy

This option concerns the endoscopic diagnostic tests and does not alter the use of rigid sigmoidoscopy, barium enema or CT scans. Complete colonoscopy allows for visualisation of the entire colon to the caecum, whilst flexible sigmoidoscopy only allows for the visualisation of the distal portion of the bowel. Whilst colonoscopy allows for the detection of both distal and proximal neoplasia, it is more expensive, potentially more time consuming, more uncomfortable and more dangerous than sigmoidoscopy.

Within the model, the proportion of patients undergoing diagnostic colonoscopy was increased by 20% whilst the proportion of patients undergoing flexible sigmoidoscopy was decreased by 20% to reflect this option for change. The additional cost of colonoscopies is also explicitly modelled.

5. Improving colonoscopy completion rates via national training programmes

National training programmes are currently in place to improve the quality of existing endoscopy services. These are expected to improve current services in terms of "gold standard" diagnostic work-up, possible reduced perforation rates, reduced demand for follow-up colonoscopy in those patients for whom colonoscopy was initially incomplete, and potentially some minor reduction in pressure on radiology services for non-completers.

Within the model, the percentage of patients in whom a complete colonoscopy would be achieved was increased. Such improvements in completion rates are accompanied by additional costs of endoscopy training and implementation in the model.

4.2.2 Treatment Options for Bowel Cancer

6. The use of laparoscopic versus open surgery in colon cancer

Evidence suggests that laparoscopic surgery may improve health-related quality of life, and may result in fewer complications and a shorter hospital stay as compared to open surgery. However, laparoscopic surgery requires a higher level of surgical expertise.

As there has been no preference-based examination of the effect of laparoscopic surgery on health-related quality of life, utility scores for laparoscopic and open surgery are assumed to be the same within the options model, NICE HTA 105 (2006). In addition, current evidence suggests that the use of laparoscopic surgical techniques may reduce hospital stay and associated costs. NICE HTA 105 (2006).

7. Assessment of the impact of surgical expertise on outcomes and/ or developing specialist pathology services

Additional specialist training may be provided to surgeons so as to improve clinical outcomes e.g. reduced complication rates and reduced recurrence rates. Developing specialist pathology services will help to maintain quality control over surgery, may result in more appropriate post-operative treatment, and may improve patient outcomes. However, this is likely to result in additional resource requirements, for example, if pathologists found more lymph nodes, indicating Duke's C disease, this would lead to more adjuvant chemotherapy (Personal communication, Dr Rob Glynne-Jones, Mount Vernon Hospital, Middlesex).

This option was modelled by altering parameter values describing complication rates, disease-free survival and overall survival. Again, initial and ongoing costs of training and "knock-on" resource use is included in the options model.

8. Pre-operative versus post-operative radiotherapy for rectal cancer

Post-operative radiotherapy avoids the over-treatment provided as a result of pre-operative radiotherapy, although a higher dose is required, resulting in increased toxicity. The

percentage of patients receiving each treatment was varied, thus resulting in a different profile of quality of life gains and costs.

The number of rectal cancer patients experiencing disease recurrence is likely to be reduced using more pre-operative radiotherapy.

9. a. The use of alternative adjuvant chemotherapy regimensb. The use of alternative sequences of palliative chemotherapy

There are numerous therapeutic agents available for the adjuvant and palliative treatment of bowel cancer. NICE has recently recommended oxaliplatin and capecitabine as options for the adjuvant treatment of colon cancer. Irinotecan and oxaliplatin are now standard treatment options for advanced bowel (colon and rectum) cancer, based upon NICE's recommendations.

The effect of adjuvant treatment was modelled according to disease-free survival durations associated with alternative cytotoxic therapies. The effect of the cytotoxic agents for metastatic disease was modelled based upon expected overall survival durations and quality of life impacts. Costs associated with these therapies include drug acquisition, administration, hospitalisation and the management of adverse events. The analysis of these options is intended to examine the degree of improvement in disease-free and overall survival benefit required in order for a new therapy to be considered cost-effective.

10. The use of enhanced recovery programmes (ERP) following surgery

Enhanced Recovery Programmes can be used to speed up recovery following surgery, leading to improvements upon quality of life. The impact of ERP was modelled by varying length of hospital stay; evidence to inform these parameters was identified from the available literature.

11. Intensive versus relaxed follow-up

Follow-up strategies for patients following resection of the primary tumour vary considerably across the UK, and there is limited proven comparative benefit of intensive or relaxed follow-up strategies. More intensive follow-up schedules may enable recurrence to be identified earlier, yet direct improvements in survival or quality of life have not yet been demonstrated within individual RCTs.

This option was modelled by assuming a more intensive follow-up schedule than that used in the baseline activity model. The impact of such follow-up regimes is currently unknown; therefore, the overall survival duration for relapsing patients was increased by 5% and 10% to explore the impact of such improvements on costs and health outcomes.

12. Increased liver/lung resection for metastatic disease

For patients who develop metastatic disease, liver resections offer the only real chance of a cure. However, our current estimates suggest that only around 10% of all patients with metastases undergo hepatic/lung resection. This could be increased by either enhancing follow-up (see above) or through the development of more effective chemotherapy agents for downstaging.

The cost-effectiveness of this option was modelled by increasing the probability that an individual receives liver resection following downstaging chemotherapy.

4.2.3 Palliative Care Options

13. Increasing palliative surgery (e.g. palliative bypass) and stenting

There may be potential for increasing the use of palliative bypasses and stenting in patients with inoperable tumours, which may lead to improvements in quality of life. However, this option this is likely to also have training and resource implications.

This option was modelled by increasing the number of palliative bypasses and stenting and through considering associated improvements in health-related quality of life and costs associated with each intervention. Additional training and implementation costs were also included in the options analysis. The reader should note that evidence surrounding these costs and outcomes is severely lacking, hence parameter values surrounding this option are based on subjective assumptions.

4.3 METHODOLOGY

4.3.1 Overview of the Bowel Cancer Options Model

The bowel cancer options model was produced using the computer software, SIMUL8. As the underlying model of the natural history of bowel cancer and the treatment pathways are complex, standard health economic modelling techniques such as simple decision analysis and Markov processes are not sufficiently flexible to accurately capture this level of detail for option modelling across the entire bowel cancer service. Instead, a more sophisticated discrete event simulation (DES) approach has been used. This simulation model estimates the expected costs and resource use resulting from the diagnosis, treatment and follow-up of bowel cancer, as well as health outcomes such as number of cancers diagnosed, life years gained and QALYs gained for the modelled population. The pathways upon which the simulation model is based are described in Section 2.

The model operates on an individual patient-level basis. Each individual patient is assigned a specific set of characteristics (Appendix C, Table A) before entering into the model which will influence the pathways that the patient follows (i.e. event probabilities), times to event occurrence, and the duration of events. This process is based upon Monte Carlo sampling techniques (Appendix C, Table B). This allows the model to generate distributions of costs, health outcomes, and resource use resulting from alternative configurations of the bowel cancer service in England.

Model parameters are also used to describe whether patient presents at A&E or via their GP, whether the GP will refer the patient (Appendix C, Table C), whether or not a correct diagnosis will be made (Appendix C, Tables D) and whether an additional diagnostic test will be required for each patient (Appendix C, Table E). Operative mortality and death from other causes has been explicitly modelled (Appendix C, Tables F and G). Some parameters have been elicited with the help of clinicians using statistical software developed by statisticians from the Open University (Section 1.6 and Appendix B).

The probability of underlying disease progression prior to diagnosis has been modelled using the ScHARR screening model which was calibrated against national incidence and mortality data (Appendix C, Table G).

First-order uncertainty, that is variation in the sample data, was modelled using trials consisting of 25 runs based on a different set of random numbers for each parameter distribution in the model. Each of these trials was run 50 times to incorporate second-order uncertainty, that is, the uncertainty surrounding the population mean. Therefore, the results of each option are taken from a total of 1,250 runs to comprehensively capture the uncertainty surrounding all of the parameters simultaneously.

4.3.2 Scope of the Options Model

It is important to note that other individuals besides those patients with sporadic bowel cancer consume resources within the bowel cancer service. The population included within the model (and hence the boundary around the modelled service) is any person presenting with potential bowel cancer symptoms or requiring the diagnostic services in England (with the exclusion of people who are at increased risk of bowel cancer such as people with FAP, HNPCC, ulcerative colitis and Crohn's disease). Therefore, the model includes 4 groups of patients:

- 1. People who are diagnosed with an underlying bowel cancer;
- 2. People who present to their GP or at A&E with symptoms of bowel cancer (but have no underlying colorectal pathology);
- **3.** People who present to their GP or at A&E with symptoms of bowel cancer (with other non-malignant colorectal pathology e.g. diverticulitis, ulcerative colitis, haemorrhoids);
- 4. People in whom adenomatous polyps have been identified.

The model estimates direct costs and health outcomes from the perspective of the UK NHS and PSS. In line with current practice, future costs and health outcomes are discounted at a rate of 3.5%.

A schematic of the model can be observed in Figure 4.1 overleaf.



4.3.3 Health Economic Outcomes Included in the Model

The model estimates the following outcomes in terms of the effectiveness of each option:

- Life years gained (LYGs);
- Quality adjusted life years (QALYs) gained;
- Cancers avoided (reduction in incidence);
- Cancer stage and polyp distributions.

4.3.4 Modelling the Patient Pathways

A cohort of 10,000 patients has been modelled, where the probability of presenting with cancer or polyps is based on age-based data (ONS data and autopsy studies). Each patient has the following characteristics:

- Underlying disease status;
- Age;
- Fit for surgery or not;
- Health utility;
- Colon or rectal cancer;
- If colon cancer, proximal or distal;
- Obstructed or not;
- Palpable mass or not;
- If rectal, R0 or R1/R2 (predicted);
- If fit for surgery, emergency or elective.

The proportion assigned to each of the above is shown in Table A, Appendix C. Owing to weaknesses in the evidence base, several assumptions have been made concerning the relationship between these characteristics:

- The distribution of Dukes' stage at presentation is the same for colon and rectal cancers;
- The distribution of Dukes' stage at presentation is the same for proximal and distal cancers;
- A patient's level of health-related quality of life is related to age, but not to Dukes' stage;
- The way in which a patient presents does not have an effect on their probability of having colon or rectal cancer;
- The probability that a patient is obstructed is dependent upon the stage of their underlying cancer;
- The probability of having a palpable mass is independent of the stage and site of cancer;
- Patients presenting from secondary care have the same distribution of characteristics as patients presenting to their GP;
- The probability of being fit for surgery is assumed to decrease with age.

4.3.5 Model Assumptions

The model also employs a number of further assumptions which are summarised below. In some cases, these assumptions simplify the process considerably or propose parameters based on limited evidence. Further research in some of these areas would reduce the number of assumptions required in the model, and would reduce the degree amount of uncertainty within the model.

1. Assumptions concerning patient presentation

- If a patient in the model does not have bowel cancer or polyps, they will always present to their GP, rather than presenting at A&E or through secondary care;
- If a patient is obstructed, the probability that they present initially at A&E is 0.47. Otherwise they will present initially to their GP and will then be referred to A&E;
- If a patient is not obstructed, the probability that they present through secondary care is 0.26, with the remainder presenting to their GP;
- If a patient is not obstructed and presents to their GP, they have a 2% chance of being referred to A&E.

2. Assumptions concerning patient referral

- A patient who has been incorrectly sent home by the GP will return for a further appointment or present at A&E;
- Prior to referral, a patient may die as a result of other causes, but not as a result of bowel cancer;
- A patient who presents at A&E will always receive a CT scan, x-ray and blood test before receiving emergency surgery or stenting;
- In the model, all who patients who present through secondary care have bowel cancer and are always diagnosed;
- Data surrounding patient referral provided by Dr. W. Hamilton can be generalised nationally;
- Due to lack of further research in this area, the data provided from Dr. W. Hamilton of patients diagnosed between 1998 and 2002 inclusive, from all of the 21 practices in the Exeter PCT has been used to model the sensitivity and specificity of current GP practise and time taken from onset of symptoms to referral, and from referral to diagnosis, for both elective and emergency cases.

3. Assumptions concerning the treatment of patients with increased risk (adenomatous polyps)

- Patients in whom adenomas are identified and who are considered high-risk, will undergo colonoscopic surveillance every three years until two consecutive negative results are received;
- The probability of an adenoma recurring in the first year following removal of the initial adenoma is 18% and 25% for low- and high-risk adenomas respectively. In

years 2 and 3 following excision of the initial polyp, the probability of recurrence is 5% and 6% for low- and high-risk adenomas respectively;

- If a high-risk polyp recurs, it will be identified through polyp surveillance and the patient will not return to their GP or present at A&E before the 3-yearly colonoscopy surveillance. The patient will not progress to a high-risk polyp before returning to colonoscopy surveillance;
- If an adenoma is not identified at endoscopy, the patient will have a 50% or 75% chance of not using bowel cancer resources again in their lifetime for high and low risk cancers respectively. Otherwise, they are assumed to return to their GP after a year, where the polyp has around a 2% chance of progressing within this time (Appendix C, Table G).
- All patients with adenomas are assumed to have the same life expectancy as the average person in England and Wales, unless the adenoma progresses to bowel cancer.

4. Assumptions concerning diagnostic investigations

- Patients will not die as a direct result of bowel cancer following diagnosis if they are treated via surgery, unless they have a metastatic recurrence;
- The choice of diagnostic test (colonoscopy or flexible sigmoidoscopy) at endoscopy is independent of which other tests have been given to the patient;
- The perforation rate for colonoscopy and flexible sigmoidoscopy is 1.3%. Of these there is a probability of 5.8% that the patient who suffers perforation will die;
- The probability that a patient with proximal cancer will be sent for a colonoscopy following a flexible sigmoidoscopy due to the presence of an adenoma in the distal portion of the colon is assumed to be 29% (Dinning, 1994);
- All patients will receive CT scans. All rectal cancer patients will also receive MRI scans;
- There is no difference in health utility for an individual with pre-clinical bowel cancer and an individual with clinical bowel cancer;
- It could be argued that if a person is unaware of an underlying disease they would have a higher level of quality of life than if they were aware of the disease. Due to lack of evidence surrounding health utility scores, the model assumes this is not the case;
- No patients are treated following diagnostic investigations if they do not have cancer.

