Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health technology assessment (HTA) of a population-based colorectal cancer screening programme in Ireland

25 March 2009

About the Health Information and Quality Authority

The Health Information and Quality Authority is the independent Authority which has been established to drive continuous improvement in Ireland's health and social care services. The Authority was established as part of the Government's overall Health Service Reform Programme.

The Authority's mandate extends across the quality and safety of the public, private (within its social care function) and voluntary sectors. Reporting directly to the Minister for Health and Children, the Health Information and Quality Authority has statutory responsibility for:

Setting Standards for Health and Social Services - Developing personcentred standards, based on evidence and best international practice, for health and social care services in Ireland (except mental health services)

Monitoring Healthcare Quality - Monitoring standards of quality and safety in our health services and implementing continuous quality assurance programmes to promote improvements in quality and safety standards in health. As deemed necessary, undertaking investigations into suspected serious service failure in healthcare

Health Technology Assessment - Ensuring the best outcome for the service user by evaluating the clinical and economic effectiveness of drugs, equipment, diagnostic techniques and health promotion activities

Health Information - Advising on the collection and sharing of information across the services, evaluating information and publishing information about the delivery and performance of Ireland's health and social care services

Social Services Inspectorate - Registration and inspection of residential homes for children, older people and people with disabilities. Monitoring day- and pre-school facilities and children's detention centres; inspecting foster care services.

Foreword

In Ireland, colorectal cancer is the second most frequently diagnosed cancer in both men and women. During the time period 2002 to 2005, an average of 2,040 new cases of colorectal cancer was diagnosed each year. During the same time period, an average of 925 people died from the disease each year. The incidence rates of colorectal cancer for men and women in Ireland are among the highest in Europe, and we have the highest mortality rate for colorectal cancer for men in Western Europe.

In November 2007, the Health Information and Quality Authority agreed to carry out a health technology assessment (HTA) of a population-based colorectal cancer screening programme in Ireland in response to a request by the National Cancer Screening Service (NCSS) Board.

A population-based screening programme involves inviting a defined population who are at average risk for the disease (that is, do not have medical conditions that put them at higher risk of developing colorectal cancer or a strong family history of colorectal cancer) to attend for screening. Such a programme would not only identify individuals with colorectal cancer at an earlier stage, but would also identify people who have pre-cancerous adenomas at risk of developing colorectal cancer. Screening for colorectal cancer has been recommended by the Europe Against Cancer programme of the European Union, the International Union Against Cancer and the Preventative Services Task Force in the United States. Screening has been shown to reduce the number of new cases of cancer, through the detection and removal of pre-cancerous tumours (that is, polyps or adenomas). Screening also allows cancers to be detected at an earlier stage. For the individual patient this can mean an improved quality of life and, or a longer duration of life. For the population, this can mean a reduced risk of developing or dying from the disease.

The purpose of this assessment was to evaluate the cost-effectiveness of various options for a population-based colorectal cancer screening programme in Ireland compared to a policy of no screening and relative to each other. The HTA also estimated the resource requirements and health outcomes that would result in the first ten years following implementation of a population-based colorectal cancer screening programme.

The Authority commissioned a multi-disciplinary team led by the National Cancer Registry to conduct the HTA on its behalf. The team included groups from the National Centre for Pharmacoeconomics, the School of Health and Related Research (ScHARR) at the University of Sheffield and Dublin City University. To lead and oversee the process and advise the Authority, a multidisciplinary Expert Advisory Group was convened. An ethical commentary on the results was provided by Dr. Deirdre Madden, Faculty of Law, University College Cork.

It should be noted that it was not within the remit of this HTA to estimate the budgetary impact of establishing a population-based screening programme in Ireland. This process was undertaken by the NCSS, the body responsible for the implementation of population-based screening programmes, and is described in a business implementation plan included in their report of December 2008, that outlined their recommendations for a colorectal cancer screening programme in Ireland.

This HTA evaluated a number of proposed screening options for colorectal cancer in Ireland and found that any of these options would be highly cost-effective compared with a policy of no screening. A screening programme based on biennial immunochemical faecal testing (FIT) for individuals aged 55 to 74 years was found to be the optimal strategy as it would provide the greatest health gain while remaining highly cost-effective compared to the other options considered. Although implementation of screening would require investment in resources, a screening programme based on FIT would avert a significant number of colorectal cancer cases and deaths in the population, with the effect on colorectal cancer deaths seen from year two of the programme being implemented.

The draft report was endorsed by the Expert Advisory Group in February 2009. The Board of the Authority subsequently approved the report in March 2009 and has submitted it to the Minister for Health and Children, the Health Service Executive and the NCSS. A decision on the adoption and implementation of a colorectal cancer screening programme will be taken by the Minister for Health and Children following due consideration of all available evidence.

The following report contains an outline of the health technology assessment that was prepared by the Authority, the technical report that was prepared by the evaluation team and the ethical commentary prepared by Dr. Deirdre Madden.

The Authority would like to thank the Evaluation Team, the members of the Expert Advisory Group, Dr. Deirdre Madden and all who contributed to the production of this report.

Dr. Tracey Cooper
Chief Executive Officer
Health Information and Quality Authority

Health Technology Assessment Process

In November 2007, the Health Information and Quality Authority agreed to carry out a health technology assessment (HTA) of a population-based colorectal cancer screening programme in Ireland in response to a request by the National Cancer Screening Service Board. To lead and oversee the process and advise the Authority, a multidisciplinary Expert Advisory Group (EAG) was convened, the inaugural meeting of which was held in February 2008. Following a competitive tendering process and refinement of the scope of the HTA in consultation with the EAG, a contract to conduct the HTA on behalf of the Authority was signed by a multidisciplinary team led by the National Cancer Registry in May 2008. The team included groups from the National Centre for Pharmacoeconomics, the School of Health and Related Research (ScHARR) at the University of Sheffield and Dublin City University. These groups had extensive experience in economic modelling, health technology assessment and health services research. Dr Deirdre Madden, Senior Lecturer, Faculty of Law, University College Cork agreed to prepare an ethical commentary on the HTA. The overall project was managed by staff in the HTA directorate of the Authority.

The Terms of Reference for the Expert Advisory Group were to:

- Contribute to the provision of high quality and considered advice to the Minister for Health and Children.
- Contribute fully to the work, debate and decision making processes of the group by providing expert guidance, as appropriate.
- Be prepared to occasionally provide expert advice on relevant issues outside of group meetings, as requested.
- Provide advice to the Authority on the refinement of the scope of the evaluation including, but not limited to such factors as the screening methodologies to be compared, the screening interval, patient age groups, specifics of the modelling approach, etc.
- Support the Evaluation Team led by the National Cancer Registry during the assessment process by assisting with the population of the economic model (e.g. epidemiological data, cost data, screening programme uptake rates, etc.) by providing expert opinion and access to pertinent data, as appropriate.
- Review the project plan outline and advise on priorities, as required.
- Review the draft report from the Evaluation Team and recommend amendments as appropriate.
- Contribute to the Authority's development of its approach to HTA by participating in an evaluation of the process on the conclusion of the assessment.

The membership of the group was as follows:

Chairperson: Mr Jon Billings, Director of Healthcare Quality and Safety, Health Information and Quality Authority

Professor Niall O'Higgins, Professor of Surgery, Formerly at University College, Dublin, Ireland, and St. Vincent's University Hospital, Dublin

Professor Colm Ó' Móráin, Consultant Gastroenterologist, Adelaide & Meath Hospital, incorporating the National Childrens' Hospital, Dublin and Trinity College Dublin

Dr Pádraic Mac Mathúna, Consultant Gastroenterologist, Mater Misericordiae University Hospital

Professor Ronan O'Connell, Professor of Surgery, University College Dublin (UCD) and Mater Misericordiae University Hospital

Dr Conor O'Keane, Consultant Pathologist, Mater Misericordiae

Ms Anne Murphy, Clinical Nurse Specialist, Cork University Hospital

Dr Helen Fenlon, Consultant Radiologist, BreastCheck and Mater Misericordiae University Hospital

Dr Michael Flynn*, General Practitioner, Irish College of General Practitioners

Professor Diarmuid O'Donoghue, St. Vincent's University Hospital, Dublin and University College Dublin

Professor Mark Sculpher, Professor of Health Economics, Centre for Health Economics, University of York, England

Mr Liam McDonough, Patient Representative, Irish Cancer Society

Mr Stephen McMahon, Patient / Public Representative, Irish Patients Association

Dr Deirdre Murray, Consultant in Public Health Medicine, Department of Public Health, Health Service Executive

Dr Seamus O'Reilly, Consultant Medical Oncologist, Irish Society of Medical Oncologists

Dr Alan Smith, Consultant in Public Health Medicine, National Cancer Screening Service

Mr Patrick Cafferty, Planning and Risk Manager, National Cancer Screening Service

Dr Deirdre Madden, Senior Lecturer, Faculty of Law, University College Cork

Ms Diana Reerman, Danish Centre for Health Technology Assessment (DACEHTA), National Board of Health, Denmark

Dr Máirín Ryan, Director of Health Technology Assessment, Health Information and Quality Authority

Dr Patricia Harrington, Acting Director of Health Technology Assessment, Health Information and Quality Authority

Dr Caroline Waldron, Project Manager, Health Information and Quality Authority

* *Regretfully, Dr Flynn passed away in August 2008 following a brief illness.*

No Conflicts of Interest declared.
This HTA will be considered for review in 2012

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Outline Report

1 Introduction

In November 2007, the Health Information and Quality Authority (the Authority) agreed to carry out a health technology assessment (HTA) of a population-based colorectal cancer screening programme in Ireland, in response to a request by the National Cancer Screening Service (NCSS) Board.

The purpose of this assessment was to evaluate various options for a population-based colorectal cancer screening programme in Ireland with a view to establishing (i) the cost-effectiveness of these options compared to the current policy of no screening and relative to each other, (ii) the key additional resource implications and health outcomes associated with these options in the first ten years of a screening programme and (iii) the ethical considerations arising from these findings.

In Ireland, colorectal cancer is the second most frequently diagnosed cancer in men, after prostate cancer, and the second most frequently diagnosed cancer in women, after breast cancer. An average of 2,040 new cases of colorectal cancer were diagnosed each year during the period 2002 to 2005, with an average of 925 deaths from colorectal cancer each year during the same period. Almost half of these deaths (49%) occur in people aged 75 and older, 8% in those aged 55 and under, 15% in those aged 55 to 64 years and 28% in those aged 65 to 74 years[1].

The incidence of colorectal cancer increases with increasing age. The number of cases diagnosed each year in Ireland is therefore expected to increase as our population ages. By 2020, the number of new cases diagnosed each year in Ireland is projected to have increased by 79% in men and 56% in women, compared to the average annual number recorded for the period 1998 to 2002[2]. The incidence rates of colorectal cancer in Ireland rank among the highest in Western Europe for both men and women[3], while the death rate (mortality) from colorectal cancer is higher for men in Ireland than elsewhere in Western Europe[4].

Population-based colorectal cancer screening involves systematically inviting individuals in a defined population to participate in a programme aimed at detecting colorectal cancer and pre-cancerous lesions that may develop into colorectal cancer. The aim of a screening programme is to save lives by preventing premature deaths from colorectal cancer. Organised screening for colorectal cancer is already underway or is in the process of being rolled out in several countries, either at a regional or national level[5,6].

The following section explains what HTA is and summarises the findings of this assessment. A more detailed description of the HTA and its findings can be read in the technical report and in the ethical commentary. A glossary of technical terms used in the report can be found at the end of the technical report.

2 Background

2.1 What is the role of the Health Information and Quality Authority in health technology assessment (HTA)?

The Health Information and Quality Authority is an independent Authority reporting to the Minister for Health and Children which was established on May 15, 2007. The Authority is the statutory organisation in Ireland with a responsibility to carry out national health technology assessments (HTAs) and to develop standards for the preparation of these and other HTAs across our health system.

2.2 What is HTA?

Health technology assessment is a form of health research that generates information about the clinical and cost-effectiveness of health interventions (technologies), as well as information on their wider impact. The term 'technology' includes drugs, medical equipment, diagnostic techniques, surgical procedures, and public health programmes, for example, cancer screening programmes. This information is for use by the public, service providers and policy makers. The main issues investigated as part of any HTA are:

- Does the intervention (technology) work?
- For whom does it work?
- What is the benefit to the individual?
- At what cost?
- How does it compare to the alternative options available?

2.3 How is a HTA carried out?

A HTA usually consists of two interlinked parts:

i. a systematic review of the available published and unpublished literature

ii. an economic evaluation to see whether an intervention is cost-effective compared with the current situation (or another comparator).

However, a HTA can also look at broader issues, such as resource implications and potential ethical issues associated with a technology or intervention.

The literature review is used to collect important information on the disease process that the intervention is targeting, and the efficacy and safety of the technology/ intervention (for example, how well the technology works in identifying disease and reducing deaths). In this case it included information on the relative efficacy and safety of various screening tests for colorectal cancer, as well as information on the cost-effectiveness of strategies or programmes using these screening tests in other settings. The literature review also examined the natural history of colorectal cancer, that is, how the disease is thought to develop.

The economic evaluation includes a cost-effectiveness analysis, in which alternative courses of action are compared. In this case, proposed options for a colorectal screening programme were individually compared with a policy of no screening. Subsequently, these options for a screening programme were compared directly to each other. As in this assessment, an evaluation of the resources that may be required to implement the intervention may be undertaken as part of an HTA.

2.4 What measurements are used?

In a cost-effectiveness analysis, the costs and effects (health benefits) of each intervention being evaluated must be measured. In this instance, the total costs incurred by the health services to provide the different screening options where estimated (for example, the cost of the screening test and the cost of diagnosing and treating the disease). The health benefit of the intervention or programme may be measured in a number of ways. Life years gained (LYG) measures the impact of an intervention on patient length of life (survival). If the effects of an intervention on the health-related quality of life of a patient, as well as on survival, are to be considered, both are combined into a single common unit of measure called the Quality Adjusted Life Year (QALY). Both LYG and QALYs are widely used in HTAs in other countries.

In this HTA, both LYG and QALYs gained were calculated while costs were measured in euro. The advantage of calculating health benefits in terms of QALYs gained is that is allows the effect of screening on both the quality of life of patients (morbidity) as well as on survival (mortality) to be estimated, rather than estimating the effect on mortality alone.

When comparing two or more interventions, the question is then, what is the additional cost involved for the additional benefit achieved. To answer this question, the incremental cost-effectiveness of one therapy over the other is calculated, with the results presented as an incremental cost-effectiveness ratio (ICER)[7].

The ICER for two healthcare interventions A and B can be calculated as follows:

$$\text{ICER} = (\text{Cost A} - \text{Cost B})/(\text{Effect A} - \text{Effect B})$$

One of the implications of making comparisons between the cost-effectiveness of different interventions is that there is a threshold ratio above which a programme would not be considered cost-effective. In practice, there is no fixed threshold above which an ICER would not be considered cost-effective. However, if an intervention has an ICER that is significantly higher than other healthcare interventions that are already reimbursed, other factors such as the innovative nature of the technology, or the wider costs and benefits to patients and society, would need to be taken into consideration.

The ICER is a measurement that allows the cost-effectiveness of different technologies to be compared and should not be considered as putting a monetary value on a year of life.

3 Natural History of Colorectal Cancer

Colorectal cancer refers to cancer of the lower bowel, that is, the colon and rectum. Evidence suggests that most colorectal cancers develop from benign polyps (non-cancerous tumours) in the lining of the bowel described medically as 'adenomas' or 'adenomatous polyps.' This is known as the adenoma-carcinoma sequence[8, 9,].

Adenomas are classified as low, intermediate or high risk in terms of their ability to cause cancer[10]. Most adenomas do not cause severe symptoms and although they can produce blood in the stools, this can go undetected, that is, occult (hidden) blood. The true prevalence of adenomatous polyps in the population is unknown[9]. The progression from pre-cancerous adenoma to cancer is generally considered to be slow and may take 10 to 15 years to occur[9].

When a cancer is diagnosed, it is usually 'staged.' That is, a series of tests are carried out that measure the size and spread of the cancer at that point. Like other cancers, colorectal cancer can spread into the surrounding lymph nodes (stage III) and to other parts of the body (stage IV). Stages I and II refer to more localised disease[11]. Data from the National Cancer Registry show that during the period 2002 to 2005 in Ireland, 11% of colorectal cancer cases were stage I at diagnosis, 24% were stage II, 26% stage III and 22% at stage IV. Seventeen percent of the cancers were not staged[1].

Cancer that has advanced to stages III and IV is more complex to treat and usually requires additional treatments. In addition, patients diagnosed at these later stages have a lower chance of survival. Data from the National Cancer Registry show that for patients diagnosed with colon cancer between 1997 and 2001 in Ireland, approximately three-quarters of those with stage I disease were still alive five years after diagnosis, compared to just over 60% with stage II, around half with stage III and less than 10% with stage IV[12].

Adenomas and colorectal cancer can be detected by a variety of screening tests and are removed by colonoscopy or surgery. In this way a cancer may either be prevented from occurring in the first place or it can be diagnosed and treated at an earlier stage where it is associated with a better chance of survival.

4 Screening for Colorectal Cancer

As noted, the purpose of a screening programme for cancer is to save lives by preventing the disease from occurring or by detecting the disease at an earlier stage. The existence of the adenoma-carcinoma sequence, and the strong association between the stage of disease at diagnosis and survival, provides the rationale for colorectal cancer screening.

A population-based screening programme for colorectal cancer involves inviting a defined population who are at average risk for the disease (that is, do not have medical conditions that put them at higher risk of developing colorectal cancer or a strong family history of colorectal cancer) to attend for screening. Such a programme would not only identify individuals with colorectal cancer at an earlier stage, but would also identify people who have pre-cancerous adenomas who are at risk of developing colorectal cancer. Several countries already have organised screening programmes in place either at a national or regional level[5,6]. In the United Kingdom (UK), it is expected that full national programmes will be in place by 2010.

A range of potential screening tests are available for colorectal cancer. Options include invasive diagnostic tests such as colonoscopy and flexible sigmoidoscopy that involve an examination of the bowel by a medical professional. There are also various non-invasive tests that can detect occult (hidden) blood in stool, which may indicate the presence of cancer or adenomas. These tests are known as faecal occult blood tests and can be completed by the individual in their home. Individuals who have a positive test are then referred for further screening, usually involving a direct examination of the bowel by colonoscopy.

The World Health Organisation (WHO) criteria for screening state that screening tests should be effective, safe and acceptable to the population and that the economic costs to the health service should be acceptable[13]. Therefore, a screening programme for colorectal cancer not only needs to be cost-effective, but its implementation also must be feasible, in terms of having sufficient resources available to deal with the new cancers and adenomas detected.

Screening tests can result in false positive results and false negative results. The ability of a test to accurately identify persons who truly have a disease and those who truly do not have a disease is called its sensitivity and specificity[14]. Sensitivity is the proportion of persons with disease in a screened population who are identified as having the disease by the screening test. Tests with a high sensitivity have a better chance of detecting disease. Specificity is the proportion of persons without disease in a screened population who are identified as being disease-free by a screening test. Tests with a high specificity limit the numbers of people with false positive screening test results.

4.1 Description of selected screening tests

A brief description of three screening tests frequently used in colorectal screening programmes (and that are evaluated in this HTA) is given below:

4.1.1 Guaiac-Based Faecal Occult Blood Test (gFOBT)

The faecal occult blood test (FOBT) is a test for blood in the stool (faeces)[15]. The presence of blood may be an indicator for cancer or adenomas. The test is based on a reaction between guaiac, which is present in the test, and the enzyme peroxidase which is found in blood. Peroxidase is not however specific to human blood and high peroxidase-containing foods such as red meat and certain raw plant foods can result in a false-positive result[16]. In addition, the gFOBT test can detect blood from the stomach and small intestine that may be due to bleeding associated with certain drugs, such as non-steroidal anti-inflammatory drugs like aspirin. Therefore, it is not selective for blood of colorectal origin. To minimise the effect of these interactions, those completing the test may have to restrict their diet or the use of certain drugs for several days prior to using the test[17].

The test is relatively easy for individuals to carry out in their own homes. Testing kits are readily available in a format that is suitable for outward and return posting[18]. The test involves taking samples from a number of stools using a sampler and placing these samples on cards. The test kit is returned by mail and is processed in a laboratory to determine if the card samples are positive or negative for blood.

The analysis of the samples in the laboratory is not always straightforward and can be subjective[15]. Equivocal results can arise when some, but not all, of the test samples are positive. Repeat testing is required usually every two years in screening programmes as a once-off test is not sufficiently sensitive.

Programmes based on guaiac-based tests usually use a second round of testing in positive cases, with either the same guaiac-based test or another type of faecal test. This is known as 'reflex testing.' Reflex testing has been shown to reduce the number of false positive results arising from screening, thus reducing the number of further diagnostic tests required[19]. In this HTA, the gFOBT-based screening programme that was evaluated used a reflex FIT test (see below) in all those who had an equivocal or positive test with gFOBT.

A range of gFOBT tests are available[20]. Some more recently developed tests seem to have a higher sensitivity than the older tests, but may be more susceptible to the effects of diet[15].

Four randomised controlled trials have been conducted to assess the efficacy of gFOBT-based colorectal cancer screening programmes. A 2008 Cochrane review that included a meta-analysis of these trials showed that repeat gFOBT testing is associated with a 25% reduction in mortality compared with no screening[21]. In other words, a screening programme based on regular gFOBT has been proven to be effective in reducing the number of deaths from colorectal cancer.

Numerous national and regional screening programmes are based on gFOBT, including those in the UK[19], Ontario[22], France[23], Spain[24] and Italy[25].

4.1.2 Faecal Immunochemical Test (FIT)

The faecal immunochemical test (FIT) is also based on the detection of occult blood in the stool. It depends on antibodies specific for human haemoglobin to react with blood[15,16]. It is more selective for blood originating from the colon and rectum than the gFOBT test. Therefore, dietary and drug restrictions are not required with FIT. In theory, this should cut down on the number of false positive results[16]. An advantage of FIT is that the processing and reading of FIT tests can be automated, allowing for more objective interpretation of the results. However, FIT test kits are more expensive than gFOBT test kits. As with gFOBT, repeat testing is likely to be required in a screening programme for colorectal cancer.

Several randomised controlled trials are underway to evaluate the efficacy of FIT-based screening programmes, but as yet they have not been reported. This means that there is currently no evidence that screening by FIT would be effective in reducing colorectal cancer mortality in the population. Nevertheless, screening programmes based on FIT have been adopted in Australia[26] and parts of Italy[5, 27] and a change from gFOBT to FIT testing has been recently recommended in the French screening programme[28]. It has been argued that it is not necessary to demonstrate in trials that FIT reduces mortality as it has already been proven from the gFOBT trials that faecal occult blood testing is effective[15]. Despite the absence of conclusive evidence, FIT has been adopted in a number of screening programmes on the basis that the tests may have better performance characteristics such as sensitivity and specificity and because they may be more acceptable to screening participants because there are no dietary or drugs restrictions.

There is no clear evidence whether gFOBT or FIT has better sensitivity or specificity[20, 29]. Newer tests tend to perform better than the older tests, so the performance of gFOBT or FIT very much depends on the type of test chosen.

4.1.3 Flexible Sigmoidoscopy (FSIG)

Flexible sigmoidoscopy is a procedure in which a slender, hollow, flexible, lighted tube is placed into the rectum to help find polyps or cancers in the rectum and lower part of the colon. The rationale for the use of FSIG as a screening tool for colorectal cancer is the observation that 50 to 75% of adenomatous polyps are within reach of the 60cm instrument[30]. An advantage of FSIG as a screening test is that screening and diagnosis can be combined, that is, for the majority of those with adenomas, the lesion can be removed at the time of testing. Another advantage is that a single screening examination (once-off with no repeat testing) may be sufficient to provide protection against colorectal cancer, unlike the requirement for biennial testing with the faecal tests[31].

No randomised controlled trials of flexible sigmoidoscopy demonstrating reduced mortality have been published in full yet. Results from a number of trials are awaited including that of a large UK population-based trial in 40,674 individuals with results relating to colorectal mortality expected in 2010[32].

Flexible sigmoidoscopy (FSIG) is used for colorectal screening in parts of Italy, Australia, Canada and the USA[5].

4.2 Screening and resource implications

Following an initial screening test, a screening programme will require resources to follow up those individuals who have a positive test. Pathology (including biopsy and/or relevant blood tests) will be required to categorise adenomas removed during colonoscopy or flexible sigmoidoscopy and to stage the cancers detected. Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scans, Positron Emission Tomography (PET) scans and transrectal ultrasound (TUS) will be required for the diagnosis and staging of cancers detected to varying degrees. For example, all colorectal cancers are likely to require a CT scan, but only 10% of colorectal cancers are likely to require a PET scan[33].

Surgery and treatment with post-operative chemotherapy and/or radiotherapy will be required for most colorectal cancers that are diagnosed. All cancers will require follow-up after treatment to detect recurrence or spread of the cancer.

Some individuals with adenomas diagnosed during the screening process will require ongoing surveillance, usually by colonoscopy, the frequency of which depends on the size, nature and number of adenomas detected. Current UK surveillance guidelines recommend annual colonoscopy for those classified as high risk and colonoscopy every three years for those that are at an intermediate risk[10]. Individuals that are classified as low risk return to routine screening.

It is important to consider the resource implications for existing services (cancer treatment, surveillance) as well as the costs of conducting screening when evaluating screening programmes. Establishing a screening service requires investment in new and existing resources. However, in time, screening programmes are expected to reduce the number of cancers occurring in the population or to allow these cancers to be diagnosed at an earlier stage and therefore have the potential to reduce overall cancer resource requirements in the future.

4.3 Screening and health outcomes

Studies investigating screening programmes usually measure health outcomes in terms of LYG or QALYs gained in the main analysis. Health outcomes may also be evaluated in other ways including: reduction in colorectal cancer cases, reduction in colorectal cancer deaths, stage–distribution of screen-detected cancers, and rates of complications.

Complications of screening can arise at the screening or diagnostic stages and include bowel perforation, bleeding and rarely, death[32, 34, 35, 36]. While the risk to an individual of complications occurring may be low, it is important to consider potential negative and positive outcomes when evaluating any screening programme.

5 Health Technology Assessment on a Population Based Colorectal Cancer Screening Programme

Colorectal cancer screening presents an opportunity to reduce the risk of developing colorectal cancer and dying from the disease in Ireland. Currently, there is no nationally organised or 'population-based' screening programme for individuals that are at an average risk of developing colorectal cancer in Ireland. That is not to say that screening does not take place. Screening for colorectal cancer is conducted within research programmes and on a case by case basis for individual patients identified by their doctors. Hereafter, this situation is referred to as 'no screening' in relation to this HTA.

5.1 Objectives

The objectives were to:

- evaluate the cost-effectiveness of various options for a colorectal cancer screening programme compared to a policy of no screening
- compare these options with one another in terms of their relative cost-effectiveness
- estimate the key additional resource requirements (for example, colonoscopy capacity) and key health outcomes (for example, numbers of cases of adenomas and cancer detected) in the initial ten years of the programme.

The ethical considerations arising from these findings were also evaluated separately as part of the HTA.

It should be noted that it was not within the remit of this HTA to estimate the budgetary impact of establishing a population-based screening programme in Ireland. This process was undertaken by the NCSS, the body responsible for the implementation of population-based screening programmes, and is described in a business implementation plan issued as part of a December 2008 report from the NCSS that outlined their recommendations for a colorectal cancer screening programme in Ireland.

5.2 Evaluation process

Following a request from the NCSS in November 2007, the Board of the Authority agreed to undertake the HTA and a competitive tender process was initiated to select an evaluation team. To lead and oversee the process, and to advise the Authority, a multidisciplinary Expert Advisory Group was convened. This group included clinical experts, experts in public health, international experts in HTA, key stakeholders, patient and public representatives.

The scope of the HTA was refined following consultation with the Expert Advisory Group and a multi-disciplinary team, led by the National Cancer Registry Ireland, was subsequently appointed in May 2008 to conduct the HTA on its behalf. The team included groups from the National Centre for Pharmacoeconomics in Dublin, the School of Health and Related Research (ScHARR) at the University of Sheffield, and Dublin City University. These groups had extensive experience in economic modelling, health technology assessment, health services research and expertise in the epidemiology of colorectal cancer. This project was managed by the HTA directorate within the Authority.

Dr Deirdre Madden from the Faculty of Law, University College Cork provided the ethical commentary.

5.3 Screening options

The advice of the Expert Advisory Group was taken in selecting the screening options to be evaluated as part of this HTA. There are several screening options for colorectal cancer – evaluation of all of which would be a time consuming, resource intensive exercise. In selecting the screening options to be evaluated, consideration was given to the timeframe within which the HTA needed to be completed, the volume and strength of the scientific evidence supporting the different options, screening practices in other countries, and factors such as the acceptability, feasibility and risk of serious adverse events associated with different screening options. The appropriate age-range for a programme based on faecal testing was agreed by the Expert Advisory Group to be 55 to 74 years and is in line with international recommendations and screening programmes implemented in other countries. Three core screening options were recommended by the Group:

- Biennial immunochemical faecal testing (FIT) at ages 55 to 74 years to be fully implemented over two consecutive years, hereafter, referred to as ('Biennial FIT at ages 55 to 74 years')
- Biennial guaiac-based faecal occult blood test (gFOBT) at ages 55 to 74 years (with reflex FIT testing) to be fully implemented over two consecutive years, (hereafter referred to as 'Biennial gFOBT at ages 55 to 74 years')
- Flexible sigmoidoscopy (FSIG) once only at age 60 (hereafter, referred to as once-off FSIG at age 60').

The cost-effectiveness of age-related variations of the three core scenarios were also evaluated by the Evaluation Team to aid decision making and included:

- Biennial FIT at ages 55 to 64 years
- Biennial FIT at ages 65 to 74 years
- Biennial gFOBT at ages 55 to 64 years
- Biennial gFOBT at ages 65 to 74 years
- FSIG once only at age 55 years.

The HTA also investigated a staggered implementation of the FIT-based screening option (55 to 74 years) incorporating different ages over several years to determine the impact on resources and health outcomes.

5.4 Outcomes evaluated

The main analysis in this HTA (the cost-effectiveness analysis) examined health outcomes in terms of QALYs gained and LYG for each of the three main screening options. Secondary health outcomes evaluated in this analysis included:

- Reduction in the lifetime incidence of colorectal cancer (that is, the number of new cases of colorectal cancer occurring)
- Reduction in the lifetime number of deaths due to colorectal cancer
- Percentage of all cases of colorectal cancer that would be detected by screening
- Stage distribution of cancers detected in the screening programme compared with stage distribution of cancers detected without screening (henceforth referred to as 'symptomatically-detected cancers')
- Rates of complications (major bleeding, bowel perforation, deaths due to perforation)
- Lifetime rates of endoscopy procedures.

In a separate analysis on resources and health outcomes in the first ten years of a screening programme, the following health outcomes were examined:

- The number of deaths due to colorectal cancer in the first ten years of a screening programme
- The number of cases of colorectal cancer occurring in the first ten years of a screening programme.

Costs involved for each screening option, as well as the costs involved in managing colorectal cancers and surveillance of intermediate and high-risk adenomas, were evaluated in this HTA. Costs were measured in euro and were examined from the perspective of the Health Service Executive (HSE). This means that only direct costs to the HSE were taken into account. Costs incurred by the patient (for example, travel expenses, time off work) or costs to society (for example, carers' time, loss of productivity) were not taken into account. ICERs were computed for each option compared to no screening and subsequently were calculated for the various screening options compared to each other.

5.5 Economic modelling approach

As the HTA required the prediction of outcomes and costs occurring in the future, it was necessary to use economic modelling in the evaluation. An independent economic model, the ScHARR colorectal cancer screening model that was previously used to conduct an economic evaluation of screening in England, was updated and modified to the Irish setting[37]. Estimates and data on the efficacy of the screening tests, likely uptake of screening, frequency of disease, treatment patterns and resource use were incorporated into the model. These data were mainly obtained by literature review as described earlier and came from published trials and studies, other population-based screening programmes, Irish databases, and where relevant data was not available in the literature, from expert opinion. All estimates were approved by the Expert Advisory Group.

Within the timeframe of the HTA it was not possible to conduct specific micro-costing exercises. Therefore, cost estimates were compiled from a range of sources, including from single hospitals and pharmacies in Ireland, from the Diagnostic Related Group (DRG) costs (HSE Casemix unit), and from other studies.

The base-case analysis refers to the evaluation conducted using a set of agreed parameters. To deal with uncertainty in the true values of the parameters and to assess the robustness of the results, extensive sensitivity analysis was conducted. This involved repeating each evaluation using a range of parameter values in order to see whether the results were significantly affected by changing any particular parameter or all parameters simultaneously.

Following consultation with the National Cancer Screening Service (NCSS) and the National Cancer Control Programme, and with the agreement of the Expert Advisory Group, it was decided that the definition of a colorectal screening programme would encompass all procedures up to and including the completion of primary treatment. Thus for individuals with:

- Adenomas, screening would include everything up to and including removal of the polyp
- Colon cancer, screening would include everything up to and including removal of the cancer by surgery
- Rectal cancer, screening would include everything up to and including removal of the cancer by surgery. Since pre-operative radiotherapy is the standard of care, this would also be included in the screening programme.

Thereafter, the individual would enter the symptomatic services for further treatment or follow-up. This would include surveillance of individuals who had adenomas removed, with the frequency of follow-up depending on whether the individual was considered as low, intermediate or high risk.

Once individuals left the screening programme, they would return to the care of their General Practitioner (GP) or routine clinical services.

The impact of screening versus a policy of no population-based screening on health service resources was calculated for the ten years following commencement of a screening programme. These resources were agreed with the Expert Advisory Group and included:

- Colonoscopy resources (diagnosis and ongoing surveillance)
- Pathology for diagnosis and staging/risk classification
- Surgery for colon and rectal resection
- Radiology procedures (PET, CT scan, TUS, MRI) for work-up of cancers.

5.6 Assumptions

In conducting the HTA the following assumptions were made:

- Under the gFOBT and FIT options, test kits would be dispatched by post to screening invitees and returned by post for laboratory processing and analysis
- All lesions (cancers and adenomas) would be removed at detection by FSIG or colonoscopy
- No further surveillance would occur beyond 80 years of age
- Because of a lack of data on the performance characteristics (sensitivity and specificity) of combinations of screening tests (gFOBT with reflex FIT), it was assumed that the performance characteristics of gFOBT and reflex FIT are independent
- All those who have a positive gFOBT test will complete a FIT test
- All individuals in whom colonoscopy was incomplete or unsuitable will undergo CT colonography.

The resource model was structured to predict resource requirements if a screening programme were implemented immediately. That is, for biennial FIT- and gFOBT-based programmes, 50% of the eligible population (55 to 74 year olds) would be offered screening in year one (equating to 357,812 individuals) and the remaining 50% in year two (362,535 individuals).

Costs and outcomes occurring in the future were discounted (that is, adjusted for time-preference for costs (later) and benefits (now)) at a rate of 4% in accordance with recommendations of the Department of Finance.

6 Findings

6.1 Cost-effectiveness of possible screening options for a population-based screening programme in Ireland

As outlined in further detail below, the key finding of the economic evaluation in the primary analysis was that a population-based colorectal cancer screening programme based on, (i) biennial FIT at ages 55 to 74 years, (ii) biennial gFOBT at ages 55 to74 years or (iii) once-off FSIG at age 60 would be highly cost-effective compared to the current policy of no screening.

Secondary analysis demonstrated that a screening programme based on biennial FIT at ages 55 to 74 years (i) provided the greatest health gain (measured as QALYs gained) compared with no screening and (ii) was highly cost-effective when compared with all other screening options evaluated. It therefore represents the optimal screening strategy for a population-based colorectal screening programme.

6.1.1 Cost-effectiveness of core screening options compared to no screening

Each of the three screening options proposed by the Expert Advisory Group was compared to the current standard of care, that is, no population-based screening (Table 1).

Table 1: Cost-Effectiveness of Core Screening Options Compared to No Screening

Screening Option	ICER (€ / QALY)
Biennial FIT at ages 55 to 74 years	€1,696
Biennial gFOBT at ages 55 to 74 years	€4,428
Once-off FSIG at age 60 years	€589

When the analysis was repeated with LYG as the outcome, the above results changed little. This means that any of these options would be considered highly cost-effective in the Irish healthcare setting and compare favourably with recent economic evaluations of other interventions that have been recommended and approved for reimbursement. These include evaluations of universal infant pneumococcal conjugate vaccination (€5,997/LYG) and universal infant hepatitis B vaccination (€37,018/LYG)[38,39]. Internationally, screening for colorectal cancer has been considered to be cost-effective, and occasionally cost-saving, in most of the settings in which it has been evaluated.

Of the three core screening options evaluated, while a screening programme based on biennial FIT at ages 55 to 74 years was found to be the most costly, it was also found to be the most effective option, that is to say it would provide the greatest health gain as measured in QALYs gained compared to a policy of no screening.

6.1.2 Cost-effectiveness of core screening options compared to each other

In comparing the three core screening options with one another the following results were found (Table 2):

Table 2: Cost-Effectiveness of Core Screening Options Compared to Each Other

Screening Option	ICER (€ / QALY)
Biennial gFOBT at ages 55 to 74 years vs. Biennial FIT at ages 55 to 74 years Once-off FSIG at age 60	Dominated*
Biennial FIT at ages 55 to 74 years vs. Once-off FSIG at age 60	€2,058

* *More costly and less effective than a combination of these two screening options. An ICER was therefore not calculated for gFOBT vs FIT or FSIG.*

A screening programme based on biennial gFOBT was found to be the least favourable of the three options. In technical terms it is described as "dominated," that is more expensive and less effective than a combination of the other two options.

The ICER associated with investing in FIT compared to FSIG was €2,058 / QALY gained, which would be considered to be highly cost-effective in the context of the Irish healthcare setting.

Therefore, based on the evidence that it would provide the greatest health gain (QALYs) compared to a policy of no screening, while remaining highly cost-effective compared to the other screening options evaluated (gFOBT and FSIG), a screening programme based on biennial FIT for those aged 55 to 74 years was found to be the optimal screening option.

6.1.3 Cost-effectiveness of the age-related variations of the core screening options

When age-related variations of the core screening scenarios were compared to no screening, the most cost-effective strategies were biennial FIT at ages 55 to 74 years, biennial FIT at ages 55 to 64 years, and once-off FSIG at age 60. All other options were found to be dominated by these three options. When the three options were compared to each other, biennial FIT at ages 55 to 74 years:

- Provided the greatest health gain of the three screening options
- Had an ICER of €3,221 per QALY gained compared to biennial FIT at ages 55 to 64 years, that is to say, it would be considered highly cost-effective compared with restricting implementation to ages 55 to 64 years.

6.1.4 Robustness of the findings

Extensive sensitivity analysis was conducted to test the robustness of the findings and to identify circumstances that may alter the results. The results were sensitive to (that is to say, were changed by) a range of factors including the discount rate, cost of the screening tests, the cost of managing colorectal cancer, utility values (measure of patient preference or desirability for a specific health outcome), and, for gFOBT and FIT, the sensitivity of the test.

However, even when these parameters were set at their most extreme values, all three core options remained cost-effective; in some instances, they became cost-saving compared to no screening. The probabilistic sensitivity analysis confirmed the ranking of the three screening options in terms of their cost-effectiveness. It was noteworthy that if one of the newer, more sensitive guaiac-based tests were to be used, instead of one of the older, less sensitive tests, this could increase the cost-effectiveness of gFOBT compared to no screening.

6.1.5 Health gains

Significant improvements in health outcomes were predicted for each option compared with no screening. Biennial FIT at ages 55 to 74 years was associated with the greatest health gain (QALYs gained) in the primary analysis. Other health gains evaluated in the secondary analysis are summarised in Table 3.

Table 3: Predicted Reduction in Incidence and Mortality from Colorectal Cancer with Core Screening Options Compared to No Screening

Screening Option	% Reduction in lifetime incidence rate	% Reduction in lifetime mortality rate
Biennial FIT at 55 to 74 years	14.7	36.0
Biennial gFOBT at 55 to 74 years (with reflex FIT testing)	1.0	11.8
FSIG once only at 60 years	4.9	7.5

Of the three screening options, a programme based on biennial FIT at ages 55 to 74 years was associated with the largest predicted reduction in colorectal cancer incidence (-15%) and mortality rates (-36%). It was also associated with a much higher percentage of cancers detected by screening (30%) than either a programme based on biennial gFOBT (14%) or once-off FSIG (3%) (Figure 1). Screen-detected cancers are typically detected at an earlier stage than cancers detected symptomatically. For all three core screening options, over 70% of screen-detected cancers would be stage 1 or stage II.

Figure 1: Estimated Lifetime Percentage of Cancers Detected through Screening, Surveillance and Symptomatic Presentation for the Core Screening Options

Figure 1.1: Biennial FIT at Ages 55 to 74 Years

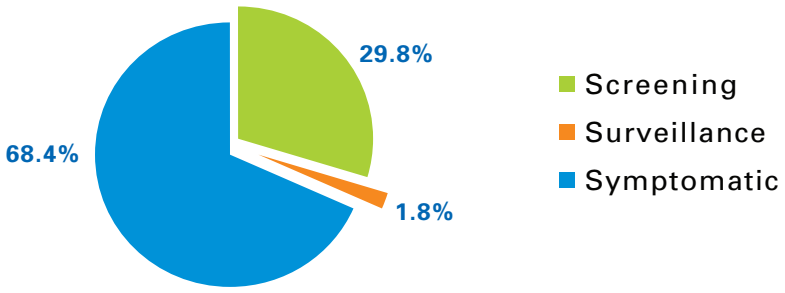


Figure 1.2: Biennial gFOBT at Ages 55 to 74 Years

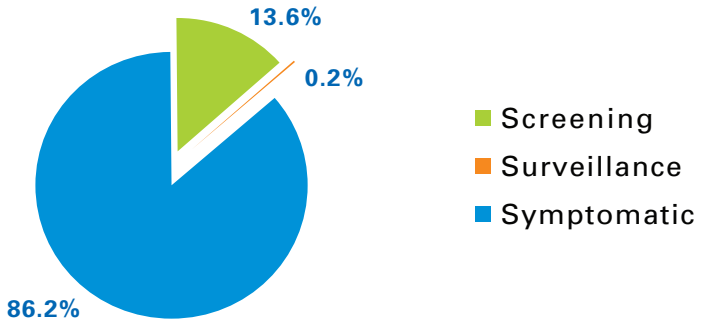
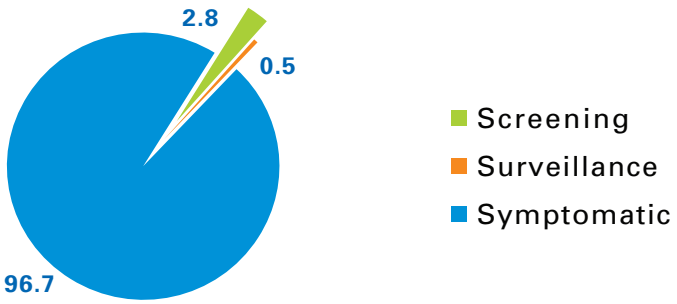


Figure 1.3: Once-off FSIG at Age 60



6.1.6 Summary of cost-effectiveness analysis

Of the three core screening options evaluated (FIT, gFOBT, FSIG), a screening programme based on biennial FIT for those aged 55 to 74 years would provide the greatest health gain (QALYs) compared to a policy of no screening while remaining cost-effective compared to the other screening options. Therefore, FIT was found to be the optimal screening option.

Consideration of the age-related variations in the core scenarios did not affect the key findings of the analysis. When the analysis was repeated with LYG as the outcome, the above results changed little. The findings remained cost-effective for all options in extensive sensitivity analysis to test the robustness of the findings.

6.2 Resource requirements and health outcomes

Implementation of a screening programme requires resources to (i) implement the screening programme in the first instance and (ii) to follow up individuals who test positive during screening. One of the key criteria for establishing a screening programme is that there should be sufficient facilities available for the diagnosis and treatment of individuals who have a positive screening test or disease detected through screening.

The resources evaluated in this HTA included those required for the diagnosis, treatment and follow-up surveillance of adenomas and cancers detected through the screening programme. A summary of the key screening related resource use and health outcomes is presented below. Overall, it was predicted that the resource requirements in the first ten years of screening would be greatest for a programme based on FIT compared to programmes based on gFOBT or FSIG. This would include significantly greater requirements for colonoscopies as well as the increased requirements to diagnose, treat and follow-up on the ensuing greater yield of screen-detected cancers and adenomas.

6.2.1 Participants in screening programme

Assuming a 53% uptake for a screening programme based on FIT or gFOBT, an estimated 189,640 test kits would be returned for processing in year one. Likewise, for a programme based on FSIG, assuming 39% uptake, an estimated 18,617 patients would present for screening in year one. These figures would increase by between 11% (FSIG) and 16 to 17% (FIT / gFOBT) by year ten of the screening programme being implemented due to projected increases in the population. (Table 4)

Table 4: Summary of estimated screening-related resource use and health outcomes (number) by year of programme

Screening scenario	gFOBT at 55 to 74 years		FIT at 55 to 74 years		Once-off FSIG at 60 years	
Resource/health outcome	**Year 1**	**Year 10**	**Year 1**	**Year 10**	**Year 1**	**Year 10**
Participants						
Invited to Screen	357,812	420,151	357,812	417,464	30,520	33,811
Screened[1]	189,640	222,637	189,640	220,999	18,617	20,625
Endoscopy Requirements						
FSIG[2]	0	0	0	0	18,617	20,625
Diagnostic colonoscopies[3]	967	1,103	11,095	12,414	381	423
Ssurveillance colonoscopies[3]	0	297	0	2,406	0	620
Complications of Screening						
Major bleeding following endoscopy	4	6	48	62	7	10
Perforation following endoscopy	2	2	21	27	1	2
Death following perforation	0	0	1	1	0	0
Adenomas & Cancers Detected						
Screen-/ surveillance-detected adenomas	366	537	3,320	4,327	808	1,128
Screen- /surveillance-detected colorectal cancers	309	336	853	687	64	78
Procedures Required						
Colorectal resections	281	307	779	635	59	71

1 *Assuming 53% uptake of FIT and gFOBT-based options and 39% uptake of FSIG*

2 *All individuals that attend for screening are screened using FSIG*

3 *Diagnostic colonoscopies would be delivered as part of the screening programme; surveillance colonoscopies would be delivered as part of the routine symptomatic services programme.*

6.2.2 Impact on colonoscopy/CT colonography resources

The number of colonoscopies required for FIT-based screening was predicted to be ten times higher than that for screening based on gFOBT, due to the greater sensitivity of the immunochemical test. This would result in much larger numbers initially being referred for diagnostic investigation and subsequently entering surveillance for intermediate and high-risk adenomas.

For FIT in year one of the programme, resources would be required to perform over 11,000 additional diagnostic colonoscopies increasing to 12,414 colonoscopies by year ten. The diagnostic resources required for gFOBT would be one-tenth of those required for FIT. With once-off FSIG, the estimated number of diagnostic colonoscopies required ranged from 381 in year one to 423 in year ten. (Table 4) The estimated number of surveillance colonoscopies required was predicted to increase to 297, 2,406 and 620, for screening programmes based on gFOBT, FIT and once-off FSIG, respectively.

Requirements for CT colonography for the diagnostic investigation of those with a positive test would also be much greater for a screening programme based on biennial FIT (55 to 74 years) than screening based on gFOBT or FSIG. For FIT in year one of the programme, resources would be required to perform 1,442 CT colonographies; rising to 1,614 scans in year ten. The diagnostic resources required with gFOBT would be one-tenth of those required for FIT.

6.2.3 Impact on pathology/radiotherapy

A screening policy based on biennial FIT in the 55 to 74 age group would result in the largest number of cancers detected and hence would have the greatest requirements for histopathology. This number would fall in time with repeated screening. In year one of the programme, capacity would be required nationally for histopathology of an additional 824 cancers. However, from year six onwards the predicted national pathology capacity for colorectal cancer would be lower with a screening programme than with the current policy of no screening. A similar pattern is predicted for other resources related to cancer diagnosis and treatment (although the impact on surgery is not predicted until year 9).

For example, in year one, increased capacity would be required to provide pre-operative radiotherapy for an additional 192 rectal cancers detected by screening, but by year ten the requirements for radiotherapy would be less than those predicted for a policy based on no screening.

6.2.4 Impact on surgery

The requirement for colon and rectal resections would increase for all screening options, but would be highest for a screening programme based on FIT, as a function of the larger number of cancers detected by this screening option. (Table 4). However, by year 10, the predicted national requirement for colorectal surgery would be lower with a screening programme based on FIT than with a policy of no screening.

6.2.5 Overall impact on colorectal cancer resources (screening or symptomatic services)

While a screening programme based on any of three core screening options would require an initial investment in new resources, after the first five years of a screening programme based on FIT there would be a potential to bring about reductions in overall requirements for pathology, pre-operative radiotherapy, colorectal resections, PET, MRI, CT scans and TUS (transrectal ultrasound) compared with a policy of no screening. For example, by year ten of a screening programme based on FIT, the overall requirement for surgery (patients presenting through screening or symptomatic services) would be lower than with the current policy of no screening (26 fewer colon resections and three fewer rectal resections). This effect was most notable with an FIT-based programme. It should be noted, however, that screening uptake rate was found to significantly impact on the resources required.

6.2.6 Health Outcomes

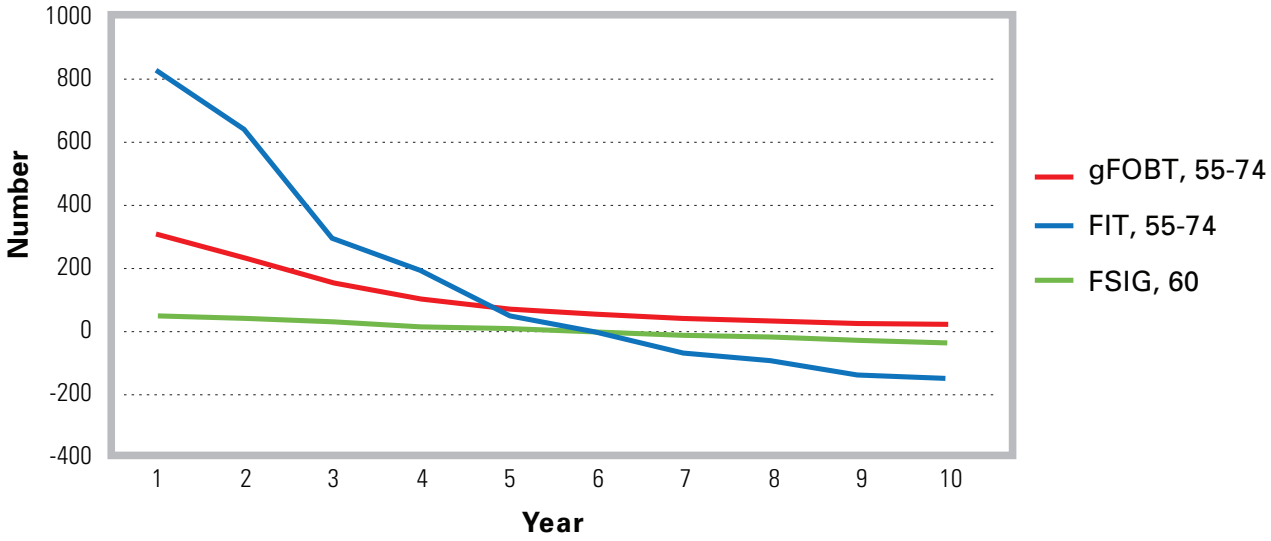
A consequence of the improved detection of cancers through a screening programme based on FIT is that over 30% of colorectal cancers diagnosed in Ireland would be expected to come from screening services rather than the symptomatic services, with in excess of 70% of these cancers diagnosed at stage I or II. However, as noted previously, colonoscopies are invasive procedures that are not without risk. While the risk to the individual patient would remain low, an important consequence of the increased number of colonoscopies associated with a screening programme based on FIT is that there would be a proportionate increase in the projected incidence of potential complications such as colonoscopy-associated major bleeding, bowel perforation and rarely, death. (Table 4) Based on international evidence from established screening programmes, the estimated risk for the individual patient would be low, nonetheless, these negative outcomes are an important consideration when evaluating population-based screening programmes.

Compared to a policy of no screening, screening based on biennial FIT in the 55-74 age group would be expected to bring about a greater reduction in the number of cases of colorectal cancers occurring and the numbers of deaths from colorectal cancer than the other two core options. The model predicted that, with an FIT-based programme, a reduction in the total number of colorectal cancers in Ireland would be expected from year six of the programme onwards, with approximately 160 cases averted in year ten. A reduction in mortality would be expected from year two onwards, with approximately 270 deaths from colorectal cancer avoided in year ten. (Figure 2) As noted previously, the potential to realise these benefits will depend greatly on the uptake of screening in the population.

Figure 2: Estimated difference in numbers of cases of, and deaths from, colorectal cancer in the population with screening versus a policy of no screening, over years 1-10, core screening scenarios

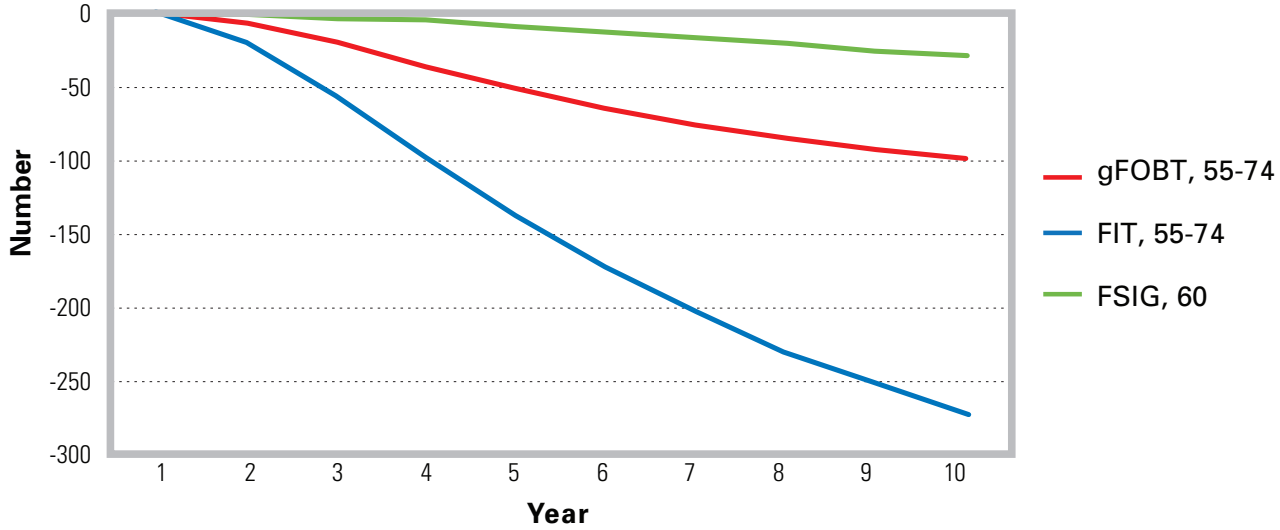
(a) Colorectal cancer cases

Difference between total colorectal cancers detected in the population with screening versus no screening, by year and scenario



(b) Deaths from colorectal cancer

Difference between total colorectal cancer deaths in the population with screening versus no screening, by year and scenario



6.3 Alternatives to an immediate and full implementation of a biennial FIT (ages 55 to 74 years) programme

There are various options for reducing the initial resource requirements associated with implementing biennial FIT-based screening. Rather than screening the full age-group immediately in the first two years of the programme, different implementation options could be considered, such as restricting screening to those aged 55 to 64 years, or staggered implementation of screening across the 55 to 74 year age-group.

The advantage of the options based on staggered implementation is that they would allow for capacity to be built-up gradually over the initial years of the programme. The details of the staggered implementation (for example, the number of years it would take to encompass the entire 55 to 74 age group in the programme) could be designed to match the speed at which capacity could be made available.

In considering the different implementation options, a staggered implementation of screening in the 55 to 74 age group would be preferable to immediate implementation in the 55 to 64 age group. This is because the cost-effectiveness results indicate that, in future years, when a programme based on the 55 to 74 age group was fully operational, it would result in a greater overall health gain than a programme limited to the 55 to 64 age group.

A screening programme based on biennial gFOBT, with reflex FIT, in the 55 to 74 age group, or FSIG once at age 60, would also remain highly cost-effective compared to a policy of no screening. However, it should be borne in mind that neither of these programmes would achieve the same health gains as a programme based on FIT.

6.4 Limitations

As with any HTA, the findings of this type of economic analysis are dependent on the quality of the data on which the model is based. There were important limitations in the evidence-base. The evidence relating to the performance characteristics of the screening and diagnostic tests was of particular concern.

In addition, there is a lack of robust Irish cost data. However, extensive sensitivity analysis has been conducted as part of the HTA and the key findings were not found to be altered.

6.5 Ethical Commentary

The ethical commentary highlighted the importance of an effective and comprehensive informed consent process, appropriately trained personnel, and robust quality assurance procedures in relation to the handling and communication of risks associated with implementation of screening in asymptomatic individuals.

7 Conclusions

The following conclusions arise from this HTA:

1 Compared to a current policy of no screening, a population-based screening programme for colorectal cancer in Ireland based on biennial FIT or gFOBT in individuals aged 55 to 74 years old or once-off FSIG in individuals aged 60 years old would be highly cost-effective.

2 Of the three core screening options evaluated (FIT, gFOBT, FSIG), a screening programme based on biennial FIT for those aged 55 to 74 years would provide the greatest health gain (QALYs) compared to a policy of no screening. This strategy would also result in:

   a. The highest estimated lifetime reduction in the incidence (14.7%) and mortality (36.0%) from colorectal cancer

   b. The highest percentage of screen-detected cancers.

3 A screening programme based on FIT would cost most more than programmes based on gFOBT or FSIG, however, it would provide the greatest health gain (QALYs) compared to a policy of no screening, while remaining highly cost-effective relative to the other screening options, and was therefore determined to be the optimal screening option.

4 In the first ten years of programme implementation, a screening programme based on FIT at ages 55 to 74 would detect the highest number of adenomas and cancers. In addition, compared to a policy of no screening, it would result in more colorectal cancer cases and deaths averted in the population than either of the other screening options evaluated. These gains would be seen within this ten-year window. In the cases of deaths averted, the benefit would be seen by the second year of programme implementation.

5 All screening options would be associated with increased resource requirements in the first ten years of a programme, with FIT placing the greatest demand on resources due to the large number of colonoscopies and the additional resources required to diagnose, treat and provide follow-up for cancers and adenomas detected during screening and surveillance.

6 In considering alternative options to full and immediate implementation of biennial FIT (ages 55 to 74 years), staggered implementation of screening in the 55 to 74 year age group over several years would be cost-effective once fully implemented and would allow screening capacity to be built gradually in the system.

7 Notwithstanding the fact that a programme based on FIT would be the optimal strategy in terms of cost-effectiveness, a screening programme based on biennial gFOBT with reflex FIT in the 55 to 74 age group, or FSIG once at age 60, would also be considered highly cost-effective compared to a policy of no screening.

8 The Ethical Commentary highlighted the importance of an effective and comprehensive informed consent process, appropriately trained personnel, and robust quality assurance procedures in relation to the handling and communication of risks associated with implementation of screening in asymptomatic individuals.

Advice to the Minister for Health and Children

The Health Act 2007 states that one of the functions of the Health Information and Quality Authority is 'to evaluate the clinical and cost-effectiveness of health technologies including drugs and provide advice arising out of the evaluation to the Minister and the Executive.'

The advice to the Minister for Health and Children on a population-based colorectal cancer screening programme is outlined below.

As economic models incorporate a number of assumptions and are dependent on the quality of data available, the results are subject to a degree of uncertainty. Bearing in mind the estimates and assumptions that were used in this analysis, the following conclusions can be drawn:

1 Each of the three screening options (biennial FIT (55 to 74 years), biennial gFOBT (55 to 74 years) or once-off FSIG at age 60) proposed by the Expert Advisory Group would be considered highly cost-effective compared to a policy of no screening in the Irish healthcare setting and would compare very favourably with recent economic evaluations of other interventions that have been recommended and approved for reimbursement. These include evaluations of universal infant pneumococcal conjugate vaccination (€5,997/LYG) and universal infant hepatitis B vaccination (€37,018/LYG).

2 Compared to no screening, the following ICERs were obtained for the core screening scenarios:

- Biennial FIT (55 to 74 years): €1,696/QALY
- Biennial gFOBT (55 to 74 years): €4,428/QALY
- Once-off FSIG at age 60 years: €589/QALY.

3 Of the three core screening options evaluated (FIT, gFOBT, FSIG), a screening programme based on biennial FIT for those aged 55 to 74 years would provide the greatest health gain (QALYS or LYG) compared to a policy of no screening. This strategy would also result in:

- The highest estimated lifetime reduction in the incidence (14.7%) and mortality (36.0%) from colorectal cancer;
- The highest percentage of lifetime cases of screen or surveillance-detected cancers (31.6% of all cancers versus 13.8% for gFOBT and 3.3% for FSIG) and adenomas. Screen-detected cancers are more likely to be detected at an earlier stage (stage I or II) than those detected symptomatically and therefore would be associated with improved survival rates.

4 In comparing the three screening options with one another:

- Biennial FIT at ages 55 to 74 years would be the most effective screening option providing the greatest health gain (QALYs and LYG gained).
- Biennial FIT at ages 55 to 74 would be more costly than once-off FSIG at 60 years. However, at an ICER of €2,058 per additional QALY, investing in FIT compared to FSIG would be considered highly cost-effective in the Irish healthcare setting.
- A screening programme based on biennial gFOBT was found to be the least favourable option in the cost-effectiveness analysis, as it would be more costly and less effective than a combination of the other two options.

5 In summary, the results of the cost-effectiveness analysis show that a screening programme based on FIT would cost most more than programmes based on gFOBT or FSIG, however, it would provide the greatest health gain (QALYs or LYG) compared to a policy of no screening, while remaining highly cost-effective relative to the other screening options, and is therefore recommended as the optimal screening option.

6 The resource analysis showed that the resource requirements in the first ten years of programme based on biennial FIT at ages 55 to 74 years would be greater than those required for the other screening options. This includes resources for the diagnosis, management and surveillance of screen-detected adenomas and cancers.

7 In the first ten years of programme implementation and compared to a policy of no screening, a screening programme based on FIT at ages 55 to 74 years would:

- Detect the highest number of adenomas and cancers
- Avert more colorectal cancer cases and deaths in the population than either of the other screening options evaluated. Approximately 160 cases of cancer and 270 deaths from colorectal cancer would be avoided in year ten of a screening programme based on FIT. In the case of deaths averted, the benefit would be seen by the second year of programme implementation
- Have the highest endoscopy requirement with an additional 11,000 to 15,000 colonoscopies being required each year
- Result in the highest number of individuals suffering adverse consequences of screening (for example, major bleeding, bowel perforation or rarely, death from perforation) as a consequence of the higher number of colonoscopies
- Require the largest number of resources to manage and treat screen-detected adenomas and cancers (for example, histopathology, radiology, radiotherapy and surgery) due to the higher yield of adenomas and cancers detected.

8 These resource requirements for a programme based on FIT, are based on an assumed screening uptake rate of 53%. Should uptake be considerably higher or lower than this, then, the resources required, yield of screen-detected cancers and adenomas, health outcomes gained (cases and deaths of colorectal cancer averted) and number of screening-related adverse events suffered would vary accordingly. However, in the context of all the resources examined as part of this evaluation, only a screening programme based on FIT has the potential to reduce several of these cancer resource requirements from year six onwards compared to continuing a policy of no screening.

9 A number of options were evaluated that would reduce the initial resource requirements associated with implementing population-based screening and to allow capacity to build gradually in the system. Of the options considered, a programme based on staggered implementation of FIT for those in the 55 to 74 year age group was found to be the optimal strategy and preferable to limiting screening to a restricted age group (such as 55 to 64-year-olds), as once fully operational, this option would provide the greatest overall health gain. The details of the staggered implementation (how many years it would take to encompass the entire 55 to 74 year age group) could be designed to match the speed at which capacity could be made available in the system.

10 Notwithstanding the fact that a programme based on FIT would be the optimal strategy in terms of cost-effectiveness, a screening programme based on biennial gFOBT in the 55 to 74 age group, or FSIG once at age 60, would still be considered highly cost-effective compared to a policy of no screening.

11 No particular areas of concern were noted in the ethical commentary when colorectal cancer screening was compared to other population-based screening programmes. It was noted, however, that while the absolute risk of screening-related adverse events for the individual is low, the risk of death from perforation of the bowel under a policy of biennial FIT at ages 55 to 74 at a population level, emphasises the importance of informed consent, the availability of trained personnel to assist with the informed consent process and the requirement for appropriate quality assurance in the governance and running of a screening programme to mitigate some of the risks that may be associated with implementation of screening in asymptomatic individuals.

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Technical Report

Health technology assessment (HTA) of a population-based colorectal cancer screening programme in Ireland

13 March 2009

Report Prepared by

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for the **Health Information and Quality Authority**

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Conflicts of interest

None declared

Abbreviations and acronyms

AJCC	American Joint Committee on Cancer
ASR	age-standardised rate
CC	colon cancer
CEA	carcinoembryonic antigen
CEAC	cost-effectiveness acceptability curve
CEAF	cost-effectiveness acceptability frontier
CI	confidence interval
COL	colonoscopy
CRC	colorectal cancer
CRD	Centre for Reviews and Dissemination
CSO	Central Statistics Office
CT	computed tomography
CTC	CT colonography ("virtual" colonoscopy)
DALY	disability adjusted life year
DCBE	double contrast barium enema
DES	discrete events simulation
DNA	deoxyribonucleic acid
DRG	diagnostic related group
EGFR	human epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
FA	folinic acid
FAP	familial adenomatous polyposis
FIT	faecal immunochemical test
FOLFIRI	folinic acid, 5-FU and irinotecan
FOLFOX	folinic acid, 5-FU and oxaliplatin
FSIG	flexible sigmoidoscopy
gFOBT	guaiac faecal occult blood test
HIQA	Health Information and Quality Authority
HNPCC	hereditary non-polyposis colorectal cancer
HRQoL	health-related quality of life
HSE	Health Service Executive
HTA	health technology assessment
IBD	inflammatory bowel disease
ICD	International Classification of Diseases

ICER	incremental cost-effectiveness ratio
LCR	laproscopic colonic resection
LYG	life years gained
MIMS	the Monthly Index of Medical Specialties
MLE	maximum likelihood estimation
MRI	magnetic resonance imaging
NICE	National Institute for Clinical Excellence
NCCP	National Cancer Control Programme
NCRI	National Cancer Registry Ireland
NCSS	National Cancer Screening Service
NHS	UK National Health Service
NORCCAP	Norwegian Colorectal Cancer Prevention study
OCR	open colonic resection
PET	positron emission tomography
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
PPV	positive predictive value
PRT	preoperative radiotherapy
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life years
RC	rectal cancer
RCT	randomised controlled trial
RR	relative risk
ScHARR	School for Health and Related Research
SCORE/2/3	Italian colorectal cancer screening trial(s)
SIG	(rigid) sigmoidoscopy
TME	total mesorectal excision
TUS	transrectal ultrasound
UICC	International Union Against Cancer
UK	United Kingdom
US	United States
USPSTF	United States Preventive Services Task Force
VEGF	human vascular endothelial growth factor
WHO	World Health Organisation
YLS	years of life saved
5-FU	fluorouracil

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Executive Summary

Background

In Ireland, colorectal cancer is the second most commonly diagnosed cancer in both men and women. Each year, during 2002 to 2005, an average of 2,040 new cases were diagnosed, 1,160 in men and 880 in women. During the same time period an average of 925 people died from the disease each year. Incidence rates in Ireland rank among the highest in Western Europe for both men and women. For mortality, rates in men in Ireland exceed those in other Western European countries, while mortality among women is in the mid-range of rates reported across the continent. Survival for those diagnosed with colorectal cancer in Ireland is below the European average. However, in common with trends in other countries, survival has been increasing in Ireland: five-year relative survival was around 52% for those diagnosed in 1997-2001 and is estimated to be 57% for those diagnosed in 2002-05. Stage is an important predictor of prognosis. Currently in Ireland, 11% of cases are diagnosed at stage I, 24% at stage II, 26% at stage III and 22% at stage IV; for the remaining 17% the stage is unknown. By 2020, the number of new cases of colorectal cancer diagnosed each year in Ireland is projected to increase by 79% in men and 56% in women, compared to 1998-2002. This increase is due mainly to predicted demographic changes.

Several strands of evidence suggest that the majority of colorectal cancers develop from adenomatous polyps (adenomas). Various screening tests are available which can detect adenomas or early colorectal cancers. A variety of international organisations now recommend that men and women aged 50 and older should participate in colorectal cancer screening. Currently in Ireland there is no organised colorectal cancer screening of average-risk individuals outwith the context of specific research studies or opportunistic activities.

The ultimate aim of a screening programme is to reduce mortality from colorectal cancer in the population. This is achieved by detecting the cancer at an earlier stage in its natural history than it would have otherwise been found in the absence of screening. Earlier detection of disease through screening can also reduce morbidity and improve health outcomes. However, the establishment of a screening programme also brings with it the possibility of harms (e.g. anxiety due to false positive results, complications associated with diagnosis and treatment). In addition, there are significant costs in setting-up and running the programme. The issue for decision-makers is the relative balance of these costs (including harms) and health benefits in the population.

Economic evaluations of different options for colorectal cancer screening in average-risk populations have been conducted in various countries. Although these studies are not directly comparable, in most settings screening was considered to be cost-effective. In some settings it was cost-saving compared to no screening. The extent to which these conclusions can be generalised to Ireland are unclear. Local factors such as underlying prevalence of adenomas, screening uptake, compliance with follow-up and costs of treatment will impact on cost-effectiveness.

Aim and objectives

The purpose of this health technology assessment (HTA) was to evaluate various options for a population-based colorectal cancer screening programme in Ireland.

The objectives were, to estimate:

(i) for each screening option, the cost-effectiveness of a colorectal cancer screening programme compared to a policy of "no screening" (i.e. the status quo);

(ii) the incremental cost-effectiveness of the alternative screening options; and

(iii) for each screening option, the key resource requirements (e.g. colonoscopy capacity) and health outcomes (e.g. numbers of individuals with adenomas detected) in the initial ten years of a programme.

Methods

An Expert Advisory Group (EAG), comprising clinical experts, key stakeholders and patient and public representatives was established by the Health Information and Quality Authority to advise on various aspects of the HTA. An important role of the EAG was to consider which screening scenarios should be evaluated. Giving due cognisance to the timeframe within which the HTA had to be completed, the scenarios were defined based on the volume and strength of the available scientific evidence, knowledge of screening practice in other countries, and considerations such as likely acceptability and feasibility.

In that context, three core screening scenarios were endorsed by the EAG:

- biennial immunochemical faecal testing (FIT) at ages 55-74;
- biennial guaiac-based faecal occult blood testing (gFOBT) at ages 55-74, with those with a positive gFOBT subsequently undergoing FIT (i.e. reflex FIT);
- flexible sigmoidoscopy (FSIG) once only at age 60.

The EAG endorsed suggestions from the Evaluation Team (ET) that, in order to inform the decision-making process, the cost-effectiveness of a series of age-related variants of the core scenarios should be evaluated in secondary analyses. The additional scenarios evaluated were:

- biennial FIT at ages 55-64;
- biennial FIT at ages 65-74;
- biennial gFOBT at ages 55-64;
- biennial gFOBT at ages 65-74; and
- FSIG once only at age 55.

Under the gFOBT and FIT scenarios it was assumed that test kits would be dispatched by post to screening invitees, completed, and returned by post for laboratory processing and analysis. It was further assumed that in each two-yearly screening round approximately half of all eligible individuals would be invited for screening in the first year and the remainder in the second year. FSIG would be conducted in designated screening centres by health professionals. Diagnostic investigation would be mainly by colonoscopy, with CT colonography offered to those unfit for colonoscopy or in whom colonoscopy was incomplete. Lesions would be removed by polypectomy where possible. Post-polypectomy surveillance of those with adenomas considered to be intermediate- or high-risk would follow current UK consensus recommendations.

An economic modelling approach was adopted for the evaluation of the scenarios. The model used was a modified version of the colorectal cancer screening model originally developed by ScHARR (School of Health And Related Research, University of Sheffield). The model comprised three sub-models relating to the natural history of colorectal neoplasia, the various screening scenarios, and mortality. Various modifications were made, including updates to incorporate advances in knowledge about the natural history of colorectal neoplasia and current post-polypectomy surveillance guidelines.

Two approaches were taken to running the model. The first employed a single cohort approach, in which a cohort of 55-year old individuals was followed over their lifetime (since 55 is the age at which screening would start). This approach was used to assess cost-effectiveness. The second approach was based on the whole population, and was used to calculate resource requirements and health outcomes in the first 10 years of implementation of a screening programme. The model was adapted to the Irish setting by calibrating to colorectal cancer incidence and mortality data for Ireland. Since one of the main reasons that economic models are used in decision making is to bridge the gaps in the available data or evidence, this inevitably means that the values of some of the data items used in the models (the model parameters) are not known precisely. The model was further modified to incorporate extensive sensitivity analyses, in which the robustness of the results to changes in parameter values was assessed.

Systematic reviews of the literature were undertaken to inform estimates for the key model parameters including those relating to the performance of the screening and diagnostic tests, harms of screening (major bleeding, bowel perforation, death from perforation), screening uptake, compliance with diagnostic tests, and health-related quality of life. Where relevant data was not available, parameter estimates were based on expert clinical opinion. Costs of screening and diagnostic tests, and the lifetime costs of managing colorectal cancer were estimated for Ireland. For each parameter, a base-case value and range were identified, the latter for use in sensitivity analyses. Also for sensitivity analyses, each parameter was assigned a probability distribution, based on consideration of the properties of the parameter and the data informing it. The parameters and their ranges were endorsed by the EAG.

Both cost-utility and cost-effectiveness analyses were undertaken, with health outcomes measured in terms of quality-adjusted-life-years gained (QALYs) and life years gained (LYG), respectively. Incremental cost-effectiveness ratios (ICERs) were computed for each screening scenario compared with a policy of no screening.

Scenarios which were not dominated (i.e. those which were least costly and most effective) were then compared with one another in terms of ICERs. The healthcare payer perspective (i.e. HSE/Department of Health and Children) was adopted and costs and benefits were discounted at 4%. The models were run with parameters set at their base-case values. The values of key model parameters were then allowed to vary in one-way and multi-way sensitivity analyses. A comprehensive probabilistic sensitivity analysis, in which all parameters were varied simultaneously, was also conducted. From this, cost-effectiveness acceptability curves were created.

In the analysis of resource requirements and health outcomes, the specific resources to be estimated were agreed with the EAG and included requirements for: colonoscopy for diagnostic and surveillance purposes, pathology for adenomas and cancers, diagnostic radiology for cancers, neo-adjuvant radiotherapy and colorectal resection. Health outcomes estimated included harms of screening and numbers of individuals diagnosed with adenomas and cancers.

The primary analysis estimated, for each scenario: (i) the screening-related resources required; and (ii) the screening-related health outcomes achieved, each year over the first 10 years of programme implementation. Secondary analyses estimated, for each screening scenario versus a policy of no screening, (i) the additional resources required at the population level; and (ii) the health gains achieved at the population-level, over the first 10 years of programme implementation. Thus the primary analyses related to the absolute resources required to deliver a screening programme, while the secondary analyses related to resources required across the population relative to a policy of no screening. The whole population approach was taken to running the model with parameters set at base-case values. Sensitivity analyses were undertaken to explore the impact of changing assumptions around (i) screening uptake, and (ii) the relationship between the performance characteristics of gFOBT and the reflex FIT. In order to assist in the decision-making process regarding the feasibility of implementing FIT-based screening, resources required for three alternative implementation options were also evaluated: immediate implementation in the 55-64 age group, and two options associated with staggered age-based implementation in the 55-74 age group.

Cost-effectiveness results

Table S.1 Incremental cost-effectiveness ratios (ICER) for core screening scenarios, versus no screening

Scenario	Incremental cost per person	Incremental QALYs per person	ICER -Incremental cost per QALY gained
gFOBT at 55-74 years	€ 33.63	0.0076	€ 4,428
FIT at 55-74 years	€ 40.17	0.0237	€ 1,696
FSIG once at 60 years	€ 3.43	0.0058	€ 589

Core scenarios

The results of the base-case analysis indicated that all three core scenarios were highly cost-effective compared to no screening (Table S1). Compared with no screening, FSIG once at age 60 had the lowest ICER (€589 per QALY gained), followed by FIT at 55–74 years (ICER €1,696 per QALY gained), and gFOBT at ages 55–74 (ICER €4,428 per QALY gained).

gFOBT was dominated by a combination of the other two scenarios, that is to say it was more costly and less effective, and from a cost-effectiveness perspective it would therefore be considered the least desirable of the three core options. In determining the optimal strategy in terms of cost-effectiveness, further consideration was therefore limited to FIT at ages 55-74 and FSIG once at age 60. Compared to no screening, FIT at ages 55-74 was associated with a much greater health gain (i.e. incremental QALYs) than FSIG at age 60 (Table S1). However, FIT at ages 55-74 was also associated with a greater cost per person, compared to no screening, than FSIG at age 60. When the two strategies were compared directly, the ICER associated with investing in FIT at ages 55–74 years compared to FSIG once at age 60 was €2,058 per QALY gained. This would be considered highly cost-effective. Therefore, in the base-case analysis, the optimal strategy was biennial FIT at ages 55-74.

Of the three core scenarios, biennial FIT at ages 55-74 was associated with the greatest lifetime reductions in colorectal cancer incidence (-15%) and mortality rates (-36%) for the cohort of 55-year old individuals. It also resulted in a much higher percentage of cancers which were screen-detected (30%) than gFOBT (14%) or FSIG (3%).

For each scenario, compared with symptomatically-detected cancers, greater percentages of screen-detected cancers were stage I or II and lower percentages were stage III or IV. For example, for biennial FIT at ages 55-74, 78% of cancers detected by screening were stage I or II, compared to 42% of those detected symptomatically.

Age-related variant scenarios

When age-related variations in the screening scenarios were evaluated, the most cost-effective strategies compared to no screening were: FSIG once at age 60, biennial FIT at ages 55-64, and biennial FIT at ages 55–74. All other scenarios were dominated. In directly comparing these three options with one another, the optimal strategy was FIT at age 55-74 (ICER of €3,221 per QALY gained compared to FIT at ages 55-64), followed by FIT at age 55-64 (ICER of €1,436 per QALY gained compared to FSIG once at age 60) and then by FSIG once at age 60. This ranking was mainly due to the fact that FIT in the 55-74 age group was associated with the greatest health gain.

Sensitivity analyses

When the analysis was repeated with LYG as the outcome, the results changed little. The sensitivity analyses showed that the results were robust to variations in the parameter estimates. In one-way and multi-way sensitivity analyses, several of the variables which were subject to the most uncertainty, such as screening uptake, had a negligible influence on cost-effectiveness. The most influential parameters were: the discount rate; the cost of the screening tests; the cost of managing colorectal cancer; utility (for gFOBT); test sensitivity (for gFOBT and FIT); and costs of colonoscopy (for FIT). Even for these parameters all three screening scenarios remained cost-effective when the parameters were set at their most extreme values. For example, the factor which had the biggest impact on the ICERs was the discount rate and, for FIT at 55-74 years, the ICER ranged from -€1,399 to €4,938 per QALY as the discount rate was varied from 0% to 6%. In addition, in every run of the probabilistic sensitivity analysis all scenarios remained cost-effective. This analysis also confirmed the rankings of the policies in terms of cost-effectiveness. Moreover, the cost-effectiveness acceptability curves indicated that FIT in the 55-74 age group was likely to be the most cost-effective strategy across a range of willingness-to-pay thresholds.

Resource requirements and health outcome results

Table S2: Summary of estimated screening-related resource requirements and health outcomes of the screening programme, by year of programme

Screening scenario, resource/ health outcome and year of programme	gFOBT at 55-74 years		FIT at 55-74 years		FSIG once at 60 years	
	Year 1	Year 10	Year 1	Year 10	Year 1	Year 10
No. screened	189,640	222,637	189,640	220,999	18,617	20,625
No. of diagnostic colonoscopies	967	1,103	11,095	12,414	381	423
No. of surveillance colonoscopies	0	297	0	2,406	0	620
No. with major bleeding following endoscopy	4	6	48	62	7	10
No. with perforation following endoscopy	2	2	21	27	1	2
No. of deaths from perforation following endoscopy	0	0	1	1	0	0
No. with screen- or surveillance-detected adenomas	366	537	3,320	4,327	808	1,128
No. with screen- or surveillance-detected colorectal cancers	309	336	853	687	64	78
No. undergoing colorectal resection	281	307	779	635	59	71

Screening-related resource requirements and health outcomes of screening

In year one of a programme based on gFOBT or FIT in those aged 55-74, assuming uptake of 53%, approximately 189,600 individuals would be screened (Table S2). With a programme based on FSIG once at age 60, assuming uptake of 39%, approximately 18,600 individuals would undergo screening. Between years one and 10 the number screened by FIT or gFOBT would increase by 16-17% and the number screened by FSIG would increase by 11%. This is entirely a result of demographic changes (i.e. an increase in the number of individuals of screening age in the population).

One of the key criteria for establishing a screening programme is that there should be sufficient facilities available for the diagnosis and treatment of individuals who have a positive screening test or disease detected via screening. Resource requirements for biennial FIT at ages 55-74 would be greater than those for screening based on gFOBT at ages 55–74 or FSIG once at age 60 (Table S2). Endoscopy requirements would be a major consideration for any screening programme. In the first 10 years of a programme, FSIG once at age 60 would require capacity to undertake 18,600-21,600 flexible sigmoidoscopies and between 380 and 1,050 colonoscopies annually for diagnostic or surveillance purposes. For the other two core scenarios, there would be no requirements for flexible sigmoidoscopy, but greater capacity would be needed within the screening programme for colonoscopies. For gFOBT at ages 55-74, capacity would be required for 1,000-1,400 diagnostic and surveillance colonoscopies each year. For FIT at ages 55-74, capacity would be required for 11,000-15,000 colonoscopies each year.

