PROTOCOL

1 PROJECT TITLE
Frequency of follow-up for patients with low-, intermediate- and high-risk colorectal adenomas.

2 PLANNED INVESTIGATION

2.1 Research objectives
Overall objectives:
- To examine the optimum frequency of surveillance in people found to have low-, intermediate- and high- risk colorectal adenomas.

- To examine the risks and benefits to the patient with respect to prevention of cancer and the development of advanced adenomas; anxiety, morbidity and mortality; costs and cost-effectiveness and implications for the NHS.

2.1.1 Aims of the statistical analysis
The aim of the statistical analysis is to answer the following questions:
- Is there substantial heterogeneity of results at subsequent examination in terms of detection rates of advanced adenomas or colorectal cancer (CRC) according to baseline characteristics and interval to first follow-up colonoscopy?
- If so, is there a subgroup that does not need subsequent examination identifiable at baseline, and is the magnitude of this subgroup meaningful?
- For those who do need follow-up can we identify a group for whom an interval of 3 years is too long? Similarly is there a group for whom 3 years is too short?
- For the latter group, how long can the interval safely be extended to?
- Is there a subgroup who needs a second examination but no further follow-up thereafter, and if so, how is the group identified from the baseline and first follow-up examination results?
- What is the risk of CRC in each adenoma risk-group defined according to current adenoma surveillance guidelines:
  - What is the long-term CRC risk in those who have no surveillance?
  - What is the long-term CRC risk in those who have at least one, or two or more surveillance exam(s)?
  - Are there sub-groups in which CRC risk is low enough not to warrant surveillance?
  - Among those whose risk is determined high enough to require surveillance, when would CRC risk become sufficiently low to safely stop surveillance?
- Should risk-groups be redefined based on long-term CRC risk such that some patients might be reclassified as lower risk?
- What are appropriate surveillance intervals within defined risk groups to warrant colonoscopy but not result in unacceptably high interval cancers?

2.1.2 Aims of the psychological impact analysis
To answer the question:
- What are the anxiety-inducing effects of colonoscopic surveillance or being told that colonoscopy surveillance is required?

2.1.3 Aims of the economic analysis
The aims of the economic analysis are:
- To estimate the incremental cost-effectiveness of alternative adenoma follow-up strategies, including a policy of no follow-up, for individuals who have intermediate-risk colorectal adenomas;
- To estimate the impact of alternative adenoma follow-up strategies on colonoscopy services in England and Wales;

- To estimate the total cost impact of alternative adenoma follow-up strategies in England and Wales.
- To determine the health and economic impacts of the refined risk groups and surveillance intervals.

2.2   Background

2.2.1   Evidence that adenoma detection and removal prevents the development of colorectal cancer

It is now widely accepted that most colorectal cancers (CRCs) develop from adenomas and, by extension, that the detection and removal of adenomas will lead to a reduction in the incidence of CRC. Evidence to support this supposition is sparse and based on epidemiological data rather than randomised controlled trials (RCT). For example, the USA National Polyp Study (NPS) observed a 70-90% lower than expected incidence of CRC in patients undergoing colonoscopic surveillance compared to three reference populations [1].   Several case-control studies have shown reductions in incidence and mortality rates of distal CRC following sigmoidoscopy screening of the order of 60 – 80% [2-5]. However these study designs cannot eliminate the possibility of selection bias which can only be achieved by a RCT design. Several trials are in progress [6-9], the largest of which, the UK Flexible Sigmoidoscopy Screening trial (UKFSST), is examining the efficacy of flexible sigmoidoscopy (FS) screening with removal of all adenomas detected in reducing CRC incidence and mortality rates, but this trial will not report for 3 years.

The US Task Force [10] has described the evidence base for the efficacy of adenoma detection and removal in prevention of CRC as 'fair'. Evidence for the efficacy of regular colonoscopic surveillance is almost non-existent yet the procedure is widely practised at enormous cost to health care providers. Evidence is based primarily on the high recurrence rate of adenomas at repeat colonoscopy within 3 years of endoscopic removal of all visible polyps, which is of the order of 30%-50% [11-16]. At least 10% of these so-called recurrences are thought to be polyps missed at the initial examination and it has been suggested that two colonoscopies are required to achieve a 'clean colon' free of all visible polyps [17] (although this practice has since been mostly abandoned except for people with numerous polyps). As a result of these observations, several expert groups in the US began to recommend follow-up by regular colonoscopy for all patients with colorectal adenomas [18-20]

Autopsy and endoscopy studies indicate that adenomas are present in at least one third of individuals aged over 60 years. To offer prophylactic polypectomy followed by surveillance colonoscopy to all those at risk would be a formidable task, graphically illustrated by Kern in his presidential address to the American Gastroenterological Association in 1976 when he visualised ''an endless train of people colonoscoping each other, end to end, like elephants in a circus''.