5. Assumptions concerning adjuvant treatment of colon and rectal cancer

- Around 89% of patients are considered fit for surgery. This is based upon data from the Wessex audit. The remaining 11% would have palliative care;
- Complications during surgery do not affect patient quality of life;
- The probability of having a stoma following resection is 14.5% and 67% for colon cancer and rectal cancer respectively, based on data from HES (2004). Of these, the proportion of stomas that become permanent is 73%;

- Operative mortality for elective and emergency surgery is 5.5% and 21.7% respectively, based on data from Mella (1997);
- Disease-free survival durations observed within recent clinical trials are broadly generalisable. The methodology and assumptions applied are outlined in Section 4.3.5.7;
- Local recurrence is highly unlikely to occur in colon cancer patients;
- Local recurrence will occur in 5% of rectal cancer patients who have received preoperative radiotherapy and 11% of rectal cancer patients who have received postoperative radiotherapy, based on data from the CR07 trial;
- Local recurrence has an impact on costs, but not on overall survival or quality of life;
- If a patient with rectal cancer in whom an R1/R2 resection is predicted is not successfully downstaged during preoperative radiotherapy, they will go on to have palliative chemotherapy rather than best supportive care or palliative surgery;
- If a patient has an emergency stent, they will always go on to have elective surgical resection apart from 0.5% which die from the stenting operation;
- If a patient is considered unfit for curative surgical resection, they have a 50:50 chance of receiving best supportive care and palliative surgery.

6. Assumptions concerning treatment of metastatic disease

- The expected duration of overall survival following the onset of metastatic disease is assumed to be independent of previous adjuvant treatments received;
- Around 83% of patients will receive palliative chemotherapy for metastatic disease. The expected overall survival for these patients is modelled using data from the FOCUS trial (2004);
- Of those patients who do not receive palliative chemotherapy, 50% will receive palliative surgery, whilst the remaining 50% will receive best supportive care. There is assumed to be no difference in overall survival for these two groups. Owing to the lack of evidence in this area, the expected overall survival duration for this population has been elicited from clinical experts;
- If a patient receives palliative surgery, they have a 50:50 chance of having palliative stent or palliative bypass;
- If a patient receives best supportive care instead of palliative stenting or bypass they have a relative health utility decrement of an average of 50%. (Uniform[0,1]);
- If metastatic disease is not successfully downstaged to allow for a liver or lung resection to be undertaken, the patient will go on to receive palliative chemotherapy.

4.3.6 General assumptions

- The patient pathways are as described in Section 2. However, some pathways have been simplified in the model where the detail was not required for the options analysis;
- All patients have the same probability of death from other causes in the model, based on their age (Appendix C, Table J).

It is likely that a patient's level of quality of life would be differentially affected by many of the treatments included in the bowel cancer options model. However, due to the paucity of evidence concerning health-related quality of life available from the literature, the model assumes little or no difference in terms of health utility scores between many of these interventions. Further research in this area would be valuable.

4.3.7 Modelling Time-To-Event Outcomes

4.3.7.1 Modelling disease-free survival

Within the bowel cancer options model, time to relapse or death was modelled using parametric survival curves based upon empirical disease-free survival curves, which have been reported in recent RCTs of adjuvant chemotherapy, surgery and radiotherapy. Weibull distributions were fitted to the disease-free survival data in order to estimate a parametric model allowing extrapolation beyond the duration of the clinical trials. The uncertainty surrounding these curves was modelled using multivariate normal distributions. As the hazard of relapse declines after around 5-years following surgical treatment, the model assumes that the risk of relapse is zero beyond this point in time for both colon and rectal cancers. The survival duration for patients who do not relapse was then assumed to follow that of the age-matched general population of England.

4.3.7.2 Colon cancer

Patients with Dukes' A colon cancer

For patients with Dukes' A disease, the probability of relapse over time is very low, and this subset of patients is assumed not to receive adjuvant chemotherapy. The distribution of disease-free survival for these patients has been derived from the open surgery arm of the recent COST trial (2004), as this trial presented disease-free survival curves stratified by stage of cancer. Empirical and modelled disease-free survival curves are shown in Figure 4.1.


Figure 4.1: Disease-free survival for patients with Dukes' A bowel cancer

Patients with Dukes' B colon cancer

A proportion of patients with Dukes' B colon cancer are assumed to receive oxaliplatin in combination with 5-FU/FA (FOLFOX) or capecitabine. Disease-free survival curves for patients receiving FOLFOX have been derived from the recent MOSAIC trial (2004). The equivalent curve is assumed for patients receiving capecitabine. The probability of relapse in patients with Dukes' B colon cancer who do not receive adjuvant chemotherapy is assumed to be the same as for those who do receive adjuvant chemotherapy.



Figure 4.2: Disease-free survival for patients with Dukes' B colon cancer receiving adjuvant chemotherapy

Patients with Dukes' C colon cancer

The majority of patients with Dukes' C colon cancer receive adjuvant chemotherapy. This is most likely to be either capecitabine or FOLFOX, based on the findings of the recent MOSAIC and X-ACT trials. Empirical and parametric disease-free survival curves for these patients are shown in Figures 4.3 and 4.4.

Figure 4.3: Disease-free survival for patients with Dukes' C colon cancer receiving adjuvant FOLFOX



Figure 4.4: Disease-free survival for patients with Dukes' C colon cancer receiving adjuvant capecitabine



4.3.7.3 Rectal cancer

Disease-free survival outcomes for rectal cancer patients receiving either pre-operative radiotherapy or selective post-operative chemoradiation were modelled using data from the MRC CR07 trial results presented at ASCO 2006 and from a study of outcomes for patients with borderline resectable or unresectable rectal cancer reported by Mawdsley *et al.* (2005) Disease-free survival outcomes for patients in whom an R0 resection is predicted were modelled exclusively using data from the CR07 trial, as shown in Figure 4.5.





Disease-free survival outcomes for patients in whom an R1/R2 resection is predicted were modelled using data from Mawdsley *et al.*, based on the probability of CRM involvement (2005). More favourable disease-free survival outcomes were assumed for the proportion of patients who were expected to be CRM-negative (see Figure 4.5).

Figure 4.6: Disease-free survival outcomes for patients undergoing an R1/R2 resection according to CRM involvement



A proportion of patients in whom an R1/R2 resection is predicted will not be successfully downsized by neo-adjuvant treatment. The model assumes that most of these patients will receive palliative chemotherapy; their expected overall survival time was based on data from trials of palliative chemotherapy described below.

Table 4.1:	Summary of modelled 5-year disease-free survival outcomes
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Disease-free survival outcomes	Modelled 5-year DFS
Dukes' A colon cancer	94.71%
Dukes' B colon cancer (with chemotherapy)	74.76%
Dukes' B colon cancer (without chemotherapy)	74.76%
Dukes' C colon cancer (FOLFOX)	53.20%
Dukes' C colon cancer (capecitabine)	47.36%
Dukes' C colon cancer (without chemotherapy)	50.00%
Pre-operative radiotherapy (CR07)	73.33%
Selective post-operative radiotherapy (CR07)	64.75%
Borderline/inoperable R0 (Mawdsley)	42%
Borderline/inoperable R1/R2 (Mawdsley)	8%

4.3.8 Overall Survival

Time to death following relapse is modelled using data from the FOCUS trial which evaluated the use of chemotherapy in patients with metastatic bowel cancer. The empirical and parametric overall survival curve used in the model for these patients is shown in Figure 4.7.

Figure 4.7: Overall survival for patients receiving oxaliplatin plus 5-FU/FA



7. Survival duration for unfit patients receiving best supportive care alone

There is very limited information concerning the survival duration for patients who are insufficiently fit to receive any chemotherapy. An expected survival duration of 3 - 4 months is assumed; this was modelled using a simple uniform distribution.

Table 4.2:	Summary of modelled overall survival outcomes used in model
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Overall survival outcomes	Modelled mean survival (years)
Metastatic bowel cancer (FOCUS regimen)	1.54
Metastatic bowel cancer (FOLFIRI/FOLFOX regimen)	2.18
Metastatic bowel cancer (Liver resection)	3.30
Metastatic bowel cancer (best supportive care only)	0.29

4.4 METHODS FOR ESTIMATING HEALTH UTILITIES

Systematic searches were undertaken to identify evidence relating to the impact of bowel cancer and its treatment on health-related quality of life. There exist a large number of quality of life studies in patients with bowel cancer; most commonly, these have been undertaken using cancer specific questionnaires such as the EORTC QLQ C-30 or the FACT instrument. Whilst these questionnaires have been highly validated and provide valuable information on the impact of health interventions on quality of life, they do not allow for the calculation of single index preference-based health utilities which are required for economic evaluation. A total of six studies were identified which attempted to estimate utility scores for patients with metastatic CRC.1-6 Details of the methods used within these studies are reported in Table 4.3.

Table 4.3: Summary of characteristics of utility studies for bowel cancer

Study	Study population	Method of preference elicitation and details of scenarios used
Ko et al.	Colon cancer subgroup included 169 patients.	The Health and Activities Limitation Index was mapped onto a utility scale. This does not appear to be preference-based but is a conversion of a numerical Likert rating scale.
Ness et al.	90 individuals who had previously undergone removal of colorectal adenoma. 81 of these patients were included in study.	Seven health states describing various states of severity of colon and rectal cancer. Scenarios F and G were "Stage IV metastatic/unresectable disease with/without ostomy." Preferences elicited using standard gamble.
Ramsey <i>et al.</i>	173 subjects with CRC (various stages) sampled from US SEER database completed the survey	Preferences elicited using the Health Utilities Index Mark 3 (HUI3)
Petrou and Campbell	30 nurses experienced in oncology care	Utility scores for six chemotherapy-specific scenarios elicited using the standard gamble technique
MRC FOCUS trial	Subset of clinical trial population with metastatic bowel cancer	EQ-5D questionnaire
Merck MABEL trial	Clinical trial population with metastatic bowel cancer	EQ-5D questionnaire

Tables 4.3 - 4.7 present the utility scores reported for each of the scenarios used within the six identified studies.

Table 4.4:Utility scores relating to stage of bowel cancer

Health state description	Ness et al.	Ramsey et al.	Focus	Mabel
Self-valuation (no CRC)	0.84			
	(0.88 to 0.80)			
Stage I rectal / stage I/II colon	0.74			
cancer treated with resection	(0.78 to 0.69)			
only				
Stage III colon cancer treated	0.7			
with resection and	(0.77 to 0.63)			
chemotherapy without				
significant side effects				
Stage III colon cancer treated	0.63			
with resection and	(0.7 to 0.56)			
chemotherapy with significant				
side effects				
Stage II/III rectal cancer	0.59			
treated with	(0.64 to 0.54)			
resection/chemotherapy/radiot				
nerapy	0.5			
Stage II/III rectal cancer	0.5			
treated with	(0.56 to 0.44)			
resection/cnemotherapy/radiot				
Store IV	0.04			
Stage IV	0.24			
disease without esterny	(0.32 to 0.16)			
	0.07			
Stage IV	0.27			
diagona with actomy	(0.36 (0 0.16)			
Store I		0.04 (1/0.17)		
		0.04 (+/-0.17)		
		0.86(+/-0.14)		
		0.85 (+/-0.14)		
Stage IV		0.84 (+/-0.12)	A sectore is it.	0.70 (0.00)
Stage IV metastatic bowel			Academic in	0.73 (+/-~0.20)
cancer			confidence	

Health state description	Ko et al.	Ramsev et al.
<1yr post-diagnosis (no stage information available)	0.67 (+/- 0.21)	
1-5 vrs post-diagnosis (no stage information	0.68 (+/- 0.24)	
available)	· · · · ·	
>5yrs post-diagnosis (no stage information	0.71 (+/-0.25)	
available)	· · · · · ·	
All stages (13-24months)		0.80 (+/-0.20)
All stages (25-36months)		0.88 (+/-0.12)
All stages (37-60months)		0.84 (+/-0.14)
All stages (>60months)		0.90 (+/-0.90)
Stage I (13-24months)		0.72 (+/-0.27)
Stage I (25-36months)		0.89 (+/-0.11)
Stage I (37-60months)		0.90 (+/-0.06)
Stage I (>60months)		0.89 (+/-0.05)
Stage II (13-24months)		0.85 (+/-0.15)
Stage II (25-36months)		0.87 (+/-0.13)
Stage II (37-60months)		0.79 (+/-0.18)
Stage II (>60months)		0.91 (+/-0.11)
Stage III (13-24months)		0.82 (+/-0.15)
Stage III (25-36months)		0.95 (standard error not
		estimable)
Stage III (37-60months)		0.79 (+/-0.25)
Stage III (>60months)		0.92 (+/-0.05)
Stage IV (13-24months)		0.95 (standard error not
		estimable)
Stage IV (25-36months)		0.92 (+/-0.04)
Stage IV (37-60months)		0.76 (+/-0.11)
Stage IV (>60months)		0.84 (+/-0.13)

Table 4.5:Relationship between health-related quality of life and time since
diagnosis

Table 4.6: Relationship between health-related quality of life and treatment

Health state description	Ramsey <i>et al.</i>
Surgery in last month (all stages)	0.584
No surgery in last month (all stages)	0.85
Chemotherapy in last month (all stages)	0.80
No chemotherapy in last month (all stages)	0.84
Radiotherapy in last month (all stages)	0.68
No radiotherapy in last month (all stages)	0.85
Colostomy appliance	0.85
No colostomy appliance	0.84

Table 4.7:Relationship between health-related quality of life and response
(metastatic disease)

Health state description	Petrou and Campbell
Best possible health	1.0 (standard error not available)
Worst possible health	0 (standard error not available)
Partial response	1.0 (standard error not available)
Stable disease	0.95 (standard error not available)
Progressive disease	0.575 (standard error not available)
Terminal disease	0.10 (standard error not available)

Tables 4.3 – 4.7 do not demonstrate a clear relationship between health-related quality of life and stage of cancer, treatment, phase of disease, or time since diagnosis. Importantly, only two studies have attempted to estimate health utility scores for patients according to stage of cancer. Whilst Ness *et al.* (1999) suggests a substantial difference between early- and latestage cancers, this study was undertaken using hypothetical health status scenarios; Ramsey (2000), which was undertaken using long-term survivors of bowel cancer does not demonstrate this relationship between cancer stage and declining health-related quality of life. The results of the MABEL study (Corrie (2005)) lend further weight to this suggestion, as the sample of patients included in this study had metastatic bowel cancer and had failed on at least one prior line of chemotherapy.