Although the absolute numbers of procedures would be much smaller, similar patterns to those seen for colonoscopy would be evident in requirements for CT colonography for diagnostic and surveillance purposes.

An important consequence of the greater numbers of colonoscopies associated with screening by biennial FIT at ages 55-74 than by the other core scenarios is that there is potential for more individuals to suffer screening-related complications (e.g. major bleeding, bowel perforation, and death from perforation: Table S2). However, the absolute risk to individuals of experiencing these events is small. Moreover, these harms should be offset against the much larger yield of adenomas and cancers that would be achieved with biennial FIT at ages 55–74 (Table S2). With FIT at ages 55-74, each year during years one to 10, approximately 3,300-4,300 individuals would have adenoma(s) detected by screening or surveillance, and 690-850 individuals would have cancer detected. This compares to 800-1,100 with adenoma(s) and 50 with cancers each year with FSIG-based screening and 370-540 with adenoma(s) and 310-340 with cancers with gFOBT-based screening.

The higher yield of cancers with FIT at ages 55-74 than with the other core scenarios, means that more resources would be required within the screening programme for cancer work-up and treatment (i.e. histopathology, radiology, neo-adjuvant radiotherapy and colorectal resection). Tables S2 illustrates these requirements for colorectal resection.

Population-level health gains and resource requirements

Biennial FIT at ages 55-74 would be expected to bring about a greater reduction in colorectal cancer incidence and mortality at the population-level (compared to no screening) than the other two screening options. Under this scenario, a reduction in the total number of colorectal cancers in Ireland would be expected from year six of the programme onwards, with approximately 160 cases averted in year 10. Since, by year 10, almost 30% of all colorectal cancer cases diagnosed in the population would result from FIT-based screening, and screen-detected cancers are more likely to be at an early stage than those found symptomatically, this strategy also has the potential to bring about a shift (albeit modest) in the overall stage distribution of cancers. Also with biennial FIT at ages 55-74, a decrease in the numbers of colorectal cancer deaths in the population would be expected from year two of the programme onwards, with approximately 270 deaths avoided in year 10.

Since screening has the potential to reduce numbers of colorectal cases diagnosed in the population, this means that it could also reduce requirements for (at least some of the) resources associated with work-up and treatment nationally. These potential reductions would be greatest for screening based on biennial FIT at ages 55-74 years.

Sensitivity analyses

Sensitivity analyses showed that the resources requirements and health outcomes would be heavily influenced by screening uptake. For example, if uptake of FIT-based screening was less than 53% (the base-case estimate), requirements for colonoscopies and pathology would fall. However, the number of screen-detected adenomas and cancers would also decrease. If uptake was higher (e.g. 70%), there would be an increase in the capacity required by the screening programme for diagnostic and surveillance colonoscopy, pathology, and cancer work-up and treatment, but the numbers of individuals found with adenomas and screen-detected cancers would also increase.

Alternative FIT-based implementation options

The alternative options for implementing biennial FIT screening evaluated included immediate implementation in the 55-64 age group, and two options associated with staggered age-based implementation across the 55-74 age group. All of these options would be less resource intensive (either overall or in the initial years) than immediate implementation of biennial screening across the full 55-74 age group. However, as a consequence, they would result in fewer screen-detected adenomas and cancers.

Discussion

The success of a population-based colorectal cancer screening programme will, ultimately, depend both on uptake among the population invited to be screened and on the capacity to diagnose, treat and follow-up those found to have adenomas and cancers. The cost-effectiveness analysis demonstrated that biennial FIT at ages 55–74 was the optimal screening strategy, resulting in the greatest health gain over

the lifetime of those invited for screening. In addition, this strategy would result in the greatest yield of screen-detected adenomas and cancers. Furthermore, it would have the greatest potential to save lives, averting the largest number of colorectal cancer cases and deaths (compared to no screening) in the population. However, the decision to select a particular screening strategy should also depend on resource considerations, and these are considerably larger for FIT at ages 55-74 than for the other core scenarios. Moreover, there is potential for more individuals to suffer screening-related complications although the absolute risk to an individual is low. These are the key issues which need to be weighed against one another in the decision-making process.

There would be various options for reducing the initial resource requirements associated with implementing biennial FIT based screening by adopting a staggered, age-based, implementation. This approach is attractive because it would allow for capacity to be gradually built up over the initial years of the programme and, once fully implemented, would be associated with the same cost-effectiveness as immediate implementation across the full 55-74 age group.

It is worth noting that if screening based on FIT was considered unfeasible for any reason, then a screening programme based on biennial gFOBT, with reflex FIT, in the 55-74 age group, or FSIG once at age 60, would still be considered highly cost-effective compared to a policy of no screening.

Costs to society (e.g. lost productivity among those diagnosed with cancer) were not included in the cost-effectiveness evaluation. This means that the results are likely to be conservative (i.e. to under-estimate the cost-effectiveness of screening compared to no screening). In terms of the resource use and health outcomes in the first 10 years of a screening programme, it should be borne in mind that these analyses were run at the base-case values of the parameter estimates. The actual resources required to deliver a population-based screening programme in Ireland, and the health outcomes that would be achieved by this programme, and in the population, will be highly dependent on a range of factors, including uptake of screening, compliance with diagnostic investigations, and the performance characteristics of the specific screening test implemented. In particular, screening uptake is likely to have a major influence on the health gains attainable at the population-level by screening.

Finally, it should be noted that findings of this type of economic analysis are dependent on the quality of the data on which the model is based. There were important limitations in the evidence-base and these need to be acknowledged. The evidence relating to the performance characteristics of the screening and diagnostic tests was of particular concern; the available data was weak and all of it was drawn from settings outside Ireland. This necessitated that various assumptions be made in the analysis as regards particular parameters. In addition, there were considerable uncertainties around the cost estimates. It was reassuring, therefore, that the extensive sensitivity analyses conducted did not alter the cost-effectiveness findings.

Conclusions

- A population-based screening programme for colorectal cancer in Ireland - based on biennial FIT at ages 55-74, FISG once only at age 60, or biennial gFOBT with reflex FIT at ages 55-74 - would be highly cost-effective compared to a policy of no screening.
- Of the options evaluated, biennial FIT at ages 55-74 would be associated with the greatest health gain (QALYs) compared to no screening. This strategy would also produce the greatest reductions in lifetime colorectal cancer incidence and mortality rates compared to no screening. Furthermore, it would result in a higher percentage of screen-detected cancers. Biennial FIT at ages 55-74 is therefore considered to be the optimal screening strategy.
- In the first 10 years of a screening programme, the requirements for diagnostic, treatment and follow-up surveillance services would be much greater for a programme based on biennial FIT at ages 55-74 than for a programme based on gFOBT or FSIG. However, screening by FIT at ages 55-74 would detect more adenomas and cancers. In addition, compared to a policy of no screening, it would result in more colorectal cancer cases and deaths averted in the population than the other options evaluated, and these gains would be expected to be seen within 10 years of programme implementation.

Chapter 1

Introduction

1.1 Colorectal cancer and screening

Colorectal cancer is a major health problem worldwide. Each year over a million new cases are diagnosed[1]. As five-year survival rates average about 55% in developed areas of the world, and just under 40% in less developed areas, mortality is about half of incidence, so that about 500,000 people die from the disease each year[1, 2]. Around two-thirds of the incident cases occur in developed countries, where colorectal cancer is the third most common cancer in men and the second most common in women.

The International Union Against Cancer (UICC) has argued that colorectal cancer fulfils long-established World Health Organization (WHO) criteria for screening - Appendix 1[3] and have strongly recommended that screening programmes are put into place[4]. The European Code against Cancer recommends that men and women aged 50 or older should participate in colorectal cancer screening, and that this should be within programmes with integrated quality assurance procedures[5]. In the USA, in an update of their 2002 statement[6], the Preventive Services Task Force has recently recommended screening for all adults beginning at age 50 and continuing until age 75[7].

There is considerable colorectal cancer screening activity underway internationally[8, 9, 10]. A 2007 review identified a total of 35 organised initiatives in 17 countries[8]. In some countries organised screening programmes are in place, or in the process of being rolled-out (for example, Australia, Austria, Canada, England, France, Germany, Italy, Poland, Scotland). In other countries, screening programmes are under evaluation in large, population-based, randomised controlled trials (for example, Finland, Netherlands, Norway). Elsewhere (for example, USA) there are strong recommendations that citizens undergo screening, but the organisation of this is left to the individual and/or their health-care practitioners.

1.2 Aim of population-based cancer screening programmes

A population-based screening programme is one where screening is systematically offered, by invitation, to a defined population. The ultimate aim of a such a programme is to reduce mortality from the disease (in this case, cancer) of interest in the population[11]. In some instances, depending on the natural history of the disease and the characteristics of the screening test (for example, whether there is a pre-cancerous lesion which can be detected by the screening test), it may also be possible to bring about a reduction in disease incidence in the population. These reductions in the disease burden are generally achieved by detecting the disease at an earlier stage in its natural history than it would have been found clinically and treating it, thus either preventing cases from occurring and/or preventing deaths. A further benefit that can result from treatment at an earlier stage is improved quality-of-life and reduced morbidity amongst those with the disease. However, these benefits are not free. Any screening brings possibilities of harms (for example, anxiety due to false

positive results, false reassurance of false negative results, complications or deaths associated with diagnosis or treatment). In addition there are costs associated with setting up and running the programme, as well as opportunity costs associated with the programme (i.e. costs spent on screening cannot be spent elsewhere). The issue for a screening programme is the relative balance of these costs (including harms) and benefits in the population[12].

1.3 Economic evaluation

Economic evaluation involves the comparative analysis of alternative courses of action (for example, screening versus no screening, or alternative screening tests versus one another) in terms of both their costs and their benefits (for example, health outcomes). Economic evaluations fall into three major categories: cost-effectiveness analysis; cost-utility analysis; and cost-benefit analysis. Although they employ similar methods to define and evaluate costs, the methods differ in the way in which the health benefits are assessed. In a cost-effectiveness analysis, the health benefit is measured in natural units (for example, life years gained (LYG)). This approach, however, is limited in that only a single measure can be used in comparing the cost-effectiveness of the alternatives. In particular, it cannot reflect the effects of one intervention on both the quantity and (health-related) quality of life (HRQoL)[13]. Cost-utility analysis enables the effects of treatment on HRQoL and survival to be considered together, by converting both into a common unit of measure. The most widely used outcome measure in cost-utility analysis is the quality-adjusted life-year (QALY; see section 1.3.2). In effect, cost-utility analysis is generally considered to be a particular type of cost-effectiveness analysis. Henceforth, the term cost-effectiveness is used to refer to both types of analyses. In cost-benefit analysis there is a requirement to convert both costs and consequences to monetary terms and determine the net present value as a difference in value between costs and benefits. The use of this method is limited by the methods used to translate benefits to monetary values[14].

1.3.1 Modelling in economic evaluation

Economic models provide a framework for decision making about alternative options or interventions (for example, for screening or treatment) under conditions of uncertainty[13]. They provide a way to bring together diverse sources of evidence and translate them into estimates of costs and effects, taking into account the uncertainty relating to the model structure and input parameters, thus allowing the alternatives to be compared.

Modelling is a particularly useful strategy for assessing the cost-effectiveness of screening. Randomised controlled trials (RCTs) and other studies of screening interventions rarely have a sufficiently lengthy time horizon to allow cost-effectiveness to be evaluated. Modelling facilitates the combination of data on costs and benefits from different sources and extrapolation into the future. The introduction of a population-based screening programme would incur substantial set-up costs and considerable ongoing running costs, while the benefits - such as reduced colorectal cancer mortality (and, possibly, incidence) and reduced expenditure on treatment - would take many years to accrue. Modelling allows the short-term nature of some costs to be offset against the long-term nature of the benefits. Factors such as underlying disease prevalence, screening uptake, compliance with follow-up, and costs of treatment impact on cost-effectiveness of screening. For this reason, the results of an economic modelling exercise in one setting cannot simply be extrapolated to another setting; cost-effectiveness modelling needs to be undertaken in each particular setting to which it is being applied.

In addition to incurring costs and benefits, implementation of a new screening programme has implications for existing clinical services, and may generate a requirement for extensions to current services or the establishment of new services (for example, for the follow-up of those with screen-detected lesions). These resource implications are entirely context-specific, and the analysis of resource requirements is sometimes performed side-by-side with a cost-effectiveness evaluation.

1.3.2 LYG and QALYs

The QALY is often considered the outcome of choice for economic evaluations of healthcare interventions[15] because it is recognized that most health treatments and programmes impact upon both length and quality-of-life. An alternative (and sometimes more conservative) estimate of cost-effectiveness is obtained by limiting the evaluation of consequences to mortality only (LYGs), rather than morbidity and mortality combined (QALYs).

QALYs combine survival and HRQoL into a single index. HRQoL is measured as a utility value on a cardinal scale of zero to one, such that a year of life in perfect health has a score of one and death a score of zero[15].* A utility value is a preference weight reflecting the relative value that individuals place on different health states. Several methods exist for obtaining utility values for health states and the choice of method depends on the study setting and on whose values are considered to be the most relevant (for example, patients, care-givers, or the general population)[16]. In addition, the health state valuations should ideally be relevant to the population(s) under study, since valuation is believed to be influenced by culture and income.[17, 18]. The use of QALYs in economic modelling exercises is predicated on there being reliable and robust estimates of utility available for the population of interest; this is not always the case.

* *LYG are in effect equivalent to QALYs with the assumption that all years are spent in perfect health (i.e. with a utility score of one)*

1.3.3 Comparison of alternatives - ICERs and their interpretation

In comparing two healthcare interventions, such as screening options, in a cost-effectiveness analysis, one wants to be able to determine how much additional benefit is achieved for the additional cost incurred for one intervention compared to the other. This is done by calculating the "incremental cost-effectiveness ratio" (ICER), which describes the difference in the costs and benefits of the two interventions[13]. Note that one of these interventions may be "no intervention" or "no screening".

The ICER for intervention A compared to intervention B is calculated as follows:

ICER = (costs of A - costs of B) / (effects of A - effects of B)

= incremental costs / incremental effects (benefits)

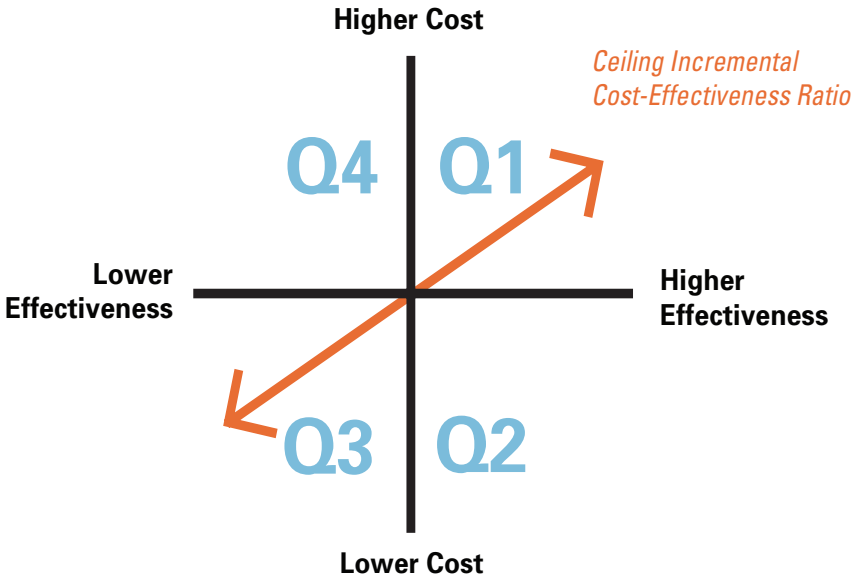
ICERs present the incremental cost per additional unit of outcome. This could be the cost per LYG, cost per case successfully diagnosed, cost per patient treated or cost per QALY gained. As the ICER becomes smaller the intervention A is said to be more cost-effective compared to the alternative B[19]. ICERs may be less than zero; in some circumstances this indicates that not only is intervention A cost-effective compared to intervention B, but that it is also cost-saving.

To aid interpretation, the point-estimates for costs and effects (benefits) for the strategies are often plotted on a cost-effectiveness plane (figure 1.1). The incremental effects are shown on the horizontal axis (i.e. the difference in effects between the new intervention (for example, a particular colorectal cancer screening scenario) and the comparator/alternative (for example, no screening)). The incremental costs are shown on the vertical axis (i.e. difference in costs between the new intervention and the comparator). The cost-effectiveness plane can be considered in four quadrants, Q1-Q4. If the new intervention is less costly and more effective than the comparator (i.e. the point-estimate is in Q2), it is said to dominate the alternative and would be the preferred option.

Conversely, if the new intervention is more costly and less effective than the comparator (point-estimate in Q4) then it would not be considered a cost-effective approach; in this situation the alternative is the dominant strategy. When the new intervention is more costly and more effective than the comparator (point estimate in Q1), a line can be drawn from the origin to the point-estimate for the new intervention and the slope of this line represents the ICER. In this situation, the decision on which intervention is preferable would depend on how much decision-makers are willing to pay for the additional benefits associated with the new intervention. If the point estimate lies in Q3, this indicates that the new intervention is less costly but less effective than the alternative. The decision of the preferred strategy would be based on whether the lower cost makes the lower effectiveness acceptable.

Typically, when a series of interventions are being compared, such as various screening strategies, the first step would be to calculate an ICER for each strategy versus the alternative of no screening. As a second step, the strategies might be compared with one another by computing the ICERs for one strategy versus another. This estimates how much additional benefit is achieved for the additional cost incurred for one strategy compared to another.

Figure 1.1 Cost-effectiveness plane



1.3.4 Dealing with uncertainty

One of the main reasons that economic models are used in decision making is to bridge the gaps in the available data or evidence[20]. This inevitably means that the values of some of the data items used in the models (the model parameters; for example, sensitivity of a screening test) are not known precisely. It then becomes important to consider how the cost-effectiveness results are affected by changes in these values of these parameters. Sensitivity analysis is the conventional approach for handling this uncertainty. The values of key parameters can be varied one at a time (one-way sensitivity analysis) or together (multi-way sensitivity analysis) to assess their impact on cost-effectiveness. However, this approach is likely to underestimate the true uncertainty in the parameters and probabilistic sensitivity analysis (PSA), which allows multiple model parameters to vary simultaneously, is thought to provide a more realistic reflection of the uncertainty. The results of a PSA can be summarised on a single cost-effectiveness plane using cost-effectiveness acceptability curves (CEACs). The CEAC for an intervention gives the probability that it is cost-effective across a range of willingness to pay thresholds. CEACs permit decision-makers to use their own criteria for how much they would be willing to pay for an additional QALY, for example; they can set their own threshold ICER and see the probability that the intervention would be cost-effective at this threshold[13]. When a series of interventions are being considered, a cost-effectiveness acceptability frontier (CEAF) can be plotted. This shows the probability that the optimal option (the one with the greatest expected net benefit) is cost-effective at different willingness-to-pay thresholds.

1.3.5 Cost-effectiveness threshold

One of the implications of making comparisons of different interventions (or screening scenarios) is that there is some threshold ICER above which an intervention would be deemed not cost-effective. In practice there is no fixed threshold. What generally happens, therefore, is that decision-makers examine the ICER for the new intervention to see whether it compares favourably with other healthcare interventions in the same setting. In addition, in making the decision, other factors may be taken into consideration besides estimated cost-effectiveness, such as budgetary considerations (and constraints) and the opportunity costs of investing in a particular intervention[21].

In Ireland, although it is not a formal threshold, in the past, the Department of Health and Children have agreed to reimburse most drug interventions with an ICER of less than €45,000 per QALY gained[22]. However, cost-effectiveness is only one factor that is considered in the decision making process and some interventions with an ICER above €45,000 per QALY gained have been funded (e.g. sunitinib for gastrointestinal tumour and metastatic renal cell carcinoma). Moreover, an ICER below this notional threshold is not a guarantee that the intervention will be funded.

The cost-effectiveness of other population-based cancer screening programmes in Ireland, BreastCheck and CervicalCheck, is not known.

1.3.6 Discounting

The technique of discounting allows comparison between costs and benefits that occur at different times. Since costs incurred and outcomes realised today are not equivalent to costs and outcomes in the future, discounting is used to calculate the present value of future events[23]. The further away into the future the event occurs, the lower the (discounted) present value today. This is particularly important in economic evaluations of screening programmes where the costs of screening occur immediately and benefits (such as deaths averted) may occur many years in the future.

1.4 Aim and objectives of this HTA

The purpose of this HTA was to evaluate various options for a population-based colorectal cancer screening programme, in average-risk individuals, in Ireland.

The objectives were, to estimate:

(i) for each screening option, the cost-effectiveness of a colorectal cancer screening programme compared to a policy of no screening;

(ii) the incremental cost-effectiveness of the alternative screening options; and

(iii) for each screening option, the key resource requirements (for example, colonoscopy capacity) and health outcomes (for example, numbers of individuals with adenomas detected) in the initial ten years of a programme.

Chapter 2

Epidemiology of colorectal cancer

The process of colorectal tumourgenesis involves the transformation of the normal epithelium of the colorectum to hyperproliferative epithelium followed by benign changes (polyps) and the development of invasive carcinoma (cancer). This histological progression is thought to result from the accumulation of multiple genetic changes[24].

This chapter describes the epidemiology of colorectal cancer in Ireland, and provides an overview of the development of colorectal cancers from polyp precursors, and considers the relevance of this to screening.

2.1 Descriptive epidemiology in Ireland

2.1.1 Incidence

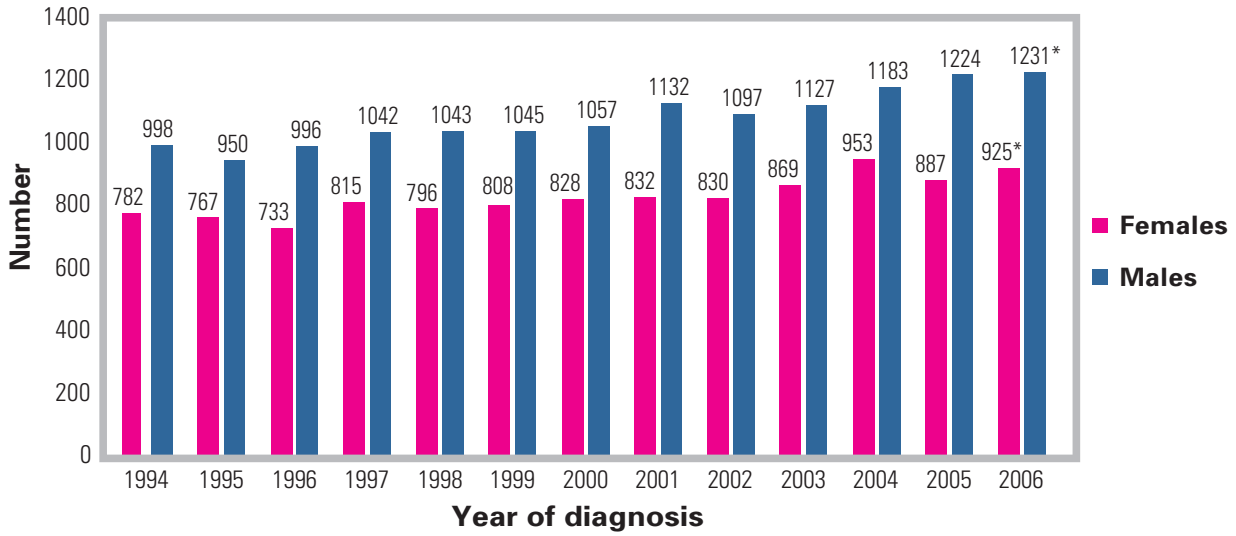
Colorectal cancer is the second most commonly diagnosed cancer in both men and women in Ireland[25]. Each year in Ireland, during 2002-2005, an average of 2040 new cases of colorectal cancer were diagnosed, 1160 cases in men and 880 cases in women (source: National Cancer Registry; www.ncri.ie). Approximately two-thirds of cases (64%) arise in the colon and one-third (36%) in the rectum.

Between 1994-1996 and 2004-2006 the number of new cases of colorectal cancer in Ireland rose by more than 20% (figure 2.1). This increase was almost entirely due to an increase in the size of the population and to population ageing. There was no notable change in age-standardised incidence rates (which take into account the size and age-distribution of the population) over the period 1994 to 2006 (figure 2.2).

By 2020, the number of new cases of colorectal cancer diagnosed each year in Ireland is projected to increase by 79% in men and 56% in women, compared to 1998-2002[26]. This predicted growth is mainly due to projected demographic changes.

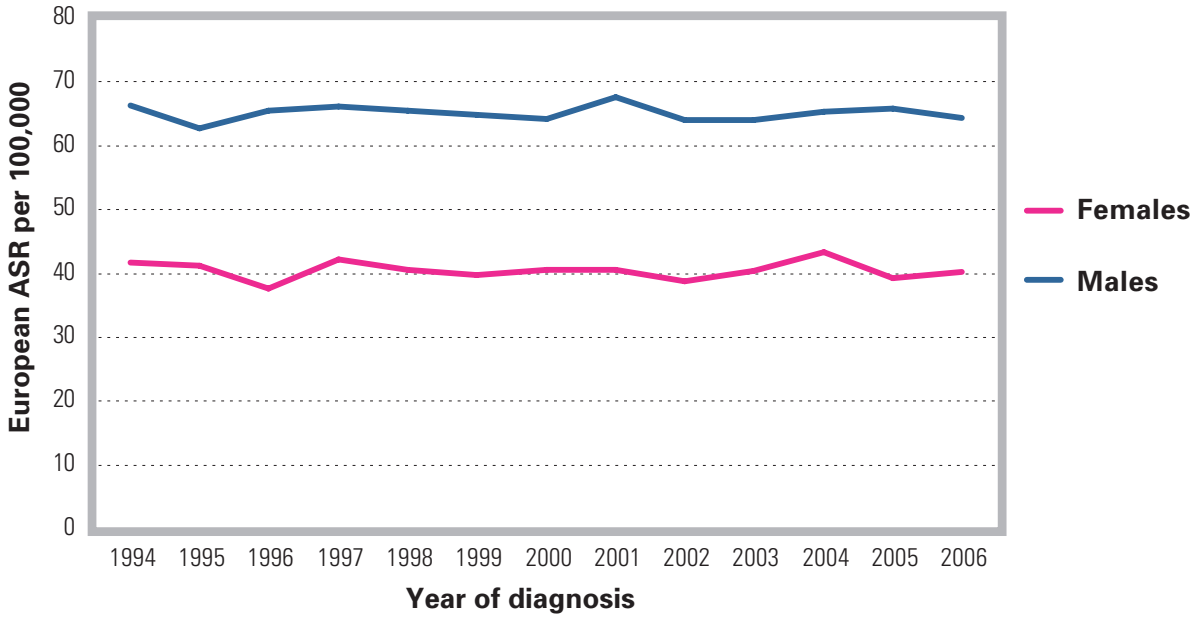
Figures 2.1-2.4 Colorectal cancer incidence in Ireland

2.1 Numbers of new cases of colorectal cancer (ICDO2 C18-C21) by year and sex, Ireland 1994-2006



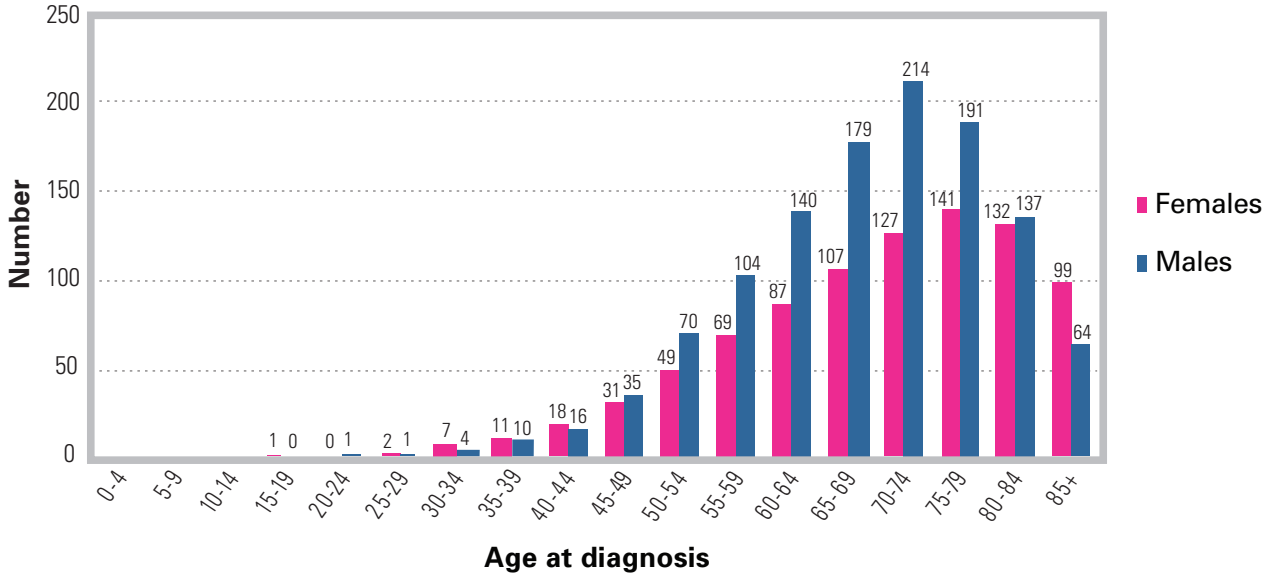
** figures for 2006 are provisional*

2.2 Age-standardised* incidence rates of colorectal cancer per 100,000 population by year of diagnosis and sex, Ireland 1994-2006

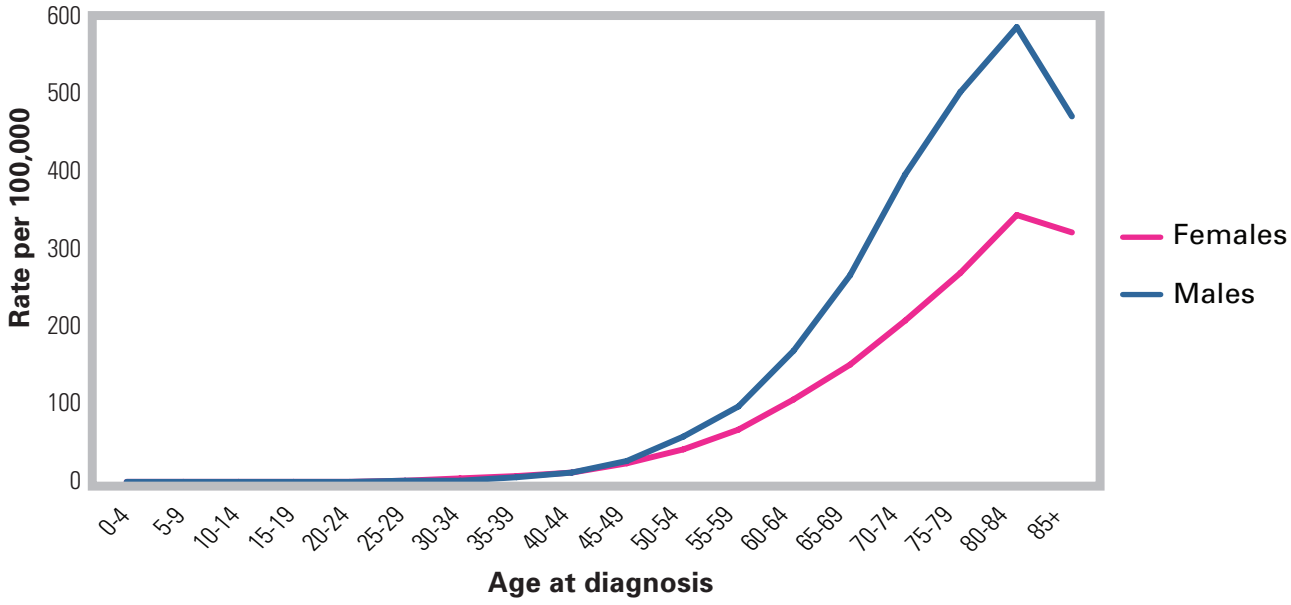


** standardised to the European Standard Population*

2.3 Average annual number of cases of colorectal cancer by age at diagnosis and sex, Ireland 2002-05



2.4 Colorectal cancer age-specific incidence rates per 100,000 population by sex, Ireland 2002-05



Colorectal cancer incidence rates generally increase with increasing age (figure 2.4). The numbers of cases peak in the seventh decade of life (figure 2.3). Overall, 12% of cases are diagnosed in those aged 55 or younger, while 20% occur in the 55-64 age group and 31% in the 64-74 age group. The remaining 37% are diagnosed in persons aged 75 and older.

The stage of a colorectal cancer depends on the depth of invasion of the primary tumour, the presence of locoregional lymph node involvement, and the presence of distant metastasis[27, 28]. In Ireland, during the period 2002-2005, 11% of cases were stage I at diagnosis, 24% were stage II, 26% stage III and 22% stage IV; stage was not known or not recorded for the remaining 17% (table 2.1).

Table 2.1 Stage distribution of colorectal cancers in Ireland, 2002-05[1]

AJCC/TNM Stage[2]	Definition	% of cases
Stage I	No nodal involvement, no distant metastasis; tumour invades submucosa (T1, N0, M0), or muscularis propria (T2, N0,M0)	11%
Stage II	No nodal involvement, no distant metastasis; tumour invades subserosa (T3, N0, M0), or into other organs (T4, N0, M0)	24%
Stage III	Nodal involvement, no distant metastasis; 1-3 regional lymph nodes involved (any T, N1, M0) or 4 or more regional lymph nodes involved (any T, N2, M0)	26%
Stage IV	Distant metastasis (any T, any N, M1)	22%
Unknown stage		17%

1 NCRI data, assuming cases with missing information on metastases have no metastases (i.e. Mx=M0)

2 O'Connell et al., 2004[27]

2.1.2 Mortality

Colorectal cancer is the second most common form of cancer death among men in Ireland and the third most common among women[25]. Data from the Central Statistics Office, supplied to the National Cancer Registry, show that during 2002-2005, approximately 925 people - 520 men and 405 women - died from colorectal cancer each year in Ireland.

Annual numbers of deaths did not change over the period 1994 to 2005 (figure 2.5). However, when age-standardised rates were considered, decreasing mortality is seen in both males and females (figure 2.6). This is consistent with trends in other developed countries over the past 20-30 years[29]. Projections of these trends until 2017 suggest that death rates from colorectal cancer in Ireland will continue to decline in both sexes[30] even without the introduction of screening.

Mortality rates for colorectal cancer increase steadily with increasing age (figure 2.8). Numbers of deaths in men peak in the seventh decade of life, while in women there are more deaths in those aged 85 and older than in other age groups (figure 2.7). Overall, almost half of deaths (49%) are in people aged 75 and older. 8% of deaths occur in those aged 55 and under, 15% occur in the 55-64 age group and 28% in those aged 65-74.

2.1.3 Survival

Five-year relative survival for colon cancers diagnosed in 1997-2001 was 52% (95% CI 51%-53%); for rectal cancers it was 51% (95% CI 49%-53%). Survival has increased slightly over time[31] and 5-year relative survival for those diagnosed in 2002-05 is estimated to be approximately 57% (95% CI 54%-60%).

Stage is strongly associated with survival (table 2.2). Approximately three-quarters of patients diagnosed with stage I disease are still alive at 5-years after diagnosis, compared to just over 60% with stage II, around half with stage III and less than 10% with stage IV.

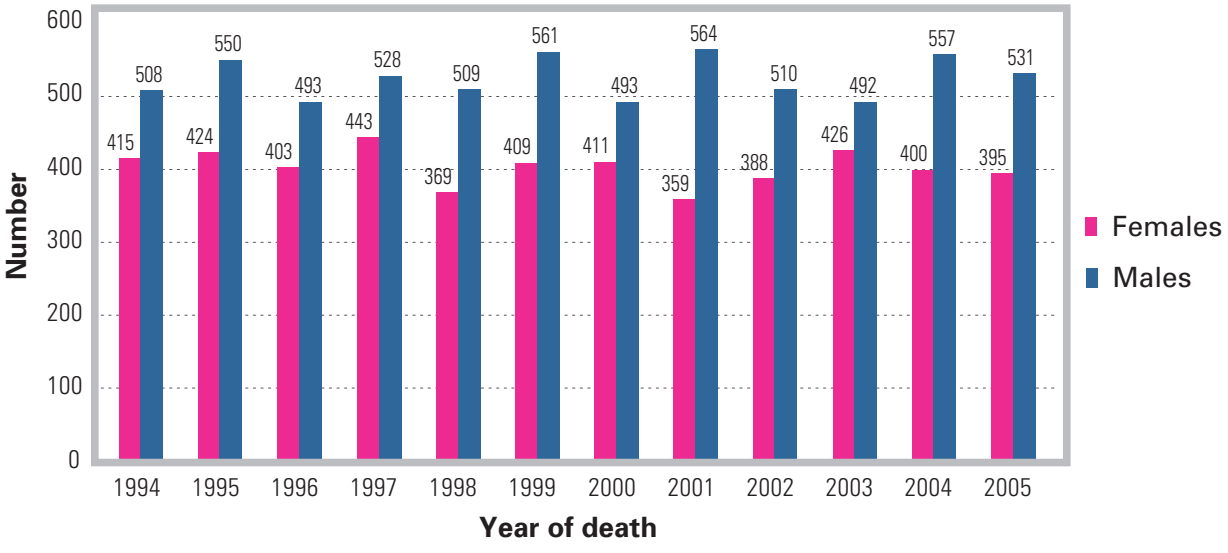
Table 2.2 5-year crude survival (%), with 95% CI, colon and rectal cancers by stage, 1997-2001[1]

AJCC/TNM Stage	Colon cancers (ICDO2 C18)		Rectal cancers (ICDO2 C19-20)	
	%	95% CI	%	95% CI
Stage I	80	73-85	77	69-82
Stage II	62	57-66	62	58-67
Stage III	48	43-53	53	48-58
Stage IV	9	7-12	8	4-14
Unknown stage	30	25-34	35	29-41

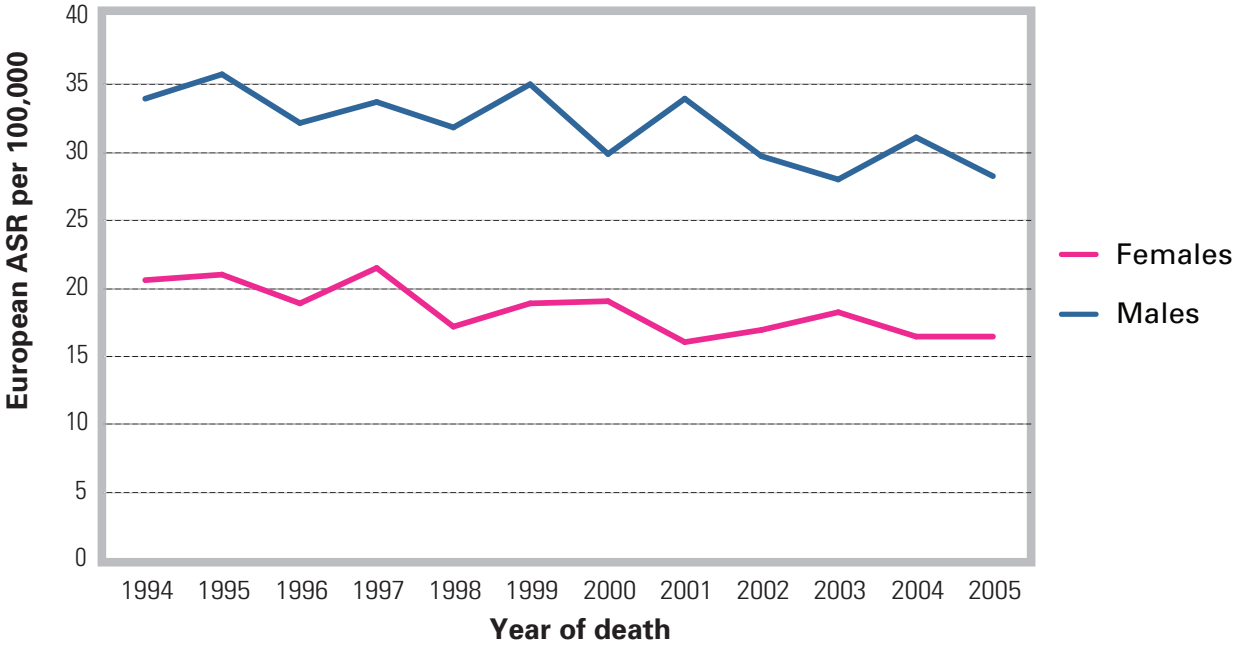
1 NCRI data; with follow-up until 31/12/2006

Figures 2.5-2.8 Colorectal cancer mortality in Ireland

2.5 Numbers of deaths from colorectal cancer by year and sex, Ireland 1994-2005

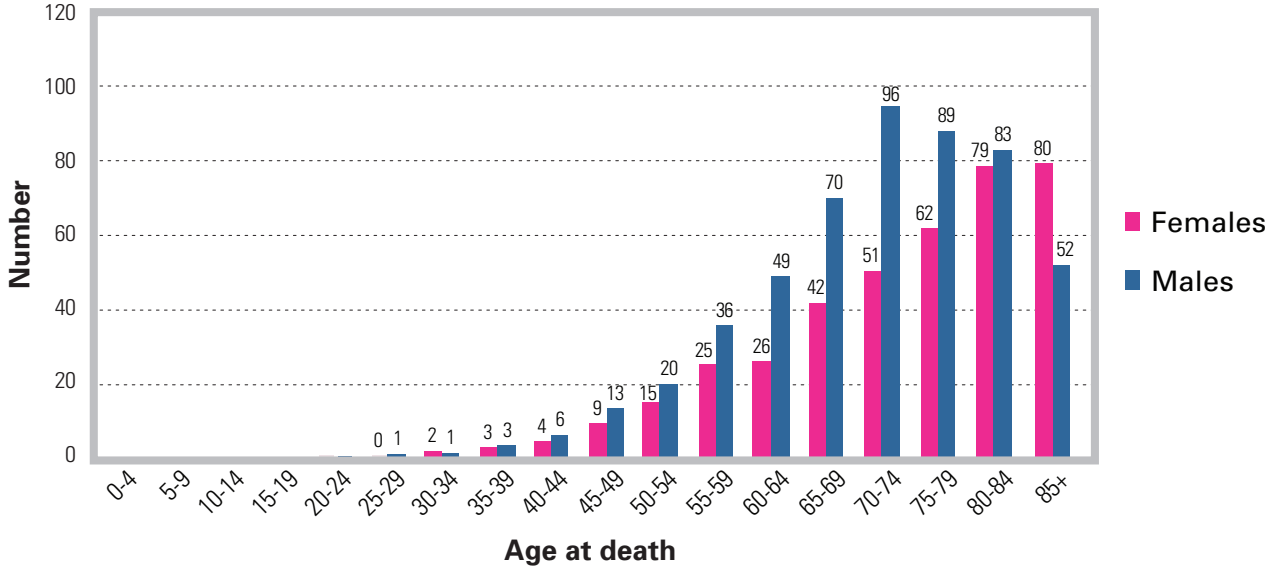


2.6 Age-standardised* mortality rates from colorectal cancer per 100,000 population by year of death and sex, Ireland 1994-2005

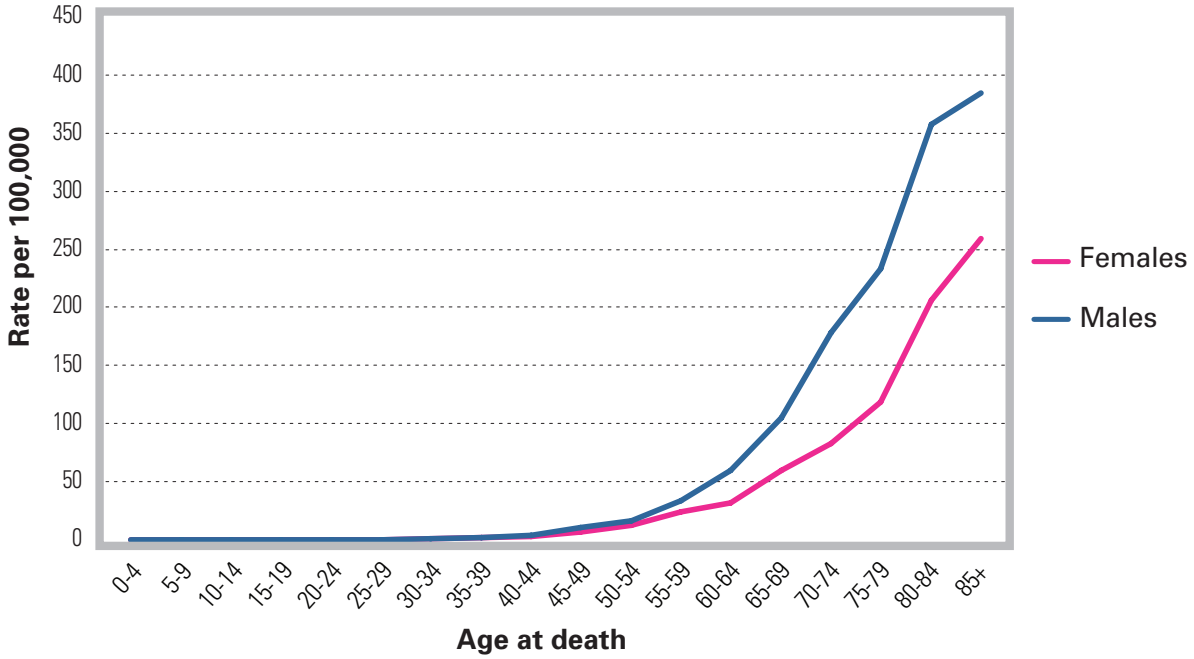


** standardised to the European Standard Population*

2.7 Average annual number of deaths of colorectal cancer by age at death and sex, Ireland 2002-05



2.8 Colorectal cancer age-specific mortality rates per 100,000 population by sex, Ireland 2002-05



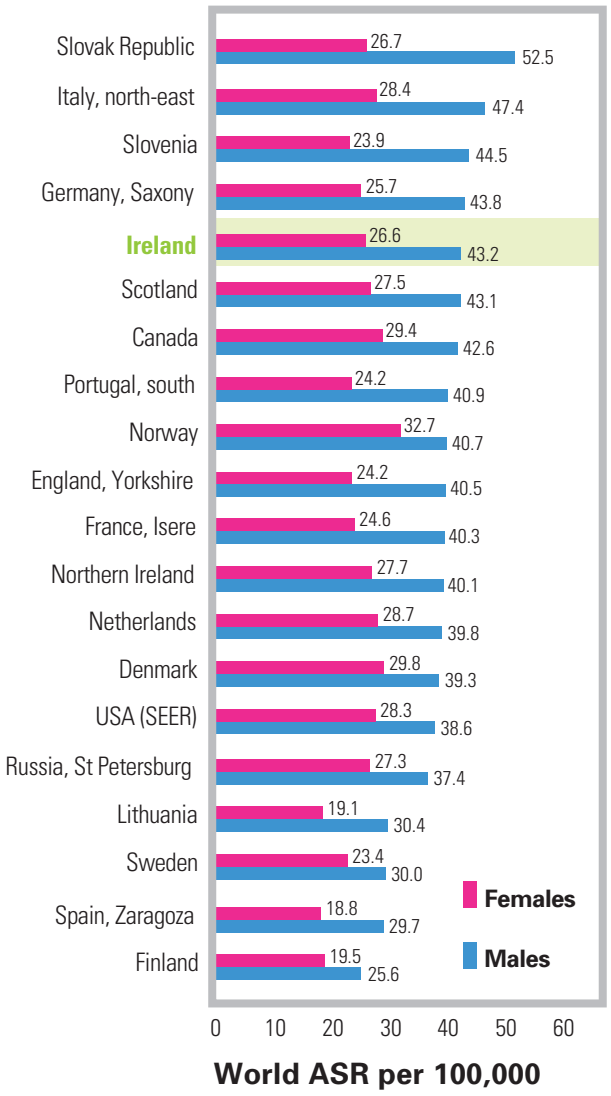
2.1.4 International comparisons

Internationally there is major variation in incidence of colorectal cancer, with rates varying at least 25-fold between the countries with lowest and highest incidence[1]. The highest rates are seen in Japan, Australia/New Zealand, North America and central and western Europe. Within Europe, incidence rates in males and females in Ireland rank amongst the highest observed (figure 2.9 [32]).

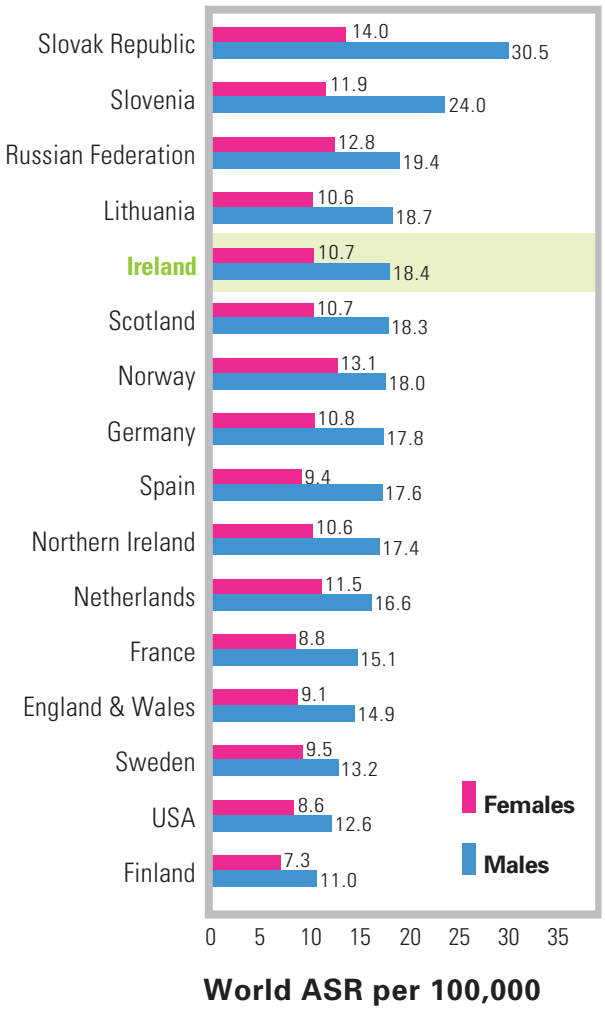
Similar variation is evident in mortality rates[33]. Within Europe, for 2002-2005, only countries in central and Eastern Europe had a higher colorectal cancer mortality rate for men than Ireland (figure 2.10). The mortality rate for women ranks in the middle of those seen across Europe.

Five-year survival for colorectal cancer patients diagnosed 1995-1999 in Ireland (50.6%, 95% CI 49.3-52.0) was somewhat lower than the European average (54.3%, 95% CI 53.9-54.5) (Source: EUROCARE 4). Survival in Ireland was similar to that in the countries of the UK, but lower than in most other countries in Northern and Western Europe.

2.9 Age-standardised* incidence rates of colorectal cancer (ICDO2 C18-C21) per 100,000 by country and sex, 1998-2002



2.10 Age-standardised* mortality rates for colorectal cancer per 100,000 by country and sex, 2002-2005



** standardised to the World Standard Population*

** standardised to the World Standard Population*

2.2 Polyps

Most polyps do not cause severe symptoms and, in the absence of screening, tend to be detected incidentally[34], after which they are usually removed. Evidence from colonoscopy series suggest that approximately 70% of polyps removed are polypoid adenomas[35], and it is this group that are most relevant as regards screening for colorectal cancer.

2.2.1 Adenomatous polyps and the adenoma-carcinoma sequence

Studies of adenomatous polyps left in situ show progression to cancer (reviewed in[36]). This observation, coupled with several strands of indirect evidence, supports the view that most colorectal cancers develop from adenomas (see, for example,[36, 37]). This is the so-called adenoma-carcinoma sequence. While the exact time from the formation of an adenoma to its progression to cancer is uncertain, it is thought that a small polyp may grow for around 10-15 years before it is transformed into a malignant

growth[37]. Malignant potential is related to the number of lesions, size, histopathology and the degree of dysplasia[36] with risk of malignancy increasing with increasing dysplasia and villous structure of the adenoma[37]. In data from the 1970s, the annual conversion rate (percentage of individuals with adenomas who develop cancers each year) was estimated to be 0.25% overall; for those with large adenomas, adenomas with villous structures, or severe dysplasia, the annual conversion rates were 3%, 17% and 37% respectively[38].

Between 30% and 40% of individuals who have had an adenoma removed by colonoscopic polypectomy will have a new (metachronous) adenoma found within three years[39, 40]. Although some of these lesions will be newly incident, others are likely to have been present, but missed, at the time of the original colonoscopy. The most consistently reported risk factor for the development of new adenomas is multiplicity of adenomas at the baseline colonoscopy[37]. Other risk factors for recurrence, such as size, villous/tubulovillous structure, and the age of the individual, have been less consistently reported[37]. Some, but not all, studies suggest that those who have adenomas removed are also at increased risk of developing colorectal cancer[41]. The risk of subsequent neoplasia in those who have had adenomas removed provides the rationale for ongoing colonoscopic surveillance in these individuals.

The true underlying prevalence of adenomatous polyps in the population (of Ireland and elsewhere) is unknown. Most of the available evidence comes either from autopsies series or studies of individuals undergoing colonoscopy[37]. Both sources suffer from considerable selection bias and their findings as regards prevalence differ. However, it seems clear that there is likely to be a considerable burden of undiagnosed adenomas in the middle-aged and older populations of most developed countries.

2.2.2 Polyps of other types

In the past, serrated polyps, a group which encompasses hyperplastic polyps, sessile serrated adenomas, admixed polyps and traditional serrated adenomas[42], were considered to be non-neoplastic[34]. However, it is now thought that they may have malignant potential and provide an alternative pathway to colorectal cancer[42, 43, 44]. For example, there is evidence that hyperplastic polyps could be precursors of some right-sided colon cancers[45, 46].

The role of flat adenomas (superficial, non-polypoidal, depressed polyps) in colorectal carcinogenesis is controversial. Flat type colorectal cancers have been described which have pathological and molecular similarities to flat adenomas, which may indicate that flat adenomas are precursors to some flat or de novo colorectal cancers[47].

Screening inevitably results in the detection and removal of some of these other types of polyps, but whether this has any impact on subsequent colorectal cancer mortality is unknown.

2.3 Rationale for colorectal cancer screening

The existence of the adenoma-carcinoma sequence and the strong association between stage at diagnosis and survival provide the rationale for screening for colorectal cancer.

Chapter 3

Review of clinical and cost-effectiveness of colorectal cancer screening

3.1 Screening test options for colorectal cancer

There is a range of potential screening tests for colorectal cancer including various faecal tests (gFOBT, FIT, faecal DNA testing), rigid and flexible sigmoidoscopy, colonoscopy, and CT colonography. An important feature of these tests is that, in addition to detecting early-stage colorectal cancers, they can also detect adenomas. This means that screening programmes for colorectal cancer have the potential to reduce both incidence of, and mortality from, the disease in the population.

The scope of this HTA was agreed with an Expert Advisory Group (EAG), established by the Health Information and Quality Authority (HIQA) to oversee the process, and includes three screening tests: gFOBT, FIT and flexible sigmoidoscopy. (Further details on the specific screening scenarios to be evaluated in this HTA are given in chapter 4.) The WHO criteria for screening state that a screening test should be effective, safe, and acceptable to the population, and that the economic costs to the health services should be acceptable (Appendix 1[3]). This chapter describes the tests, their strengths and limitations, summarises available evidence on efficacy and effectiveness, and reviews evidence on cost-effectiveness in screening for colorectal cancer.

3.2 Assessing the performance of screening tests

3.2.1 Efficacy and effectiveness

Efficacy is the extent to which a screening test produces a beneficial result (such as, identifying disease, reducing mortality) under ideal conditions. Effectiveness is the extent to which a screening test when used in routine circumstances does what it is intended to do (i.e. whether a screening test "works" in the real world)[48].

The determination of efficacy is generally based on the results of RCTs. These are generally held to provide the strongest evidence on whether a screening test "works"[11]. If an RCT is large enough, the process of randomisation will ensure that the characteristics of participants in the trial arms will be similar, thereby controlling confounding factors, and making the comparison between the arms internally valid. If the trial is population-based (i.e. all eligible individuals in a specified population are invited to participate), it increases the possibility that the results will be externally valid, that is they will be generalisable to other populations. Other study designs (for example, non-randomised trials, or observational designs such as case-control studies, or time trend studies) can also be used to evaluate screening tests. However, since these designs are potentially subject to bias (systematic errors) and confounding, the evidence from them is not considered to be as strong or convincing as that from RCTs[12]. A particular concern is the issue of self-selection of participants; those who choose to be screened may differ systematically from those who chose not to be screened and from the population as a whole, which can affect the external validity of the results.

Even if a screening test is efficacious in a research study, this does not mean that it will be effective when applied in the "real world". Issues such as the ability to identify all eligible persons in the screening target population, uptake and acceptability of the test to the population, the availability of sufficient diagnostic and treatment facilities will impact on how a test will perform when used in a screening programme.

3.2.2 Sensitivity, specificity and positive predictive value

The performance characteristics of a screening test, such as sensitivity and specificity, describe how well the test discriminates between people who do and do not have disease[49]. The assessment of these characteristics typically involves a series of individuals undergoing both the screening test and a "gold standard" diagnostic test, which is used to confirm presence or absence of disease. The individuals are classified by whether the screening test was positive or negative and whether the gold standard test was positive (disease present) or negative (disease absent), as shown in table 3.1. From the data in the table, various performance characteristics can be calculated.

Sensitivity is the ability of the screening test to accurately identify those who have disease. It is the proportion of individuals with disease who were identified as diseased by the screening test (i.e. they had a positive screening test). In the notation of table 3.1, this is calculated as a/(a+c).

Specificity is the ability of the screening test to correctly identify those who do not have disease. It is the proportion of individuals without disease who were identified as non-diseased by the screening test (i.e. they had a negative screening test). In the notation of table 3.1, d/(b+d). The positive predictive value of a screening test is the probability that an individual who had a positive screening test actually has the disease. From table 3.1, this is calculated as a/(a+b).

Table 3.1 Classification of individuals by screening test result and disease status

		True disease status[1]	
		disease present	disease absent
Screening test result[2]	positive	True positives (group a)	False positives (group b)
	negative	False negatives (group c)	True negatives (group d)

1 As determined by the gold-standard diagnostic test.

3.3 gFOBT

3.3.1 Description of test

The faecal occult blood test (FOBT) is a test for blood or blood products in faeces; the presence of blood is an indicator for the presence of neoplasia[50]. It is a guaiac-based test and, as such, it may react positively to any peroxidase in the faeces, not just to the peroxidase activity of heme. High peroxidase-content foods (for example, red meat and certain raw plant foods) can result in a false-positive test result[51]. Hence, sometimes (although not always[52]) gFOBTs will be used with a requirement for users to restrict dietary intake (usually red meat) for several days prior to using the test. The difficulties with this in the context of a screening programme are, firstly, whether dietary restriction will discourage individuals from participating in screening, and secondly, whether those who participate will comply adequately with the restrictions. In addition, the tests may detect bleeding from any site in the gastrointestinal tract, including the stomach[51]. This means that drug restriction may also be required since use of non-steroidal anti-inflammatory drugs (such as aspirin) can result in false positive results because of their propensity to cause gastro-intestinal bleeding[50].

A range of gFOBTs are available (see[53] for a description of several of these). The older Hemoccult® tests (Beckman Coulter), which have been extensively evaluated at the population-level, have been criticised for low sensitivity and/or poor specificity[50]. It is generally accepted that the performance characteristics of a single one-off gFOBT are poor[54] and successful screening requires repeat tests, typically either annually or biennially. Performance characteristics also depend on whether the sample has been rehydrated prior to analysis. The current view is that rehydration is not recommended because it causes the activation of plant peroxidases in the faecal smears[55, 56, 57] and results in high test positivity rates, a high rate of referral for diagnostic investigation, and poor specificity[50]. More recently developed tests, such as Hemoccult® SENSA®, seem to offer higher sensitivity than the older tests[50], but appear more susceptible to the effects of diet[56, 57].

Typically gFOBT-based screening programmes involve sending screening invitees a kit through the mail for completion at home, and return by mail to a central laboratory (see, for example, the pilot programmes in England and Scotland[58]). The main advantages of gFOBTs are that they are relatively cheap, relatively easy for screening participants to perform in their own homes, and are readily available in a format that is suitable for outward and return posting. These are all important considerations for a screening programme. Analysing, reading and interpreting the test results is not always straightforward, however. The Hemoccult II® test, for example, is based on detection of blue colouration. This is subjective, and may also be transient[50]. In addition, there are many situations in which the test may be false positive or false negative because of sampling issues (for example, the sample is thick or has dried out). To try to limit these, population-based programmes which employ gFOBT generally ask individuals to complete a test card with multiple samples, typically two samples

from each of three separate bowel movements. The disadvantage of this is that results may be clearly positive (for example, five or six samples positive), clearly negative (i.e. all six samples negative) or equivocal (for example, one to four samples positive). In the event of an equivocal result, individuals are asked to do another test (either a gFOBT or FIT)[59]. This increases the cost of screening and potentially raises issues with compliance.

Careful adherence to manufacturers' instructions and the use of newer forms of the developing agent have improved the readability of gFOBTs[50], but there is still an element of subjective interpretation. Personnel involved in developing the test and reading the end-points need to be experienced and well trained[55, 60]. This means that quality control is a particularly important issue for a screening programme. For example, in the pilot programmes in Scotland, extensive and rigorous laboratory quality control procedures have been out in place (Callum Fraser, personal communication). A limitation of gFOBTs is that they do not readily lend themselves to automation.

3.3.2 Summary of evidence on efficacy and effectiveness

There have been four RCTs of colorectal cancer screening using repeated gFOB testing[61, 62, 63, 64]. These are summarised in Appendix 2 (table APP2.1).

Three trials took place in Europe - in Sweden[62], Denmark[64] and Nottingham, England[63] - and one in the USA[61]. The three European trials were population-based. All four trials evaluated repeated screening with Hemoccult® gFOBTs, generally on a biennial basis, although the US trial also included an annual screening arm. Follow-up in these trials has now reached 12-18 years. All four trials found a reduction in colorectal cancer mortality in the screened arm compared to the non-screened arm. They also observed a change in the stage distribution of cancers in the screened arm, with a greater proportion in Duke's A or B in the screening than in the non-screened arm.

A 2008 Cochrane review conducted a combined analysis of the trials and estimated, based on an intention-to-screen approach, that repeated gFOBT screening results in a statistically significant relative reduction in colorectal cancer mortality of 16% (fixed and random effects models: RR=0.84, 95% CI 0.78-0.90)[65]. Excluding results for annual screening from the Minnesota trial had little impact on this estimate. An intention-to-screen analysis includes all those invited to take part in screening, irrespective of whether they attended and is likely to under-estimate the true effect in attendees. The authors of the review therefore repeated the analysis adjusting for screening attendance and estimated that the relative mortality reduction associated with gFOBT screening was 25% (RR=0.75, 95% CI 0.66-0.84).

There has been a range of other studies of gFOBT screening, including two non-randomised trials[40,66] and several case-control studies[67, 68, 69, 70, 71, 72, 73].

Numerous national and regional screening programmes are based on gFOBT[8], including those in the UK[59], Ontario[74], France[75], Spain[76] and Italy[77].

3.4 FIT

3.4.1 Description of test

The faecal immunochemical test is a stool-based test which depends on antibodies specific for human haemoglobin[50, 51]. In theory this should cut down on false-positive test results as compared with the gFOBT. In addition, the tests are highly selective for occult bleeding of colorectal origin[51]. Moreover, dietary and/or drug restriction is not required[51] and some studies have suggested that this might improve participation[78].

There are several immunochemical tests available (see[53] for a description of several of these), but not all of these have been comprehensively evaluated at the population level[50]. Ideally, it might be anticipated that a FIT-based screening programme based would operate in the same way as one organised around gFOBT, in that test kits would be posted to screening invitees, completed at home and returned to the laboratory by post. Most of the currently available FITs are not particularly suitable for this. Several require the collection of faeces into tubes containing buffer and such tubes are difficult and expensive to send to screening participants by post[79]. In addition, the material in the tubes generally needs to be processed within a week or so of faecal collection, which may cause logistical difficulties in a screening programme[80]. Some more stable card-collection systems are becoming available[80]. In addition, some groups (notably the Scottish Bowel Cancer Screening Programme) have worked with manufacturers to develop kits that can be distributed through the mail and are in a format familiar to participants who have already completed a gFOBT (Callum Fraser, personal communication).

At the moment most immunochemical tests are qualitative in that they produce a dichotomous result, with individuals categorised as either positive or negative if the amount of haemoglobin in the faecal sample is above or below a specific analytical detection limit set by the manufacturers. Research studies show that higher haemoglobin concentrations are strongly associated with increased severity of colorectal neoplasia[51, 79, 81, 82, 83, 84]. This has stimulated the development of more quantitative tests where the ratio of sensitivity: specificity can be determined by the user. These tests offer the possibility of flexibility in setting cut-offs suitable for local circumstances[79], in particular being able to set a test positivity rate that is manageable in terms of available colonoscopy resources while still maintaining an adequate neoplasia detection rate. The challenge, however, is to be able to determine what constitutes a colonoscopy referral rate high enough to ensure screening is effective, but low enough that it does not cause problems with capacity[51].

The interpretation of immunochemical tests in the laboratory is generally more straightforward than for gFOBT, and analytical staff are not required to be as experienced (Callum Fraser, personal communication). A further advantage is that some tests can be automated, both in terms of sample processing and development and subsequent reading of end-points.

The disadvantage of immunochemical tests as compared with gFOBTs is that the test kits are generally more expensive[80]. In addition, the analytical detection limit of the qualitative test is generally lower than for gFOBTs[80]. This means that, in a programme based on FIT compared to one based on gFOBT (as implemented in England and

Scotland, where individuals who have an equivocal result complete a second test), it would be expected that more individuals would test positive and be referred for diagnostic investigation, making resource requirements for colonoscopy, CT colonography and barium enema an important consideration. Strategies might be devised to limit the referral rate to colonoscopy in an FIT-based programme, such as (i) asking individuals to complete two tests initially, or offering a second test to those who are positive on the first test, and referring only if both tests are positive, or (ii) applying a quantitative test and using a higher limit to define test positivity.

3.4.2 Summary of evidence on efficacy and effectiveness of FIT as a primary screening test

There is currently no evidence from RCTs that immunochemical faecal tests are effective in reducing mortality from colorectal cancer. Several population-based RCTs are underway and results from these are awaited. These include two trials in the Netherlands[85, 86, 87] two in Italy (SCORE2 and SCORE3;[88,89]) and the NORCAPP trial in Norway which is comparing flexible sigmoidoscopy alone with flexible sigmoidoscopy plus FIT[90]. In addition, in Australia, following a pilot programme[91], the recently established National Bowel Cancer Screening Program is using an immunochemical test[92]. Some of the regional screening programmes in Italy also use FITs[8, 93].

It has been argued that since the efficacy of the older Hemoccult® gFOBTs has been established, it is not necessary to show that newer tests, such as FIT, decrease mortality, but simply that they have better performance characteristics (for example, sensitivity) than the Hemoccult® tests[50]. Comparing only diagnostic characteristics does not, of course, take into account the fact that the gFOBTs and FITs measure somewhat different things. Nor does it consider the likely differences in costs and requirements for diagnostic investigation associated with the newer, compared to the older, tests.

Several observational studies have compared the sensitivity and specificity of gFOBT and FIT in the same individuals (see, for example,[94] and references therein), but most have methodological limitations. These limitations include the inclusion of high-risk subjects rather than an average-risk screening population[56, 95, 96, 97], small sample size, and lack of randomisation[53, 87, 94]). Several studies asked participants to perform both FIT and gFOBT tests at the same time[83, 98]. Van Rossum et al[87] argue that this is likely to reduce participation and may induce selection bias in favour of highly motivated participants. Others used a non-quantitative immunochemical test[98].

Preliminary results have been reported from a large, ongoing, population-based screening trial in the Netherlands, in which subjects were randomised to gFOBT or FIT screening[87]. A random sample of 20,623 individuals aged 50-75 years was identified from municipal databases and invited to participate in screening; symptomatic individuals were excluded. Individuals were randomised to receive either a gFOBT or an immunochemical test by post. The guaiac test was Hemoccult II®, which consisted of three cards to be completed on consecutive days by taking two samples from different parts of the stool. The immunochemical test was the automated semi-quantitative OC-Sensor (Eiken Chemical Co) which

consisted of a single sampling tube, with an integrated faecal probe which was to be used to scrape different parts of the stool. The gFOBT was not rehydrated before analysis and positivity was defined as blue colouration in any of the six stool samples within 30-60 seconds after applying the developing solution. The cut-off level to define a positive FIT was 100ng/mL corresponding to +/- 20µg haemoglobin per gram of faeces. All those who were positive on either test were offered colonoscopy. Participation was higher among the group randomised to FIT than among those randomised to gFOBT. 10,301 individuals were invited to complete the gFOBT, 4,836 of whom (46.9%, 95% CI 46.0-47.9) did so. 10,322 were randomised to FIT and 6,157 (59.6%, 95% CI 58.7-60.6) completed the test. The test positivity rate was twice as high for FIT as for gFOBT (5.5% vs 2.4%) and this difference was statistically significant ($p<0.01$). 88% of those with a positive gFOBT underwent colonoscopy compared to 83% with a positive FIT. The primary analysis was based on intention-to-screen. The frequency of all polyps and cancer was significantly higher in the FIT arm (2.1%; 95% CI 1.8-2.4) than the gFOBT arm (0.8%; 95% CI 0.6-0.9; $p(\text{difference})<0.01$). The same pattern was evident when advanced adenomas and cancers were analysed separately. However, the positive predictive values (ppv) of the tests did not differ significantly. For all adenomas and cancer, the ppv was 69.9% for gFOBT and 71.8% for FIT. For all advanced adenomas and cancers, it was 55.3% for gFOBT and 51.8% for FIT. The estimated specificity of FIT for all adenomas and cancer was slightly, but significantly, lower than that for gFOBT (gFOBT: 99.0%; FIT:97.8%; $p(\text{difference})<0.01$).

The conclusion from a systematic review of the performance characteristics of faecal tests undertaken by the Centre for Reviews and Dissemination (CRD) was that there was no clear evidence, from either direct or indirect comparisons, to suggest whether guaiac or immunochemical tests had better sensitivity or specificity[53, 94].

Limiting consideration to FITs, one of the major findings of the CRD review was that there was extreme heterogeneity in diagnostic performance among different tests. The authors concluded that it was not possible to compute overall estimates of performance characteristics, nor to determine whether one test performed better than the other. Others studies published since the review have also demonstrated large differences between tests in diagnostic performance (see, for example,[100]). This serves to illustrate the uncertainty about how well these tests would perform in a population-based screening programme.

3.4.3 Summary of evidence on efficacy and effectiveness of FIT as adjunct to gFOBT ("two-tier" approach)

An alternative use of the immunochemical test is as an adjunct to primary gFOB testing. Individuals who have an equivocal gFOBT result would be asked to complete an FIT rather than another gFOBT; those who are positive on the immunochemical test would then be referred onwards for diagnostic investigation. This approach has been suggested as being suitable for screening in settings where colonoscopy resources are limited and/or population compliance with dietary or drug restrictions for guaiac-based tests may be uncertain[50]. It is worth noting, however, that the available data on this as a screening strategy, from either research studies or screening programmes is extremely limited.

This strategy began to be used in the latter part of the second round of the colorectal screening pilot in Scotland and has been used throughout the third round. Several pilot studies have been undertaken to demonstrate the feasibility of the approach, the potential for decreasing the numbers of false positives from gFOBTs (if an appropriate cut-off for the FIT is used), and the ability to identify individuals with high-risk neoplasia[79, 80, 101] Performance indicators illustrate the impact on the overall programme[102]. The rate of individuals who were screen-positive declined from 2.07% in the first round, to 1.90% in the second round, and 1.16% in the third round. The numbers of individuals undergoing colonoscopy similarly fell from 2,961 in round 1, to 2,795 in round 2 and 1,661 in round 3. Although some of these trends may be due to differences between rounds in numbers screened, characteristics of those screened, and colonoscopy compliance, the greater part is likely to be due to the change to using an immunochemical reflex test. It should be noted that these data reflect the performance characteristics of the specific gFOBT and FITs used in Scotland, the details of the screening protocol, and the underlying disease prevalence in the population and would not necessarily generalise to other settings, or other combinations of tests. In addition, the long-term effectiveness of this approach is not yet established.

3.5 Flexible sigmoidoscopy

3.5.1 Description of test

The rationale for the use of flexible sigmoidoscopy as a screening tool for colorectal cancer is the observation that 50-75% of adenomatous polyps are within reach of the 60cm instrument[103]. The main advantage that flexible sigmoidoscopy would offer over faecal tests is that a single screening examination may be sufficient to provide protection against colorectal cancer[104]. This assertion follows from case-control studies which have shown that individuals who have had a rigid or flexible sigmoidoscopy have reduced risk of being diagnosed with distal (left-sided) colorectal cancer compared to those who have not had the procedure, and that this reduction persists for between 7 and 16 years[104, 105, 106, 107]. In addition, it has been suggested that if the procedure is done at the age of 60, the protection afforded may be even longer than found in the case-control studies[104].

One advantage of flexible sigmoidoscopy as a screening test is that often the screening and diagnostic step can be combined: for the majority of those with adenomas, the lesion(s) can be removed at the time of the flexible sigmoidoscopy. This reduces the requirements for diagnostic colonoscopy as compared with screening based on faecal tests. However, some individuals will require further endoscopic examination after the flexible sigmoidoscopy, and there is a lack of a clear consensus on who to send for colonoscopy based on sigmoidoscopy findings[54]. The other main disadvantage of flexible sigmoidoscopy is that the full bowel is not visualised, meaning that neoplasia located in the right (proximal) colon are likely to be missed. In addition, the procedure itself is associated with a risk of perforation (albeit low) and subsequent death[108].

Since the procedure needs to be undertaken by a health professional (trained nurse or gastroenterologist) in an out-patient setting, this means that the costs of offering an individual screening using flexible sigmoidoscopy are likely to be much higher than offering screening using a faecal test. However, this needs to be offset against the requirements for repeated faecal tests, and greater numbers undergoing diagnostic investigation with faecal tests.

3.5.2 Summary of evidence on efficacy and effectiveness of flexible sigmoidoscopy

An RCT reported in the 1980s found a reduced risk of death from colorectal cancer in the group allocated to an annual multiphasic health check which included rigid sigmoidoscopy[109]. A range of other studies have also evaluated sigmoidoscopy as a screening tool (reviewed in[36]) but these have been non-randomised and are potentially subject to bias.

In terms of flexible sigmoidoscopy, no RCTs of efficacy have so far been reported. Several small trials have been completed[110, 111, 112, 113, 114]. Other large RCTs, several of which are population-based, are underway and findings relating to mortality are awaited; those which have published baseline findings are summarised in Appendix 2 (table APP2.2)[85, 86, 88, 89, 90, 115, 116, 117]. These trials have demonstrated feasibility, safety and a high yield of neoplasia of flexible sigmoidoscopy-based screening. Further research studies are also in progress in several European countries, including Belgium, Spain and Switzerland[8].

The published trials include the large, population-based, trial of once-only flexible sigmoidoscopy between the ages of 55 and 63 in the UK[116]. 40,674 individuals were screened, 39% of those invited. Of these, 72% did not have any pathological specimens removed and were discharged. A further 22% were discharged after histopathology showed no significant pathology or low-risk polyps only. Most of the remainder (n=2,131, 5%) were referred for colonoscopy and 2,051 underwent colonoscopy. Overall, 25% of those screened had one or more distal polyps removed at flexible sigmoidoscopy or colonoscopy. One or more distal adenomas were found in 12% of those screened. High-risk lesions were found in 4.7% and the cancer detection rate was 3.4 per 1000 screened. Results relating to colorectal cancer mortality are anticipated in 2010 (Wendy Atkin, personal communication).

There are several screening initiatives based on flexible sigmoidoscopy, either administered once-only or repeated at regular intervals[8]. These include organised screening (through mailed invitations) in parts of Italy and Australia, and opportunistic screening (associated with visits to family practitioners) in Canada and parts of the USA.

3.6 Cost-effectiveness of colorectal cancer screening in average risk populations

This section reviews the evidence on the cost-effectiveness of screening for colorectal cancer screening in average-risk populations. The purpose of the review was two-fold: (i) to identify and evaluate the methodological and modelling methods used by other groups with the intention of using this in the further development of the economic model used in this HTA; and (ii) to set the findings of this HTA in the context of those from other settings.

3.6.1 Search strategy

A review of existing literature on the economic evaluation of options for colorectal cancer screening was performed in June 2008 and updated in December 2008. Studies published in the English language since 2003 were eligible for inclusion and added to those identified in an earlier review by Tappenden et al[118]. The search was limited to studies which included evaluation of at least one of gFOBT, FIT or sigmoidoscopy (flexible or rigid); studies which focussed solely on other technologies (for example, colonoscopy, CT colonography, faecal DNA testing) were not included. Studies were limited to those which pertained to average-risk populations; studies in populations at high genetic risk were excluded. Databases searched included Medline (PubMed), Embase and the NHS economic evaluation database. Relevant MeSH headings including "colorectal neoplasms", "mass screening", "economics", "quality of life" and "cost and cost analysis" were combined with text words such as "colorectal", "immunochemical", "cost-effectiveness" and "economic evaluation" to identify potentially relevant papers. Additional papers were identified by hand-searching the reference lists of published papers. Other HTAs were included where relevant and publicly available. The studies and HTAs identified by this search strategy and included in the review are summarised in Appendix 3 (table APP3.1).

3.6.2 Colorectal cancer screening models

The core of an economic model generally involves a description of the natural history of the condition in the population, in this case colorectal neoplasia. Interacting with this will be a description of the clinical scenario (here, screening and diagnosis of polyps or cancer) and the management strategies (here, treatment and surveillance of adenomas and cancer).

In the studies reviewed, a variety of different approaches were used to model the natural history of colorectal neoplasia. These included simple decision tree models, Markov and semi-Markov processes, and discrete events simulation (DES). The major advantage of the decision tree models is their simplicity, but their main limitation is that they do not generally have a temporal element. Both Markov models and micro-simulation models have a temporal element and this allows individuals to move (transition) from one health state to another over time. These methods are useful for modelling diseases or conditions where risk is ongoing over time, where events may occur more than once, and where the timing of events is important[119, 120, 121]. The Markov and semi-Markov state-transition

models simulate the behaviour of a population cohort and describe the progression of the cohort through a number of disease states over a defined period of time[119]. The micro-simulation or discrete events simulation models work at the patient-level. They allow for the representation of a disease transition process as a chronological sequence of events with each event occurring at a moment in time and representing a change in state within the process[122]. This approach provides greater detail than Markov models but the models are complex and require additional assumptions to be made in populating the model[119, 120]. This means that Markov models are the most commonly used method in models of screening interventions.

Appendix 3 contains further details of the natural history models used and methods of the studies included in the review.

3.6.3 Cost-effectiveness of gFOBT, FIT and flexible sigmoidoscopy screening strategies

3.6.3.1 gFOBT

The majority of studies examining the cost-effectiveness of screening for bowel cancer have evaluated gFOBT as a methodology. In one of the earliest studies, England et al[123] compared gFOBT to double contrast barium enema (DCBE) and endoscopy and found it to be the most cost-effective strategy when used in combination with DCBE for an American population. Numerous other studies have found gFOBT testing to be a cost-effective method of screening for colorectal cancer[58, 118, 124-141]. Where estimates were made in US Dollars, ICERs ranged from $2,500 per LYG[131] up to $35,000 per LYG[142], with most studies concluding that gFOBT cost less than $20,000 per LYG. In a French population, Berchi et al[140] estimated the cost-effectiveness of gFOBT was €2,980 per LYG. In the UK, Alexander and Weller[58] estimated the cost-effectiveness of gFOBT to be £2,600-£8,000 depending on the demographic group being considered. Also in the UK, Tappenden et al[118, 139] found that while the ICER for gFOBT in those aged 50-69 year was between €551 and €7992 per additional QALY, it was not as cost-effective as screening based on flexible sigmoidoscopy. However, it was recommended as a more attractive, or feasible, screening strategy than flexible sigmoidoscopy because of limitations in endoscopy capacity.

Both annual and biennial administration models of gFOBT screening have been evaluated. Generally the different studies are not easily comparable, but a few studies have compared the two options directly. A Canadian study by Flanagan et al[138] found that biennial gFOBT in those aged 50-74 was preferable in terms of cost-effectiveness to a similar strategy implemented on an annual basis. O'Leary et al[143] also favoured biennial over annual screening (AUS$41,183 versus AUS$46,900 per LYG) though both options were found to be significantly less cost-effective than endoscopic screening modalities.

Most studies which specified a particular gFOBT evaluated Hemoccult® or Hemoccult II®. Zauber et al[144] assessed cost-effectiveness of annual screening with the more sensitive Hemoccult® SENSA® test and found that it provided similar LYG to colonoscopy-based screening every 10 years. In contrast, annual screening with Hemoccult II® did not provide the same effectiveness as using the more sensitive test.

3.6.3.2 FIT

Seven economic assessments of FIT-based screening were identified for inclusion in the review[136, 140, 141, 144-147]. Using an economic model to extrapolate from screening study data, Chen et al[147] found that FIT was less costly and more effective than no screening. Zauber et al[144] concluded that, for the 50-75 age group in the USA, annual FIT screening provided similar LYG to screening by colonoscopy every 10 years. Tsuiji et al[145], in a study comparing FIT, DCBE, sigmoidoscopy and colonoscopy, and Shimbo et al[146], in a study comparing FIT, gFOBT and sigmoidoscopy, found FIT to be the most cost-effective modality when compared to no screening. Parekh et al[141] concluded that with perfect adherence FIT could be said to dominate colonoscopy every 10-years as a screening strategy.

In contrast, in Singapore, Wong et al[136] found that FIT was less cost-effective than gFOBT when rolled out annually (Singapore dollars (SGD$)162 versus SGD$368 when weighted across age groups from 50-69). Similarly, Berchi et al[140] reported that while the effectiveness of biennial gFOBT (Hemoccult II®) and FIT (Magstream) was similar, FIT cost €59 more per person due to the larger number of colonoscopies required under screening with FIT; FIT was therefore less cost-effective than gFOBT as a screening strategy.