Furthermore, the results of the studies reported by Ko *et al.* (2003) and Ramsey *et al.* (2000) suggest that time since diagnosis do not dramatically influence health utility scores, irrespective of whether they are stratified by cancer stage. The most notable difference in health utility appears to derive from the Ramsey analysis of utility according to treatment. A significantly lower utility score was reported for patients who had undergone surgery in the previous month compared to those who had not (p = 0.001).

The study reported by Petrou and Campbell (1997) suggests a notable difference in quality of life for difference phases of metastatic disease. However, this study was undertaken using nurses acting as a proxy for bowel cancer patients; the stage-specific utilities estimated from Corrie (2005) and the Ramsey *et al.* (2000) suggest that such differences would not be observed had the elicitation focussed on the preferences of patients with metastatic bowel cancer.

The current state of evidence concerning the relationship between health utilities, stage of cancer, treatment and time since diagnosis is not entirely consistent. Observed relationships between utility and other covariates (e.g. stage, phase of treatment) reported in studies in which individuals without bowel cancer are not substantiated by patients with bowel cancer. The precise reasons for this are not clear. This is clearly an area in which further research is merited.

4.4.1 Modelling the Impact of Health-Related Quality of Life

Simplistic assumptions were made in the options model due to the limited evidence concerning the relationship between utility, stage of cancer and time since diagnosis. Two health states were assumed: (1) patient does not have bowel cancer (2) patient has bowel cancer. Age-specific utility scores were assigned to patients without bowel cancer based upon the 1996 General Health Survey for England. Age-specific utilities were modelled using a narrowly defined normal distribution. The relative utility of patients with bowel cancer versus the normal population was modelled using a highly skewed beta distribution, whereby the mean relative utility was very close to 1, yet the long tail of the distribution allows for the utility of patients with bowel cancer to be substantially lower than that for the general population.

4.5 MODELLING THE COSTS OF DIAGNOSIS, TREATMENT AND FOLLOW-UP OF BOWEL CANCER

The model includes the costs associated with diagnosis, treatment and follow-up. Where available, these estimates have been taken from NHS Reference Costs, and from previous NICE assessments. Further details of these parameters are detailed in Appendix A.

Section 5: Summary: Option Model Results

This section presents the cost-effectiveness results from the base case model and the expected marginal costs and outcomes resulting from the fourteen options for change evaluated. It should be noted that these options are based on limited data and require further research. No attempt has been made to derive a detailed cost of the interventions within the scope of this study and whilst there has been some consultation with clinical experts throughout the course of this study, further research would be desirable prior to implementing any of the options. However, the illustrative findings presented herein do allow the interventions considered to be ranked based on their cost effectiveness and may help in prioritising interventions that warrant further research.

The results for the options are presented in Table 5.i. The table presents the estimates for both the current service and each of the individual options for change. The results presented include the total costs, Life years gained (LYG), Quality Adjusted Life Years (QALYs), marginal LYG and marginal QALYs. The final columns of this table rank the costs and rank the QALYs in comparison with the baseline option model results. For example, the lowest marginal cost (in some circumstances the option will be cost saving) and highest marginal QALY will receive a rank of 1.

The model suggests that the most cost-effective option for improving outcomes for bowel cancer patients is to increase the use of colonoscopy from 70% to 90% as an alternative to flexible sigmoidoscopy. Whilst the assumptions in the model may affect the extent to which this option will benefit patients, it is expected to improve health outcomes and produce cost-savings (i.e. the option is expected to "dominate" the current service). Future research concerning the natural history of the disease and the probability of polyps and cancers being detected in patients with distal colon cancer would be valuable. The introduction of an Enhanced Recovery Programme is also cost saving with initial indications of a low associated risk of detrimental clinical outcomes. This option is again relatively robust and at an advanced stage of development for implementation.

The model suggests that the most costly option would be the further development of GP referral criteria guidelines, although this is also expected to be associated with a reasonable improvement in LYGs. This assumes that improving GP referral criteria will allow GPs to detect the cancer at an earlier presentation, and hence an earlier stage in some patients. This option is highly uncertain due to the lack of evidence surrounding disease progression and the cost of implementation. It would also require substantial further research in order to assess how changes in referral criteria will affect GP referrals, such that specificity is not decreased as a result of increasing sensitivity (since this is expected to lead to worse health outcomes). Further research is required surrounding the relationship between symptoms and disease progression.

Increasing the use of emergency stenting is expected to be very effective for a small number of patients consuming bowel cancer resources, but is associated with a relatively high cost. Options 7 and 9, to improve surgical resection and/or pathology and to improve adjuvant or

palliative chemotherapies, are associated with improvements in health outcomes at a relatively low cost; providing that for option 7 the cost of improvements in pathology are not greater than the modelled costs, and for option 9 that the new chemotherapy regimens are not considerably more expensive than the current standard chemotherapies. All of these options would provide health benefits; however there is considerable uncertainty surrounding the necessary costs required to provide the amount of health benefit. In the case of option 9, this will depend upon new and currently unknown costs and outcomes of future chemotherapies.

Many of the options assessed within the model display huge variability due to the large amount of uncertainty associated with both the base case model and the options. The confidence intervals around the results suggest that it is unlikely that increasing the use of colonoscopy and introducing an Enhanced Recovery Programme will not be cost saving. However, since there is very little evidence regarding health utility scores for bowel cancer services, there is a considerable degree of uncertainty associated with all of these options in terms of their impact upon health-related quality of life. This is a clear area in which further research would be of value.

The effect of introducing bowel cancer screening across England upon the costeffectiveness of the treatment options is expected to be minimal; the total costs and benefits may be reduced slightly, yet the relative effects of each of the treatment options are not expected to be substantially different. Furthermore, the current FOBT test has been shown to have a low sensitivity. The options surrounding presentation and referral are likely to be affected considerably by the introduction of screening throughout England. The effectiveness of these options is likely to be reduced due to screening; however the ScHARR screening model (Tappenden *et al.* 2007) suggests that they do have the potential to provide some additional benefit.

Table 5.i:The option model results

0	lion	Cost			Marginal aget (C)	Marginal life	Morginal OAL Va	Cost	QALY
Op	lion	(£)	Life years	QALIS	Marginal Cost (£)	years	Marginal QALTS	rank	rank
	Baseline	908.18	10.4691	8.1981					
1	GP referral criteria - sensitivity	933.02	10.4708	8.2026	24.85 (-32.33, 84.23)	0.0017 (-0.0724, 0.0722)	0.0045 (-0.0508, 0.0586)	14	2
2	Media campaign	909.50	10.4702	8.1986	1.32 (-64.38, 63.31)	0.0011 (-0.0772, 0.074)	0.0005 (-0.0601, 0.0567)	7	10
3	Emergency stenting	919.52	10.4731	8.2008	11.34 (-46.85, 65.58)	0.0040 (-0.0678, 0.0767)	0.0027 (-0.0525, 0.0589)	13	4
4	Colonoscopy versus flexi sig	843.79	10.4802	8.2006*	-64.39 (-120.52, -11.54)	0.0111 (-0.0615, 0.0839)	0.0025 (-0.054, 0.0586)	1	5
5	Colonoscopy completion rates	912.29	10.4713	8.1998	4.11 (-49.75, 56.92)	0.0022 (-0.0725, 0.0765)	0.0017 (-0.0545, 0.0589)	10	7
6	Pre versus postop RT	912.64	10.4695	8.1986	4.46 (-46.71, 58.97)	0.0004 (-0.0674, 0.074)	0.0004 (-0.0527, 0.0566)	11	11
7	Improve surgery/pathology	907.15	10.4763	8.2035*	-1.03 (-51.7, 45.75)	0.0072 (-0.0626, 0.0811)	0.0054 (-0.0481, 0.0617)	5	1
8	Lap versus open	911.01	10.4680	8.1973	2.84 (-53.97, 62.71)	-0.0011 (-0.0745, 0.0688)	-0.0008 (-0.0569, 0.0538)	9	14
9a	Alternative adjuvant chemotherapies	902.84	10.4714	8.2000*	-5.34 (-31.83, 24.61)	0.0023 (-0.0596, 0.0647)	0.0019 (-0.0464, 0.05)	3	6
9b	Alternative palliative chemotherapies	905.24	10.4751	8.2016*	-2.94 (-6.65, -0.31)	0.0060 (0.0006, 0.0128)	0.0035 (0.0004, 0.0074)	4	3
10	Enhanced recovery programme	859.25	10.4702	8.1989*	-48.93 (-107.93, 12.75)	0.0011 (-0.0707, 0.08)	0.0008 (-0.0535, 0.0616)	2	9
11	Intensive versus relaxed follow-up	916.75	10.4714	8.1996	8.57 (-54, 73.56)	0.0023 (-0.0697, 0.0781)	0.0015 (-0.0531, 0.0598)	12	8
12	Increased liver/lung resection	909.02	10.4695	8.1983	0.84 (-43.06, 41.23)	0.0004 (-0.0653, 0.0696)	0.0002 (-0.0501, 0.0536)	6	12
13	Increase palliative surgery	910.66	10.4691	8.1982	2.48 (1.12, 4.27)	0.0000 (0, 0)	0.0001 (0, 0.0002)	8	13

5.1 INTRODUCTION

This section presents the cost-effectiveness results obtained from the base case model and details the expected marginal costs and outcomes resulting from the variety of options evaluated within the analysis. The model population includes all patients using bowel cancer resources (see Section 4.3), and not only patients with bowel cancer. It should be noted that bowel cancer patients make up around 3% of all of the people using all bowel cancer resources. Around half of the non-cancer patients will use the GP resource only. The remainder of the non-cancer patients will require diagnostic resources and patients with polyps may undergo surveillance via colonoscopy. Therefore, while some of the options may have a large impact on a number of bowel cancer patients, they only have a small impact the broader population of patients who consume bowel cancer resources. The options are assessed using limited data, and in some cases, cost and effectiveness data have been produced using data from a single weak source. Therefore there is considerable uncertainty around all of the option results and further research in many areas would be valuable.

5.2 BASE CASE SCENARIO MODEL RESULTS

Table 5.1 presents the estimates of life years gained (LYG), quality adjusted life years (QALYs) gained and total costs per patient in the base case model.

Table 5.1:	Estimates of health	outcomes and	costs per patient
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Scenario	LYs	QALYs	Total cost
Base case	10.4691	8.1981	£908.18

These results have been used to provide a baseline from which to estimate the marginal cost per LYG and the marginal cost per QALY gained associated with each option. These outcomes thus describe the additional cost required to produce one extra unit of benefit for each option relative to the costs and outcomes associated with the current service. The first line of each of the tables presents the relevant base case parameter and the base case costs and outcomes. Owing to a lack of empirical evidence, many of the options are based on assumptions and subjective judgements surrounding the costs of staff training and other resources, and differences in these costs may affect the cost-effectiveness of the option considerably.

The following sections outline the results of each option together with a discussion of each. A list of the assumptions underpinning the results is presented. Further research in each area would be required to validate these assumptions to ensure that the results of the options are reliable. It should also be noted that the costs of many of these options may decrease over time if the option were to become standard procedure, particularly for changes in procedure such as the introduction of an Enhanced Recovery Programme. The options are presented in two sections; access to service options (Section 5.3) and treatment, follow-up and palliative care options (Section 5.4). As the model population relates to all people consuming colorectal cancer resources, the treatment, follow-up and palliative care options have also been re-scaled to represent the bowel cancer population in order to present a more comprehensive evaluation.

Bowel cancer screening using Faecal occult blood testing (FOBT) for individuals aged 60-69 is currently being rolled out across the country. Importantly, bowel cancer screening has the potential to both reduce the incidence of cancer and change the distribution of disease stage at the expense of increasing the use of diagnostic services and prospective treatment services for of people with polyps. Currently screening has been piloted, but has not been fully rolled out across England. The anticipated effect of implementing screening is discussed for each option. The effect upon the cost-effectiveness of bowel cancer treatment options is expected to be minimal, in that the total costs and benefits may be reduced slightly; however the relative effects of each of these options are not expected to be substantially different. Furthermore, the current FOBT test has been shown to have a low sensitivity. However, the options around presentation and referral are likely to be largely affected by the introduction of screening throughout England. Screening is expected to reduce the effect of these options by detecting the disease in many of the patients that would otherwise present at their GP at some later date. The first two options have therefore been assessed alongside screening using ScHARR's screening model (Tappenden et al. 2007), whilst the impact of screening upon the remaining options have been discussed without being explicitly modelled.

Each of the results has also been subjectively graded according to the uncertainty surrounding the model parameters and the ease of implementation. All of the options are associated with uncertainty surrounding the initial model assumptions and because of the uncertainty surrounding the potential changes to costs and benefits. The uncertainty scale shown below is a subjective measure which has been used with the aim to provide additional information around the estimated effect of this uncertainty upon the results.

Table 5.2: Uncertainty grade scale

Uncertainty	Grade
Robust	1
Some uncertainty	2
Highly uncertain	3

Grade 1 suggests that the evidence-base surrounding the option is strong and that we are fairly confident that the option is unlikely to result in a negative impact on benefits (and it is unlikely to be costly) despite the underlying uncertainties. Grade 2 suggests that there is some uncertainty in the model or the parameters of the options which could lead to negative benefit or a greater cost than predicted. Finally, Grade 3 suggests that the results of the

modelled option are highly uncertain as there is very little or no evidence around the costs and/or effects of the options.

The level at which implementation is possible has also been graded.

Table 5.3: Implementability grade scale

Implementability	Grade
Implementable with modest development requirements	А
Research surrounding implementation required	В
Basic research required	C

Grade A is used for options where trials have been undertaken, the option has usually been piloted and minimal, if any, and further research is required before the option could be implemented. Grade B suggests that research has been carried out around the option, but some additional research is required before the option could be implemented. Finally, Grade C suggests that there is very little evidence available around the costs and/ or benefits of the option and relevant parameters basic further research is required in order to understand the potential of the suggested option. There is clearly some correlation between the two grade scales since those options which have already been trialled and piloted are more likely to have data available and hence reduce the uncertainty involved than those options where lesser amount of research is required.

Following the evaluation of each individual option, a table and graph comparing the costs and QALYs of each option are shown in Section 5.5 (summary results), along with a table of a number of secondary model outcomes such as costs of each part of the pathway and the number of people diagnosed with each cancer stage.

5.3 ACCESS TO SERVICE OPTIONS

5.3.1 Option 1: Changing GP Referral Criteria

Table 5.4:Expected impact of changing GP referral criteria upon marginal cost-
effectiveness

Parameters changed	Parameter value	LYs	QALYs	Total cost	Marginal cost per LY gained	Marginal cost per QALY gained
Sensitivity	77%	10.4691	8.1981	£908.18		
Sensitivity	82%					
Cost of	£20	10.4708	8.2026	£933.02	£14,622	£5,566
implementation	£40			£953.02	£26,393	£10,046
Sensitivity	87%					
Cost of	£20	10.4714	8.2058	£938.75	£13,543	£3,969
implementation	£40			£958.75	£22,402	£6,565

GP referral criteria may be altered such that more or less people, both with cancer and without cancer, may be sent for diagnostic tests. Increasing sensitivity would mean that people may be diagnosed at an earlier stage in the disease progression, such that they may not develop bowel cancer from their polyps, or they may not reach such an advanced stage of bowel cancer. The reduction in GP appointments would reduce costs, whilst the cost of implementation would increase them. Assuming a cost of implementation of £20, the marginal cost per QALY gained would be £5,566 and £3,969 for a 5% and 10% absolute improvement in sensitivity. If this cost per patient was doubled, the marginal cost per QALY gained would become £10,046 and £6,565, respectively.

The results for this option are highly dependent upon the following assumptions:

a. The transition probabilities are reasonable for modelling the disease natural history

The transition probabilities describing underlying disease progression were derived from ScHARR's colorectal cancer screening model (Tappenden *et al.* 2007), which was calibrated against national colorectal incidence and mortality data. If the probabilities are excessively high, the effectiveness of this option will be overestimated. Research suggests that there is no significant correlation between the time taken to be diagnosed and the outcome at diagnosis, (Khattak *et al.* 2006; Bharucha *et al.* 2005; Gonzalez-Hermoso *et al.* 2004) implying that this effect may be over-predicted in the model; however the ScHARR screening model provides the best available evidence surrounding the rate of progression.

b. It is possible to improve GP referral criteria such that sensitivity is improved whilst specificity is not reduced

There is no evidence around how GP criteria can be improved to increase sensitivity without decreasing specificity. This is an area requiring further research. The options analysis assumes that sensitivity can be improved by 5% and 10%; there is currently no evidence to suggest whether these are reasonable estimates. The model does not consider a scenario whereby specificity decreases as a result of an increase in sensitivity.

c. All people who die of bowel cancer are captured in the model

People who have underlying bowel cancer but die of other causes prior to diagnosis and hence do not consume bowel cancer resources are assumed to be outside of the scope of the economic analysis. Changing referral criteria may result in some of these people being identified, diagnosed and treated. The associated error is assumed to be small.

d. The cost of disseminating GP guidelines is £150,000

This is based on a subjective estimate for the production and dissemination of clinical guidelines.

e. The cost of training a GP is £100

In order for the revised guidelines to be valuable, the GPs must be trained to use them correctly. Based on the GRAF trial, (Jiwa, 2004), training is included as a one-off cost; further costs may be incurred for ongoing training, although these have not been included in the options analysis. The cost-effectiveness of improving the GP referral criteria is highly dependent on the cost of training and implementation.

f. Each GP refers around 10 patients with suspected bowel cancer pathology per year

This is clearly variable across the country, and is not supported by empirical evidence.

The effect of implementing screening in England has been assessed alongside this option using the ScHARR screening model (Tappenden *et al*, 2007). Since the disease may be detected by screening for many people who would have otherwise presented to their GP, screening is expected to reduce the effectiveness of this option. The ScHARR screening model assumes a cost of producing and disseminating guidelines of 50p per person who is over the age of 50 years old in England. Since there is no evidence around the potential effectiveness of this option, three different levels of effectiveness have been assessed by altering the probability of presenting symptomatically with each Dukes stage, shown in Table 5.5 below. The results of the analysis are shown in Table 5.6 overleaf.

Table 5.5: Sensitivity analysis of the probability of presenting symptomatically

	Effectiveness					
Probability of presenting symptomatically	Base case	Low	Medium	High		
With Dukes A	7.00%	9.50%	12.00%	14.50%		
With Dukes B	32.00%	33.25%	34.50%	35.75%		
With Dukes C	49.00%	49.63%	50.25%	50.88%		
With Dukes D	85.40%	85.71%	86.02%	86.33%		

	Absolutes				Marginals			Marginal cost effectiveness ratios	
Intervention	Costs	LYs	QALYs	Costs	LYs	QALYs	LYs	QALYs	
GP referral	£414.14	16.8653	14.3229	-	-	-	-	-	
criteria not									
revised									
Low									
effectiveness									
GP referral	£410.33	16.8696	14.3258	-£3.81	0.0043	0.0029	Dominates	Dominates	
criteria							no change	no change	
revised									
GP referral	£432.69	16.8816	14.3346	£22.36	0.0120	0.0088	£1866.82	£2531.54	
criteria									
revised plus									
screening									
Medium									
<u>CD</u> referrel	C405.07	16 0720	14 2207	C0 1C	0.0096	0.0059	Dominataa	Dominataa	
GP relefial	£405.97	10.07.39	14.3207	-20.10	0.0000	0.0056	Dominates	Dominates	
revised							no change	no change	
GP referral	£428.80	16 8853	1/ 3371	£22.82	0.011/	0.008/	£2006.62	£2709.83	
criteria	2420.00	10.0000	14.5571	222.02	0.0114	0.0004	22000.02	22109.00	
revised plus									
screening									
High									
effectiveness									
GP referral	£401.09	16.8781	14.3316	-£13.05	0.0128	0.0087	Dominates	Dominates	
criteria							no change	no change	
revised							_	_	
GP referral	£424.38	16.8889	14.3396	£23.29	0.0108	0.0080	£2162.71	£2906.65	
criteria									
revised plus									
screening									

Table 5.6: Revising GP referral criteria

This Table suggests that for a cost of 50p per person in England over the age of fifty years, improving GP referral criteria would provide additional health gains. Introducing screening in England in addition to improving GP referral criteria will increase costs and benefits, producing a marginal cost per QALY gained of around £2500 to £3000. Under currently acceptable levels of cost-effectiveness, this option could be considered cost-effective when combined with screening. However, it is important to note that this effect has been assessed simplistically by altering the probability of presenting symptomatically with Dukes A, Dukes B, Dukes C and Dukes D. Therefore, an underlying assumption has been made that revising GP referral criteria has the potential to improve Dukes stage at diagnosis without additional non-cancer patients being referred.

5.3.1.1 Uncertainty and implementability grading: 3C

The results of this option are highly dependent on a number of assumptions which are based on extremely limited data. Research is required concerning the way in which GP guidelines could be improved in order to increase sensitivity without decreasing specificity of the referral before this option could be considered in further depth.

5.3.2 Option 2: Increased Bowel Cancer Awareness

Parameters changed	Parameter value	LYs	QALYs	Total cost	Marginal cost per LY gained	Marginal cost per QALY gained
Probability of	Base case	10.4691	8.1981	£908.18		
cancer	Reduce by 1%	10.4702	8.1986	£909.50	£1,154	£2,572

Table 5.7: Estimated cost-effectiveness of increased bowel cancer awareness campaigns

There is limited evidence surrounding the costs or benefits which would be expected to result from the inception of a media campaign to raise awareness of the symptoms of bowel cancer. Assuming that the probability of developing cancer is reduced by around 1% due to earlier presentation, that the distribution of Dukes stage is altered to allow for diagnosis at an earlier stage for around 2% of people, and the cost for a media campaign per person in the model were £10, the marginal cost per QALY gained for this option is estimated to be £2,572.

Importantly, this estimate is likely to be optimistic. The costs included for this option include the cost of a small number of additional people presenting without bowel cancer. However, the media campaign may result in only a few more bowel cancer patients presenting and a large number of non-bowel cancer patients presenting who are worrying unnecessarily and increasing costs and pressures for diagnostic services. This extreme scenario has not been modelled, but should be taken into account if this option were to be considered in further detail.

The results for this option are highly dependent upon the following assumptions:

a. The probability of developing cancer is reduced by 1% due to earlier presentation

b. The cost per person in the model for a media campaign is £10

The cost of a media campaign will be dependent upon the type of campaign carried out. We are assuming that a cost of £10 per person consuming colorectal cancer resources will decrease the probability of developing cancer by 1%. There is no evidence around this relationship.

Screening is another means of encouraging patients to present earlier. Therefore, the rollout of screening throughout England will be a direct 'competitor' for this option. This option was also assessed using the ScHARR screening model, which assumed that the cost of a media campaign per person over the age of 50 years in England is £1. The results are shown in Table 5.8 below with a sensitivity analysis around the potential effectiveness of a media campaign as modelled for the GP referral criteria (see Table 5.3).

	Absolutes			Marginals			Marginal cost- effectiveness ratios	
Intervention	Costs	LYs	QALYs	Costs	LYs	QALYs	LYs	QALYs
No media campaign	£414.14	16.8653	14.3229	-	-	-	-	-
Low effectiveness								
Media campaign	£410.83	16.8696	14.3258	-£3.31	0.0043	0.0029	Dominates no media campaign	Dominates no media campaign
Media campaign plus screening	£433.19	16.8816	14.3346	£22.36	0.0120	0.0088	£1866.82	£2531.54
Medium effectiveness								
Media campaign	£406.47	16.8739	14.3287	-£7.66	0.0043	0.0058	Dominates no media campaign	Dominates no media campaign
Media campaign plus screening	£429.30	16.8853	14.3371	£22.82	0.0120	0.0084	£2006.62	£2709.83
High effectiveness								
Media campaign	£402.09	16.8781	14.3316	-£12.05	0.0128	0.0087	Dominates no media campaign	Dominates no media campaign
Media campaign plus screening	£425.38	16.8889	14.3396	£23.29	0.0108	0.0080	£2162.71	£2906.65

Table 5.8: Introducing a media campaign

The model suggests that implementing screening across England in addition to carrying out a media campaign produces a marginal cost per QALY gained of around £2500 - £3000. Again, however, the effectiveness of the option is highly uncertain.

5.3.2.1 Uncertainty and implementability grading: 3B

Given that there is limited evidence available surrounding the relationship between the costs and effects of a media campaign for bowel cancer, and that further research is likely to be required before a media campaign may be carried out, this option has been given a grade of 3B.

5.3.3 Option 3: Management of Emergency Presentations

Table 5.9: Estimated cost-effectiveness of increased stenting

Parameters changed	Parameter value	LYs	QALYs	Total cost	Marginal cost per LY gained	Marginal cost per QALY gained
Percent of	2.4%	10.4691	8.1981	£908.18		
emergency cases	10%	10.4696	8.1984	£910.38	£4,654	£6,757
stented	47.5%	10.4731	8.2008	£919.52	£2,860	£4,150

Using stenting as a bridge to surgery has been shown to improve patient outcomes, decrease complication rates and decrease the use of stomas (Targownick, 2004). Currently, only around 2% of emergency cases are stented. Increasing the use of emergency stenting to 10% would have only a small effect on costs or outcomes due to the small amount of people that may potentially benefit from a stent. However, increasing the use of emergency stenting to 47.5% (the maximum percent achievable suggested from the elicitation process), increases both costs and outcomes further; with an estimated marginal cost per QALY gained of £4,150.

The results of this option are highly dependent upon the following assumptions:

- a. Emergency stenting will have no effect upon quality of life, unless the patient dies during the stenting procedure (0.5%);
- b. There is a stenting success rate of 88% (Khot, 2002);
- c. Emergency stenting will reduce the number of stomas required by around 16%;
 Stomas may potentially increase the cost of treatment substantially; hence this

assumption could have a large impact on costs of treatment for stented patients.

- d. There is no difference in quality of life between people with or without an emergency stent;
- e. The cost of training is £1,250 per surgeon and 1 surgeon is required for every 3 patients able to receive emergency stenting in the model;
- f. If stenting is to be provided to 47.5% of all emergency patients, every patient that requires emergency stenting needs to be demographically able to be treated by a trained surgeon.

The roll-out of screening in England is expected to reduce the number of emergency presentations since the disease is anticipated to be detected at an earlier stage for those people in the screening age group. Therefore, the effectiveness of this option will be reduced following the implementation of screening. However, the cost of training surgeons may also be reduced if demographics allow. Therefore, whilst screening may reduce the total cost-effectiveness of this option, the relative cost-effectiveness per person should remain approximately the same.

5.3.3.1 Uncertainty and implementability grading: 2A

There is a little uncertainty surrounding the cost of training and patient quality of life, but with additional training stenting can be implemented imminently.