Chen et al[147] explored the optimum cut-off for a quantitative FIT test. They allowed this to range from 30 to 200 ng/mL and identified the point at which the ICER (compared to no screening) was lowest. Cost-effectiveness increased as the cut-off by which a positive test was defined increased, reaching its optimum value at a cut-off of 110ng/mL. At a cut-off level of above 110ng/mL, cost-effectiveness decreased slightly.

3.6.3.3 Flexible sigmoidoscopy

The cost-effectiveness of screening based on sigmoidoscopy and flexible sigmoidoscopy has frequently been evaluated[118, 123, 124, 127, 129, 130, 132, 133, 136, 137, 139, 142-144, 148-151]. Studies have considered a variety of different scenarios with screening participants scoped "once only" (at a variety of different ages) and repeatedly (every 3, 5 or ten years). Flexible sigmoidoscopy has been considered as a standalone test and in combination with gFOBT.

Using the MISCAN-COLON microsimulation model, Loeve et al[151] found that five-yearly sigmoidoscopy could be cost-saving compared to no screening. Similarly, in the UK, Tappenden et al[118, 139] found flexible sigmoidoscopy to be cost-saving compared to no screening when offered once only at 55 or 60 years. It continued to be cost-saving when offered in combination with biennial screening gFOBT between the ages of 61 and 70 years. The authors noted, however, that resource constraints inherent to the delivery of a flexible sigmoidoscopy screening programme (i.e. the endoscopy capacity) required careful consideration.

Vijan et al[133] also evaluated flexible sigmoidoscopy in combination with gFOBT and found this strategy to be cost-effective compared to no screening. Zauber et al[144] concluded that 5-yearly flexible sigmoidoscopy was less effective in terms of LYG than a strategy which offered 5-yearly examinations together with a mid-interval gFOBT. In addition, the combined strategy resulted in similar LYG to 10-yearly colonoscopies, but required fewer colonoscopies to be performed.

Conversely, Bolin et al[129] did not find evidence for substantial cost-effectiveness for flexible sigmoidoscopy either as a standalone screening test or in combination with gFOBT. Sonnenberg et al[148] ranked standalone flexible sigmoidoscopy as the least cost-effective strategy in their study, when compared to no screening. Wu et al[137] found that while five-yearly flexible sigmoidoscopy dominated faecal DNA testing that it was inferior to both ten-yearly colonoscopies and annual gFOBT.

3.6.4 Resource requirements and health services impact of screening

While most studies evaluated costs of screening only in monetary terms, a few studies considered outcomes related to the likely resource and health service implications of colorectal cancer screening. In a study in Australia, O'Leary et al[143] investigated the likely impact of screening on demand for colonoscopy services. They concluded that screening was only viable if adequate colonoscopy capacity could be provided, and felt that while this was deliverable in urban areas, the picture in rural Australia was likely to be more complex. Tappenden et al[118, 139] developed a model which estimated additional resource use for each screening scenario compared to the resources used under a policy of no screening. They concluded that although flexible sigmoidoscopy was the most cost-effective strategy, the additional endoscopy capacity needed to deliver a population-based programme using this screening test would be difficult to provide. Zauber et al[144] considered the numbers of surplus colonoscopy and non-colonoscopy tests under screening. The authors considered 10-yearly colonoscopy screening to be the most resource-efficient modality due to the burden of non-colonoscopy tests associated with other, more frequent methods of screening, such as FIT, gFOBT or repeated flexible sigmoidoscopy. Ho et al[150] examined the likely numbers of extra gastroenterologists and radiologists required to efficiently implement screening in terms of the available resources. They found that, for all screening scenarios considered – including one based on gFOBT- the numbers required were a multiple of the available capacity.

3.6.5 Comments

The evidence-base on the cost-effectiveness of gFOBT and flexible sigmoidoscopy is extensive, but to date relatively few studies have considered FIT. Overall it is not clear whether one screening strategy dominates. Different screening tests, combinations of tests, age ranges and screening intervals have been assessed in different studies. Studies took different approaches with regard to what costs were included, and the base year for costs differed. Comparison between studies is further complicated by the range of different modelling methodologies that have been employed. In particular, the screening models varied in their interpretation of key aspects of the natural history of colorectal neoplasia, including the extent to which cancer develops from adenomatous polyps.

Despite this heterogeneity, it is clear that in most settings where screening for colorectal cancer in average risk populations has been evaluated, it has been considered to be cost-effective. In some settings it is cost-saving compared to no screening. However the extent to which these conclusions generalise to Ireland are unclear. Local factors such as underlying prevalence of adenomas, screening uptake, compliance with follow-up and costs of treatment are likely to impact on cost-effectiveness. Several studies included in this review highlighted the health service implications of different screening strategies on existing services. In a number of cases this resulted in the recommendation of a screening strategy other than the one which was most cost-effective. This illustrates the importance of considering both cost-effectiveness of screening and its feasibility (in terms of the ability of the programme or the health services to deliver the required resource capacity) in this HTA.

Chapter 4

Methods

4.1 Screening scenarios

An Expert Advisory Group (EAG), comprising clinical experts, key stakeholders and patient and public representatives was established by the HIQA to advise on various aspects of the HTA. One important role of the EAG was to consider which screening scenarios should be evaluated. The timeframe within which the HTA had to be completed meant that it was not possible to evaluate all potential screening tests. In recognition of this, a decision was taken to focus on a small number of key scenarios. These scenarios were defined based on the volume and strength of the available scientific evidence, knowledge of screening practices in other countries, and considerations such as likely acceptability and feasibility and the risk of serious adverse events. The development of the scenarios was also informed by the deliberations of the Expert Advisory Group on Colorectal Cancer Screening which had been established by the National Cancer Screening Service (NCSS), and which had reported in December 2007[152].

Three core screening scenarios were endorsed by the HIQA EAG for evaluation in this HTA:

1. biennial gFOBT, with reflex FIT testing, in those aged 55-74 years;
2. biennial FIT, in those aged 55-74 years;
3. once-only flexible sigmoidoscopy (FSIG), at age 60.

These are described further below and are illustrated in Appendix 4. The decision as to which age group should be included in screening by faecal tests was based on the deliberation of the NCSS expert group; this group had recommended screening in those aged 55-74 years since colorectal cancer incidence is relatively low in those under 50 and increases with age[152]. The age at which FSIG would be undertaken was based on the mid-range of the age group included in the UK Flexible Sigmoidoscopy Screening Trial[116].

To assist with the decision- and policy-making process, the EAG endorsed a suggestion from the Evaluation Team (ET) that the cost-effectiveness of a series of variants of the core scenarios should be evaluated in secondary analyses. These scenarios were designed by the Evaluation Team and were differentiated from the core scenarios by various age restrictions or changes (see below).

4.1.1 Core scenarios

Under the gFOBT and FIT scenarios it was assumed that test kits would be dispatched by post to screening invitees, completed, and returned by post for laboratory processing and analysis. It was further assumed that in each two-yearly screening round approximately half of eligible individuals would be invited for screening in the first year and the remainder in the second year. FSIG would be conducted in designated screening centres by health professionals.

The EAG advised on the procedures which would be used for diagnostic investigation and post-polypectomy surveillance of screened individuals. For the majority of individuals, diagnostic investigation of a positive screening test would be by colonoscopy. Individuals who are unfit or otherwise unsuitable for colonoscopy, in whom the colonoscopy is incomplete (the caecum not reached), or who decline colonoscopy, would be offered CT colonography. Lesions seen at colonoscopy would be removed (by polypectomy) where possible and appropriate. If a cancer is suspected, the individual would be referred for diagnostic work-up, and treatment as required.

Individuals who have adenomas detected and removed would undergo follow-up/ surveillance in line with the most recent UK guidelines ([153]; Appendix 4). Those with low-risk adenomas (defined as 1-2 adenomas, both of which are small (<10mm) would be returned to routine screening, or if screening by once-only flexible sigmoidoscopy, would be discharged. Those with intermediate-risk adenomas (3-4 small adenomas or at least one adenoma ≥10mm) would have colonoscopies at 3-yearly intervals. Two consecutive clear colonoscopies would be needed before surveillance ceases and, if appropriate, the individual is returned to routine screening. If any colonoscopy shows high-risk adenomas (≥5 small adenomas or ≥3 adenomas, with at least one ≥10mm), the individual would revert to the surveillance strategy for high-risk adenomas. Those with high-risk adenomas would have yearly colonoscopy. If the examination is negative, or low or intermediate-risk adenomas are found, they would be followed-up according to the protocol for intermediate-risk adenomas. Consistent with the situation for diagnostic investigation, in the post-polypectomy surveillance protocol, individuals who are unfit or otherwise unsuitable for colonoscopy, in whom the colonoscopy is incomplete, or who decline colonoscopy, would be offered CT colonography.

4.1.2 Additional age-variant scenarios

The addition scenarios evaluated were:

- biennial gFOBT (with reflex FIT) in those aged 55-64
- biennial gFOBT (with reflex FIT) in those aged 65-74
- biennial FIT in those aged 55-64
- biennial FIT in those aged 65-74
- once-only FSIG at age 55

Diagnostic investigation, treatment and surveillance under these scenarios would be the same as for the core scenarios.

4.2 Interface between screening programme and existing services

It was the view of the NCSS and National Cancer Control Programme (NCCP) that a colorectal screening programme would be likely to encompass all procedures up to and including the completion of primary treatment (and the cancer is staged, if appropriate). Thus,

- for individuals with adenomatous polyps: Screening would include everything up to, and including, the removal of the polyp(s)
- for individuals with colon cancer: Screening would include everything up to and including surgery/colorectal resection
- for individuals with rectal cancer: Screening would include everything up to and including surgery/colorectal resection. Since pre-operative radiotherapy is standard care, this would be delivered under the auspices of the screening programme.

Post-colonoscopy follow-up and surveillance of individuals with intermediate-risk and high-risk adenomas removed would not be done as part of the screening programme, but would be a responsibility of the routine services. Adjuvant (post-surgery) chemotherapy and chemoradiation would not be delivered under the auspices of the screening programme. Once individuals have primary treatment, they would return to the care of their GP or local/routine clinical services for further treatment or follow-up as required.

This approach mirrors the screening model used by BreastCheck.

4.3 Comparator

In the main cost-effectiveness analyses, each screening scenario was compared with "no screening". "No screening" represents the status quo in Ireland, since there is no organised screening of average-risk individuals outside the context of specific research studies or opportunistic activities.

In further analyses, particular scenarios were compared against one another.

4.4 Cost perspective

The cost-effectiveness analysis was conducted from the perspective of the healthcare payer, in this context the Health Service Executive (HSE)/ Department of Health & Children. Therefore, only direct costs were included in the evaluation. Indirect costs, such as those associated with lost productivity, or out-of-pocket expenses incurred by individuals attending for a screening or diagnostic test, were not included.

4.5 Discounting

In the cost-effectiveness analysis, both costs and health outcomes were discounted at an annual rate of 4% starting at age 55. This is based on an estimate of the Social

Rate of Time Preference in Ireland and accordingly is considered, by HIQA, to be the appropriate rate for economic evaluations in Ireland. Discounting is not necessarily straightforward; it is not always clear at what point to begin discounting, and the appropriate rate is a matter of some debate (see chapter 7). Other discounting scenarios were, therefore, explored in sensitivity analyses (see section 4.9.1).

4.6 Outcomes

Because of the limitations of the available data on HRQoL for colorectal cancer (see Appendix 5), it was agreed with the EAG that health outcomes would be measured in both QALYs gained and LYG, and that these outcomes would be considered to have equal weight. The cost-effectiveness results are presented as costs per QALY gained and costs per LYG .

Secondary outcomes in the cost-effectiveness analysis included: (1) percentage reduction in the colorectal cancer incidence rate compared to no screening; (2) percentage reduction in the colorectal cancer mortality rate compared to no screening; (3) stage distribution of screen-detected and symptomatically detected cancers (i.e. those found clinically); (4) lifetime rates of complications (major bleeding, bowel perforation, and deaths due to perforation); (5) lifetime rates of endoscopy procedures; (6) costs of screening; and (7) costs of managing colorectal cancers.

4.7 Economic model

Cost-effectiveness and resource requirements/health outcomes were assessed within the same model structure. The model is an adaptation of the ScHARR colorectal cancer screening model, which was used to conduct an economic evaluation of gFOBT and flexible sigmoidoscopy screening in England. The model is described below. Further details can be found in Tappenden et al[118], together with discussion of the strengths and limitations of this model compared to the others available in the literature. Some of the modifications to the model were made for the purpose of incorporating the screening scenarios under evaluation in this HTA, and others were made to adapt it to a new setting (i.e. Ireland), with a different colorectal cancer incidence and mortality from that in England. Several modifications were made to deal with acknowledged limitations in the previous version of the model and how it was calibrated; others were for the purpose of updating the model to reflect advances in knowledge about the disease, and the availability of additional data.

The main modifications which have been made for this HTA are as follows:

- the inclusion of FIT and gFOBT with reflex FIT testing as screening tests;
- a refinement to the natural history component of the model to allow a proportion of colorectal cancers to develop without going through the adenoma-carcinoma pathway;
- sourcing of improved data sources for calibrating/fitting the natural history model (for example, prevalence of polyps, and undiagnosed colorectal cancer);
- a different method of calibrating the natural history model;
- calibrating the model to Irish colorectal cancer incidence and mortality data;
- populating the model with more up-to-date data, including data from recently established population-based or pilot screening programmes, recent RCTs and other studies;
- modification of the surveillance strategy for individuals with adenomas removed by polypectomy, to include categories of low, intermediate and high-risk polyps, more closely reflecting current follow-up recommendations[153];
- sourcing of improved data on metachronous adenomas and carcinomas in individuals under surveillance;
- incorporation of comprehensive probabilistic sensitivity analysis;
- inclusion of "a whole population" component within the model so that resource use and health outcomes for years 1-10 of screening implementation can be calculated within the same framework as cost-effectiveness;
- modification of the structure to compare different strategies for screening implementation.

4.7.1 Model structure: Natural history, screening and mortality components

The economic model is implemented within EXCEL® (Microsoft Corporation). It contains three sub-models: (1) a state-transition model which simulates the natural history of colorectal cancer; (2) a model of the screening intervention (and subsequent adenoma surveillance for intermediate and high-risk individuals) which interacts directly with the natural history model; and (3) a model of mortality, which is used to reflect age-specific 'other-cause' mortality, mortality due to colorectal cancer and mortality resulting from perforation due to endoscopic procedures. These components are described in more detail below.

Two approaches can be taken to running the model - a single cohort approach and a whole population approach. The single cohort approach is used to estimate the cost-effectiveness of screening. The economic model was initially developed around the single cohort approach and the descriptions below reflect this. Essentially, this model "works" as follows. A single cohort of individuals aged 30 is followed through the model, simulating progression throughout their lifetime. As the cohort ages some develop adenomatous polyps, some develop cancers, and some die. The simulation continues until the cohort is aged 100, by which time almost all members will have

been absorbed into the "death" health-state. The size of the cohort in this analysis is based on the estimated number of 55-year old individuals in Ireland in the year 2020 (n=64,420[154]). The cohort were aged 55 since this is the age at which screening starts in the scenarios under consideration. Since the cohort model evaluates cost-effectiveness when a programme is fully implemented in the population, the 2020 population was used to allow time for programme set-up and implementation and to accommodate demographic changes anticipated between 2008 and 2020. The cost-effectiveness analysis relates to all costs, events (e.g. diagnostic tests, treatment procedures, health outcomes) which occur over the lifetime of this single cohort.

The whole population approach is used to calculate the resource use requirements and health outcomes in the initial years of implementation of a screening programme. This approach follows 70 different age-cohorts (i.e. a cohort of 30 year-olds, a cohort of 31 year-olds, a cohort of 32 year-olds, etc) through the model for a defined number of years (in this case, 10 years). Annual resource use and health outcomes are accumulated for all 70 age-cohorts (i.e. across the whole population). The number of individuals in each age-cohort was chosen to match the 2008 population distribution for Ireland[154], so the outputs essentially reflect resources requirements (and health outcomes) for the first 10 years of the programme should a screening programme be established immediately.

4.7.1.1 Natural history model for colorectal neoplasia

The natural history model is a Markov model. Central to this methodology is the division of the given disease process into a finite number of mutually exclusive health states, and the division of the relevant time horizon for the analysis into equal increments of time (Markov cycles of one year). At any point in time, all "patients" must exist within one of the defined health states. The distribution of "patients" across the health states over time is governed by a series of transition matrices which describe the probability of transiting from the current health state to an alternative health state during each model cycle. Costs and utilities are associated with spending time in each health state or with the transition between health states; these are aggregated over the time horizon to provide an estimate of the expected costs and health outcomes of each screening option.

The natural history model simulates the progression from normal epithelium to adenomatous polyp to colorectal cancer and eventually, death. As the Markov methodology requires mutually exclusive states, health states describing the presence of adenomas and pre-clinical cancers are defined in terms of the 'index' lesion; that is, the greatest malignant potential of the adenoma present, or the most advanced cancer present. Individuals with adenomas are classified as either low-risk (<10mm) or higher-risk (≥10mm), with "higher-risk" broadly corresponding to a combination of the categories of intermediate-risk and high-risk defined by Atkins & Saunders[153]. Intermediate and high-risk adenomas are not modelled separately due to limitations in the evidence-base regarding the rate at which individuals progress from low-risk to intermediate-risk and from intermediate-risk to high-risk[118]. Discrete cancer states are modelled individually according to AJCC staging (i.e. stages I, II, III and IV)[27]. The presence of adenomatous polyps and cancers located in the distal and proximal colon is considered separately in order to

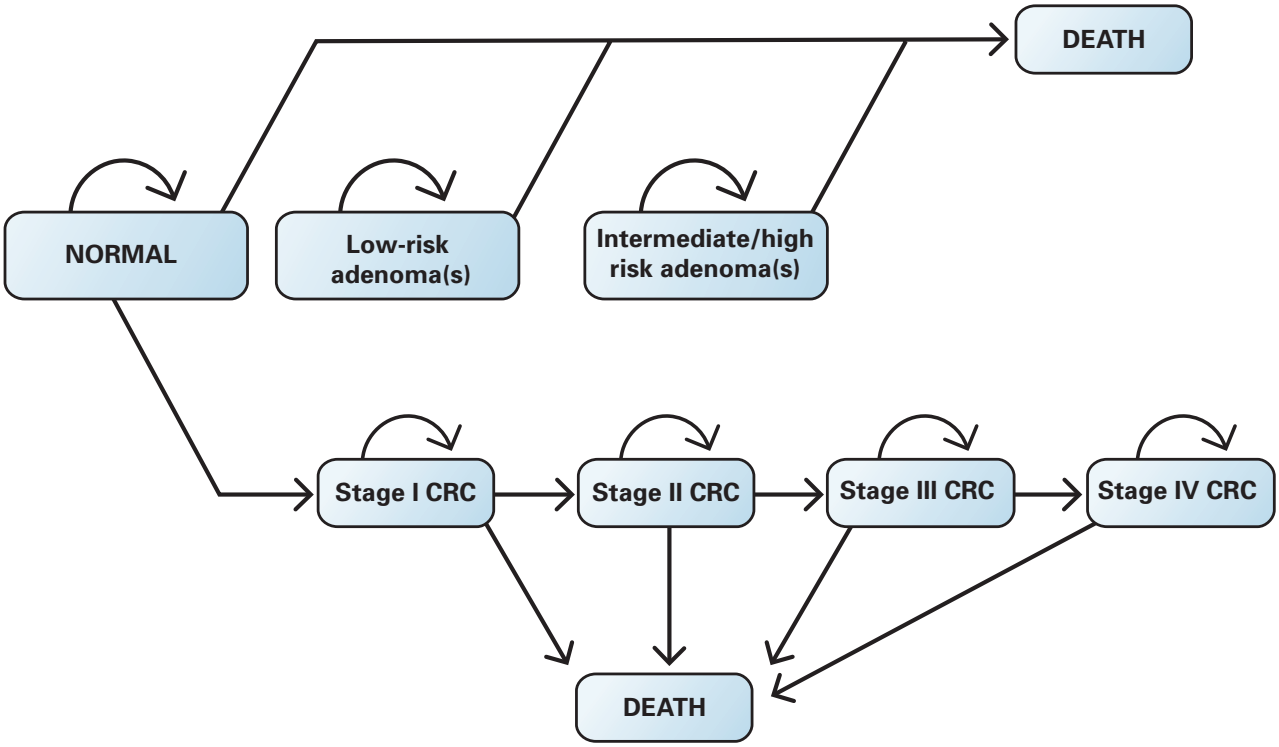
account for the reach of flexible sigmoidoscopy (although some correlation between the two is implicitly modelled, essentially by assuming that 70% of adenomas arise in the distal colon and 30% in the proximal colon).

Since a proportion of colorectal cancers may arise without a prior adenoma, the model allows for some cancers to develop without progressing through the adenoma pre-cursors; thus, some in the cohort can transition directly from normal epithelium to stage I colorectal cancer. This aspect of the model was agreed with the EAG.

Due to difficulties in defining the true prevalence of adenomas and pre-clinical cancers at the time of the first screening round, the cohort enters the simulation at age 30, at which point it is assumed that the prevalence of pre-clinical adenomas and cancers is zero. This is likely to be a reasonable assumption for colorectal cancers that arise in those without specific genetic syndromes such as FAP or HNPCC (i.e. "sporadic" cancers). The prevalence of adenomas at the time of the first screen is thus built up over the pre-screening period. (i.e. during ages 30-54). Time-homogeneous transition probabilities are used to describe adenoma growth, progressions to pre-clinical cancer, and the rate at which pre-clinical cancers progress from early local cancer to regional disease and subsequently, metastatic disease. Time-varying probabilities are used to reflect different incidence rates for adenomas arising in the distal and proximal colon, and age-specific probabilities of other cause mortality. The probability that an individual with colorectal cancer is diagnosed is assumed to vary according to the stage of cancer. Individuals with cancer who present symptomatically transition to one of four clinically diagnosed cancer health states, depending on the stage of the cancer. The stage of the cancer at diagnosis determines the annual probability of dying from colorectal cancer, the subsequent treatment and follow-up strategies, and the utility associated with the health state.

All transitions in the model are progressive; 'backwards' transitions are not allowed for within the model. Figure 4.1 illustrates the Markov states in the natural history model, and the transitions possible in each annual cycle.

Figure 4.1 Markov states in natural history model



low-risk polyp(s): <10 mm; intermediate/high-risk adenomas: ≥10mm; CRC=colorectal cancer

4.7.1.2 Screening intervention model

Superimposed upon the natural history model is a screening intervention model which allows for the detection and removal of adenomas through endoscopy and the detection and treatment of colorectal cancer. The test characteristics of gFOBT, FIT, flexible sigmoidoscopy, colonoscopy and CT colonography are defined in terms of the probability of achieving positive or negative test results given an individual's true underlying histological state (i.e. the true sensitivity and specificity of the test). The impact of the different screening tests, diagnostic colonoscopy or CT colonography, and management of adenomas and cancers are modelled by re-distributing the model cohort across the health states at the point of screening. For example, an individual in whom a low-risk adenoma is detected by flexible sigmoidoscopy is assumed to undergo polypectomy and is subsequently moved to the 'low-risk post-polypectomy' health state.

The effectiveness of each screening modality is thus modelled as a function of an individual's true histological state, the probability of completing a screening test, the characteristics of the screening test, the probability of attending for a diagnostic investigation, the characteristics of the diagnostic test, and the probability of death due to the diagnostic test. For example, an individual with stage I colorectal cancer who is offered FIT has a probability of completing and

returning the test kit, a probability of testing positive for FIT, a probability of attending for diagnostic colonoscopy, a probability of testing positive for colorectal cancer on colonoscopy, and a probability of dying due to endoscopic perforation of the bowel.

Because of a lack of data on the diagnostic performance of combinations of screening tests, the model assumes that the performance characteristics of the gFOBT and reflex FIT tests are independent. It further assumes that all of those who have a positive gFOBT will complete a FIT.

While most adenomas are removed via polypectomy, in practice some cases (for example, large adenomas) may require surgery. For the sake of simplicity, the model assumes that all identified adenomas are removed at the point of detection (i.e. at polypectomy during colonoscopy following a positive gFOBT/FIT, or during the flexible sigmoidoscopy screen) regardless of risk status of the individual.

For simplicity, the model also assumes 100% compliance with CT colonography in those who are offered it because they are unfit or unsuitable for colonoscopy, they have declined to undergo colonoscopy, or they have had a colonoscopy and it was incomplete.

Individuals in whom colorectal cancer is detected by flexible sigmoidoscopy at diagnostic investigation or at post-polypectomy surveillance enter one of four "screen-detected clinical management" health states depending on the stage of the disease at the point of detection.

4.7.1.3 Surveillance for individuals with adenomas detected

A further three health states are used to model the subsequent risk of developing new adenomas following polypectomy: "low-risk post-polypectomy", "intermediate-risk post-polypectomy" and "high-risk post polypectomy". The probability of developing a new adenoma for individuals in these states is higher than for those with no prior history of adenomas. The surveillance strategy follows Atkin and Saunders ([153]; Appendix 4). It was assumed that no further surveillance of adenomas would be undertaken beyond 80 years of age; this was based on a combination of the upper oldest age at which screening would be offered (by gFOBT or FIT: 73 years), and the minimum number of years an individual with a high-risk screen detected adenoma would be under surveillance (7 years).

4.7.1.4 Mortality model

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

surveillance process. For gFOBT and FIT screening options, the probability of death due to perforation of the bowel is applied at the point of diagnostic investigation only, whereas for flexible sigmoidoscopy screening options, this risk is applied both at the point of screening, as well as at diagnostic colonoscopy for those individuals found to have high-risk or malignant neoplasia. The risk of perforation due to surveillance colonoscopy is modelled in the same way for the first and subsequent colonoscopies for all screening scenarios.

4.7.2 Costs and health outcomes

Costs incurred after age 55 are included in the model, since this is the age at which screening starts in the scenarios which were modelled. Costs of screening include: the screening test and any associated processing, diagnostic investigation, pathology and treatment of complications. Since surveillance colonoscopy and CT colonography are a consequence of screening, the costs of these procedures are included in the costs of screening. Costs of cancer management relate to the lifetime costs of managing both screen-detected cancers and those which present symptomatically. LYG (and QALYs gained) for an average 55-year old as a result of implementing screening are calculated as the sum of the number of people alive at the beginning of each of the model cycles starting at age 55 (i.e. from age 55 to age 100) and are based on the difference between the expected life years for a strategy of screening compared to no screening. The model incorporates adjustments for HRQoL associated with different states of health by applying different utility weights to each year spent in the respective model health states. The same utility score is applied to all "non-cancer" states.

4.7.3 Model calibration - fitting the natural history model

Parameter values for the transition probabilities in the natural history part of the model are largely unobservable, primarily because they relate to events which are difficult to measure and/or for which data are unavailable, such as the rate of progression through the stages of colorectal cancer. Estimates for these unobservable parameters are obtained through a process of model calibration, which involves fitting the model to available data on the incidence and mortality of colorectal cancer and the likely prevalence of adenomas and undiagnosed cancers in Ireland. The sources of data used in the model fitting are described in Appendix 4.

The natural history parameters were estimated by using a the Metropolis-Hastings algorithm, which is a Markov Chain Monte Carlo (MCMC) method. The algorithm is a stochastic method which generates multiple sets of parameters from a probability distribution that is compatible with the observed data (i.e. the data on colorectal cancer incidence and mortality and adenoma prevalence). It starts by using arbitrary initial values for the parameters, and then proposing nearby candidate values. The chance that the chain moves to these values depends on the relative likelihood of these compared with the previous values for the chain. After an initial number of iterations, the values that are selected come from the joint distribution of the parameters given the data. This approach is commonly used in Bayesian statistical inference and is well described elsewhere[155-157].

The approach was implemented in Visual Basic for Applications within the EXCEL®

(Microsoft Corporation) model and the results were subsequently examined for convergence using the package CODA in R v2.8.0 (R Development Core Team). A normal likelihood function was used for the observations about mortality, incidence and prevalence. The model was run using three independent chains with a burn-in of 2000 iterations for each. The parameter set with the highest likelihood was used for the transition probabilities when the cost-effectiveness model was run using the base-case parameters and in the one-way and multi-way sensitivity analyses (see section 4.9). Thinned sets from all of the chains were used in the probabilistic sensitivity analysis (see section 4.9). Since the values are samples from the joint posterior probability distribution, they reflect the residual uncertainty about the natural history parameters conditional on the data that are available for the fitting process.

The results of the calibration process are shown in Appendix 7.

4.8 Model parameters

There are three main types of model parameters: (1) those relating to costs; (2) those relating to issues such as test performance, uptake, and so forth; and (3) those used in the model fitting. For the first two categories of parameters, the most likely value of the parameter (for use in the base-case analysis), and the range or variability around this (for use in the sensitivity analysis; see section 4.9) were determined. To ensure that all methods and assumptions are explicit, the data sources, methods and assumptions used to derive the parameters are described in detail in Appendices 6 and 7.

The primary source of information for the non-cost parameter estimates was literature review. This was augmented by reports and data from ongoing population-based screening programmes, pilot programmes (such as the pilots in England and Scotland[59]) and randomised controlled trials (such as the UK Flexible Sigmoidoscopy Trial[116]). The data sources cited by the authors of the cost-effectiveness evaluations (see chapter 3 and Appendix 3) published since 2003 were also reviewed in detail. Where information could not be obtained from these sources, expert clinical opinion was sought. In these situations, the experts were asked to provide both the most likely value for the parameter estimate and some indication of the likely range.

The main source for the literature review was Medline (PubMed). For those parameters which had been included in the original ScHARR model[118], the focus was on identifying papers published since 2003 (i.e. after the literature review for that model was conducted). For "new" parameters (for example, performance characteristics of FIT), no time limit was placed on the search. Searches used a range of MeSH headings and text words relevant to colorectal cancer, adenomas, the screening and diagnostic tests, including "adenomatous polyps", "colonic polyps", "colorectal neoplasms", "colon cancer", "rectal cancer", "FOBT" and "faecal immunochemical test". Alternative spellings were allowed and wild-cards used to ensure relevant papers were not missed. Combinations of search terms were used to help focus on potentially relevant papers. Searches were limited to studies relating to adults (aged 19 and older) and published in the English language. Particular efforts were made to identify systematic reviews, meta-analyses or

pooled analyses. Reference lists of published articles were hand-searched to identify further relevant papers. Abstracts of papers thus identified were carefully reviewed. Full copies of papers which appeared relevant were obtained; details were extracted and tabulated. To identify parameters on HRQoL, additional searches were done of Tufts Medical Centre CEA Registry. The term "colorectal cancer" was used to search for utility weights over a 10 year period between 1995 and 2005 (the most recent data for which data was available at the time of the search). Separate reviews were conducted for each model parameter. The searches were done during May to November 2008.

In selecting parameter estimates, a range of features of the reviewed data sources were considered. These included: whether the data were from a population-based screening programme or pilot programme; study design; quality; size; characteristics of the participants; definitions of the outcomes of interest and likely applicability of the results to Ireland. Detailed information on the review process for the non-cost parameter estimates are contained in Appendix 5. This appendix also describes the data sources used in the model fitting.

Appendix 6 is a technical report describing in detail the derivation of the costs of screening tests, diagnostic tests, follow-up surveillance and management of colorectal cancer.

The base-case values, ranges and distributions of the model parameters are shown in table 4.1. The parameter estimates used were endorsed by the EAG.

Table 4.1 Parameter estimates, with base-case values, range, distributions and sources

	Model parameter	Base-case estimate	Range for sensitivity analyses	Distribution for PSA[1]	Source
Performance of screening tests					
1	gFOBT sensitivity for adenomas	11%	10% - 12%	Beta (11.40,92.10)	Allison et al, 1990, Allison et al, 1996, Brevinge et al, 1997, Castiglione et al, 1991, Collins et al, 2005, Foley et al, 1992, Lieberman et al, 2001, Niv et al, 2002, Sung et al, 2003[158-166]
2	gFOBT sensitivity for CRC	36%	31% - 42%	Beta (105.00,186.60)	
3	gFOBT specificity for adenomas and CRC	97%	96% - 98%	Beta (1083.40,33.50)	
4	FIT sensitivity for adenomas	21%	19% - 22%	Beta (594.62,2236.92)	Allison et al, 1996, Allison et al, 2007, Chen et al, 1997, Cheng et al, 2002, Gondal et al, 2003, Itoh et al, 1996, Liu et al, 2003, Morikawa et al, 2005, Morikawa et al, 2007, Nakama et al, 2000, Nakama et al, 2001, Nakazato et al, 2006[82, 159, 167-176]
5	FIT sensitivity for CRC	71%	67% - 75%	Beta (35.29,143.08)	
6	FIT specificity for adenomas and CRC	95%	94% - 96%	Beta (1732.57,91.19)	
7	FSIG sensitivity for low-risk distal adenomas	65%	60% - 70%	Beta (235.00,126.54)	Expert opinion, informed by Lieberman et al, 2001, Rozen et al, 1987, Sung et al, 2003[164, 166, 167]
8	FSIG sensitivity for intermediate/ high-risk distal adenomas	74%	68% - 78%	Beta (180.00,63.24)	Lieberman et al, 2001, Rozen et al, 1987, Sung et al, 2003[164, 166, 167]
9	FSIG sensitivity for distal CRC	90%	85% - 95%	Beta (90.00,10.00)	Expert opinion, informed by Bressler et al, 2007, Lieberman et al, 2001, Rozen et al, 1987, Sung et al, 2003[164, 166, 177, 178]
10	FSIG specificity for distal adenomas and CRC	92%	90% - 95%	Beta (250.00,21.74)	Expert opinion

Uptake and non-compliance with screening tests					
11	gFOBT uptake	53%	32% - 70%	Uniform	Information Services Division, 2008, UK Colorectal Cancer Screening Pilot Group, 2004, Verne et al, 1998, Weller et al, 2006[59, 102, 111, 179]
12	FIT uptake	53%	32% - 70%	Uniform	Bowel Cancer Screening Pilot Monitoring and Evaluation Steering Committee, 2005, Grazzini et al, 2004, Ho et al, 2008, Sali et al, 2008, Segnan et al, 2005, Segnan et al, 2007[88, 89, 92, 93, 150, 180]
13	FSIG uptake	39%	24% - 67%	Uniform	Brotherstone et al, 2007, Gray and Pennington, 2000, UK Flexible Sigmoidoscopy Screening Trial Investigators, 2002[114, 116, 181]
14	% of individuals who never accept an offer of screening[2]	13%	0% - 41%	-	Weller et al, 2006[179]
Compliance with diagnostic tests[3]					
15	COL compliance (diagnostic test)	86%	81% - 90%	Uniform	Cotton et al, 2004, Information Services Division, 2008, Weller et al, 2006[102, 179, 182]
Performance of diagnostic tests and related parameters					
16	COL sensitivity for low-risk adenomas	77%	73% - 80%	Beta (350.00,104.55)	Bressler et al, 2007, Rex et al, 1997, Rockey et al, 2005, van Rijn et al, 2006[178, 183-185]
17	COL sensitivity for intermediate/ high-risk adenomas	98%	93% - 99%	Uniform	
18	COL sensitivity for CRC	98%	95% - 99%	Uniform	
19	COL specificity for adenomas and CRC	97%	96% - 98%	Beta (970.00,30.00)	Expert opinion
20	CTC sensitivity for low-risk adenomas	53%	45% - 60%	Beta (80.00,70.94)	Expert opinion, informed by Mulhall et al, 2005[186]
21	CTC sensitivity for intermediate/ high-risk adenomas	85%	48% - 100%	Beta (4.50,0.79)	Johnson et al, 2008, Mulhall et al, 2005[186, 187]

22	CTC sensitivity for CRC	85%	75% - 95%	Beta (50.00,8.82)	Expert opinion, informed by Cotton et al, 2004, Halligan et al, 2005, Johnson et al, 2008, Rockey et al, 2005[182, 184, 187, 188]
23	CTC specificity for adenomas and CRC	86%	80% - 90%	Beta (140.00,22.79)	Expert opinion, informed by Johnson et al, 2008, Mulhall et al, 2005[186, 187]
24	Average no. adenomas removed per person	1.9	-	-	Winawer et al., 1993[40]
Harms of screening					
25	FSIG probability of perforation (with or without polypectomy)	0.002%	0% - 0.051%	Uniform	Gondal et al, 2003, Kelly et al, 2008, Levin et al, 2002, Shapero et al, 2007, UK Flexible Sigmoidoscopy Screening Trial Investigators, 2002[116, 169, 189-191]
26	FSIG probability of death following perforation	6.452%	0% - 9.070%	Uniform	Gatto et al, 2003, Misra et al, 2004[108, 192]
27	Probability of (major) bleeding following FSIG	0.029%	0.002% - 0.054%	Uniform	Levin et al, 2002, Pabby et al, 2005, UK Flexible Sigmoidoscopy Screening Trial Investigators, 2002[116, 190, 193]
28	COL probability of perforation (with polypectomy)	0.216%	0.168% - 0.298%	Uniform	Dafnis et al, 2001, Gondal et al, 2003, Misra et al, 2004, Regula et al, 2006, UK Flexible Sigmoidoscopy Screening Trial Investigators, 2002[116, 169, 192, 194, 195]
29	COL probability of perforation (without polypectomy)	0.107%	0.010% - 0.249%	Uniform	
30	COL probability of death following perforation	5.195%	0% - 9.070%	Uniform	Gatto et al, 2003, Misra et al, 2004[108, 192]
31	Probability of (major) bleeding following COL	0.379%	0.065% - 0.412%	Uniform	Bowles et al, 2004, UK Flexible Sigmoidoscopy Screening Trial Investigators, 2002, Weller et al, 2006[116, 179, 196]
Resource use parameters - inadequate or incomplete endoscopic procedures[4]					
32	FSIG probability of incomplete/ inadequate procedure	9%	5%-14%	Beta (14.00,141.56)	Gondal et al, 2003, Segnan et al, 2007, UK Flexible Sigmoidoscopy Screening Trial Investigators, 2002, Weissfeld et al, 2005[89, 116, 117, 169]
33	COL probability of incomplete/ inadequate procedure	13%	8% -16%	Uniform	Shah et al, 2007[197]; range based on expert opinion

Health-related QoL/utility					
34	Utility cancer free	0.94	-	-	Fryback and Lawrence, 1997[198]
35	Utility stage I	0.80	0.43-0.94	0.94*Beta (3.92,0.69)	Ramsey et al, 2000[199]
36	Utility stage II	0.80	0.43-0.94	0.94*Beta (3.92,0.69)	
37	Utility stage III	0.80	0.43-0.94	0.94*Beta (3.92,0.69)	
38	Utility stage IV	0.80	0.43-0.94	0.94*Beta (3.92,0.69)	
Surveillance of screen-detected adenomas					
39	% of those in with intermediate/ high-risk adenomas removed in whom the adenoma was high-risk	29%	-	-	Alexander and Weller, 2003, Weller et al, 2006[58, 179]
40	COL compliance (surveillance)	86%	81% - 90%	Uniform	Assumption
Resource use parameters – costs					
41	gFOBT kit[5]	€1.70	€1.36-€2.04	Uniform	Estimated by ET (see Appendix 6 for full details)
42	gFOBT processing/ analysis[6]	€7.81	€6.25-€9.37	Uniform	
43	FIT kit[5]	€3.75	€3-€4.50	Uniform	
44	FIT processing/ analysis[6]	€11.60	€9.28-€13.92	Uniform	
45	Cost of FSIG (with/without polypectomy)	€150	€120-€180	Uniform	VHI Healthcare; Whynes et al, 2003[200]
46	Cost of COL	€650	€520-€780	Uniform	Based in DRGs (HSE Casemix Unit, 2008;[201])
47	Cost of CTC	€550	€440-€660	Uniform	Expert opinion
48	Cost of treating bowel perforation	€10,200	€8,160-€12,240	Uniform	Based in DRGs (HSE Casemix Unit, 2008;[201])
49	Cost of admittance for bleeding	€3,079	€2,463-€3,695	Uniform	Based in DRGs (HSE Casemix Unit, 2008;[201])
50	Pathology cost for adenoma	€65	€52-€78	Uniform	Tappenden et al, 2004[118]
51	Pathology cost for cancer	€530	€424-€636	Uniform	Tappenden et al, 2004[118]

52	Lifetime cost stage I CRC-symptomatic	€23,688	€18,950 - €28,425	Uniform	Estimated by ET (see Appendix 6 for full details)
53	Lifetime cost stage II CRC -symptomatic	€37,180	€29,744 - €44,616	Uniform	
54	Lifetime cost stage III CRC-symptomatic	€48,835	€39,068 - €58,602	Uniform	
55	Lifetime cost stage IV CRC-symptomatic	€36,602	€29,281 - €43,922	Uniform	
56	Lifetime cost stage I CRC - screen-detected	€22,885	€18,308 - €27,462	Uniform	
57	Lifetime cost stage II CRC - screen-detected	€36,377	€29,102 - €43,652	Uniform	
58	Lifetime cost stage III CRC - screen-detected	€48,032	38,426 - €57,638	Uniform	
59	Lifetime cost stage IV CRC-screen-detected	€35,799	28,639 - €42,959	Uniform	

COL=colonoscopy; CRC=colorectal cancer; CTC=CT colonography; ET=Evaluation Team; FIT=faecal immunochemical test; gFOBT=guaiac faecal occult blood test; FSIG=flexible sigmoidoscopy; low-risk adenoma(s), <10mm; intermediate/high-risk adenoma(s), ≥10mm.

1 *if not distribution given, parameter was not varied in the PSA*

2 *relevant to gFOBT and FIT scenarios only; varied in one-way sensitivity analysis, but not varied in PSA*

3 *for simplicity the model assumes that all those who are referred for CT colonography attend*

4 *used in model to estimate percentage who require another procedure; if FSIG is incomplete or inadequate, the individual will have another FSIG; if COL is incomplete or inadequate, the individual will have CT colonography*

5 *cost per kit dispatched (cost per individual invited to participate in screening)*

6 *cost per kit completed and returned (cost per screening participant)*

4.9 Sensitivity analyses

4.9.1 One-way and multi-way sensitivity analyses

Table 4.2 shows the key parameters which were varied in one-way and multi-way sensitivity analyses. The cost-effectiveness analysis was repeated setting each specified parameter at its lower or upper limit as shown in table 4.1, or the values described below. Some parameters were varied simultaneously because they would be expected to be correlated. For example, when screening test sensitivity was varied, it was varied simultaneously for adenomas and carcinomas; when utility was varied, this was done simultaneously for all stages of colorectal cancer; and when costs of managing colorectal cancer were varied, this was done for all stages and both screen-detected and non-screen detected cases simultaneously.

Because of the uncertainty in the costs of the screening tests (Appendix 6), and the potential for these to have a major impact on the costs of screening, it was decided to conduct additional sensitivity analyses around these. The costs were allowed to vary within 10%, 20%, 30%, 40% and 50% of the base-case estimates and cost-effectiveness was computed at each of these points. Costs of colonoscopy were allowed to vary by up to 50% either side of the base-case value. Because of the variation in the results of the studies of HRQoL (see Appendix 5), two sensitivity analyses were undertaken relating to utility. In the first, the utility estimates were varied around the base-case values from Ramsey et al[199]. The second used utility estimates from the study of Ness et al[202], and assumed that utility decreased with increasing stage (stage I: base-case=0.74, range 0.69-0.78; stage II: 0.69, 0.64-0.73; stage III: 0.64, 0.59-0.69, stage IV: 0.25, 0.20-0.31: see Appendix 5).

Because of the increasing range of faecal tests available, and the heterogeneity in the reported performance characteristics[53, 94] additional sensitivity analyses were run to further explore the effect of using gFOBTs or immunochemical tests with higher sensitivity. Using data from the study of Allison et al[82], which employed the gFOBT Hemoccult® SENSA®, alternative estimates for gFOBT sensitivity were derived (adenomas: 20%; carcinomas: 64%). Cost-effectiveness of screening if this test (or another gFOBT test with similar sensitivity) was to be used for a primary screening test was then estimated. Data from Nakama et al[203], who reported the immunochemical OC-Hemodia test with a cut-off of 50 ng/mL, was used to define alternative values for FIT sensitivity (adenomas: 32%; carcinomas: 89%). The analysis was re-run exploring the impact on cost-effectiveness if a more sensitive immunochemical test was used as a primary screening tool. A further sensitivity analysis was undertaken specifically in relation to the gFOBT scenario, to consider the impact on cost-effectiveness if the performance characteristics of the gFOBT and FIT were not independent (independence was assumed in the base-case). For this analysis, the combined sensitivity and specificity of the two tests was estimated from data on the ppv and positivity rate of the combination of tests from the third round of the pilot programme in Scotland[102], data on average age of screening participants from the second round of the pilot programme in England[179], and estimates from the current model on prevalence of adenomas and colorectal cancers. From this process the sensitivity of the combined tests was estimated to be 14.5% for cancers and 3.8% for adenomas; the combined specificity was estimated to be 99.2%.

Since the discount rate is likely to be a key determinant of cost, the analyses were repeated setting it at 0% (i.e. undiscounted) and 6% for both costs and outcomes.

Table 4.2 Parameters included in one-way and multi-way sensitivity analyses

Model parameter(s)	Model parameter(s)
Test characteristics	**Costs**
gFOBT sensitivity (for adenomas and CRC)	Cost of gFOBT (kits and processing/analysis)
Sensitivity (for adenomas and CRC) and specificity of the combination of gFOBT and reflex FIT[1]	Cost of FIT (kits and processing/analysis)
FIT sensitivity (for adenomas and CRC)	Cost of FSIG
FSIG sensitivity (for distal adenomas and CRC)	Life time cost of managing CRC (symptomatic and screen-detected)
COL sensitivity (for adenomas and CRC)	
Uptake and compliance	**HRQoL**
Proportion who never participate in screening (gFOBT and FIT-based scenarios only)	Utility based on Ramsey et al, 2000[199]
gFOBT uptake	Utility based on Ness et al, 1999[202]
FIT uptake	**Discount rate**
FSIG uptake	Costs and benefits
COL compliance (diagnostic test)	

1 analysis assuming the performance characteristics of the tests are not independent

4.9.2 Probabilistic sensitivity analysis

The PSA involved running the model with 1,200 different parameter sets, and calculating the costs, LYG and QALYs gained for each run. In each simulation (run) the value for each parameter was sampled from its probability distribution (shown in table 4.1). The choice of the probability distributions was based on consideration of the properties of the parameters and the data informing them (specifically the ranges from the literature review). Beta distributions were used for preference. In some cases, where probabilities were very small, or the parameter range was very skewed. it was not possible to fit a beta distribution to the range, so a uniform distribution was used. In the simulations, most parameters were considered to be independent of one another but some were thought to be inter-dependent and so their distributions were correlated. For example, the sensitivities of a screening test for low-risk adenomas and intermediate/high-risk adenomas were considered to be related so these parameters were modelled using correlated distributions. The natural history parameters were sampled from the natural history parameter sets obtained in the calibration process as described in section 4.7.3, with 400 sets sampled from each of the three chains.

Chapter 5

Cost-effectiveness of colorectal cancer screening in Ireland

Key findings

- No screening was the least expensive policy. Once-only FSIG at age 60 was associated with the smallest increase in costs compared to no screening (€3.43 per person), followed by biennial gFOBT for 55-74 years (€33.63 per person) and biennial FIT for 55-74 years (€40.17 per person).
- All three core scenarios were associated with gains in life years and QALYs compared to no screening. The maximum health gain was for FIT-based screening (0.0237 QALYs per person compared to no screening), followed by gFOBT (0.0076 QALYs) and FSIG (0.0058 QALYs).
- Each of the three core scenarios was highly cost-effective compared to no screening. Compared to no screening, FSIG once at age 60 had the lowest ICER (€589 per QALY gained), followed by FIT at 55-74 years (€1,696), and by gFOBT at 55-74 years (€4,428).
- gFOBT at age 55-74 was dominated (i.e. it was more costly and less effective than a combination of the other two strategies).
- FIT at age 55-74 was associated with the maximum health gain. However, as well as being more effective than FSIG at age 60, it was more costly. The ICER for FIT at age 55-74 versus FSIG at age 60 was €2,058 per QALY gained, which would be considered highly cost-effective. This indicates that FIT at age 55-74 is the optimal strategy.
- The results were robust to variations in parameter estimates. Following extensive one/multi-way and probabilistic sensitivity analyses the conclusions were unchanged.
- When age-related variations in the screening scenarios were considered, the three most cost-effective scenarios were biennial FIT at age 55-74, biennial FIT at age 55-64 and FSIG once at age 60. All other scenarios were dominated. In comparing these three options with one another, the optimal strategy was FIT at age 55-74 (ICER of €3,221 per QALY gained compared to FIT at ages 55-64), followed by FIT at age 55-64 (ICER of €1,436 per QALY gained compared to FSIG at age 60).
- The cost-effectiveness acceptability curves indicated, that if decision-makers were willing-to-pay a maximum of around €1000 per additional QALY, the most cost-effective strategy would be expected to be FSIG once age 60. At a willingness-to-pay threshold of between approximately €1,000 and €3,000 per additional QALY, biennial FIT in the 55-64 age group would be likely to be the most cost-effective option.

If decision-makers were willing to pay €4,000 per additional QALY or more, the preferred option would be biennial FIT in the full age range, 55-74 years. Moreover, if decision-makers were willing-to-pay approximately €13,000 per additional QALY, this strategy would be expected to be cost-effective approaching 100% of the time.

- As well as depending on decision-makers' willingness-to-pay, any decision to invest in FIT would depend on resource considerations; these are considered in detail in chapter 6. It is worth noting that if FIT was considered unfeasible (due to resource considerations, for example) gFOBT at age 55-74 and FSIG once at age 60 would be considered highly cost-effective options compared to a policy of no screening.
- In conclusion, biennial FIT at age 55-74 is the optimal strategy as it would result in the greatest health gain of all the scenarios evaluated.

5.1 Base-case analysis for core scenarios

Tables 5.1 and 5.2 show the lifetime costs and benefits, in terms of QALYs and LYG, respectively, for the three core screening scenarios compared to no screening for a population of 64,420 55-year old individuals in Ireland. No screening option was the least expensive policy. Once-only FSIG at age 60 was associated with the smallest increase in costs compared to no screening (€3.43 per person), followed by biennial gFOBT for 55-74 years (€33.63 per person) and biennial FIT for 55-74 years (€40.17 per person).

Table 5.1 Incremental cost-effectiveness ratios (ICER), based on QALYs, for core screening scenarios

Scenario	Cost of screening & CRC management per person	Incremental cost per person[1]	Expected QALYs per person	Incremental QALYs per person[1]	ICER -Incremental cost per QALY gained
No screening	€ 1074	-	10.96	-	-
gFOBT at 55-74 years	€ 1107	€ 33.63	10.97	0.0076	€ 4,428[2]
FIT at 55-74 years	€ 1114	€ 40.17	10.98	0.0237	€ 1,696
FSIG once at 60 years	€ 1077	€ 3.43	10.97	0.0058	€ 589

CRC=colorectal cancer; FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; gFOBT=guaiac-based faecal occult blood test; QALY=quality-adjusted life year. Costs and outcomes discounted at 4%

1 Each incremental values compares value for that strategy to common baseline of no screening

2 gFOBT considered dominated by a combination of FIT and FSIG

Table 5.2 Incremental cost-effectiveness ratios (ICER), based on LYG, for core screening scenarios

Scenario	Cost of screening & CRC management per person	Incremental cost per person1	Expected life years per person	Incremental LYG per person[1]	ICER- Incremental cost per LYG
No screening	€ 1074	-	11.68	-	-
gFOBT at 55-74 years	€ 1107	€ 33.63	11.69	0.0101	€ 3,332
FIT at 55-74 years	€ 1114	€ 40.17	11.71	0.0273	€ 1,470
FSIG once at 60 years	€ 1077	€ 3.43	11.69	0.0059	€ 583

CRC=colorectal cancer; FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; gFOBT=guaiac-based faecal occult blood test; LYG=life years gained. Costs and outcomes discounted at 4%

1 Each incremental value compares values for that strategy to common baseline of no screening

All three screening scenarios were associated with gains in life years and QALYs compared to no screening. These gains were small and, as would be expected, were slightly larger for LYG than for QALYs. The maximum health gain was for FIT-based screening (0.0237 QALYs per person compared to no screening), followed by gFOBT (0.0076 QALYs) and FSIG (0.0058 QALYs). Combining costs and benefits, and comparing each scenario with no screening, the incremental cost per QALY gained was smallest for FSIG (€589), intermediate for FIT (€1,696) and highest for gFOBT (€4,428). These ICERs were all much lower than the historical notional cost-effectiveness threshold of €45,000 per QALY, indicating that all three options would be considered highly cost-effective compared to no screening.

The additional costs and QALYs for each screening strategy are illustrated on a cost-effectiveness plane (figure 5.1). The ICERs for FSIG and FIT can be connected with a line of lower slope than a line connecting any other two scenarios (indicating a lower cost-effectiveness ratio). Any strategy that has an ICER above the line joining FSIG and FIT, as is the case for gFOBT, would be considered dominated (i.e. it was more costly and less effective than one, or a combination, of the other strategies). Therefore, gFOBT was dominated by a combination of FSIG and FIT.†

Since FIT was associated with the greatest health gain compared to no screening, but FSIG was less costly, any decision to adopt FIT in preference to FSIG depends on decision-makers' willingness-to-pay. Investing in FIT as compared to FSIG would result in an increase in the total costs by €36.74 (i.e. €40.17-€3.43) and in the QALYs by 0.0179 (i.e. 0.0237-0.0058), yielding an ICER of €2,058 per QALY gained. This would be considered highly cost-effective. Therefore, in this base-case analysis, the optimal strategy would be FIT at age 55-74.

When incremental costs per LYG were considered the scenarios were ranked in the same order (table 5.2), and the conclusions were unchanged.

† Technically, gFOBT is eliminated by extended dominance. The principle of extended dominance eliminates from consideration strategies whose costs and benefits are improved by a mixed strategy of two other alternatives.

Figure 5.1 Cost-effectiveness plane for core screening scenarios, based on QALYs

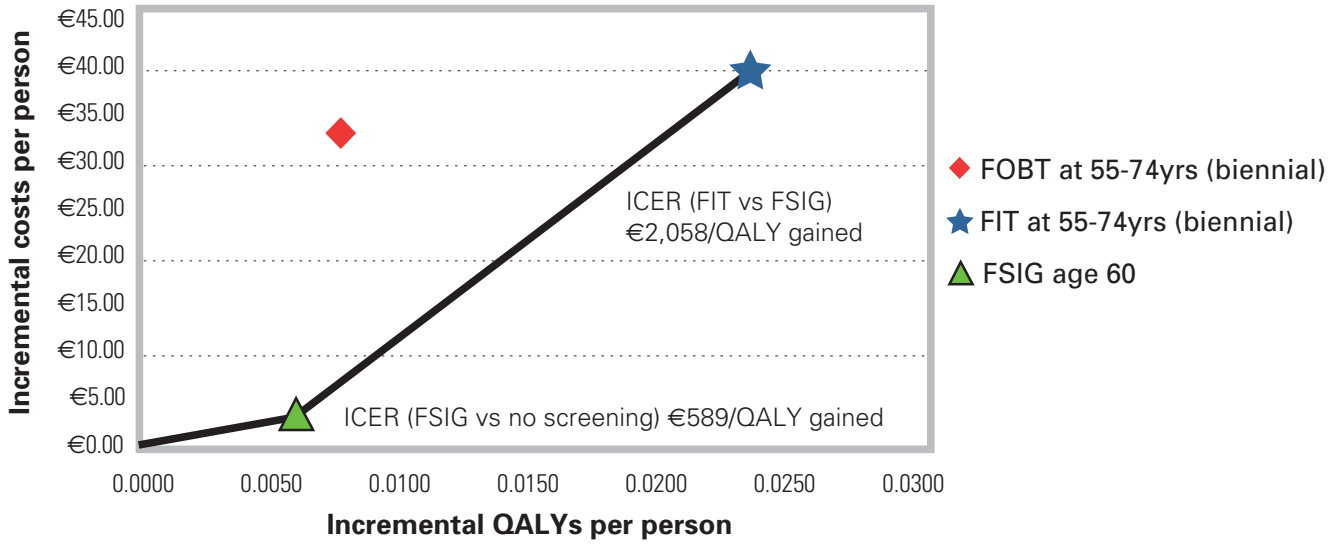


Table 5.3 shows the overall impact of the core screening scenarios on colorectal cancer incidence and mortality. The model suggests that once screening is fully rolled out, biennial gFOBT screening in the 55-74 age group would result in a reduction in colorectal cancer mortality of almost 12%, but there would be almost no change in incidence compared to no screening. A policy based on biennial FIT in the 55-74 age group would result in the highest rates of (a) screen-detected cancers and (b) cancers detected in individuals under surveillance for intermediate/high-risk adenomas. This policy would also result in the greatest reduction in the colorectal cancer incidence (-14.7%) and mortality rates (-36.0%), compared to a policy of no screening. This is most likely due to the higher sensitivity of FIT than gFOBT. Compared to no screening, FSIG at age 60 would result in a 5% reduction in the incidence rate and 7.5% reduction in mortality.

Table 5.3 Lifetime rates[1] of colorectal cancer incidence and mortality per 100,000 population, and percentage reductions in incidence and mortality compared to no screening, for core screening scenarios

Scenario	Incidence				Mortality	
	Screen detected CRC rate	Surveillance-detected CRC rate[2]	Symptomatic CRC rate	% reduction in CRC incidence[3]	CRC mortality rate	% reduction in CRC mortality[3]
No screening	0	0	5158	-	2287	-
gFOBT at 55-74 years	695	11	4401	1.0%	2016	11.8%
FIT at 55-74 years	1313	78	3010	14.7%	1465	36.0%
FSIG once at 60 years	138	25	4742	4.9%	2116	7.5%

CRC=colorectal cancer; FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; gFOBT=guaiac-based faecal occult blood test

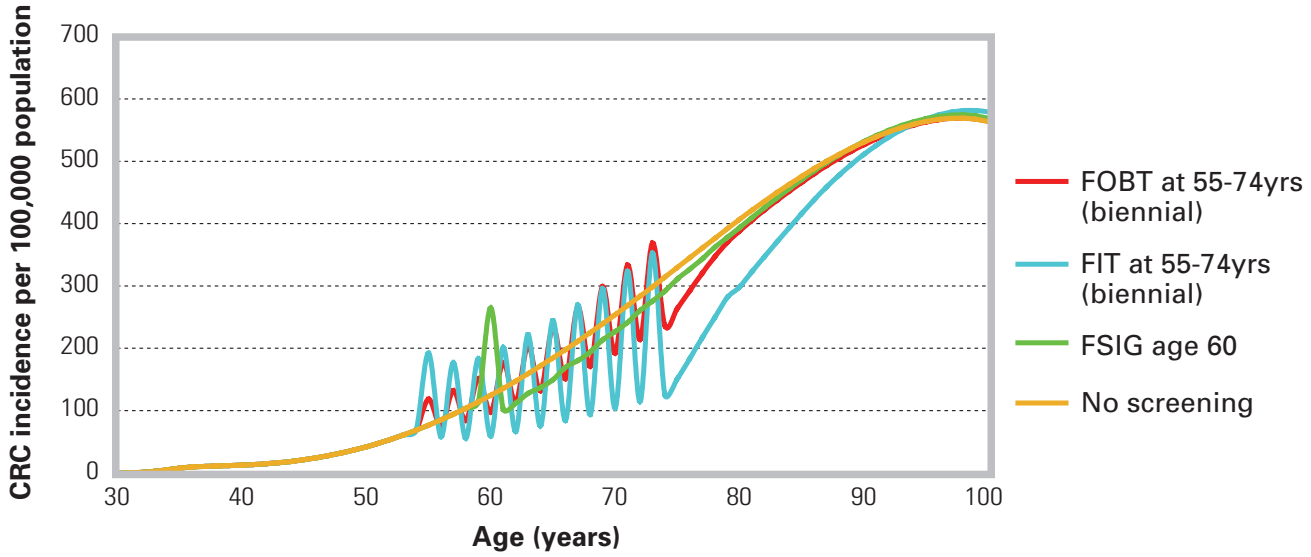
1 Over the entire lifetime of the cohort, therefore for gFOBT and FIT includes 10 screening rounds

2 CRC detected at surveillance among those with intermediate/high-risk adenomas found at screening

3 Each incremental value compares values for that strategy to common baseline of no screening

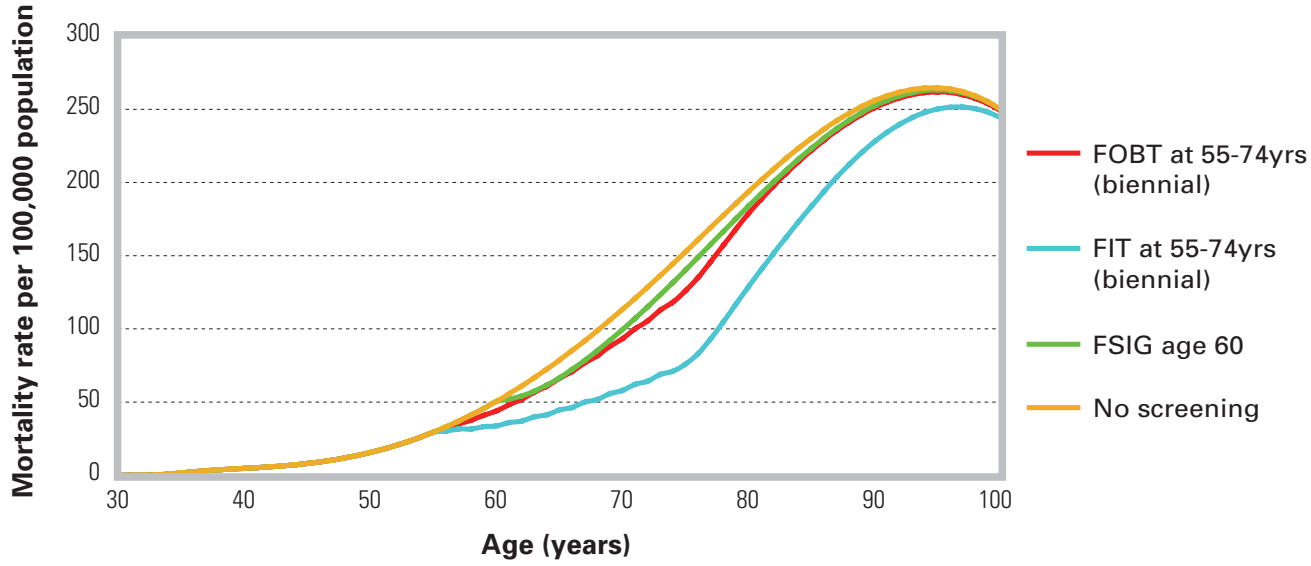
Figures 5.2(a) and (b) show the predicted lifetime colorectal cancer incidence and mortality rates per 100,000 population by age. For incidence, there are peaks during screening years due to the detection of cancers in individuals who would either have presented symptomatically later or not at all, and troughs due to reductions in symptomatic cancers following screening. The figure illustrates that offering biennial FIT-based screening to those aged 55-74 years would result in the greatest long-term reduction in incidence compared to no screening. As regards colorectal cancer-specific mortality, all three screening options result in a lifetime reduction. This is greatest for biennial FIT screening. The reductions for screening with gFOBT or FSIG are similar, but lower than that for FIT-based screening.

Figure 5.2(a) Predicted impact of core screening options on colorectal cancer incidence, over lifetime of cohort[1]



1 Over the entire lifetime of the cohort, therefore for gFOBT and FIT includes 10 screening rounds

Figure 5.2(b) Predicted impact of core screening options on colorectal cancer mortality, over lifetime of cohort[1]



1 Over the entire lifetime of the cohort, therefore for gFOBT and FIT includes 10 screening rounds

The percentages of all cases of colorectal cancer occurring over the lifetime of the cohort which would be detected by screening, surveillance and symptomatically are shown in table 5.4. With no screening, all cases of colorectal cancer would present clinically (i.e. would be detected symptomatically). Biennial FIT at 55-74 years results in the greatest proportion of cases detected by screening (29.8%) or surveillance (1.8%). Under a policy of once-only FSIG at age 60, less than 4% of colorectal cancer cases are detected by screening or surveillance.

Biennial gFOBT in those aged 55-74 years is intermediate between FSIG and FIT, with approximately 14% of colorectal cancers detected by screening or surveillance.

Table 5.4 Percentage of lifetime cases of colorectal cancer detected by screening, surveillance[1], and symptomatically

Scenario	Screen detected CRC (%)	Surveillance-detected CRC[1] (%)	Symptomatic CRC (%)	Total
No screening	-	-	100.0%	100.0%
gFOBT at 55-74 years	13.6%	0.2%	86.2%	100.0%
FIT at 55-74 years	29.8%	1.8%	68.4%	100.0%
FSIG once at 60 years	2.8%	0.5%	96.7%	100.0%

CRC= colorectal cancer; FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; gFOBT=guaiac-based faecal occult blood test

1 Surveillance of those found to have intermediate/high-risk adenomas at screening

Table 5.5 shows the stage distribution of screen-detected and symptomatically-detected colorectal cancers occurring over the lifetime of the cohort under a policy of no screening and the three core scenarios. Under each screening scenario, compared with symptomatically-detected cancers, greater percentages of screen-detected cancers are stage I or II and lower percentages are stages III and IV. For example, for biennial FIT at ages 55-74, 78% of cancers detected by screening were stage I or II, compared to 42% of those detected symptomatically. This means that all of the screening options have the potential to change the overall stage distribution of cancers detected, such that more disease is detected at an earlier stage. There was relatively little difference between the three screening policies in the stage of the screen-detected cancers.

Table 5.5 Percentages of lifetime cases of screen-detected and symptomatic colorectal cancer by stage at diagnosis

Scenario	Screen-detected CRC by stage					Symptomatic CRC by stage				
	I (%)	II (%)	III (%)	IV (%)	Total	I (%)	II (%)	III (%)	IV (%)	Total
No screening	-	-	-	-	-	11.6%	25.1%	34.6%	28.7%	100.0%
gFOBT at 55-74 years	38.4%	34.4%	20.4%	6.8%	100.0%	12.7%	26.0%	34.1%	27.2%	100.0%
FIT at 55-74 years	43.7%	34.7%	17.0%	4.6%	100.0%	14.5%	27.1%	33.2%	25.2%	100.0%
FSIG once at 60 years	36.8%	34.3%	22.1%	6.8%	100.0%	11.9%	25.3%	34.5%	28.3%	100.0%

Table 5.6 shows the expected lifetime rates (per 100,000) of endoscopy procedures. The model suggests that once FSIG screening is established, the lifetime rate of flexible sigmoidoscopy procedures would exceed 40,000 per 100,000. The rate of colonoscopies (for diagnostic or surveillance purposes) would be considerably lower for a policy of once-only FSIG at age 60 than for policies based on either of the two faecal tests. The rate of colonoscopies for FIT-based screening would be 10-times higher than that for screening based on gFOBT, due to the much greater sensitivity of the immunochemical test, which results in much larger numbers referred for diagnostic investigation and subsequently entering surveillance for intermediate/high-risk adenomas (discussed further in chapter 6).

Table 5.6 Lifetime rates[1] per 100,000 population of screening-related flexible sigmoidoscopy, colonoscopy[2] and polypectomy, for the core screening scenarios

Scenario	Flexible sigmoidoscopy	Colonoscopy	Polypectomy
gFOBT at 55-74 years	-	3,386	1,215
FIT at 55-74 years		34,632	9,486
FSIG once at 60 years	40,177	2,543	2,487

FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; gFOBT=guaiac-based faecal occult blood test

1 *Over the entire lifetime of the cohort, therefore for gFOBT and FIT includes 10 screening rounds*

2 *Includes diagnostic and surveillance colonoscopies*

Table 5.7 summarises the lifetime rates (per 100,000) of complications incurred under each screening scenario. The rates of major abdominal bleeding and bowel perforation are highest for FIT-based screening, due to the greater numbers of colonoscopy procedures that will be done under this policy than for the others. A further consequence of the high referral rate to colonoscopy is that there would be an estimated 3 deaths per 100,000 over the lifetime of a cohort of 55-year olds invited for screening.

Table 5.7 Lifetime rates[1] of complications[2] per 100,000, for core screening scenarios

Scenario	Major bleeding[3]	Bowel perforation	Deaths due to perforation
gFOBT at 55-74 years	12	5	0.26
FIT at 55-74 years	132	57	3.00
FSIG once at 60 years	22	5	0.25

CRC=colorectal cancer; FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; gFOBT=guaiac-based faecal occult blood test.

1 *Over the entire lifetime of the cohort, therefore for gFOBT and FIT includes 10 screening rounds*

2 *Complications associated with diagnostic and surveillance colonoscopy and, where relevant, FSIG*

3 *Major abdominal bleeding, requiring admission or intervention*

Table 5.8 breaks down the incremental costs of each core scenario into components relating to costs of screening and costs of managing colorectal cancer. A strategy based on biennial gFOBT is associated with the lowest screening cost (€56 per person), closely followed by once-only FSIG at age 60 (€61 per person). The per person cost associated with FIT-based screening is considerably higher (€222 per person). This is a function of several factors including the slightly higher costs of the immunochemical test than the guaiac test, and the greater proportions of individuals who test positive and require colonoscopy or CT colonography, have adenomas removed, and who require surveillance following intermediate/high-risk adenomas, and the higher numbers of perforations and episodes of major bleeding. In contrast, the per person cost of managing colorectal cancers is lower for FIT-based screening than for screening by gFOBT or FSIG. This is likely due to the greater yield of screen-detected cancers under this strategy, which results in a more favourable stage distribution of cancers overall.

Table 5.8 Lifetime costs of screening and managing colorectal cancer[1] per person, and incremental costs[2], for core scenarios

Scenario	Costs of screening per person	Costs of managing CRC per person[1]	Total costs of screening & CRC management per person	Incremental cost per person[2]
No screening	-	€ 1,074	€ 1,074	-
gFOBT at 55-74 years	€ 56	€ 1,051	€ 1,107	€ 33.63
FIT at 55-74 years	€ 222	€ 892	€ 1,114	€ 40.17
FSIG once at 60 years	€ 61	€ 1,016	€ 1,077	€ 3.43

CRC=colorectal cancer; FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; gFOBT=guaiac-based faecal occult blood test

Cost of screening include: faecal testing kit and processing, or FSIG examination; diagnostic colonoscopy/CTC; pathology; perforations and bleeds; adenoma surveillance; plus any other costs not included in total lifetime cost of managing CRC. Cost of managing CRC include: total lifetime costs per person.

1 Weighted average of costs of managing screen-detected and symptomatic CRC

2 Each incremental value compares value for that strategy t o common baseline of no screening

5.2 Sensitivity analysis for core scenarios

5.2.1 One-way and multi-way sensitivity analysis

Figures 5.3(a), (b) and (c) summarise the key findings, expressed in terms of incremental costs per QALY, from the one-way and multi-way sensitivity analyses. The full results for both QALYs and LYG are in Appendix 8.

Most of the factors considered had relatively little impact on the estimates of cost-effectiveness. Given that all three scenarios were highly cost-effective at the base-case, variations of this limited magnitude would make no difference to the overall conclusions. Several of the variables which were subject to most uncertainty, such

as screening uptake and non-compliance, and compliance with colonoscopy, had a negligible influence on cost-effectiveness.

The most influential parameters were the discount rate, the cost of the screening tests, the cost of managing colorectal cancer, utility (for gFOBT), test sensitivity (for gFOBT and FIT) and costs of colonoscopy (for FIT). However, even for these most influential parameters, all three screening scenarios remained cost-effective when the parameters were set at their most extreme values. In some instances, screening became cost-saving compared to no screening (i.e. an ICER < €0 per QALY gained).

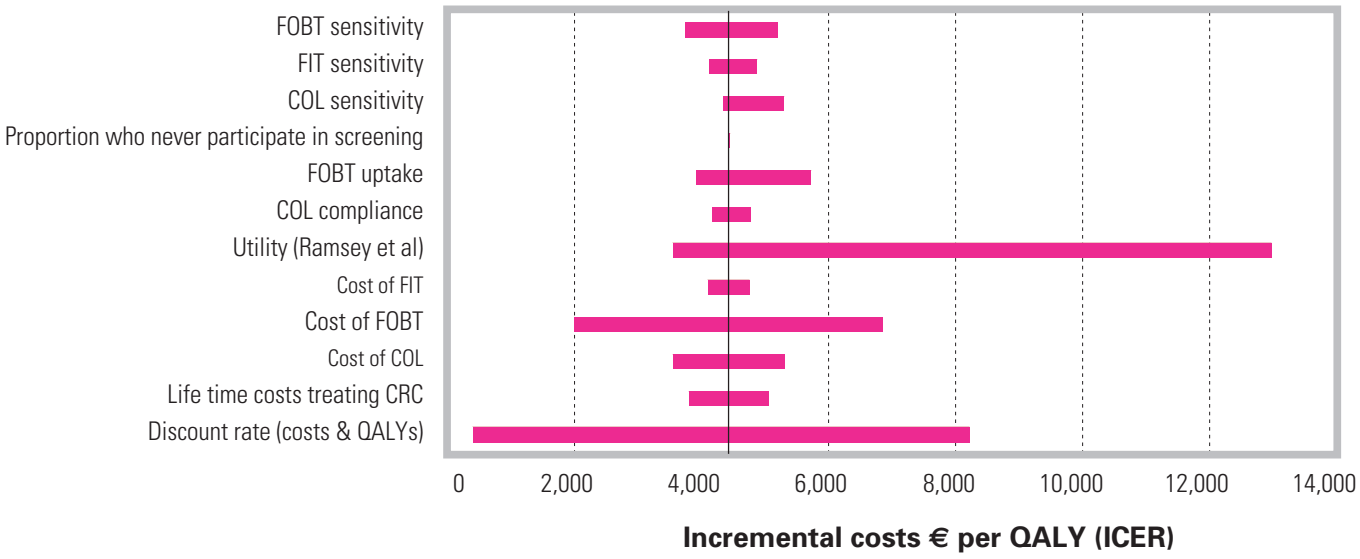
For screening based on gFOBT, if a more sensitive test were used, the programme would become considerably more cost-effective (ICER of €1,701 per QALY gained, compared to €4,428 for the base-case). It is worth noting that this ICER is very similar to that for biennial FIT in the base-case analysis (€1,696 per QALY gained). If it was assumed that the performance characteristics of the gFOBT and reflex FIT are not independent, screening would be slightly more costly and less effective (ICER €6,241 per QALY gained). The ICERs were very sensitive to utility values (figure 5.4(a)). If HRQoL in those with cancer were lower than the base-case, the programme would be considerably less cost-effective compared to no screening (€12,965 per QALY gained); cost-effectiveness would improve slightly if HRQoL was higher (€3,544 per QALY gained). If the cost of the gFOBT kit and associated processing were 50% less than the base-case estimate, the programme would become more cost-effective (€1,997 per QALY gained), and if it were 50% higher, the programme would be less cost-effective (€6,863 per QALY gained). If costs and benefits were not discounted the ICER would fall to €410 per QALY gained; if they were discounted at 6% per annum it would rise to €8,217 per QALY gained.

For biennial FIT screening in the 55-74 age group, the most influential parameters were the discount rate and costs of colonoscopy. If costs and benefits were not discounted, screening would be cost-saving compared to no screening (ICER -€1,399 per QALY gained; base-case €1,696). If they were discounted at 6%, the ICER would rise to €4,938. If the cost of colonoscopy were 50% higher than the base-case, the ICER would be €4,704 per QALY gained. Conversely, if cost of colonoscopy were 50% lower, this scenario would be cost-saving with an ICER of -€1,312. Variations in costs of FIT kits and processing had a less pronounced impact on cost-effectiveness; if these were 50% less than estimated for the base-case, the programme would cost €383 per QALY gained, whereas if they were 50% higher, it would cost €3,012 per QALY gained. When the lifetime costs of managing colorectal cancer were varied by 50% around the base-case the ICER ranged from €105 to €3,288 per QALY gained. If a more sensitive FIT test were to be used, the programme would become more cost-effective, but it is worth remembering that in this situation the numbers undergoing colonoscopy, and experiencing associated harms, would inevitably increase.

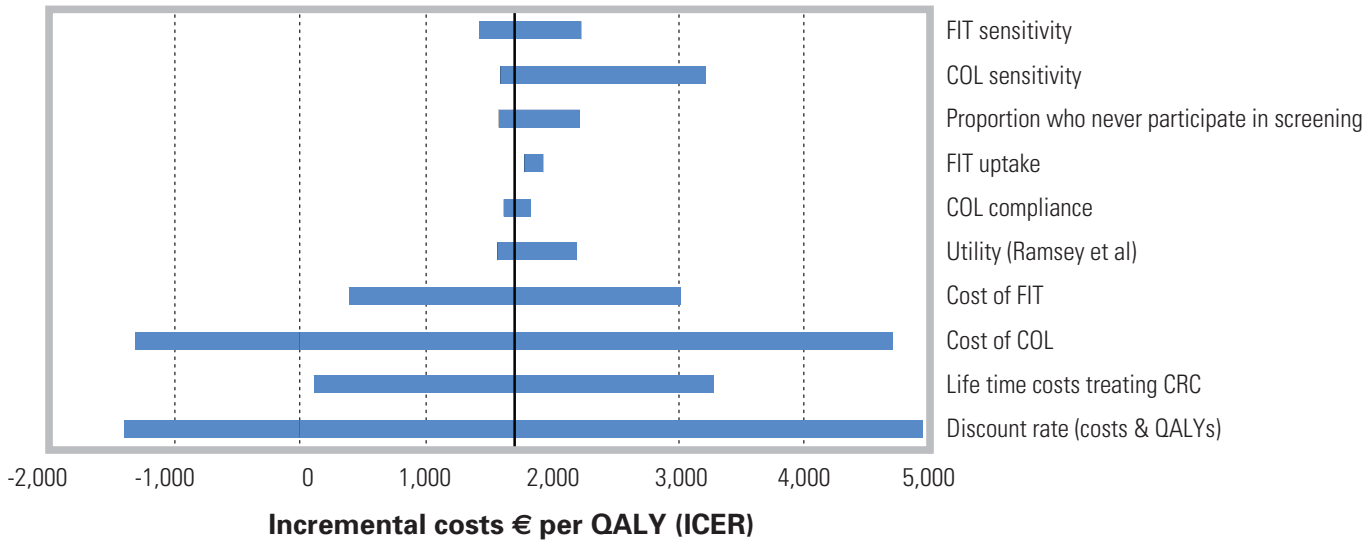
The cost of flexible sigmoidoscopy had an important impact on the cost-effectiveness of once only FSIG screening at age 60. If this were 50% less than the base-case estimate, FSIG would become cost-saving compared to no screening (ICER -€3,650 per QALY gained; base-case €589). If this were 50% higher than the base-case, it would be less cost-effective (€4,827 per QALY gained). A similar variation was seen when the discount rate was changed. Not discounting costs and benefits reduced the ICER to -€2,012 per QALY gained, whereas discounting at 6% per annum resulted in an increase in the ICER to €3,671 per QALY gained. Varying the sensitivity of FSIG for the detection of adenomas and carcinomas had a modest impact on cost-effectiveness: the ICER ranged from €131 to €1,327 per QALY gained. Increasing the life-time costs of managing CRC also resulted in FSIG becoming cost-saving (-€1,447 per QALY gained) while conversely were such costs to be 20% lower than the base-case the ICER rose to €2,624 per QALY gained.

Figure 5.3 One/multi-way sensitivity analysis: cost-effectiveness (incremental costs per QALY gained) when key parameters are varied independently, for core scenarios

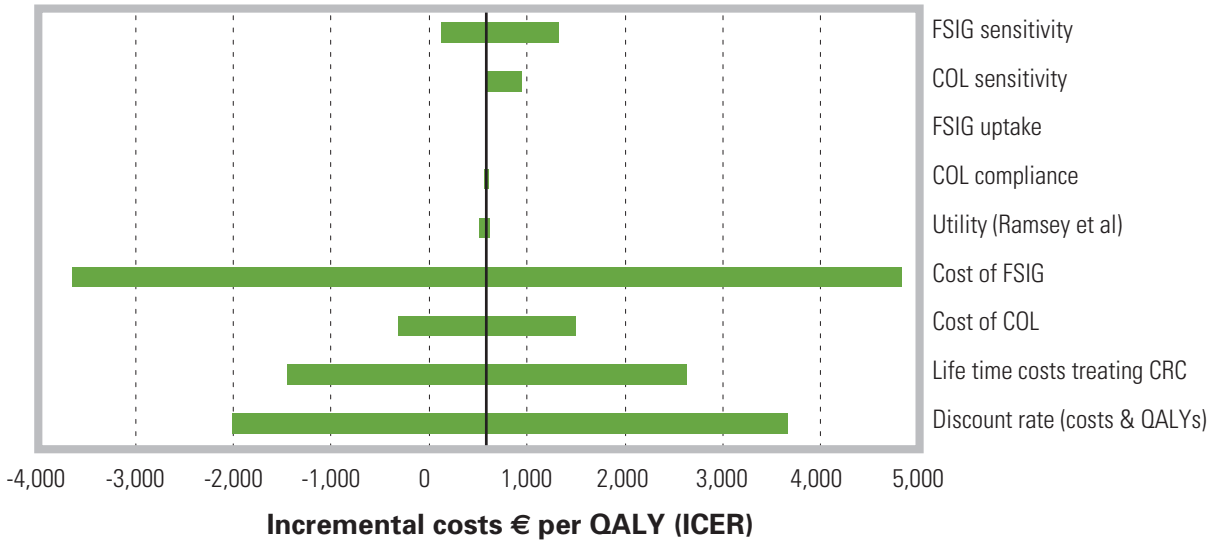
(a) gFOBT at 55-74 years



(b) FIT at 55-74 years



(c) FSIG once at 60 years



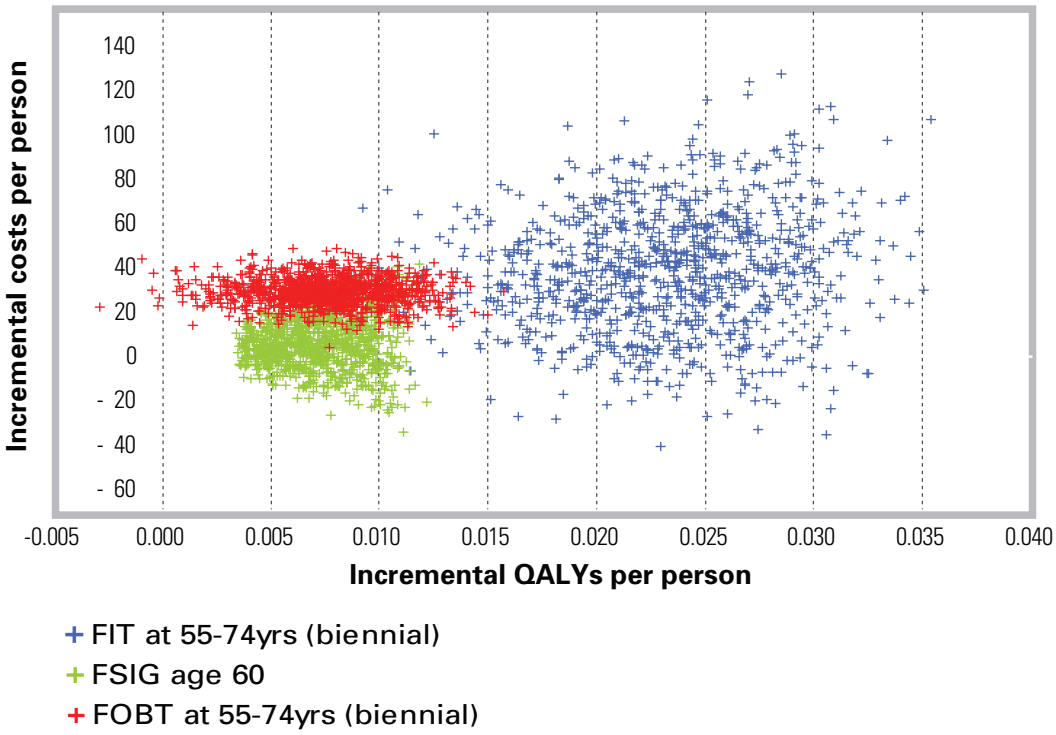
5.2.2 Probabilistic sensitivity analysis

Figure 5.4 shows the scatterplot of the costs and QALYs from the individual runs of the PSA. Given the uncertainty in the model parameters, it is noteworthy that all three screening options are always economically attractive compared to a policy of no screening (i.e. they were cost-effective in all simulations). There were instances where both FSIG and FIT-based screening appear to be cost-saving compared to no screening.

Uncertainty was greatest for screening by biennial FIT in the 55-74 age group. The spread of both the incremental costs and QALYs was wider for this scenario than for the others. This is most likely due to the greater "activity" associated with FIT-based screening (i.e. greater numbers of colonoscopies, adenomas, screen-detected cancers, cases of bleeding, bowel perforations, etc). There was a clear distinction in terms of incremental QALYs between FIT screening on one hand and screening

based on gFOBT or FSIG on the other; in almost all simulations FIT-based screening is associated with greater gains in QALYs than the other two options. In the majority of simulation, the incremental costs of screening using gFOBT exceed those for FSIG.

Figure 5.4 Cost-effectiveness of the core scenarios: probabilistic sensitivity analysis

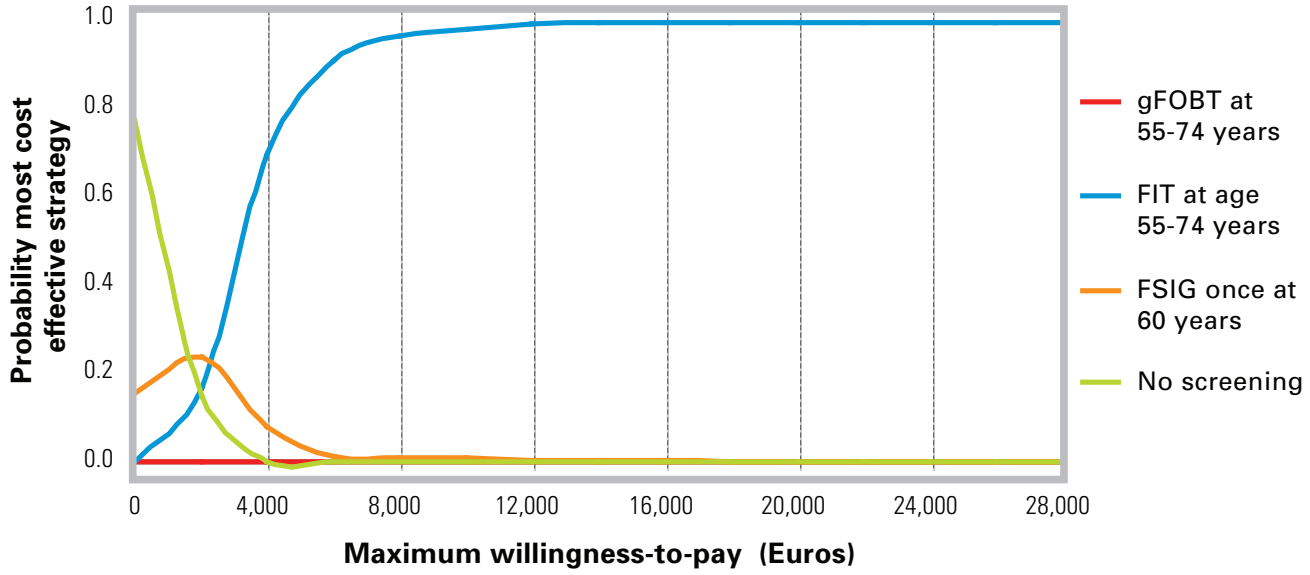


** each symbol represents one simulation of the parameter set*

5.2.3 Cost-effectiveness acceptability curves

Figure 5.5 shows cost-effectiveness acceptability curves (CEACs) for the option of no screening and the core screening scenarios. The CEACs show the probability that each scenario results in the greatest expected net benefit over a range of willingness-to-pay thresholds. The figure indicates that if decision-makers were willing-to-pay around €2,500 per QALY gained, FSIG at age 60 would be likely to be the most cost-effective option. At a willingness-to-pay threshold of €4,000 per additional QALY or higher, FIT screening for the full age range 55-74 years would be likely to be the most cost-effective strategy. Moreover, if decision-makers were willing-to-pay approximately €13,000 per additional QALY, this strategy would be likely to be cost-effective approaching 100% of the time. (The line for gFOBT cannot be seen on the graph as it is not likely to be the most cost-effective option at any willingness-to-pay threshold.)

Figure 5.5 Cost-effectiveness acceptability curves for core screening scenarios



5.3 Analysis of additional age-variant scenarios

5.3.1 Base-case analysis

Table 5.9 shows the costs and benefits, in terms of QALYs, for the core scenarios and the five additional age-variant scenarios. In these analyses, the incremental costs and benefits for all scenarios were computed relative to a policy of no screening, and the model was run throughout using the base-case estimates. The ICERs for all screening options were less than €6,000 per QALY gained, which would be considered highly-cost effective.

For screening based on gFOBT or FIT, the incremental cost per QALY, compared to no screening, was lower when screening was restricted to the younger$^{(55\text{-}64)}$ age group than for the full age group, meaning that screening is more cost-effective in the younger age group than in the full age group. Screening was less cost-effective, compared to no screening, in the older age group (65-74 years) than in the full age group or among those aged 55-64 years. All of the FIT-based screening options were more cost-effective, compared to no screening, than any of the options based on gFOBT. For FSIG, incremental costs were greater when screening was offered once-only at age 55 than when it was offered at age 60. The incremental QALY was slightly greater for screening at 55 but this was not sufficient to make-up for the increased costs. Therefore, FSIG at age 55 was less cost-effective than at age 60.

The base-case analysis for the eight scenarios with LYG as the outcome is contained in Appendix 8.

Table 5.9 Incremental cost-effectiveness ratios (ICER), based on QALYs, for core and additional screening scenarios

Scenario	Cost of screening & CRC management per person	Incremental costs per person[1]	Expected QALYs per person	Incremental QALYs per person[1]	ICER -Incremental cost per QALY gained
No screening	€ 1,074	-	10.961	-	-
gFOBT at 55-74 years	€ 1,107	€ 33.63	10.968	0.0076	€ 4,428[2]
gFOBT at 55-64 years	€ 1,092	€ 18.35	10.966	0.0051	€ 3,6132
gFOBT at 65-74 years	€ 1,089	€ 15.66	10.963	0.0026	€ 5,919[2]
FIT at 55-74 years	€ 1,114	€ 40.17	10.984	0.0237	€ 1,696
FIT at 55-64 years	€ 1,094	€ 20.06	10.978	0.0175	€ 1,153
FIT at 65-74 years	€ 1,088	€ 13.94	10.969	0.0082	€ 1,698[2]
FSIG once at 60 years	€ 1,077	€ 3.43	10.966	0.0058	€ 589
FSIG once at 55 years	€ 1,092	€ 18.19	10.968	0.0069	€ 2,659[2]

CRC=colorectal cancer; FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; gFOBT=guaiac-based faecal occult blood test; QALY=quality-adjusted life year. Costs and outcomes discounted at 4%.

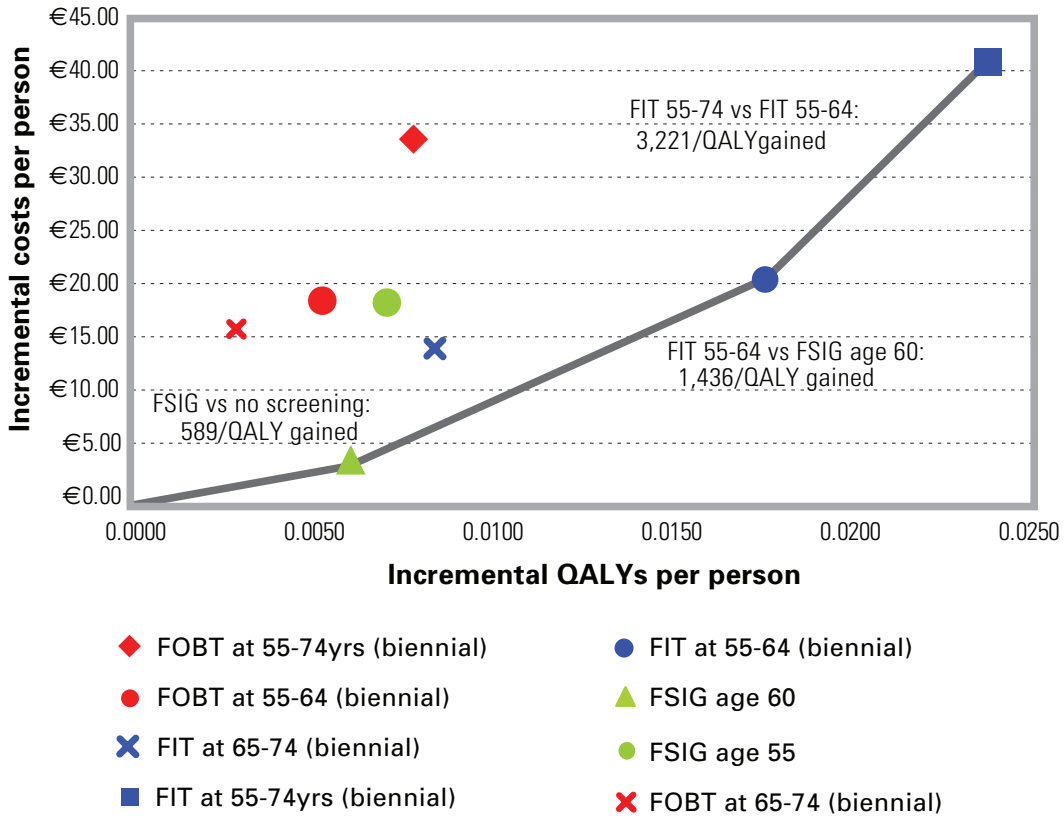
Core screening scenarios are shaded.

1 Each incremental values compares values for that strategy to common baseline of no screening

2 Strategy considered dominated by FSIG at age 60, FIT at age 55-74, FIT at age 55-64 or combinations of these

Figure 5.6 is the cost-effectiveness plane for all eight strategies. The figure shows that FSIG at age 60, FIT between ages 55-74 and FIT at age 55-64 can be connected with a line of lower slope (i.e. lower cost-effectiveness ratios) than a line between any other strategies. Any strategy that has a cost-effectiveness ratio above this line would be considered dominated. Therefore, gFOBT at age 65-74 was dominated (more costly and less effective) by FSIG at age 60; gFOBT at age 55-74 was dominated by FIT at age 55-64; gFOBT at age 55-64 was dominated by FSIG at age 60; FSIG at age 55 was dominated by FIT at age 65-74 and, finally, FIT at age 65-74 was dominated by a combination of the other FIT scenarios.

Figure 5.6 Cost-effectiveness plane for core scenarios and age-based variant scenarios, based on QALYs



Of the three remaining strategies, compared to no screening, FIT at age 55-74 was associated with the maximum health gain (0.0237 QALYs per person), followed by FIT between 55-64 years (0.0175 QALYs) and then FSIG at age 60 (0.058 QALYs; table 5.9). FIT for the 55-74 age group was also associated with the highest incremental cost compared to no screening (€40.17 per person) followed by FIT for the 55-64 age group (€20.06 per person) and then FSIG at age 60 (€3.43; table 5.9). Therefore any decision to adopt FIT for the full age group in preference to FSIG at age 60, or FIT at age 55-64, would depend on the willingness-to-pay of decision-makers (and resource considerations which are dealt with in chapter 6). Table 5.10 shows the results of a comparative analysis of these three scenarios. Investing in FIT at ages 55-74, compared to FIT at ages 55-64, changes total costs by €20.04 and QALYs by 0.006, yielding an ICER of €3,221 per QALY gained. Investing in FIT at ages 55-64, compared to FSIG at age 60, yields an ICER of €1,436 per QALY gained. Therefore, in terms of cost-effectiveness only, the optimal screening strategy would be FIT for the 55-74 age group, followed by FIT at ages 55-64, followed by FSIG at age 60.

5.3.2 Probabilistic sensitivity analysis

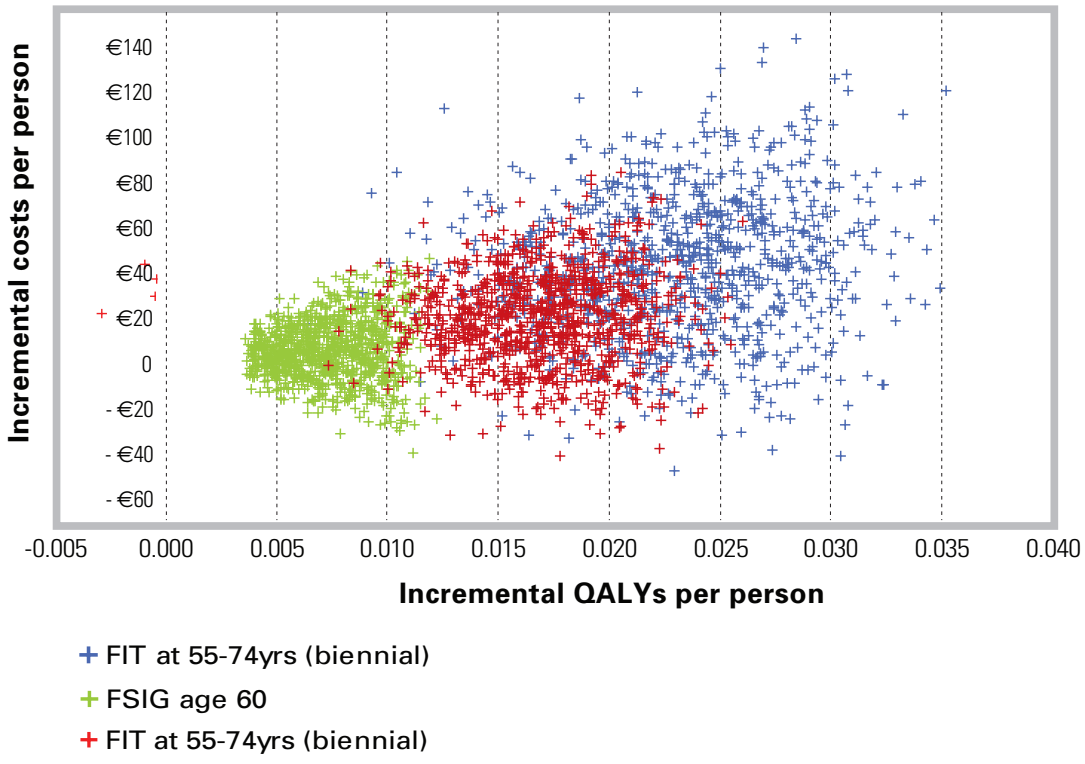
Figure 5.7 shows the scatterplot of the costs and QALYs from the individual runs of the probabilistic sensitivity analysis for the three remaining scenarios. This confirms the conclusions from the base-case analysis as regards the relative rankings of the policies (i.e. the optimal strategy is FIT at ages 55-74, followed by FIT at ages 55-64, followed by FSIG at age 60).

Table 5.10 Incremental cost-effectiveness ratios (ICER), based on QALY per persons, for FSIG once at age 60 years, FIT at ages 55-64 and FIT and ages 55-74

Scenario	Cost of screening & CRC management	Incremental cost (compared to preceding scenario)	Expected QALYs	Incremental QALYs (compared to preceding scenario)[1]	ICER (compared to preceding scenario)
No screening	€ 1,074	-	10.961		
FSIG once at 60 years	€ 1,077	€ 3.43	10.966	0.0058	€ 589
FIT at 55-64 years	€ 1,094	€ 16.70	10.978	0.012	€ 1,436
FIT at 55-74 years	€ 1,114	€ 20.04	10.984	0.006	€ 3,221

CRC=colorectal cancer; FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; gFOBT=guaiac-based faecal occult blood test; QALY=quality-adjusted life year. Costs and outcomes discounted at 4%

Figure 5.7 Cost-effectiveness for FSIG once at age 60 years, FIT at ages 55-64 and FIT and ages 55-74: Probabilistic sensitivity analysis*



** Each symbol represents one simulation of the parameter set*

5.3.3 Cost-effectiveness acceptability curves and cost-effectiveness acceptability frontier

Figure 5.8 shows CEACs for FIT at age 55-74, FIT at age 55-64 and once-only FSIG at age 60 and figure 5.9 adds the cost-effectiveness acceptability frontier (CEAF). If decision-makers were willing-to-pay a maximum of around €1,000 per additional QALY, the most cost-effective strategy would be expected to be FSIG once-only at age 60. At a willingness-to-pay threshold of between approximately €1,000 and €3,000 per additional QALY, biennial FIT in the 55-64 age group is likely to be the most cost-effective screening option. If decision-makers were willing to pay €4,000 per additional QALY or more, the preferred option would be biennial FIT in the full age range, 55-74 years. The CEAF shows the probability that the "optimal" option is cost-effective. It indicates that at a threshold of €10,000 per additional QALY or above, there is a greater than 95% probability that screening would be cost-effective.

Figure 5.8 Cost-effectiveness acceptability curves for FSIG once at age 60 years, FIT at ages 55-64 and FIT and ages 55-74

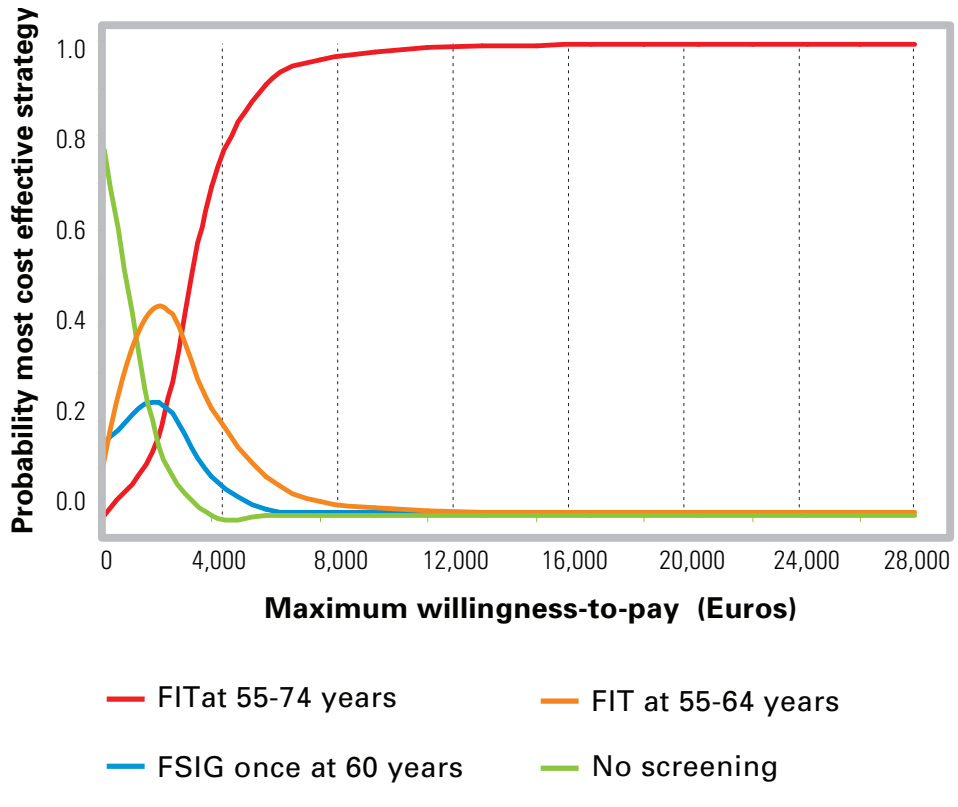
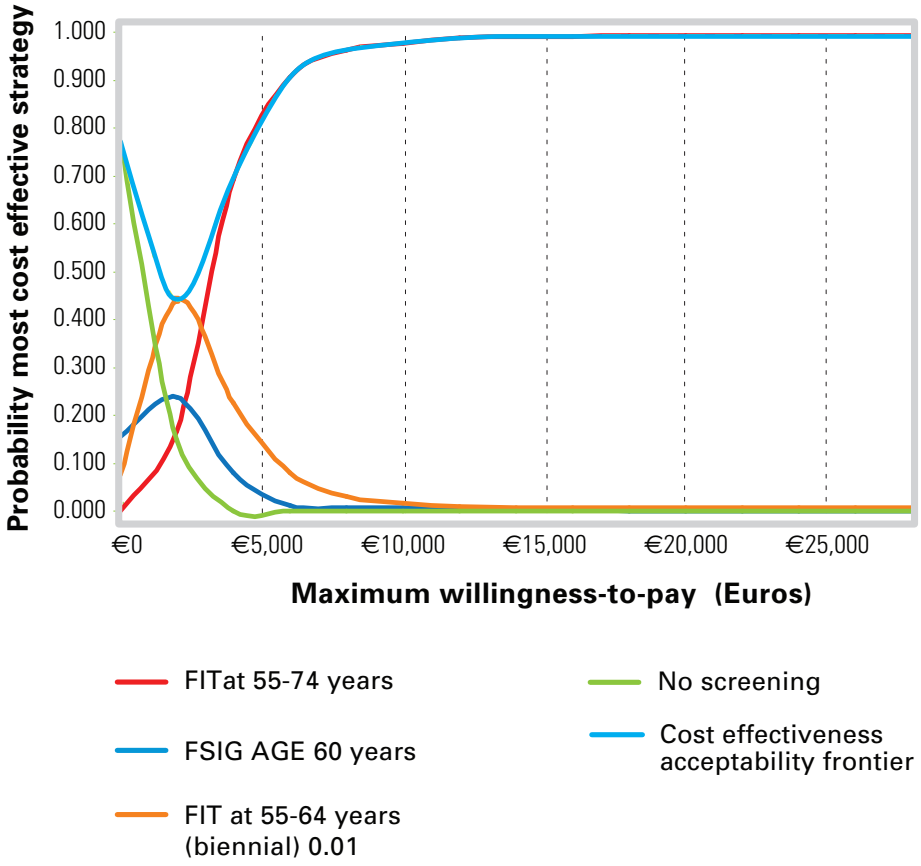


Figure 5.9 Cost-effectiveness acceptability curves and cost-effectiveness acceptability frontier for FSIG once at age 60 years, FIT at ages 55-64 and FIT and ages 55-74



Chapter 6

Resource requirements and health outcomes associated with colorectal cancer screening in Ireland

Key findings

- The resource requirements for a screening programme based on biennial FIT for 55-74 years would be greater than those for screening based on biennial gFOBT for age 55-74 or once-only FSIG at age 60.
- In year one of a programme based on gFOBT or FIT in those aged 55-74 years, 357,812 individuals would be sent test kits. Assuming uptake of 53%, 189,640 completed kits would be returned for laboratory processing. With a programme based on FSIG once at age 60, assuming uptake of 39%, 18,617 individuals would undergo screening. Because of demographic changes (i.e. increase in the population of screening age), assuming uptake remains constant, between years one and 10 the number screened by FIT or gFOBT would increase by 16-17% and by FSIG would increase by 11%.
- Requirements for colonoscopy and CT colonography for the diagnostic investigation of those with a positive screening test would be much greater for a screening programme based on biennial FIT at ages 55-74, than screening based on gFOBT for aged 55-74 or FSIG once at age 60. For FIT at ages 55-74, in year one of the programme, resources would be required to perform 11,000 diagnostic colonoscopies and 1,400 CT colonographies; this would rise to 12,400 colonoscopies and 1,600 colonographies in year 10. The diagnostic resources required under gFOBT for 55-74 years would be one tenth of those required for FIT (1,000 colonoscopies in year one and 130 CT colonographies). With once-only FSIG, between 380 and 420 individuals would be required to undergo colonoscopy each year.
- Similar patterns are evident in the colonoscopy and CT colonography resources required for surveillance of those with intermediate/high-risk adenomas. With biennial FIT at age 55-74, 300 individuals would undergo a surveillance colonoscopy in year two, rising to 2,400 in year 10.
- A consequence of the greater numbers of colonoscopies with FIT than the other core scenarios is that this scenario would lead to more individuals suffering adverse consequences of screening each year (major bleeding, bowel perforation, and death from perforation), than the other core scenarios.

- The resources required in a screening programme for histopathology, radiology (PET scans, CT scans, MRI), neo-adjuvant radiotherapy and colorectal surgery are a function of the numbers of individuals with screen-detected adenomas and cancers. The yield of disease is much higher for biennial FIT in the 55-74 age group than for the other two core options, therefore the resources required to manage these is much greater. For example, with FIT at age 55-74, 6,300-8,200 adenomas would require pathological analysis each year, compared to 1,200-1,700 adenomas with FSIG at age 60, and 700-1000 with gFOBT at ages 55-74. Resources would be required to conduct 780 colorectal resections in those with screen-detected cancers in year one under FIT screening, compared to less than 300 under gFOBT screening and approximately 60 with FSIG. In year 10, the screening programme would require resources to conduct slightly less than 650 colorectal resections with FIT-based screening, 300 with gFOBT-based screening, and 70 with FSIG-based screening.
- Compared to a policy of no screening, screening based on biennial FIT in the 55-74 age group would be expected to bring about a greater reduction in colorectal cancer incidence and mortality at the population-level than the other two strategies. Under this strategy, a reduction in the total number of colorectal cancers in Ireland would be expected from year six of the programme onwards, with approximately 160 cases averted in year 10. A reduction in mortality would be expected from year two onwards, with approximately 270 deaths from colorectal cancer avoided in the population in year 10.
- Since screening has the potential to reduce the number of colorectal cases diagnosed in the population, this means that it could also reduce requirements for (at least some of the) resources associated with work-up and treatment nationally. These potential reductions would be greatest for screening based on biennial FIT at ages 55-74 years.
- Various options are available to reduce the resource requirements associated with a programme based biennial FIT screening, either overall or in the initial years. For example, if screening was limited to the 55-64 age group, the requirements for numbers of tests, and diagnostic colonoscopies, would be about 60% of those for the 55-74 age group. Alternatively, screening of the 55-74 age group could be implemented gradually over several years, with the speed of implementation determined by the speed at which the required capacity would become available.
- If capacity was available, the optimal screening option would be full and immediate implementation of biennial FIT-based screening in the 55-74 age group. If capacity was not available initially, a gradual implementation of screening in the 55-74 age group would be preferable to immediate implementation in the 55-64 age group. In future years, when a programme based on the 55-74 age group is fully operational it would result in a greater overall health gain than a programme limited to the 55-64 age group. If, however, there was no possibility that capacity could be built-up over the initial years of the programme, then screening in the 55-64 age group would be an acceptable and cost-effective option compared to no screening.

- Finally, it should be noted that the actual resource requirements and health outcomes for a colorectal cancer screening programme in Ireland will be a function of a number of factors, including screening uptake, compliance with diagnostic investigations and the performance characteristics of the specific tests used. The figures in this chapter are subject to uncertainty and should be interpreted as broad indications rather than precise estimates. Screening uptake, for example, will be a very important determinant of resource requirements and health outcomes. Specifically, compared to the health gains attained assuming uptake of FIT-based screening of 53%, lower uptake would reduce the potential number of colorectal cancers that could be averted at the population-level by screening, whereas higher uptake would increase the potential number of cancers averted in the population.

6.1 Resources and health outcomes assessed

One of the key WHO criteria for the establishment of a screening programme is that there should be sufficient facilities available for the diagnosis and treatment of cases of the disease detected by screening (Appendix 1[3]). This chapter is concerned with the requirements for facilities for screening and those required for diagnosis and treatment that would be generated by the various screening options (i.e. the resources required to diagnose, treat and follow-up individuals with adenomas and colorectal cancers).

The objectives of the primary analysis were, to estimate, for each screening scenario: (i) the screening-related resources required; and (ii) the health outcomes achieved, over the first 10 years of implementation of a screening programme. Secondary analyses were conducted to estimate, for each screening scenario versus a policy of no screening, (i) the additional resources required at the population level ; and (ii) the health gains achieved at the population-level, over the first 10 years of programme implementation. Thus the primary analyses relate to the absolute resources required to deliver a screening programme, while the secondary analyses relate to resources required across the population relative to policy of no screening.

6.1.1 Primary analysis: screening-related resources and health outcomes

The screening-related resources to be estimated were agreed in discussions with the NCSS and the NCCP, and were subsequently endorsed by the EAG, and are shown in table 6.1. They were based, in the main, on assumptions about which diagnostic and treatment procedures would be conducted under the auspices of a screening programme (as compared to within routine services; see section 4.2). Procedures related to surveillance of individuals who had had screen-detected adenomas removed were included in the analysis since the resources required for these are generated by a screening programme. The Evaluation Team were not asked to consider resources which would fall outwith the remit of the programme, such as adjuvant chemotherapy or follow-up investigations post-resection, responsibility for which would be likely to remain within the realm of the routine services.

Table 6.1 Screening-related resources modelled

Resource	Estimate
Colonoscopy	Number of individuals undergoing diagnostic colonoscopy[1] Number of individuals undergoing surveillance colonoscopy[2]
CT colonography	Number of individuals undergoing diagnostic CT colonography[1] Number of individuals undergoing surveillance CT colonography[2]
Pathology	Number of screen-detected adenomas requiring pathology[3] Number of individuals with screen-detected colorectal cancers undergoing pathology
Diagnostic radiology	Number of individuals who will undergo a PET scan, MRI scan, CT scan(s), and transrectal US as part of work-up for screen-detected colorectal cancers
Neo-adjuvant radiotherapy (+/- chemotherapy)	Number of individuals with screen-detected rectal cancer who will undergo pre-operative radiotherapy, given with or without chemotherapy
Colorectal surgery	Number of individuals with screen-detected colon cancer who will undergo colon resection Number of individuals with screen-detected rectal cancer who will undergo rectal resection

1 *Those referred following a positive screening test*

2 *Those undergoing surveillance following removal of screen-detected intermediate/high-risk adenoma(s)*

3 *Since individuals are detected with, on average, >1 adenoma each, this is based on numbers of adenomas, not number of individuals who have adenomas*

In addition, the following screening test associated resources were estimated:

- number of gFOBT kits dispatched;
- number of gFOBT kits returned;
- number of FIT kits dispatched;
- number of FIT kits returned;
- number of FSIG screening examinations conducted;

Several screening-related health outcomes were estimated, including:

- numbers of individuals who will have a major abdominal bleed or a bowel perforations as a result of screening and the number who will die as a result of a perforation;

- number of individuals with screen-detected adenoma(s), by risk status (low, intermediate/high) and in total;
- number of individuals with screen-detected colorectal cancers, by stage at diagnosis, and in total.

6.1.2 Secondary analysis: additional resources and health gain at the population-level

Screening can impact on the overall burden of disease in the population, and the cancers detected as part of a screening programme can be offset against those that would have been detected symptomatically under a policy of no screening. Therefore, in secondary analyses, for each core screening scenario, the additional resources that would be needed for the diagnosis and treatment of colorectal cancer, and the health gain achieved, at the population level were computed. For additional resources, this involved comparing the pathology, diagnostic radiology, radiotherapy and surgery resources required for each screening scenario with those required under a policy of no screening. For health gain, the total numbers of cancers detected in the population under each screening scenario (screen-detected, surveillance-detected and symptomatic) was compared with those that would have been detected with no screening (all symptomatic). Similarly, the reduction in numbers of deaths from colorectal cancer by subtracting the deaths under each scenario from those under the no screening option was computed.

6.2 Model, time horizon, population and parameters

The whole population model was used to estimate the resources and health outcomes (see chapter 4). The results relate to the 2008 population of Ireland (chapter 4).

A 10-year time horizon was adopted. Thus the resources and health outcomes were estimated for each year from year one to year 10 after set-up of a screening programme. Here, year one relates to the first year in which individuals would be screened.

The estimates generated by the model are based on the base-case parameter estimates (chapter 4) and the resource utilisation values used in estimating the lifetime costs of managing colorectal cancer (Appendix 6). For example, the results are based on assumptions that screening uptake would be 53% for FIT and gFOBT and 39% for FSIG, that compliance with diagnostic and surveillance colonoscopy would be 86%, that sensitivities of screening and diagnostic tests are as stated in table 4.1, and so forth.

The assumptions inherent in the model are specified in chapter 4.

6.3 Screening scenarios and alternative implementation options

The main focus was on the three core scenarios - gFOBT at age 55-74 years, FIT at age 55-74 years and FSIG once at age 60. Since the cost-effectiveness analysis indicated that FIT was the optimal scenario, it was agreed with the EAG that various alternative options for implementation of FIT-based screening should be evaluated, in order to inform the decision-making process relating to screening implementation. The specific implementation options were developed by the Evaluation Team and designed so that they would have less intensive resource requirements than the core scenario, and might therefore prove more feasible in the short-term. Screening-related resources and health outcomes were computed for these implementation options and compared with those required/achieved under the core FIT scenario. It should be noted that these options were designed for illustrative purposes rather than with the aim of recommending a particular implementation strategy.

The first option (option 1) concerned restricting the screening age group to 55-64 years (as modelled in chapter 5). As compared to the core scenario, this option would always involve screening few individuals therefore the resource requirements, and the costs, would always be lower. The second and third options (labelled "medium" and "slow" implementation respectively) concerned different possibilities for staggered implementation of biennial screening in the 55-74 age group. Rather than providing screening to the full age range in years one and two, these options assume that screening would gradually be offered to people of different ages over several years, encompassing the full 55-74 age range after several years. Option 2 - "medium implementation" - would involve inviting individuals aged 55 and 65 in year one; in year two those aged 55, 57, 65 and 67 would be invited; in year three, those aged 55, 57, 59, 65, 67 and 69 would be invited, and so on until the full age range is included in year five. Under option 3 - "slow implementation" - individuals aged 55 would be invited in year one; those aged 55 and 57 would be invited in year two; those aged 55, 57 and 59 would be invited in year three and so on until year 10 when the full age range would be included. The advantage of these scenarios is that they would allow for capacity for endoscopy or radiology, for example, to be built up over the initial years of the programme, eventually reaching the levels required for screening the entire 55-74 age group. These options would also be less costly in initial years than implementing screening in the full age range at one time.

Figure 6.1 Illustration of the points at which FIT-based screening would be offered for the core scenario, and the three alternative options for implementation

Core scenario										
biennial FIT, 55-74 years, full implementation										
	Year									
age	1	2	3	4	5	6	7	8	9	10
55	x	x	x	x	x	x	x	x	x	x
56										
57	x	x	x	x	x	x	x	x	x	x
58										
59	x	x	x	x	x	x	x	x	x	x
60										
61	x	x	x	x	x	x	x	x	x	x
62										
63	x	x	x	x	x	x	x	x	x	x
64										
65	x	x	x	x	x	x	x	x	x	x
66										
67	x	x	x	x	x	x	x	x	x	x
68										
69	x	x	x	x	x	x	x	x	x	x
70										
71	x	x	x	x	x	x	x	x	x	x
72										
73	x	x	x	x	x	x	x	x	x	x
74										

Implementation option 1: age-restricted screening										
biennial FIT, 55-64 years										
	Year									
age	1	2	3	4	5	6	7	8	9	10
55	x	x	x	x	x	x	x	x	x	x
56										
57	x	x	x	x	x	x	x	x	x	x
58										
59	x	x	x	x	x	x	x	x	x	x
60										
61	x	x	x	x	x	x	x	x	x	x
62										
63	x	x	x	x	x	x	x	x	x	x
64										

Implementation option 2: medium implementation										
biennial FIT, 55-74 years										
	Year									
age	1	2	3	4	5	6	7	8	9	10
55	x	x	x	x	x	x	x	x	x	x
56										
57		x	x	x	x	x	x	x	x	x
58										
59			x	x	x	x	x	x	x	x
60										
61				x	x	x	x	x	x	x
62										
63					x	x	x	x	x	x
64										
65	x	x	x	x	x	x	x	x	x	x
66										
67		x	x	x	x	x	x	x	x	x
68										
69			x	x	x	x	x	x	x	x
70										
71				x	x	x	x	x	x	x
72										
73					x	x	x	x	x	x
74										

Implementation option 3: slow implementation										
biennial FIT, 55-74 years										
	Year									
age	1	2	3	4	5	6	7	8	9	10
55	x	x	x	x	x	x	x	x	x	x
56										
57		x	x	x	x	x	x	x	x	x
58										
59			x	x	x	x	x	x	x	x
60										
61				x	x	x	x	x	x	x
62										
63					x	x	x	x	x	x
64										
65						x	x	x	x	x
66										
67							x	x	x	x
68										
69								x	x	x
70										
71									x	x
72										
73										x
74										

x - indicates point at which individual of specified age would be invited to take part in screening

6.4 Sensitivity analyses

One-way sensitivity analyses were undertaken to explore the impact of variations in screening uptake on the estimates of resource requirements and health outcomes. For each of the core scenarios, the whole population model was re-run assuming lower and higher uptake than at the base-case. The values used were: for gFOBT at 55-74 years: 32% and 70%; for FIT at 55-74 years: 32% and 70%; and for FSIG once at 60 years: 24% and 67%.

A further sensitivity analysis was conducted to investigate the effect of using different estimates for the sensitivity and specificity of the combination of gFOBT and the reflex FIT. This was to explore the effect of the assumption in the model that the characteristics were independent. The whole population model was re-run using the same estimates for the performance of the combination of tests as were used as in the cost-effectiveness sensitivity analysis (see chapter 5; sensitivity of gFOBT with reflex FIT for adenomas, 3.8%; sensitivity of gFOBT with reflex FIT for colorectal cancers, 14.5%; specificity of gFOBT with reflex FIT for adenomas or cancers, 99.2%).

6.5 Primary analysis: Screening-related resources and health outcomes for core scenarios

Tables 6.2(a), (b) and (c) show the screening-related resource use and health outcomes for the three cores scenarios. For all scenarios, assuming uptake does not change, the number of screening tests, and number of individuals screened, will increase from years one to 10 of the programme; this is a function of population changes and growth in the numbers eligible for screening in coming years. For screening based on gFOBT or FIT, the numbers eligible and screened would increase by 16-17% between years 1-10; for FSIG there would be a rise of 11% in the number of procedures between year one and 10. In terms of numbers of tests, between 360,000 and 420,000 faecal tests would be dispatched each year, with 190,000-220,000 returned and requiring processing (assuming uptake at the base-case level of 53%). For FSIG, approximately 18,600 procedures would be conducted in year one (assuming uptake at the base-case value of 39%) with 20,600 in year 10.

In terms of diagnostic investigations, because a proportion of those who are screened by FSIG and found to have an adenoma would have the lesion removed immediately, only 400 or so individuals would require colonoscopy each year with this screening option, and a further 50 or so would have CT colonography. Biennial gFOBT at age 55-74 would entail around 1,000 individuals undergoing colonoscopy each year to follow-up a positive test result, with a further 130-140 having CT colonography for diagnostic purposes. The numbers of individuals who would require diagnostic colonoscopy or CT colonography would be more than 10-fold higher for biennial FIT in the 55-74 age group than for screening based biennial gFOBT in the same age group. With FIT, 11,000-12,400 individuals would undergo colonoscopy each year because of a positive immunochemical test, with an additional 1,400-1,600 undergoing CT colonography. A similar pattern is seen when resource use associated with surveillance of those with intermediate/high-risk adenomas is considered. The annual number of surveillance colonoscopies for gFOBT-based screening rises

from around 30 in year two to 300 in year 10. For FIT-based screening, the number undergoing surveillance colonoscopy would increase from approximately 300 in year two to 2,400 in year 10. Figure 6.2(a) illustrates the overall colonoscopy resource requirements for the three core scenarios.‡ It is worth noting that the endoscopy (and CT colonography) requirements associated with various screening options would be greater than estimated here if screening uptake, or compliance with diagnostic investigations or surveillance, exceeded the base-case values (53% and 86% respectively; see sensitivity analyses). Similar comments apply to the other resource estimates.

One of the consequences of the much higher numbers of individuals undergoing colonoscopy for biennial FIT than for the other scenarios is the higher frequency of complications (figure 6.2(b)). It is estimated that 50-60 individuals would sustain major abdominal bleeding (requiring intervention or hospitalisation) each year in the first 10 years of screening with biennial FIT in the 55-74 age group. A further 25 or so will have a bowel perforation and, on average, each year one individual would die from a bowel perforation sustained by participating in screening. The much lower frequency of colonoscopy for gFOBT in the 55-74 age group and once-only FSIG means that with these screening options between 6 and 12 individuals on average would have major bleeding or a bowel perforation each year. In addition, the risk of a screening-related death occurring is much lower for these options than for biennial FIT. It should be noted that the FSIG scenario, the harms include both harms of colonoscopy and those associated with FSIG itself.

Figures 6.2(c) and 6.2(d) show the average annual numbers of individuals found, by screening, to have adenomas and colorectal cancer each year for the three core scenarios. Biennial FIT in the 55-74 age group is associated with a much higher yield of disease than the other two options. With FIT screening, in year 1, approximately 3,300 individual would have one or more screen-detected adenomas and 850 would have a screen-detected cancer. In year 10 there would be 4,300 individuals diagnosed with adenomas and 690 with cancers through screening. The decline in screen-detected cancers over time is due to repeated screening with FIT detecting and treating adenomas and thus preventing the onset of colorectal cancer; people who may have developed cancer in the absence of screening would have been screened biennially, reducing their likelihood of developing cancer over time. With FSIG once at age 60, the estimated yield of individuals with adenomas would rise from approximately 800 in year one to 1,100 in year 10. There would be around 65-80 screen-detected cancers each year under this screening option. Compared to once-only FSIG, biennial gFOBT would result in fewer individuals with adenomas each year (approximately 370 in year one rising to 540 in year 10) but a higher number with cancers (approximately 310 in year one and 340 in year 10).

The yield of screen-detected adenomas and cancers is the main driver of the resources required in the screening programme for histopathology, diagnostic radiology, neo-adjuvant radiotherapy and colorectal surgery. The higher disease yield for biennial FIT at age 55-74 compared to the other two core options means that

‡ *Note that colonoscopies required for post-resection follow-up of screen-detected colorectal cancer are not included in these figures, nor elsewhere in this chapter.*

the resource requirements would be much greater for a programme based on this test than for a programme based on the other two tests. For example, allowing for the fact that a substantial proportion of individuals found to have adenomas have multiple lesions, FIT-based screening would result in 6,300 adenomas requiring pathology in year 1, rising to 8,200 in year 10. The comparable figures for FSIG would be 1,500-2,100, and for gFOBT, 700-1,000. As regards surgery for screen-detected cancers, responsibility for which is likely to fall within the screening programme (see section 4.2), with screening based on biennial FIT in those aged 55-74, resources would be required to conduct 420-520 colon resections each year and 220-260 rectal resections. Under gFOBT screening, around 200 colon resections and 100 rectal resections would require to be conducted annually, and for once only FSIG, approximately 40 colon resections and 20 rectal resections would require to be done.

Table 6.2(a) Estimated screening-related resource use and health outcomes by year: gFOBT at 55-74 years

		Year of programme									
		1	2	3	4	5	6	7	8	9	10
Screening-related resource use											
Screening tests	No. of gFOBT kits sent out	357,812	362,535	370,335	374,800	383,945	389,295	397,478	404,573	414,394	420,151
	No. of gFOBT kits processed	189,640	192,143	196,257	198,624	203,460	206,294	210,625	214,385	219,586	222,637
COL/CTC	No. of diagnostic COL	967	980	977	990	1,006	1,022	1,041	1,060	1,085	1,103
	No. of diagnostic CTC	126	127	127	129	131	133	135	138	141	143
	No. of surveillance COL	0	33	39	117	147	155	223	250	260	297
	No. of surveillance CTC	0	4	5	15	19	20	29	33	34	39
Pathology	No. of adenomas requiring pathology[1]	695	704	714	789	827	844	915	950	975	1,020
	No. of CRC requiring pathology	309	313	300	305	306	311	316	323	330	336
CRC work-up and treatment	No. receiving PET scan	31	31	30	30	31	31	32	32	33	34
	No. receiving MRI scan	111	113	108	110	110	112	114	116	119	121
	No. receiving CT scan(s)	310	314	300	305	306	311	316	323	330	336
	No. receiving TUS	16	16	15	15	15	16	16	16	17	17
	No. receiving pre-operative radiotherapy (+/- chemotherapy)[2]	71	72	67	68	68	70	71	72	74	75
	No. undergoing colon resection	186	189	181	184	185	188	191	195	200	203
	No. undergoing rectal resection	95	96	92	94	94	96	98	100	102	104

			Year of programme									
			1	2	3	4	5	6	7	8	9	10
Screening-related health outcomes												
Harms[3]	No. with major bleeding following endoscopy		4	4	4	5	5	5	5	5	6	6
	No. with perforation following endoscopy		2	2	2	2	2	2	2	2	2	2
	No. of deaths from perforation following endoscopy		0	0	0	0	0	0	0	0	0	0
Adenomas and CRC	No. with adenoma(s)[4]	Total	366	371	376	415	435	444	481	500	513	537
		low-risk	229	232	236	259	271	276	299	311	319	333
		intermediate/high-risk	137	138	140	157	164	168	182	189	194	204
	No. with CRC[5]	Total	309	313	300	305	305	311	316	324	330	336
		stage I	111	112	113	115	117	119	122	125	128	130
		stage II	105	107	102	104	105	107	109	111	113	115
		stage III	69	70	63	64	62	64	64	66	67	68
		stage IV	24	24	22	22	21	21	21	22	22	23

COL=colonoscopy; CRC=colorectal cancer; CTC=CT colonography; gFOBT=guaiac-based faecal occult blood test; FIT= faecal immunochemical test; FSIG= flexible sigmoidoscopy; TUS= ultrasound

intermediate/high-risk=adenoma(s) ≥10mm; low-risk=adenoma(s) <10mm;

1 assuming average of 1.9 adenomas per person; includes screen-detected and surveillance-detected adenomas

2 includes radiotherapy given with or without chemotherapy

3 includes complications from diagnostic and surveillance endoscopy, including FSIG where relevant

4 includes individuals with screen-detected and surveillance-detected adenomas

5 includes individuals with CRC detected at screening and at surveillance

Table 6.2(b) Estimated screening-related resource use and health outcomes by year: FIT at 55-74 years

		Year									
		1	2	3	4	5	6	7	8	9	10
Screening-related resource use											
Screening tests	No. of FIT kits sent out	357,812	362,535	369,155	373,602	382,043	387,356	395,084	402,134	411,758	417,464
	No. of FIT kits processed	189,640	192,143	195,538	197,894	202,301	205,113	209,167	212,899	217,981	220,999
COL/CTC	No. of diagnostic COL	11,095	11,242	11,164	11,303	11,433	11,599	11,767	11,981	12,237	12,414
	No. of diagnostic CTC	1,442	1,461	1,451	1,469	1,486	1,508	1,530	1,558	1,591	1,614
	No. of surveillance COL	0	301	355	1,039	1,311	1,312	1,900	2,098	2,121	2,406
	No. of surveillance CTC	0	39	46	135	170	171	247	273	276	313
Pathology	No. of adenomas requiring pathology[1]	6,308	6,393	6,124	6,803	6,918	7,018	7,501	7,775	7,867	8,222
	No. of CRC requiring pathology	853	864	697	715	664	675	661	677	671	687
CRC work-up and treatment	No. receiving PET scan	85	86	70	72	66	67	66	68	67	69
	No. receiving MRI scan	307	311	251	257	239	243	238	244	241	247
	No. receiving CT scan(s)	853	864	697	715	664	675	661	677	671	687
	No. receiving TUS	43	44	35	36	33	34	33	34	34	35
	No. receiving pre-operative radiotherapy (+/- chemotherapy)[2]	196	199	152	155	143	145	141	145	143	146
	No. undergoing colon resection	516	522	423	434	404	411	403	413	409	419
	No. undergoing rectal resection	263	266	217	223	208	212	208	213	211	216

			Year									
			1	2	3	4	5	6	7	8	9	10
Screening-related health outcomes												
Harms[3]	No. with major bleeding following endoscopy		48	48	48	51	53	54	57	59	60	62
	No. with perforation following endoscopy		21	22	21	23	24	24	25	26	26	27
	No. of deaths from perforation following endoscopy		1	1	1	1	1	1	1	1	1	1
Adenomas and CRC	No. with adenoma(s)[4]	Total	3,320	3,365	3,223	3,580	3,641	3,694	3,948	4,092	4,141	4,327
		low-risk	2,081	2,109	2,048	2,253	2,311	2,345	2,520	2,610	2,656	2,770
		intermediate/ high-risk	1,239	1,256	1,175	1,328	1,330	1,349	1,428	1,483	1,485	1,558
	No. with CRC[5]	Total	853	864	697	715	664	675	661	677	671	687
		stage I	308	312	286	297	286	291	290	297	296	303
		stage II	293	297	239	244	229	233	228	234	231	237
		stage III	192	195	131	133	115	117	112	115	113	115
		stage IV	60	61	41	41	33	33	31	32	31	31

COL=colonoscopy; CRC=colorectal cancer; CTC=CT colonography; gFOBT=guaiac-based faecal occult blood test; FIT= faecal immunochemical test; FSIG= flexible sigmoidoscopy; US= ultrasound; intermediate/high-risk=adenoma(s) ≥10mm; low-risk=adenoma(s) <10mm;

1 assuming average of 1.9 adenomas per person; includes screen-detected and surveillance-detected adenomas

2 includes radiotherapy given with or without chemotherapy

3 includes complications from diagnostic and surveillance endoscopy, including FSIG where relevant

4 includes individuals with screen-detected and surveillance-detected adenomas

5 includes individuals with CRC detected at screening and at surveillance

Table 6.2(c) Estimated screening-related resource use and health outcomes by year: FSIG once at age 60

		Year of programme									
		1	2	3	4	5	6	7	8	9	10
Screening-related resource use											
Screening tests	No. of FSIG done[1]	18,617	18,736	18,926	18,870	18,993	19,757	19,466	20,151	20,091	20,625
COL/CTC	No. of diagnostic COL	381	384	388	387	389	405	399	413	412	423
	No. of diagnostic CTC	50	50	50	51	51	53	52	54	54	55
	No. of surveillance COL	0	65	76	233	293	307	448	506	530	620
	No. of surveillance CTC	0	8	10	30	38	40	58	66	69	81
Pathology	No. of adenomas requiring pathology[2]	1,535	1,545	1,561	1,688	1,744	1,816	1,909	2,011	2,022	2,144
	No. of CRC requiring pathology	64	64	65	67	68	71	72	75	75	78
CRC work-up and treatment	No. receiving PET scan	6	6	6	7	7	7	7	7	7	8
	No. receiving MRI scan	23	23	23	24	24	25	26	27	27	28
	No. receiving CT scan(s)	64	64	65	67	68	71	72	75	75	78
	No. receiving TUS	3	3	3	3	3	4	4	4	4	4
	No. receiving pre-operative radiotherapy (+/- chemotherapy)[3]	15	15	15	15	15	16	16	17	17	17
	No. undergoing colon resection	39	39	39	40	41	43	43	45	45	47
	No. undergoing rectal resection	20	20	20	21	21	22	22	23	23	24

			Year of programme									
			1	2	3	4	5	6	7	8	9	10
Screening-related health outcomes												
Harms[4]	No. with major bleeding following endoscopy		7	7	7	7	8	8	9	9	9	10
	No. with perforation following endoscopy		1	1	1	1	1	1	2	2	2	2
	No. of deaths from perforation following endoscopy		0	0	0	0	0	0	0	0	0	0
Adenomas and CRC	No. with adenoma(s)[5]	Total	808	813	821	888	918	956	1,005	1,058	1,064	1,128
		low-risk	544	548	553	591	609	634	663	697	700	740
		intermediate/ high-risk	264	265	268	297	309	322	342	361	364	388
	No. with CRC[6]	Total	64	64	65	67	68	71	72	75	75	78
		stage I	23	24	24	25	26	27	28	29	29	31
		stage II	22	22	22	23	23	24	24	25	25	26
		stage III	14	14	14	14	14	15	15	16	16	16
		stage IV	4	4	4	4	4	5	5	5	5	5

COL=colonoscopy; CRC=colorectal cancer; CTC=CT colonography; gFOBT=guaiac-based faecal occult blood test; FIT= faecal immunochemical test; FSIG= flexible sigmoidoscopy; US= ultrasound

intermediate/high-risk=adenoma(s)≥10mm; low-risk=adenoma(s)<10mm;

1 includes FSIG with and without polypectomy

2 assuming average of 1.9 adenomas per person; includes screen-detected and surveillance-detected adenomas

3 includes radiotherapy given with or without chemotherapy

4 includes complications from diagnostic and surveillance endoscopy, including FSIG

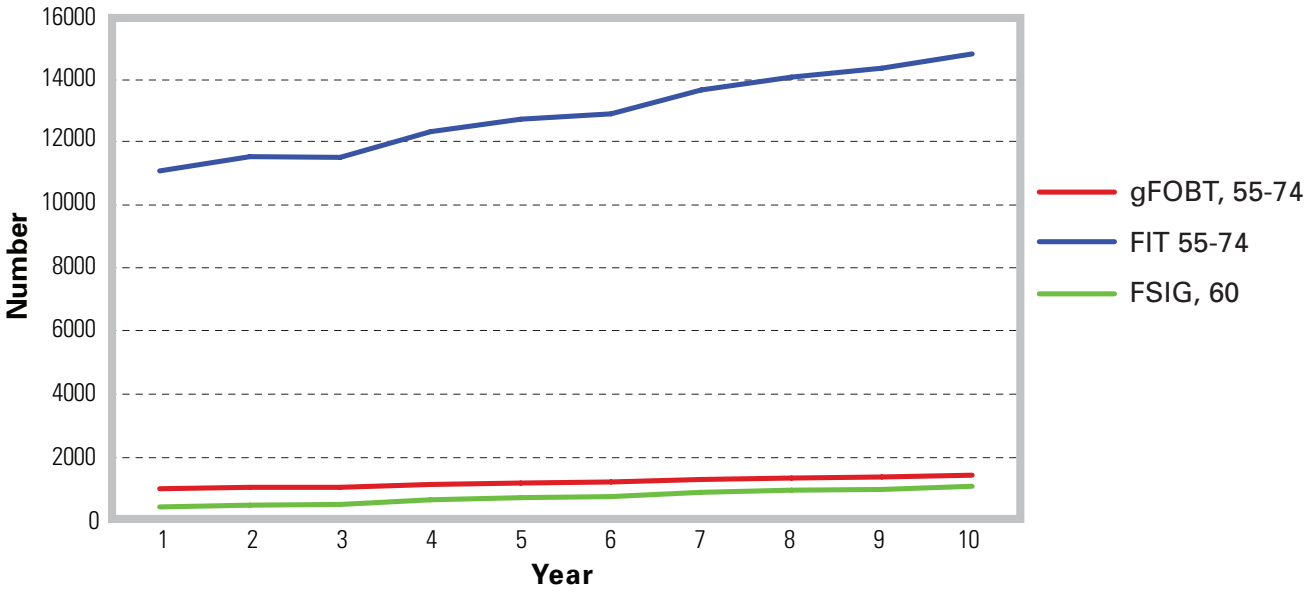
5 includes individuals with screen-detected and surveillance-detected adenomas

6 includes individuals with CRC detected at screening and at surveillance

Figures 6.2 (a)-(d) Estimated screening-related resource requirements and health outcomes for years 1-10, for core screening scenarios

(a) Diagnostic and surveillance colonoscopy

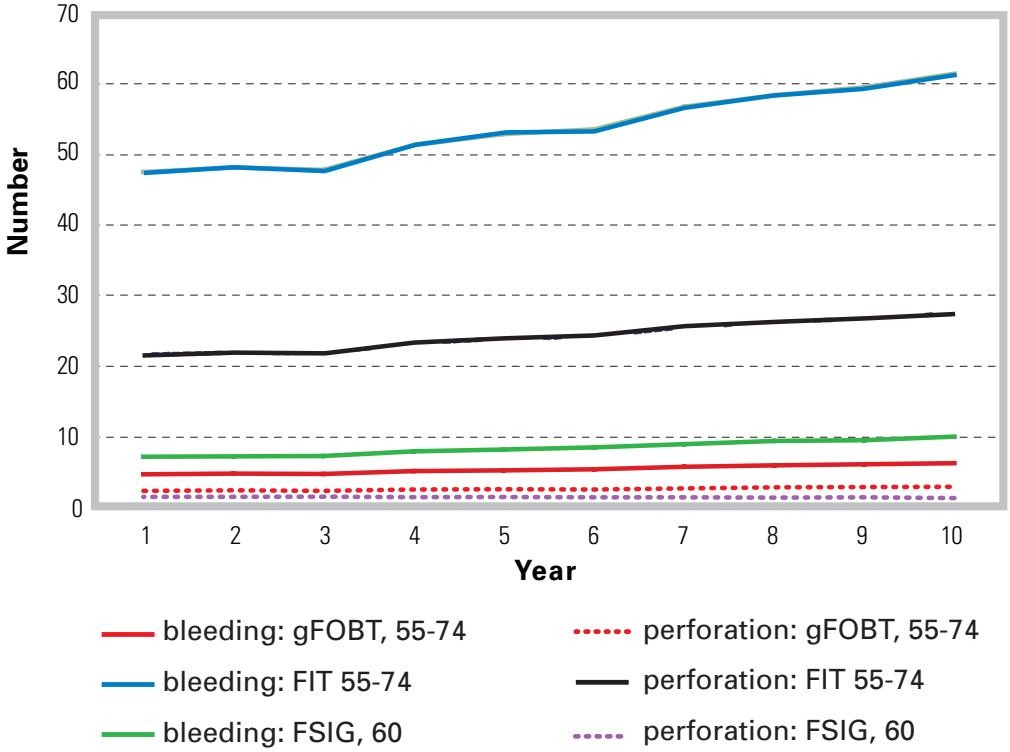
No. of individuals undergoing colonoscopy*, by year and scenario



** includes diagnostic and surveillance procedures*

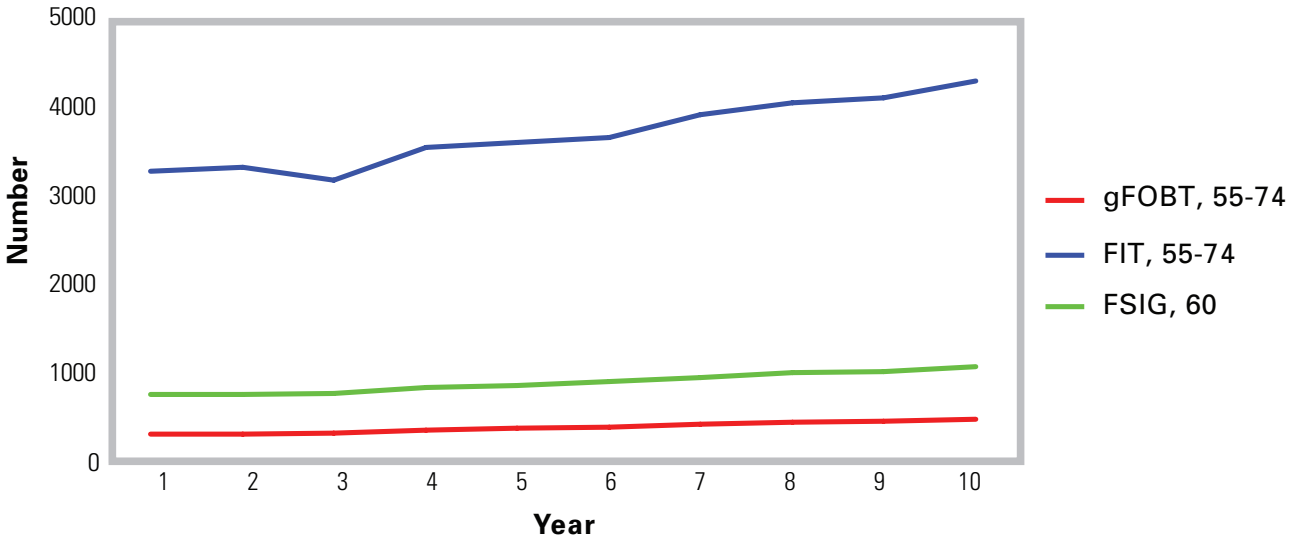
(b) Complications of screening

No.of individuals experiencing complications
(major bleeding and bowel performations), by year and scenario



(c) Screen and surveillance-detected adenomas

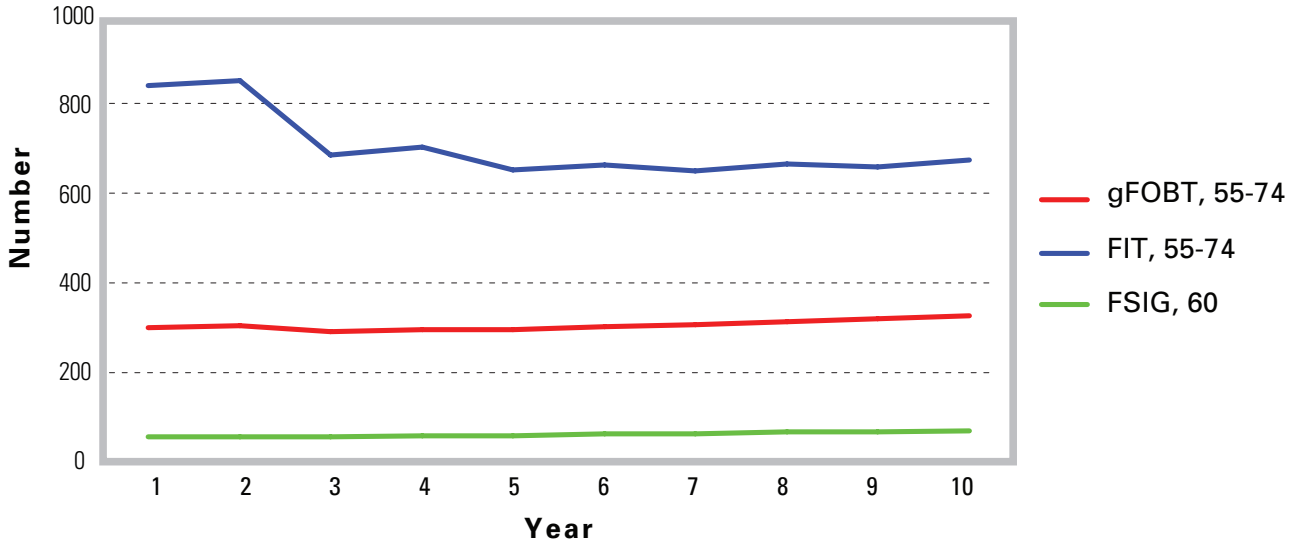
Total number of adenoma(s) detected*, by year and scenario



**includes low-risk and intermediate/high risk, from screening and surveillance*

(d) Screen and surveillance-detected cancers

No. of screen-detected colorectal cancers*, by year and scenario



** includes small number of cancers detected in those undergoing surveillance*

6.6 Secondary analysis: additional resources and health gains at the population-level for core scenarios

Tables 6.3 (a), (b) and (c) show the additional resource requirements and the health gains at the population level for each of the three core screening scenarios compared to a policy of no screening. The results are limited to resources related to the diagnosis, work-up and treatment of cancer, since resources related to, for example, screening tests, or pathological analysis of adenomas, would be considered to be generated entirely by the screening programme, and hence all such resources would be "additional" to those incurred under no screening (see above for these resource requirements).

6.6.1 Colorectal cancers diagnosed in the population compared to no screening, and associated resource requirements

Because the yield of screen-detected cancers is greatest for the FIT in the 55-74 age group, the additional resources required for work-up and treatment of cancers is greatest under this scenario. In year one of the programme, for example, capacity would be required nationally for histopathology of an estimated additional 800 cancers (figure 6.3(a)). This number would fall over time as biennial FIT screening begins to prevent cancers, and from year 5 onwards the required pathology capacity would be lower with screening than with no screening. By year 10, FIT-based screening would result in approximately 160 fewer cancers in the population than would be detected under a policy of no screening. A similar pattern is evident for other resources related to cancer diagnosis and treatment. For example, in year one, across the entire population, capacity would be required to provide pre-operative radiotherapy for an additional 190 rectal cancers, but by year 10 the requirements for radiotherapy would be less with a biennial FIT-based screening programme in place than with no screening.

Similar patterns are seen in the additional resources required with a policy of biennial gFOBT screening in the 55-74 age group, but the increased capacity required in the early years is less pronounced than with screening based on FIT. In addition, by year 10, gFOBT would not result in any reductions in capacity required nationally compared with no screening. For example, in year 1, at the population level an additional 300 colorectal cancers would require histopathology under gFOBT-based screening than compared to a policy of no screening (figure 6.3(a)). By year 10, there would still be a requirement for pathological analysis of an additional 20 colorectal cancers with screening compared to no screening.

The annual additional cancer-related resources requirements associated with screening based on once-only FSIG at age 60 would be small, due to the small numbers of additional cancers detected (approximately 60 in year one falling to approximately five in year five; figure 6.3(a)). In years six to 10, there would be fewer cancers detected in the population under a policy of FSIG than with no screening, but even by year 10, the difference would remain small (approximately 50 fewer cancers with screening than without screening).

The proportion of all colorectal cancers which would be detected through screening (and surveillance) in years one and 10 under each screening scenario is shown in figure 6.4. With biennial FIT, 26% of all cancers diagnosed in the first year and 30% of those

diagnosed in year 10 would be found as a result of screening. Screening based on biennial gFOBT would detect 11% of all colorectal cancers diagnosed in year one and 14% of those diagnosed in year 10. The comparable figures for FSIG would be 3% in both year one and year 10.

Under all three scenarios the stage distribution of the symptomatically detected cancers in year one of the programme would be as follows: stage I, 12%; stage II, 25%; stage III, 35% and stage IV, 28%. With all scenarios the screen-detected cases would have a more favourable stage distribution than those detected symptomatically. In the first year of the programme, for example, 36% would be expected to be stage I at diagnosis, another 34%-35% would be stage II, 22-23% would be stage III and only 7-8% would be stage IV.

As a consequence of the greater proportion of cases which would be detected via screening, biennial FIT at age 55-74 years would have the potential to change the stage distribution of all colorectal cancer in the population during the first ten years of a screening programme; this would not be seen for the other core scenarios. Under this strategy, between year one and year 10, the percentage of cases diagnosed at stage I would increase from 18% to 23% and the percentage stage II would rise from 28% to 30% (figures 6.5 (a), (b)). There would be slight falls in the percentages diagnosed at stage III (from 32% to 28%) and stage IV (22% to 19%).

6.6.2 Deaths from colorectal cancer in the population compared to no screening

All three screening scenarios would result in a decrease in the estimated numbers of deaths from colorectal cancer in the population compared to no screening; this decrease would begin to become evident by year two of the establishment of a screening programme, and would increase over time (figure 6.3(b)). The fall in numbers of deaths would be greatest for screening based on biennial FIT, intermediate for a policy of biennial gFOBT, and smallest for FSIG-based screening.

With biennial FIT screening, in year two there would be 21 fewer deaths with screening than with no screening; figure 6.3(b)). By year 10 there would be an estimated 272 fewer deaths under a policy of screening as compared to no screening. With biennial gFOBT, by year 10 there would be almost 100 fewer deaths from colorectal cancer in the population, compared to no screening. For FSIG at age 60, by year 10, there would be approximately 40 fewer deaths with screening compared to no screening.

Table 6.3(a) Estimated additional resource requirements and health gains by year: gFOBT at age 55-74 versus no screening

	Year of programme									
	1	2	3	4	5	6	7	8	9	10
Additional resource requirements for CRC diagnostic work-up and treatment										
No. of CRCs requiring pathology	299	232	152	104	65	45	33	26	22	18
No. receiving PET scan	30	23	15	10	7	5	3	3	2	2
No. receiving MRI scan	107	83	55	38	24	16	12	9	8	6
No. receiving CT scan(s)	299	232	152	104	65	45	33	26	22	18
No. receiving TUS	15	12	8	5	3	2	2	1	1	1
No. receiving pre-operative radiotherapy (+/- chemotherapy)[1]	69	54	33	23	15	12	10	8	8	7
No. undergoing colon resection	182	146	103	79	61	52	47	44	43	41
No. undergoing rectal resection	93	75	54	43	34	30	27	26	25	24
Population health gain										
Total no. with CRC	2,700	2,606	2,511	2,455	2,416	2,402	2,399	2,407	2,420	2,436
No. with symptomatic CRC	2,391	2,293	2,211	2,150	2,111	2,091	2,083	2,083	2,090	2,100
stage I	284	273	269	266	265	265	265	266	268	270
stage II	605	581	559	548	543	541	540	541	544	547
stage III	827	793	762	737	721	713	710	710	711	714
stage IV	675	646	621	599	582	572	568	566	567	569
No. with screen-detected CRC[2]	309	313	300	305	305	311	316	324	330	336
stage I	111	112	113	115	117	119	122	125	128	130
stage II	105	107	102	104	105	107	109	111	113	115
stage III	69	70	63	64	62	64	64	66	67	68
stage IV	24	24	22	22	21	21	21	22	22	23
Additional CRC cases detected (versus no screening)	299	232	152	104	65	45	33	26	22	18
Total no. of CRC deaths	1,052	1,029	1,006	986	969	958	951	949	949	952
Reduction in CRC deaths (versus no screening)	0	8	21	37	52	65	76	85	92	99

COL=colonoscopy; CRC=colorectal cancer; CTC=CT colonography; gFOBT=guaiac-based faecal occult blood test; FIT= faecal immunochemical test; FSIG= flexible sigmoidoscopy; US= ultrasound

1 includes radiotherapy given with or without chemotherapy

2 includes CRC detected at surveillance; numbers of these are very small

Table 6.3(b) Estimated additional resource requirements and health gains by year: FIT at age 55-74 versus no screening

	Year of programme									
	1	2	3	4	5	6	7	8	9	10
Additional resource requirements for CRC diagnostic work-up and treatment										
No. of CRCs requiring pathology	824	642	295	194	45	-6	-72	-97	-143	-164
No. receiving PET scan	82	64	29	19	4	-1	-7	-10	-14	-16
No. receiving MRI scan	297	231	106	70	16	-2	-26	-35	-52	-59
No. receiving CT scan(s)	824	642	295	194	45	-6	-72	-97	-143	-164
No. receiving TUS	42	32	15	10	2	0	-4	-5	-7	-8
No. receiving pre-operative radiotherapy (+/- chemotherapy)[1]	192	150	59	35	3	-7	-22	-28	-39	-44
No. undergoing colon resection	504	406	210	159	80	55	20	8	-16	-26
No. undergoing rectal resection	257	209	112	88	49	37	20	14	2	-3
Population health gain										
Total no. with CRC	3,227	3,016	2,653	2,545	2,396	2,351	2,295	2,283	2,254	2,254
No. with symptomatic CRC	2,374	2,152	1,956	1,830	1,733	1,676	1,634	1,606	1,583	1,568
stage I	283	258	246	239	234	230	226	224	223	222
stage II	604	548	494	470	453	443	434	428	423	420
stage III	822	745	672	620	583	563	547	537	529	523
stage IV	665	601	544	500	463	441	426	416	409	403
No. with screen-detected CRC[2]	853	864	697	715	664	675	661	677	671	687
stage I	308	312	286	297	286	291	290	297	296	303
stage II	293	297	239	244	229	233	228	234	231	237
stage III	192	195	131	133	115	117	112	115	113	115
stage IV	60	61	41	41	33	33	31	32	31	31
Additional CRC cases detected (versus no screening)	824	642	295	194	45	-6	-72	-97	-143	-164
Total no. of CRC deaths	1,052	1,015	969	923	883	850	825	805	790	779
Reduction in CRC deaths (versus no screening)	0	21	58	99	138	173	203	228	251	272

COL=colonoscopy; CRC=colorectal cancer; CTC=CT colonography; gFOBT=guaiac-based faecal occult blood test; FIT= faecal immunochemical test; FSIG= flexible sigmoidoscopy; US= ultrasound

1 includes radiotherapy given with or without chemotherapy

2 includes CRC detected at surveillance; numbers of these are very small

Table 6.3(c) Estimated additional resource requirements and health gains by year: FSIG once-only at age 60 versus no screening

	Year of programme									
	1	2	3	4	5	6	7	8	9	10
Additional resource requirements for CRC diagnostic work-up and treatment										
No. of CRCs requiring pathology	62	48	33	19	5	-7	-20	-30	-43	-52
No. receiving PET scan	6	5	3	2	1	-1	-2	-3	-4	-5
No. receiving MRI scan	22	17	12	7	2	-2	-7	-11	-15	-19
No. receiving CT scan(s)	62	48	33	19	5	-7	-20	-30	-43	-52
No. receiving TUS	3	2	2	1	0	0	-1	-2	-2	-3
No. receiving pre-operative radiotherapy (+/- chemotherapy)[1]	14	9	6	3	1	-2	-5	-7	-9	-11
No. undergoing colon resection	38	30	22	15	8	2	-5	-10	-17	-21
No. undergoing rectal resection	19	16	12	8	5	2	-2	-4	-7	-9
Population health gain										
Total no. with CRC	2,465	2,422	2,391	2,370	2,357	2,350	2,347	2,350	2,355	2,366
No. with symptomatic CRC	2,401	2,357	2,326	2,304	2,289	2,280	2,275	2,276	2,280	2,288
stage I	284	279	276	274	272	271	271	272	273	274
stage II	606	595	587	582	578	576	575	575	577	579
stage III	830	814	802	794	789	786	784	783	784	787
stage IV	682	669	660	654	649	647	646	645	646	648
No. with screen-detected CRC[2]	64	64	65	67	68	71	72	75	75	78
stage I	23	24	24	25	26	27	28	29	29	31
stage II	22	22	22	23	23	24	24	25	25	26
stage III	14	14	14	14	14	15	15	16	16	16
stage IV	4	4	4	4	4	5	5	5	5	5
Additional CRC cases detected (versus no screening)	62	48	33	19	5	-7	-20	-30	-43	-52
Total no. of CRC deaths	1,052	1,035	1,022	1,014	1,008	1,005	1,004	1,005	1,008	1,012
Reduction in CRC deaths (versus no screening)	0	2	5	8	13	18	23	28	34	39

COL=colonoscopy; CRC=colorectal cancer; CTC=CT colonography; gFOBT=guaiac-based faecal occult blood test; FIT= faecal immunochemical test; FSIG= flexible sigmoidoscopy; US= ultrasound

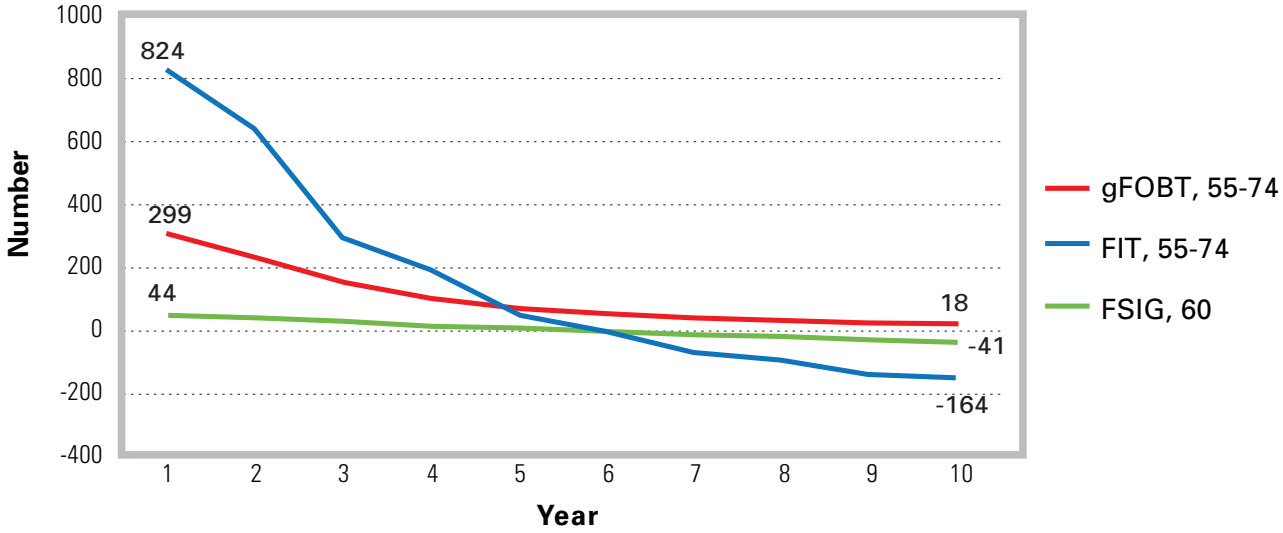
1 includes radiotherapy given with or without chemotherapy

2 includes CRC detected at surveillance; numbers of these are very small

Figure 6.3 (a), (b) Estimated difference in numbers of cases of, and deaths from, colorectal cancer in the population with screening versus a policy of no screening, over years 1-10, core screening scenarios

(a) Colorectal cancer cases

Difference between total colorectal cancers detected in the population with screening versus no screening, by year and scenario



(b) Deaths from colorectal cancer

Difference between total colorectal cancer deaths in the population with screening versus no screening, by year and scenario

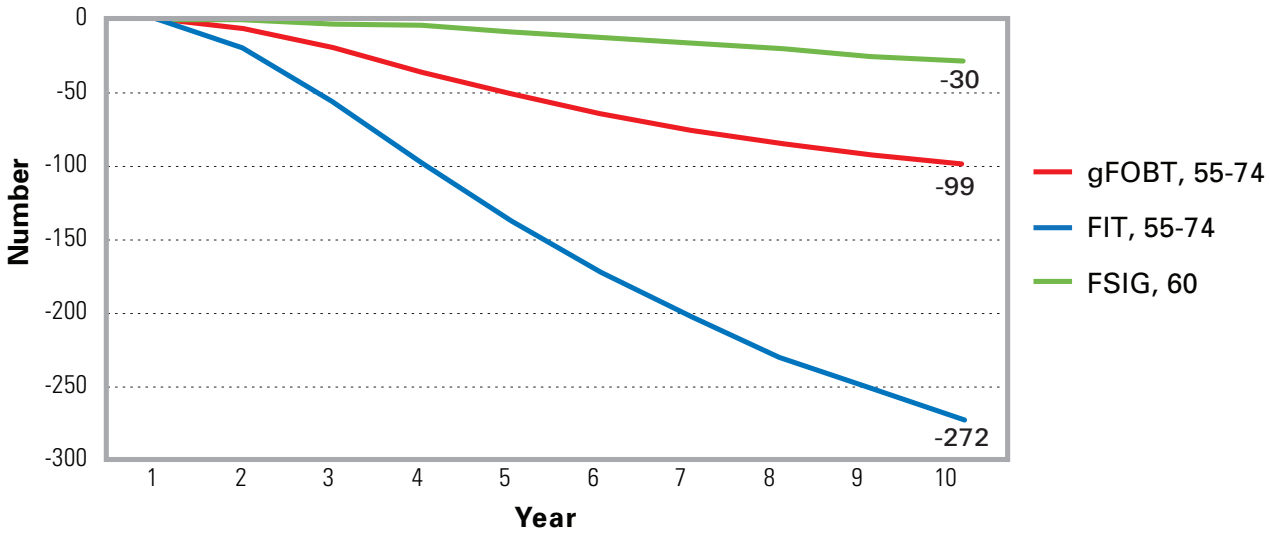
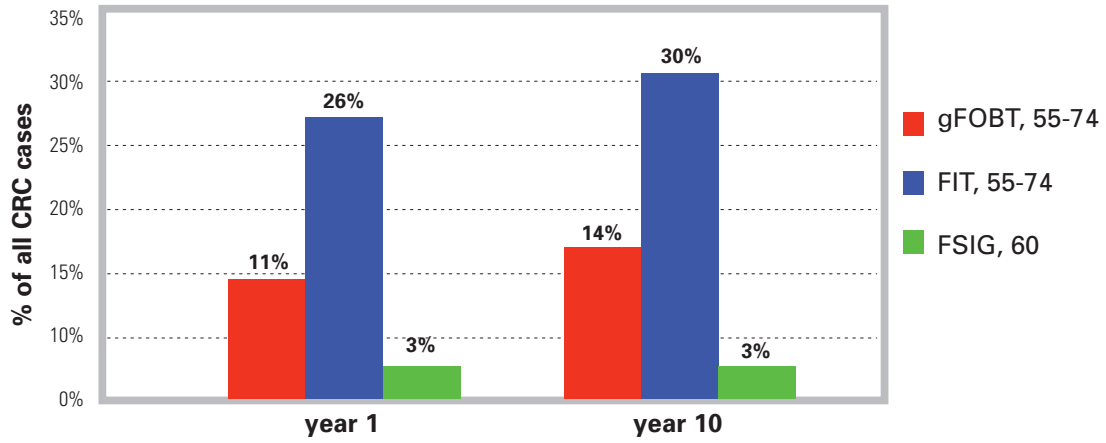


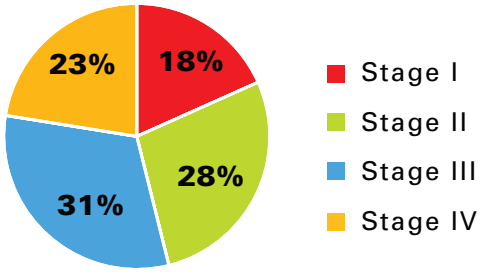
Figure 6.4 Estimated percentage of all cases of colorectal cancer in the population which would be screen-detected*, in years one and 10, core screening scenarios



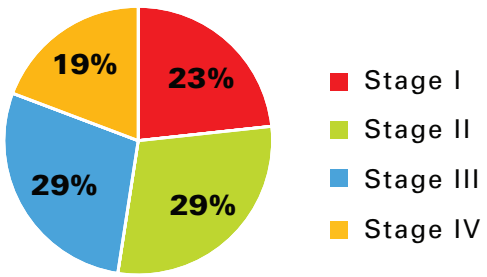
** includes cancers detected by individuals undergoing surveillance*

Figure 6.5 (a), (b) Stage distribution of all* colorectal cancer in years one and 10 of programme, biennial FIT at age 55-74

(a) Year one of programme



(b) Year 10 of programme



** detected by screening, surveillance or symptomatically*

6.7 Sensitivity analysis for core scenarios

6.7.1 Screening uptake

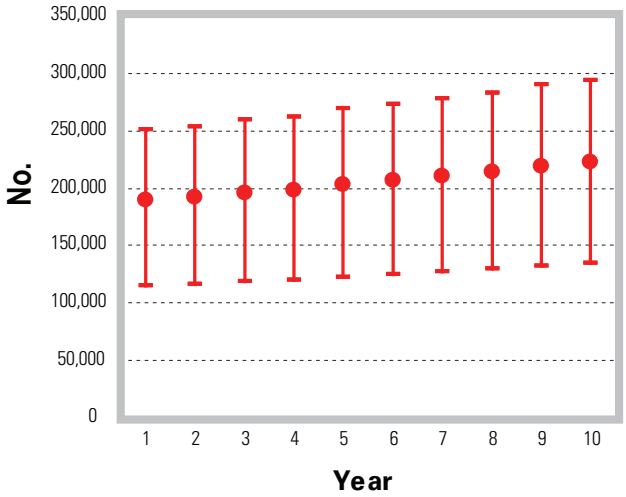
Figures 6.6(a)-(d), 6.7(a)-(d) and 6.8(a)-(d) show the results of the sensitivity analysis relating to screening uptake for scenarios based on gFOBT, FIT or FSIG respectively. Selected resources and outcomes are shown: number of individuals screened, number of diagnostic colonoscopies conducted, number of adenomas requiring pathology (detected by screening or surveillance), and number of individuals with screen-detected cancers (including those detected at surveillance).