5.3.4 Option 4: Increasing the Use of Colonoscopy from 70% to 90% as an Alternative to Flexible Sigmoidoscopy

Parameters changed	Parameter value	LYs	QALYs	Total cost	Marginal cost per LY gained	Marginal cost per QALY gained
Percent of	70%	10.4691	8.1981	£908.18		
colonoscopies versus flexible sigmoidoscopies	90%	10.4802	8.2006	£843.79	-£5,812	-£25,661

Table 5.10: Estimated cost-effectiveness of increased colonoscopy use as an alternative to flexible sigmoidoscopy

Proximal cancers and adenomas which may not be picked up with a flexible sigmoidoscopy may be detected using colonoscopy. As complete colonoscopy can visualise the entire colon up to the caecum, the single-test sensitivity of colonoscopy is higher than hat for flexible sigmoidoscopy. This means that a small proportion of neoplasia which would have been missed at sigmoidoscopy would now be identified. This health effect is expected to be beneficial in terms of patient outcomes since more polyps and cancers are expected to be identified at an earlier stage, and also in terms of the avoidance of costs of patients representing and having further diagnostic tests or emergency surgery. It is anticipated that there would be a small cost of training for the staff carrying out a colonoscopy, which has been included in the total cost and is estimated to be £5 for each person in the model. This option is expected to dominate the base case scenario (i.e. the option produces a greater number of QALYs at a lesser cost than the base case scenario).

The results of this option are highly dependent upon the following assumptions:

a. There is a 29% chance that patients with distal colon cancer who receive a flexible sigmoidoscopy will be sent for a colonoscopy due to a polyp being found in the proximal colon;

This estimate is based on one American source from over ten years ago (Dinning, 1994). If the proportion of polyps which may be found in the proximal colon is greater than 29%, colonoscopy would have a reduced advantage over flexible sigmoidoscopy.

b. The transition probabilities are reasonable for modelling the disease natural history;

The transition probabilities were derived from ScHARR's colorectal cancer screening model (Tappenden *et al.* 2007). If these probabilities are excessively high, the effectiveness of this option will be overestimated.

c. If a person's polyp or cancer is undetected at endoscopy, they will not represent for a year;

If, for example, an individual with a high risk polyp remains undiagnosed despite diagnostic tests they have a probability of transiting to Dukes' A colorectal cancer

each year. Individuals may re-present and undergo subsequent endoscopic tests within a shorter interval than 1-year.

- d. There is a 25% and 50% chance that a person with a low- and high-risk adenoma respectively will re-present following a negative diagnosis; Around a third of people in the general population above age 50 are thought to have a polyp, and the majority of these never develop into cancer. There is limited evidence around the number of people with an adenoma that present with cancer and even less around what happens to those following a negative diagnosis. Therefore, based on personal communication, it has been assumed that some of the people who have been negatively diagnosed will re-present; hence there is a small probability that the adenoma will progress to being cancerous during this time.
- The cost of training to increase the use of colonoscopy would be around £50 e. per person that requires diagnostic testing for colorectal cancer.

This is difficult to predict, given the shift in who performs endoscopies; increasingly, nurses may now be trained to carry out these tests. The cost which is attributed to the increase in colonoscopies rather than the change in workmanship is subjective.

Screening is expected to increase the use of colonoscopy due to the additional tests required following a positive FOBT. Therefore, capacity and resource constraints may cause difficulties in using additional colonoscopies when screening has been rolled out However, the per-patient cost-effectiveness is unlikely to change significantly, unless many more diagnostic clinics are required to accommodate the additional colonoscopies.

5.3.4.1 Uncertainty and implementability grading: 2B

Whilst the proportion of adenomas/cancers detected by flexible sigmoidoscopy and the disease natural history are both based on limited data, this option is anticipated to be cost saving despite these uncertainties and relatively easily to implement without much further work.

5.3.5 **Option 5: Improving Colonoscopy Completion Rates via National Training** Programmes

Table 5.11:	Estimated cost-effectiveness of improved colonoscopy completion rates

Parameters changed	Parameter value	LYs	QALYs	Total cost	Marginal cost per LY gained	Marginal cost per QALY gained
Number of	10%	10.4691	8.1981	£908.18		
inadequate colonoscopies	5%	10.4713	8.1998	£912.29	£1,842	£2,432

Halving colonoscopy inadequacy rates means that 5% of people requiring diagnostic tests for bowel cancer who would have needed a barium enema following incomplete colonoscopy will no longer require a second, less sensitive test. This reduces the cost of the test, although additional training would be required to improve completion rates. The model suggests that improving colonoscopy completion rates would result in a slight increase in both costs and outcomes.

The results of this option are highly dependent upon the following assumptions:

a. The number of inadequate colonoscopies can be halved through training;

b. The cost of training will be around £50 per person requiring diagnostic tests.

This option will help to reduce the costs of screening by reducing the number of barium enemas required following an inadequate colonoscopy. Therefore, this option may be considered slightly more effective than without screening, although additional costs of training may also be required.

5.3.5.1 Uncertainty and implementability grading: 2A

The relationship between the cost and the effectiveness of this option is uncertain, although training programmes have already been piloted to improve completion rates; hence implementation is unlikely to require much additional research.

5.4 TREATMENT, FOLLOW-UP AND PALLIATIVE CARE OPTIONS

The costs and QALYs for these options are presented in terms of the model population (people consuming colorectal cancer resources) throughout this section; so that they are directly comparable with options 1 - 5. However, Table 5.22, at the end of this section presents the marginal cost per LY and QALY gained by the colorectal cancer population within the model.

5.4.1 Option 6: Pre-Operative versus Selective Post-Operative Radiotherapy for Rectal Cancer Patients

Table 5.12: Estimated cost-effectiveness of greater uptake of pre-operative radiotherapy for the adjuvant treatment for rectal cancer interval i

Parameters changed	Parameter value	LYs	QALYs	Total cost	Marginal cost per LY gained	Marginal cost per QALY gained
Percentage of patients undergoing pre- operative versus	Based on CR07 and expert elicitation	10.4691	8.1981	£908.18		
post-operative radiotherapy	All postop become pre-op	10.4695	8.1986	£912.64	£10,408	£9,980

The CR07 trial suggests that pre-operative radiotherapy may improve disease-free survival in rectal cancer patients in comparison to selective postoperative radiotherapy. Within this study, only a small proportion of patients received postoperative radiotherapy. Therefore, using disease-free survival curves from this trial, we have assumed that all of the patients that would receive postoperative radiotherapy could receive preoperative radiotherapy instead. This results in an estimated marginal cost per QALY gained of £9,980.

The results of this option are highly dependent upon the following assumptions:

- a. Pre-operative radiotherapy improves disease-free survival in rectal cancer patients as in CR07;
- b. There is a 5% and 11% probability of local recurrence for patients receiving pre- and post-operative radiotherapy respectively;
- c. Pre-operative radiotherapy costs the same per patient as post-operative radiotherapy;
- The cost of training per surgeon is £1250;
 There is limited evidence around the cost of training surgeons, although this estimate is loosely based on personal communication.

e. There would be approximately 1 surgeon trained for every 2 patients requiring preoperative instead of postoperative radiotherapy.

Screening is expected to affect this option by marginally decreasing the required use of radiotherapy. Therefore, the cost of training and the effectiveness of the option will decrease almost linearly, producing the same relative effect.

5.4.1.1 Uncertainty and implementability grading: 2A

The cost of training for a surgeon to be capable of carrying out preoperative radiotherapy is highly uncertain and the effectiveness data is based only on one trial (CR07), although it is large and recent. Therefore, since this option could be implemented without a large amount of additional research it has been given a grade of 2A.

5.4.2 Option 7: Improving Pathology and/or Surgical Expertise

Table 5.13: Estimated cost-effectiveness of improving pathology and/or surgical expertise

Parameters changed	Parameter value	LYs	QALYs	Total cost	Marginal cost per LY gained	Marginal cost per QALY gained
Hazard ratio	1	10.4691	8.1981	£908.18		
for DFS curve	0.85	10.4763	8.2035	£907.15	-£142	-£190
	0.7	10.4836	8.2090	£892.94	-£1,048	-£1,405

Improving surgical expertise is expected to reduce complications and operative mortality, but will incur a cost of training. Therefore, improved outcomes are modelled through the application of a relative hazard to the disease-free survival curves and by halving the probability of operative mortality. The simulation suggests that there is a benefit in life years and QALYs gained as a result of improving pathology or surgical expertise. However, because the model predicts that over 50% of patients will be alive after 5 years, a small change in the hazard ratio such as 0.95 or 0.9 does not have a large effect on the disease-free survival.

In addition, there is a considerable degree of uncertainty surrounding the costs and health impacts resulting from the implementation of this option. Firstly, metastatic recurrence rates may be reduced further and disease-free survival may last longer as a result of improvements in pathology or surgical expertise; therefore we consider our estimate to be conservative. However, the cost of improving pathology services is also very uncertain and may be much greater than our estimate of £1500 per bowel cancer patient. Our assumption that one pathologist will examine around 10 colorectal specimens per year is also uncertain. However, under the assumptions outlined above, this option is dominating (decreases costs whilst improving outcomes) until the cost per bowel cancer patient becomes greater than around £2000. The results are sensitive to any changes to these costs.

The results of this option are highly dependent upon the following assumptions:

- a. Improving surgical resection or pathology will halve operative mortality;
- Improving surgical resection or pathology is expected to improve diseasefree survival by a relative risk of 0.7;
 As a result of this, the number of metastatic recurrences is expected to decrease and, therefore, overall survival will increase.
- c. The improvements have no effect upon quality of life;

d. The cost of improving surgical resection or pathology is around £1500 per colorectal cancer patient.

This cost of this option is variable across England, and according to whether the improvement is being made in surgery or pathology expertise. There is no evidence around the cost of improvements in these areas.

Screening is expected to reduce the number of people requiring surgery and pathology, however the per-person cost-effective result is expected to be the same.

5.4.2.1 Uncertainty and implementability grading:

- Surgical expertise: 2A;
- Developing pathology services: 3B.

There is very little evidence surrounding the cost required in order to produce the assumed effectiveness, particularly with regards to developing pathology services. However, trials have been undertaken to evaluate the extent to which improvements in surgery can improve health outcomes (Martling *et al.* 2000).

5.4.3 Option 8: The Use of Laparoscopic versus Open Colon Surgery

Table 5.14:	Estimated cost-effectiveness increasing the use of laparoscopic surgery
	for the treatment of colon cancer

Parameters changed	Parameter value	LYs	QALYs	Total cost	Marginal cost per LY gained	Marginal cost per QALY gained
Percentage of	5%	10.4691	8.1981	£908.18		
versus open surgery	50%	10.4680	8.1973	£911.01	-£2,646	-£3,397

There is little evidence in terms of a difference in quality of life between laparoscopic and open surgery and the evidence regarding disease-free survival and overall survival suggests no significant difference. Therefore, the model assumes no difference between health outcomes, although some uncertainty is modelled around this. In terms of cost, the model suggests that laparoscopic surgery is marginally more expensive despite the reduced hospital stay owing to the cost of surgery and training. Therefore, the option to increase the use of laparoscopic surgery is dominated (more expensive and slightly lower effectiveness) by the base case scenario. Importantly, however, the difference in the cost is very small and some surgeons would suggest that there are health benefits in using laparoscopic surgery. Furthermore, in the future patients may opt for laparoscopic surgery given the choice.

The results of this option are highly dependent upon the following assumptions:

- a. There is no difference in patient quality of life between those receiving open and laparoscopic surgery;
- b. Laparoscopic surgery does not increase disease-free survival or overall survival.

Screening is again expected to reduce the number of people requiring surgery; however, the per-person cost-effectiveness is expected to be the same.

5.4.3.1 Uncertainty and implementability grading: 1A

A number of trials have compared laparoscopic versus open surgery and there is a relatively large amount of information regarding the impact on health outcomes and costs. Currently, significant differences in health utilities have not been demonstrated, and further research may be warranted in this area. However, the intervention has been recommended as an alternative to open surgery by NICE and may be implemented immediately.

5.4.4 Option 9: The Use of Alternative Adjuvant and Palliative Chemotherapies

Parameters changed	Parameter value	LYs	QALYs	Total cost	Marginal cost per LY gained	Marginal cost per QALY gained
		10.4691	8.1981	£908.18		
Hazard ratio for	0.85	10.4714	8.2000	£902.84	-£2,288	-£2,879
DFS curve	0.7	10.4745	8.2023	£896.67	-£2,148	-£2,777
Overall survival	OS from	10.4751	8.2016	£905.24	-£487	-£836
increase	Hurwitz 2004					

Table 5.15: Estimated cost-effectiveness using alternative adjuvant and palliative chemotherapies for the treatment of colon cancer

The option to use alternative adjuvant or palliative chemotherapy to improve disease-free survival improves both costs and outcomes, assuming that the new chemotherapy costs the same as current standard treatments. However, it is highly likely that a new chemotherapy would be more costly than existing treatments. The threshold at which improving adjuvant chemotherapy is not cost-saving is when the drug costs an additional £200 or £400 per bowel cancer patient, according to whether the disease-free survival is improved by a hazard ratio of 0.85 or 0.7 respectively. For palliative chemotherapy, the option is no longer cost saving when the new chemotherapy costs an additional £100 per bowel cancer patient. For adjuvant chemotherapy, the assumptions concerning improvements in disease-free survival are likely to be conservative. However, in terms of palliative chemotherapy, the AVF2107g Bevacizumab trial reported by Hurwitz and colleagues (2004) presents substantially better overall survival outcomes than that estimated by the FOCUS trial used within the base case model. Therefore, a considerable improvement in palliative chemotherapy would be required to provide the cost-effectiveness scenario suggested by the model.

The results of this option are highly dependent upon the following assumptions:

- a. A relative hazard ratio of 0.70-0.85 represents an achievable target for future adjuvant chemotherapies;
- b. The observed survival benefits within the AVF2107g Bevacizumab trial reported by Hurwitz (2004) represent an achievable target for future palliative chemotherapies;

c. In order to achieve this effectiveness, the cost of a new chemotherapy is similar to the current standard treatment.

Screening is expected to reduce the number of patients requiring chemotherapy, although the per-patient cost-effectiveness is expected to remain approximately the same.

UNCERTAINTY AND IMPLEMENTABILITY GRADING: 2B

NICE Technology Assessments provide estimates around the relationship between the cost and effectiveness of new chemotherapies for bowel cancer. These results are optimistic since they assume that the new drug incurs no additional cost in comparison to the current standard chemotherapy. However, this option could be implemented following approval of the technology by NICE. The further research and development of the new chemotherapy regimen would most likely be undertaken by its manufacturer and would not incur a cost to the NHS.