Screening uptake has a major influence on all resource requirements and health outcomes. For example, for FIT screening in the 55-74 age group, if uptake was 32% 114,500 individuals would be screened in year one, compared to 189,640 with uptake at 53%, or 250,469 if uptake was 70% (figure 6.7(a)). With uptake at 53%, the screening programme would be required to conduct approximately 11,000 diagnostic colonoscopies in year one (figure 6.7(b)). If uptake was 32%, this number would fall to approximately 6700; if uptake was 70%, capacity would be needed for 14,600 colonoscopies. By year 10, uptake of 70% would generate a requirement for more than 16,000 diagnostic colonoscopies, compared to 12,500 with uptake at 53% (note that these figures do not include surveillance colonoscopies). Taking multiple adenomas in the same individual into account, in year one, at 32% uptake, 3,800 screen-detected adenomas would require to undergo pathological analysis; at 53% uptake, 6,300 adenomas would require analysis; and at 70% uptake, pathology capacity would be required to analyse 8,300 adenomas (figure 6.7(c)). If uptake was less than 53%, the number of cancers detected by screening would fall (500 in year one with uptake at 32% compared to 850 with uptake at 53%; figure 6.7(d)). If uptake was higher than 53%, the number of screen-detected cancers would rise (from 850 to 1100 in year one). Similar proportionate falls and rises would occur in resources required by the screening programme for work-up and treatment of screen-detected cancers (data not shown).

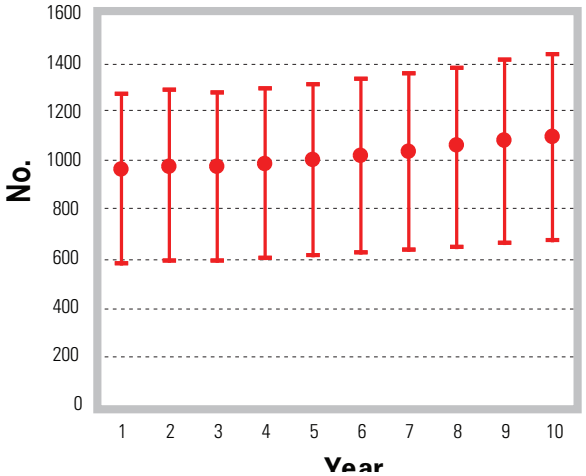
An implication of these figures is that low uptake (for example, less than 53%) would reduce the potential number of colorectal cancers that could be averted at the population-level by screening, whereas if high uptake could be achieved (for example, more than 53%), the potential number of cases averted in the population would increase.

Figures 6.6 (a)-(d) Sensitivity analysis of estimated screening-related resource requirements and health outcomes for years 1-10, for gFOBT at 55-74 years with low (32%), base-case (53%) and high (70%) uptake.

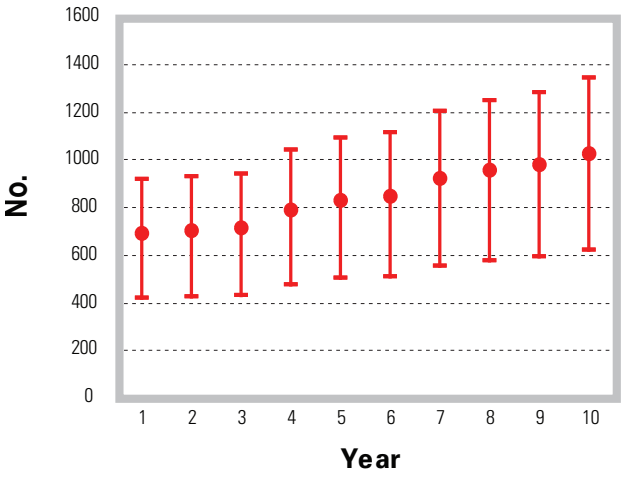
(a) No. of individuals screened



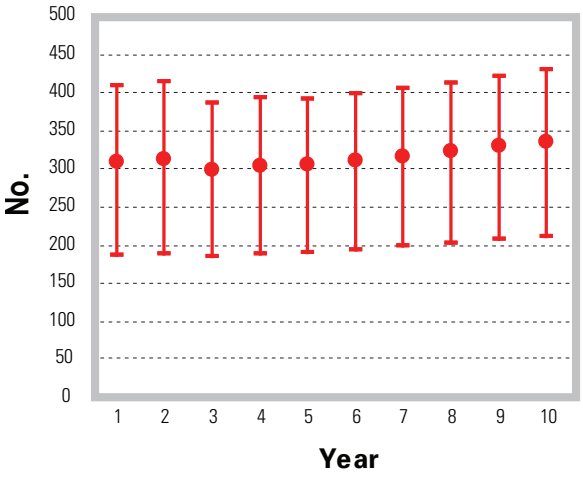
(b) No. of diagnostic colonoscopies



(c) No. of adenomas requiring pathology

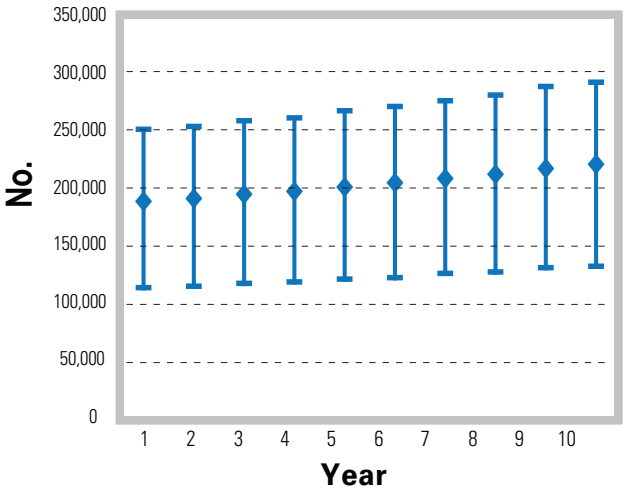


(d) No. of screen-detected cancers

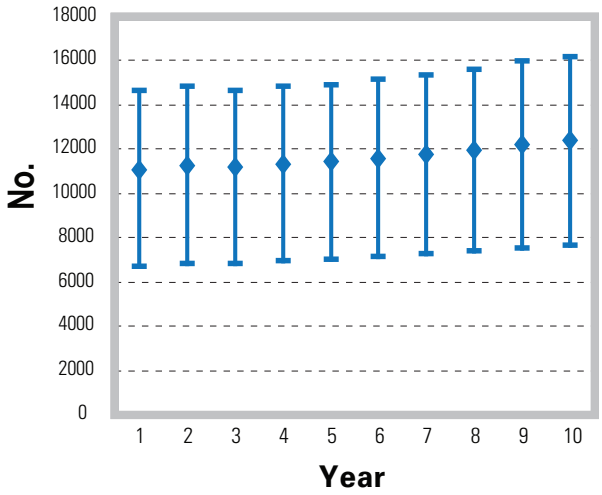


Figures 6.7 (a)-(d) Sensitivity analysis of estimated screening-related resource requirements and health outcomes for years 1-10, for FIT at 55-74 years with low (32%), base-case (53%) and high (70%) uptake.

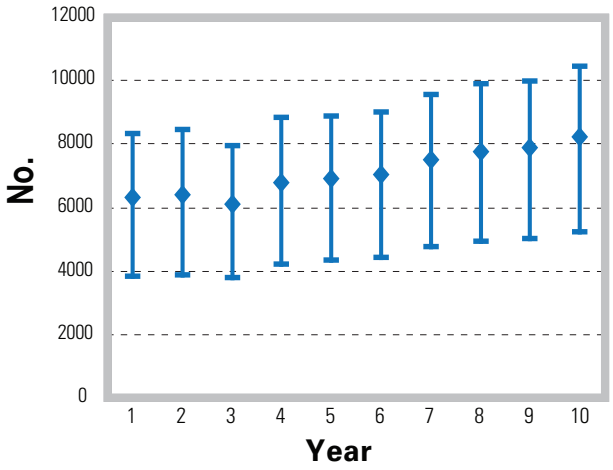
(a) No. of individuals screened



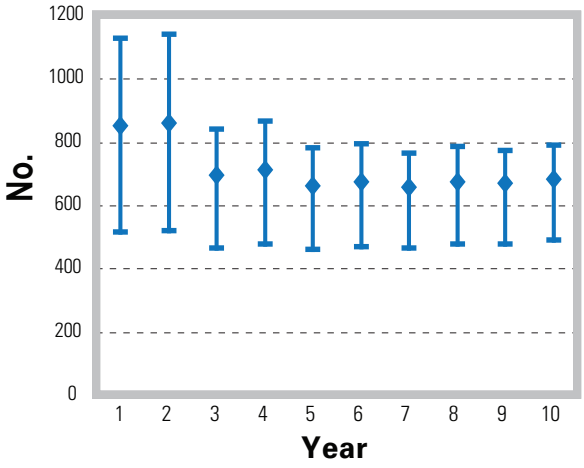
(b) No. of diagnostic colonoscopies



(c) No. of adenomas requiring pathology

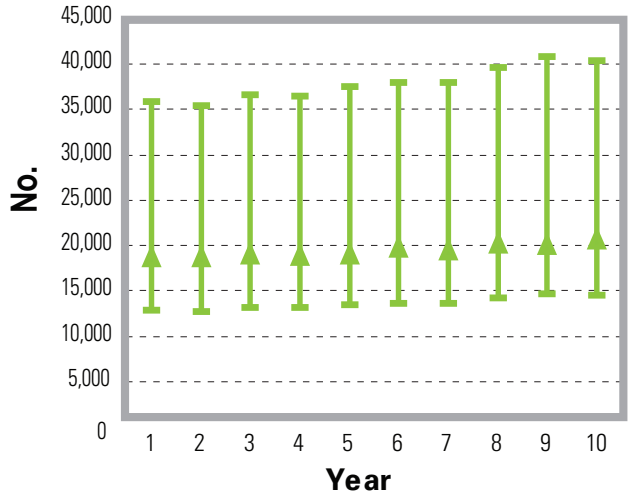


(d) No. of screen-detected cancers

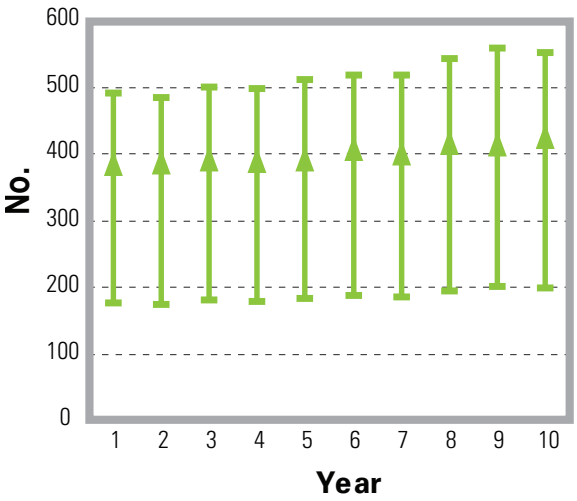


Figures 6.8 (a)-(d) Sensitivity analysis of estimated screening-related resource requirements and health outcomes for years 1-10, for FSIG once-only at 60 years with low (24%), base-case (39%) and high (67%) uptake.

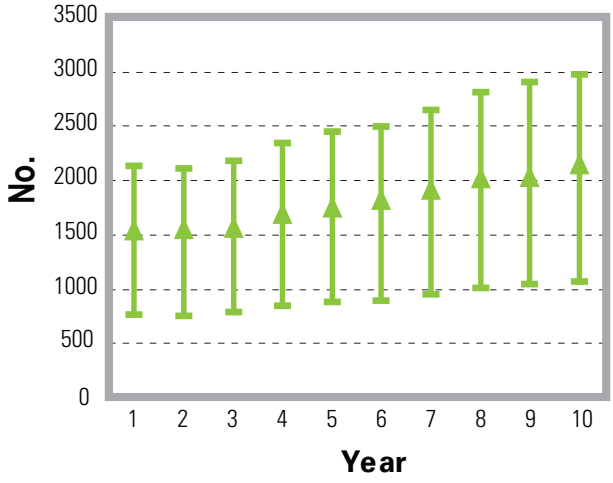
(a) No. of individuals screened



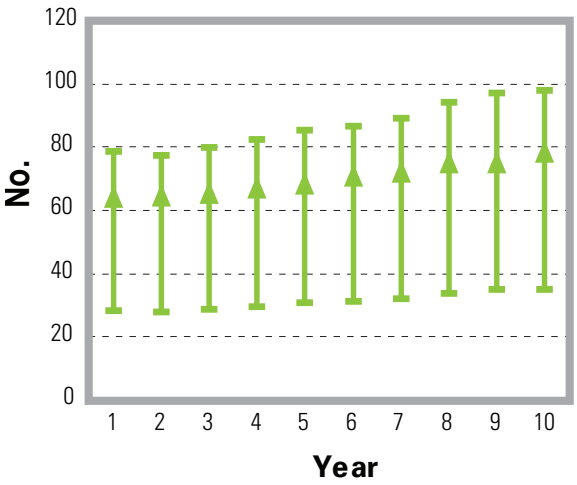
(b) No. of diagnostic colonoscopies



(c) No. of adenomas requiring pathology



(d) No. of screen-detected cancers



6.7.2 gFOBT with reflex FIT

Table 6.4 summarises selected screening-related resource requirements and health outcomes for the sensitivity analysis which explored the effect of changing the assumption used in the base-case analysis that the performance characteristics of gFOBT and reflex FIT are independent. The sensitivity analysis used a higher value for combined test sensitivity for adenomas than the base-case analysis, and this resulted in increases in the numbers of (i) colonoscopies that would be undertaken, (ii) individuals found to have adenomas, (iii) adenomas requiring pathology and (iv) individuals sustaining harms, compared to the estimates from the base-case analysis. The combined sensitivity for cancers used in the sensitivity analysis was lower than that in the base-case analysis, and hence the numbers of screen-detected cancers was lower than in the base-case.

Table 6.4 Estimated screening-related resource use and health outcomes by year: gFOBT at 55-74 years. Sensitivity analysis[1]

			Year of programme									
			1	2	3	4	5	6	7	8	9	10
Screening-related resource use												
COL/CTC	No. of diagnostic COL		2,045	2,072	2,102	2,129	2,172	2,205	2,247	2,289	2,343	2,378
	No. of diagnostic CTC		266	269	273	277	282	287	292	298	305	309
	No. of surveillance COL		0	55	64	192	242	253	364	408	423	483
	No. of surveillance CTC		0	7	8	25	31	33	47	53	55	63
Pathology	No. of adenomas requiring pathology[2]		1,142	1,157	1,168	1,292	1,350	1,377	1,491	1,548	1,587	1,660
	No. of CRC requiring pathology		180	182	178	182	183	186	190	194	198	202
Screening-related health outcomes												
Harms[3]	No. with major bleeding following endoscopy		9	9	9	10	10	10	11	11	11	12
	No. with perforation following endoscopy		4	4	4	4	4	4	5	5	5	5
	No. of deaths from perforation following endoscopy		0	0	0	0	0	0	0	0	0	0
Adenomas and CRC	No. with adenoma(s)[4]	Total	601	609	615	680	710	725	784	815	835	874
		low-risk	377	382	386	424	443	451	489	507	521	544
		intermediate/ high-risk	224	227	228	256	268	273	296	308	315	330
	No. with CRC[5]	Total	180	182	178	182	183	186	190	194	198	202
		stage I	63	64	64	66	67	68	70	72	73	75
		stage II	60	61	59	60	61	62	63	65	66	67
		stage III	39	40	38	38	38	39	39	40	41	42
		stage IV	18	18	17	17	17	17	17	18	18	18

COL=colonoscopy; CRC=colorectal cancer; CTC=CT colonography; gFOBT=guaiac-based faecal occult blood test; FIT= faecal immunochemical test

intermediate/high-risk=adenoma(s)≥10mm; low-risk=adenoma(s) <10mm;

1 assuming that the performance characteristics of gFOBT and the reflex FIT are not independent

2 assuming average of 1.9 adenomas per person; includes screen-detected and surveillance-detected adenomas

3 includes complications from diagnostic and surveillance endoscopy

4 includes individuals with screen-detected and surveillance-detected adenomas

5 includes individuals with CRC detected at screening and at surveillance

6.8 Results for alternative FIT-based implementation options

The screening-related resource requirements and health outcomes for the three alternative options for implementation of FIT screening (option 1: biennial FIT at age 55-64; option 2: biennial FIT at age 55-74, "medium implementation"; option 3: biennial FIT at ages 55-74, "slow implementation") are shown in tables 6.5(a), (b) and (c). Figures 6.9 (a)-(g) summarise the findings graphically.

In terms of screening test kits and individuals screened, the number of kits dispatched and number of persons screened under the age-restricted option (FIT at age 55-64) would be approximately 60% of those for years 1-10 for the core scenario (biennial FIT at age 55-74 with immediate implementation across the full age group; figure 6.9(a)). Both strategies which relate to staged implementation of screening in the 55-74 age group (implementation options 2 and 3), would involve much lower numbers of kits dispatched in early years, with a steady increase over time. This, of course, corresponds to much lower numbers of individuals screened, and kits requiring processing, than with the full implementation option. For option 2 (medium implementation), approximately 83,000 individuals would be invited to participate in year 1, with around 44,000 expected to do so. By year 10 this would have risen to almost 420,000 invited and 221,500 participating; the same number as under the core option. For the slow implementation option (option 3), just under 50,000 kits would be dispatched in year one with an estimated 26,000 returned; by year 10 the figures would be 247,500 dispatched and 131,000 individuals screened.

The same pattern is seen as regards colonoscopy resources required for diagnostic investigation of those with a positive screening test. Under implementation option 1, 6,500-7,000 individuals would undergo diagnostic colonoscopy each year as part of the screening programme, compared to the 11,000-12,400 required under the core scenario. Option 2 would allow for a build-up in colonoscopy capacity, with a requirement for approximately 2,400 diagnostic procedures in year one, rising to 7,500 in year five and 12,600 in year 10. A more gradual build-up in capacity would be allowed for under option 3, with 1,400 individuals requiring diagnostic colonoscopy in year one, 4,100 in year five and 7,000 in year 10. As regards colonoscopy resources for the surveillance of those with intermediate/high-risk screen-detected adenomas, the three alternative strategies result in substantially lower requirements than the core scenario. Figure 6.9(b) illustrates the overall resources required for diagnostic and surveillance colonoscopies under the core scenarios and the three options.

Since CT colonography requirements are estimated as a function of those for colonoscopy, the same patterns are apparent in the resources required for CT colonography for diagnostic and surveillance purposes as for colonoscopy.

The lower numbers of colonoscopies required for the three variant options than for the core scenario means that these policies would result in lower numbers of participants experiencing adverse outcomes (figures 6.9(c) and 6.9(d)). Screening the 55-64 age group would result in between 28-35 individuals sustaining a major abdominal bleed and around 15 bowel perforations, compared to approximately 50-60 bleeds and 25 perforations for the core scenario. There would be around 10 bleeds and 5 perforations in the early years of screening under the medium implementation strategy (option 2) rising to the same levels as the core strategy by year 9. Under the slow implementation option (option 3), 6 individuals would experience bleeding and 3 would have a

perforation in years one and two, increasing to around 30 and 15 respectively in year 10. It is worth noting that the absolute risk to the individual of sustaining a complication is the same regardless of the implementation strategy.

The annual numbers of individuals who would have screen-detected adenomas or cancers for each FIT-based scenario are shown in figures 6.9(e) and 6.9(f). Taking the first 10 years in total, screening only those aged 55-64 years would result in just under half of the total yield of individuals with adenomas and cancers compared to the core scenario. Implementation option 2 (medium implementation) would result in about 60% of the numbers with adenomas and cancers over 10 years as would be found under the core scenario, and option 3 (slow implementation) would yield just over one quarter of the numbers detected under the core scenario. Under the two options for roll-out in the 55-74 age group (options 2 and 3), the numbers of screen-detected cancers would continue to rise over time, rather than falling slightly as would be seen for the core scenarios and the "full" implementation in the younger age group (option 1). This is because, by year 10, on average individuals screened under options 2 and 3 would have completed fewer screening rounds than for the other two scenarios, thus the full preventive effect of repeated screening on colorectal cancer would not yet be apparent.

The resources required for histopathology are a function of the numbers of adenomas and cancers detected (figure 6.9(g)). Under the core scenario, there would be more than 6,000 adenomas requiring pathological analysis in year one. Under the medium and slow implementation options, the comparable figures would be approximately 1,200 and 500 adenomas respectively. Screening the 55-64 age group only would result in around 3,100 adenomas requiring pathology in year one.

Resources required in the screening programme for diagnostic radiology, radiotherapy and colorectal surgery are a function of the number of individuals diagnosed with screen-detected cancers. Therefore, under the core scenario and implementation option 1 (full implementation for ages 55-64) the resources required would decrease slightly over time, while for the medium and slow implementation options, they would increase (figure 6.9(h)). For example, screening the 55-64 age group would require resources to undertake around 300-450 resections each year (approximately 200-230 colon resections and 100-120 rectal resections); this compares to 630-780 under the core scenario (420-520 colon and 220-260 rectal). Under the medium implementation strategy, the number of resections would increase from around 150 in year 1, to 400 in year 5 and 700 in year 10. With slow implementation, capacity would be required to undertake slightly more than 50 resections in year 1, 160 in year 5 and 290 in year 10.

Table 6.5(a) Estimated screening-related resource use and health outcomes by year: FIT at 55-64 years (implementation option 1)

		Year of programme									
		1	2	3	4	5	6	7	8	9	10
Screening-related resource use											
Screening tests	No. of FIT kits sent out	219,171	222,828	226,895	227,622	232,301	232,835	237,262	239,792	245,927	247,425
	No. of FIT kits processed	116,161	118,099	120,209	120,594	123,052	123,335	125,670	127,011	130,259	131,052
COL/CTC	No. of diagnostic COL	6,437	6,551	6,550	6,573	6,662	6,677	6,787	6,857	7,029	7,070
	No. of diagnostic CTC	837	852	852	855	866	868	882	891	914	919
	No. of surveillance COL	0	138	164	489	621	628	918	1037	1050	1236
	No. of surveillance CTC	0	18	21	64	81	82	119	135	136	161
Pathology	No. of adenomas requiring pathology[1]	3,086	3,151	3,039	3,334	3,411	3,420	3,686	3,805	3,881	4,059
	No. of CRC requiring pathology	377	386	320	325	309	310	311	315	320	325
CRC work-up and treatment	No. receiving PET scan	38	39	32	33	31	31	31	32	32	33
	No. receiving MRI scan	136	139	115	117	111	112	112	114	115	117
	No. receiving CT scan(s)	377	386	320	325	309	310	311	315	320	325
	No. receiving TUS	19	19	16	16	16	16	16	16	16	16
	No. receiving pre-operative radiotherapy (+/- chemotherapy)[2]	86	88	70	70	66	67	66	67	68	69
	No. undergoing colon resection	228	234	194	198	188	189	190	192	195	198
	No. undergoing rectal resection	117	119	100	101	97	97	98	99	101	102

			Year of programme									
			1	2	3	4	5	6	7	8	9	10
Screening-related health outcomes												
Harms[3]	No. with major bleeding following endoscopy		28	28	28	30	30	31	32	33	34	35
	No. with perforation following endoscopy		13	13	13	13	14	14	15	15	15	16
	No. of deaths from perforation following endoscopy		1	1	1	1	1	1	1	1	1	1
Adenomas and CRC	No. with adenoma(s)[4]	Total	1,624	1,658	1,599	1,755	1,795	1,800	1,940	2,003	2,042	2,136
		low-risk	1,063	1,085	1,058	1,146	1,178	1,181	1,272	1,312	1,340	1,397
		intermediate/ high-risk	561	574	542	609	617	619	668	691	702	739
	No. with CRC[5]	Total	377	386	320	325	309	310	311	315	320	325
		stage I	139	142	132	136	133	133	135	137	140	142
		stage II	129	132	109	111	106	107	107	108	110	111
		stage III	83	85	60	60	54	55	54	55	55	56
		stage IV	25	26	18	18	15	16	15	15	16	16

COL=colonoscopy; CRC=colorectal cancer; CTC=CT colonography; gFOBT=guaiac-based faecal occult blood test; FIT= faecal immunochemical test; FSIG= flexible sigmoidoscopy; US= ultrasound

intermediate/high-risk=adenoma(s)≥10mm; low-risk=adenoma(s)<10mm;

1 assuming average of 1.9 adenomas per person; includes screen-detected and surveillance-detected adenomas

2 includes radiotherapy given with or without chemotherapy

3 includes complications from diagnostic and surveillance endoscopy, including FSIG where relevant

4 includes individuals with screen-detected and surveillance-detected adenomas

5 includes individuals with CRC detected at screening and at surveillance

Table 6.5(b) Estimated screening-related resource use and health outcomes by year: FIT at 55-74 years, "medium implementation" (option 2)

		Year of programme									
		1	2	3	4	5	6	7	8	9	10
Screening-related resource use											
Screening tests	No. of FIT kits sent out	82,602	82,846	165,384	168,068	249,474	253,455	331,182	337,725	412,527	418,242
	No. of FIT kits processed	43,779	43,909	87,631	89,052	13,2157	134,265	175,404	178,869	218,449	221,473
COL/CTC	No. of diagnostic COL	2,441	2,452	4,894	4,983	7,415	7,543	9,896	10,096	12,389	12,567
	No. of diagnostic CTC	317	319	636	648	964	981	1286	1312	1611	1,634
	No. of surveillance COL	0	54	64	250	313	517	702	961	1165	1,503
	No. of surveillance CTC	0	7	8	33	41	67	91	125	151	195
Pathology	No. of adenomas requiring pathology[1]	1,195	1,206	2,454	2,624	3,961	4,162	5,620	5,895	7,384	7,722
	No. of CRC requiring pathology	150	152	288	298	434	446	584	599	738	754
CRC work-up and treatment	No. receiving PET scan	15	15	29	30	43	45	58	60	74	75
	No. receiving MRI scan	54	55	104	107	156	160	210	216	266	271
	No. receiving CT scan(s)	150	152	288	298	434	446	584	599	738	754
	No. receiving TUS	8	8	15	15	22	22	29	30	37	38
	No. receiving pre-operative radiotherapy (+/- chemotherapy)[2]	34	35	64	66	96	98	128	131	161	164
	No. undergoing colon resection	91	92	174	180	264	271	355	364	449	459
	No. undergoing rectal resection	46	47	89	92	135	139	182	187	231	236

			Year of programme									
			1	2	3	4	5	6	7	8	9	10
Screening-related health outcomes												
Harms[3]	No. with major bleeding following endoscopy		10	11	21	22	32	34	44	46	57	59
	No. with perforation following endoscopy		5	5	10	10	15	15	20	21	25	26
	No. of deaths from perforation following endoscopy		0	0	0	1	1	1	1	1	1	1
Adenomas and CRC	No. with adenoma(s)[4]	Total	629	635	1,292	1,381	2,085	2,191	2,958	3,102	3,886	4,064
		low-risk	408	411	835	887	1,340	1,402	1,892	1,979	2,479	2,585
		intermediate/ high-risk	221	224	456	494	745	789	1,065	1,123	1,407	1,479
	No. with CRC[5]	Total	150	152	288	298	434	446	584	599	738	754
		stage I	55	56	112	116	175	181	241	248	310	318
		stage II	51	52	99	102	149	153	201	206	255	260
		stage III	33	34	59	61	84	86	109	112	135	137
		stage IV	10	10	18	19	25	26	32	33	39	40

COL=colonoscopy; CRC=colorectal cancer; CTC=CT colonography; gFOBT=guaiac-based faecal occult blood test; FIT= faecal immunochemical test; FSIG= flexible sigmoidoscopy; US= ultrasound; intermediate/high-risk=adenoma(s) ≥10mm; low-risk=adenoma(s) <10mm;

1 assuming average of 1.9 adenomas per person; includes screen-detected and surveillance-detected adenomas

2 includes radiotherapy given with or without chemotherapy

3 includes complications from diagnostic and surveillance endoscopy, including FSIG where relevant

4 includes individuals with screen-detected and surveillance-detected adenomas

5 includes individuals with CRC detected at screening and at surveillance

Table 6.5(c) Estimated screening-related resource use and health outcomes by year: FIT at 55-74 years, "slow implementation" (option 3)

		Year of programme									
		1	2	3	4	5	6	7	8	9	10
Screening-related resource use											
Screening tests	No. of FIT kits sent out	49,072	48,350	98,105	97,249	147,119	146,947	19,5341	197,600	245,927	247,425
	No. of FIT kits processed	26,008	25,626	51,986	51,533	77,946	77,855	103,479	104,676	130,259	131,052
COL/CTC	No. of diagnostic COL	1,369	1,349	2,748	2,724	4,145	4,140	5,542	5,605	7,029	7,070
	No. of diagnostic CTC	178	175	357	354	539	538	720	729	914	919
	No. of surveillance COL	0	22	25	103	127	217	292	410	498	657
	No. of surveillance CTC	0	3	3	13	16	28	38	53	65	85
Pathology	No. of adenomas requiring pathology[1]	534	526	1,109	1,145	1,794	1,843	2,574	2,669	3,463	3,585
	No. of CRC requiring pathology	59	58	115	114	175	175	240	243	314	317
CRC work-up and treatment	No. receiving PET scan	6	6	11	11	17	18	24	24	31	32
	No. receiving MRI scan	21	21	41	41	63	63	86	88	113	114
	No. receiving CT scan(s)	59	58	115	114	175	175	240	243	314	317
	No. receiving TUS	3	3	6	6	9	9	12	12	16	16
	No. receiving pre-operative radiotherapy (+/- chemotherapy)[2]	13	13	25	25	38	38	52	53	67	68
	No. undergoing colon resection	36	35	70	69	106	107	146	148	191	193
	No. undergoing rectal resection	18	18	36	36	55	55	75	76	98	99

			Year of programme									
			1	2	3	4	5	6	7	8	9	10
Screening-related health outcomes												
Harms[3]	No. with major bleeding following endoscopy		6	6	12	12	18	18	25	25	32	32
	No. with perforation following endoscopy		3	3	5	5	8	8	11	12	14	15
	No. of deaths from perforation following endoscopy		0	0	0	0	0	0	1	1	1	1
Adenomas and CRC	No. with adenoma(s)[4]	Total	281	277	584	602	944	970	1,355	1,405	1,822	1,887
		low-risk	192	189	397	407	636	650	905	935	1,210	1,248
		intermediate/ high-risk	89	88	187	196	309	320	450	470	613	639
	No. with CRC[5]	Total	59	58	115	114	175	175	240	243	314	317
		stage I	22	22	46	46	73	73	102	104	135	137
		stage II	20	20	39	39	60	60	82	84	108	109
		stage III	13	12	23	22	32	32	43	44	55	55
		stage IV	4	4	7	7	9	9	12	12	15	16

COL=colonoscopy; CRC=colorectal cancer; CTC=CT colonography; gFOBT=guaiac-based faecal occult blood test; FIT= faecal immunochemical test; FSIG= flexible sigmoidoscopy; US= ultrasound

intermediate/high-risk=adenoma(s)≥10mm; low-risk=adenoma(s)<10mm;

1 assuming average of 1.9 adenomas per person; includes screen-detected and surveillance-detected adenomas

2 includes radiotherapy given with or without chemotherapy

3 includes complications from diagnostic and surveillance endoscopy, including FSIG where relevant

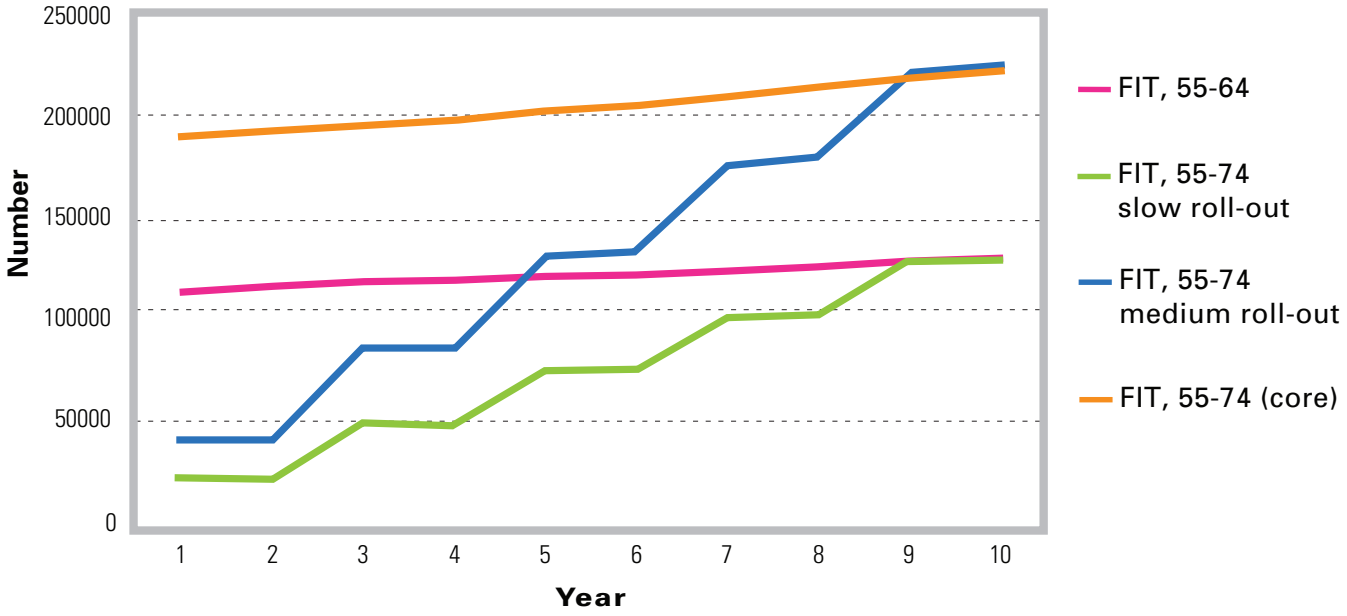
4 includes individuals with screen-detected and surveillance-detected adenomas

5 includes individuals with CRC detected at screening and at surveillance

Figures 6.9 (a)-(d) Estimated screening-related resource requirements and health outcomes for years 1-10, for the FIT core scenario and three alternative implementation options

(a) FIT kits processed/returned (no. of individuals screened)

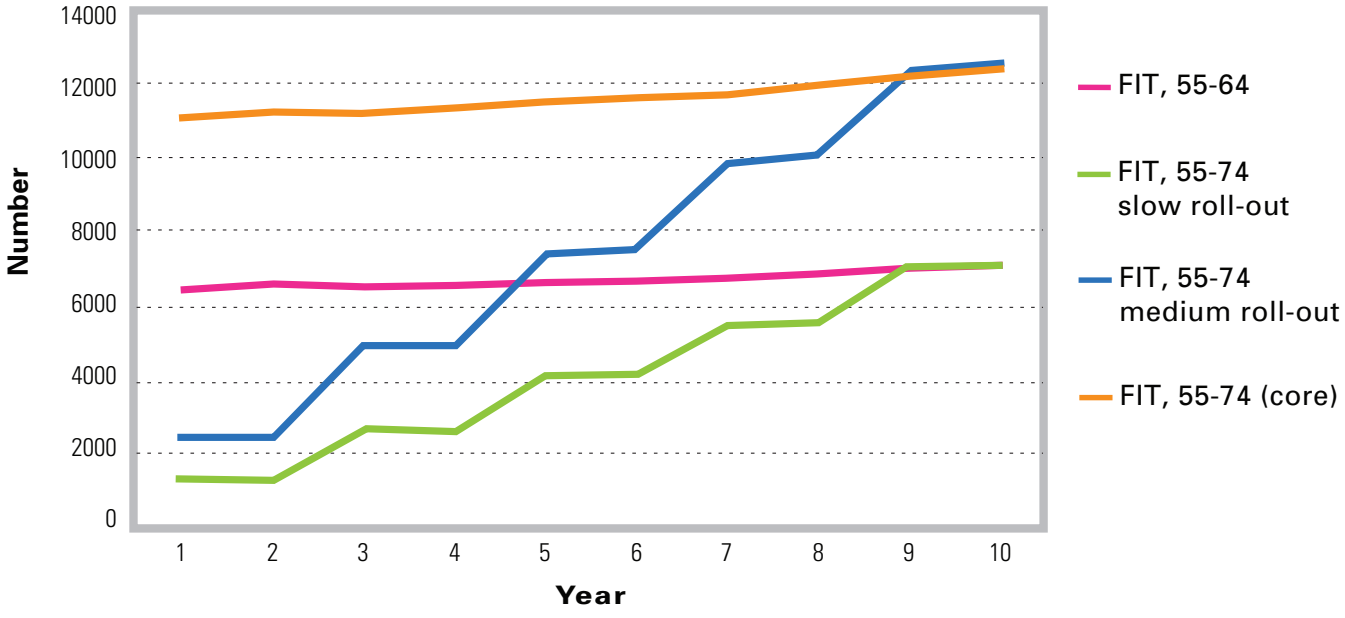
No. of FIT kits processed/returned, by year and scenario: alternative FIT options



**includes diagnostic and surveillance procedures*

(b) Diagnostic and surveillance colonoscopy

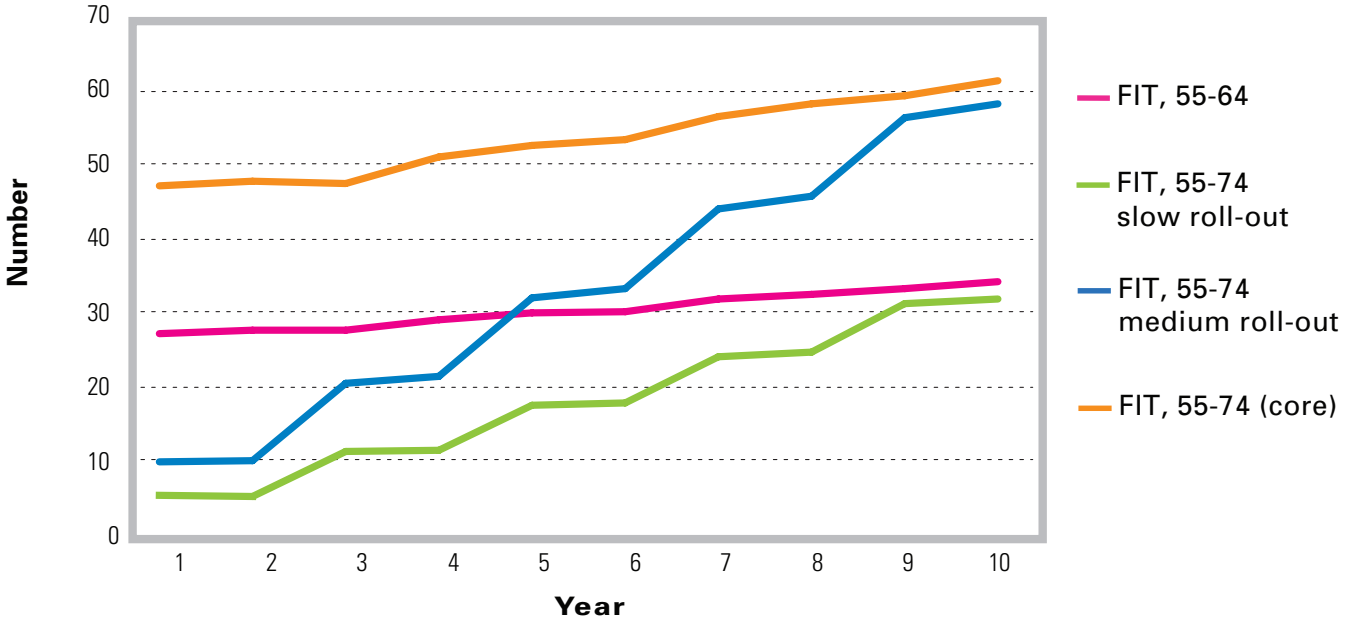
Total no. of individuals undergoing colonoscopy, by year and scenario: alternative FIT options



**includes diagnostic and surveillance procedures*

(c) Complications of screening: bleeding

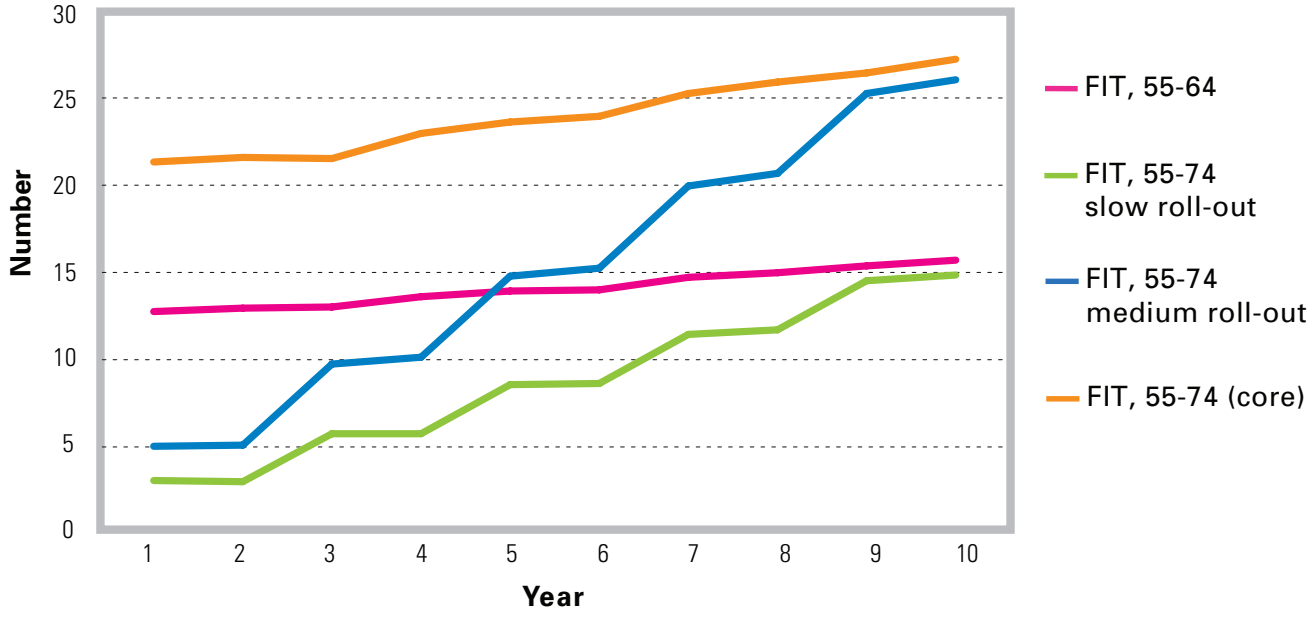
No. of individuals experiencing major bleeding following colonoscopy, by year and scenario: alternative FIT options



*includes diagnostic and surveillance procedures

(d) Complications of screening: perforation

No. of individuals experiencing bowel perforation following colonoscopy, by year and scenario: alternative FIT options

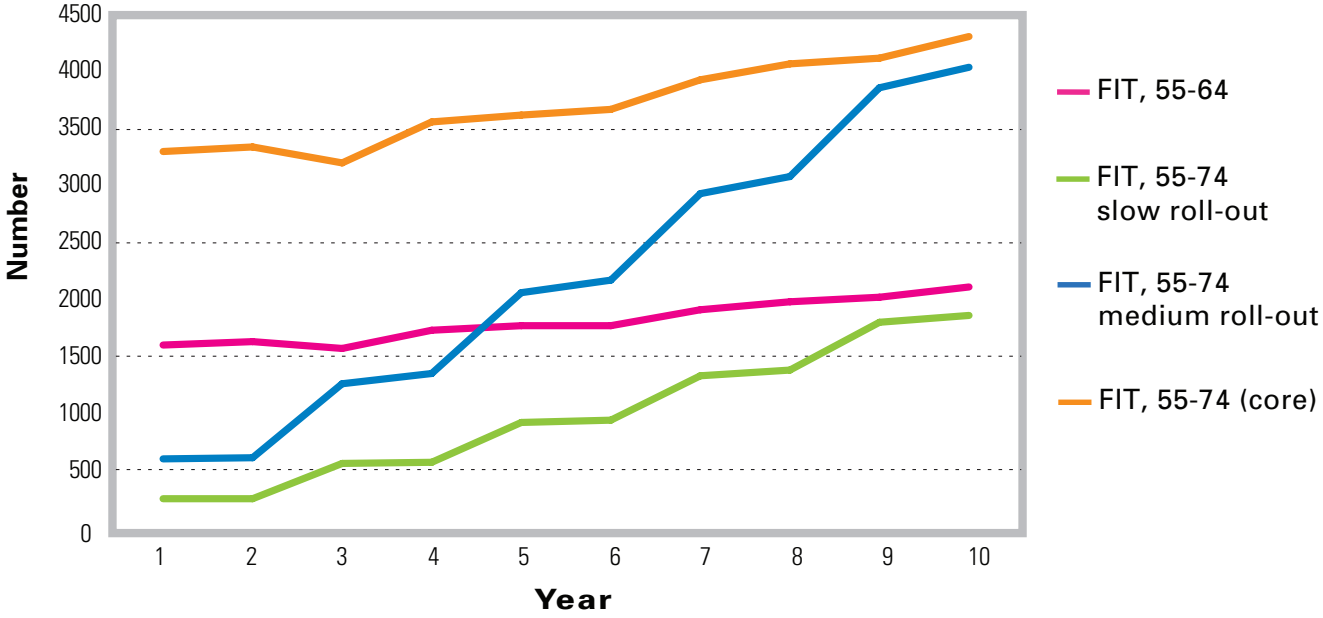


*includes diagnostic and surveillance procedures

Figures 6.9 (e)-(h) Estimated screening-related resource requirements and health outcomes for years 1-10, for the FIT core scenario and three alternative implementation options

(e) Screen and surveillance-detected adenomas

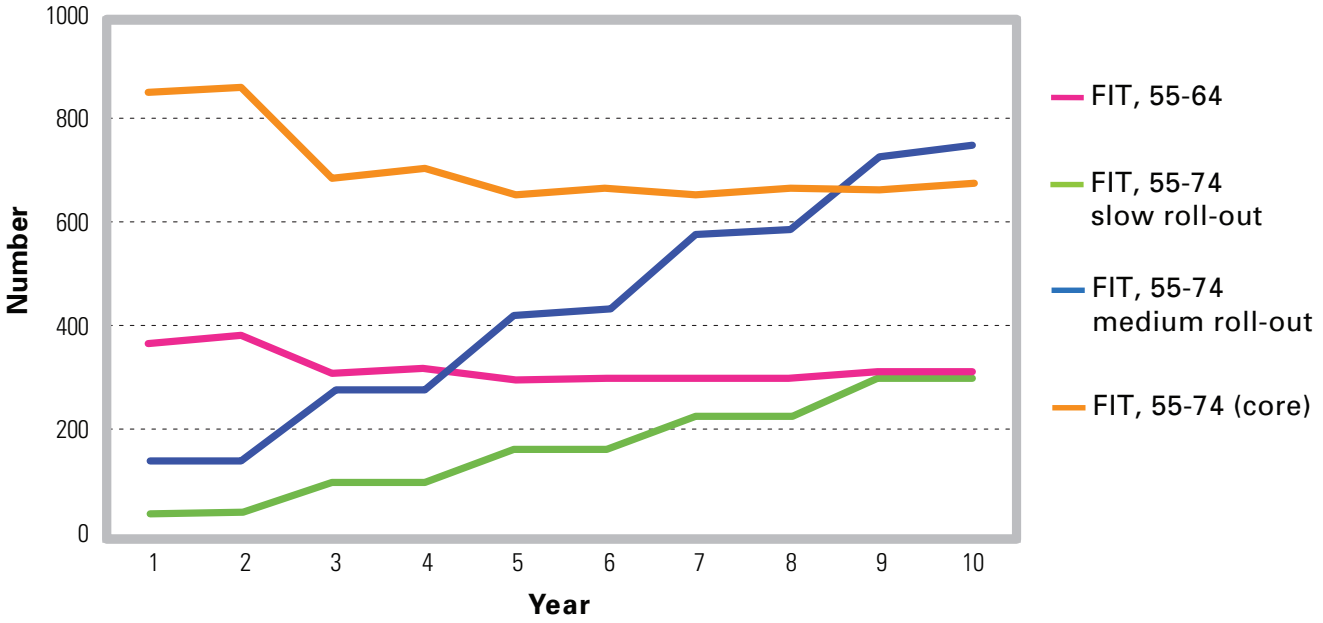
Total no. of individuals with adenoma(s)*, by year and scenario: alternative FIT options



** includes low-risk and intermediate/high risk, from screening or surveillance*

(f) Screen and surveillance-detected cancers

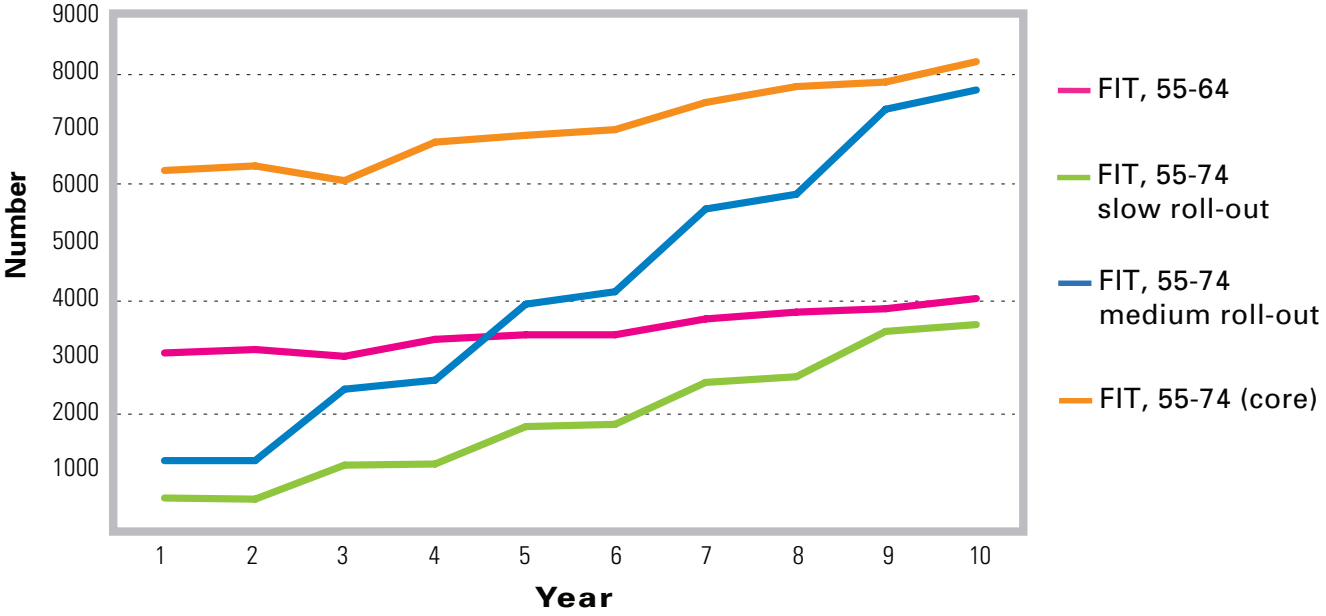
Total no. of screen-detected colorectal cancers*, by year and scenario: alternative FIT options



**includes small number of cancers detected in those undergoing surveillance*

(g) Numbers of adenomas requiring pathology

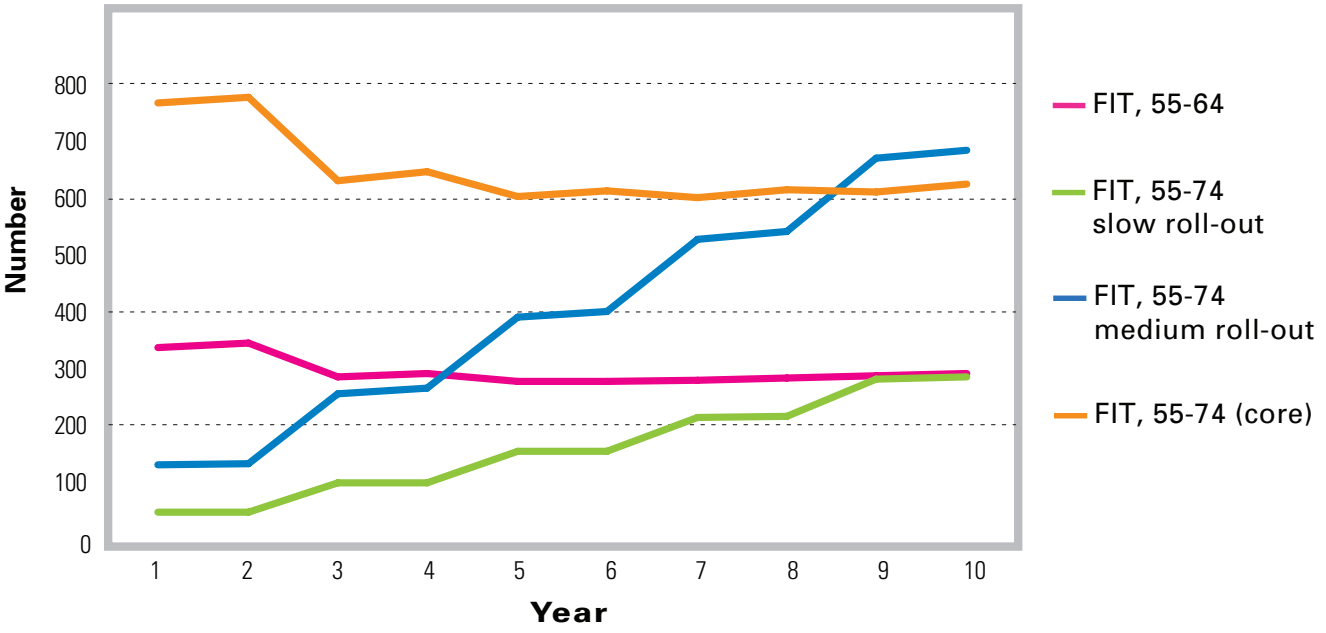
Total no. of adenomas* requiring pathology, by year and scenario: alternative FIT options



** assuming average of 1.9 adenomas detected per person*

(h) Numbers of colon and rectal resections

Total no. of colon and rectal resections required for screen-detected cancers, by year and scenario: alternative FIT options



**includes small number of cancers detected in those undergoing surveillance*

6.9 Synthesis of results

In making a decision about which of the core strategies to invest in (all of which are highly cost-effective), the balance to be struck is between the resource requirements, the complications resulting from diagnostic investigation and surveillance, and the yield of screen-detected adenomas and cancers and resultant potential health gains at the population level compared to a policy of no screening. The analyses in this chapter indicate that while biennial FIT in the 55-74 age group - the optimal scenario from the cost-effectiveness analysis - results in the greatest number of individuals detected with adenomas and cancers, and the greatest potential for reductions in colorectal cancer cases and deaths in the population, this comes at a cost. The costs include the substantially greater requirements for colonoscopy (both diagnostic and surveillance), histopathology, diagnostic radiology, radiotherapy and colorectal surgery with this strategy than with the others. In addition, there would be much higher occurrences of bleeding, bowel perforation and screening-related deaths, following from the greater numbers of individuals undergoing colonoscopy.

The three alternative implementation options for FIT-based screening all designed to be less resource intensive than implementing the core scenario fully in years one and two. If screening was restricted to the younger age group (55-64 years), the resource requirements for the programme would always be lower than those for a programme based on the core scenario. This comes at a cost however; this strategy is not as desirable in terms of cost-effectiveness than screening the full 55-74 age group (as shown in chapter 5). The two options for gradual implementation in the 55-74 age group would allow for capacity to be gradually increased as screening is extended to incorporate individuals of different ages. The disadvantage of all of these implementation options is that fewer individuals would be found with adenomas and cancers over the first 10 years of screening than under full, immediate, implementation across the entire 55-74 age group (the core scenario). This is where the trade-off lies in comparing the various implementation options.

If capacity were available at the time the screening programme starts to meet requirements for colonoscopy, pathology, and so forth, clearly the best strategy would be full and immediate implementation across the entire 55-74 age group; this is because it is highly cost-effective and results in the maximum health gain (as shown in chapter 5). If capacity were not available, but could be built-up over time, then an implementation option which would involve age-based implementation across the 55-74 age group could be considered in order to reduce resource requirements initially. Two such implementation scenarios were presented in this chapter, but other strategies might be designed. The choice of the most appropriate implementation strategy would depend on how much capacity was available in year one and how quickly capacity would be likely to be increased. Once fully implemented and operational (any of) these options would eventually be associated with the same health gains, and cost-effectiveness, as the full and immediate implementation in those aged 55-74. A strategy of this type would, therefore, be more cost-effective in the long-term than limiting screening to the 55-64 age group. These options are therefore an attractive way to allow the programme and health services to plan for the implementation of screening over a number of years.

If, however, capacity were limited at the start of the programme, and unlikely to increase over time, then biennial screening of the 55-64 age group would be an acceptable option. While it is less cost-effective than screening the 55-74 age group, it is still considerably more cost-effective than no screening.

Finally, it should be noted that the calculations of resource requirements and health outcomes used the base-case values of the model parameters. Therefore, as with the cost-effectiveness results, they are subject to uncertainty and should be interpreted as broad indications rather than precise estimates. It should not be assumed that the same factors which influenced the cost-effectiveness estimates will influence the resource estimates. For example, screening uptake did not affect cost-effectiveness to any great extent, but would be a very important determinant of the resources required to deliver a colorectal cancer screening programme in Ireland and the health outcomes achieved by the programme. It would also have a major influence on the health gains that could be achieved at the population-level. Specifically, compared to the health gains attained assuming uptake of FIT-based screening of 53%, lower uptake would reduce the potential numbers of colorectal cancers that could be averted at the population-level by screening, whereas higher uptake would increase the numbers of cases averted in the population.

Chapter 7

Discussion

The aim of this HTA was to conduct an economic evaluation of various options for a population-based colorectal cancer screening programme in Ireland. There are various limitations in this methodology, some inherent to the particular models, others related to the availability and robustness of the data used to populate the models and still others related to the general approach. These limitations, and their likely impact on the findings, are discussed below. A range of other issues pertinent to the interpretation of the findings are also discussed.

7.1 Limitations of the HTA

7.1.1 Natural history of colorectal neoplasia

One of the main limitations of this cost-effectiveness modelling exercise (and all of the others in the literature) relates to the lack of certainty about the natural history of colorectal neoplasia. This problem is exacerbated by the fact that some simplifying assumptions need to be made about the natural history of the disease in order to be able to programme the model. Various assumptions were made. While these can be justified to some extent from the literature, they are by no means certain. For example, it was assumed that there is a linear progression from normal epithelium through low-risk, to intermediate/high-risk adenomas to stage I colorectal cancer, and then linearly through the stages of colorectal cancer to death. Although this seems reasonable, whether it is true or not is not known.

In recognition of the fact that understanding of the natural history of the disease is advancing all the time, the original model developed by ScHARR was revised to incorporate the assumption that a proportion of colorectal cancers arise other than through the adenoma-carcinoma pathway. This seems likely to be true and acknowledges what is now known about hyperplastic and other polyps[42]. The uncertainty lies in the fact that it is not clear what proportion of colorectal cancers develop without a prior adenoma. From a review of the literature and consultation with experts, it was decided to set this value at 14% and the structure of the model meant that it could not be varied. Since the screening tools which were evaluated aim to detect and manage adenomas (rather than other types of polyps), if the proportion of cancers which arise from other pathways is higher, it is likely that the effectiveness of screening was over-estimated; if the proportion of cancers which arise from other pathways is lower, then the effectiveness of screening is likely to have been under-estimated. Had more time been available for this HTA, it would have been possible to have explored the effect of changing this value, in order to quantify the impact that this assumption has on cost-effectiveness.

It is worth bearing in mind that most other modelling studies have assumed that all colorectal cancers developed from adenomas (see chapter 3). The studies which make this simplifying assumption are likely to have over-estimated the cost-

effectiveness of screening by any modality, compared to no screening, in their populations.

A major area of uncertainty relates to the underlying prevalence of adenomatous polyps in the population of Ireland (and, indeed, elsewhere). This is one of the sets of data to which the model is calibrated so it has considerable importance. In previous applications of the model used in this HTA[118, 139], the model was calibrated against the results from several autopsy studies from Europe and the US[204-209]. These studies had several limitations. They were conducted several decades ago and the underlying disease prevalence may have changed over time. In addition, they were small in size and some did not clearly distinguish between adenomatous and other types of polyps[210]. In general they provided little information on the source populations and, in particular, whether the series included individuals who had colorectal cancer or polyps during their lifetime and/or whether individuals who had died from colorectal cancer were included or excluded. The age-specific prevalence estimates from these studies varied substantially and some were as high as 50% in older persons. The effect of calibrating the current version of the model against these studies was explored; this produced estimates of 10% of the population aged 80 and over with undiagnosed colorectal cancer. This seems unlikely and suggests that these older studies over-estimated the underlying prevalence of adenomas in the population.

This HTA was fortunate to be able to take advantage of data from the pilot Bowel Cancer Screening Programmes in Scotland and England[58] to estimate adenoma prevalence in individuals aged 50-69 years. These estimates were much lower than those from the autopsy studies, but they were close to estimates from a recently reported large, well-conducted, autopsy study from the Mayo clinic[(211]; see chapter 5). Although recent autopsy studies also suffer from limitations, chiefly in relation to the fact that the autopsy rate has declined dramatically over time, and hence the characteristics of deaths subject to autopsy are likely to have changed, the decision was taken to calibrate the model against these two sources rather than the older autopsy series. This is likely to have meant that the estimates of cost-effectiveness produced in this HTA are relatively lower than those from similar modelling exercises which calibrated against the older autopsy series. It should be noted that there is no way of knowing whether the estimates of prevalence that were used for model calibration are in any way representative of prevalence among the population of Ireland (and this also holds for other evaluations of cost-effectiveness of colorectal cancer screening).

7.1.2 Costs and cost perspective

This HTA was conducted from the perspective of the health service payer, the HSE/ Department of Health & Children. It is possible that a small proportion of individuals with private medical insurance who have a positive screening test would opt to have diagnostic investigation and necessary treatment or surveillance outwith the HSE. This would slightly reduce the costs incurred by the HSE, and hence improve the cost-effectiveness of screening compared to no screening.

Like most previous studies (see chapter 3), this HTA did not include any costs from the perspective of the individual or society as a whole. Those who participate in screening will have non-medical costs associated with the screening test (particularly

so for flexible sigmoidoscopy), attending for diagnostic investigations and, if found to have intermediate or high-risk adenomas, ongoing surveillance. These costs are likely to include time and travel costs to attend appointments, and lost income from time away from work. There will also be costs associated with cancer diagnosis and these would be incurred both for screen-detected cancers and for cancers found in the absence of screening. There is very limited information internationally on "patient"-related and societal costs of colorectal screening or colorectal cancer diagnosis and treatment[200, 212], and no such data for Ireland. Some of the screening costs would be likely to vary according to the screening test used. This makes it difficult to assess the impact that the "patient"-related costs would have had on the cost-effectiveness of the various screening scenarios. However, exclusion of societal costs, such as lost productivity among those diagnosed with colorectal cancer, would be expected to mean that the comparison of each screening scenario with no screening would be conservative (i.e. cost-effectiveness would be under-estimated).

In some settings, for example the UK, many hospitals now employ nurses and other non-medical professionals to conduct diagnostic and therapeutic endoscopies[213]. This raises the possibility that screening-related endoscopies could be delivered by appropriately trained and supervised nurses, rather than consultant gastroenterologists. This strategy might offer advantages in terms of the time it would take to get appropriate staff in place to deliver a screening programme. It might also be less costly. It was not possible to explore the impact of this on cost-effectiveness of screening in Ireland since information was not available on the costs of flexible sigmoidoscopy or colonoscopy conducted by different types of health professionals.

7.1.3 Budgetary impact and costs not included

It was not the purpose of this HTA to estimate the budgetary impact of establishing a population-based screening programme in Ireland. The responsibility for this lies with the NCSS, the statutory body responsible for the implementation of population-based screening programmes. The NCSS have recently prepared a business plan for the implementation of biennial FIT-based screening which has been submitted to the Minister for Health and Children for consideration[214].

Clearly, there will be many costs associated with operating a screening programme which are not encompassed in the costs of screening and management of colorectal cancers which were included in the model. These are likely to include, for example, costs of programme publicity, quality assurance, monitoring and evaluation, ongoing staff training, information technology support, maintenance and replacement of equipment, and storage of biopsy samples. There are also a range of one-off costs related to programme set-up (including staff recruitment and training, acquisition of office and/or clinic space, and setting-up screening/diagnostic centres including purchasing equipment). By convention economic modelling exercises tend not to incorporate these types of costs, probably because they are too difficult and complex to estimate a priori, especially when different types of screening scenarios are being evaluated. Since they will be dependent on the business model adopted by the NCSS in the set-up and organisation of the screening programme, this HTA did not attempt to estimate or include such costs. However, it is important to acknowledge that these

costs exist and will impact on the cost-effectiveness of the various screening options; some are likely to affect all screening modalities to the same extent while others are likely to impact differentially on one modality rather than another.

There are some other, less major, costs associated with screening which were not included. For example, the screening scenarios modelled assumed that a proportion of those who had a positive screening test would undergo CT colonongraphy. A well known feature of CT colonography is its ability/propensity to detect extra-colonic lesions and other conditions. Such findings are relatively common[215-217]. The detection of other conditions incurs a cost for the health services and, by placing individuals in another health state following screening; they would also impact on HRQoL. Because it is not clear what proportions of individuals undergoing diagnostic CT colonography in Ireland would be likely to be found to have other conditions, and what these conditions would be, the costs of managing these were not included in the costs of screening. A recent study has noted that such costs may be an important consideration in the cost-effectiveness of colorectal cancer screening[218]. Because of the much greater numbers of individuals undergoing CT colonography for screening based on FIT than that based on flexible sigmoidoscopy or gFOBT, this issue would be likely to impact disproportionately on FIT-based screening scenarios.

A variety of non-adenomatous polyps are likely to be detected in a proportion of individuals who undergo screening. Since the prevalence of other types of polyps is unclear, and there is a lack of clarity about whether removing them would impact on colorectal cancer incidence or mortality, costs for the removal or histopathology of these lesions were not included.

In terms of harms of screening, the focus was on major bleeding and perforation at endoscopy. Colonoscopy can also result in cardiovascular complications. Although such events are relatively rare[195], managing them is likely to be costly. Had they been included, the various screening options would have been likely to be slightly more costly and hence less cost-effective. Related to this issue, it is worth bearing in mind that any medico-legal costs that might be associated with serious adverse events were not considered.

7.1.4 HRQoL, QALYs and LYG

At the outset of the HTA, the intention had been that the primary outcome would be QALYs, since these accommodate both morbidity and mortality due to the condition of interest. In conducting the literature review, it became clear that there were major deficiencies in the available data on HRQoL. For that reason it was decided that there would be two main outcomes in this HTA: QALYs gained and LYG.

Although 14 studies have reported on HRQoL in those with colorectal cancer, few contained data in a form suitable for the model (i.e. by stage of colorectal cancer). They tended to measure HRQoL at a single point in time, although it is likely that the valuations which individuals with cancer place on their health state may change over time. For example, it seems plausible that utility values may be particularly low if assessed during chemotherapy but could rise once chemotherapy is completed. The current model incorporates utilities over time and because this data was unavailable, it was necessary to include an average of values that were collected at intervals over a

five year period. In addition, most studies were small so that the utility estimates lacked precision. Moreover, the findings were contradictory. It was reassuring therefore, that when the analysis was repeated based on LYG rather than QALYs gained, the main findings were unchanged. In addition, although varying utility values in the sensitivity analysis had some impact on cost-effectiveness, this was relatively modest and would not have impacted on the overall conclusions.

A further related issue is that the model structure only allowed utility values to be incorporated for cancer and non-cancer health states; this means that all those who did not have cancer detected were assumed to have the same health utility values. This may not be true. It is well established that screening can have an adverse psychosocial impact on individuals[112]. For example, in cervical cancer screening, a substantial proportion of women who have a positive screening test result, but who do not have cancer, suffer from anxiety, depression and cancer-related worries, and these effects can be long lasting (see, for example,[219]). By analogy, it seems likely that a positive colorectal cancer screening test and, in particular, being found to have an adenoma, especially one which requires ongoing surveillance, is likely to have an adverse psychosocial impact on individuals. By extension, this could well negatively impact on their HRQoL valuations. If this were true, it would mean that the benefits of screening will have been over-estimated.

7.1.5 Other limitations

The final limitation of the HTA which should be acknowledged is that some of the available screening tests for colorectal cancer were not evaluated. Colonoscopy, CTC colonography and faecal DNA testing might all be used for population-based screening and the cost-effectiveness of these in other settings has been modelled (for example,[220-225]). While it would be possible to modify the screening component of the current model to include screening scenarios based on these tests, it is worth noting that populating the model would not be a trivial exercise given the volume of literature available on colonoscopy and CT colonography in particular.

7.2 Limitations of the economic and resource models

7.2.1 Natural history model

One limitation of the natural history model related to the fact that the only distinction between categories of adenomas was between low and intermediate/ high-risk adenomas, thus intermediate-risk and high-risk adenomas were not included as separate categories. This meant that it was not possible to allow for different performance characteristics of the screening tests for intermediate and high-risk adenomas, for example. This categorization was made because at the time the model was developed there was a lack of data about this aspect of the natural history of colorectal neoplasia[118]. Nowadays there remains a lack of data on the transition probabilities from low to intermediate and from intermediate to high-risk adenomas.

A further related limitation was that low and intermediate/high-risk adenomas were defined primarily based on size (<10mm, ≥10mm). There are other predictors of the malignant potential of adenomas and of the risk of recurrence[37]. However, this simplifying assumption was necessary so that the natural history and the adenoma surveillance strategy could be modelled.

A further limitation described by Tappenden et al[118] is that most of the transition probabilities estimated within the model are assumed to be constant and this is unlikely to be accurate. However, the absence of direct evidence means that this assumption cannot be verified or modified.

7.2.2 gFOBT with reflex FIT

In the gFOBT scenario modelled two assumptions were made. The first was that the performance characteristics of the gFOBT and reflex FIT tests were independent. In the absence of any information on the true relationship between the tests, and the sensitivity and specificity of the combination of tests in an average-risk screening population, this assumption was necessary. Under the assumption of independence, the combined sensitivity of the gFOBT and reflex FIT test was computed as a multiple of the sensitivities of each test. If the performance characteristics of the tests were not independent, it is likely that the true sensitivity would differ in some way from this estimate. The extent to which the true sensitivity (and specificity) of the combined tests is under or over-estimated in the model is completely unknown as it depends on the performance characteristics of the specific tests used (which are known to be extremely heterogeneous[53, 100]) and the underlying disease prevalence in the population screened.

The sensitivity analysis was conducted to provide some idea of the possible impact on the cost-effectiveness and resource requirement if the tests were not independent. However, this analysis is subject to an important caveat - the data on which is was based was extremely uncertain. The sensitivity and specificity of the combined tests was estimated from data from various sources. Compared to the estimates of the combined sensitivity of gFOBT and FIT used in the base-case analysis, those generated by this process were higher for adenomas, and lower for cancers. If different tests were used in a screening programme in Ireland the combined sensitivity and specificity might be completely different to these. Therefore, the findings of the sensitivity analysis should be viewed as illustrative rather than definitive. They serve to demonstrate the problem associated with the deficiencies in the evidence-base; this is discussed further below.

The second assumption was that all of those who were positive on gFOBT would go on to complete a FIT. In actual fact, probably only those who had a weak/moderate positive test would be invited to do an FIT and only a proportion of those would comply; others would be referred directly for colonoscopy. For example, if the Hemoccult II® test was to be used, it is likely that individuals who had six "positive" cells/specimens would probably be referred to colonoscopy. This assumption was necessary since: (1) the specific gFOBT test that would be used was not specified a priori and definitions of strong/clear and moderate or weak positives might vary by test; (2) the proportions who would have strong/clear positive and weak/moderate positive are hard to estimate reliably. This will have meant that the costs of the gFOBT

scenario are slightly over-estimated, and that the numbers undergoing diagnostic colonoscopy are slightly under-estimated.

7.2.3 Resource model

The resource model was based on an assumption that all existing services were operating to full capacity and would not be able to cope with any additional individuals requiring colonoscopy, CT colonography, and related procedures. Therefore, it was effectively assumed that all resources required would be over and above existing services. This was necessary since there is no national information available on the capacity of existing endoscopy services or those for treatment of colorectal cancer. In reality it is likely that some of the resources required as a result of screening would be available though spare capacity in existing services.

7.3 Availability, robustness and quality of data used to populate models

7.3.1 Strategies to deal with uncertainty in data

There is considerable uncertainty around many of the parameters used in the model. For other parameters no data was available and it was necessary to make assumptions based on limited information from other settings or on clinical opinion. The sensitivity analyses provide some indication of how this uncertainty is likely to have affected the estimates of cost-effectiveness. It was reassuring that in every simulation in the PSA all of the core screening scenarios were well below the historical, notional, cost-effectiveness threshold of €45,000 per QALY. In addition, in the one/multi-way sensitivity analyses, even when set at extreme values (for example, 50% higher than the base-case for costs of screening and diagnostic tests), none of the parameters influenced the costs or the effectiveness of any of the scenarios to such an extent that the ICER threshold was exceeded. However, it should be noted that in all the sensitivity analyses the parameter estimates were permitted to vary between set bounds, and it is possible that the true values in the population may be outwith these limits. Moreover, although PSA is thought to provide a more realistic reflection of uncertainty in parameter estimates than one-way or multi-way sensitivity analyses, the possibility remains that it could be misleading if there were relationships between the parameters which were not taken into account.

7.3.2 Medical cost data

A particular concern was the lack of data on the costs in Ireland of the (1) diagnostic tests among those who have a positive screening test (i.e. colonoscopy and CT colonography) and (2) procedures associated with work-up and treatment of colorectal cancer. This important limitation was also noted in a previous HTA of HPV vaccination published by HIQA[22].

Within the time-frame of the HTA it was not possible to conduct specific micro-costing exercises. It was necessary therefore to rely on cost estimates which were obtained

from a range of sources. Some originated from single hospitals/pharmacies in Ireland, others were derived from DRG costs, and yet others were estimated from studies in other countries. It is not possible to be certain how robust these costs are or the extent to which they reflect the real costs of these procedures across the hospitals in Ireland. Although costs were varied in sensitivity analyses, the same caveat applies as above; that is, it is possible that the true costs may be greater or less than the bounds used in the sensitivity analyses and so some uncertainty must remain in terms of the true cost-effectiveness of colorectal cancer screening in Ireland.

7.3.3 Resource use data

It is fortunate that data on all colorectal cancers diagnosed in Ireland and their treatment was available from the NCRI. This data had some limitations. For example, it did not contain information on specific chemotherapy or radiotherapy regimes, or recurrence. In addition, it related to cases diagnosed a few years ago and some aspects of treatment (particularly the use of biological agents) has changed in recent years. This data was therefore augmented with several small hospital series and clinical opinion. The data, and expert clinicians whose views were sought, generally originated from large specialised centres, where advances in treatment (for example, biological agents) or guideline therapies (for example, radiotherapy before surgery for rectal cancer rather than afterwards) might be more likely to be used than in smaller hospitals. In addition, clinical opinion is probably more likely to reflect recommended or guideline treatment than the actual treatment received by patients.

It is likely that, currently, there is considerable variation in colorectal cancer treatment across the country[226]. However, the moves towards centralisation of cancer treatment under the NCCP would be expected to reduce some of these variations, and to maximise the proportions of patients who are treated in line with best practice. Therefore, the estimates of resource use may be reasonably consistent with what might be expected on a national basis in coming years.

7.3.4 Performance characteristics of the screening and diagnostic tests

Important questions remain about the efficacy and effectiveness of the screening tools which were evaluated in this HTA. Only gFOBT has been thoroughly evaluated in RCTs; comparably robust data on efficacy are lacking for flexible sigmoidoscopy and FIT.

Because gFOBT has been implemented in several population-based screening programmes or pilot programmes, this meant that there was much more "real world" information available for gFOBT than for FIT or FSIG which could be used to inform the parameter estimates. Despite this, there remains a lack of certainty about the true performance characteristics of gFOBT. The results of the available studies are very heterogeneous[53]. In addition, there are several different gFOBTs available (described in[53]) and some of the newer tests appear to have better performance characteristics than the older tests, particularly increased sensitivity[50]. However, because of a lack of data from high-quality studies of appropriate design on the sensitivity and specificity of the newer tests, it was necessary to base the parameter estimates on studies which used the older tests (Hemoccult® and Hemoccult® II). Therefore, the potential cost-

effectiveness of screening using gFOBT may have been under-estimated. A one-way sensitivity analysis was conducted to investigate the effect of using a gFOBT with higher sensitivity (with reflex FIT) and this suggested that if a more sensitive gFOBT were to be used, the cost-effectiveness of a programme based on gFOBT may be a good as that for a programme based on FIT. This is an important finding. However, the values used in the sensitivity analysis were based on a single study, test specificity was not adjusted in the analysis and the resource requirements associated with primary screening using a more sensitive gFOBT as compared to an FIT were not estimated; the latter issue would need careful consideration in any decision-making process.

Although there is also a wide range of immunochemical tests available (reviewed in[50]), the volume of evidence on these is much more limited than for gFOBT. The evidence also suffers from the same over-riding concern as that for gFOBT; the findings of the studies on sensitivity and specificity are heterogeneous[53] and the true performance characteristics are unclear. In addition, the HTA was conducted without guidance as to what specific immunochemical test would be likely to be used in a screening programme in Ireland, so it was necessary to synthesize information from a range of tests, used in a variety of settings (all of them outside Ireland), to come up with overall parameter estimates. A particular issue for quantitative immunochemical tests is what cut-off level would be used to define a positive test result and the fact that sensitivity and specificity depend on the cut-off used. It is likely that different cut-offs would be appropriate depending on whether the test was used for primary screening or reflex testing (i.e. after a gFOBT). Unfortunately, due to a lack of suitable high-quality data it was not possible to comprehensively assess cost-effectiveness at different cut-offs. A single sensitivity analysis which assumed higher test sensitivity (i.e. a lower cut-off) was run, but this is subject to the same caveats as the sensitivity analysis for gFOBT. Finally, it is worth noting that there is also a lack of data on the performance characteristics - and, indeed, efficacy and effectiveness - of repeated FIT testing (i.e. after several screening rounds).

The lack of certainty about the true sensitivity and specificity of flexible sigmoidoscopy was also a major concern. There have, unsurprisingly, been few studies, since these would require individuals to undergo flexible sigmoidoscopy and then another colonic investigation (the gold standard). Usually colonoscopy is taken as the gold standard, but since this may also miss lesions, it is possible that the performance characteristics of flexible sigmoidoscopy are over-estimated. In turn, this would entail the effectiveness of flexible sigmoidoscopy screening being over-estimated.