5.4.5 Option 10: The Use of Enhanced Recovery Programme Following Surgery

Parameters changed	Parameter value	LYs	QALYs	Total cost	Marginal cost per LY gained	Marginal cost per QALY gained
Cost of ERP		10.4691	8.1981	£908.18		
		10.4702	8.1989	£859.25	-£44,112	-£60,536

Table 5.16: Estimated cost-effectiveness of enhanced recovery programmes

Enhanced Recovery Programmes lead to a decrease in hospital stay and hence a reduction in costs. Consequently the analysis suggests that this option would dominate the current service. It should also lead to improved availability of beds. However, there is a lack of large scale RCT evidence on the quality of life and mortality impact of the ERP initiative. Early studies indicate no marked increase in complication rates or readmission rates indicative of a marked detrimental impact on quality of life. Shortened lengths of hospital stay may be associated with improved QALYs, although the main impact of this intervention is to reduce associated costs. The central estimate therefore is based on no adverse or beneficial QALY impact. The small evidence base makes it difficult to estimate the costs associated with setting up and running an ERP. The cost savings shown are based upon an assumed average additional running cost of £140 per bowel cancer patient.

The results of this option are highly dependent upon the following assumptions:

- a. An Enhanced Recovery Programme has no effect upon quality of life; There is no evidence to suggest that ERPs result in any negative health outcomes or improvements in patient quality of life; although some uncertainty has been incorporated around this.
- b. An Enhanced Recovery Programme shortens hospital stay by between 2 and 10 days for open surgery, and between 1 and 6 days for laparoscopic surgery;
- c. The initial costs of setting up an ERP are estimated to be around £140 per colorectal cancer patient.

Screening is expected to reduce the number of people requiring surgery and hence the number of people requiring an Enhanced Recovery Programme. Again, there is no evidence to suggest that this will have any real effect upon the cost-effectiveness of the option per patient.

5.4.5.1 Uncertainty and implementability grading: 1A

Whilst it may be useful to carry out further research surrounding the effects of ERPs on health utility, the analysis suggests that this option is unlikely to result in any negative health outcomes, whilst being cost saving. Research may be required at each hospital to determine the most efficient way of setting up this programme; however the major research into ERPs has been carried out via trials and pilot sites.

5.4.6 Option 11: Intensive Follow-Up

Table 5.17: Estimated cost-effectiveness of intensive follow-up

Parameters changed	Parameter value	LYs	QALYs	Total cost	Marginal cost per LY gained	Marginal cost per QALY gained
Percent increase in	Base case	10.4691	8.1981	£908.18		
overall survival	5%	10.4714	8.1996	£916.75	£3,736	£5,651
	10%	10.4720	8.2000	£916.53	£2,856	£4,330

Table 5.18: Follow-up tests currently assumed in the model

	Year 1	Year 2	Year 3	Year 4	Year 5
CEA	3	2	2	0	0
СТ	1	1	1	0	0
General examination	1	1	1	1	1
Colonoscopy	0	0	0	0	1

Table 5.19: Additional tests to those assumed in the model

	Year 1	Year 2	Year 3	Year 4	Year 5
CEA			1		1
СТ	1	1		1	

There is little evidence surrounding the effect of intensity of follow-up regimes upon health outcomes. The ongoing FACS trial aims to improve overall survival by 4% using a more intensive follow-up regime. Therefore, based on this estimate, we have estimated the cost-effectiveness of the above intense follow-up regime if it could provide a 5% or 10% improvement in survival for those patients who suffer metastatic recurrence. If a 5% improvement were made the cost per QALY gained would be around £5,631, in comparison to a 10% improvement which would provide a marginal cost per QALY gained of around \pounds 4,330. The evidence concerning the benefits of follow-up is very limited; if intensive follow-

up provided no improvement in health outcomes, this option would certainly not be worthwhile considering as it would be dominated by more relaxed follow-up schedules.

The results of this option are highly dependent upon the following assumptions:

a. The current and future follow-up regimes are as shown in Tables 5.18 and 5.19;

The current strategy is based upon data collected from around 30 centres around England. This is extremely variable. The future strategy is based upon the most intensive of these.

b. The effect of increasing follow-up intensity is to improve overall survival by 5% or 10%;

The FACS trial suggests that a more intense regime would increase survival by 4%.

c. Increasing follow-up intensity has no effect upon disease-free survival;

d. No further training is required in order to increase follow-up intensity.

Screening is expected to affect this option by reducing the number of people requiring followup as a result of catching the disease at an earlier stage. However, the cost-effectiveness per patient is again expected to be similar.

5.4.6.1 Uncertainty and implementability grading: 3B

Although a large trial has been carried out in this area (FACS), there is limited evidence surrounding the extent to which a more intensive follow-up programme improves health outcomes. Before a more intensive programme may be considered, further research would be required around what is the 'optimal' intensity of follow-up.

5.4.7 Option 12: Increased Liver/Lung Resection for Metastatic Disease

Table 5.20: Estimated cost-effectiveness of increasing liver/lung resections for patients with metastatic bowel cancer

Parameters changed	Parameter value	LYs	QALYs	Total cost	Marginal cost per LY gained	Marginal cost per QALY gained
Percentage of people with metastatic	10%	10.4691	8.1981	£908.18		
cancer receiving liver resection	20%	10.4695	8.1983	£909.02	£1,993	£4,460

If more effective chemotherapies were available for downsizing liver/lung tumours, a greater number of bowel cancer patients would become eligible for liver or lung resections. Assuming that the probability of successful downstaging was increased from 50% to 75%,

approximately 20% of metastatic patients would be suitable to have liver or lung resections. The benefits would be minimal due to the small number of people that this would affect, however, the costs are also reasonably low (assuming that the new downstaging chemotherapy would be no more expensive than the current chemotherapies). However, if in order to improve downstaging chemotherapies the cost of the drugs would increase, this option is unlikely to be considered cost-effective.

The results of this option are highly dependent upon the following assumptions:

- a. Downstaging chemotherapies can be improved such that 75% of metastatic tumours can be downstaged rather than around 50%;
- b. The downstaging chemotherapy will bear no additional costs;
- c. The cost of training will be £1250 per surgeon; and each surgeon will perform around 4 liver/ lung resections per year.

This cost estimate is based loosely on personal communication since there is limited evidence around the cost of training surgeons.

The number of people following this route is so small that screening is likely to have a minimal effect upon this option.

5.4.7.1 Uncertainty and implementability grading: 2B

There is uncertainty around the effect of improvements in downstaging chemotherapies upon the potential use of liver or lung resections for metastatic disease. There is also some uncertainty around the cost of this option. However, following research around downstaging chemotherapies, this option would be reasonably easy to implement.

5.4.8 Option 13: Increasing Palliative Bypass and Palliative Stenting

Table 5.21: Estimated cost-effectiveness of increasing palliative bypass and palliative stenting

Parameters changed	Parameter value	LYs	QALYs	Total cost	Marginal cost per LY gained	Marginal cost per QALY gained
Percentage of metastatic patients who are unfit for	50%	10.4691	8.1981	£908.18		
palliative surgery rather than best supportive care	75%	10.4691	8.1982	£910.66	Dominated	£24,137

Assuming that the proportion of palliative surgery (bypass and stenting) carried out in comparison to best supportive care is increased from 50% to 75%, increasing the use of palliative surgery is unlikely to represent value for money for the NHS. Assuming that the

option does not extend survival, the only health outcome which is improved in the model is quality of life. Since there is little evidence in terms of quality of life for palliative surgery or best supportive care, we have modelled the relative health utility associated with best supportive care has been modelled using a uniform distribution of between 0 and 1. Therefore, we have assumed an average relative decrement of 0.5. Since we have assumed that a patient will survive for an average of three to four months following palliative surgery *or* best supportive care, the small increase in health-related quality of life has little effect on the resulting cost-effectiveness estimates. Therefore, costs are incurred for minimal benefit.

The results of this option are highly dependent upon the following assumptions:

- a. People receiving palliative care who are unable to receive chemotherapy have a 50:50 probability of receiving best supportive care and palliative surgery;
- b. There is no additional training cost to increase the use of palliative surgery;
- c. There is a quality of life decrement for patients receiving best supportive care of 0.5 (Uniform [0,1]). Whilst there is no evidence surrounding this assumption, clinical experts have suggested that a disutility should be applied to patients receiving best supportive care in comparison to those receiving active palliative treatment.

The number of people requiring palliative care may be reduced slightly, although the perpatient cost-effectiveness is not expected to be significantly different.

5.4.8.1 Uncertainty and implementability grading: 3B

There is limited evidence surrounding the effects of increasing the use of palliative surgery and stenting upon quality of life. The proportion of people currently receiving surgery or stenting instead of best supportive care is also unknown. However, given further research around the benefits of surgery, the option could be implemented with relative ease.

Each of the costs, life years and QALYs gained for the above treatment, follow-up and palliative care options have been expressed in terms of the bowel cancer population in the model. The marginal cost per LY and QALY gained estimates remain the same.

Opti	on	Marginal cost	Marginal LYs	Marginal QALYs
			gained	gained
6	Pre versus postop RT	£12.96	0.0012	0.0013
7	Improve surgery/pathology	-£44.31	0.0423	0.0158
8	Lap versus open	£8.24	-0.0031	-0.0340
	Alternative adjuvant			
9a	chemotherapies	-£15.53	0.0068	0.0078
	Alternative palliative			
9b	chemotherapies	-£8.55	0.0176	-0.0018
	Enhanced recovery			
10	programme	-£142.25	0.0032	-0.0079
11	Intensive vs relaxed follow-up	£24.92	0.0067	0.0021
12	Increased liver/lung resection	£2.45	0.0012	-0.0051
13	Increase palliative surgery	£7.21	0.0000	-0.0003

Table 5.22: Results of the options expressed in terms of the bowel cancer subgroup

5.5 SUMMARY RESULTS

Figure 5.1 overleaf presents the marginal costs and QALY impact for each option compared to the baseline estimates for the current bowel cancer service. This clearly demonstrates that Options 1, 3, 4, 7, 9 and 10 stand out from the set of options considered as worthy of special consideration. Table 5.23 overleaf presents the central estimate results for the baseline and each of the options considered for a person consuming bowel cancer service resources, including patients with a negative diagnosis of bowel cancer. The uncertainty surrounding the results is clear from the confidence intervals around the central estimates for both costs and QALYs. In nearly all cases, these confidence intervals span zero; suggesting that all of the options could potentially have a minimal effect upon costs and/ or QALYs. The quality of life impacts of all options lie within +/- 0.01 QALYs for the average person in the bowel cancer system. The option to improve GP referral criteria incurs additional costs in excess of £20 per person in the system and the options to increase the use of colonoscopy instead of flexible sigmoidoscopy and to introduce an Enhanced Recovery Programme demonstrate a large cost saving. The options to improve GP referral criteria (option 1), increase the use of stenting as a bridge to elective surgery (option 3), increase the use of colonoscopy (option 4), improve surgical expertise or develop pathology services (option 7) and to improve adjuvant or palliative chemotherapy (option 9) produce the greatest improvements in QALYs.




Marginal effectiveness (QALYs)

Table 5.24 presents the difference from the base case in the cost of each part of the pathway and the number of people in each cancer stage for each option. Where zero difference is expressed there is no more than five units' difference in the results between the option and the base case. This table suggests that these outcomes are predominantly affected by the options to improve GP referral criteria (option 1), introduce a media campaign (option 2) and increase the use of colonoscopy as an alternative to flexible sigmoidoscopy (option 4).

Option		Cost (£)	Life years	QALYs	Marginal cost (£)	Marginal life years	Marginal QALYs	Cost rank	QALY rank	
	Baseline	908.18	10.4691	8.1981						
1	GP referral criteria -	033.03	10 4709	8 2026	24.85	0.0017	0.0045	1/	2	
	sensitivity	933.02	10.4706	0.2020	(-32.33, 84.23)	(-0.0724, 0.0722)	(-0.0508, 0.0586)	14		
2	Modia campaign	000 50	10 4702	9 1096	1.32	0.0011	0.0005	7	10	
2	Media campaign	909.00	10.4702	0.1900	(-64.38, 63.31)	(-0.0772, 0.074)	(-0.0601, 0.0567)	I	10	
3	Emorgonovictonting	010 52	10 /731	0 2000	11.34	0.0040	0.0027	13	1	
3	Emergency stenting	919.52	10.4731	0.2000	(-46.85, 65.58)	(-0.0678, 0.0767)	(-0.0525, 0.0589)	15	4	
1	Colonoscopy versus	942 70	10 4902	8 2006	-64.39	0.0111	0.0025	1	Б	
4	flexi sig	043.79	10.4602	0.2000	(-120.52, -11.54)	(-0.0615, 0.0839)	(-0.054, 0.0586)	I	Э	
5	Colonoscopy	012.20	10 4712	9 1009	4.11	0.0022	0.0017	10	7	
5	completion rates	912.29	10.4715	0.1990	(-49.75, 56.92)	(-0.0725, 0.0765)	(-0.0545, 0.0589)	10	1	
6	Bro vorque poston BT	012.64	10 4605	9 1096	4.46	0.0004	0.0004	11	11	
0	Fie versus postop KT	912.04	10.4095	0.1900	(-46.71, 58.97)	(-0.0674, 0.074)	(-0.0527, 0.0566)	11		
7	Improve	007 15	10 4762	9 2025	-1.03	0.0072	0.0054	5	1	
'	surgery/pathology	907.15	10.4703	0.2035	(-51.7, 45.75)	(-0.0626, 0.0811)	(-0.0481, 0.0617)	5		
Q		011 01	10.4680	8 1073	2.84	-0.0011	-0.0008	0	14	
0	Lap versus open	911.01	10.4000	0.1975	(-53.97, 62.71)	(-0.0745, 0.0688)	(-0.0569, 0.0538)	9		
02	Alternative adjuvant	902.84	10/171/	8 2000	-5.34	0.0023	0.0019	З	6	
34	chemotherapies	302.04	10.4714	0.2000	(-31.83, 24.61)	(-0.0596, 0.0647)	(-0.0464, 0.05)	5	0	
Qh	Alternative palliative	905 24	10 /751	8 2016	-2.94	0.0060	0.0035	1	3	
55	chemotherapies	505.24	10.4751	0.2010	(-6.65, -0.31)	(0.0006, 0.0128)	(0.0004, 0.0074)	-	3	
10	Enhanced recovery	859 25	10 4702	8 1989	-48.93	0.0011	0.0008	2	a	
10	programme	000.20	10.4702	0.1505	(-107.93, 12.75)	(-0.0707, 0.08)	(-0.0535, 0.0616)	Ľ	5	
11	Intensive versus	916 75	10 4714	8 1996	8.57	0.0023	0.0015	12	8	
	relaxed follow-up	510.75	10.4714	0.1000	(-54, 73.56)	(-0.0697, 0.0781)	(-0.0531, 0.0598)	12	<u> </u>	
12	Increased liver/lung	909.02	10 4695 8 1983	9 02 10 4695 8 1983	8 1983	0.84	0.0004	0.0002	6	12
	resection	000.02	10.4000	0.1000	(-43.06, 41.23)	(-0.0653, 0.0696)	(-0.0501, 0.0536)	0	12	
13	Increase palliative	910.66	10 4691	8 1082	2.48	0.0000	0.0001	8	13	
	surgery	510.00	10.4001	0.1002	(1.12, 4.27)	(0, 0)	(0, 0.0002)	0	10	

Table 5.23: Summary of central estimate results for the options

	Base	Option													
	case	1	2	3	4	5	6	7	8	9a	9b	10	11	12	13
Mean time until death	5206	0	0	0	0	0	0	8	0	0	0	0	0	0	0
St dev of time until death	3454	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cost of diagnosis: no cancer	17905	0	0	15	-6	0	6	8	18	0	0	7	13	19	0
Cost of diagnosis: polyps	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cost of diagnosis: CRC	42	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cost of rectal cancer treatment	1948	47	40	0	-326	10	6	-26	0	-20	0	-41	7	0	0
Cost of colon cancer treatment	807	-6	0	-7	10	0	0	0	0	0	0	0	0	0	0
Total number of polyps	20329	22	-64	446	545	15	352	-802	63	-117	-109	-1744	298	9	89
Total number of cancers	15167	104	-19	-78	381	-24	6	-596	2322	-516	-94	45	254	11	81
No. of low risk polyps diagnosed	1645	21	-35	0	0	-14	0	0	0	0	0	0	0	0	0
No. of high risk polyps diagnosed	345	0	0	0	-33	0	0	0	0	0	0	0	0	0	0
No. of cancers treated electively	38	0	0	0	-20	-14	0	0	0	0	0	0	0	0	0
No. of elective Dukes A diagnosed	1607	19	-36	0	17	0	0	0	0	0	0	0	0	0	0
No. of elective Dukes B diagnosed	289	0	0	0	-28	0	0	0	0	0	0	0	0	0	0
No. of elective Dukes C diagnosed	43	0	0	0	-14	0	0	0	0	0	0	0	0	0	0
No. of elective Dukes D diagnosed	93	0	0	0	0	0	0	0	0	0	0	0	0	0	0
No. of emergency cases	90	0	0	0	0	0	0	0	0	0	0	0	0	0	0
No. of Dukes A (emergency)	64	0	0	0	-19	0	0	0	0	0	0	0	0	0	0
No. of Dukes B (emergency)	56	0	0	0	0	0	0	0	0	0	0	0	0	0	0
No. of Dukes C (emergency)	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
No. of Dukes D (emergency)	19	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 5.24: Summary of other model outcomes for each option

5.6 CONCLUSIONS ON THE OPTIONS ASSESSMENT

The model suggests that the most cost-effective option for improving outcomes for bowel cancer patients is to increase the use of colonoscopy from 70% to 90% as an alternative to flexible sigmoidoscopy. Whilst the assumptions in the model may affect the extent to which this option will benefit patients, it is expected to both improve health outcomes and produce cost-savings. Future research concerning the natural history of the disease and the probability of polyps and cancers being detected in patients with distal colon cancer would be valuable. The introduction of an Enhanced Recovery Programme is also cost saving with initial indications of a low associated risk of detrimental clinical outcomes. This option is again relatively robust and at an advanced stage of development for implementation.

The model suggests that the most costly option would be the further development of GP referral criteria guidelines, although this is also associated with a reasonable improvement in life years gained. This assumes that improving GP referral criteria will allow GPs to detect the cancer at an earlier presentation, and hence an earlier stage in some patients. This option is highly uncertain due to the lack of evidence surrounding disease progression and the cost of implementation. It would also require substantial further research in order to assess how changes in referral criteria will affect GP referrals, such that specificity is not decreased as a result of increasing sensitivity since this would lead to worsened health outcomes. Greater knowledge is required regarding the relationship between symptoms and disease progression.

Increasing the use of emergency stenting is expected to be very effective for a small number of patients consuming bowel cancer resources, but is associated with a relatively high cost. Options 7 and 9, to improve surgical resection and/or pathology and to improve adjuvant or palliative chemotherapies, are associated with improvements in health outcomes at a relatively low cost; providing that for option 7 the cost of improvements in pathology are not greater than the modelled costs, and for option 9 that the new chemotherapies. All of these options would provide health benefits; however there is uncertainty surrounding the necessary costs required to provide the amount of health benefit. In the case of option 9, this will depend upon new and currently unknown chemotherapy costs and effectiveness.

Many of the options assessed within the model display huge variability due to the large amount of uncertainty associated with both the base case model and the options. The confidence intervals around the results suggest that it is unlikely that increasing the use of colonoscopy and introducing an Enhanced Recovery Programme will not be cost saving. However, since there is very little evidence regarding health utility scores for bowel cancer services, there is a considerable degree of uncertainty associated with all of these options in terms of their impact upon quality of life. This is a clear area in which further research would be merited.

The effect of introducing bowel cancer screening across England upon the treatment options is expected to be minimal, in that the total costs and benefits may be reduced slightly; however the relative effects of each of the treatment options are not expected to be

markedly different. Furthermore, the current FOBT test has been shown to have a low sensitivity. However, the options around presentation and referral are likely to be largely affected by the introduction of screening throughout England. The effect of these options is likely to be reduced because of screening, although the ScHARR screening model (Tappenden *et al.* 2007) suggests that they do have the potential to provide some benefit alongside screening using the FOBT 60-69 screening test.

6.1 SUMMARY OVERVIEW

The main results consist of two components:

- The total current baseline cost model estimates (sub-section 6.2);
- The options model estimates (sub-section 6.3).

6.2 CURRENT BASELINE COST SUMMARY

Table 6.1:Summary of baseline costs

	Patients	Total mean cost (£)	Mean cost per patient	95% CI Lower bound (£)	95% CI Upper bound (£)	
			(£)			
А	Diagnosis all patients	£290,724,484	£379	£335	£414	
В	Total primary rectal treatment	£71,868,979	£12,037	£11,110	£12,940	
С	Total primary colon treatment	£128,759,653	£8,808	£8,305	£9,322	
D	Total follow-up	£271,056,209	£11,183	£9,448	£12,520	
Е	Total stoma care	£52,076,567	£1,279	£1,107	£1,448	
F	Total palliative care	£118,552,980	£7,360	£5,963	£8,880	
G	High-risk patients	£53,758,184	£1,978	£1,978	£1,978	
Н	Screening Cost	£112,828,886	-	-	-	
Ι	(A+B+C+D+E+F+G+H)	£1,099,625,942	-	-	-	
J	Incidence patients	£419,562,097	£16,099	£15,078	£17,276	
Κ	Prevalence patients	£662,909,679	£6,257	£5,831	£6,610	
L	Non-cancer patients	£270,129,193	£365	£322	£399	
Μ	Total cost of illness (also = I)	£1,099,625,942	£1,242	£922	£1,654	

The total cost of illness was estimated at £1.1bn. The total cost consists of the prevalence cost (£662.9m), non-cancer patient costs (£270.1m), screening cost (£112.8m) and the cost of high-risk patients; (£53.8m) (Table 6.1 rows K+L+G+H). The incidence cost was estimated at £419.6m which represents the treatment cost of all newly diagnosed patients within one year.

The breakdown of the costs by their respective point in the treatment pathway is summarised in Table 6.1. The largest cost as a proportion of the total cost of illness is the cost of diagnosis which makes up 26.4% of the overall cost. The next significant cost is that of the prevalent patients follow-up cost estimated at 24.7% of the total cost of illness.

A very large proportion of the diagnosis cost is due to the cost of those patients who are found not to have cancer but who present as suspected bowel cancer cases (non-cancer patients). The cost of the non-cancer patients going through diagnosis and returning as negative bowel cancer patients was £270.1m. Those patients who were diagnosed as positive bowel cancer cases were estimated in the model to cost £20.6m.

The mean cost per patient for rectal cancer treatment was estimated at £12,037 in comparison with the mean cost of colon cancer treatment of £8,808. Rectal cancer treatment was estimated to cost more than colon cancer treatment due to three reasons. The first reason was because in the baseline model there are a higher proportion of patients who undergo stomas and stoma reversal for rectal cancer. Secondly, a proportion of rectal cancer patients undergo pre-/post-operative chemoradiation. The third reason is due to the overall higher numbers of rectal cancer patients undergoing adjuvant chemotherapy.

The total cost of rectal follow-up of $\pounds 68.6m$ comprises surveillance costs of $\pounds 6.9m$ and recurrence treatment costs of $\pounds 61.8m$. The total cost of colon follow-up of $\pounds 207.5m$ comprises surveillance costs of $\pounds 17.6m$ and recurrence treatment costs of $\pounds 189.9m$.

The stoma care cost has been estimated as an annual cost of all prevalent permanent stoma costs related to bowel cancer. The total cost of stoma care was estimated at $\pm 52m$. This consisted of a stoma care cost of $\pm 27.7m$ for those previously undergoing rectal surgery and $\pm 24.3m$ for that previously undergoing colon surgery. The mean cost per year was calculated as $\pm 1,279$ per patient.

The total palliative care costs can be broken down by the palliative intervention costs and the end of life costs in the treatment of bowel cancer. The estimated total palliative care cost for bowel cancer in England was £118.6m.

The total screening cost is estimated at £112.8m. This cost includes the cost of the screening programme for those aged 60 to 69 and the additional treatment cost in the first year for those patients who are diagnosed.

Increased-risk patients account for a smaller proportion of the cost at 5.5% of the overall total cost of illness and are estimated at £53.8m. There is a high degree of uncertainty surrounding this as data sources were very limited for the estimation of this cost.

6.3 OPTIONS MODEL RESULTS SUMMARY

The second phase of this study involved the development of a discrete event simulation model to estimate the expected costs and health gains resulting from a number of potential options for service reconfiguration.

Rather than modelling the incident and prevalent cohorts of patients who currently consume bowel cancer services, the options model estimates the expected lifetime costs and health outcomes for a hypothetical cohort of 10,000 individuals who consume bowel cancer resources at some point in their lifetime; the selection of this model population was driven by the specification of model options for appraisal. As two of these options concern the general

population rather than specifically those patients with clinically diagnosed bowel cancer, the marginal impact of each option on cost and QALYs gained is small, as the vast majority of the model cohort does not have bowel cancer.

The model suggests that the most cost-effective option for improving outcomes for bowel cancer patients is to increase the use of colonoscopy from 70% to 90% as an alternative to flexible sigmoidoscopy. Whilst the assumptions in the model may affect the extent to which this option will benefit patients, it is expected to improve health outcomes and produce cost-savings. Future research concerning the natural history of the disease and the probability of polyps and cancers being detected in patients with distal colon cancer would be valuable. The introduction of an Enhanced Recovery Programme is also cost saving with initial indications of a low associated risk of detrimental clinical outcomes. This option is again relatively robust and at an advanced stage of development for implementation.

The model suggests that the most costly option would be the further development of GP referral criteria guidelines, although this is also associated with a reasonable improvement in life years gained. This assumes that improving GP referral criteria will allow GPs to detect the cancer at an earlier presentation, and hence an earlier stage in some patients. This option is highly uncertain due to the lack of evidence surrounding disease progression and the cost of implementation. It would also require substantial further research in order to assess how changes in referral criteria will affect GP referrals, so that specificity is not decreased as a result of increasing sensitivity since this would lead to worsened health outcomes. Greater knowledge is required regarding the relationship between symptoms and disease progression.

Increasing the use of emergency stenting is expected to be very effective for a small number of patients consuming bowel cancer resources, but is associated with a relatively high cost. Options 7 and 9, to improve surgical resection and/or pathology and to improve adjuvant or palliative chemotherapies, are associated with improvements in health outcomes at a relatively low cost; providing that for option 7 the cost of improvements in pathology are not greater than the modelled costs, and for option 9 that the new chemotherapies. All of these options would provide health benefits; however there is uncertainty surrounding the necessary costs required to provide the amount of health benefit. In the case of option 9, this will depend upon new and currently unknown chemotherapy costs and effectiveness.