The scenario which was evaluated was once-only flexible sigmoidoscopy. Although this has been suggested as an appropriate, and potentially effective, strategy[104], there is actually very limited evidence to support it. In the USA, screening with flexible sigmoidoscopy has been recommended on a 5-yearly basis, although some suggest that a 10-yearly interval would be adequate after a confident examination of the splenic flexure[54]. In addition, the US Preventive Services Task Force advocate screening by a combination of flexible sigmoidoscopy and faecal tests[7]. It would be possible to modify the current model to evaluate one or more of these alternative flexible sigmoidoscopy-based screening scenarios for Ireland.

It is also worth noting that the evidence-base on the performance characteristics of the diagnostic tests is limited. There are relatively few relevant studies and none were conducted in Ireland. Therefore, questions must remain about the true sensitivity and specificity of colonoscopy and CT colonography.

7.4 Harms of screening

Screening based on biennial FIT was associated with a greater frequency of harms than screening based on either gFOBT or FSIG. This higher frequency of complications with FIT-based screening is because the performance characteristics of the test result in much greater numbers of individuals undergoing diagnostic (or surveillance) colonoscopy that under the other two screening scenarios. Colonoscopy is an invasive procedure and carries an inherent risk of complications. This risk is well recognised and is one of the reasons that some do not consider colonoscopy to be a suitable primary screening test for colorectal cancer[227]. However, it is generally held to be the most appropriate diagnostic test in those who require further investigation following screening by another modality. The absolute risk to an individual of sustaining a complication at colonoscopy is low. For example, in the first three rounds of the quality-assured pilot screening programme in Scotland, in which 7417 individuals underwent diagnostic colonoscopy, complications were rare and there were no deaths resulting from screening-related colonoscopy[102]. The literature review on complications of colonoscopy (Appendix 5) focussed on data from very large clinical series and population-based screening programmes, and used base-case estimates for the risk of perforation of 0.216% for colonoscopy with polypectomy and 0.107% for colonoscopy without polypectomy. The probability of death in those who had a perforation was 5.195%. Translating these figures to the screening population in Ireland, this corresponded to 21 perforations in the 11,095 individuals undergoing colonoscopy in year one of a programme based on FIT in the 55-74 age group (1 per 528 colonoscopies) and one death (1 per 11,095 colonoscopies). One of the issues in any screening programme is balancing the risks to the individual against the benefits that can be achieved for the population; colorectal cancer screening is no different in this regard.

7.5 Discounting

There are two important issues with regard to discounting in this HTA. The first issue relates to what the appropriate discount level is and whether costs and benefits should be discounted at the same rate in cost-effectiveness analyses; this is a matter of some debate[228-230]. In the base-case analysis, costs and benefits were discounted at 4%, which is a slightly higher rate than the convention in England and Wales at the National Institute for Health and Clinical Excellence (NICE). The sensitivity analysis indicated that the discount rate was the parameter which had the greatest influence on cost-effectiveness. However, it was reassuring that even when costs and benefits were undiscounted, or were discounted at 6%, all three core screening scenarios remained highly cost-effective compared to no screening.

A second issue relates to how discounting operates with regard to the different screening options. Flexible sigmoidoscopy (one test at age 55 or 60) represents a one-off cost, whereas the costs of gFOBT and FIT (biennial tests between ages 55-74)

are recurring and are spread over a period of 10-20 years. Therefore the discounted cost of gFOBT and FIT are relatively lower than the discounted cost of flexible sigmoidoscopy, compared to the undiscounted costs of these screening tests. Thus the discounted analyses "favour" the gFOBT or FIT screening options over flexible sigmoidoscopy in that these options would appear more cost-effective when compared to no screening than would flexible sigmoidoscopy at age 60.

7.6 Screening participation

The level of participation is likely to be a key issue in any colorectal cancer screening programme in Ireland. Participation is a key determinant of both effectiveness and cost-effectiveness of screening; while lower compliance may reduce effectiveness it will also reduce costs associated with the programme. It was noteworthy that in the sensitivity analyses, the participation rate had little impact on estimates of cost-effectiveness, but the parameter was only allowed to vary between 32% and 59% for gFOBT and FIT and between 24% and 67% for flexible sigmoidoscopy.

Achieving high uptake is likely to be challenging. In the base-case analysis uptake was set at 53% for programmes based on faecal tests, which is likely to be reasonably ambitious given the range of uptakes achieved in various population-based programmes and pilots (described in Appendix 5). In addition, particular sub-groups of the population may be less likely to accept an offer of screening. Uptake has been found to be lower in younger individuals, those of lower socio-economic status and in particular ethnic groups[179, 231, 232]. If this were to be the case in Ireland, the uptake in other groups of the population would have to be higher than the base-case value to compensate for lower participation in some subgroups.

Once screening progresses beyond the first round the issue of retention becomes important (i.e. the ability of the programme to retain participation amongst those who were screened in earlier rounds). In the gFOBT pilot programmes in both England and Scotland, uptake fell between the first and later rounds and was lower in those who were invited for the first time in later rounds than in the first round[102, 179]. In England this was ascribed, in part, to less extensive and wide-ranging publicity strategies in the second than the first screening round[179]. In the cost-effectiveness modelling for gFOBT and FIT, it was assumed that uptake was maintained at the same level in each round. If uptake were to fall in later rounds in Ireland, the costs of screening would decrease as would effectiveness, but the overall impact on the ICERs for gFOBT and FIT is not clear. It is worth noting that there is currently a lack of evidence on strategies that might be effective for the retention of individuals in colorectal cancer screening programmes.

Some preliminary data are starting to accrue regarding potential uptake of colorectal cancer screening in Ireland. In a survey of 465 out-patients attending gastroenterology clinics at Beaumont Hospital, 77% indicated that they would be willing to undergo colorectal cancer screening[233]. In pilot work in Dublin, 473 male construction workers aged over 50 were offered a 3-day, home use, gFOBT, during April 2006 and March 2008; 221 returned a completed test kit, giving a response rate of 47% (Cillin Condon, personal communication). In another pilot study, 3,500 patients aged 50 and older from general practices in south Dublin were offered FIT screening from June 2008 onwards; by the start of December 2008, 32%

(n=1,111) had completed a test kit, and 11% had declined (Cillin Condon, personal communication). Of those who had completed the FIT, 11.3% (n=126) had at least one test with a haemoglobin level of >100ng/ml.

7.7 Post-colonoscopy surveillance

One of the significant enhancements which was made to the ScHARR model concerned refining the part of the model which dealt with post-colonoscopy surveillance in those who had had adenomas removed. This now allows for different surveillance strategies for those with low, intermediate and high-risk adenomas. This refinement is particularly valuable since this aspect of screening has important implications for the health services and there is a lack of other models which consider it in any detail. There appears to be only one other surveillance model, which was published while this HTA was being conducted[234]. This model assumed gFOBT-based screening and contained a series of simplifying assumptions, meaning that the follow-up strategy did not reflect current recommendations[153] as closely as the model used in this HTA.

Evidence is accumulating[235, 236] that the surveillance schedule proposed by Atkin and Saunders[153] for individuals who have had adenomas removed may be unnecessarily intensive. The current US consensus recommendations suggest that those with ≥3 adenomas, high-grade dysplasia or villous features should have three-yearly colonoscopy, while those with other categories of adenomas can be followed-up in 5-10 years[237]. While less frequent surveillance would be less costly, it may also be less effective hence the impact of any change in post-polypectomy surveillance on the screening scenarios is not immediately clear. The availability of the enhancement to the ScHARR model means that the impact of different surveillance strategies on cost-effectiveness and resource requirements of screening could be modelled.

7.8 Research recommendations

The process of conducting this HTA and reviewing the literature on the natural history of colorectal neoplasia, colorectal screening, and management of colorectal cancer has suggested several areas where further research would be valuable. Some key research questions are listed below. While several of these relate specifically to Ireland, others are more widely applicable.

- What proportions of colorectal cancers arise through the adenoma-carcinoma pathway, through the hyperplasic polyp/sessile polyp pathway, and without a prior history of polyps?
- What is the true population prevalence of adenomatous polyps by age and sex? Similarly, what is the prevalence of other types of polyps in these same groups?
- What role do gFOBT, FIT and flexible sigmoidoscopy have in the detection and management of hyperplastic polyps and what impact, if any, would this have on the incidence and mortality from colorectal cancer in the population?

- How are colorectal cancers in Ireland managed at the moment? What proportions of patients receive each type of diagnostic test and treatment? What variations in management are there? Which resources, and what quantity of these, are used?
- What are the current local and distant recurrence rates for colon and rectal cancers, and how do these vary by stage?
- What follow-up strategies are used for colorectal cancer in Ireland? How does this vary across the country? What investigations do survivors receive and when? What is the level of attendance?
- What are the true direct medical costs of different types of treatment for colorectal cancer - and removal and surveillance of adenomas – in Ireland?
- What are the "patient"-related and societal costs of screening, undergoing follow-up and surveillance for adenomas and colorectal cancer diagnosis and treatment in Ireland?
- What are the utility valuations for various health states associated with colorectal cancer screening, in the population of Ireland and elsewhere (including having a positive screening test result, low-risk, intermediate-risk and high-risk adenomas, and colorectal cancer)? How does HRQoL vary over time for individuals in these health states?
- What strategies might be used to maximise retention to screening after the first round (for screening tests which are not one-off)?
- How might uptake be maximised in groups most likely to decline to take part (for example, younger individuals, low socio-economic status, etc)?

Chapter 8

Conclusions

Summary of key conclusions

- A population-based screening programme for colorectal cancer in Ireland - based on biennial FIT at ages 55-74, FISG once only at age 60, or biennial gFOBT with reflex FIT at ages 55-74 - would be highly cost-effective compared to a policy of no screening.
- Of the options evaluated, biennial FIT at ages 55-74 would be associated with greatest health gain (QALYs) compared to no screening. This strategy would also produce the greatest reductions in lifetime colorectal cancer incidence and mortality rates compared to no screening. Furthermore, it would result in a higher percentage of screen-detected cancers. Biennial FIT at ages 55-74 is therefore considered to be the optimal screening strategy.
- In the first 10 years of a screening programme, the requirements for diagnostic, treatment and follow-up surveillance services would be much greater for a programme based on biennial FIT at ages 55-74 than for a programme based on gFOBT or FSIG. However, screening by FIT at ages 55-74 would detect more adenomas and cancers. In addition, compared to a policy of no screening, it would result in more colorectal cancer cases and deaths averted in the population than the other options evaluated, and these gains would be expected to be seen within 10 years of programme implementation.

- All three core scenarios considered - biennial gFOBT at ages 55-74 (with reflex immunochemical testing), biennial FIT at ages 55-74, and FSIG once at age 60 - were highly cost-effective compared to no screening. Compared to no screening, in the base-case analysis, FSIG once at age 60 had the lowest ICER (€589 per QALY gained), followed by FIT at 55-74 years (€1,696), and by gFOBT at 55-74 years (€4,428). These are all well below the historical, notional, cost-effectiveness threshold of €45,000 per QALY.
- When the analysis was repeated using LYG as the outcome, because of concerns about the quality and applicability of the available data on HRQoL, the results were slightly more conservative (i.e. the ICERs were slightly higher), but all three scenarios remained highly cost-effective compared to a policy of no screening.

- In comparing the three core scenarios with one another, gFOBT at age 55-74 was dominated (i.e. it was more costly and less effective than a combination of the other two strategies). FIT at age 55-74 was associated with a much greater health gain compared to no screening than FSIG at age 60. However, as well as being more effective than FSIG at age 60, FIT at age 55-74 was more costly. Any decision to adopt FIT in preference to FSIG would therefore depend on what decision-makers were willing to pay for the additional health gain. The ICER associated with investing in FIT as compared to FSIG was €2,058 per QALY gained, which would be considered highly cost-effective. Therefore, in the base-case analysis the optimal strategy was FIT at age 55-74.

- The results were slightly sensitive to a range of factors including the discount rate, costs of the screening tests, the cost of managing colorectal cancer, utility values, and, for gFOBT and FIT, the sensitivity of the test. However, even when these parameters were set at their most extreme values, all three core scenarios remained cost-effective compared to no screening; in some instances, they became cost-saving compared to no screening. It was noteworthy that if one of the newer, more sensitive, gFOBT tests were to be used, instead of one of the older, less sensitive, tests, this could make this screening option more cost-effective compared to no screening. It was reassuring that some of the parameters which were subject to most uncertainty (for example, screening uptake) had almost no impact on cost-effectiveness. When probabilistic sensitivity analyses, which are thought to better reflect the true uncertainty in the parameter estimates, were run the conclusions from the base-case analysis were unchanged.

- When age-related variations in the core scenarios were considered, the three most cost-effective scenarios, compared to no screening, were biennial FIT at age 55-74, biennial FIT at age 55-64 and FSIG at age 60. All other scenarios were dominated. In comparing these three options with one another, the optimal strategy was FIT at age 55-74 (ICER of €3,221 per QALY gained compared to FIT at ages 55-64) followed by FIT at age 55-64 (ICER of €1,436 per QALY gained compared to FSIG at age 60). This was mainly based on the fact that FIT in the 55-74 age group resulted in a greater health gain than FIT in the 55-64 age group. This relative ranking of the strategies was robust to uncertainty in the parameter estimates and the results were unchanged after probabilistic sensitivity analyses. When the results were combined in the form of cost-effectiveness acceptability curves, these indicated that if decision-makers were willing-to-pay a maximum of around €1,000 per additional QALY, the most cost-effective strategy would be FSIG once at age 60 (but the health gain would be less than for FIT-based strategies). At a willingness-to-pay threshold of between approximately €1,000 and €3,000 per additional QALY, biennial FIT in the 55-64 age group would be likely to be the most cost-effective screening option. If decision-makers were willing to pay €4,000 per additional QALY or more, the preferred option would be biennial FIT in the full age range, 55-74 years.

- As well as depending on decision-makers' willingness-to-pay, any decision as regards which screening test to invest in depends on resource considerations. Resource requirements - in terms of diagnostic colonoscopy and CT colonography, histopathology for screen-detected adenomas and cancers, and

work-up and initial treatment of screen-detected cancers - in the first 10 years of a screening programme were estimated. In general, these would be much greater for a screening programme based on biennial FIT for 55-74 years, than for one based on biennial gFOBT for age 55-74 or once-only FSIG at age 60. This is an inevitable function of the higher pick-up rate of adenomas and cancers with FIT than with the other two screening tests.

- In year one of a programme based on gFOBT or FIT in those aged 55-74 years, assuming uptake of 53%, approximately 189,600 individuals would be screened. With a programme based on FSIG once at age 60, assuming uptake of 39%, approximately 18,600 individuals would undergo screening. Because of demographic changes (i.e. increase in the population of screening age), assuming uptake remains constant, between years one and 10 the number screened by FIT or gFOBT would increase by 16-17% and by FSIG would increase by 11%.
- Endoscopy requirements would be a major consideration for any screening programme. In the first 10 years of a programme, FSIG once at age 60 would require capacity to undertake 18,600-21,600 flexible sigmoidoscopies and between 380 and 1,050 colonoscopies annually for diagnostic or surveillance purposes. For the other two core scenarios, there would be no requirements for flexible sigmoidoscopy, but greater capacity would be needed within the screening programme for colonoscopies. For gFOBT at ages 55-74, capacity would be required for 1,000-1,400 diagnostic and surveillance colonoscopies each year. For FIT at ages 55-74, capacity would be required for 11,000-15,000 colonoscopies each year.
- Although the absolute numbers of procedures would be much smaller, similar patterns to those seen for colonoscopy would be evident in requirements for CT colonography for diagnostic and surveillance purposes.
- A consequence of the greater numbers of colonoscopies with FIT than the other core scenarios is that this scenario would lead to greater numbers of individuals suffering adverse consequences of screening (major bleeding, bowel perforation and death from perforation). This was evident in both the analysis of cost-effectiveness and that of resource requirements. A particular concern was the risk of deaths from perforation under a policy of biennial FIT at ages 55-74. In the first 10 years of a programme it was estimated that, on average, one individual would die as a result of a bowel perforation sustained at colonoscopy each year.
- The resources required in a screening programme for histopathology, radiology (PET scans, CT scans, MRI), neo-adjuvant radiotherapy and colorectal surgery are a function of the numbers of individuals with screen-detected adenomas and cancers. The yield of disease would be much higher for biennial FIT in the 55-74 age group than for the other two core options, therefore the resources required to manage these would be much greater. For example, with FIT at age 55-74, 6,300-8,200 adenomas would require pathological analysis each year, compared to 1,500-2,100 adenomas with FSIG at age 60 and 700-1,000 with gFOBT at ages 55-74. Resources would be required to conduct 780 colorectal resections in those with screen-detected cancers in year one under FIT screening, compared to fewer than 300 under gFOBT screening and approximately 60 with FSIG.

- Because FIT is more effective than the other two core screening scenarios, it would be expected to bring about a greater reduction in colorectal cancer incidence and mortality at the population-level than the other two screening options. With FIT screening in the 55-74 age group, a reduction in the total number of colorectal cancers in Ireland would be expected from year six onwards, with approximately 160 cases averted in year 10. A reduction in mortality would be expected from year two onwards, with approximately 270 deaths from colorectal cancer avoided in the population in year 10.

- Since screening has the potential to reduce the number of colorectal cases diagnosed in the population, this means that it could also reduce requirements for (at least some of the) resources associated with work-up and treatment nationally. These potential reductions would be greatest for screening based on biennial FIT at ages 55-74 years.

- Sensitivity analyses showed that the resource requirements and health outcomes would be heavily influenced by screening uptake. For example, if uptake of FIT-based screening was less than 53% (the base-case estimate), requirements for colonoscopies and pathology would fall. However, the number of screen-detected cancers would also decrease. If uptake was higher (e.g. 70%), numbers of screen-detected cancers would rise, but this would be at a cost of increases in the capacity required by the screening programme for diagnostic and surveillance colonoscopy, pathology, and cancer work-up and treatment.

- If capacity were available, the optimal screening option would be full and immediate implementation of biennial FIT-based screening in the 55-74 age group, as it is cost-effective, and provides the maximum health gain. If capacity is likely to be problematic (for example, to deliver diagnostic colonoscopies), there would be various options for reducing the initial resource requirements associated with implementing biennial FIT-based screening. Rather than screening the full age group immediately in the first two years of the programme, different implementation options could be considered such as restricting screening to the 55-64 age group or gradually rolling-out screening across the 55-74 age group. The advantage of the staggered implementation options is that they would allow for capacity to be built-up gradually over the initial years of the programme. The details of implementation (in terms of how many years it would take to encompass the entire 55-74 age group in the programme) could be designed to match the speed at which capacity would be planned to be available. In considering the different options, if capacity were not available initially, a gradual implementation of screening in the 55-74 age group would be preferable to immediate implementation in the 55-64 age group. This is because the cost-effectiveness results indicate that, in future years, when a programme based on the 55-74 age group is fully operational it would result in a greater overall health gain than a programme limited to the 55-64 age group. If, however, there was no possibility that capacity could be built-up over the initial years of the programme, then screening in the 55-64 age group would be an acceptable, and cost-effective, option compared to no screening.

- It is worth noting that if screening based on FIT was considered unfeasible due to resource requirements then a screening programme based on biennial gFOBT, with reflex FIT, in the 55-74 age group or FSIG once at age 60, would also be considered highly cost-effective compared to a policy of no screening.

- Societal costs (for example, lost productivity among those diagnosed with cancer) were not included in this evaluation. This means that the cost-effectiveness results are likely to be conservative. In terms of the analysis of resource use and health outcomes, it should be borne in mind that these were run at the base-case values of the parameter estimates. The actual resources required by a population-based screening programme in Ireland, and health outcomes that would be achieved by the programme and in the population, will be highly dependent on a range of factors, including compliance with diagnostic investigations, the performance characteristics of the specific screening test implemented and, especially, uptake of screening.

- Findings of this type of economic analysis are dependent on the quality of the data on which the model is based. There were important limitations in the evidence-base and these need to be acknowledged. The evidence relating to the performance characteristics of the screening and diagnostic tests was of particular concern; the available data was weak and all of it was drawn from settings outside Ireland. This necessitated that various assumptions be made in the analysis as regards the values of particular parameters. In addition, there were considerable uncertainties around the cost estimates. It was reassuring, therefore, that the extensive sensitivity analyses which were conducted did not alter the cost-effectiveness findings.

- In conclusion, the success of a population-based colorectal cancer screening programme will, ultimately, depend both on uptake among the population invited to be screened and on the capacity to diagnose, treat and follow-up those found to have adenomas and cancers. The cost-effectiveness analysis demonstrated that biennial FIT at ages 55–74 was the optimal screening strategy, resulting in the greatest health gain over the lifetime of those invited for screening. In addition, this strategy would result in the greatest yield of screen-detected adenomas and cancers. Furthermore, it would have the greatest potential to save lives, averting the largest number of colorectal cancer cases and deaths (compared to no screening) in the population. However, the decision to select a particular screening strategy should also depend on resource considerations, and these are considerably greater for FIT at ages 55-74 than for the other core scenarios. Moreover, there is potential for more individuals to suffer screening-related complications although the absolute risk to an individual is low. These are the key issues which need to be weighed against one another in deciding the most appropriate strategy for population-based screening for colorectal cancer in an average-risk population in Ireland.

Appendix 1:

WHO criteria for establishing a screening programme[1]

Disease	Is the disease an important public health problem?
	Is the natural history understood?
	Is there an identifiable latent or early symptomatic stage of disease?
Screening test	Is the test effective?
	Is the test safe and acceptable to the population?
Diagnosis and treatment	Is there a strategy for determining who should and should not be treated?
	Is there effective treatment for localised/early stage disease? (i.e. does treatment in the early stages have a favourable impact on prognosis?)
	Are the diagnostic test and the treatment safe and acceptable to the population?
Organisation and cost	Are facilities for diagnosis and treatment available?
	Is the psychological impact on participants not too high?
	Is the economic cost of screening (to participants and the health services) acceptable?

1 Based on Wilson and Junger, 1968[3]

Appendix 2

Colorectal cancer screening trials

Table APP2.1 summarises the results from the four RCTs of gFOBT. Table APP2.2 summarises the baseline findings from the large, ongoing, trials of flexible sigmoidoscopy.

Table APP2.1 RCTs of gFOBT in colorectal cancer screening (adapted from Hewitson et al, 2007 (65))

Area and time period	Trial population	Screening	Results			References
		Protocol, test, uptake and follow-up	Test +ve rate	Stage distribution of CRC cases (screening vs control)	CRC morality reduction[1] (screening vs control)	
USA, Minnesota; 1975-82 and 1986-92	Volunteers, aged 50-80 years recruited from American Cancer Society, veterans and employee groups; randomised to no screening (n=15,394) or annual (n=15,570) or biennial (n=15,587) screening; individuals with CRC, IBD or familial polyposis, were ineligible	Annual or biennial Hemmoccult® - 83% were rehydrated At least one screen: 75% of those on annual screening and 78% on biennial screening Follow-up: 18 years	Unrehydrated: 1.4%-5.3% Rehydrated: 3.9%-15.4%	Annual screening: A: 30% vs 22% B: 29% vs 31% C: 23% vs 21% D: 9% vs 17%	Annual: 33% Biennial: 21%	Mandel et al, 1993, Mandel et al, 1999, Mandel et al, 2000[61, 238, 239]
Sweden, Göteborg; population-based trial; screening commenced 1982	Individuals aged 60-64 resident in Göteborg; randomised to screening (n=34,144) or control (n=34,164)	Two screening cycles, with the second 16-24 months after the first (mean 20 months) Hemoccult II®- most were rehydrated 1st screen uptake: 63% Follow-up: 15.5 years	Unrehydrated: 1.9% Rehydrated: 1.7%-14.3%	A: 26% vs 9% B: 28% vs 34% C: 32% vs 21% D: 14% vs 25%	16% (RR=0.84, 95% CI 0.67-0.99)	Kewenter et al, 1994, Kewenter and Brevinge, 1996[62, 240]
England, Nottingham; population-based trial; commenced 1985	Individuals aged 45-74, identified from GP records; ineligible individuals excluded by GPs; those remaining were randomised to offer of screening sent by post (n=75,253) or not (n=76,384); those who accepted offer (n=44,838) were invited to be screened	Biennial Hemoccult® - unrehydrated 1st screen uptake: 53% Follow-up: 11.7 years	1st screen: 2.1% 2nd screen: 1.2%	A: 20% vs 11% B: 32% vs 33% C: 24% vs 31% D: 22% vs 21%	13% (RR=0.87, 95% CI 0.78-0.97)	Hardcastle et al, 1996, Robinson et al, 1999, Scholefield et al, 2002[63, 241, 242]
Denmark, Funen; population-based trial; screening commenced 1985	Individuals aged 45-75 identified from population register; those with known precursor lesions and other cancers were excluded before randomisation; remainder randomised to screening (n=30,967) or control (n=30,966); postal invitations sent to eligible individuals randomised to gFOBT	Biennial Hemoccult II® - unrehydrated 1st screen uptake: 67% Follow-up: 17 years	0.8%-3.8%	A: 22% vs 11% B: 34% vs 37% C: 19% vs 23% D: 20% vs 24%	16%	Jorgensen et al, 2002, Kronborg et al, 1996, Kronborg et al, 2004[64, 243, 244]

1 from longest reported follow-up

Table APP2.2 Baseline findings from large RCTs of flexible sigmoidoscopy

Setting, centres and recruitment period	Subjects	Screening test(s)/ comparison	Screening process	Numbers invited and screened	Uptake (%)	Positive screen – definition and %	Colonoscopy (%)	Yield-adenomas (%)	Yield-cancer (%)	Reference
UK; 14 centres; 1996-99	Individuals aged 55-64 registered with general practices within catchment areas of hospital-based endoscopy centres	Once-only FSIG vs. no screening	Ineligible individuals were removed from lists (SIG or COL in previous 3 years, history of CRC, adenomas or IBD); eligible individuals were sent a questionnaire; those who indicated that they were likely to attend for FSIG were randomised	194,726 of 354,262 approached responded positively about FSIG (55%); 170,432 were randomised; 40,674 of 57,254 assigned to FSIG attended	39% of those approached; 71% of those randomised to FSIG	Biopsy at FSIG or referral for COL or surgery; 28%	5%	12%	0.34%	UK Flexible Sigmoid-oscopy Screening Trial Investigators, 2002 [116]
Italy -SCORE; 6 centres in Northern Italy; 1995-99	Individuals aged 55-64 randomly sampled from GP lists or population registers	Once-only FSIG vs. no screening	Individuals mailed a questionnaire to assess interest in FSIG; responders who were positive about FSIG but with history of CRC, polyps, IBD, or who had had endoscopy in previous 2 years were excluded; remaining individuals were randomised	56,532 of 236,568 approached responded (24%); 43,010 were positive about FSIG (76%); 34,292 were randomised; 9,999 of 17,148 assigned to FSIG attended	11% of those approached; 58% of those allocated to FSIG	Biopsy at FSIG or referral for COL or surgery; 18%	8%	11%	0.54%	Segnan et al, 2002 [115]

Setting, centres and recruitment period	Subjects	Screening test(s)/ comparison	Screening process	Numbers invited and screened	Uptake (%)	Positive screen – definition and %	Colonoscopy (%)	Yield-adenomas (%)	Yield-cancer (%)	Reference
Italy - SCORE2; 5 centres in Northern Italy; 1999-2001	Individuals aged 55-64 randomly sampled from GP lists or population registers	Five arms: (1) biennial FIT by mail; (2) biennial FIT by practitioner; (3) patient-choice of biennial FIT or once-only FSIG; (4) once-only FSIG; (5) FSIG followed by biennial FIT starting 2 years after FSIG	Ineligible individuals excluded (previous CRC, polyps, IBD); eligible individuals randomised	1,026 screened of 3,650 randomised to once-only FSIG; 3,049 screened of 10,867 randomised to FSIG+FIT	FSIG: 28% FSIG+FIT: 28%	NR	NR	FSIG or FSIG+FIT: 12% FIT (arms 1+2): 2%	FSIG or FSIG+FIT: 0.35% FIT (arms 1+2): 0.34%	Segnan et al, 2005[88]
Italy - SCORE3; 6 centres in Northern Italy; 2002-04	Individuals aged 55-64 sampled from GP lists or population registers	Three arms: (1) once-only FSIG (2) biennial FIT; (3) once-only COL	Ineligible individuals excluded (IBD, previous CRC or polyps, endoscopy or gFOBT in previous 2 years); eligible individuals randomised	1,944 screened of 6,018 randomised to FSIG	FSIG: 32% FIT: 32% COL:27%	NR	FSIG: 7%	FSIG: 11% FIT: 2% COL: 18%	FSIG: 0.62% FIT: 0.10% COL: 0.81%	Segnan et al, 2007[89]

Setting, centres and recruitment period	Subjects	Screening test(s)/ comparison	Screening process	Numbers invited and screened	Uptake (%)	Positive screen – definition and %	Colonoscopy (%)	Yield-adenomas (%)	Yield-cancer (%)	Reference
Norway – NORCCAP; Oslo/ Telemark; 1995-99	Individuals aged 50-64 selected at random from population registers	Once-only FSIG vs. once-only FSIG+ concurrent FIT	Ineligible individuals excluded (previous colorectal surgery, ongoing cytotoxic or radiotherapy); those eligible were randomised	13,288 of 20,003 were eligible; 6,694 screened in FSIG arm; 6,266 screened in FSIG+FIT arm	FSIG only: 67% FSIG+FIT: 63%	Any polyp ≥10mm or any biopsy-verified neoplasia, irrespective of size on FSIG: 20.4%	20%	FSIG: 17% FSIG+FIT: 17%	FSIG: 0.31% FSIG +FIT:0.31%	Bretthauer et al, 2002, Gondal et al, 2003[90, 169]
Netherlands	Representative sample of individuals aged 50-74	Three arms: (1) FSIG; (2) gFOBT; (3) FIT	Individuals with history of CRC, IBD or major health problems were excluded	1,278 screened of 3,993 invited	32%	NR	NR	gFOBT: 0.6%[1] FIT: 1.6%[1] FSIG: 6.3%[1]	gFOBT: 0.3% FIT: 0.4% FSIG: 1.0%	Hol et al, 2008, Hol et al, 2008[85, 86] [2]
USA- PLCO; 10 centres; 1993-2001	Individuals aged 55-74 identified from public, commercial or screening centre-specific mailing lists	Once-only FSIG vs. no-FSIG	Postal invitation to participate in trial, then randomisation; those with history of prostate, lung, ovarian or colorectal cancer, or lower GI procedure, excluded	64,658 of 77,465 randomised to FSIG	84%	Polyp or mass at screen: 23%	16%	7%	0.29%	Weissfeld et al, 2005[117]

COL=colonoscopy; CRC=colorectal cancer; FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; gFOBT=guaiac-based faecal occult blood test; GI=gastrointestinal; IBD=inflammatory bowel disease; NR=not reported; SIG=sigmoidoscopy

1 yield of advanced adenomas

2 study reported only in abstract form

Appendix 3

Economic modelling studies of colorectal cancer screening

The studies identified by the search strategy and included in the review are summarised in table APP3.1

APP3.1 Modelling the natural history of colorectal neoplasia

A variety of different approaches to modelling the natural history of colorectal neoplasia have been adopted. Tappenden et al modelled the natural history of colorectal cancer as a series of transitions between mutually exclusive health states (low and high-risk polyps, Dukes' A, B, C, and D, colorectal cancer mortality and other-cause mortality)[118, 139]. Separate health states were also assigned to both distal and proximal cancers. Due to a lack of robust evidence on which to base this aspect of the model, no cancers were assumed to arise de novo. A modified version of this model was used in the current HTA.

Whynes et al used a semi-Markov modelling approach in their cost-effectiveness analysis of gFOBT-based screening[128]. They drew on the experience of Wagner et al[142] and also on data from the Nottingham gFOBT screening trial[63]. The mathematical model of the screening process encompassed pre-symptomatic cancers or adenomas which in the absence of screening would have become clinically detected, slowly-developing adenomas or carcinomas that would not have been detected under no screening within the subject's lifetime, adenomas without the possibility of cancerous progression, and no abnormality. The authors also allowed for cancers arising from outwith the adenoma-carcinoma sequence.

Sonnenberg et al employed a simple Markov model to assess the cost-effectiveness of a number of screening alternatives for a hypothetical cohort of 100,000 50 year-old Americans[148]. In this model individuals moved from one health state to another or stayed in their current state over a one year window. The five possible true Markov states were non-compliance with screening, status after sigmoidoscopy, status after colonoscopy, status after polypectomy and colorectal cancer. Intermediate states for screening procedures were included for FSIG, gFOBT and colonoscopy. Individuals could develop colorectal cancer from any of the other true Markov states.

As part of their evaluation of the UK colorectal cancer screening pilot, Alexander and Weller used a simple Markov process to model colorectal cancer and the cost-effectiveness of gFOBT screening[58]. This model used data from the screening pilot itself and the work of Frazier and colleagues[130]. The Markov model incorporated eight different states reflecting both the underlying natural history and also the individual's place within the screening service.

Berchi et al, in their cost-effectiveness analysis of FIT versus gFOBT, developed a six-state Markov process to model the disease natural history allowing for progression from normal to adenomas <1cm, adenomas ≥1cm, Dukes' A, B, C, D, distant spread and death[140]. Lejeune et al presented a five-state model with the same states as

Berchi et al, with the exception of distant spread[140, 134]. Similarly, O'Leary et al used a Markov process to model the impact of community-based flexible sigmoidoscopy with faecal occult blood testing and colonoscopy in a cohort of average-risk Australians aged 55-64[143]. States permitting for transitions from normal to adenomas <1cm, to adenomas ≥1cm to Dukes' A, B, C, D and to death were specified. Progression directly from the normal state and from the small adenoma state to colorectal cancer was allowed.

Wong et al presented a semi-Markov process model with progression from normal epithelium to polyps to Dukes' A-B and to Dukes' C-D for a cohort in Singapore[136]. Health states were dependent on screening strategy, test outcome and the presence of complications.

Wu at al described a Markov model for simulating the progression of colorectal disease in the general population 50 to 75 years of age in Taiwan[137]. This model involved nine health states consisting of normal, small adenoma (adenoma <1 cm), large adenoma (adenoma ≥1 cm), preclinical early colorectal cancer (preclinical Dukes' stage A and B), preclinical late colorectal cancer (preclinical Dukes' stage C and D), clinical early colorectal cancer, clinical late colorectal cancer, colorectal cancer death, and other cause of death. Non-adenomatous colorectal cancer was not modelled and while multi-state transitions in one cycle (albeit unlikely) were allowed, direct progression from small adenoma to clinical colorectal cancer were not.

Parekh et al, in a theoretical cohort of 100,000 Americans, examined the cost-effectiveness of a number of stool-based screening modalities and colonoscopy using a seven-state Markov process[141]. These states covered were: normal; small (<1cm) adenomatous polyp; large adenomatous polyp; localised colorectal cancer; regionalised colorectal cancer; distant colorectal cancer; and death. Provision was made for 15% of colorectal cancers to occur without a precursor adenomatous polyp.

In a recent study, Zauber et al employed two different microsimulation models from the Cancer Intervention and Surveillance Modelling Network (MISCAN and SimCRC) to provide an update for the US Preventive Services Task Force[144]. The model structure specified five main groups of states: normal, adenomatous, preclinical and clinical cancer states, and death from colorectal cancer. Unlike most other studies, the adenomatous state was divided into adenomas of ≤ 5mm, 6-9mm, and ≥10mm. The preclinical and clinical states were divided by stage.

In a recent HTA of CT colonography, Ho et al used a Markov model with the following states: alive with no adenoma or a hyperplastic polyp (no malignant potential); alive with a missed small adenoma; alive with a missed large adenoma; alive after removal of a small adenoma; alive after removal of a large adenoma; alive with a missed cancer; alive with a cancer found through screening; alive after surviving cancer and dead[150]. Cancers were assumed to develop through the adenoma-carcinoma sequence.

APP3.2 Outcomes assessed

APP3.2.1 Primary outcome measures and comparators

The majority of studies undertook cost-effectiveness assessments and evaluated health benefits in terms of life years gained/saved. Several studies performed cost-utility analysis. Whynes et al, Alexander & Weller, Ho et al, and Tappenden et al performed their cost-utility analyses with QALYs, while Stone et al and Woo et al used disability adjusted life years (DALYs)[58, 128, 135, 139, 149, 150]. In some cases cost-utility analysis was done alongside the analyses using LYG-based outcome measures[135, 139, 150].

In most studies, the comparator for both the cost-effectiveness and cost-utility analyses was "no screening". Several studies also compared the screening options to each other and in the case of Whynes et al and Woo et al the screening scenarios were compared with screening modalities for other cancers[128, 149].

Costs included in the vast majority of analyses were limited to direct medical costs. Some studies, however, went beyond this. Norum et al incorporated lost productivity and other non-medical costs[127]. Lejeune et al included direct costs relating to programme organisation[134]. Time and travel costs for patients were included in the work conducted by Woo and colleagues[149]. Ho et al incorporated the costs of time and travel for patients and carers relating to screening procedures[150]. The cost perspectives employed by the included studies were largely a function of geography and health service provision/organisation. The US studies predominantly took the perspective of third-party payers while those studies from outside the US adopted a health-services perspective. The exception was Woo et al whose study adopted a societal cost perspective[149].

APP3.2.2 Other outcome measures

A number of other ancillary outcome measures appeared in the literature. Cured cancers were used as an outcome by Tsuji et al, while Stone et al considered life years lost, Parekh et al looked at colorectal cancer cases per 100,000, by stage, and Ho et al considered the number of cancers diagnosed and deaths from cancer[135, 141, 145, 150].

Table APP3.1 Summary of design and results of economic modelling studies of colorectal cancer

Reference	Setting	Screening modalities assessed	Modelling approach	Outcomes assessed and comparison	Discount rate	Costs included	Results
England et al, 1989[123]	USA	13 combinations DCBE, gFOBT, SIG and COL	Mathematical model	Life-years saved	NR	Direct medical costs	Most cost effective strategy is gFOBT with DCBE if test positive, followed by COL if necessary.
Eddy et al, 1987[124]	USA	gFOBT, DCBE and colonoscopy	Nine-state Markov process model; cohort aged 50 years	Life-years saved	C: 5% O: 5%	Direct medical costs	$15,000 per life-year saved for annual gFOBT
Tsuji et al, 1991[145]	Japan	FIT, 1-day collection FIT, 2-day collection combined with various work-up methods for test +ve DCBE + SIG DCBE DCBE + COL COL	Simulation model; cohort start age 40; followed until age 79	Cured cancer cases (survive 5 years); life-years saved; each FIT vs. no screening	C: 5% O: 5%	Direct medical costs; payer's perspective (govt, national health insurance; patient)	2-day FIT was more cost-effective. Combination of this with colonoscopy for work-up was most cost-effective strategy.
Wagner et al, 1991[142]	USA	annual gFOBT annual gFOBT + SIG on entry to Medicare annual gFOBT + SIG 3-yearly annual gFOBT + SIG 5 yearly	Markov model (OTA model); cohort start age 65; followed-up until 85	Life-years gained; each strategy vs. no screening	C: 5% O: 5%	Direct medical costs	Annual gFOBT would cost $35,000 per life-year saved. Addition of SIG prevents more cancers but at greater cost.

Reference	Setting	Screening modalities assessed	Modelling approach	Outcomes assessed and comparison	Discount rate	Costs included	Results
Shimbo et al, 1994[146]	Japan	Seven strategies based on combinations of FIT, gFOBT and sigmoidoscopy	Markov model; cohort start age 40; followed until 75	Life-years saved	C: 5%	Direct medical costs	Strategies including FIT were most cost-effective. Cost per life-year saved was $13,100. If compliance <100%, starting screening older than 40 years dominates younger start.
Salkeld et al, 1996[125]	Australia	Annual gFOBT	Model based on Minnesota RCT; cohort aged 50-80	Life-years saved; comparator no screening	NR	Direct health care costs	Cost per life-year saved $24,660, which is comparable to other screening programmes. Results sensitive to costs of colonoscopy and false positive rate.
Gyrd-Hansen, 1998[126]	Denmark	gFOBT (unrehydrated Hemoccult II®) 60 different options of combinations of screening interval (yearly, 18 months, 2 years), and age group (within 50-74 years)	Statistical model developed by Day and Walter, 1984 [245]	Life years gained vs. no screening	C: 5% O: 5%	Direct health services costs incurred by screening in excess of costs of null option of no screening	Six efficient programmes identified - biennial 65-74; biennial 60-74; biennial 55-74; every 18 months 55-74; annual 55-74; annual 50-74.

Reference	Setting	Screening modalities assessed	Modelling approach	Outcomes assessed and comparison	Discount rate	Costs included	Results
Norum, 1998[127]	Norway	Once-only gFOBT + FSIG, aged 60	Mathematical model	Life-years gained; screening vs no screening	C: 5% O: 5%	Direct medical costs; plus non-healthcare costs (lost productivity); health care system perspective	Screening costs £2,889 per life-year saved, which is within usual limits for what is considered cost-effective.
Whynes et al, 1998[128]	UK	gFOBT as per Nottingham trial (biennial Hemoccult®)[63]	Semi-Markov model; screening population aged 50-74 years	QALYs; compared with breast screening programme	C: 6% O: 6%	NHS perspective (costs incurred by NHS; benefits accrue to patients)	Similar cost-effectiveness to breast screening in short term; CRC screening superior in longer term. Results insensitive to assumptions about compliance. Screening of females is more cost-effective than screening of males.
Bolin et al, 1999[129]	Australia	gFOBT (annual and triennial) FSIG (3 and 5 yearly) DCBE COL(one-off at 50, 5 and 10 yearly) gFOBT + other tests	Markov (Office of Technology Assessment) model; cohort age 50, followed until 85	Life-years saved	NR	Direct health care costs of screening, diagnostic work-up, treatment and follow-up	Annual and triennial gFOBT, DCBE 3 and 5-yearly, and colonoscopy 5 and 10 yearly are all cost-effective. Less value in FSIG alone or gFOBT + FSIG.

Reference	Setting	Screening modalities assessed	Modelling approach	Outcomes assessed and comparison	Discount rate	Costs included	Results
Frazier et al, 2000[130]	USA	SIG DCBE COL Unrehydrated gFOBT Rehydrated gFOBT applied at age 55 annually every 5 years every 10 years plus combinations of strategies	Markov model; cohort age 50, followed-up until 85	Life-years gained; screening vs. no screening	C: 3% O: 3%	Direct medical costs; third party payer	Analysis done by ethnic group and sex. White men was group in whom least cost-effective. Most effective strategy for white men was annual rehydrated gFOBT plus SIG every 5 years from 50-85. Cost-effectiveness compares favourably with other cancer screening strategies.
Helm et al, 2000([131]	USA	Annual and biennial gFOBT	Deterministic model; projected RCT results to population 45-75 years in USA	Life-years saved	C: 3%	Costs of test, physicians and treatment of colorectal cancer	Cost $2,500 per life-year saved, well below threshold for cost-effectiveness. Remains cost-effective if specimens are rehydrated.
Khandker et al, 2000[132]	USA	Annual gFOBT FSIG 3-yearly FSIG 5-yearly Annual gFOBT + FSIG 3-yearly Annual gFOBT +FSIG 5-yearly DCBE 5-yearly COL 5-yearly COL 10-yearly	Dynamic state transition model; cohort age 50; followed for 35 years	Life-years saved; each modality vs. no screening	C: 3% O: 3%	Outpatient direct health care costs	All interventions, with exception of 5-yearly colonoscopy, had cost-effectiveness ratio <$19,000. Compares favourably with other cancer screening strategies. FSIG every 5 years and annual gFOBT were cost-effective under a broad range of assumptions.

Reference	Setting	Screening modalities assessed	Modelling approach	Outcomes assessed and comparison	Discount rate	Costs included	Results
Loeve et al, 2000[151]	USA	SIG every 5 years	MISCAN-COLON simulation model (NCI/Netherlands model); models costs and savings in simulated dynamic population	Costs and savings over years after screening introduced	C: 3% O: 3%	Direct medical costs; third party payer perspective	5-yearly SIG could be cost-saving. Break-even point is 35-44 years after screening starts. Assumptions are key determinants of effectiveness.
Sonnenberg et al, 2000[148]	USA	Annual gFOBT FSIG 5-yearly FSIG 10-yearly COL 10-yearly	Markov model; cohort start age 50; followed until death	Life-years saved; comparison of strategies	C: 3% O: 3%	Direct medical costs; third-party payer perspective	FSIG least cost-effective strategy. Annual gFOBT costs less than colonoscopy, but saves fewer life-years. gFOBT sensitive to assumptions about compliance and dominated by colonoscopy if less than perfect uptake.
Vijan et al, 2001[133]	USA	FSIG COL at age 60 COL at age 55 COL at 55 and 65 COL at 50 and 60 gFOBT FSIG and gFOBT	Markov model; cohort age 50	Life years gained; each modality vs no screening	C: 3% O: 3%	Direct medical costs incurred by third-party payer	Cost-effectiveness ratio of all screening strategies vs none is <$20,000 per life year gained. One-off colonoscopy at age 60 almost cost neutral; and one off colonoscopy at 65 is cost saving. FSIG and gFOBT dominated by colonoscopy.

Reference	Setting	Screening modalities assessed	Modelling approach	Outcomes assessed and comparison	Discount rate	Costs included	Results
Alexander and Weller, 2003[58]	UK	Screening using the pilot study protocol (i.e. biennial gFOBT for ages 50-74)	Markov model; 50 and 60 year-old cohorts considered	QALYs; versus no screening	NR	Direct medical costs	ICER for screening vs no screening was £2,650 per QALY gained. Screening the 60-74 age group would be less cost-effective than screening from age 50 (ICER vs no screening was in the range £6,000-£8,000 per QALY gained.)
Flanagan et al, 2003[138]	Canada	Annual gFOBT (Hemoccult II®, nonrehydrated) 50-74 years Biennial gFOBT 50-74 years	POHEM - microsimulation tool, which dynamically simulates ageing of population cohort	Life-years saved	C: 5% O: 5%	Direct costs of screening and treatment of colorectal cancer	Biennial screening cost-effective relative to commonly accepted thresholds for health interventions. Effectiveness depends greatly on reaching participation rate of 67%.
Berchi et al, 2004[140]	France	Biennial gFOBT (Hemoccult®) 50-74 years FIT (Magstream), 50-74 years	Markov model; screening performed 5-74 years; cohort followed for 20 years	Life-years saved; Magstream vs Hemoccult®	C: 3%	Direct costs for health care provider	Tests had similar effectiveness, though Hemoccult® less costly. At 20 years, ICER was €2,980 per life-year saved (FIT costs €59 more per target person and gives mean increase in life expectancy of 1 week). Added costs mainly due to increased colonoscopies due to higher test positivity rate. ICER increased as participation rate increased; extra costs due to increased participation were not compensated for by gains in effectiveness.

Reference	Setting	Screening modalities assessed	Modelling approach	Outcomes assessed and comparison	Discount rate	Costs included	Results
Lejeune et al, 2004[134]	France	Biennial gFOBT (Hemoccult II®) 50-74 years Biennial gFOBT with variations in start age (50, 55, 60, 65) and end age (54, 59, 64, 69, 74)	Markov model, described in Lejeune et al (2003); screening population 50-74 years; followed for 20 years or until 85	Life-years gained in screening group versus control group	C: 3% O: 3%	Direct costs of programme organisation, invitations, tests, analysis, polypectomy, treatment of colorectal cancer.	ICER after 20 years for 5-74 years was €3,357 per LYG, which is below commonly accepted threshold of $20,000 per QALY gained. ICERs for 50-74 and 55-74 very similar; ICERs for 60-74 and 65-74 higher. Lowest ICER 55-64, but small LYG. Colonoscopy costs, screening uptake, and specificity of test had major impact on results.
O'Leary et al, 2004[143]	Australia	Annual gFOBT (rehydrated Hemoccult®) Biennial gFOBT FSIG 10-yearly COL 10-yearly	Markov model; cohort age 55-64	Life-years saved; comparator no screening; requirements for colonoscopy.	C: 5% O:5%	Direct medical costs from health service perspective.	FSIG and colonoscopy were both more cost-effective than gFOBT. FSIG was most cost-effective. Colonoscopy requirements similar for 10-yearly colonoscopy and annual gFOBT.
Stone et al, 2004[135]	Australia	Biennial gFOBT, 55-69 years Extensions to include younger (45-54) and older (70+) age groups	Modelling of various extensions to a base-programme in "steady-state" operation	Disability adjusted life years; years of life lost; national programme vs. status quo (small local programmes offered on ad hoc basis by volunteer organisations)	C: 3% O: 3%	Health care utilisation costs	ICER for base-programme is $17,000/DALY gained (gross) or $12,000/DALY gained (net). Extension of programme to older individuals (70-74 years, or 70+) would have avoided significantly more DALYs than addition of younger age groups.

Reference	Setting	Screening modalities assessed	Modelling approach	Outcomes assessed and comparison	Discount rate	Costs included	Results
Tappenden et al, 2004, Tappenden et al, 2007[118, 139]	England	Biennial gFOBT 50-69 years Biennial gFOBT 60-69 years One-off FSIG at 55 One-off FSIG at 60 One-off FSIG at 60, followed by biennial gFOBT 61-70 years	State transition/ Markov model; natural history cohort begins at age 30	Expected costs, life-years gained (LYG), quality adjusted life years gained (QALYs) for each screening option vs no screening	C: 3.5% O: 3.5%	Direct medical costs	Screening using FSIG or gFOBT, or both, has cost-effectiveness profile which is better than many interventions funded by NHS. One-off FSIG is more effective and less expensive that a policy of no screening. Lifetime costs of gFOBT are higher than FSIG, but biennial gFOBT screening may produce health gains at acceptable cost.
Wong et al, 2004[136]	Singapore	gFOBT FIT FSIG COL DCBE	Semi-Markov	Cost per year of life-expectancy saved versus no screening	NR	Direct medical costs	Any screening strategy would increase life expectancy of population aged 50-70 years. gFOBT is most cost-effective strategy.
Wu et al, 2006[137]	Taiwan	F-DNA testing 3-yearly Annual gFOBT FSIG 5-yearly COL 10-yearly	Markov model	Cost per LYG of all options compared with no screening	C: 3% O: 3%	Direct medical costs	All strategies are reasonably cost-effective compared to no screening. Annual gFOBT and ten-year colonoscopy the most cost-effective.

Reference	Setting	Screening modalities assessed	Modelling approach	Outcomes assessed and comparison	Discount rate	Costs included	Results
Chen et al, 2007[147]	Taiwan	FIT at various cut-offs ranging from 30 to 200 ng/mL	Markov model; screening starting at age 50	Cost per LYG for each cut-off compared to no screening	C: 5% O: 5%	Societal perspective; direct medical costs and lost production	Regardless of cut-off, FIT was less costly and more effective than no screening. Average LY decreased with increasing cut-off of FIT. The lowest ICER was at a cut-off of 100ng/mL.
Woo et al, 2007[149]	Hong Kong	Annual gFOBT 50-74 years Biennial gFOBT 50-74 years SIG 3-yearly, 50-74 SIG 5-yearly, 50-74 Annual gFOBT plus SIG 5-yearly, 50-74 COL every 5, 7, or 10 years, 50-74 Limited to women only	Decision analysis	DALYs vs no screening	C: 3% O: 3%	Societal perspective; costs of screening, direct medical costs of managing screen positives; cancer treatment costs; patient time and travel costs included for screening and managing screen positives.	COL every 7 years most effective in terms of DALYs averted, but at cost of deaths and perforations. In terms of cost-effectiveness, COL every 10 years ranked highest (and higher than breast or cervical screening).
Ho et al, 2008[150]	Canada	Annual gFOBT COL CTC	Markov Model	Costs, QALYs, LYG, number of cancers, number of cancer deaths, and cost per QALY	C: 5% O: 5%	Health service perspective including patient/ caregiver time and travel costs	In base case, CTC was dominated and gFOBT excluded by extended dominance. COL delivered a cost per QALY gained of $7,937. When resources were considered gFOBT was the most feasible

Reference	Setting	Screening modalities assessed	Modelling approach	Outcomes assessed and comparison	Discount rate	Costs included	Results
Parekh et al, 2008[141]	USA	Annual gFOBT 50-80 years Annual FIT 50-80 years F-DNA 3-yearly, 50-80 years COL 10-yearly, 50-80 years	Markov model	CRC cases by stage in a cohort of 100,000; deaths; and average LY and costs per person for each scenario versus no screening	C: 3% O: 3%	Direct medical costs	In base case, gFOBT and FIT produced gain in life- years per person, and cost less, than no screening. With excellent adherence FIT dominated 10-year colonoscopies
Zauber et al, 2008[144]	USA	COL 10-yearly Annual gFOBT (Hemoccult II®), 50-75 years Annual gFOBT (Hemoccult® SENSA®), 50-75 years Annual FIT 50-75 FSIG 5-yearly, 50-75 FSIG 5-yearly, with gFOBT 3-yearly, 50-75	MISCAN and Sim CRC microsimulation models	Number of life-years gained compared with no screening; number of colonoscopies and non-colonoscopy tests required.	N/A	N/A	Assuming equally high adherence, four strategies provided similar LYG: COL every 10 years, annual gFOBT (Hemoccult® SENSA®), annual FIT, and FSIG every 5 years with midinterval gFOBT. Annual Hemoccult II® and FSIG every 5 years alone were less effective.

C=costs; COL=colonoscopy; CRC=colorectal cancer; CTC=CT colonography; DALY= disability adjusted life year; DCBE=double contrast barium enema; F-DNA=faecal DNA test; FIT=faecal immunochemical test; gFOBT=guaiac faecal occult blood test; FSIG=flexible sigmoidoscopy; ICER=incremental cost-effectiveness ratio; LYG=life years gained; N/A= not applicable; NR=not reported; O=outcomes; QALY=quality adjust life year; RCT=randomised controlled trial; SIG=sigmoidoscopy.

Appendix 4

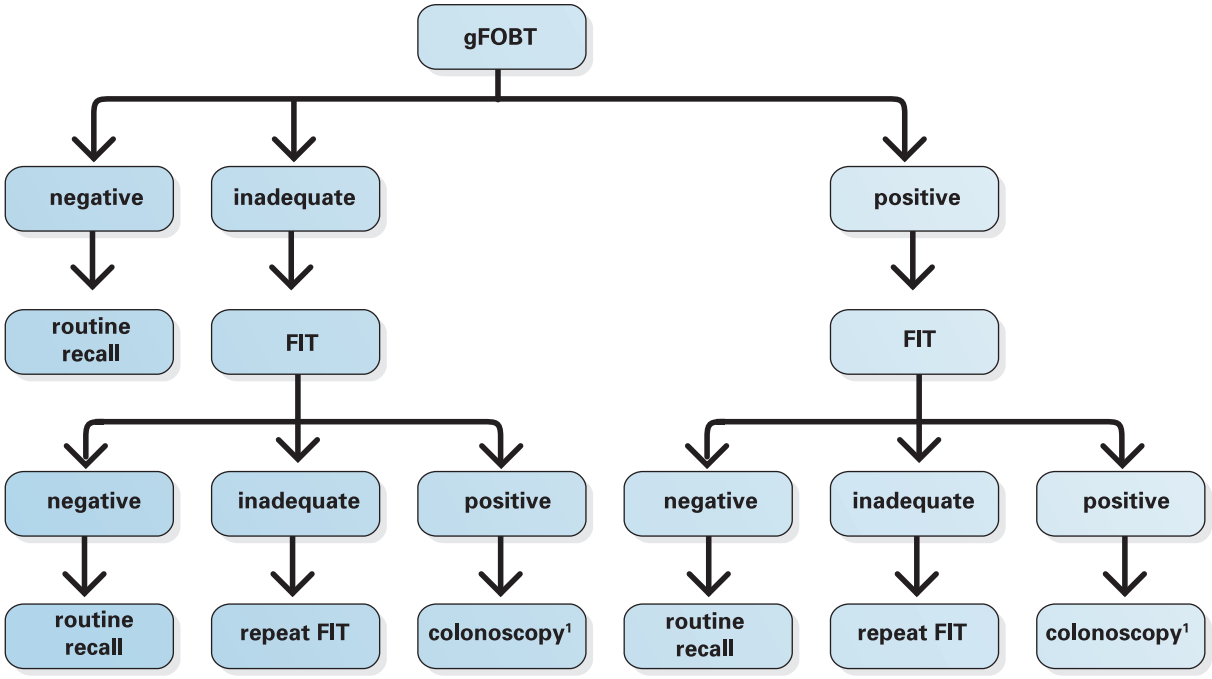
Core screening scenarios

Figures APP4.1-APP4.3 illustrate the three core screening scenarios which were evaluated in terms of cost-effectiveness and resources requirements and health services impact. Figure APP4.4 illustrates the surveillance strategy for individuals who have intermediate or high-risk adenomas removed; this is based on Atkins & Saunders[153].

Figure APP4.1 Core Scenario 1 - gFOBT, with FIT reflex testing

Age group: 55-74 years

Screening interval: 2 years

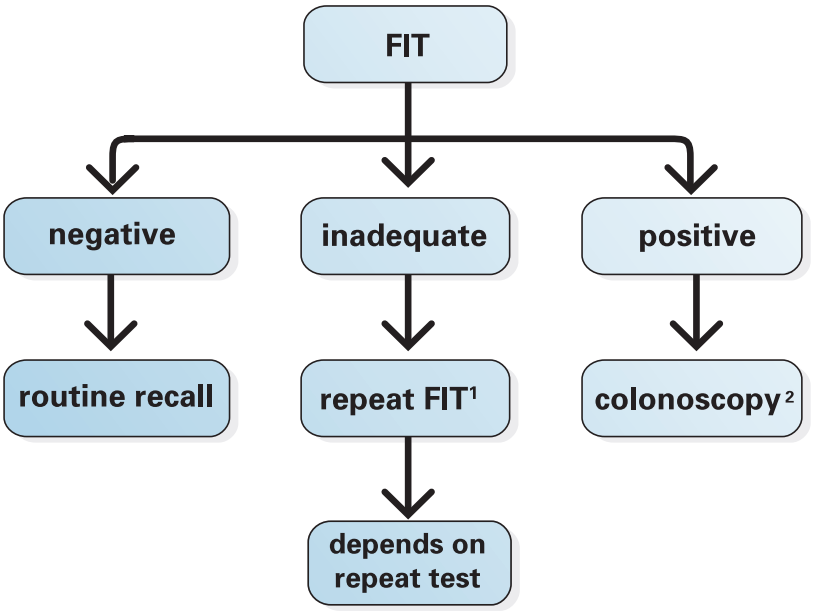


1 or CT colonography if individual unsuitable for colonoscopy or declines colonoscopy, or if colonoscopy is incomplete

Figure APP4.2 Core Scenario 2 - FIT

Screening interval: 2 years

Age group: 55-74 years

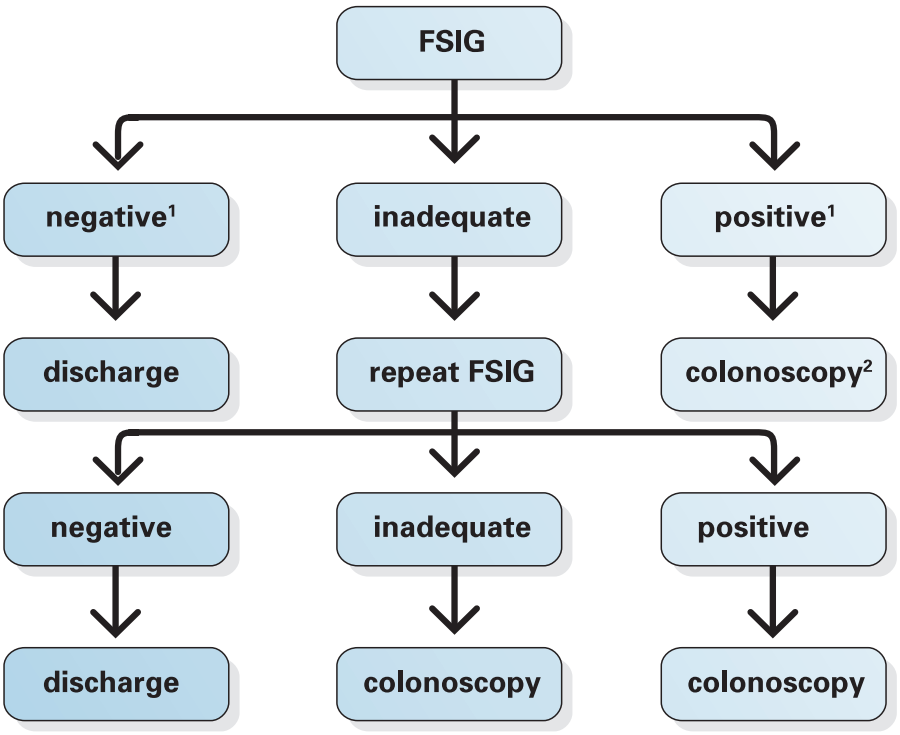


1 *if positive, refer for colonoscopy; if negative, routine recall; if inadequate, repeat FIT*

2 *or CT colonography if individual unsuitable for colonoscopy or declines colonoscopy, or if colonoscopy is incomplete*

Figure APP4.3 Core Scenario 3 - one-off flexible sigmoidoscopy (FSIG)

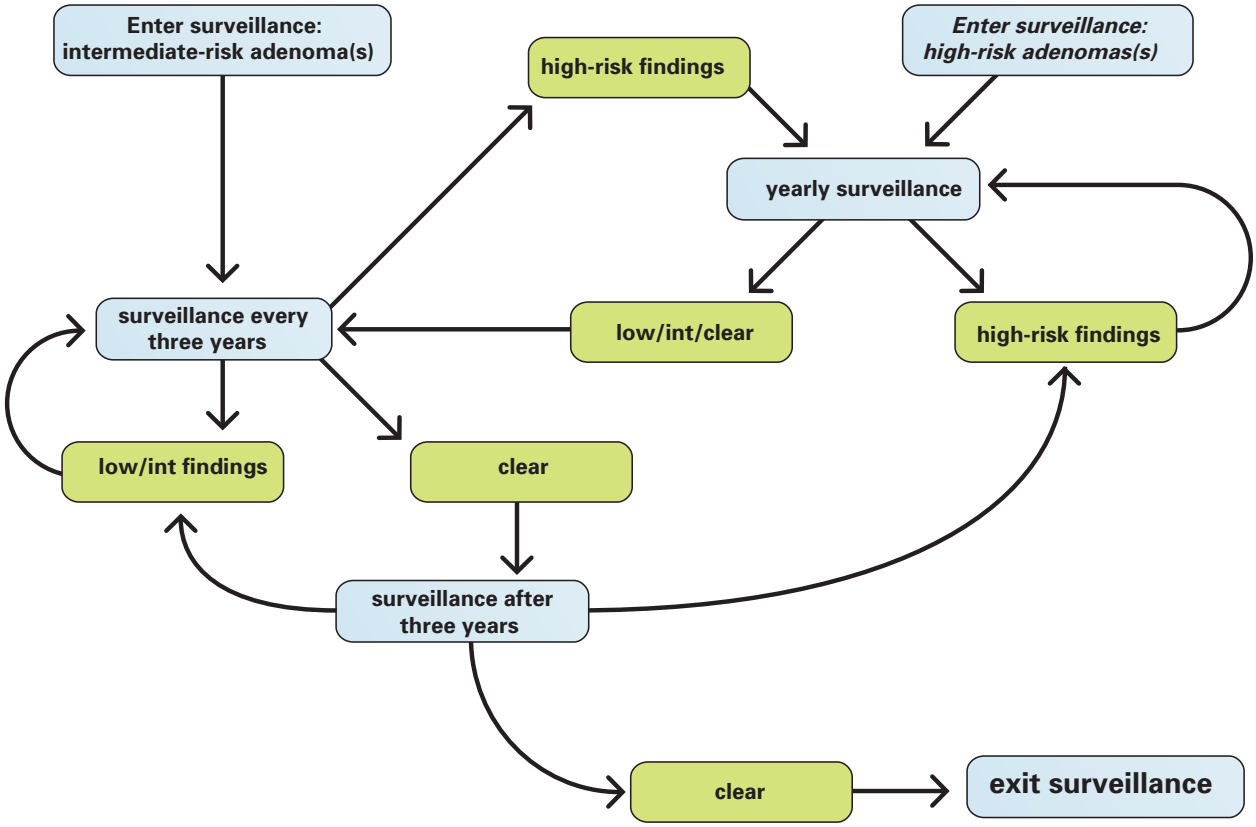
Age 60 years



1 *definitions of positive and negative FSIG as per the UK Flexible Sigmoidoscopy Trial[116]. Small polyps removed during FSIG screening and colonoscopy undertaken only 'when polyps with characteristics known to be associated with high risk of advanced proximal lesions are detected. These are defined as: large size (>1cm in diameter), tubuvillous or villous histology, severe dysplasia or malignancy, multiple small adenomas (≥3) and ≥20 hyperplastic polyps above the distal rectum. Polyps <3mm in diameter in the distal 5cm of the rectum ignored at the discretion of the endoscopist if judged on endoscopic appearance to be hyperplastic. Those with no or low-risk polyps are considered negative and discharged.*

2 *or CT colonography if individual unsuitable for colonoscopy or declines colonoscopy, or if colonoscopy is incomplete*

Figure APP4.4 Surveillance strategy for those with screen-detected intermediate or high-risk adenomas [based on Atkin and Saunders, 2002]



Appendix 5

Parameter estimates

The general process for deriving the parameter estimates is described in chapter 4 of the main report. Final estimates and their ranges were approved by the EAG.

APP5.1 Natural history parameters

As described in chapter 4, some of the natural history parameters are used for the purposes of model calibration while others are estimated from the model calibration/ fitting. The methods used to derive the natural history parameters which are used in the model calibration process are described below.

APP5.1.1 Proportion of colorectal cancers that arise without a previous adenoma

The proportion of colorectal cancers which arise from routes other than through the adenoma-carcinoma pathway is unknown. The value for this model parameter was informed by data from several sources and expert clinical opinion. Firstly, individuals with inflammatory bowel disease (IBD; Crohn's disease and ulcerative colitis) are at increased risk of developing colorectal cancer[246]. The cancers which arise in these individuals are not generally preceded by an adenoma. The upper estimate of the proportions of colorectal cancers that arise in persons with IBD is 2%[247]. Secondly, a small number of studies have reviewed the histopathology of colorectal cancers to identify the proportion that are serrated adenocarcinoma, and which presumably arose from serrated polyps. The studies generally estimate this figure to be about 8%[42, 44, 248]. Thirdly, there is increasing recognition that some colorectal cancers in Western populations may arise from flat adenomas[47]. Combining these strands of information, and taking expert gastroenterology opinion into account, the proportion of colorectal cancers which arise without going through the adenoma-carcinoma sequence was set as 14%; no range was required as this parameter was used in model calibration.

APP5.1.2 Population prevalence of adenomas and carcinomas

Two sources of data were used to estimate the prevalence of adenomas and undiagnosed carcinomas in the population: (1) a large, recently reported, autopsy study[211] and (2) data from the first (prevalent) round of the gFOBT screening pilots in England and Scotland[58].

Pendergrass et al[211] reviewed a series of all autopsies in adults aged 20 and older conducted during January 1985 and December 2004 in individuals who were hospitalised at a single large US centre. The aim of the study was to quantify adenomatous polyps that were undetected or unsuspected during life. The study procedures adhered to methodological principles for epidemiologic necropsy studies[249]. All individuals with evidence, or suspicion, of colorectal adenomas or carcinomas before death were excluded. Also excluded were individuals with previous colorectal resection, and individuals with colorectal carcinomas detected during the autopsy. Necropsies without

examination of the abdomen, and specifically the large bowel, were excluded. For eligible autopsies, the large bowel was opened and cleaned, the mucosa was inspected and any polyps seen were counted, measured and sent for histopathological evaluation. Only adenomatous polyps confirmed pathologically were included in the analysis, and each individual was counted as one observation regardless of the number of polyps found. The final study population included 3,558 individuals, 8% of whom were found to have one or more adenomatous polyps. The prevalence of polyps generally increased with increasing age, from 1.4% in those aged 20-29 years at death to 12% in those aged 80-89 years. The age-specific rates are shown in table APP5.1.

Table APP5.1 Age-specific prevalence of undiagnosed or undetected colorectal adenomas, by age at death (from[11])

Age at death	Numbers of individuals autopsied	Numbers with adenomatous polyps	Prevalence (%)
20-29	144	2	1.4%
30-39	334	8	2.4%
40-49	523	19	3.6%
50-59	558	57	10.2%
60-69	652	71	10.9%
70-79	521	57	11.0%
80-89	219	26	11.9%

For the second source of data, information was obtained on the numbers of individuals found to have (a) adenomas and (b) cancers in the first round of the screening pilots in England and Scotland, by age group[58]. The age-specific detection rates of adenomas and carcinomas were estimated by firstly adjusting for the proportion of individuals who had positive screening tests but did not undergo colonoscopy and secondly by dividing by the numbers screened. The age-specific prevalence of adenomas and carcinomas was then estimated by dividing the detection rates by the product of the base-case sensitivity of gFOBT and the base-case sensitivity of colonoscopy (see later in this Appendix). Finally a weighted average of the age-specific prevalence rates in England and Scotland was computed. The results of this process are shown in table APP5.2.

Table APP5.2 Estimated prevalence of adenomas and carcinomas, by age (derived from data in[58])

Age at screening	Adenoma prevalence (%)	Carcinoma prevalence (%)
50-54	3.72%	0.20%
55-59	5.54%	0.27%
60-64	9.14%	0.60%
65-69	9.66%	0.91%

APP5.2 Performance of screening tests

APP5.2.1 Faecal tests

The main source of information on the sensitivity and specificity of the gFOBT and FITs was the systematic review conducted by the Centre for Reviews and Dissemination[53, 94]. The review was performed in accordance with CRD and other guidelines on the meta-analysis of diagnostic tests[94, 250]. Fifteen databases were searched for studies published by November 2004[53], with a later update of the review including studies published until March 2007[94]. There were rigorous eligibility criteria; studies were eligible for inclusion if they were diagnostic cohort or case-control studies, or the screening arm of RCTs, which compared gFOBT or FIT with any reference standard (usually, but not always, colonoscopy), were conducted in an "average-risk" adult population and reported sufficient data to construct a 2x2 table from which both sensitivity and specificity could be computed. Sixty-one studies met the inclusion criteria, 24 evaluating gFOBTs, 26 FITs and 11 both types of test. There was substantial heterogeneity in the estimates of sensitivity and specificity of both tests. For gFOBTs, sensitivities for the detection of all neoplasia ranged from 6.2% to 83.3%, with specificity ranging from 65.0% to 99.0%. For immunochemical tests, sensitivities were in the range 5.4% to 62.6% and specificity was between 89.4% and 98.5%. The heterogeneity was so extreme that the authors concluded that it would be inappropriate to perform pooled analyses.

The reasons for this heterogeneity are likely to include differences in study design, the specific test used and the reference standards; differences in the study populations and the underlying prevalence of colorectal neoplasia in the populations; selection and participation biases; and the relatively small size of several of the studies. In order to obtain estimates for the current HTA the more homogeneous studies were identified and their results pooled. Studies were included in the pooled analyses if they were diagnostic cohort studies (i.e. diagnosis had not been determined prior to recruitment to the study, and all participants underwent the index test and the reference standard test) and recruited an "appropriate patient spectrum" (as defined by the authors of the CRD review). For gFOBT, studies were further limited to those which used the Hemoccult® or Hemoccult II® test. For FIT, a few large studies had been published since the updated CRD review, and these were included in the pooled analysis.

APP5.2.1.1 gFOBT

Nine studies provided information on the diagnosis of adenomas of all sizes and/or colorectal cancers and were eligible for inclusion in the pooled analysis[158-166]. These are summarised in table APP5.3. Three studies used rehydrated tests, five unrehydrated tests and one used both. A range of reference standards were used including colonoscopy, sigmoidoscopy, barium enema and follow-up through cancer registries.

Five studies were included in the pooled analysis of sensitivity for adenomas of all sizes[158, 162-164, 166]. 20,299 individuals were included; of these 321 had had a positive index test and were found to have one or more adenomas by the reference standard (true positive), 459 had a positive index test and had no adenomas (false positive) and 2,636 were negative on the index test but found to have adenomas (false negative). The pooled estimate of sensitivity from these studies was 11%, with a 95% confidence interval of 10%-12%; these values were used for the base-case estimate and the lower and upper limits of the range.

All nine studies were included in pooled analysis of the sensitivity of gFOBT for the detection of colorectal cancer. These included 46,550 individuals of whom 117 had a positive index test and were confirmed as having cancer on the reference standard (true positive), 1,396 were test positive but negative by the reference standard (false positive), and 206 were negative on the index test, but subsequently found to have cancer (false negative). When the studies were pooled the overall estimate of sensitivity was 36% and this was used for the base-case estimate. The 95% confidence interval of this estimate (31%-42%) was used to define the range of the parameter.

Considering adenomas and cancers separately, the specificity for each was 97%, and both estimates had a very narrow confidence interval. This value was therefore used as the base-case estimate of the specificity of gFOBT for the detection of adenomas and cancers, with a range of 96% to 98%.

Table APP5.3 Summary of studies included in pooled analysis of performance characteristics of gFOBT[1]

Setting & subjects	Index test	Reference standard	No. incl.[2]	Adenomas -TP[3]	Cancer – TP[3]	Reference
USA, screening population, aged 45-70+	Hemoccult II® - NR	colonoscopy, barium enema, and cancer registry	13,465	43	21	Allison et al, 1990[158]
Italy, screening population, aged 40-70	Hemoccult® - NR	sigmoidoscopy and barium enema	14,992	-	25	Castiglione et al, 1991[161]
Ireland, screening population, aged 44-85	Hemoccult®- NR Hemoccult® - R	sigmoidoscopy sigmoidoscopy	880 / 872	10 11	2 1	Foley et al, 1992[163]
USA, screening population, aged 50-70+	Hemoccult® and Hemoccult II® -NR	colonoscopy and follow up	8,065	-	13	Allison et al, 1996[159]
Sweden, population-based RCT, aged 55-56	Hemoccult® - R	flexible sigmoidoscopy and barium enema	825	-	6	Brevinge et al, 1997[160]
USA, asymptomatic men, aged 50-75	Hemoccult II® - R	colonoscopy	2,885 / 2,861	138	12	Lieberman et al, 2001[164]
Israel, asymptomatic residents of 24 randomly selected settlements, aged 40-75	Hemoccult II® - NR	colonoscopy and cancer registry	2,268	-	13	Niv et al, 2002[165]
Hong Kong, volunteers recruited from general population, aged 50-79	Hemoccult II® - NR	colonoscopy	505 / 504	28	1	Sung et al, 2003[166]
USA, screening population,aged 50-75	Hemoccult II® - R	colonoscopy	2,665 / 2,597	91	23	Collins et al, 2005[162]

NR=non-rehydrated test; R=rehydrated test; RCT=randomised controlled trial

1 *Data abstracted from Burch et al[53]*

2 *If two figures shown, first is total number included in analysis of sensitivity and specificity for colorectal cancer and second is total number included in analysis of sensitivity and specificity for adenomas*

3 *true positive (i.e. numbers with positive index test, who were confirmed to have a lesion by the reference standard)*

APP5.2.1.2 FIT

Eight diagnostic cohort studies which provided data on sensitivity and specificity for all adenomas and/or colorectal cancers were identified from the CRD review[159, 167-175]. Three further large studies had been published since the review and were taken into consideration[82, 172, 173, 176]. The studies are summarised in table APP5.4. A variety of immunochemical tests were used in the studies. In one instance the specific test used was not reported; in several other studies the definition of a positive test result was not stated. The reference standards included colonoscopy, flexible sigmoidoscopy, follow-up and health insurance claims.

Four studies provided data for the pooled analysis of sensitivity of immunochemical tests for adenomas of all sizes[168, 169, 171, 175]. These studies included 23,990 individuals, of whom 451 were true positives, 1,293 were false positives and 1,767 were false negatives on the immunochemical test. The pooled estimate of sensitivity was 21%, with a 95% confidence interval of 19%-22%. These were used for the base-case estimate and lower and upper limits of the range respectively.

The recent studies of Nakazato et al[176], Allison et al[82] and Morikawa et al[173] reported sensitivity for large (≥10mm) adenomas, which would be expected to be higher than sensitivity for all adenomas. The estimates of sensitivity for large adenomas from these studies were 25% (95% CI 12.9-36.1), 20% (95% CI 21.4%-38.9%) and 23%, respectively, which are compatible with the pooled estimate for all adenomas derived above.

As regards sensitivity for cancers, all 11 studies included relevant data. This amounted to a total of 170,685 individuals. There were 336 true positives, 8,613 false positives and 136 false negatives. The pooled estimate of sensitivity from the 11 studies was 71%, with a 95% confidence interval of 67%-75%. When the analysis was repeated and restricted to the eight studies from the CRD review, the pooled estimate was little changed (73%). Therefore 71% was used for the base-case and the range was defined as 67%-75%.

In terms of specificity, the pooled estimates for adenomas and carcinomas were 94% and 95% respectively; 95% was, therefore, used as the base-case estimate for adenomas and cancers combined. Since the confidence interval around both estimates was tight, the range for the parameter was set at 94%-96%.

Table APP5.4 Summary of studies included in pooled analysis of performance characteristics of FIT

Setting & subjects	Index test and definition of +ve test	Reference Standard	No. incl.[2]	Adenomas - TP[3]	Cancer – TP[3]	Reference
USA, screening population, aged 50-70+[1]	Immudia HemSp®; agglutination at 1:8 dilution	colonoscopy, follow up and cancer registry	7,493	-	22	Allison et al, 1996[159]
Japan, screening population, aged 40+[1]	OC Hemodia/OC Hemocatch®; agglutination within 3 minutes	colonoscopy and health insurance claims	27,860	-	77	Itoh et al, 1996[170]
China, screening population, aged 30-60+[1]	Immudia HemSp®; not reported	flexible sigmoidoscopy and follow-up	62,611	-	18	Chen et al, 1997[167]
Japan, screening population, aged 40-60[1]	Iatro HemCheck®; no agglutination within 1.5 minutes	colonoscopy	17,664	-	79	Nakama et al, 2000[174]
Japan, screening population, mean age 54[1]	Immudia HemSp®; agglutination at 1:8 dilution	colonoscopy	9,952 / 9,888	201	39	Nakama et al, 2001[175]
Taiwan, screening population, aged 20-80+[1]	OC Hemodia/OC Hemocatch®; not reported	colonoscopy	7,331 / 7,393	118	14	Cheng et al, 2002[168]
Taiwan, aged 46 +/-12 years[1]	OC Hemodia/OC Hemocatch®; not reported	colonoscopy	1,387 / 1,381	12	3	Liu et al, 2003[171]
Norway, population-based RCT, aged 50-64[1]	FlexSure®; not reported	colonoscopy and flexible sigmoidoscopy	6,136 / 5,328	120	13	Gondal et al, 2003[169]
Japan, asymptomatic participants in a health program, mean age 48 +/-9.3 years	Magstream 1000/HemSp®; not reported	colonoscopy	21,805	-	52	Morikawa et al, 2005; Morikawa et al, 2007[172, 173]
Japan, individuals enrolled for complete medical check-up, mean aged 53 +/- 7.9 years	Test not stated; not reported	colonoscopy	3,090	-	10	Nakazato et al, 2006[176]
USA, individuals at average-risk of colorectal cancer recruited by phone or GP referral, aged 50+	FlexSure OBT®; cut-off 0.3mg haemoglobin per gram faeces	colonoscopy and flexible sigmoidoscopy	5,356	-	9	Allison et al, 2007[82]

RCT=randomised controlled trial

1 *Data abstracted from Burch et al[53]*

2 *If two figures shown, first is total number included in analysis of sensitivity and specificity for colorectal cancer and second is total number included in analysis of sensitivity and specificity for adenomas*

3 *true positive (i.e. numbers with positive index test, who were confirmed to have a lesion by the reference standard)*

APP5.2.2 FSIG

Since flexible sigmoidoscopy aims to detect lesions in the distal bowel, the relevant model parameters relate to adenomas in the distal bowel (i.e. sensitivity for low-risk distal adenomas, sensitivity for intermediate/high-risk distal adenomas). There is very limited data on which to base estimates of the performance characteristics of flexible sigmoidoscopy. This is because suitable studies would require individuals to undergo both a flexible sigmoidoscopy and examination by a "gold standard" test (irrespective of the result of the flexible sigmoidoscopy) and this would usually be considered overly invasive. A further difficulty relates to the fact that there is no "gold standard" test that is 100% sensitive and specific. Generally colonoscopy would be considered to be the best reference standard, but it is known to miss lesions, particularly small or diminutive adenomas (see, for example,[183]). Therefore the true sensitivity and specificity of flexible sigmoidoscopy in clinical practice is unknown.

Three studies were identified which informed the base-case estimate of the sensitivity of flexible sigmoidoscopy[164, 166, 177]. An important limitation of two of these studies is that they did not consider actual flexible sigmoidoscopy examinations, but rather used colonoscopy as a surrogate[164, 166]. Thus, they may overestimate the sensitivity of flexible sigmoidoscopy. In the study by Rozen et al[177], 1,176 asymptomatic and previously unscreened volunteers had a flexible sigmoidoscopy and a gFOBT within one week. Those who had a lesion detected at flexible sigmoidoscopy, or a positive gFOBT, had a barium enema and then underwent colonoscopy. Lesions were resected by polypectomy or, if necessary, surgery. Forty-eight individuals had neoplasia detected by colonoscopy, of whom 45 (74%) had had lesions seen at flexible sigmoidoscopy. Thirty-six of the 38 (95%) with adenomas found at colonoscopy had had adenomas seen on flexible sigmoidoscopy; five of five (100%) individuals with carcinoma in situ at colonoscopy, and four of five (80%) with invasive cancer, had had these lesions at seen at flexible sigmoidoscopy.

Lieberman et al[164] invited asymptomatic men aged 50-75 years to complete a gFOBT before undergoing colonoscopy; 2,885 did so. Colonoscopies were repeated until examination of the entire colon was completed. All retrieved lesions underwent histopathological examination. Advanced neoplasia was considered to be an adenoma of 10mm or larger, or with villous features or high-grade dysplasia, or an invasive cancer. Examination of the rectum and sigmoid colon during colonoscopy was defined as a surrogate for flexible sigmoidoscopy. The authors estimated that one-time flexible sigmoidoscopy would detect 70% of individuals with advanced neoplasia, assuming that all those with an adenoma in the distal colon subsequently undergo complete colonoscopy.