Option		Cost (£)	Life years	QALYs	Marginal cost (£)	Marginal life years	Marginal QALYs	Cost rank	QALY rank
	Baseline	908.18	10.4691	8.1981					
1	GP referral criteria -	022.02	10 4709	0 2026	24.85	0.0017	0.0045	14	2
1	sensitivity	955.02	10.4706	0.2020	(-32.33, 84.23)	(-0.0724, 0.0722)	(-0.0508, 0.0586)	14	
2	Madia compaign	000 50	10 4702	9 1096	1.32	0.0011	0.0005	7	10
2	Media campaign	909.50	10.4702	0.1900	(-64.38, 63.31)	(-0.0772, 0.074)	(-0.0601, 0.0567)	/	10
2	Emorgonov stanting	010 50	10 4724	8 2008	11.34	0.0040	0.0027	12	
3	Emergency stenting	919.52	10.4731	0.2000	(-46.85, 65.58)	(-0.0678, 0.0767)	(-0.0525, 0.0589)	15	4
1	Colonoscopy versus	942 70	10 4902	8 2006	-64.39	0.0111	0.0025	1	Б
4	flexi sig	043.79	10.4602	0.2000	(-120.52, -11.54)	(-0.0615, 0.0839)	(-0.054, 0.0586)	I	Э
5	Colonoscopy	012.20	10 4712	9 1009	4.11	0.0022	0.0017	10	7
5	completion rates	912.29	10.4715	0.1990	(-49.75, 56.92)	(-0.0725, 0.0765)	(-0.0545, 0.0589)	10	
6	Pro vorsus poston PT	012.64	10 4605	9 1096	4.46	0.0004	0.0004	11	11
0	Fie versus postop KT	912.04	10.4095	0.1900	(-46.71, 58.97)	(-0.0674, 0.074)	(-0.0527, 0.0566)	11	
7	Improve	007 15	10 4763	8 2035	-1.03	0.0072	0.0054	5	1
'	surgery/pathology	307.13	10.4705	0.2033	(-51.7, 45.75)	(-0.0626, 0.0811)	(-0.0481, 0.0617)	5	
8		011 01	10.4680	8 1073	2.84	-0.0011	-0.0008	Q	14
0		311.01	10.4000	0.1975	(-53.97, 62.71)	(-0.0745, 0.0688)	(-0.0569, 0.0538)	3	
02	Alternative adjuvant	902.84	10 4714	8 2000	-5.34	0.0023	0.0019	З	6
54	chemotherapies	502.04	10.4714	0.2000	(-31.83, 24.61)	(-0.0596, 0.0647)	(-0.0464, 0.05)	5	
ah	Alternative palliative	905 24	10 4751	8 2016	-2.94	0.0060	0.0035	Δ	3
50	chemotherapies	505.24	10.4751	0.2010	(-6.65, -0.31)	(0.0006, 0.0128)	(0.0004, 0.0074)	т	
10	Enhanced recovery	859 25	10 4702	8 1989	-48.93	0.0011	0.0008	2	9
10	programme	000.20	10.4702	0.1000	(-107.93, 12.75)	(-0.0707, 0.08)	(-0.0535, 0.0616)	2	
11	Intensive versus	916 75	10 4714	8 1996	8.57	0.0023	0.0015	12	8
	relaxed follow-up	510.70	10.4714	0.1000	(-54, 73.56)	(-0.0697, 0.0781)	(-0.0531, 0.0598)	12	Ŭ
12	Increased liver/lung	909 02	10,4695 8	8 1983	0.84	0.0004	0.0002	6	12
	resection	000.02	10.4000	0.1000	(-43.06, 41.23)	(-0.0653, 0.0696)	(-0.0501, 0.0536)	0	
13	Increase palliative	910.66	10 4691	8 1982	2.48	0.0000	0.0001	8	13
.0	surgery	010.00	10.7001	0.1002	(1.12, 4.27)	(0, 0)	(0, 0.0002)	5	

Table 6.2: Summary results of options assessment

Many of the options assessed within the model display huge variability due to the large amount of uncertainty associated with both the base case model and the options. The confidence intervals around the results suggest that it is unlikely that increasing the use of colonoscopy and introducing an Enhanced Recovery Programme will not be cost saving. However, since there is very little evidence regarding health utility scores for bowel cancer services, there is a considerable degree of uncertainty associated with all of these options in terms of their impact upon quality of life. This is an area in which further research would be merited.

The effect of introducing bowel cancer screening across England upon the treatment options is expected to be minimal, in that the total costs and benefits may be reduced slightly; however the relative effects of each of the treatment options are not expected to be markedly affected. Furthermore, the current FOBT test has been shown to have a low sensitivity. However, the options around presentation and referral are likely to be largely affected by the introduction of screening throughout England. The effect of these options is likely to be reduced because of screening, although the ScHARR screening model (Tappenden *et al.* 2007) suggests that they do have the potential to provide some benefit alongside screening using the FOBT 60-69 screening test.

6.4 LIMITATIONS OF THE MODELS

6.4.1 Synthesising Evidence within a Decision-Analytic Framework

It is important to acknowledge that both the baseline model and the options model presented within this report are dependent on a considerable number of structural and parametric assumptions, which have been sourced from expert clinical advice and from evidence available within the literature. As with any mathematical model which attempts to synthesise a large yet incomplete evidence base, the results of the analysis are subject to a considerable degree of uncertainty. The fundamental principle that underpins decision analytic modelling is that it is better to provide a robust, transparent and reproducible analysis using the best available evidence to inform decision makers than to leave the decision-makers to implicitly synthesize the set of evidence of which they are aware. However, given this underlying rationale, the development of any health economic model inevitably involves a compromise between the ideal and making the most of the evidence that is available. The validity of any model results is dependent upon the quality of the available evidence and the appropriateness of the assumptions used to draw this evidence together. One of the key outcomes of setting out the current evidence within a formal quantitative modelling framework is that it serves to highlight those areas where further research would be of value for future clinical and policy decision-making.

6.4.2 Issues Surrounding External Validity of the Analysis

The generalisability of the model results is dependent on the external validity of the data sources used to populate both the baseline model and the options model. In particular, it is noteworthy that the populations recruited into many of the clinical trials used to inform the model are likely to be fitter and younger than the English NHS bowel cancer population; therefore, it is likely that modelled clinical outcomes appear more favourable than would be observed for the general bowel cancer population. Within both models, we have used trial data to model disease-free survival which may result in an underestimate of metastatic recurrence rates for the English bowel cancer population, thus leading to an overestimate of overall survival. Consequently, when modelling the options which are expected to improve disease-free survival, we may have underestimated the impact they may have upon life years and QALYs gained. However, we anticipate that such biases would not have a significant impact upon the overall conclusions.

6.4.3 Issues Surrounding Modelling Methodologies

This study has employed the use of two modelling methodologies: a clinical pathways decision-tree model to estimate baseline costs and outcomes, and a discrete event simulation model to estimate the expected costs and outcomes associated with each of the options for service reconfiguration. Where possible, all structural and parameter assumptions are consistent between the two models. In addition, each model has been validated against external sources, and the two models have been calibrated against one another. Whilst the methodologies used to estimate baseline cost and activity levels and the expected costs and outcomes of the options are fit for their purpose, they are subject to certain limitations. These limitations are summarised below, and should be borne in mind when interpreting the results of this study.

The baseline activity and cost model adopted a decision-tree approach. The most substantial limitation of this approach concerns the difficult in explicitly modelling time, and incorporating ongoing risk. As a consequence, incident and prevalent cases have been modelled separately, and certain assumptions about the timing of events have been required. In addition, the outcomes experienced by patients are only dependent on the patient's characteristics where these are described by a chance node; to fully incorporate conditionality of future outcomes based on previous events would make the structure of the baseline model intractable.

There are also limitations associated with the options model, which primarily concern the degree of information required to fully populate the model. Where evidence is particularly weak or even absent, assumptions have been necessary. This level of complexity has been driven by the scope of the options specified for appraisal within this study. In relation to this, the explicit consideration uncertainty within the DES model results in considerable computational expense. The use of Monte-Carlo simulation techniques is associated with a degree of random sampling error, such that when there is little or no true difference in outcomes or costs, small differences may still appear in the results. We have attempted to reduce the degree of sampling error by running the model a large number of times to ensure

stability in the results. The options model was run 1,250 times per option. Despite this, a small degree of random sampling error is still evident in the results (beyond two decimal places). This would usually be considered to be of sufficient accuracy; however, because cancer patients account for such a small percentage of the modelled population, the cost per life year and cost per QALYs may be slightly affected by these differences. This should be taken into consideration when considering the results of the options appraisal.

6.5 AREAS FOR FURTHER RESEARCH

6.5.1 Areas for Further Clinical and Economic Research

As noted above, there are a number of gaps in the current evidence base which limit the external validity of the models presented in this report. These are detailed below.

1. Health utility scores

Evidence concerning the level of health-related quality of life associated with the stages of the underlying disease, symptoms, diagnosis and treatment is very weak, and limited. Where evidence is available (see Section 4), the methodological quality of utility estimates is variable, and between-study estimates appear to be logically inconsistent. Notably, there is insufficient quality of life evidence to allow us to discriminate between the value of many of the treatments included in the model even though our prior expectation is that a difference would exist, e.g. enhanced recovery programmes, laparoscopic surgery. In some instances, the lack of evidence is unsurprising, for example, the absence of utilities for patients in best supportive care, as data collection would be ethically problematic and likely to be subject to informative censoring. Where possible, future clinical trials should include a detailed and appropriate consideration of the preferences for health using standard preference-based instruments.

2. Benefit of adjuvant chemotherapies

There currently exists limited evidence concerning the relative disease-free survival and overall survival of those patients who receive adjuvant chemotherapy against those who do not. The relative outcomes for patients who do not receive adjuvant chemotherapy is unclear, as some patients will be unfit and have a poor prognosis, whilst another group will have a better prognosis and will not require therapy. In the model, we have assumed that those patients who do not receive adjuvant chemotherapy have the same disease-free survival as those patients who do receive adjuvant chemotherapy. This is not ideal, as there is RCT evidence which has demonstrated the benefit of these therapies. Registry data, or more broadly, observational studies could provide indirect estimates of outcomes for these patients.

3. Relationship between symptoms and histological state

One of the major areas of uncertainty concerns the relationship between clinical symptoms and a patient's underlying histological state. Whilst a relationship between these factors is likely, current understanding of the natural history of the disease is limited, and for the most part, based only on indirect evidence. Within the model, we have chosen not to model the symptoms of the disease, in order to avoid unfounded assumptions. Bayesian synthesis combining clinical trial data and other sources of evidence could be used to draw out this relationship.

4. Time from onset of symptoms to presentation

There is considerable uncertainty surrounding evidence on the time from first onset of CRC symptoms and the time at which patients present to a healthcare professional. The majority of the evidence surrounding this is based upon patient memory, which often leads to inaccuracy and bias. As current evidence concerning the time from onset of symptoms to presentation is very limited, the scope of our model covers the patient pathway from the point of presentation onwards.

5. Sensitivity of endoscopy

The sensitivity of endoscopy is highly dependent on the skill and experience of the operator. Within the model, we have used estimates of endoscopy miss rates from US studies; it is possible that these do not accurately reflect the situation in England.

6. Costs of surgical techniques

Published evidence concerning the costs of various surgical techniques is very limited. Where available, we have used Department of Health Reference Costs, mapped against HES data, to provide estimates for these parameters. However, this approach is not ideal and is unlikely to sufficiently discriminate in terms of the complexity of surgical resection.

7. Audit of current practice nationally

The pathways used to structure the model have been elicited from experts and where possible, current literature. However, our experience would suggest that practice varies considerably across England. Whilst we have attempted to explicitly capture the uncertainty surrounding the costs and benefits of the current service, it is possible the variability in services has not been fully addressed. Many of the data sources used to populate the model are necessarily region-specific, as national data were not available. A large scale audit of bowel cancer diagnosis, treatment and follow-up across the country would be of considerable value in clarifying the current situation and the scope for potential improvement.

8. Prognosis for inoperable patients

There is currently very little evidence with respect to survival outcomes for patients who are inoperable. The absence of clinical trial data is unsurprising; however, this uncertainty could be addressed through an audit study or a case note review.

9. Benefit of follow-up

Current evidence concerning the relative benefits of intensive and more relaxed follow-up regimens is scant. Whilst one may expect that intensive follow-up would improve overall survival outcomes, no clinical trials have demonstrated such statistically significant improvements. In our model, we have assumed that more intensive follow-up would improve survival. It is envisaged that the FACS trial will provide evidence to support or challenge this assumption.

10. Costs and benefits for increased and increased-risk groups

The costs and benefits associated with the management of individuals who have an increased or high-risk of bowel cancer are highly uncertain. The baseline model includes estimates of these costs and outcomes, but is based primarily on assumption rather than evidence. These groups of patients have been excluded from the options model. It also of note, that the clinical management and outcomes for these individuals are likely to be highly variable by centre. Again, this area of uncertainty may be addressed through the establishment of a large scale national audit.

6.5.2 Research and Development Implications

The aim of this project was to support the Department of Health in considering how best to ensure that investment in bowel cancer services is directed to areas which will give maximum benefit to patients. These aims have been pursued through the development of a service-level model that allows the estimation of current costs and benefits and an appraisal of options for future service developments. Two key research and development initiatives are indicated:

1. Improve information collection throughout the pathway

The model developed within this study has been designed and populated using information from a large number of sources. Information is used on pathways, flows, probabilities (including baseline and relative treatment outcomes), costs, resources and health utilities. The best source for some information items such as utilities and relative treatment effects would be from clinical trials and population-based studies. However, information such as clinical pathways, flows, probabilities and baseline treatment outcomes would be best sourced directly from the bowel cancer system itself. Information systems that support the collection of detailed routine data, such as the Do Once and Share programme (which includes the establishment of comprehensive Electronic Patient Record, EPR), would be invaluable in informing such programme-level decision-making.

2. Methods development for service-level modelling

Service-level modelling covers a broader focus than typical cost-effectiveness models undertaken to support the appraisal of healthcare technologies. Guidelines also involve the development of models of clinical pathways but have a specific focus on describing best practice rather than evaluating options for programme improvement based on the current service. As far as we are aware, this is the first application of a detailed service-level model to inform decision-making at a programme-level. This study has raised a number of areas for further methodological development. In particular, further research is required concerning the methods for developing pathways of the current system that reflect both clinical consensus and variation in services. Research on the methods for the elicitation of expert judgement where there is no available evidence on the current service, and for assessing hypothetical options for change, would also be merited. Given the scale and complexity of this level of mathematical modelling, formal systematic reviewing at each node on the pathway is unlikely to be feasible, hence research into methods for identifying appropriate sources of evidence would also be of considerable value. Finally, there is a need for the development of multi-criteria decision-making approaches at the broader programme-level which consider other factors alongside incremental cost and effects.

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