Sung et al[166] recruited 505 asymptomatic individuals aged 50 and older from the general population and invited them to complete a gFOBT and undergo a colonoscopy, irrespective of the findings on the gFOBT. Lesions found on colonoscopy were photographed and had their size and site recorded and polypectomy was done. An advanced colonic neoplasm was defined as an adenoma at least 10mm in size, or with villous architecture, or with moderate or severe dysplasia, or invasive carcinoma. Findings at the distal colon 40cm

from the anal verge on withdrawal of the colonoscope were taken as a surrogate for flexible sigmoidoscopy. One hundred and twenty subjects had lesions in the distal colon. Assuming these individuals would undergo a full colonoscopy, the authors estimated that 78% of advanced neoplasia would be detected by one-time flexible sigmoidoscopy. Specificity for advanced neoplasia was estimated as 84%.

These three studies were combined to produce a pooled estimate for sensitivity of 74%. This was used for the base-case estimate for the sensitivity to detect intermediate/high-risk adenomas. The range of the parameter was taken to be 68%-78%.

As regards sensitivity of flexible sigmoidoscopy for low-risk distal adenomas, no studies were identified which included sufficient numbers of cases to permit a reliable estimate to be made. Expert opinion considered that the sensitivity of flexible sigmoidoscopy for low-risk lesions would be lower that that for larger lesions and would also be lower than that for colonoscopy. The base-case estimate was therefore set at 65% with lower and upper limits of 60% and 70% respectively. The estimates for sensitivity for colorectal cancers were also based on expert opinion (base-case 90%; range 85%-95%). The rationale for the values was that sensitivity of flexible sigmoidoscopy for the detection of cancers would be expected to be higher than that for large adenomas, but lower than the sensitivity of colonoscopy for cancers. On the basis of expert opinion, specificity of flexible sigmoidoscopy for adenomas and cancers was taken to be 92% with a range of 90%-95%.

APP5.3 Uptake and non-compliance with screening tests

Two parameters are used in the model to represent participation in screening – uptake and non-compliance. Uptake is defined as the proportion of individuals who complete a screening test in a particular screening round (or, for flexible sigmoidoscopy, individuals who accept a screening invitation and have a flexible sigmoidoscopy). For tests which are repeated (i.e. gFOBT and FIT), a proportion of individuals in the population may never undergo screening (i.e. they always refuse), no matter how many times they are invited. In this context, this is called non-compliance.

For tests which are repeated (i.e. gFOBT and FIT) uptake is assumed to be the same level in each screening round. This was because it would be usual for screening programmes to have the same target for uptake in each round.

In identifying data to inform estimates of uptake of the screening tests, the focus was on data from population-based screening programmes, or pilot programmes, in Europe and Australia. Participation rates in population-based trials and other studies in which individuals were recruited in a similar way to what would be likely to be done in a population-based screening programme (e.g. from a population register or via general practices) were also reviewed. Trials or studies which recruited volunteers or which were not population-based were not considered as the participation rates from these are unlikely to be representative of uptake in a population-based screening programme.

APP5.3.1 gFOBT uptake

Data on uptake of gFOBT-based screening is shown in table APP5.5. There is considerable variation in uptake, with values ranging from 17% in the first round of the screening programme in Catalonia[76], to 71% in the screening trial in Finland[251]. The uptake in the first round of the pilot programme in England was 59%, and in Scotland was 55%[59]. Uptake fell in the second rounds in both countries to 52% in England and 53% in Scotland[102, 179]. As regards other studies in the UK, uptake of 32% was achieved in a small community-based screening trial in Hertfordshire[111], while participation in the first round of the Nottingham gFOBT trial was 53%[63].

The base-case value for gFOBT uptake was set at 53%, with a range of 32% to 59%.

TABLE APP5.5 Uptake of gFOBT-based screening

Setting	Subjects	Screening test	Screening process	Numbers screened and invited	% uptake	Reference
Scotland; pilot programme since 2000; 3 rounds	Individuals aged 50-69 registered with GPs east and north-east of the country	Hemoccult II®; with reflex FIT in second and third rounds	Postal invitation letter, enclosing kit	1st round: 153,524 screened 2nd round: NR 3rd round: NR	1st round: 55% 2nd round: 53% 3rd round: 55%	Information Services Division, 2008[102]
England; pilot programme since 2000; 2 rounds	Individuals aged 50-69 registered with GPs in West Midlands	Hema Screen™	Postal invitation letter, enclosing kit; in 2nd round, ineligible individuals were excluded (those being treated for CRC, had bowel removed, already referred for bowel investigation, etc)	1st round: 105,878 screened 2nd round: 66,264 screened of 127,746 invited	1st round: 59% 2nd round: 52%	UK Colorectal Cancer Screening Pilot Group, 2004; Weller et al, 2006[59, 179]
England; Hertfordshire; community-based trial of screening tests	Individuals aged 50-75 registered with single general practice; randomised gFOBT or FSIG	Hemoccult®	Those randomised to gFOBT were sent kit and reply-paid envelope	393 of 1245 randomised, after exclusions due to colorectal exam in past two years or previous CRC	32%	Verne et al, 1998[111]
Finland; first phase of programme; 2004-6	Individuals aged 60-69, identified from central population register; 50% randomised to screening and 50% to no intervention	Hemoccult®	Postal invitation, including kit	37,514 of 52,994 randomised to screening	71%	Malila et al, 2007[251]

Setting	Subjects	Screening test	Screening process	Numbers screened and invited	% uptake	Reference
Italy; multiple screening programmes	Participants in screening programmes in 2005 and 20061	Details not given	Reviews of screening programmes; further details not provided	2005: 376,240 of 827,473 invited 2006: 907,306 screened of 2,106,916 invited	Crude: 45% Adjusted: 47% Crude: 43% Adjusted: 45%	Zorzi et al, 2006; Zorzi et al, 2008[77, 252]
Spain, Catalonia; pilot programme since 2000; 3 screening rounds	Individuals aged 50-69 identified from population register	Hema Screen™ (Immunostics Inc)	Postal invitation to participate in screening; those who agreed returned reply-paid envelope to request test kit; those with history of CRC, polyps, IBD, and those fulfilling HNPCC criteria were ineligible	1st round: 11,011 of 63,880 eligible 2nd round: 14,818 of 66,534 eligible 3rd round: 17,740 of 65,147 eligible	1st round: 17% 2nd round: 22% 3rd round: 27%	Peris et al, 2008[76]
Netherlands; pilot programme; 1st round; 2006-07	Individuals aged 50-75 randomly selected from population registers in two areas randomised to gFOBT or FIT	Hemoccult II® (Beckman Coulter)	Symptomatic individuals were ineligible; randomised individuals received allocated test by post, with freepost reply envelope	4,836 screened of 10,301 randomised to gFOBT	47%	Van Rossum et al., 2008[87]
Netherlands; population-based trial of gFOBT, FIT and FSIG	Representative sample of individuals aged 50-74	Hemoccult II® (Beckman Coulter)	Individuals with history of CRC, IBD or major health problems were excluded	2,019 screened of 4,125 invited	49%	Hol et al, 2008[86]

Setting	Subjects	Screening test	Screening process	Numbers screened and invited	% uptake	Reference
France; pilots for national programme	Individuals aged 50-74 in four areas (Cote d'Or, Haut-Rhin, Ile-et-Vilaine, Saone-et-Loire)	Hemoccult II® (Beckman Coulter)	Individuals invited to participate by their GP, but letter enclosing test kit; those with personal of family history of CRC or adenomas, or colonoscopy in past 5 years excluded	2007 reported figures for four areas: 324,389 screened of 621,449 invited 2008 reported figures for Ile-et-Vilaine: 96,048 screened of 187,342 eligible 2007 reported figures for Haut-Rhin: 90,706 screened of 163,707 eligible	52% 52% 55%	Lepage et al., 2007 (presentation); Manfredi et al, 2008; Denis et al, 2007[75, 253]
Original gFOBT trials						
Denmark, Funen; population-based trial; screening commenced 1985	Individuals aged 45-75 identified from population register; randomised to screening or control	Hemoccult II®	Those with known precursor lesions and other cancers were excluded before randomization; postal invitations sent to eligible individuals randomised to gFOBT	20,672 of 30,967 randomised to gFOBT had 1st screen	1st screen: 67%	Kronborg et al, 1996; Hewitson et al, 2007[64, 65]
Sweden, Goteborg; population-based trial; screening commenced 1982	Individuals aged 60-64 resident in Goteborg; randomised to screening or control	Hemoccult II®		21,511 of 34,144 randomised to screening had 1st screen	1st screen: 63%	Kewenter et al, 1994; Hewitson et al, 2007[62, 65]
England, Nottingham; population-based trial; commenced 1985	Individuals aged 45-74, identified from GP records; randomised to offer of screening or control	Hemoccult®	Ineligible individuals excluded by GPs before randomization; individual offered screening by post; those who accepted offer were invited to be screened	75,253 offered screening; 30,415 (42%) refused; of 44,838 who accepted, 16,118 completed at least one screen	1st screen: 53% of those who accepted offer of screening	Hardcastle et al, 1996; Hewitson et al, 2007[63, 65]

CRC=colorcetal cancer; gFOBT=guaiac faecal occult blood test; FSIG=flexible sigmoidoscopy; IBD=inflammatory bowel disease

1 some of the programmes are based on FIT

APP5.3.2 FIT uptake

Population-based data on uptake of FIT-based screening is more limited than that available for gFOBT (table APP5.6). In two trials in the Netherlands, uptake rates of 58% and 60% were reported[86, 87]. In Italy, in a regional screening programme, uptake was 41%[93] and in the second and third SCORE trials uptake was around 30%[88, 89]. The pilot programme in Australia had an uptake rate between the values in Italy and the Netherlands (45%[92]). In recognition of the uncertainty in uptake for FIT at the population-level, it was decided to use the same base-case estimate and range as for gFOBT (i.e. 53%; 32%-59%).

APP5.3.3 Flexible sigmoidoscopy uptake

There is extreme variation in the uptake rates for flexible sigmoidoscopy reported in population-based trials and studies (table APP5.7), with values ranging from around 11% in the first SCORE trial in Italy[115] to 67% in the NORCCAP trial in Norway[90] and in a community-based study in London[181]. In a small study in Scotland uptake of flexible sigmoidoscopy was 24%[114], and rates of around 30% are reported from screening programmes in Italy[77]. In the very large UK flexible sigmoidoscopy trial a two-stage recruitment process was used[116]. Eligible individuals were sent a questionnaire and those who indicated on this questionnaire that they would be likely to attend for flexible sigmoidoscopy went on to be randomised. Fifty-five percent of those who completed the questionnaire were positive about flexible sigmoidoscopy, and of those who were randomised, 71% attended for the examination. Therefore the uptake rate for flexible sigmoidoscopy was 39% (71% of 55%). This value was used for the base-case and the range was 24% to 67%.

TABLE APP5.6 Uptake of FIT-based screening

Setting	Subjects	Screening test	Screening process	Numbers screened and invited	Uptake (%)	Reference
Australia; pilot programme, 2002-04	Individuals aged 55-74 resident in designated postcodes in three areas	Magstream HemSp®; Inform®	Postal invitation to participate, enclosing test kit	25,840 of 56,907 invited (excluding those ineligible due to recent colonoscopy or previous CRC)	Crude: 45% Age-standardised: 45%	Bowel Cancer Screening Pilot Monitoring and Evaluation Steering Committee, 2005[92]
Netherlands; pilot programme; 1st round; 2006-07	Individuals aged 50-75 randomly selected from population registers in two areas randomised to gFOBT or FIT	OC-Sensor®	Symptomatic individuals were ineligible; randomised individuals received allocated test by post, with freepost reply envelope	6,157 screened of 10,322 randomised to FIT	60%	van Rossum et al, 2008[87]
Netherlands; population-based trial of gFOBT, FIT and FSIG	Representative sample of individuals aged 50-74	OC-Hemodia®	Individuals with history of CRC, IBD or major health problems were excluded	2,405 screened of 4,176 invited	58%	Hol et al, 2008[86]
Italy; Tuscany, population-based screening, 1st round	Individuals aged 50-70 years	OC-Hemodia®	Kits were distributed by GPs, health operators of Sanitary Districts and volunteers	78,505 screened	41%	Grazzini et al, 2004[87]

Setting	Subjects	Screening test	Screening process	Numbers screened and invited	Uptake (%)	Reference
Italy, SCORE2 population-based trial; 1999-2001	Individuals aged 55-64 randomly sampled from GP lists or population registers in five areas; randomised to various FSIG or FIT options	Immudia-HemSp®	Ineligible individuals excluded (previous CRC, polyps, IBD); eligible individuals either sent a kit or advised to contact GP or screening centre for kit	2,682 screened of 2,266 randomised to received kit by mail 5,893 screened of 1,654 randomised to obtain kit from GP or screening centre	30% 28%	Segnan et al, 2005[88]
Italy, SCORE3 population-based trial; 2002-04	Individuals aged 55-64 randomly sampled from GP lists or population registers in six areas; randomised to FSIG, FIT, or colonoscopy	Immudia-HemSp®	Ineligible individuals excluded; eligible individuals mailed an invitation signed by GP; individuals contacted GPs or screening centres to obtain kit	1,965 screened of 6,075 randomised to FIT	All: 32% 55-59: 31% 60-64: 35%	Segnan et al, 2007[89]

CRC=colorectal cancer; FIT=faecal immunochemical test; gFOBT=guaiac faecal occult blood test; FSIG=flexible sigmoidoscopy; IBD=inflammatory bowel disease

TABLE APP5.7 Uptake of flexible sigmoidoscopy-based screening

Setting	Subjects	Screening process	Numbers screened and invited	Uptake (%)	Reference
UK; Flexible Sigmoidoscopy Trial (14 centres; population-based)	Individuals aged 55-64 registered with general practices within catchment areas of 14 hospital-based endoscopy centres	Individuals were sent questionnaire; those who indicated that they were likely to attend for FSIG were randomised to screening or no intervention	194,726 of 354,262 approached responded positively about FSIG (55%); 170,432 eligible individuals were randomised; 40,674 of 57,254 assigned to flexi-sig attended (71%)	0.71 * 55%= 39%	UK Flexible Sigmoidoscopy Screening Trial Investigators, 2002[116]
England; Hertfordshire; community-based trial of screening tests	Individuals aged 50-75 registered with single general practice; randomised to FSIG or gFOBT	Individuals randomised to FSIG were sent appointment for FSIG to be undertaken by GP	582 of 1,249 randomised, after exclusions due to colorectal exam in past two years or previous CRC	47%	Verne et al, 1998[111]
England; London; community-based study	Patients aged 60-64 registered with three general practices	Invitation letter with hospital clinic appointment enclosed; nurse administered screening	280 attended of 510 invited; after exclusions due to ineligibility (incorrect contact details; ongoing bowel investigations), number invited was 419	67% after exclusions due to ineligibility	Brotherstone et al, 2007[181]
Scotland; Dundee; community-based trial of invitation styles	Patients aged 50-60 registered with one general practice	Postal invitation to take part in screening.		24%	Gray and Pennington, 2000[114]
Australia; Western Australia; community-based study	Individuals aged 55-59 on electoral commission database	Letters sent inviting attendance at single sigmoidoscopy clinic; individuals with family history of CRC; personal history of polyps or CRC, or bowel symptoms, or whose letters were undelivered, were subsequently excluded	342 screened of 2,881 invited and eligible	12%	Olynyk et al, 1999[112]
Australia; Melbourne; community-based study	Patients aged 50-60 attending 12 GPs for routine consultation	GPs discussed screening and recommended attendance at free clinic at local hospital	92 attended of 187 invited	49%	Cockburn et al, 1995[110]

Setting	Subjects	Screening process	Numbers screened and invited	Uptake (%)	Reference
Italy; screening programmes	Participants in screening programmes in 2005 and 2006	Review of six FSIG based screening programmes in 2005 and seven FSIG based programmes in 2006; further details not provided	2005: 5,821 screening of approx 40,000 invited 2006: 7,759 screened of 27,990 invited	29% Crude: 27% Adjusted: 29%	Zorzi et al, 2006; Zorzi et al, 2008[77, 252]
Italy, Lombardy; community-based trial of screening	Asymptomatic individuals aged 55-64 years, identified via 244 GPs	Invited by postal questionnaire; 20% responded and of these 27% were excluded due to ineligibility; those who indicated willingness to undergo screening were randomised to FSIG or control arms	1,582 screened of 2,885 randomised to FSIG	55%	Andreoni et al, 2000[113]
Italy, SCORE population-based trial of FSIG, 1995-99	Individuals aged 55-64 randomly sampled from GP lists or population registers in five areas	Individuals mailed a questionnaire to assess interest in FSIG; responders who were positive about FSIG but with history of CRC, polyps, IBD, or who had had endoscopy in previous two years were excluded. Remaining individuals were randomised to FSIG or no intervention	56,532 of 236,568 approached responded (24%); 43,010 were positive about FSIG (76%); 34,292 eligible individuals were randomised; 9,999 of 17,148 assigned to FSIG attended (58%)	0.58 * 0.76 * 24% = 11%	Segnan et al, 2002[115]
Italy, SCORE2 population-based trial; 1999-2001	Individuals aged 55-64 randomly sampled from GP lists or population registers in five areas; randomised to various FSIG or FIT options	Ineligible individuals excluded (previous CRC, polyps, IBD); eligible individuals mailed an invitation and appointment in letter signed by GP	1,026 screened of ,3650 randomised to once-only FSIG 3,049 screened of 10,867 randomised to FSIG followed in two years by FIT	28% 28%	Segnan et al, 2005[88]
Italy, SCORE3 trial; community-based ; 2002-04	Individuals aged 55-64 randomly sampled from GP lists or population registers in six areas; randomised to FSIG, FIT, or colonoscopy	Ineligible individuals excluded; eligible individuals mailed an invitation and FSIG appointment in letter signed by GP	1,944 screened of 6,018 randomised to FSIG	All: 32%	Segnan et al, 2007[89]

Setting	Subjects	Screening process	Numbers screened and invited	Uptake (%)	Reference
Norway; NORCCAP population-based screening trial	Individuals aged 55-64 selected at random from population registers in two areas	Invited to undergo screening; and randomised to FSIG only or FSIG + gFOBT	88,849 of 13,288 eligible, after exclusions	All: 67% FSIG only: 68% FSIG+gFOBT: 65%	Bretthauer et al, 2002[90]
Netherlands; population-based trial of gFOBT, FIT and FSIG	Representative sample of individuals aged 50-74	Individuals with history of CRC, IBD or major health problems were excluded	1,278 screened of 3,993 invited	32%	Hol et al, 2008[86]

CRC=colorectal cancer; FIT=faecal immunochemical test; gFOBT=guaiac faecal occult blood test; FSIG=flexible sigmoidoscopy; IBD=inflammatory bowel disease

APP5.3.4 Non-compliance with screening

Data from the second rounds of the gFOBT screening pilots in England and Scotland was used to derive the estimates of non-compliance[179, 254]. In the second round of the English pilot, uptake was 13% among individuals who had been invited in the first round, but who did not participate; thus the probability of an individual not attending, given that they did not attend in the previous round was 0.87. Allowing for nine prevalent screening rounds, and assuming 53% overall uptake in each round, the probability that someone will never attend for screening is estimated to be $(1-0.53)*(1-0.13)^9=0.13$. The figure derived from the data for Scotland was very close to this. Thus the base-case estimate for non-compliance for gFOBT-based and FIT-based screening was set at 13%. The lower limit for the range was taken as 0%, which is consistent with assuming that participation in each screening round is independent of previous participation/non-participation. The upper limit was set at 41%, based on the probability of non-compliance with two rounds of screening (i.e. $(1-0.53)*(1-0.13)=0.41$).

APP5.4 Compliance with diagnostic tests

Compliance with diagnostic tests was defined as the proportion of individuals referred for the test who had the test. Thus, for colonoscopy, those who do not comply would be a combination of those who refuse to have colonoscopy and those who do not attend the colonoscopy appointment. Generally data is not available on different categories of non-compliance, therefore the model includes single values for "overall" compliance with each diagnostic test.

Values for this parameter were derived from review of data from population-based screening programmes, pilot programmes and trials in Europe, and the original gFOBT population-based RCTs (table APP5.8). There was wide variation in colonoscopy compliance, ranging from 63%-65% in the first round of screening in the Czech Republic[255] and the Australian pilot programme[92] to at least 95% in the UK Flexible

Sigmoidoscopy trial[116], the SCORE2 trial in Italy[88], the third round of the screening programme in Catalonia[76], and the NORCAPP trial in Norway[169]. Three of the four sources which reported particularly high compliance involved individuals who had previously undergone flexible sigmoidoscopy. Most sources had compliance of between approximately 78% and 90%, and parameter values which represented this range were selected. The first round of the screening pilot in Scotland reported colonoscopy compliance in the middle of the range (86%[102]) and this was used for the base-case estimate. The lower limit was derived from the estimated compliance in the first round of the pilot in England (81%[179]) and the upper limit was from the second round of the pilot in Scotland (90%[102]).

TABLE APP5.8 Compliance with colonoscopy

Setting	Screening test	Numbers invited and attending	% compliance	Reference
Scotland; pilot programme since 2000; three rounds	gFOBT (with reflex FIT testing in 2nd and 3rd round)	NR	1st round: 86% 2nd round: 90% 3rd round: 81%	Information Services Division, 2008[102]
England; pilot programme since 2000; two rounds	gFOBT	1st round: 1,243 attended for colonoscopy, of whom two were unfit and had DCBE and 14 were unfit and did not have DCBE 2nd round: 1,171 tested positive, or whom 1,074 attended nurse appointment; three were unfit for colonoscopy; 1,001 referred for colonoscopy of whom 970 attended	1st round: 81% 2nd round: (970/1,171) 83%	UK Colorectal Cancer Screening Pilot Group, 2004; Weller et al, 2006[59, 179]

Setting	Screening test	Numbers invited and attending	% compliance	Reference
UK; Flexible Sigmoidoscopy Trial (14 centres; population-based)	FSIG	2,051 underwent colonoscopy of the 2,131 referred	96%	UK Flexible Sigmoidoscopy Screening Trial Investigators, 2002[116]
Finland; first phase of programme; 2004-6	gFOBT	723 of the 803 those with positive test and referred for colonoscopy underwent the procedures; in 27/80 who did not have colonoscopy, this was because they had recently had a colonoscopy	90%	Malila et al, 2007[251]
Italy; multiple screening programmes	gFOBT/FIT or FSIG	2005 review: Average attendance rate at colonoscopy among those gFOBT positive 2006 review: Average attendance rate at colonoscopy among those gFOBT positive	2004 review: 82% (range 56%-100%) 2006 review: 81% (range 38%-100%)	Zorzi et al, 2006; Zorzi et al, 2008[77, 252]
Italy, population-based screening, Tuscany, 2006-07	gFOBT	Of 1,882 with positive gFOBT test, 1,493 underwent colonoscopy	78%	Sali et al, 2008[180]
Italy, SCORE population-based trial of FSIG, 1995-99	FSIG	Of 832 in whom colonoscopy was indicated at FSIG, 775 underwent colonoscopy	93%	Segnan et al, 2002[115]
Italy, SCORE2 population-based trial; 1999-2001	FIT or FSIG	FIT: 96 underwent colonoscopy of 122 who had positive test FSIG: 332 of 341 referred for colonoscopy attended	FIT: 79% FSIG: 97%	Segnan et al, 2005[88]
Italy, SCORE3 trial; community-based ; 2002-04	FIT or FSIG	FIT: 81of 92 who had positive test result underwent colonoscopy FSIG: Of 138 referred for colonoscopy, 124 attended	FIT: 88% FSIG: 90%	Segnan et al, 2007[89]

Setting	Screening test	Numbers invited and attending	% compliance	Reference
Spain, Catalonia; pilot programme since 2000; three screening rounds	gFOBT	In 1st and second round combined, 442 of 495 test positives had a colonoscopy; raw data for 3rd round not reported	1st round: 90% 2nd round: 88% 3rd round: 95%	Peris et al, 2008[76]
Netherlands; pilot programme; 1st round; 2006-07	gFOBT or FIT	gFOBT: 103 of 117 who had positive test had a follow-up examination; this may have been CT colonography in a few subjects FIT: 280 of 339 who had positive test had a follow-up examination; this may have been CT colonography in a few subjects	gFOBT: 88% FIT: 83%	van Rossum et al, 2008[87]
Czech Republic; programme since 2001; three rounds completed	gFOBT	2001: 4,393 colonoscopies in 7,002 gFOBT positive individuals 2002: 9,462 colonoscopies in 11,578 gFOBT positive individuals 2005: 14,885 colonoscopies in 15,635 gFOBT positive individuals	2001: 63% 2002: 82% 2005: 95%	Zavoral and Zavada, 2007[255]
France; pilots for national programme	gFOBT	Four areas, 2007 reported figures: 7,927 underwent colonoscopy of 9,427 who had positive screening test One area (Ile-et-Vilaine) 2008 reported figures: 2,246 underwent colonoscopy of 2,477 who had positive screening test One area (Haut-Rhin), 2007 reported figures: 2,724 underwent colonoscopy of 3,100 with positive test	Four areas, 2007 reported figures: 84% Ile-et-Vilaine, 2008 reported figures: 91% Haut-Rhin, 2007 reported figures: 88%	Lepage et al., 2007 (presentation); Manfredi et al, 2008; Denis et al., 2007[75, 253]
Hungary; pilot programmes	faecal test	-	Centre 1: 65% Centre 2: 93% Centre 3: 78%	Dobrossy et al, 2007[256]

Setting	Screening test	Numbers invited and attending	% compliance	Reference
Hungary; pilot programmes	faecal test	-	Centre 1: 65% Centre 2: 93% Centre 3: 78%	Dobrossy et al, 2007[256]
Australia; pilot programme, 2002-04	FIT	Percentage of people referred to colonoscopy by GP who had had one by 74 weeks; some of these were referred for reasons other than positive FIT test (e.g. family history, symptoms of CRC, etc) Percentage of participants with positive FIT test recorded as having completed a colonoscopy	65% overall 55%	Bowel Cancer Screening Pilot Monitoring and Evaluation Steering Committee, 2004; Bowel Cancer Screening Pilot Monitoring and Evaluation Steering Committee, 2005[92, 257]
Norway; NORCCAP population-based screening trial	FSIG or FSIG+FIT	2,524 of the 2,639 individuals referred for colonoscopy (FSIG positive +/- FIT positive) attended	96%	Gondal et al, 2003[169]
Original gFOBT trials				
Denmark, Funen; population-based trial; screening commenced 1985	gFOBT	Percentage who had a colonoscopy	93%	Hewitson et al, 2007[65]
England, Nottingham; population-based trial; commenced 1985	gFOBT	Percentage who had colonoscopy, DCBE or both	87%	Hewitson et al, 2007[65]

CRC=colorectal cancer; DCBE= double contrast barium enema; FIT=faecal immunochemical test; gFOBT=guaiac faecal occult blood test; FSIG=flexible sigmoidoscopy; IBD=inflammatory bowel disease; NR=not reported

APP5.5 Performance of diagnostic tests and related parameters

APP5.5.1 Colonoscopy performance

The difficulty in estimating the sensitivity and specificity of colonoscopy for the detection of adenomas and cancers is that the test is normally considered to be the gold standard or reference standard for endoscopic evaluation. This means that there is no external standard to which it can be compared, and so its true performance characteristics cannot be assessed. It is generally accepted that colonoscopy misses some lesions, but the precise percentage missed is not known for certain.

Two different study designs have been used to estimate sensitivity of colonoscopy. The first design involves individuals undergoing two colonoscopies with polypectomy ('tandem' or 'back-to-back' colonoscopies), usually on the same day. The miss rate is then the number of polyps detected only during the second colonoscopy, relative to the number found during both colonoscopies; note that this is a rate per polyp, not per individual. The main difficulty with this approach is that the miss rate will tend to be under-estimated (and hence sensitivity will be over-estimated) because polyps in awkward positions are more likely to be missed during both examinations[185]. The second design involves review of colonoscopies prior to a diagnosis of polyps or cancer. Neoplasia diagnosed in individuals in whom the last colonoscopy was within a specific time (e.g. six months and three years) prior to the cancer diagnosis are considered to have been missed. The difficulty with this approach is that if the time interval is long enough between colonoscopy and diagnosis of neoplasia, a new lesion may have developed, so the miss-rate would be over-estimated since it includes both 'true' missed lesions and new lesions (and hence sensitivity will be under-estimated).

Van Rijn et al[185] undertook a systematic review of studies of tandem colonoscopies to investigate the adenoma miss rate. Six patient cohorts, involving 465 subjects, were included in the review[183, 258-261]. A total of 1,650 adenomatous polyps were reported across the cohorts. For adenomas <10mm, 167 of 711 were missed. From this, sensitivity for low-risk adenomas was estimated as 77% (i.e. 100%-miss rate), with lower and upper limits from the 95% confidence interval for this estimate (73%-80%). Of adenomas ≥10mm, two of 96 were missed, suggesting the sensitivity of colonoscopy for these lesions is 98%.

Rockey et al[184] compared the ability of colonoscopy to detect lesions with that of air contrast barium enema and CT colonography. 614 patients had all three tests. For lesions of 10mm and larger, the sensitivity of colonoscopy (taking CT colonography as the 'gold standard') was 98%. Although it has been argued that this is an inappropriate design to assess the miss rate of colonoscopy[185]), it is noteworthy that the estimate of sensitivity agreed with that from the review of van Rijn et al[185]. The base-case sensitivity for intermediate/high-risk adenomas was therefore set at 98%, with the range defined by the 95% confidence interval of the estimate from the data in the review by van Rijn et al (93%-99%[185]).

The largest study on the cancer miss rate for colonoscopy was a population-based cohort study in Ontario, Canada[178]. Individuals with an incident colorectal cancer diagnosed in Ontario during April 1997-March 2002, who had a colonoscopy within three years before the diagnosis, were identified. New or missed cancers were defined

as those who had a colonoscopy between six and 36 months before diagnosis; it was assumed that this colonoscopy did not detect the cancer. The study included 25,892 individuals with cancer, of whom 12,496 had had a colonoscopy within the three years prior to diagnosis. In total 430 individuals were defined as having a new or missed cancer (3.4%). When colonoscopies within two years where considered, the rate of new or missed cancers was 2.4%.

It was considered that the sensitivity of colonoscopy for cancers should be at least at high as for large adenomas (≥10mm). Therefore the base-case was set at 98%. The upper limit was set at 99% for consistency with that for intermediate/high-risk adenomas. Since other studies (e.g.[183]) suggest that the miss rate for cancers is in the region of 5%, the lower limit of the range was set at 95%.

There is no data on the specificity of colonoscopy for the detection of adenomas or cancers. Based on expert clinical opinion, the base-case estimate was set at 97%, and the range 96%-98%. This was justified on the basis that a proportion of polyps may be seen on colonoscopy and assumed to be adenomas, but may in fact be of other histological types.

APP5.5.2 CT colonography performance

In deriving estimates of the performance of CT colonography there is a similar difficulty as for flexible sigmoidoscopy; that is, the "gold standard" is generally taken to be colonoscopy, but this is known not to be 100% sensitive and specific. Therefore, studies will tend to over-estimate sensitivity and specificity of CT colonography.

The main sources of information used to inform the parameter estimates for CT colonography were two reviews published in 2005[186, 188]. The methods of the reviews differed, mainly in terms of the criteria for the studies which were included and excluded; generally Halligan et al[188] had more restrictive eligibility criteria. These reviews were augmented with information from newer studies. Clinical opinion was sought to synthesize the evidence and arrive at the parameter estimates used in the model.

Mulhall et al included in their review 33 studies of 6,393 individuals published between January 1975 and February 2005[186]. Halligan et al included 24 studies published between 1994 and 2003[188]. Both sets of authors observed that the sensitivity of CT colonography for adenomas was very heterogeneous. Mulhall et al[186] suggested that differences in the CT scanners used, such as width of collimation, type of detector and mode of imaging, were an important factor contributing to the heterogeneity. Another important source of heterogeneity is likely to be the difference between studies in the characteristics of subjects included (e.g. age, whether symptomatic or asymptomatic, etc) and, in particular, the underlying prevalence of colorectal neoplasia. Mulhall et al[186] further noted that most of the studies did not use the newest CT colonography technology, such as multidetector scanners which have improved image quality and spatial resolution.

In the per-person analysis for adenomas of any size, by Mulhall et al[186], the pooled estimate of sensitivity was 70%, with a 95% confidence interval of 53% to 87%. Nineteen of the studies in the review contained data on adenomas ≥10mm. The pooled estimate of sensitivity was 85%. The wide confidence interval (48%-100%)

illustrates the diversity in the estimates from the individual studies. From the review by Halligan et al[188], based on 2,610 individuals 206 of whom had larger adenomas (≥10mm), the pooled estimate of sensitivity was 93% (73%-98%). In a recently published study, 2,600 asymptomatic individuals aged 50 or older, from 15 US clinical centres, underwent CT colonography followed by (generally on the same day) conventional optical colonoscopy[187]. All radiologists had had specialised training and accreditation and examinations were done with multidetector-row CT scanners with at least 16 rows. The combined sensitivity for adenomas ≥10mm and cancers combined was 90% (95% CI 84%-96%). In light of the heterogeneity in the results of the studies included in the two reviews, 85% was taken as the base-case estimate for sensitivity for intermediate/high-risk adenomas with 48% and 100% as the lower and upper limits of the range respectively.

The model requires a single parameter estimate for sensitivity for adenomas <10mm, but this was not provided in the review of Mulhall at al[185]. Twelve studies reported data for adenomas 6-9mm in size and eight of these provided data for adenomas <6mm. The pooled estimates of sensitivity were 85% (95% CI 30%-95%) and 48% (95% CI 25%-70%) respectively, but there was significant heterogeneity in the results of the individual studies. Informed by these estimates, and based on the assumption that the majority of adenomas detected by screening would be <10mm, expert opinion advised that the base-case estimate of sensitivity of CT colonography for low-risk adenomas should be 53%, with a range of 45% to 60%.

There is also considerable uncertainty as regards the sensitivity of CT colonography for cancers. The review by Halligan et al[188] included 17 studies which provided relevant data, but overall this amounted to only 150 cases of cancer. The pooled estimate of sensitivity from these studies was 96% (95% CI 91%-99%). Several studies published since that review have provided lower estimates of sensitivity, but all have included small numbers of cancers. For example, Cotton et al[182] compared CT colonography with colonoscopy among 615 individuals aged 50 and older; CT colonography missed 2 of 8 cancers meaning that sensitivity was 75%. Rockey et al[184], in their comparison of air contrast barium enema, CT colonography and colonoscopy in 614 patients, estimated sensitivity of CT colonography for adenocarcinomas to be 78%. In the study of Johnson et al[187], described above, sensitivity for large adenomas and cancers combined was 90%. The EAG were of the view that the true sensitivity of CT colonography was likely to be lower than that for colonoscopy and was probably somewhere between 75% and 95%. This was taken as the range around a base-case estimate of 85%.

The model requires an estimate for the overall specificity of CT colonography for adenomas and carcinomas combined. Mulhall et al[186] estimated that the specificity for adenomas of all sizes was 86% (95% CI 84%-88%). Halligan et al[188] estimated that specificity for large (≥10mm) adenomas was 97% (95% CI 95%-99%) and for medium and large adenomas (≥6mm) was 86% (76%-93%). Johnson et al[187] estimated specificity for adenomas ≥10mm or cancers as 86% (95% CI 0.81-0.90); when lesions of 5mm or larger were considered, specificity was estimated to be 89% (95% CI 0.85-0.92). Informed by these estimates, expert opinion suggested that the base-case estimate should be 86% and with lower and upper limits of 80% and 90% respectively.

APP5.5.3 Average number of adenomas removed

Many studies have reported on numbers of adenomatous polyps found in individuals undergoing colonoscopy, but most of these tend to reported grouped data (e.g. 1-2, 3, 4 or more adenomas), thus average numbers of adenomas computed from these studies would tend to be under-estimates. Winawer et al[40], in data on 1,418 individuals who underwent colonoscopy as part of the US National Polyp Study, found that, on average, 1.9 adenomas were removed per person. Values estimated from other studies generally range between 1.4 to 2.4 adenomas per person, with several clustering around 1.8-1.9[262-268]. A lower estimate, of at least 1.3 adenomas per person, was obtained from the UK trial where flexible sigmoidoscopy was followed by colonoscopy[116], but this was again likely to be an under-estimated because the reported data were grouped. The base-case was taken as 1.9, with a range of 1.4 to 2.4.

APP5.6 Harms of screening

APP5.6.1 Probability of perforation following flexible sigmoidoscopy

Two perforation parameters are included in the model, one for when the procedure is done with polypectomy and the other for when it is done without polypectomy. Generally, however, most studies which report perforations following flexible sigmoidoscopy do not discriminate between whether the procedure was done with or without polypectomy. Because of this, and because the event itself is rare and estimates are based on very small numbers and are subject to considerable uncertainty, the same base-case value and range was used for the two parameters.

Nine studies were identified which reported information on perforations following flexible sigmoidoscopy[108, 115, 116, 169, 189, 190, 191, 193, 269]. One of these was limited to individuals aged 65 and older, and since it reported that the frequency of perforations increases with age, this study was felt to provide too high an estimate[108]. The two largest studies were the UK Flexible Sigmoidoscopy Trial and a US study of flexible sigmoidoscopy among Kaiser-Permanente recipients[108, 116]. Of the 40,764 individuals who underwent screening flexible sigmoidoscopy in the UK, one had a perforation (0.002%). This frequency corresponds with the figure from the US study (two perforations in 107,704 individuals), and was therefore used as the base-case estimate.

In a community-based screening programme of asymptomatic individuals in Canada, there were no perforations in 1,818 individuals screened[191]. Similarly, in a US study of 7,388 average risk individuals undergoing flexible sigmoidoscopy screening[193] and in the Norwegian NORCCAP trial, no perforations occurred[169]. The lower limit of the range was therefore set at 0%. The upper limit was set at 0.051%, which was the frequency observed in a study of 3,956 nurse-led outpatient flexible sigmoidoscopy examinations in the UK[189], and was consistent with the figure from a review of 21,157 sigmoidoscopies (flexible and rigid) conducted in one hospital in the Netherlands during 1990-2005 (0.057%[269]).

APP5.6.2 Probability of death due to perforation following flexible sigmoidoscopy

Data is limited on the probability of death in those who have a perforation during a flexible sigmoidoscopy. In a study of a random sample of 35,298 flexible sigmoidoscopies in US Medicare recipients aged 65 and older, there were two deaths within 14 days in the 31 individuals who had a perforation[108]. This formed the base-case estimate (6.452%). The lower limit was set at 0%. Because of a lack of data relating specifically to flexible sigmoidoscopy, the upper limit of 9.070% came from a review of 17 studies of colonoscopy conducted during 1975-2001([192]; table APP5.9).

APP5.6.3 Probability of (major) bleeding following flexible sigmoidoscopy

This parameter referred to major episodes of bleeding, rather than self-limiting bleeding during the procedure. Of the 40,764 who had flexible sigmoidoscopy in the UK trial, 12 individuals were admitted for bleeding (0.029%;[116]). This value was used for the base-case estimate. There were nine individuals who required a transfusion because of bleeding among the 107,704 who underwent flexible sigmoidoscopy in the Kaiser-Permanente series (0.002%;[190]). This value was used for the lower limit of the range. In the US study of Pabby et al[193], four episodes of post-polypectomy bleeding were noted among 7,388 individuals who had flexible sigmoidoscopy (0.054%), and this was used to set the upper limit of the range.

APP5.6.4 Probability of perforation following colonoscopy

As for flexible sigmoidoscopy, the model contains two parameters relating to the probability of perforation following colonoscopy – one relating to colonoscopy without polypectomy and the other to colonoscopy with polypectomy. In this case, however, there was sufficient data available to enable us to generate different base-case estimates and ranges for these two parameters.

There are many sources of information on perforations (and other complications, such as bleeding; see below) following colonoscopy. Data from population-based screening programmes, pilot programmes or trials and the original gFOBT randomised controlled trials and data from studies in non-screening (i.e. symptomatic) populations were reviewed. Because there were so many studies from non-screening populations, and because the applicability of the results to screening populations is not clear, consideration was limited to studies that were population-based, or concerned very large (>100,000) series from single centres, series from multiple centres, or audits of multiple practitioners. The data included in the review is summarised in (table APP5.9).

The major limitation of the data from the population-based programmes is that they relate to relatively small numbers of colonoscopies, because colonoscopy was generally done after a positive screening test. The exception to this is Poland, where a colonoscopy-based screening programme is underway. Of the 50,148 individuals who underwent colonoscopy in this programme, 11,913 had polypectomy[195]. The rate of perforation was very low; there was one case of perforation among those who had polypectomy (0.010%) and four cases among those who did not (0.008%).

A population-based study in Sweden reviewed all colonoscopies in the country

between 1979 and 1995[194]. This reported a rate of perforations of 0.107% in those who had a "diagnostic" colonoscopy (where no other procedures were performed) and 0.216% in those who had "therapeutic" colonoscopy (where polypectomy or another procedure was done). A review of 17 studies conducted during 1975-2001 which included 202,313 diagnostic and 53,311 therapeutic colonoscopies, reported estimates similar to those from the Swedish study (diagnostic=0.09%; therapeutic=0.24%;[192]). The values from the Swedish study were therefore used for the base-case estimates (i.e. colonoscopy without polypectomy, 0.107%; colonoscopy with polypectomy 0.216%).

For colonoscopy without polypectomy, the Polish colonoscopy-based screening programme provided the lower limit of the range (0.010%;[195]). The upper limit was the upper 95% confidence limit for the estimate from the Swedish study (0.249%;[194]).

For colonoscopy with polypectomy, data from the UK Flexible Sigmoidoscopy Trial was used to inform the lower limit (four perforations in 2,377 individuals; 0.168%;[116]). The upper limit was based on data from the Norwegian NORCAPP trial (1 perforation per 336 colonoscopies with polypectomy; 0.298%;[169]).

APP5.6.5 Probability of death due to perforation at colonoscopy

As for flexible sigmoidoscopy, there is limited data on the probability of death in those who have a perforation during at colonoscopy. The US Medicare study, described above, included 39,386 colonoscopies[108]. 77 individuals had a perforation and among these, there were four deaths within 14 days (5.195%). This value was used for the base-case estimate. The same range was used as for flexible sigmoidoscopy (0%-9.070%).

APP5.6.6 Probability of (major) bleeding following colonoscopy

As for flexible sigmoidoscopy, the intention was to estimate risk of major bleeding at, or following, colonoscopy. Thus, data on haemorrhages or episodes of bleeding requiring hospital admission or medical intervention were considered. Relevant studies were identified using the same criteria as for perforation at colonoscopy and are shown in table APP5.9.

The UK Flexible Sigmoidoscopy Trial reported nine admissions for bleeding, all after polypectomy, among 2,377 individuals who underwent colonoscopy (0.379%;[116]). This was taken as the base-case. In an audit of colonoscopy practice in 68 units in the UK, which reviewed 9,223 consecutive procedures over a four month period, there were six admissions for bleeding (0.065%;[196]). This was taken as the lower limit of the range. The upper limit came from data from the second round of the screening pilot in England, in which four cases of bleeding among 970 colonoscopies (0.412%;[179]) was reported.

Table APP5.9 Studies reporting complications of colonoscopy

Setting	Screening test	Numbers undergoing colonoscopy and numbers in whom complication occurred	% complications	Reference
Scotland; pilot programme since 2000; three screening rounds	gFOBT	Percentage of people with admissions for complications following colonoscopy	1st round: 0.3% 2nd round: 0.4%	Scottish Bowel Screening Programme, 2007[254]
England; pilot programme since 2000; two screening rounds	gFOBT	2nd round: in the 970 who attended for colonoscopy, there were 0 perforations, 4 cases of bleeding, 1 hypoxia, 1 bradycardia, and 5 hypotension	Bleeding: 0.412%	Weller et al, 2006[179]
Spain, Catalonia; pilot programme since 2000; three screening rounds	gFOBT	In 1st and 2nd round, 623 colonoscopies performed; 3 cases of bleeding, 1 perforation, and 2 bradycardia	Bleeding: 0.161%	Peris et al, 2008[76]
Norway; NORCCAP population-based screening trial	FSIG or FSIG+FIT	Six perforations, all following polypectomy (1 per 470 colonoscopies; 1 per 336 therapeutic colonoscopies); 4/6 were admitted to hospital	Perforation, all: 0.212% Perforation, COL with polypectomy: 0.298%	Gondal et al, 2003[169]
Poland; national screening programme; commenced 2000; individual aged 40-66 invited to take part	COL	50,148 individuals underwent colonoscopy; polypectomy was performed on 11,913; complications requiring medical intervention were reported; 5 cases of perforation (4 in those without polypectomy; 1 in those with polypectomy); 13 episodes of bleeding; 22 cardiovascular events and 11 other events occurred	Perforation, all: 0.001% Perforation, with polypectomy: 0.008% Perforation, w/o polypectomy: 0.010% Bleeding: 0.026%	Regula et al, 2006[195]
France; pilot for national programme; Haut Rhin results	gFOBT	2,724 underwent colonoscopy; 6 serious complications including 2 perforations requiring surgery and 4 cases of bleeding requiring additional endoscopic procedures; another 9 people admitted for overnight observation	Perforation: 0.073% Bleeding: 0.147%	Denis et al, 2007[75]
Italy, SCORE population-based trial; 1995-99	FSIG	775 underwent colonoscopy; 1 had bleeding requiring hospitalization; 7 had self-limiting bleeding; 1 had perforation	Bleeding, any: 1.032% Bleeding, hospitalized: 0.129% Perforation: 0.129%	Segnan et al, 2002[115]

Setting	Screening test	Numbers undergoing colonoscopy and numbers in whom complication occurred	% complications	Reference
Italy, SCORE2 population-based trial; 1999-2001	FSIG	332 underwent colonoscopy; 8 had self-limiting bleeding after polypectomy; 1 had severe haemorrhage requiring admission	Bleeding (haemorrhage): 0.301%	Segnan et al, 2005[88]
UK; Flexible Sigmoidoscopy Trial (14 centres; population-based)	FSIG	2,377 underwent colonoscopy in whole trial; 9 admissions for bleeding (all after polypectomy); 4 perforations (all after polypectomy)	Perforation: 0.168% Bleeding, with polypectomy: 0.379%	UK Flexible Sigmoidoscopy Screening Trial Investigators, 2002[116]
USA; comparison of colonoscopy vs CTC "screening" (2/3 of patients were symptomatic)	COL	3,163 individuals underwent colonoscopy; 7 perforations, 4 of which required surgical repair	Perforation, all: 0.221% Perforation, surgery: 0.126%	Kim et al, 2007[270]
Original gFOBT trials				
Sweden, Goteborg; population-based trial; screening commenced 1982	gFOBT	190 procedures; 2 perforations and 1 case of post-colonoscopy bleeding	Perforation: 1.053% Bleeding: 0.526%	Hewitson et al, 2007[65]
England, Nottingham; population-based trial; commenced 1985	gFOBT	1,475 procedures, in which there were 5 perforations and 1 major bleed (and 1 snare entrapment)	Perforation: 0.338% Bleeding: 0.068%	Hewitson et al, 2007[65]
USA, Minnesota; trial; screening commenced 1975	gFOBT	Of 12,256 colonoscopies, 4 perforation requiring surgery and 11 cases of serious bleeding (3 requiring surgery)	Perforation: 0.033% Bleeding: 0.090%	Hewitson et al, 2007[65]
Data from non- screening populations[1]				
USA; population-based data; random sample of 5% of Medicare beneficiaries in SEER areas; aged 65+; 1991-98	NA	39,386 colonoscopies were done; 51% were considered to be for the purposes of "screening/other" (vs for indications); 77 perforations; risk of perforation increased with increasing age; 4 deaths within 14 days in the 77 individuals who had a perforation	Perforation: 0.196% Probability of death following perforation: 5.195%	Gatto et al, 2003[108]

Setting	Screening test	Numbers undergoing colonoscopy and numbers in whom complication occurred	% complications	Reference
Sweden; population-based data; all colonoscopies in one county, 1979-1995	NA	6,066 colonoscopies in 4,304 patients; 4,677 classified as diagnostic (no procedures performed) and 1389 as therapeutic (polypectomy or other procedure done); there were 12 cases of bleeding , all of these in therapeutic colonoscopies, 10/12 were after polypectomy; 11/12 episodes of bleeding were during colonoscopy and ceased spontaneously; 8 perforations, 5 in diagnostic and 3 in therapeutic colonoscopies; 3 cases of cardiovascular morbidity related to colonoscopy - 2 in diagnostic and 1 in therapeutic procedures	Bleeding, all colonoscopies: 0.198% Bleeding, therapeutic colonoscopy: 0.864% Bleeding after polypectomy: 0.7% Perforation, all colonoscopies: 0.132% Perforation, diagnostic colonoscopy: 0.107% Perforation: therapeutic colonoscopy: 0.216%	Dafnis et al, 2001[194]
USA, network of 45 ambulatory endoscopic centres; 1999	NA	116,000 colonoscopies performed; 37 perforations reported	Perforation: 0.032%	Korman et al, 2003[271]
USA, Mayo Clinic; review of all patients undergoing colonoscopy in 1980-2006	NA	258,248 colonoscopies performed; 180 patients had a perforation; of these, 165 were managed operatively	Perforation: 0.069%	Iqbal et al, 2008[272]
UK; audit of colonoscopic practice in 68 units (including five paediatric units)	NA	9,223 consecutive colonoscopies over a 4 month period; bleeding was reported for 34 patients in total, for 13 after colonoscopy (6 required admission) and for 21 during colonoscopy and requiring active intervention; 12 patients had perforation; 10 deaths were reported within 30 days of the procedure and in 5 of these individuals, the colonoscopy had been normal; colonoscopy was considered possible factor in death of 6/10 patients	Any bleeding: 0.369% Bleeding requiring admission: 0.065% Perforation: 0.130% Death: 0.065% or 0.108%	Bowles et al, 2004[196]

Setting	Screening test	Numbers undergoing colonoscopy and numbers in whom complication occurred	% complications	Reference
Germany; survey of practice among 160 GIs; 1998-99	NA	82,416 colonoscopies and 14,249 polypectomies; 4 perforations in colonoscopies and 9 in polypectomies; 1 case of haemorrhage (arterial or venous bleeding of > 1 minute) in colonoscopies, and 37 in polypectomies; 1 death in each group	Perforation, all: 0.013% Perforation, colonoscopy: 0.005% Perforation, polypectomy: 0.063% Bleeding, all: 0.039% Bleeding, colonoscopy: 0.001% Bleeding, polypectomy: 0.260% Death, colonoscopy: 0.001% Death, polypectomy: 0.260%	Sieg et al, 2001[273]
Pooled estimate from 17 studies, 1975-2001	NA	202,313 diagnostic colonoscopies and 53,311 therapeutic colonoscopies; reported perforation rates and mortality rates (diagnostic perforations n~18,208; therapeutic perforations n~12,795; diagnostic mortality n~1,214; therapeutic mortality n~1,599)	Perforation, diagnostic: 0.09% Perforation, therapeutic: 0.24% Perforation, all: 0.121% Mortality, diagnostic: 0.006% (rate per procedure) Mortality, therapeutic: 0.03% (rate per procedure) Prob death given perforation, diagnostic: ~6.67%[1] Prob death given perforation, therapeutic: 12.50%[1] Prob death given perforation, all: 9.07%[1]	Misra et al, 2004[192]
Pooled estimate of 10 series	NA	Review of 10 series; pooled estimate based on 393 perforations in 30,366 endoscopies	Perforation: 0.24%	Lüning et al, 2007[269]
UK; survey of 28 primary care units performing endoscopy	NA	1,386 colonoscopies; 3 perforations requiring admission; 3 other complications requiring admission	All requiring admission: 0.433% Perforation: 0.216%	Galloway et al, 2002[274]

COL=colonoscopy; CRC=colorectal cancer; CTC=CT colonography; DCBE= double contrast barium enema; FIT=faecal immunochemical test; gFOBT=guaiac faecal occult blood test; FSIG=flexible sigmoidoscopy; GIs=gastroenterologists; IBD=inflammatory bowel disease; NA=not applicable; NR=not reported

1 these deaths may not all have been due to perforations

APP5.7 Inadequate or incomplete endoscopic procedures

In a relative small proportion of individuals, an endoscopic procedure (either flexible sigmoidoscopy or colonoscopy) is incomplete or inadequate and the individual would have another procedure. This constitutes an additional cost to the screening programme. It was assumed that in the event that a flexible sigmoidoscopy is incomplete or the bowel preparation is inadequate, the individual would be invited to have another flexible sigmoidoscopy. If a diagnostic colonoscopy is inadequate or incomplete, the individual would undergo CT colonography.

APP5.7.1 Flexible sigmoidoscopy

Four reliable sources of information were identified to inform the parameter estimates for inadequate flexible sigmoidoscopy; these were all trials and are summarised in table APP5.10. The lowest frequency was from the UK Flexible Sigmoidoscopy Trial, where 5% of participants had a repeat procedure[116]. In the three other trials, between 11% and 14% had either poor bowel preparation or an inadequate procedure with limited depth of insertion or only partial visualisation of the distal bowel[89, 117, 169]. The data from these studies was pooled to produce a base-case estimate of 9%. The lower and upper limits for the range were based on the estimates from the individual studies and set at 5% and 14%, respectively.

APP5.7.2 Colonoscopy

Data were available from most of the population-based screening programmes, pilot programmes or trials on the percentage of individuals in whom the caecum was not reached for any reason during colonoscopy (table APP5.11). The figures ranged from 3% in the second round of the screening pilot in England[179] to 24% in the SCORE trial in Italy[115]. Most of the estimates were in the range 11%-13%.

The base-case estimate was taken to be 13%. As well as being consistent with the data from the screening programmes, pilots and trials, this figure was reported in a review of 331,608 colonoscopies undertaken for screening purposes in individuals aged 50-74 years in Ontario, Canada[197]. It is also compatible with a figure for Ireland which became available after the review was completed; of 909 colonoscopies done in a Dublin hospital, the caecal intubation rate was 88%[275].

The view of the clinical experts on the EAG was that a population-based screening programme, with rigorous quality assurance, should be able to achieve complete colonoscopy in about 92% of individuals. This was compatible with figures from the second and third round of the pilot programme in Scotland (Paula McClements, personal communication) and the colonoscopy-based screening programme in Poland[195], and so was used for the lower limit of the range. The upper limit was set at 16%.

TABLE APP5.10 Probability that flexible sigmoidoscopy is inadequate or incomplete[1]

Setting	Procedure	Numbers undergoing FSIG and numbers in whom FSIG was incomplete/bowel prep was inadequate	% inadequate or incomplete bowel prep, or FSIG repeated	Reference
UK; Flexible Sigmoidoscopy Trial (14 centres; population-based)	FSIG	40,764 underwent FSIG; 2,141 had repeat FSIG mainly due to inadequate bowel prep	repeat FSIG: 5.26%	UK Flexible Sigmoidoscopy Screening Trial Investigators, 2002[116]
Norway; NORCCAP population-based screening trial	FSIG or FSIG+FIT	12,960 had FSIG; bowel prep considered "poor" in 1,783	poor bowel prep: 13.76%	Gondal et al, 2003[169]
Italy, SCORE3 trial; community-based; 2002-04	FSIG	1,944 FSIG attendees; 22 had inadequate bowel prep and refused to fix another date; another 192 had only a partial examination of the distal bowel	incomplete FSIG: 11.01%	Segnan et al, 2007[89]
USA; PLCO trial; volunteers aged 50-74; 1993-2001	FSIG	64,658 received initial sigmoidoscopy; procedure inadequate (depth of insertion <50cm and/or visualization of <90% of intestinal mucosa) in 7,099	inadequate FSIG: 10.98%	Weissfeld et al, 2005[117]

FIT=faecal immunochemical test; FSIG=flexible sigmoidoscopy

1 used in model to estimate proportion of individuals who have a repeat flexible sigmoidoscopy

TABLE APP5.11 Probability that colonoscopy is incomplete[1]

Setting	Screening test	Numbers undergoing colonoscopy and numbers in whom procedure is incomplete or inadequate	% incomplete	Reference
Scotland; pilot programme since 2000; three screening rounds	gFOBT	1st round: 2,961 underwent colonoscopy; complete in 2,628 2nd round: 2,795 underwent colonoscopy; complete in 2,561 3rd round: 1,661 underwent colonoscopy; complete in 1,538	1st round: 89% 2nd round: 92% 3rd round: 93%	Paula McClements (personal communication)
England; pilot programme since 2000; two screening rounds	gFOBT	2nd round: 970 underwent colonoscopy; not completed satisfactorily in 32 of these (in addition, a very small number of people (n=3) were not referred for colonoscopy because they were deemed unfit at the assessment appointment with the nurse)	2nd round: 3%	Weller et al, 2006[179]
Italy; multiple screening programmes	gFOBT/FIT or FSIG	2004 review, gFOBT/FIT screening: incompletion rate of colonoscopy 2006 review, gFOBT/FIT screening: incompletion rate of colonoscopy	2004: 9% 2006: 11%	Zorzi et al, 2006; Zorzi et al, 2008[77, 252]
Italy; population-based screening, Tuscany, 2006-07	gFOBT	Caecum not reached for 65 of 903 individuals undergoing colonoscopy	7%	Sali et al, 2008[181]
Italy, SCORE population-based trial of FSIG, 1995-99	SIG	Colonoscopy incomplete in 188 of 775	24% (variability between centres: 13%-48%)	Segnan et al, 2002[115]
Italy, SCORE3 trial; community-based ; 2002-04	FIT, FSIG or COL	FIT: caecum not reached for 9 of 81 FSIG: caecum not reached for 7 of 124 Colonoscopy: caecum not reached for 212 or 1,595 screened	FIT: 11% FSIG: 6% COL: 13% Overall: 13%	Segnan et al, 2007[89]

Setting	Screening test	Numbers undergoing colonoscopy and numbers in whom procedure is incomplete or inadequate	% incomplete	Reference
Spain, Catalonia; pilot programme since 2000; three screening rounds	gFOBT	In 1st and 2nd rounds, colonoscopies were complete in 408 of 442 individuals; raw data for 3rd round not reported	1st & 2nd round: 8% 3rd round: 9%	Peris et al, 2008[76]
France; pilot for national programme; Haut-Rhin results	gFOBT	Percentage where caecal intubation not achieved	5%	Denis et al, 2007[75]
Netherlands; pilot programme; 1st round; 2006-07	gFOBT or FIT	Caecum not reached during initial colonoscopy in 25 of 383 individuals	7%	van Rossum et al, 2008[87]
Australia; pilot programme, 2002-04	FIT	223 colonoscopies of 1,833 were considered inadequate (some of these colonoscopies were done on individuals referred for reasons other than a positive FIT test)	12%	Bowel Cancer Screening Pilot Monitoring and Evaluation Steering Committee, 2004[257]
Norway; NORCCAP population-based screening trial	FSIG or FSIG+FIT	Caecal intubation not achieved at first colonoscopic attempt in 270 of 2,524 individuals	11%	Gondal et al, 2003[169]
Poland; national screening programme; commenced 2000; individual aged 40-66 invited to take part	COL	Caecum not reached in 4,463 of 50,148 individuals screened	9%	Regula et al, 2006[195]
Data from non-screening populations				
Canada; colonoscopies in those aged 50-74 in Ontario in 1999-2003[2]	NA	43,483 of 331,608 colonoscopies were incomplete	13%	Shah et al, 2007[197]

COL=colonoscopy; CRC=colorectal cancer; FIT=faecal immunochemical test; gFOBT=guaiac faecal occult blood test; FSIG=flexible sigmoidoscopy; IBD=inflammatory bowel disease; NA=not applicable

1 *used in model to estimate proportion of individuals who will have another procedure, in this case CT colonography*

2 *authors state that this was an "approximate "screening population" since those with CRC, IBD, bowel resection, or colonoscopy in previous 5 years were excluded*

APP5.8 Utility/health-related quality of life

The search of the Tufts Medical Centre CEA Registry yielded 39 utility weights from seven publications. After combining the results with those of the PubMed search, 14 studies were identified which contained utility scores for patients with colorectal cancer and were considered most applicable to the population in the current study; these are summarised in table APP5.12.

The studies identified had several limitations, and there were large variations in the results. None of the studies was conducted in Ireland. Most included small sample populations and the characteristics of the study populations varied. There was wide variation in the instruments used to assess the HRQoL, from the cancer-specific quality of life measures, EORTC QLQ C30 and EORTC QLQ C38, to the more generic instrument, EQ 5D. The health states evaluated varied greatly between studies and no studies evaluated health states that mapped directly onto those in the economic model used in this HTA.

It was necessary to assign estimates of utility for each of the health states included in the model: (1) cancer-free; (2) stage I colorectal cancer; (3) stage II colorectal cancer; (4) stage III colorectal cancer; and (5) stage IV colorectal cancer. Because of the variations in the results of the reviewed studies, and hence the uncertainty associated with the utility scores for these health states, two sets of utility scores were selected. Those for the base-case were from the study of Ramsey et al[199], while the second set, which were explored in a sensitivity analysis, were from Ness et al[202]. This allowed the impact of incorporating different utility weights, and patterns of utility scores, in the model to be investigated. These studies represented two distinct possibilities in term of HRQoL - the first that HRQoL is reduced in all those with colorectal cancer, to a similar extent irrespective of stage, compared to the cancer-free population, and the second that HRQoL is reduced in those with colorectal cancer, but that the amount by which it is reduced increases with increasing stage.

APP5.8.1 Utility values used in the base-case analysis

Evidence from the literature suggests that the HRQoL weights reported by survivors of colorectal cancer is higher than that of individuals undergoing treatment for the disease[199, 276, 277]. This provided the rationale for the choice of the study of Ramsey et al for the base-case, since these authors evaluated HRQoL in those considered to be survivors of colorectal cancer, and reported results by stage at diagnosis[199]. One hundred and seventy-three individuals with colorectal cancer completed two self-administered questionnaires: the FACT-C and the HUI Mark III. The HUI utility scores were lower in the first three years post-diagnosis (mean 0.80) compared to five years post-diagnosis (mean 0.85). There was no variation in utility scores by stage at diagnosis: for stage I to IV, utilities were 0.84, 0.86, 0.85 and 0.84, respectively.

The utility value of 0.94, from the study of Fryback et al was assigned to the "cancer-free state" in the model[198]. This is based on the concept that HRQoL weights for individuals without chronic conditions may not be 100 (or 1.00)

because people may still suffer from other co-morbidities or acute conditions, or not identify themselves as being in "excellent health". The same utility score, of 0.85, for all stages of disease was selected from the study of Ramsey et al[199]. This was adjusted for the population average HRQoL weight (i.e. 0.85*0.94). Therefore a utility score of 0.80 was assigned to the four stages of colorectal cancer in the model. The range for the sensitivity analysis was derived from a beta distribution (0.94*Beta(3.92,0.69) and was 0.43-0.94.

APP5.8.2 Utility values used in sensitivity analysis

Ness et al[202] reported utility scores for stage-dependent outcome states of colorectal cancer. The study included individuals who had previously had colorectal adenomas removed. The authors suggest that these individuals may have had a greater aversion to outcome states of colorectal cancer and this could have led to lower utility valuations. Participants were presented with descriptions of stage-dependent outcome states and utilities were measured using the Standard Gamble technique. Data from 81 participants were analysed covering seven different outcomes states, based on combinations of cancer site, stage and treatment received (e.g. stage II/III rectal cancer treated with resection/chemotherapy/radiation). All outcome states were described as being 30 years in duration with the exception of terminal states, which were 18 months in duration. Data was selected from among the seven outcome states and assigned to stages I-IV colon and rectal cancer (table APP5.13). Weighted averages of these were computed to produce utilities for colorectal cancer stages I-IV, with 95% confidence intervals.

TABLE APP5.12 Summary of studies of health-related quality of life for colorectal cancer

Study setting	Study size and sample	HRQoL instrument	Health states	Utility value	Reference
US	N=1,142 individuals aged 45 to 85 years.	Time trade-off	Non CRC health state. Age-dependent utility for various degrees of morbidity	0.94	Fryback and Lawrence, 1997[198]
US	N=246 Patients at a veterans hospital aged 50-75 years.	Time trade-off	HRQoL associated with CRC screening: Flexible sigmoidoscopy every five years for 20 years A. Unscreened (n=62) B. Screened (n=24) Colonoscopy every five years for 20 years C. Unscreened D. Screened Colonoscopy every five years for 20 years with one perforation requiring surgery E. Unscreened F. Screened	Median no. of days patient is willing to give up (IQR): A. 91 (1-365) B. 0 (0-30) C. 183 (1-365) D. 7 (0-106) E. 365 (21-1460) F. 53 (0-365)	Dominitz and Provenzale, 1997[278]
Norway	N=94 Dukes B and C CRC patients	EQ5D, EORTC QLQ-C30, simple QoL scale	A. Dukes B and C with and without adjuvant chemotherapy - all three QoL instruments B. EQ5D C. EORTC QLQ-C30 D. Simple QoL scale	Median (range) A. 0.83 B. 0.78 (0.33-1) C. 0.83 (0.17-1) D. 0.85 (0.40-1)	Norum et al, 1997[279]

Study setting	Study size and sample	HRQoL instrument	Health states	Utility value	Reference
US	N=90 CRC patients	Standard gamble	A. Stage I RC or Stage I/II CC treated with resection only B. Stage III CC treated with resection and chemo without significant side effects. C. Stage III CC treated with resection and chemo with significant side effects D. Stage II/III rectal cancer treated with resection/chemo/ radiotherapy E. Stage II/III rectal cancer treated with resection /chemo/ radiotherapy/permanent ostomy. F. Stage IV metastatic/unresectable disease without ostomy. G. Stage IV metastatic/unresectable disease with ostomy.	Mean (95%CI) A. 0.74 (0.69,0.78) B. 0.70 (0.63,0.77) C. 0.63 (0.56,0.70) B/C 0.67 (0.62, 0.72) D. 0.59 (0.54,0.64) E. 0.50 (0.44,0.56) F. 0.24 (0.16,0.32) G. 0.27 (0.18,0.36) F/G. 0.25 (0.20,0.31)	Ness et al, 1999[202]
Netherlands	Three panels of 15 Dutch medical experts	EQ5D+C	A. CRC, state after intentionally curative primary therapy B. CRC, stage of diagnosis and primary therapy C. CRC, irradically removed or metatstatic carcinoma	A. 0.80–0.85 B. 0.50 –0.60 C. 0 – 0.20	Stouthard et al, 2000[280]
US	N=173 Survivors of CRC	HUI Mark III	A. Stage I B. Stage II C. Stage III D. Stage IV E. Mean (for survivors) F. Mean (for those who died)	Mean (sd) A. 0.84 (0.17) B. 0.86 (0.14) C. 0.85 (0.14) D. 0.84 (0.12) E. 0.85 (0.15) F. 0.65	Ramsey et al, 2000[199]

Study setting	Study size and sample	HRQoL instrument	Health states	Utility value	Reference
Japan	N=110 Post-op RC patients	EQ5D	A. Japanese tariff score for patients with a stoma B. Japanese tariff score for patients without a stoma C. Social tariff score for patients with a stoma D. Social tariff score for patients without a stoma	Mean (sd) A. 0.836 (0.713) B. 0.870 (0.163) C. 0.842 (0.191) D. 0.865 (0.220)	Hamashima, 2002[281]
Netherlands	N= 1,530 RC patients undergoing TME	EQ5D	A. Randomisation to PRT or surgery B. Time from PRT to surgery C. Time from surgery to discharge for patients with microscopically negative rectal metastases at surgery in the PRT+TME group D. Time from surgery to discharge for patients with microscopically negative rectal metastases at surgery in the TME group E. Time from surgery to discharge for patients with microscopically positive rectal metastases or incomplete local resection at surgery in the PRT+TME group F. Time from surgery to discharge for patients with microscopically positive rectal metastases or incomplete local resection at surgery in the TME group G. Time from surgery to discharge for patients with distal metastases at surgery in the PRT+TME group H. Time from surgery to discharge for patients with distal metastases at surgery in the TME group I. Local recurrence after PRT and TME J. Local recurrence after TME K. Distant recurrence after PRT and TME L. Distant recurrence after TME M. Local and distant recurrence after PRT and TME N. Local and distant recurrence after TME O. Greater than 9 months post surgery for patients with microscopically positive rectal metastases or incomplete local resection and no stoma P. Greater than 9 months post surgery for patients with microscopically negative rectal metastases and no stoma	A. 0.78 B. 0.70 C. 0.78 D. 0.11 E. 0.21 F. 0.09 G. 0.17 H. 0.73 I. 0.80 J. 0.67 K. 0.70 L. 0.64 M. 0.48 N. 0.45 O. 0.89 P. 0.86	van den Brink et al, 2004[282]

Study setting	Study size and sample	HRQoL instrument	Health states	Utility value	Reference
Netherlands	N=167 Post-op RC patients	EQ5D, EORTC QLQ-C30 & QLQ-CR38	A. Low-colorectal anastomosis B. Abdominoperineal resection C. Colo-anal J-pouch	EQ5D scores presented graphically	Gosselink et al, 2005[283]
UK	N=201 CRC patients	EORTC QLQ-C30, FACTC, SF12, EQ5D	A. CC B. RC Six weeks post curative resection for CRC.	Mean EQ5D score A. 0.824 B. 0.761	Wilson et al, 2006[284]
Netherlands	N=97 CRC patients with liver metastases	EQ5D, EORTC QLQ-C30	Group 1 - Hepatic surgery Group 2 – Inoperable disease identified during surgery Group 3 – Outpatient with inoperable disease diagnosed before surgery	EQ-5D Index scores at 2 weeks, 3 months and 6 months post surgery (presented graphically).	Langenhoff et al, 2006[285]
Sweden	N=285 Post-op CC patients	EQ5D and EORTC QLQ-C30	A. LCR Pre-op B. LCR 2 weeks C. LCR 4 weeks D. LCR 12 weeks E. OCR pre-op F. OCR 2 weeks G. OCR 4 weeks H. OCR 12 weeks	Mean EQ5D score A. 0.745 B. 0.668 C. 0.770 D. 0.856 E. 0.764 F. 0.627 G. 0.752 H. 0.875	Janson et al, 2007[286]
Japan	N=127 CRC patients over 75 years of age	EQ5D, SF-12	A. Before surgery B. Immediately after surgery C. 3 months after surgery D. 6 months after surgery	Mean EQ5D score A. 0.769 B. 0.764 C. 0.790 D. 0.806	Amemiya et al, 2007[287]

Study setting	Study size and sample	HRQoL instrument	Health states	Utility value	Reference
Netherlands	N=31 Post-op RC patients	EQ5D, EQ-VAS, EORTC QLQ C30 & CR38	A. Transanal endoscopic microsurgery B. TME	Mean EQ5D score (range) A. 0.81 (-0.18, 1) B. 0.76 (0.26, 1)	Doornebosch et al, 2007[288]
US	N=692 Patients diagnosed with breast , colon (n=169), or lung cancer, or melanoma.	HALex	Colon cancer patients: A. <1 year after diagnosis B. 1-5 years after diagnosis C. >5 years after diagnosis	Mean (sd) A. 0.67 (0.21) B. 0.68 (0.22) C. 0.71 (0.25)	Ko et al, 2003[289]

CC=Colon cancer; CRC=Colorectal cancer; EORTC=European Organisation for Research and Treatment of Cancer; HALex=Health and Activities Limitation Index; IQR=inter-quartile range; LCR= laproscopic colonic resection; OCR=open colonic resection; PRT=preoperative radiotherapy; RC=Rectal cancer; sd=standard deviation; TME=Total mesorectal excision,

Table APP5.13 Utility scores for colon and rectal cancer by stage at diagnosis (based on[202])

Stage	Colon cancer	Rectal cancer	Colorectal cancer*
	mean (95% CI)	mean (95% CI)	mean (95% CI)
I	0.74 (0.69-0.78)	0.74 (0.69-0.78)	0.74 (0.69-0.78)
II	0.74 (0.69-0.78)	0.59 (0.54-0.69)	0.69 (0.64-0.73)
III	0.67 (0.62-0.72)	0.59 (0.54-0.69)	0.64 (0.59-0.69)
IV	0.25 (0.20-0.31)	0.25 (0.20-0.31)	0.25 (0.20-0.31)

** weighted average, assuming 64% colon cancers and 36% rectal cancers*

APP5.9 Surveillance of screen-detected adenomas

APP5.9.1 Distribution of adenomas detected

The second round of the screening pilot in England classified individuals who had screen-detected adenomas into low, intermediate or high-risk[179]. The risk classification was based on size and multiplicity so was compatible with the categorisation in the surveillance guidelines used to inform the post-colonoscopy follow-up strategy in the economic model used in this HTA[153]. Of the 301 individuals who had one or more adenomas detected and classified, 132 (44%) were categorised as low-risk, 120 (40%) were categorised as intermediate-risk and 49 (16%) were categorised were high-risk; of those who had intermediate or high-risk adenomas, 71% were intermediate-risk and 29% were high-risk. This distribution was broadly similar to that reported from the first round of the pilots in Scotland and England[58]. These values were used to sub-divide the group with intermediate/high-risk adenomas entering surveillance into intermediate-risk and high-risk.

APP5.9.2 Compliance with surveillance

No data were identified on compliance with surveillance in individuals who have had adenomas removed as part of a colorectal cancer screening programme. Nor was this information available from any of the pilot programmes. In a recent review of compliance with surveillance, Rapuri et al[290] identified nine relevant sources of information, including routine and clinical data, trials and observational studies. Rates of compliance ranged from 52% to 85%. Since it is not clear the extent to which these finding will apply to population-based screening, it was assumed that compliance with follow-up colonoscopy would be the same as compliance with diagnostic colonoscopy (86%), with a range of 81% to 90%.

APP5.9.3 Rates of metachronous adenomas and carcinomas

Model the post-colonoscopy surveillance of individuals who have had adenomas removed requires data on the risk of subsequent adenomas and carcinomas, according to the whether the adenoma(s) removed were low, intermediate or high-risk. While there are now a large number of studies which include recurrence rates in individuals who have had adenomas removed, most of these do not report risk according to multiplicity and size of adenomas removed at the baseline colonoscopy. Ten studies were identified which provided some information on risk of metachronous adenomas or carcinomas classified by size or number of previous adenomas[40, 113, 264, 266, 268, 291-295]. It should be noted that none of the studies categorised previous and subsequent adenomas in a way that entirely corresponded to the categories of low, intermediate and high-risk defined in the surveillance guidelines[153], so some inferences and estimation were required in synthesizing the results of the studies to produce model parameters. Also most studies were not in screening populations, and it is not clear whether risks of subsequent adenomas and carcinomas might differ in those who have had adenomas found through screening or on a symptomatic basis. Since the model requires annual transition probabilities, it was assumed that risk of developing new adenomas was constant over time until the next colonoscopy and, on this basis, the annual risks of adenomas and carcinomas were estimated in each of the identified studies. This assumption may not be entirely true but since the current surveillance guidelines allow for another colonoscopy in a maximum of three years[153], it is not completely unreasonable. To generate estimates for the model, weighted averages were computed from the studies which provided relevant data for each category of previous and subsequent neoplasia. These estimates are shown in table APP5.14.

Table APP5.14 Metachronous adenomas and carcinomas: annual transition probabilities

Subsequent neoplasia	Adenoma history[1]		
	Low	Intermediate	High
N*-low	11%	15%	18%
N*-intermediate	2%	4%	6%
N*-high	2%	4%	6%
N*-any adenoma	15%	23%	30%
N*-cancer[2]	0.19%	0.31%	1.13%

N: normal epithelium (i.e. after having had adenoma(s) removed)*

1 category of most serious adenoma(s) removed at baseline colonoscopy

2 colorectal cancer of any stage

APP5.10 Other data

APP5.10.1 Colorectal cancer incidence data

The data on incidence of colorectal cancer used for the model calibration was obtained from the National Cancer Registry Ireland (www.ncri.ie). It related to numbers of incident, primary, invasive colorectal cancers (ICDO2 C18-C20) in the years 2002-2005. Four cases were omitted because of missing information on age and gender. The 8,172 remaining incident cancers were tabulated by age and stage at diagnosis.

APP5.10.2 Mortality data

The model incorporates three causes of mortality: deaths due to colorectal cancer, deaths due to perforations of the bowel at endoscopy and deaths due to other causes. The data sources and parameter estimates for deaths due to bowel perforations are described above.

APP5.10.2.1 Deaths from colorectal cancer

Information on all deaths from colon or rectal cancer during 2002-05 (ICD9 153 and 154), registered by the Central Statistics Office, was obtained from the National Cancer Registry, and tabulated by age. This data was used for model calibration.

APP5.10.2.2 Deaths from other causes

The annual probability of dying from causes other than colorectal cancer was estimated using standard life expectancy tables for the years 2001-2003 obtained from the Central Statistics Office[296]. These describe the probability of dying from all causes during a given year depending on age and sex. The life tables were adjusted by subtracting deaths from colorectal cancer thus providing estimates of deaths from other causes.

APP5.10.3 Colorectal cancer survival

Estimates of relative survival, based on deaths from all causes, were obtained from the National Cancer Registry Ireland, for individuals diagnosed during 2002-2005. Cases where diagnosis was made at autopsy were excluded along with instances of multiple primary tumours; when such cases were excluded 8,012 incident cancers remained.

APPENDIX 6

Cost estimates

APP6.1 Costs of screening tests and associated issues

APP6.1.1 Faecal tests

A wide range of guaiac and immunochemical-based test are available and their unit costs vary. In undertaking this HTA it was not possible to assume that a specific test would be used. If, and when, a screening programme is set-up, it is likely that suppliers would be invited to tender to provide and analyse screening tests within a specific cost (as happened for CervicalCheck) or the programme would negotiate a special rate with a specific provider (as was done in the Scottish programme; Callum Fraser, personal communication). This means that there is considerable uncertainty in the likely costs of faecal tests.

In estimating costs, the starting point was an assumption from the NCSS that an immunochemical test would be likely to cost approximately €10 per person screened (Patrick Cafferty, personal communication). Since the technical effort involved in analysing gFOBTs and immunochemical tests differs, it was decided to partition costs into two components. The first (fixed) cost related to all tests dispatched to screening invitees, and was assumed to include the costs of the kit itself and associated consumables, such as a letter of invitation to participate in screening, and outward postage and packing ("cost of kits"). The second (variable) cost related to all tests returned by screening participants and included the costs of return postage, analysis and associated quality control, and reporting results ("cost of processing/analysis"). Several suppliers and users of kits provided costs of kits, reagents and disposables (Cillin Condon, Ian Cowie, Paudy Gorman, Bart Vandecasteele, personal communications). Access was available to workforce planning modelling undertaken by the Scottish Bowel Cancer Screening Programme, which provided information on workload and numbers and grades of staff required to book in, analyse, quality control and report results of guaiac and immunochemical tests (Callum Fraser, personal communication). Staff costs in Ireland were estimated from Department of Health and Children salary scales. Population statistics were used to estimate numbers of kits dispatched per annum. Base-case estimates of uptake were applied to compute numbers of kits returned. From this information, the unit cost of a gFOBT kit was estimated to be €1.70 per person invited and the unit cost of processing/analysis was estimated to be €7.81 per kit analysed. The unit cost for an FIT kit was estimated as €3.75 per person invited the cost of processing/analysis was estimated to be €11.60 per kit analysed. To accommodate the considerable uncertainty in these costs, the upper and lower limits for the range for each of these parameters were set at 20% above and below the base-case estimate respectively.

APP6.1.2 Flexible sigmoidoscopy

The direct health care cost of a flexible sigmoidoscopy was based primarily on an audit of resource use among almost 40,000 individuals taking part in the UK Flexible Sigmoidoscopy Trial[200]. The resources included labour, consumables, capital and overheads. At 2000 prices, the cost of a flexible sigmoidoscopy, based on an annual throughput of 2,000 procedures per centre, was estimated as £56. When converted to Euro using the exchange rate published by the Central Bank of Ireland, and inflated to 2008 values using the consumer price index for health, this resulted in an estimated cost of €120. This figure was lower than most other estimates from the literature (reviewed in Whynes et al[200]). Also considered were the VHI Healthcare schedule of fees (€92.80), and expert opinion which suggested that the cost of a flexible sigmoidoscopy was unlikely to be more than double this amount. The base-case was set at €150, with a lower and upper limit of €120 and €180 respectively (i.e. +/- 20%). The same values were used irrespective of whether the flexible sigmoidoscopy involved polypectomy or not.

APP6.1.3 Diagnostic and surveillance tests

The unit cost of a colonoscopy was estimated from Diagnostic Related Group (DRG) costs[201]. It was computed as a weighted average of the DRGs for other, same-day, colonoscopy (DRG G44C), other day-case colonoscopy (G44O) and complex day-case colonoscopy (G43O), which gave a base-case estimate of €650. The lower and upper limits were set at 20% below (€520) and 20% above (€780) this estimate.

For CT colonography, the unit cost was based on expert opinion and the cost paid by the HSE for a patient to have the procedure in a private facility. The base-case estimate was €550 and the range was taken as +/-20% around this (i.e. €440-€660).

APP6.1.4 Histopathology

In considering the time, consumables, and tasks involved, expert opinion suggested that the pathology costs for a colorectal cancer were likely to be around eight times higher than those for a single adenoma. However, no information could be obtained on the pathology costs for adenomas and colorectal cancers in Ireland. The estimates were, therefore, based on the ones used by Tappenden et al - £30 for an adenoma and £250 for a cancer[118]. These were converted to Euro using the exchange rate published by the Central Bank of Ireland, and inflated to 2008 values using the consumer price index for health, giving base-case estimates of €65 for an adenoma and €530 for a cancer. The lower and upper limits were again set at +/-20% around the base-case (i.e. €52-€78 for adenomas and €424-€636 for cancers).

APP6.1.5 Harms of screening

The costs of treating a bowel perforation and of managing a major bleed following endoscopy procedures were estimated from DRG costs[201]. The cost of treating a bowel perforation was computed as a weighted average of the DRG costs for minor small and large bowel procedures with and without complication or comorbidity (DRG G05A and G05B). This provided a base-case estimate of €10,200. As for other costs, the lower and upper limits were set at +/-20% around the base-case (i.e. €8,160, €12,240). Major bleeding was assumed to result in hospital admission, and the cost was estimated as a weighted average of DRGs for gastrointestinal haemorrhage (G61A and G61B). The base-case estimate was €3,079, and the range €2,463-€3,695 (+/-20%).

APP6.2 Lifetime costs of managing colorectal cancer in Ireland

Cost of managing colorectal cancer data are country specific and highly dependent on the structure of the system within which healthcare is delivered. The overall costs are essentially composed of two parts: the quantity of resources used, and the cost per unit for each type of resource. Both the quantity of resources and the unit cost of each resource vary between countries and at different points in time. Therefore, an essential component of the HTA was to establish the cost of managing colorectal cancer in Ireland.

Briefly, the lifetime costs of managing colon and rectal cancer, which included costs of diagnosis, treatment and follow-up, were simulated using (static) decision tree analysis of colorectal cancer treatment pathways. The analysis was undertaken in Microsoft® Excel. The treatment pathways were developed from guidelines[297-301] and expert opinion, and were site (colon/rectum)- and stage-specific. Costs associated with diagnosis, hospitalisation, surgery, radiotherapy, chemotherapy, supportive care, clinician visits and other healthcare professional staff costs, laboratory costs, other ancillary medications and follow-up were considered. A range of options are available for diagnosis, treatment and follow-up of colorectal cancer, and it was necessary to establish which are used, and in what proportions of patients, in Ireland. Resource use estimates were based on data derived from several sources including the National Cancer Registry Ireland (NCRI), local hospital databases and protocols, literature review and expert clinical opinion. Resource use items were then valued using Irish unit cost data. Follow-up was assumed to continue for 5-years post-diagnosis. Separate cost estimates were produced for screen-detected and symptomatic cancers (i.e. all those not detected by screening). Estimates were produced for colon and rectal cancer separately and combined, assuming 64% of cases arise in the colon and 36% in the rectum. Costs were discounted at 4% per annum.

There is a lack of robust Irish data on the costs of medical procedures, so these had to be estimated from a variety of sources. In addition, most of the available treatment data for Ireland is "high-level" (e.g. databases tend to record that a patient had chemotherapy or radiotherapy, but not the specific drugs administered or regimes used), and data regarding some aspects of management is scant or non-existent (e.g. use of newer biological agents, attendance at follow-up, recurrence, etc). Thus it was necessary to make many assumptions regarding resource use. This was done based on expert opinion and hospital protocols, where available, but this, together with the

limitations of the unit cost data, means that there is considerable uncertainty regarding the overall estimates of direct medical costs. This uncertainty was explored in sensitivity analyses. The sensitivity analysis was used to determine the lower and upper limits of the cost estimates used in the model.

Because of these uncertainties in the Irish data, a literature review of studies published since 1996 which reported stage-specific costs of managing colorectal cancer was conducted. This allowed comparison of the cost estimates derived in this HTA with those from other settings.

APP6.2.1 Unit cost data

The unit cost data included in the model are summarised in table APP6.1. Unit cost data for in-patient procedures were obtained from 2006 Diagnosis Related Group (DRG) costs[201]. Unit costs for diagnostic procedures were obtained from local hospital finance departments. Costs of laboratory tests were obtained from a Dublin university teaching hospital. The cost of radiotherapy was estimated by expert clinical opinion from a specialist Dublin radiotherapy centre and was based on the recent study by Ploquin and Dunscombe[302]. Every effort was made to incorporate Irish unit cost data. However, where data were not available it was adapted from the UK. The cost of best supportive care for colon cancer was obtained from a study conducted by Guest et al[303]. UK costs were converted to Euro using the exchange rate published by the Central Bank of Ireland. The unit cost data included in the treatment pathway decision trees were inflated to 2008 values using the consumer price index for health.

APP6.2.1.1 Chemotherapy costs

Table APP6.2 summarises the costs of chemotherapy and associated biological agents (bevacizumab, cetuximab) included in the estimates of costs of management. Details of how these costs were derived are given below for each regime separately. Costs were based on protocols from a Dublin university teaching hospital and expert clinical opinion. The ingredient cost of chemotherapy (excluding VAT), as well as the pharmacists and pharmacy technicians time to compound the chemotherapy, were also obtained from a Dublin university teaching hospital. Drug acquisition costs of chemotherapy were based on an individual with a body surface area of 1.75m^2 or a body weight of 75kg, with allowance for wastage. Costs of ancillary medications (e.g. anti-emetics) were obtained from MIMS Ireland[304]. Staff costs for nursing and pharmacy staff as well as clinical consultants were estimated from the Department of Health and Children consolidated salary scales. Monitoring costs (e.g. laboratory tests) and hospital visits were also included in the cost estimates for chemotherapy.

APP6.2.1.1.1 Fluourouracil (5-FU) infusion

Different regimens and different dosages of 5-FU are used in different settings. The unit cost for this economic evaluation was based on the dosage regimen used in a Dublin university teaching hospital (225mg/m^2 per day as a continuous infusion for 5-6 weeks). The total cost per patient for six weeks 5-FU infusion, including ancillary medications (ondansetron, dexamethasone, domperidone, Corsodyl® mouthwash, Mycostatin mouthwash), staff costs, laboratory tests and hospital visits was estimated at €5,580.

APP6.2.1.2 FOLFOX

FOLFOX is a combination regimen which includes calcium leucovorin (folinic acid (FA)), fluorouracil (5-FU) and oxaliplatin (Eloxatin®). On days one and 15, oxaliplatin 85mg/m^2 and folinic acid 400mg/m^2 are given simultaneously over two hours. This is then followed by an intravenous bolus of 5-FU 400mg/m^2 followed by a 46 hour intravenous infusion of 5-FU 2,400/m^2 (administered via a home pump). The chemotherapy is prepared in the pharmacy compounding unit. The total time taken to prepare the regimen was obtained from the Pharmacy Compounding Unit of a Dublin university teaching hospital. Ancillary medications, such as include anti-emetics and mouth care preparations, were included. The total cost of FOLFOX per patient over a six month period is estimated at €22,500.

APP6.2.1.2.1 Capecitabine (Xeloda®)

Capecitabine is indicated for the adjuvant treatment of patients following surgery of stage III colon cancer. Given as a single agent, the recommended starting dose in the adjuvant treatment of colon cancer is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to 2,500 mg/m^2 total daily dose) for 14 days followed by a seven day rest period. Treatment is recommended for a total of 6 months. Assuming usual body surface area of 1.75/m^2, the average person would receive a dose of 2,150mg twice daily and there would be approximately eight cycles of treatment in a six month period.

Capecitabine is reimbursed in the community under the High-Tech Drug Scheme. Pharmacists are paid a monthly patient care fee of €60.52 to dispense drugs covered under this scheme[305]. It was assumed that patients attend one out-patient appointment each cycle. Therefore the total cost (including monitoring costs, dispensing fees, hospital visits as well as the ingredient cost of medication) of capecitabine per patient over six months is approximately €5,300.

APP6.2.1.2.2 FOLFOX plus bevacizumab (Avastin®)

Bevacizumab, a biologic agent, is a recombinant humanised monocloncal antibody that acts as an angiogenesis inhibitor. It targets the biological activity of human vascular endothelial growth factor (VEGF), which stimulates new blood vessel formation in the tumour. It is licensed in combination with fluorouracil regimens for the treatment of patients with metastatic carcinoma of the colon or rectum[306]. Bevacizumab is administered over 30 – 90 minutes on days one and 15. The usual dose is 5mg/kg and the regimen is given every 28 days. If vial wastage is assumed, a 75kg person would receive a dose of 375mg and a single 400mg vial of bevacizumab would be used to prepare this. The total cost of FOLFOX and bevacizumab, including hospital visits, pharmacy and nursing time, laboratory tests and ancillary medications per patient for three months is estimated at €18,255.

APP6.2.1.1.3 FOLFIRI and cetuximab (Erbitux®)

FOLFIRI is a combination regimen which includes calcium leucovorin (folinic acid (FA)), fluorouracil (5-FU) and irinotecan (Campto®). On days one and 15, irinotecan 180mg/m^2 and folinic acid 400mg/m^2 are given simultaneously over two hours. This is then followed by a bolus of 5-FU 400mg/m^2 followed by a 46 hour infusion of 5-FU 2,400mg/m^2 (administered via a home pump).

Cetuximab, a biologic agent, is a recombinant monoclonal antibody that blocks the human epidermal growth factor receptor (EGFR) and thus inhibits the proliferation of cells that depend on EGFR activation for growth. It is indicated for the treatment of patients with metastatic colorectal cancer who over-express EGFR, in combination with chemotherapy or as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan[307].

The very first dose is 400mg/m^2 and subsequent weekly doses are 250mg/m^2. Cetuximab is available as 100mg and 500mg vials. Therefore, an average person with a body surface area of 1.75m^2 would receive two 100mg and one 500mg vial for the very first dose and one 500mg vial for subsequent weekly doses. The total cost of FOLFIRI and cetuximab, including hospital visits, pharmacy and nursing time, laboratory tests and ancillary medications per patient for five months is estimated at €59,265.

Panitumumab (Vectibix®), the most recently approved chemotherapy, was not included in this analysis, as it is currently not widely used in practice.

It is expected that the use of biologic agents will increase in coming years. In addition a genetic test has very recently become available which aims at identifying those likely to respond to the biological agents. The costs of this test were not included in the cost estimates. Overall, therefore, the chemotherapy cost estimates in this HTA are likely to be conservative.

Table APP6.1 Unit cost data included in the model (€2008)

Description	Unit cost (€)	Source
A&E	334	Health Service Executive
Outpatient visit	169	Health Service Executive
Biopsy/histopathology	130	VHI Healthcare
CT scan	106	Dublin university teaching hospital
CT thorax, abdomen and pelvis	119	Dublin university teaching hospital
Colonoscopy	649	Weighted average DRG G44C, G44O and G43O
CT colonography	550	Private hospital fee; expert clinical opinion
Rigid sigmoidoscopy	903	Weighted average DRG G11S (day-case)
MRI (pelvis)	467	Health Service Executive
TUS	160	VHI Healthcare
PET scan	1,700	Dublin university teaching hospital; Private hospital; expert clinical opinion
CEA test	13	Dublin university teaching hospital
Full blood count	18	Dublin university teaching hospital
Coagulation	52	Dublin university teaching hospital
Biochemistry	59	Dublin university teaching hospital
Pre-operative / post-operative radiotherapy	5,250	Ploquin and Dunscombe, 2008[302]; Dublin specialist radiotherapy centre (€4,500 – 6,000)
Chemotherapy in combination with radiotherapy (5-FU infusion)	5,580	Dublin university teaching hospital
Chemotherapy post radiotherapy (5-FU infusion + folinic acid)	5,000	Dublin university teaching hospital
Rectal resection	18,933	Weighted average DRG G01A/B
Colon resection	17,974	Weighted average DRG G02A/B
GI stoma/stent /bypass	2,887	Weighted average DRG G05A/B/S and G0511A/B/S
Lung resection	16,744	Weighted average DRG E01A/B
Liver resection	22,959	Weighted average DRG H01A/B
Minor GI procedure (local excision)	9,057	Weighted average DRG G05A/B/S

A&E=accident and emergency; CEA=carcinoembryonic antigen; CT=computed tomography; DRG=diagnostic related group; GI=gastrointestinal; MRI=magnetic resonance imaging; PET=positron emission tomography; TUS=transrectal ultrasound

Table APP6.2 Cost of chemotherapy regimens (€ 2008)

Description	Cost of 1 cycle (€)	Duration of treatment	Total cost (€)
Pre-op chemotherapy in combination with radiotherapy			
5-FU infusion in combination with radiotherapy	5,580	6 weeks	5,580
Radiotherapy	5,250		5,250
Total cost			**10,830**
Post-op chemotherapy and radiotherapy			
5-FU infusion in combination with radiotherapy	5,580	6 weeks	5,580
Chemotherapy post radiotherapy (5-FU infusion + folinic acid)	5,000	3 x 6 week cycles	15,000
Radiotherapy	5,250		5,250
Total cost			**25,830**
Adjuvant chemotherapy			
FOLFOX (80%)	3,743	6 months	17,966
Capecitabine (20%)	885	6 months	1,062
Total cost			**19,028**
Chemotherapy for metastatic disease			
FOLFOX+bevacizumab (100%)	6,085	3 months	18,255
FOLFIRI + cetuximab (100%)	11,778	5 months	59,265
Total cost[1]			**77,520**

1 assuming patient receives 3 months FOLFOX+bevacizumab and 5 months FOLFIRI+cetuximab

APP6.2.2 Resource utilisation

APP6.2.2.1 Databases used

APP6.2.2.1.1 National Cancer Registry Ireland (NCRI)

Data from the NCRI for cancers diagnosed in 2004-2005 was used to estimate resource utilisation. Colon cancers included cancers coded to ICDO2 C18.0 to C18.9 and rectal cancers included those code to ICDO2 C19 (recto-sigmoid junction) and C20 (rectal ampula). A total of 4,268 cases (36% rectal; 64% colon cancers) were diagnosed in 2004-2005.

The NCRI records information on treatment received within approximately one year of diagnosis. The number of cases who had following therapies, alone and in combination, was obtained by site and stage and diagnosis: (a) local excision; (b) colon/rectal resection; (c) liver or lung resection; (d) chemotherapy; (e) radiotherapy; (f) other procedures (e.g. stents, GI bypass, etc). Information on date of procedures was used to categorise chemotherapy and radiotherapy by whether they were delivered pre or post-operatively.

Details about type, dose and duration of chemotherapy and radiotherapy, and follow-up surveillance were not available.

APP6.2.2.1.2 Local hospital databases

Data from the colorectal cancer databases from St James' Hospital, Dublin (155 patients seen in 2007) and St Vincent's Hospital, Dublin (142 patients seen in 2007) were made available to the evaluation team. Colleagues from Cork University Teaching Hospital also provided estimates based on their series of rectal cancers (n=46). These datasets were primarily used for the estimation of the diagnostic procedures for colon and rectal cancers. Some information about the radiotherapy regimens and chemotherapy regimens was also available but patient numbers were very small, therefore the data was supplemented and verified by expert clinical opinion.

APP6.2.2.2 Diagnosis

Evidence on presentation of patients with colon and rectal cancer is limited. Several assumptions were made and endorsed by the EAG. A summary of the resource utilisation associated with diagnosis is shown in table APP6.3.

It was assumed that 30% of unscreened patients present as emergency cases via Accident & Emergency and 70% are referred to a hospital outpatient clinic via their general practitioner. Approximately 10% of colorectal cancers recorded by the NCRI are not histologically confirmed and so it was assumed that some 90% of patients would be biopsied. It was assumed that 10% of patients would not have a colonoscopy. These patients, and those who have an incomplete colonoscopy, would undergo CT colonography; from literature review (Appendix 5) it was assumed this would apply to 13% of cases. Based on local data, it was assumed that 33% of rectal cancer patients would have rigid sigmoidoscopy. A PET scan is performed if recommended by the multidisciplinary team, and it was assumed, based on data from St James' Hospital, that this would apply in 10% of cases. All patients would have a CEA test, full blood count, coagulation and biochemistry. All colon cancer patients would have a CT scan. Patients with rectal cancer are also assumed to undergo CT scans of the thorax, abdomen and pelvis and an MRI, and 15% would have transrectal ultrasound (US).

It was assumed that all resource items are included in the cost of diagnosis for unscreened/symptomatically-detected individuals whereas the initial hospital visit and colonoscopy are excluded from the cost of diagnosis for the screened individuals, as this would be captured as part of the cost of screening.

Applying these resource estimates to the unit costs, costs associated with the diagnosis of screen-detected and non-screen detected colon and rectal cancers were derived (table APP6.4).

Table APP6.3 Summary of resource utilisation for the diagnosis of colon and rectal cancer

Resource use item	Colon cancer probability	Rectal cancer probability
Location of diagnosis		
Emergency presentation via A&E	0.3	0.3
Outpatient referral	0.7	0.7
Diagnostic procedures		
Biopsy/histology	0.9	0.9
CT scan	1.0	1.0
Colonoscopy	0.9	0.9
CT Colonography	0.13	0.13
PET scan	0.1	0.1
CEA blood test	1.0	1.0
Rigid sigmoidoscopy	0	0.33
MRI pelvis	0	1.0
TUS	0	0.14
Laboratory tests		
Full blood count	1.0	1.0
Coagulation	1.0	1.0
Biochemistry	1.0	1.0

A&E=accident and emergency; CEA=carcinoembryonic antigen; CT=computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography; TUS=transrectal ultrasound

Table APP6.4 Estimated cost of diagnosis for screened and unscreened colon and rectal cancers (€ 2008)

	Colon cancer	Rectal cancer
Unscreened cases	€1,346	€2,146
Screened cases	€543	€1,344

APP6.2.2.3 Treatment

Treatment pathways for stages I-IV colon and rectal cancer were developed and verified by expert clinical opinion (figures APP6.1-APP6.4). While it is recognised that some patients may have very individualised treatment, these pathways are intended to represent the treatment course of a "typical" patient with a particular disease site and stage.

Figure APP6.1 Stage I-III colon cancer

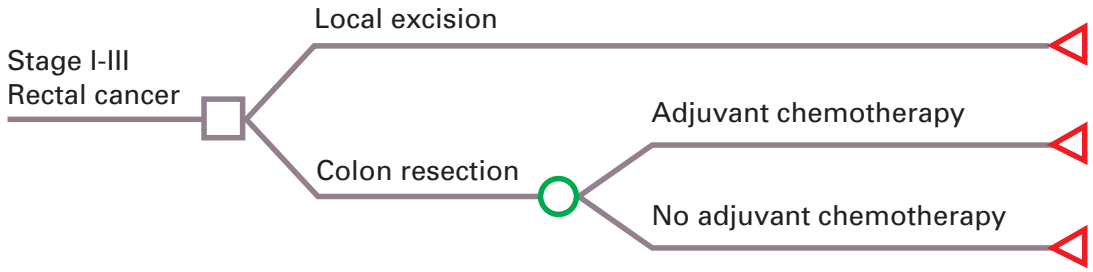


Figure APP6.2 Stage IV colon cancer

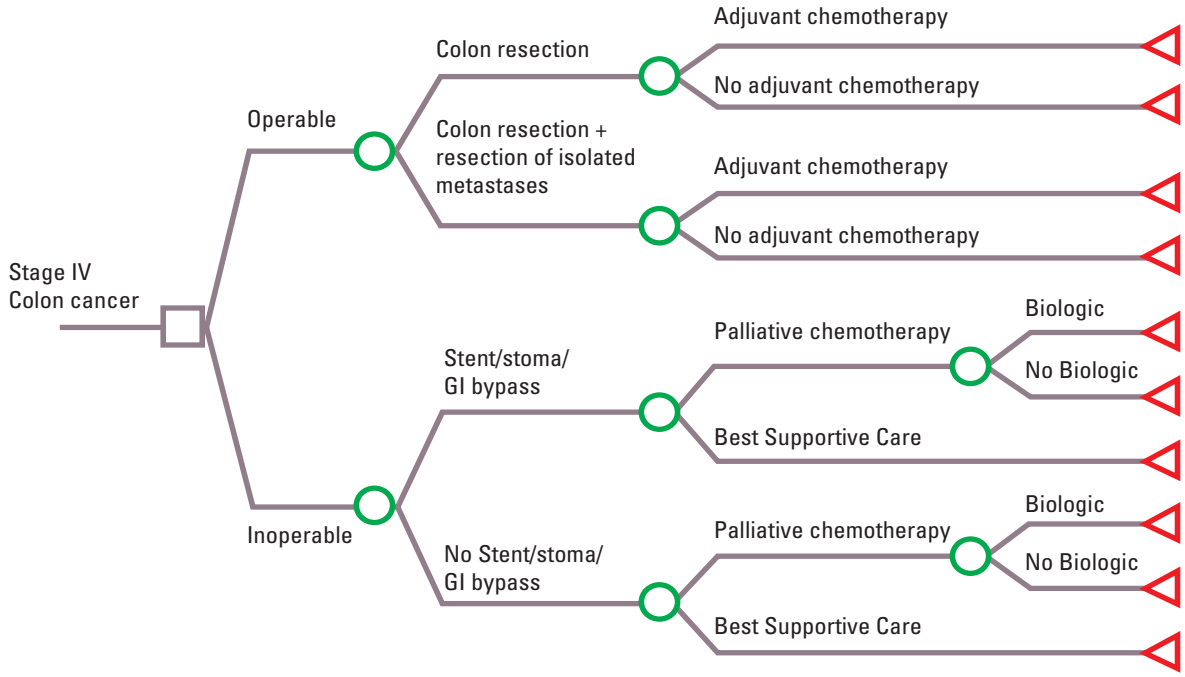


Figure APP6.3 Stage I-III rectal cancer

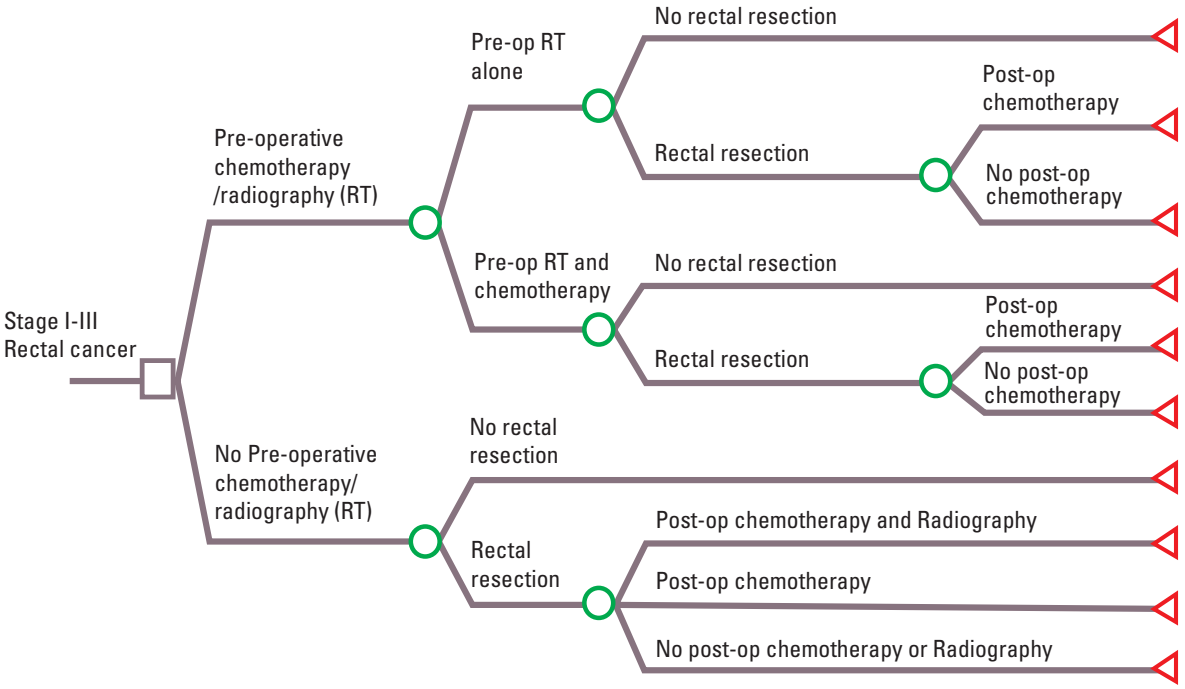
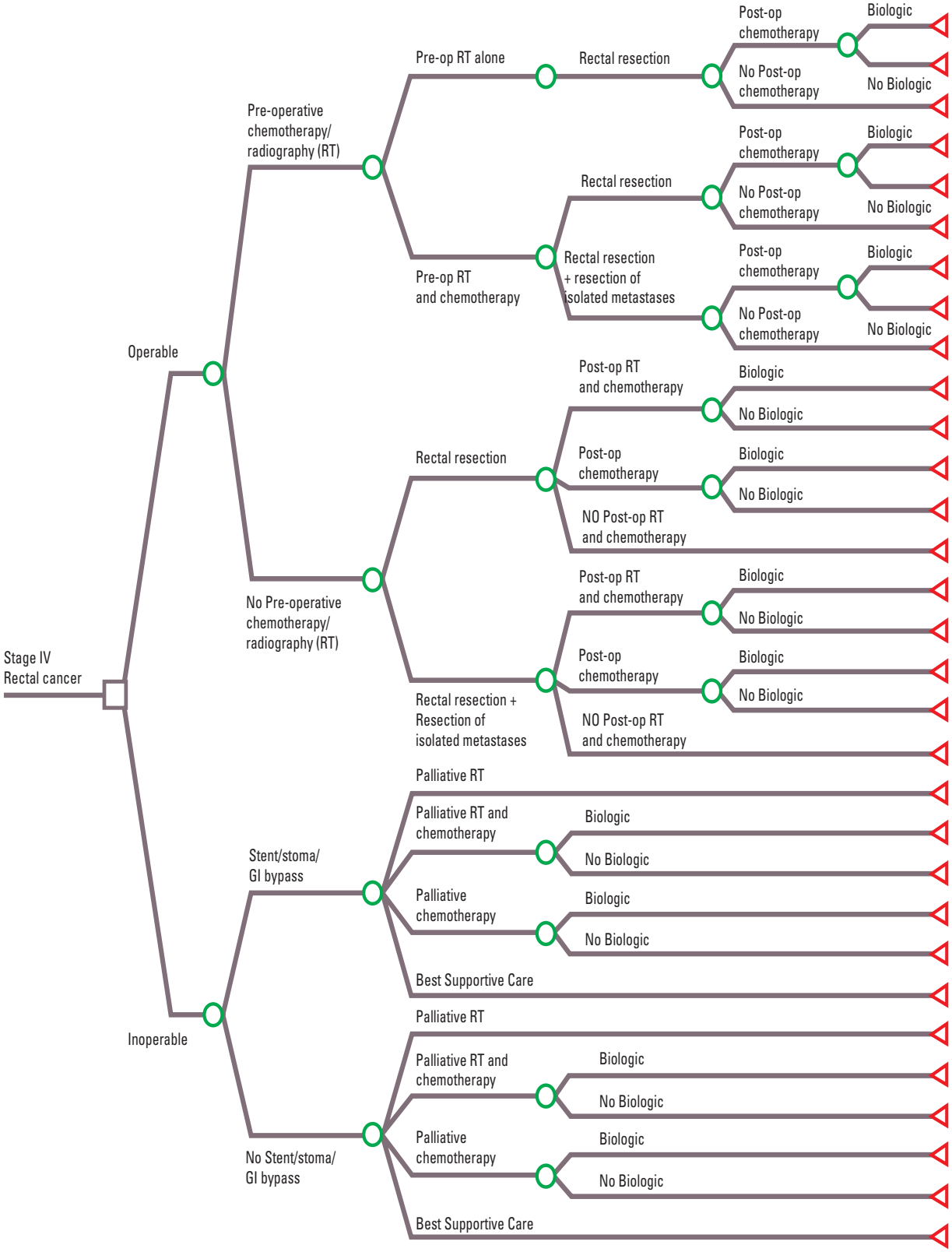


Figure APP6.4 Stage IV rectal cancer



APP6.2.2.3.1 Surgical resection

Based on NCRI data, 5% of stage I colon cancers were assumed to undergo local excision and the remainder to have a colon resection. It was assumed that 100% of stage II and III colon cancers would have a colon resection. A proportion of stage IV colon cancers (53%) were assumed to be inoperable and 10% of those were assumed to have a stoma, stent or a bypass to relieve obstruction. Of the operable stage IV colon cancers, it was assumed that 85% had a colon resection only with the remaining 15% also having a liver or lung resection for metastatic disease.

For rectal cancer, 5% of stage I patients were assumed to undergo local excision and the remainder have a rectal resection. From NCRI data, the overwhelming majority of stage II and III patients have a rectal resection. 60% of stage IV rectal cancers were assumed to be inoperable and 10% of these were assumed to undergo stoma, stent or bypass to relieve obstruction. Of the operable stage IV cancers, it was assumed 87% had a rectal resection only and the other 13% had both rectal resection and a resection for metastatic disease.

APP6.2.2.3.2 Chemotherapy

APP6.2.2.3.2.1 Adjuvant chemotherapy (stage II and III colon cancer)

Although adjuvant chemotherapy for patients with stage II colon cancer is not routinely used, some patients may be considered for chemotherapy, particularly those with poor prognostic features (e.g involved lymph nodes, T4 lesions, perforation, or poorly differentiated histology)[308]. Based on NCRI data, it was assumed 28% of stage II patients would received chemotherapy. Adjuvant chemotherapy is recommended for patients with stage III colon cancer and, based on NCRI data, it was assumed that 58% would receive this. Some stage II, III and IV rectal cancer patients would received post-operative chemotherapy (without radiotherapy), and these figures were estimated from NCRI data.

Based on expert opinion and hospital protocols, it was assumed that adjuvant chemotherapy would be administered for a period of six months, with approximately 80% of patients given FOLFOX as first line treatment and the remaining 20% prescribed the oral agent capecitabine (Xeloda®).

APP6.2.2.3.2.2 Chemotherapy for metastatic disease (stage IV disease)

On the basis of expert opinion and hospital protocols, it was assumed that stage IV patients with colorectal cancer are administered FOLFOX in combination with bevacizumab (Avastin®) first line. The duration of treatment for patients with metastatic disease varies; it was assumed first-line therapy would have an average duration of approximately three months. A combination of FOLFIRI and cetuximab (Erbitux®) is usually prescribed as second line therapy. Duration of therapy of five months was assumed. From expert opinion, it was assumed that 67% with stage IV disease would receive biological agents with chemotherapy. The impact of varying this proportion and the duration of therapy on these agents was explored in sensitivity analysis.

APP6.2.2.3.3 Radiotherapy

Radiotherapy, with or without chemotherapy, is given before or after surgery in patients with stage II-IV rectal cancer, with pre-operative administration preferred[309]. No pre-operative radiotherapy or chemotherapy would be given to stage I patients. Based on NCRI data and expert opinion, it was assumed that pre-operative radiotherapy is used in approximately 80% of patients with stages II and III rectal cancer. Approximately 10% of stage IV patients (i.e. those with metastatic disease, whose good prognosis dictates that local control may become an issue) would also be also given pre-operative radiotherapy. It was assumed, from expert opinion, that approximately 30% of patients are given radiotherapy alone and the remainder are administered radiotherapy in combination with fluorouracil infusion (225mg/m^2 per day administered as a continuous infusion for five to six weeks). If patients received pre-operative radiotherapy, it was assumed that it would not be given post-operatively. The proportion who would get post-operative radiotherapy was estimated from NCRI data (18% of stage II and 34% of stage III who were resected and did not have pre-operative radiotherapy). Different radiotherapy regimens are used in different hospitals. On the basis of expert opinion, it was assumed that patients receive long-course therapy (i.e. 45-50 Gray in 25 fractions over five weeks).

APP6.2.2.3.4 Recurrence

Both local and distant recurrences usually occur within two years of surgery[310]. Of those who recur, 80% occur within two years and recurrence after five years is rare[28]. Recurrence rates appear to have declined over time[311, 312], but they may vary according to the type of surgical procedure[313]. A systematic review of the literature was conducted to identify data on recurrence. Data was sought primarily from population-based registries or series, since data from individual clinical series and most RCTs is unlikely to be generalisible. Population-based data is limited and only six population-based series were identified[311, 314-318]. Studies vary in size, outcomes assessed and length of follow-up. Furthermore, the frequency of recurrence is likely to be underestimated since post-mortem examinations are not routinely performed.

It was assumed that stage I cancer would not recur. Recurrence rates for colon cancer were drawn from a population-based study of 2,657 colon cancer patients who underwent resection with curative intent between 1975 and 2000 in France[311]. The five-year overall recurrence rate was 27% for stage II and 56% for stage III colon cancer. The recurrence rate at five-years for stage II and III rectal cancer was estimated at 20% and 36% respectively[310, 317]. The cost of treating recurrence was assumed to be the same as the cost of managing stage IV disease, and these costs were included in the overall cost of managing stage II and III colon and rectal cancers.

APP6.2.2.3.5 Costs of treatment of colon and rectal cancer

The resource use estimates were applied to the unit cost data to derive estimates of the costs of treating each stage of colon and rectal cancer (table APP6.5). These costs were assumed to be the same for screen-detected and non-screen detected cancers.

Table APP6.5 Summary of estimated cost of treatment of colon and rectal cancer by stage (€ 2008)

	Stage I	Stage II	Stage III	Stage IV
Colon cancer	€18,613	€31,155	€45,299	€29,087
Rectal cancer	€18,439	€36,001	€45,599	€41,779

APP6.2.2.4 Follow-up

Individuals with colorectal cancer are followed up in a hospital outpatient setting, with the aim of the early detection of potentially resectable recurrent or metastatic disease. There is a lack of consensus about the optimal modality, frequency and overall duration of follow-up[319] and, within Ireland, follow-up protocols vary between hospitals.

Protocols were obtained from three Irish teaching hospitals([320], and unpublished protocols) and combined based on expert opinion. The resource utilisation and associated costs of follow-up were estimated over a period of five years. It was assumed that follow-up would consist of three-monthly outpatient attendances (including a CEA test) for the first six months, followed by six-monthly attendances for a further 18 months and then annual visits until year five (table APP6.6). It was also assumed that patients would have a CT scan at years one, two and five, and a colonoscopy at years one, three and five.

For stages I-III, it was assumed that follow-up would be for five years and all patients would follow the same protocol. A proportion with stage II and III disease would drop-out from follow-up due to recurrent disease. It was assumed that patients with stage IV disease would be followed up for 15 months (mean survival of stage IV colorectal cancer patients;[118]). Costs of follow-up in years two to five were discounted at a rate of 4% in the base-cases analysis; sensitivity analyses were conducted to explore the impact of incorporating undiscounted follow-up costs.

The estimated cost of follow-up is shown in table APP6.7.

Table APP6.6 Estimated resource use during 5 year follow-up surveillance

Time (months)	CEA test	CT	Colonoscopy	Clinic visit
0	Surgical resection			
3	1			1
6	1			1
12	1	1	1	1
18	1			1
24	1	1		1
36	1		1	1
48	1			1
60	1	1	1	1
Total	**8**	**3**	**3**	**8**

CEA= carcinoembryonic antigen

Table APP6.7 Estimated cost of follow-up of colon and rectal cancer by stage (€ 2008)

	Stage I	Stage II	Stage III	Stage IV
Colon cancer	€3,503	€2,557	€1,541	€1,311
Rectal cancer	€3,503	€2,802	€2,242	€1,311

APP6.2.2.5 Summary of direct medical costs of managing colorectal cancer in Ireland

The estimated costs associated with diagnosis, treatment and follow-up were summed and a weighted average total cost produced for screen-detected and symptomatic (non-screen detected) cancers (tables APP6.8 and APP6.9). These were used as the base-case estimates.

Table APP6.8 Estimated cost[1] per parson of diagnosis, treatment and follow-up of symptomatic colorectal cancer[2] by stage at diagnosis (€ 2008)

	Stage I	Stage II	Stage III	Stage IV
Diagnosis	€1,634	€1,634	€1,634	€1,634
Treatment	€18,550	€32,900	€45,407	€33,656
Follow-up	€3,503	€2,646	€1,794	€1,311
Total	**€23,688**	**€37,180**	**€48,835**	**€36,602**

1 discounted at 4% per annum

2 all cancers which are not detected through a screening programme; assuming 64% are in the colon and 36% in the rectum

Table APP6.9 Estimated cost[1] per person of diagnosis, treatment and follow-up of screen-detected colorectal cancer[2] by stage at diagnosis (€ 2008)

	Stage I	Stage II	Stage III	Stage IV
Diagnosis	€832	€832	€832	€832
Treatment	€18,550	€32,900	€45,407	€33,656
Follow-up	€3,503	€2,646	€1,794	€1,311
Total	**€22,885**	**€36,377**	**€48,032**	**€35,799**

1 discounted at 4% per annum

2 assuming 64% are in the colon and 36% in the rectum

APP6.2.2.5.1 Sensitivity analysis

One-way sensitivity analysis was undertaken to explore the impact of variation of key parameters (e.g. % treated with a biological agent) on the total costs of managing colorectal cancer (table APP6.10). This showed that the total cost estimates varied by a maximum of approximately +/- 20% around the base-case estimates. Thus, the costs of managing colorectal cancer were allowed to vary by +/-20% in the economic model.

Table APP6.10 One-way sensitivity analysis on key parameters: lifetime costs by stage at diagnosis (€ 2008)

Parameter and base-case values	Value of /change in parameter	Lifetime costs			
		stage I	stage II	stage III	stage IV
Base case estimates (symptomatically-detected colorectal cancers)	-	€ 23,688	€ 37,180	€ 48,835	€ 36,602
Total cost estimates	+20%[1]	€ 28,425	€ 44,616	€ 58,602	€ 43,922
	-20%[1]	€ 18,950	€ 29,744	€ 39,068	€ 29,281
Follow-up costs discounted at 4%	follow-up costs undiscounted	€ 24,073	€ 37,471	€ 49,032	€ 36,654
Duration of treatment with FOLFIRI/ cetuximab: 3 months	8 months	€ 23,688	€ 38,910	€ 52,187	€ 44,129
Percentage of eligible stage IV patients prescribed a biologic agent: 67%	80%	€ 23,688	€ 37,739	€ 49,918	€ 39,039
Costs of chemotherapy and biological agents	+20%[1]	€ 23,024	€ 39,164	€ 52,795	€ 40,274
	-20%[1]	€ 23,549	€ 34,497	€ 44,204	€ 32,139
Proportion of stage II and III rectal cancer patients given pre-operative chemotherapy and radiotherapy: 80%	60%	€ 23,688	€ 36,976	€ 49,056	€ 36,602
Recurrence of stage II and III colon and rectal cancer: colon - 27% and 56%; rectum - 20% and 36%	+20%[1]	€ 23,688	€ 38,786	€52,003	€36,602
	-20%[1]	€23,688	€ 35,573	€ 45,607	€ 36,602

1 +/- 20% of base-case value

APP6.2.2.5.2 International comparisons of the cost of managing colorectal cancer

Studies published since 1996 which reported stage-specific costs of colorectal cancer treatment are summarised in table APP6.11[118, 321-325]. In addition to these, a review by Jansman et al[326] of studies relating to north American and Europe from the years 1996 to 2006 was identified.

It is difficult to compare overall costs of managing colorectal cancer between studies. Studies differ in terms of length of follow-up, cost perspective, type of costs included and whether disease recurrence and/or follow-up surveillance were included. Furthermore diagnostic and treatment pathways may differ between healthcare settings. Several published studies include patients diagnosed from the late 1980s and 1990s and oncology practice has changed dramatically since this time, particularly with regard to the use of biological agents. In a study limited to metastatic disease, from the USA, published in 2006, it was suggested that lifetime costs for treatment and care for these patients are close to $100,000[327]. This reflects at least a doubling of the costs compared with studies performed during the 1990s[321], illustrating the impact of newer therapies on the disease treatment costs. It is likely that

the costs of managing colorectal cancer will further increase with increasing use of biological agents, and the development and introduction of similar new therapies as adjuvant treatment for stage III and possibly stage II disease.

The costs estimated in the current HTA are somewhat higher than those from a study from France[324], although the difference is less for stage I and IV disease than for stages II and III. Unlike the current study, the French study did not include costs of recurrence, which was a notable component of the estimated costs for stage II and III tumours in the current HTA. Costs in Ireland are more than double those estimated for England in the ScHARR HTA of colorectal screening[118], but the English data relate to individuals diagnosed several years ago, and treatment is likely to have become much more expensive over time especially with the introduction of the biological agents. A recent small study in Switzerland estimated that the cost of treatment was slightly higher than in the current study[323]. Generally, the estimates for Ireland fall within the range of data reported suggesting that they are probably reasonable.

Table APP6.11 Summary of studies of direct medical costs of managing colorectal cancer in different countries, by stage at diagnosis

Country	Stage I	Stage II	Stage III	Stage IV	Sample size (n)	Study perspective/ costs included	Price year	Additional comments	Reference
Ireland (no screening)	€ 23,688	€ 37,180	€ 48,835	€36,602	4,268	Direct medical costs	2008	Includes colon and rectal cancer costs separately. Costs during first 5 years after diagnosis. Discounted at 4%.	Current HTA
France	€17,596	€20,472	€29,013	€35,059	384	Direct costs; mean cost	2004/5	1st year after diagnosis. Follow-up and recurrence not included.	Clerc et al, 2008[324]
US	US$41,134					Direct medical costs; mean cost	2002 (Medicare payments)	65 and older only. 1st year after diagnosis.	Warren et al, 2008[325]
Switzerland	US$19,638 US$31,254	US$25,547 US$31,547	US$27,784 US$35,682	US$39,298 US$48,156	83	Direct hospital costs only; Median cost; Mean cost	Resource use: 1997-8 Costs: not specified	Includes colon and rectal cancer costs separately. Costs during first 3 years after diagnosis	Delco et al, 2005[323]
UK (no screening)	€9,859 (£8,299)	€14,781 (£12,441)	€22,665 (£19,077)	€14,192 (£11,945)	-	Direct medical costs	2004	New biologic agents not included. Resource use mainly based on expert opinion.	Tappenden et al, 2004[118]

Country	Stage I	Stage II	Stage III	Stage IV	Sample size (n)	Study perspective/ costs included	Price year	Additional comments	Reference
5 EU countries - Belgium, Germany, France, Italy, UK [1]			CC €13,630 (549,833 BF) RC €21,859 (881,778 BF)	CC €18,647 (752,221BF) RC €17,763 (716,564BF)	200 (10 centres)	Direct hospital costs; Mean costs from 5 EU countries.	Resource use: Average from Belgium, Germany, France, Italy and UK in 1998 Costs: Belgian Francs 1998		Neymark and Adriaenssen, 1999[322]
US	CC US$32,700 RC US$33,000	CC US$34,400 RC US$39,300	CC US$41,600 RC US$49,500	CC US$29,400 RC US$30,100	40,094 in continuing phase care	Direct medical cancer related costs covered by Medicare (total costs also reported)	Medicare payments from 1990-1994	65 and older only. Long-term cost (up to 25 years after diagnosis). Discounted at 3%	Brown et al, 1999[321]

1 Costs in study reported in Belgian Francs; costs in Euro based on Council of the European Union recommendations for exchange rates between currencies on 31st December 1998
CC=colon cancer; RC=rectal cancer

Appendix 7

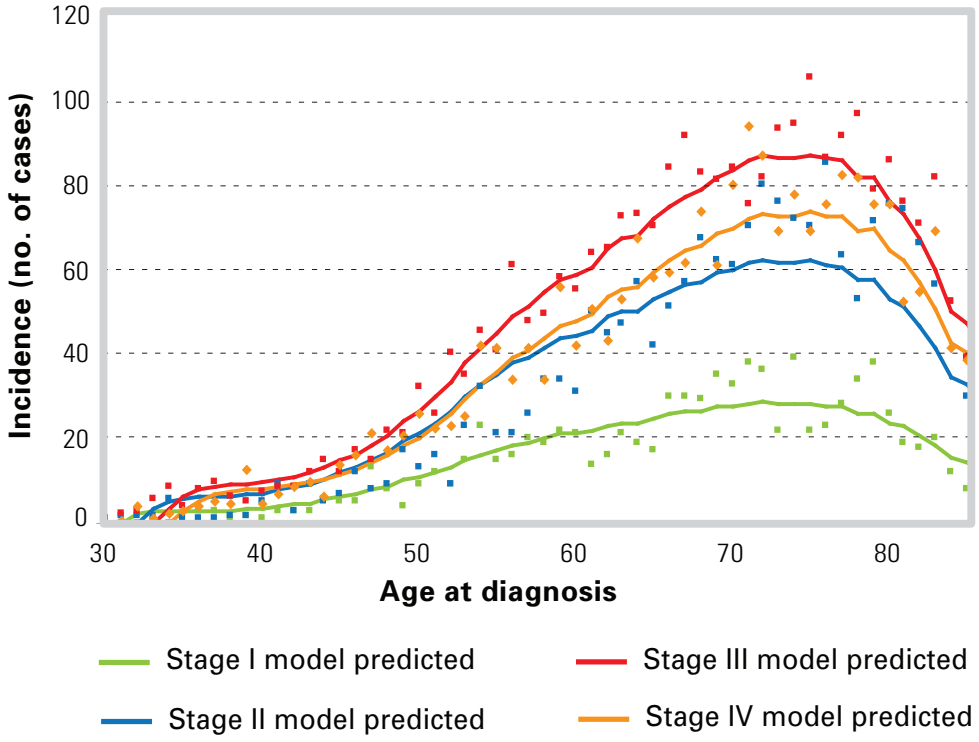
Results of the model calibration

In the calibration process the model was run under the assumption of "no screening" and the natural history parameter values were varied so that a good fit to the observed data was obtained. Figures APP7.1(a)-(d) show the outcome of this process. For colorectal incidence and morality, the predicted values from the model closely followed the distributions in the population. The model slightly underestimated mortality from colorectal cancer in the oldest age group, but this is probably the group in whom the mortality data are least reliable. For adenoma prevalence, the model predictions for younger age groups lay between those from the study by Pendergrass et al[211] and those derived from the screening pilots in England and Scotland[58]. The predicted adenoma prevalence for older age groups was higher than the observed data. For undiagnosed colorectal cancer, for ages up to 69, the model predictions of the prevalence were close to the figures estimated from the screening pilots. Prevalence was predicted to continue to increase with increasing age thereafter, which does not seem unreasonable.

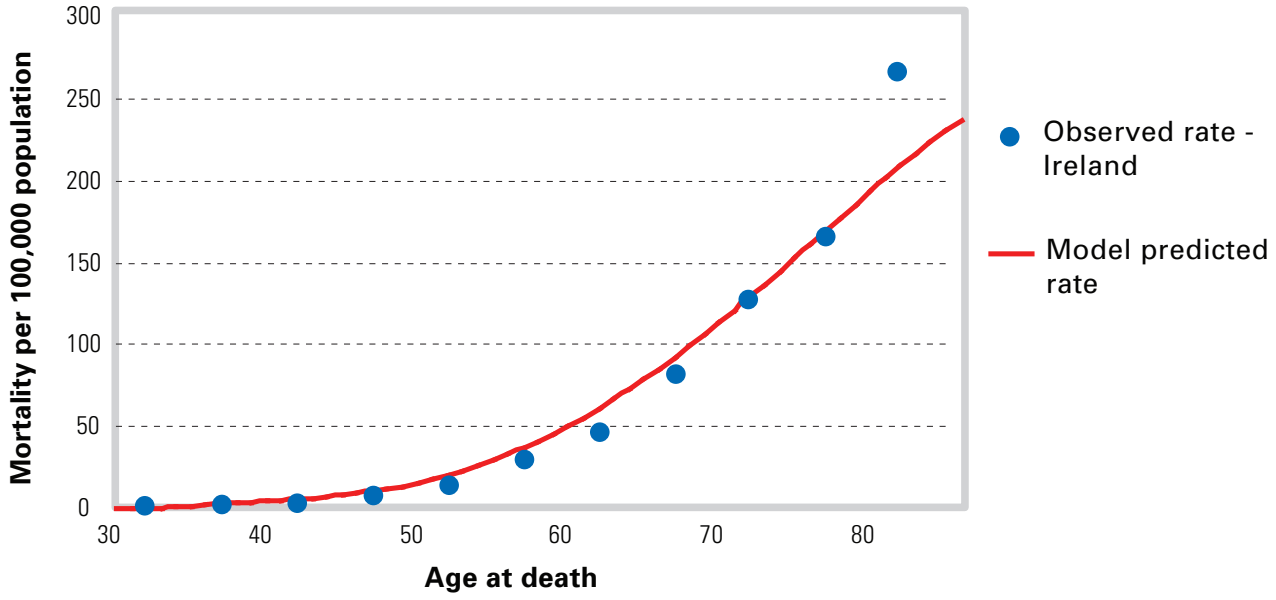
The natural history parameter values estimated from the calibration and used when the model was run deterministically (i.e. base-case and one/multi-way sensitivity analysis), are shown in table APP7.1.

Figures APP7.1 (a)-(d) Results of model calibration

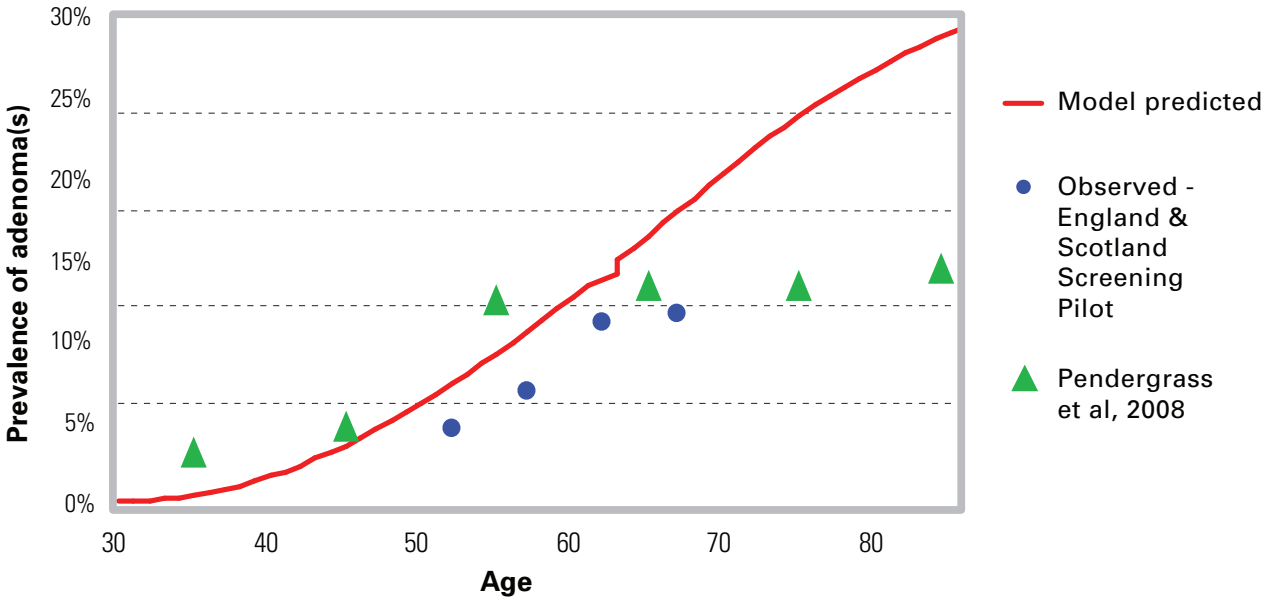
(a) Actual and model predicted stage-specific incidence of colorectal cancer



(b) Actual and model predicted mortality from colorectal cancer



(c) Adenoma prevalence from published sources and predicted by the model



(d) Prevalence of undiagnosed colorectal cancer from published sources and predicted by the model

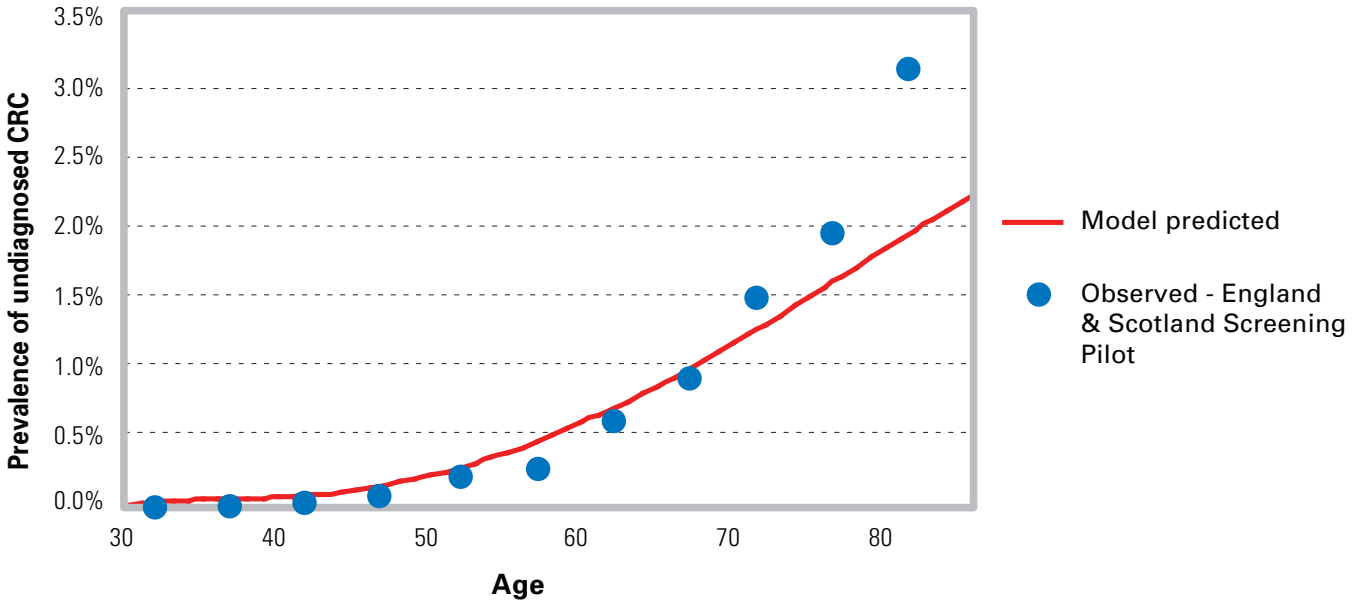


Table APP7.1 Parameters in natural history model, and values estimated from the calibration[1]

Parameter	Value
Adenoma and cancer annual transition probabilities	
normal epithelium to low-risk adenoma[2]	age 30: 0% age 70: 1.07% age 100: 1.04%
low-risk adenoma to intermediate/high-risk adenoma	5.73%
intermediate/high-risk adenoma to stage I cancer	5.82%
stage I cancer to stage II cancer	90.47%
stage II cancer to stage III cancer	72.00%
stage III cancer to stage IV cancer	63.12%
normal epithelium to stage I cancer[3]	14%
Symptomatic cancer presentation	
probability of presenting symptomatically with stage I cancer	23.80%
probability of presenting symptomatically with stage II cancer	32.16%
probability of presenting symptomatically with stage III cancer	48.14%
probability of presenting symptomatically with stage IV cancer	90.41%
Mortality rates	
annual CRC-specific mortality rate for stage I	0.23%
annual CRC-specific mortality rate for stage II	0.65%
annual CRC-specific mortality rate for stage III	4.03%
annual CRC-specific mortality rate for stage IV	30.49%

CRC=colorectal

1 *based on the parameter set with the highest likelihood*

2 *This is an age dependent variable; probability increases from age 30 to 70, and falls slightly thereafter*

3 *To allow for cancers to develop through alternative pathways (e.g. serrated polyps, de novo CRC); the proportion is estimated from literature review, and not from the model calibration*

APPENDIX 8

Additional cost-effectiveness results

Tables APP8.1-8.3 show the results of the one-way and multi-way sensitivity analysis carried out with respect to the core scenarios of gFOBT 55-74, FIT 55-74 and once-off FSIG at 60.

Table APP8.4 shows the incremental cost-effectiveness ratios (ICER), based on LYGs, for the three core scenarios and the additional five age-variant scenarios.

Table APP8.1 One-way and multi-way sensitivity analysis for gFOBT at 55-74 years: ICERs (incremental cost per LYG and per QALY gained) compared with no screening

					Incremental cost per LYG				Incremental cost per QALY gained			
Model parameter[1]	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**
gFOBT sensitivity												
- adenomas	11%	10%	12%	20%[2]	€3,332	€3,937	€2,811	€1,285	€4,428	€5,213	€3,752	€1,701
- CRC	36%	31%	42%	64%[2]								
FIT sensitivity												
- adenomas	21%	19%	22%	32%[2]	€3,332	€3,666	€3,110	€2,079	€4,428	€4,888	€4,135	€2,718
- CRC	71%	67%	75%	89%[2]								
Combined gFOBT/FIT sensitivity and specificity[3]												
- adenoma sensitivity				3.8%				€5,213				€6,241
- CRC sensitivity				14.5%								
- specificity				99.2%								
COL sensitivity												
- low-risk adenoma	77%	73%	80%		€3,332	€3,994	€3,270		€4,428	€5,315	4,345	
- intermediate/high-risk adenoma	98%	93%	99%									
- CRC	98%	95%	99%									
Proportion who never participate in screening	13%	0%	41%		€3,332	€3,326	€3,357		€ 4,428	€ 4,454	€ 4,421	

					Incremental cost per LYG				Incremental cost per QALY gained			
Model parameter[1]	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**
gFOBT uptake	53%	32%	59%		€3,332	€4,300	€2,963		€ 4,428	€ 5,722	€ 3,933	
COL compliance (diagnosis)	86%	81%	90%		€3,332	€3,595	€3,143		€ 4,428	€4,783	€ 4,172	
Utility (Ramsey et al, 2000[199])												
- Cancer free state	0.94	0.94	0.94	0.94					€4,428	€12,965	€3,544	
- Stage I	0.80	0.43	0.94	0.80								
- Stage II	0.80	0.43	0.94	0.80								
- Stage III	0.80	0.43	0.94	0.80								
- Stage IV	0.80	0.43	0.94	0.80								
Utility (Ness et al, 1999[202])												
- Cancer free state									-4	-€5,505	€4,591	
- Stage I												
- Stage II												
- Stage III												
- Stage IV												
Cost of gFOBT[5]												
- kits	€1.70	€0.85	€2.55		€3,332	€1,503	€5,164		€ 4,428	€ 1,997	€ 6,863	
- processing and analysis	€7.81	€3.91	€11.72									

					Incremental cost per LYG				Incremental cost per QALY gained			
Model parameter[1]	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**
Cost of COL[5]	€650	€3255	€975		€3,332	€2,671	€3,993		€ 4,428	€3,550	€5,306	
Life time cost of CRC: Symptomatic[6]												
- Stage I	€23,668	€18,950	€28,425		€3,332	€3,807	€2,857		€4,428	€ 5,059	€3,796	
- Stage II	€37,180	€29,744	€44,616									
- Stage III	€48,835	€39,068	€58,602									
- Stage IV	€36,602	€29,281	€43,922									
Screen-detected[6]												
- Stage I	€22,885	€18,308	€27,462									
- Stage II	€36,377	€29,102	€43,652									
- Stage III	€48,032	€38,426	€57,638									
- Stage IV	€35,799	€28,639	€42,959									
Discount rate (costs and benefits)	4%	0%	6%		€3,332	€322	€6,031		€4,428	€410	€8,217	

1 parameters which are grouped (e.g. sensitivity for adenomas and cancers) were varied simultaneously in multi-way analyses

2 to represent a more sensitive test

3 analysis assuming that the performance characteristics of gFOBT and reflex FIT are not independent

4 base-case not shown as relates to Ramsey et al[199]

5 allowed to vary +/-10%, +/-20%, +/-30%, +/-40% and +/-50% around base-case estimate; values shown are for +/-50%

6 discounted at 4% per annum

Table APP8.2 One-way and multi-way sensitivity analysis for FIT at 55-74 years: ICERs (incremental cost per LYG and per QALY gained) compared with no screening

					Incremental cost per LYG				Incremental cost per QALY gained			
Model parameter[1]	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**
FIT sensitivity												
- adenomas	21%	19%	22%	32%[2]	€1,470	€1,918	€1,234	-€219	€1,696	€2,230	€1,423	-€243
- CRC	71%	67%	75%	89%[2]								
COL sensitivity												
- low-risk adenoma	77%	73%	80%		€1,470	€2,703	€1,382		€ 1,696	€3,216	€1,594	
- intermediate/high-risk adenoma	98%	93%	99%									
- CRC	98%	95%	99%									
Proportion who never participate in screening	13%	0%	41%		€1,470	€1,356	€1,944		€1,696	€1,570	€2,215	
FIT uptake	53%	32%	59%		€1,470	€1,651	€1,548		€ 1,696	€ 1,925	€ 1,771	
COL compliance (diagnosis)	86%	81%	90%		€1,470	€1,573	€1,399		€ 1,696	€ 1,821	€ 1,610	
Utility (Ramsey et al, 2000[199])												
- Cancer free state	0.94	0.94	0.94						€ 1,696	€2,185	€ 1,564	
- Stage I	0.80	0.43	0.94									
- Stage II	0.80	0.43	0.94									
- Stage III	0.80	0.43	0.94									
- Stage IV	0.80	0.43	0.94									

					Incremental cost per LYG				Incremental cost per QALY gained			
Model parameter[1]	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**
Utility (Ness et al, 1999[202])												
- Cancer free state		0.94	0.94						-[3]	€1,817	€1,717	
- Stage I		0.69	0.78									
- Stage II		0.64	0.73									
- Stage III		0.59	0.69									
- Stage IV		0.20	0.31									
Cost of FIT[4]												
- kits	€3.75	€1.88	€5.63		€1,470	€332	€2,610		€1,696	€383	€3,012	
- processing and analysis	€11.60	€5.80	€17.40									
Cost of COL[4]	€650	€3255	€975		€1,470	-€1,137	€4,077		€ 1,696	-€1,312	€4,704	
Life time cost of CRC: Symptomatic[5]												
- Stage I	€23,668	€18,950	€28,425		€1,470	€2,849	€91		€ 1,696	€3,288	€105	
- Stage II	€37,180	€29,744	€44,616									
- Stage III	€48,835	€39,068	€58,602									
- Stage IV	€36,602	€29,281	€43,922									
Screen-detected[5]												
- Stage I	€22,885	€18,308	€27,462									
- Stage II	€36,377	€29,102	€43,652									
- Stage III	€48,032	€38,426	€57,638									
- Stage IV	€35,799	€28,639	€42,959									
Discount rate (costs and benefits)	4%	0%	6%		€1,470	-€1,251	€4,193		€1,696	-€1,399	€4,938	

1 parameters which are grouped (e.g. sensitivity for adenomas and cancers) were varied simultaneously in multi-way analyses

2 to represent a more sensitive test (e.g. a quantitative test used with a lower cut-off to define those with a positive result)

3 base-case not shown as relates to Ramsey et al[199]

4 allowed to vary +/-10%, +/-20%, +/-30%, +/-40% and +/-50% around base-case estimate; values shown are for +/-50%

5 discounted at 4% per annum

Table APP8.3 One-way and multi-way sensitivity analysis for FSIG once at years: ICERs (incremental cost per LYG and per QALY gained) compared with no screening

					Incremental cost per LYG				Incremental cost per QALY gained			
Model parameter[1]	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**
FSIG sensitivity												
- low-risk distal adenomas	65%	60%	70%		€583	€1,311	€130		€589	€1,327	€131	
- high-risk distal adenomas	74%	68%	78%									
- CRC	90%	85%	95%									
COL sensitivity												
- low-risk adenoma	77%	73%	80%		€583	€930	€569		€589	€946	€574	
- intermediate/high-risk - adenoma	98%	93%	99%									
- CRC	98%	95%	99%									
FSIG uptake	39%	24%	67%		€583	€583	€583		€589	€589	€589	
COL compliance (diagnosis)	86%	81%	90%		€583	€570	€596		€589	€576	€601	
Utility (Ramsey et al, 2000 [199])												
- Cancer free state	0.94	0.94	0.94						€589	€518	€621	
- Stage I	0.80	0.43	0.94									
- Stage II	0.80	0.43	0.94									
- Stage III	0.80	0.43	0.94									
- Stage IV	0.80	0.43	0.94									

					Incremental cost per LYG				Incremental cost per QALY gained			
Model parameter[1]	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**	**Base-case**	**Lower estimate**	**Upper estimate**	**Other values**
Utility (Ness et al, 1999 [202])												
- Cancer free state	0.94	0.94							-[2]	€566	€584	
- Stage I	0.69	0.78										
- Stage II	0.64	0.73										
- Stage III	0.59	0.69										
- Stage IV	0.20	0.31										
Cost of FSIG[3]	€150	€75	€225		€583	-€3,619	€4,786		€589	-€3,650	€4,827	
Cost of COL[3]	€650	€3255	€975		€583	-€311	€1,478		€589	-€313	€1,490	
Life time cost of CRC: Symptomatic[4]												
- Stage I	€23,668	€18,950	€28,425		€583	€2,602	-€1,435		€589	€2,624	-€1,447	
- Stage II	€37,180	€29,744	€44,616									
- Stage III	€48,835	€39,068	€58,602									
- Stage IV	€36,602	€29,281	€43,922									
Screen-detected[4]												
- Stage I	€22,885	€18,308	€27,462									
- Stage II	€36,377	€29,102	€43,652									
- Stage III	€48,032	€38,426	€57,638									
- Stage IV	€35,799	€28,639	€42,959									
Discount rate (costs and benefits)	4%	0%	6%		€583	-€2,021	€3,604		€589	-€2,012	€3,671	

1 parameters which are grouped (e.g. sensitivity for adenomas and cancers) were varied simultaneously in multi-way analyses

2 base-case not shown as relates to Ramsey et al (199)

3 allowed to vary +/-10%, +/-20%, +/-30%, +/-40% and +/-50% around base-case estimate; values shown are for +/-50%

4 discounted at 4% per annum

Table APP8.4 Incremental cost-effectiveness ratios (ICER), based on LYGs, for core and additional screening scenarios

Scenario	Cost of screening & CRC management per person	Incremental cost per person[1]	Expected life years per person	Incremental LYG per person[1]	ICER -Incremental cost per LYG
No screening	€ 1,074	-	11.684	-	-
gFOBT at 55-74 years	€ 1,107	€ 33.63	11.694	0.0101	€ 3,332
gFOBT at 55-64 years	€ 1,092	€ 18.35	11.691	0.0065	€ 2,808
gFOBT at 65-74 years	€ 1,089	€ 15.66	11.688	0.0037	€ 4,187
FIT at 55-74 years	€ 1,114	€ 40.17	11.712	0.0273	€ 1,470
FIT at 55-64 years	€ 1,094	€ 20.13	11.704	0.0197	€ 1,020
FIT at 65-74 years	€ 1,088	€ 13.94	11.694	0.0101	€ 1,385
FSIG once at 60 years	€ 1,077	€ 3.43	11.690	0.0059	€ 589
FSIG once at 55 years	€ 1,092	€ 18.22	11.691	0.0068	€ 2,659

CRC=colorectal cancer; FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; gFOBT=guaiac-based faecal occult blood test; LYG=life-years gained. Costs and outcomes discounted at 4%
Core screening scenarios are shaded.
1 Each incremental value compares value for that strategy to a common baseline of no screening.

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Glossary

ADENOMA/ ADENOMATOUS POLYP
A particular type of benign (non-invasive) neoplasm (tumour) in the epithelial tissue of the colorectum.

ADENOCARCINOMA
A cancer which develops in glandular tissue, usually of the lining or inner surface of an organ (e.g. the colon).

ADJUVANT THERAPY
A treatment, such as chemotherapy or radiotherapy, which is given in addition to the main treatment (usually surgery) for cancer. It may be given before or after surgery; if given before it is often called neo-adjuvant therapy. The aim of adjuvant therapy is to increase the chances of curing the disease or to stop it spreading.

AGE-STANDARDISED RATE
A method used when comparing rates of disease between countries/areas or over time. The method involves adjusting the rates to remove the effect of differences in the population distributions. between the countries, or over time.

ASYMPTOMATIC
Having no symptoms of disease.

BENEFIT
The sum of the effects on well-being (positive or negative) which a particular intervention or programme bestows upon society. May be expressed in money terms to make it commensurate with cost.

BIAS
A systematic error.

BIOPSY
The examination of tissue removed from a patient to discover the presence, extent and cause of disease.

CANCER REGISTRY
Collection of information about the types of cancer that have been diagnosed and treated in a given area or region. Governments and health services run cancer registries so that they can keep a count of cancer rates and monitor how effective their prevention, diagnosis and treatment strategies are.

CARCINOMA
A malignant tumour derived from epithelial tissue. Carcinomas are the most common type of cancer.

CARCINOMA IN SITU
An early cancer that has not invaded (grown into) surrounding tissues. Considered as the most severe cell change just prior to invasive cervical cancer.

CASE-CONTROL STUDY
A type of study in which individuals who have a disease of interest (e.g. cancer) are compared with those who are free from the disease, to identify factors associated with increased or reduced risk of developing the disease.

CARCINOEMBRYONIC ANTIGEN (CEA)
A biological marker thought to help predict recurrence of colorectal cancer.

CHEMOTHERAPY
The treatment of disease, usually cancer, using chemical substances (drugs), the aim of which is to destroy cancer cells.

COLONOSCOPY
An examination of the colon with a long. Flexible, lighted tube called a colonoscope.

COMORBIDITY/ CO-MORBID CONDITION
The presence of one of more health condition/disease in an individual at the same time (e.g. cancer plus another condition such as diabetes or heart disease).

COMPUTED TOMOGRAPHY (CT SCAN)
An image produced by a CT scanner. X-rays are taken from different angles and are put together by a computer to generate a series of cross-sections of the part of the body being scanned. This can build up a very detailed picture of the inside of the body, and provide accurate information on the size and position of a tumour.

CONFOUNDING
When the effects of two factors on an outcome (e.g. results of a study) cannot be separated.

CONFIDENCE INTERVAL
This refers to the range of values within which the true prevalence or percentage is likely to lie. These intervals provide an estimate of the uncertainty about underlying parameters given data. For example a 95% confidence interval has a 95% chance of including the true value for that parameter. As the amount of data increases, confidence intervals for parameters get narrower in width.

COST-EFFECTIVENESS ANALYSIS
A form of economic evaluation which assesses the costs and consequences or benefits of an intervention and where the consequences/benefits are measured in terms of natural units, such as life years gained.

COST-UTILITY ANALYSIS
A form of economic evaluation which assesses the costs and consequences or benefits of an intervention and where the consequences/benefits are adjusted by health state preferences or utility weights, such as quality adjusted life years (QALYs).

CT COLOGRAPHY/VIRTUAL COLONOSCOPY
A procedure that uses CT scanning (see above) to obtain an interior view of the colon.

DISCOUNTING
A technique which allows comparison between costs and benefits that occur at different times. Since costs incurred and outcomes realised today are not equivalent to costs and outcomes in the future, discounting is used to calculate the present value of future events.

DISCRETE EVENTS SIMULATION
A process in which the operation of a system (for example, the development of colorectal cancer) is represented as a chronological sequence of events. Each event occurs at an instant in time and marks a change of state in the system.

DISCOUNT RATE
The amount by which costs and benefits are discounted each year.

DOMINATED
When one intervention is less costly and more effective than the alternative, it is said to dominate the alternative.

ECONOMIC EVALUATION
The systematic appraisal of costs and benefits of projects, normally undertaken to determine the relative economic efficiency of interventions or programmes.

EFFECTIVENESS
The extent to which an intervention, procedure, regimen, when used in routine circumstances, does what it is intended to do for the specified population.

EFFICACY
The extent to which an intervention, procedure or regimen, when assessed in ideal circumstances, (usually in a randomised controlled trial) does what it is intended to do

EVIDENCE-BASED
Based on valid empirical information.

FALSE NEGATIVE
A negative test result in a person who does have the condition being tested for.

FALSE POSITIVE
A positive test result in a person who does not have the condition being tested for.

FLEXIBLE SIGMOIDOSCOPY (FSIG)
A procedure in which a slender, hollow, flexible, lighted tube is placed into the rectum, to help find polyps or cancers in the rectum and part of the colon.

HISTOLOGICAL
Study of a biopsy.

HEALTH-RELATED QUALITY-OF-LIFE (HRQOL)
An individual's satisfaction or happiness with domains of life (for example, physical functioning, cognitive functioning, psychosocial/emotional well-being, etc) insofar as they affect, or are affected by, "health".

INCIDENCE
Number of new cases during a period of time, typically specified in number per year. May also be expressed as a rate (i.e. number of cases per 100,000 population).

INCREMENTAL COSTS
Difference in costs (differential costs) between two comparable interventions.

INCREMENTAL EFFECT
Difference in effect (e.g., life expectancy) between two comparable interventions.

INTENTION-TO-SCREEN
Study results from patients who were randomly assigned to a screening, regardless of whether or not they completed the study protocol.

LIFE YEARS GAINED (LYG)
Number of years of prolongation of a patient's/individual's life by means of a particular intervention.

MAGNETIC RESONANCE IMAGING (MRI)
Method that uses a magnetic field to produce pictures of the structures inside the body. Produces better images of organs and soft tissues than other scanning technologies such as X-rays. Particularly useful for imaging the brain and spine, as well as the soft tissues of joints and the interior structure of bones.

MARKOV PROCESS
A mathematical model/random process in which the distribution of future states depends only on the present state and not on any past states (i.e. the system is "memoryless").

MEAN
Calculated by adding all the individual values in the group and dividing by the number of values in the group.

MEDIAN
Any value that divides the probability distribution of a random variable in half. For a finite population or sample, the median is the middle value of a odd number of values (arranged in ascending order) or any value between the two middle values of an even number of values.

META-ANALYSIS
The process of using statistical methods to combine the results of different studies.

MORTALITY RATE
The number of deaths from a specified disease that are diagnosed or reported during a defined period of time in a given population.

NATURAL HISTORY
The course of disease from onset to resolution.

NEGATIVE PREDICTIVE VALUE
The probability a person does not have the disease when the screening test is negative.

NEOPLASM
A growth of abnormal tissue. Maybe be benign or invasive. Also known as a tumour.

OBSERVATIONAL STUDY
A type of study in which individuals are observed or certain outcomes are measured. No attempt is made to affect the outcome (for example, no treatment is given and no intervention is made).

OCCULT BLOOD
Blood which is not visible to the naked eye, but which may be detectable by chemical means. The term usually relates to blood in the stool (faeces).

ONCOLOGIC
Related to cancer (oncology is the study of tumours, their origin, development and treatment).

PET SCAN
Short for positron emission tomography scan. A PET scan is a way to find cancer in the body. In a PET scan, the patient is given radioactive glucose (sugar) through a vein. A scanner then tracks the glucose in the body. The scanner's pictures can be used to find cancer, since cancer cells tend to use more sugar than other cells.

POLYP
A benign (non-invasive) neoplasm (tumour) in the epithelial tissue of the colorectum. There are various types of polyps including adenomas (see above), hyperplastic polyps, serrated adenomas, and flat polyps.

POOLED ANALYSIS
The process of using statistical methods to combine data from different studies.

POPULATION-BASED SCREENING PROGRAMME
A programme in which screening is systematically offered by invitation to a defined population.

POSITIVE PREDICTIVE VALUE
The probability that a person actually has the disease when the screening test is positive.

PREVALENCE
The proportion of the population with the disease at a given point in time.

PROBABILITY DISTRIBUTION
A function which defines the chance that a random variable takes particular values. In the case of model parameters, a probability distribution can be used to summarise uncertainty, with the function being larger for "likely" values of the parameter and smaller for "unlikely" values of the parameter.

QUALITY ADJUSTED LIFE YEARS (QALYS)
A measure of both the quality and quantity of life lived. QALYs gained are the number of years of prolongation of a patient's/individual's life by means of a particular intervention, incorporating adjustments for quality of life (morbidity).

RADIOTHERAPY
Cancer treatment that uses high-energy electromagnetic radiation such as x-rays to kill cancer cells. During radiotherapy, a significant amount of healthy normal tissue is sometimes irradiated. To reduce the side effects caused by this, the radiation dose is often split into a number of treatments, enabling the normal healthy tissue to recover before the next treatment is given.

Randomised controlled trial (RCT)

A study in which participants are randomly (i.e. by chance) assigned to one of two or more interventions.

RELATIVE SURVIVAL
The survival of a group of people with a disease relative to the survival of a group of individuals of the same age and sex who do not have the disease. It, therefore, describes how well those with the disease survival in comparison to those without the disease.

SCREENING
A search for cancer, or precancerous lesions, in people who do not have symptoms.

SENSITIVITY ANALYSIS
A method used to test the robustness of an assessment by examining the extent to which results are affected by changes in methods, parameters or assumptions.

SENSITIVITY
The proportion of truly diseased persons in a screened population who are identified as diseased by a screening test.

SPECIFICITY
The proportion of truly non-diseased persons in a screened population who are identified as disease free by a screening test.

STAGING/STAGE
Staging is a process of finding out whether a cancer had spread from the site or origin and, if so, how far it has spread.

(CRUDE) SURVIVAL
The proportion/percentage of people with a disease who are still alive at a specified time (e.g. 5 years) after diagnosis.

SYMPTOMATIC
Individuals who have one or more symptoms (e.g. rectal bleeding) that may be due to a disease (e.g. colorectal cancer).

TIME TREND STUDY
A type of study which examines trends in disease incidence and/or mortality rate over several years. Sometimes used to assess the impact of screening in the population, by comparing rates before and after the introduction of screening.

TRUE NEGATIVE
A test correctly identifying a person without a disease.

TRUE POSITIVE
A test correctly identifying a person with a disease.

UTILITY
A measure of the preference for, or desirability of, a specific level of health status or specific health outcome. Utility is generally measured on a scale of zero to one, where a year of life in perfect health has a score of one and death a score of zero.

Ethical Commentary

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Ethical issues

In the context of public health policy, considerations such as screening for disease, or the provision of a vaccine to the population at large, ethical discussion must take into account not only the application of the principles to individuals, but also the benefit, costs and risks to the public. Ethical criteria play an important role in developing any new healthcare technology or intervention.

There are four principles of medical ethics that are commonly used to assess issues in health care. These are:

- Autonomy
- Beneficence
- Non-maleficence
- Justice.

The first three criteria are more commonly applied to individual relationships between doctors and patients, whereas the final criterion is applied in discussions relating to the fair allocation of health care resources. Considerations of fairness in the context of a screening programme would include access to screening irrespective of ability to pay, fair distribution across all socio-economic groups, fairness as between genders unless the disease is gender specific, and fairness in relation to the prioritisation of expenditure on a screening programme for one particular disease at the expense of others.

Screening for colorectal cancer presents an opportunity to develop preventative tools to maximise benefit to the population. From an ethical perspective therefore, it may be seen as having a positive effect due to the prevention of disease. This would be in keeping with the utilitarian model of resource allocation which recommends the provision of services which will have the greatest effect on the largest number of people.

However, there is no progress without cost and investment, and all healthcare expenditure has both positive and negative implications. The conditions and context of each new development needs assessment on a case-by-case basis to ensure maximum benefit and minimum risk. For a screening test such as one for colorectal cancer to have an impact in terms of population health, it is necessary to ensure a high uptake of the screening programme, the minimisation of any risks associated with the screening and diagnostic tests by the implementation of quality assurance processes, and a comprehensive and adequately resourced follow-up treatment programme for those who need it.

The European Commission recommends that in all screening programmes measures must be in place to ensure that the tests are meaningful, the condition is serious, the test is highly predictive and follow-up actions must be available in terms of healthcare interventions. It also states that the relevance of the condition being screened for must be validated and regularly evaluated within the public health context; that the appropriate environment for providing information prior to testing and relevant post-test counselling be in place prior to offering such screening; that pilot programmes be undertaken prior to general introduction; and that the economic dimension of screening programmes be considered carefully. The following issues therefore arise for consideration:

- reliability and quality assurance
- transparency
- autonomy and respect for personal choice
- the provision of information and consent
- the protection of vulnerable groups
- confidentiality - the right to know and not to know, the duty to disclose and warn others
- equity in access
- control over samples and data
- the management and communication of uncertainty.

As well as the importance of the clinical aspects involved in ensuring reliable and high quality testing, the provision of information and counselling is considered an essential requirement in screening for serious disorders. Screening for colorectal cancer involves the testing of individuals, both men and women, who have no symptoms of the disease and are apparently well. It is important therefore to ensure that all relevant information is discussed with those individuals being tested to ensure that their consent to the test is voluntary and truly an informed choice. This requires the expertise of professionals who have specific training in the field. Simple printed information should be made available to anyone who has undergone testing, as well as the opportunity for further explanation and discussion offered.

In the context of disclosure of information prior to screening there are a number of ethical issues that need to be carefully considered and discussed in relation to the analysis of risks and benefits. Although the early detection of symptoms of colorectal cancer may be of life-saving benefit, there is also the potential for negative effects such as:

- false positive test results which may give rise to unnecessary distress for the individual and his/her family, as well as the possibility of further investigations being carried out on healthy individuals
- false negative results, which may give false security and ultimately delay the accurate diagnosis, with potentially fatal consequences

- physical side-effects or risks of testing, investigation and treatment, such as perforation of the colon or bleeding, including possible death
- psychological difficulties in informing an apparently healthy individual that they have signs of early cancer.

Increased public awareness of the disease through media and other information campaigns may serve to familiarise the public with general information regarding the benefits of early detection through testing, but in order to achieve the objectives of informed consent, further and more comprehensive information must be provided to ensure that the individual who chooses to be tested understands the purpose, potential risks and benefits, the possibility of misdiagnosis, and the alternatives to being tested. Communication of test results must respect the dignity, privacy and confidentiality of the individual, and counselling should be offered to enable the individual to understand the consequences of the test result for him/her and other family members. Guidelines should be developed to assist in the communication of the risks and benefits of screening.

The recommendation in this report favours the FIT based programme in 55 -74 year olds as the optimal strategy due to its greater overall effectiveness in reducing colorectal cancer mortality rates. However, it is also acknowledged that there may be a small risk of death, one per year, arising from the increased number of colonoscopies. The question may be posed as to whether this small risk is acceptable from an ethical perspective given that the majority of those who are screened will not have cancer. This raises two issues – the potential benefit of screening to those who test positive and who may therefore receive early and effective intervention, and the possibility that someone may be inadvertently harmed by the screening procedure. Public health measures generally rely upon the importance of maximising the benefit to the community as well as minimising, to the greatest extent possible, any possible risks or side-effects inherent in the measure to be taken.

In relation to the screening methods adopted in this report, it is ethically justifiable to recommend FIT on the basis of its expected benefit to society while at the same time ensuring that the colonoscopy procedures are carried out to the highest standards in order to minimise to the greatest degree possible any inadvertent risk of harm.

In relation to the proposed expenditure which the screening programme will necessarily entail, it is important to also recognise the long-term resource savings in terms of colorectal cancer treatment, and more importantly, the health gains for those whose length and quality of life will be enhanced by a screening programme. Allocation of healthcare resources is inevitably a question of balancing different priorities. Given the potential ultimate cost-saving and overall expected health gain it is therefore considered ethically justifiable to recommend expenditure on the FIT programme.

All other options evaluated in this HTA as alternatives to the recommended strategy (biennial FIT implemented within two years in ages 55 to 74 years) do not raise any additional ethical issues other than those already discussed in this commentary.