It appears, though, that many practitioners have lost sight of the primary purpose of colonoscopic polypectomy which is the prevention of cancer rather than the removal of polyps. The lifetime risk of developing CRC is only 5% suggesting that almost 90% of individuals found to have adenomas at baseline will not develop cancer. Results from the NPS [12] in which patients were randomised to either one or two colorectal examinations within the first 3 years after entry, indicated that, compared with adenomas at entry, new adenomas at follow-up tend to be mostly diminutive (<5 mm), and only mildly dysplastic. Radiological studies suggest that the rate of growth of small adenomas is very slow and some may stay dormant for long periods [21]. There is little evidence that most of these small adenomas pose a risk of cancer during the remaining lifetime of the majority of patients. Independent studies undertaken on the US NPS dataset [22] showed that the observed reduction in incidence of CRC could be accounted for entirely by the initial colonoscopic polypectomy. Thus the NPS does not provide evidence that colonoscopic surveillance reduces risk further than achieved by the initial clearing colonoscopy.

However, endoscopists are faced with a dilemma. Without firm evidence of the absence of risk of cancer in an individual patient with adenomas, it was not considered ethical until recently, in the light of prevailing recommendations, to withhold colonoscopic surveillance where it is

available. Furthermore, there are anecdotal reports of carcinomas appearing within a short period of achieving a clean colon [23, 24]. It is not clear whether these cancers have arisen in missed adenomas or whether in some cases, progression is rapid [25]. It does seem, however, that while the majority of patients may be at very low risk of developing subsequent cancer after achieving a clean colon at entry, there is a small proportion, which is at high risk, and for this group colonoscopic surveillance is warranted.

2.2.2 Evidence of heterogeneity of risk among patients with adenomas
The strongest evidence that CRCs arise from adenomas is derived from the observation that remnants of adenomatous tissue are often seen in CRCs and a focus of malignancy is sometimes seen in adenomas. Muto et al [26] showed that the probability that an adenoma would contain a focus of malignancy was higher if the adenoma was larger than 1 cm, had tubulovillous or villous histology or severe dysplasia.

A long-term cohort study undertaken at St Mark's by Atkin et al. [27], was the first study to demonstrate that these features are predictive not only of the presence of malignancy in an adenoma but also of future risk in patients from whom adenomas have been removed. We examined the lifetime risk of developing CRC following removal of adenomas via the 25 cm rigid sigmoidoscope and identified a low-risk group in whom risk was no higher than the general population. This group, which comprised more than half of all patients with adenomas, included those with only 1 or 2 small, tubular adenomas. Risk was increased 3-fold compared with the general population in patients from whom large, tubulovillous or villous polyps were removed and by 5-fold in patients from whom both multiple and large, villous or tubulovillous adenomas had been removed.

The concept of the "advanced adenoma" was first described by the US NPS investigators [28] to include adenomas which are large, have tubulovillous or villous histology or severe dysplasia, and therefore a higher "malignant potential. It was concluded that the aim of colonoscopy is to detect these high-risk lesions and not the removal of small adenomas, the vast majority of which will never become malignant. The NPS showed that around 3% of individuals from whom an adenoma was removed developed an advanced adenoma by 3 years. Several studies, including NPS and St Mark's, [12, 14-16] have shown that the features associated with an increased risk of developing an advanced adenoma are increasing number, size, and more advanced histology or dysplasia.

Thus it appears that whether the outcome is an advanced adenoma or cancer, future risk is low among patients with one to two small adenomas. We have suggested that colonoscopic surveillance is probably not justified in such patients. Recent guidelines from the American Gastrointestinal Association [29] have cautiously recommended that the first follow-up colonoscopy may be delayed until 5 years or possibly even longer, but comments that evidence is evolving. The definitive study to examine risk of CRC in this sub-group compared with people with no adenomas is being undertaken as part of the UK FS Screening Trial [7]. In this trial people found at screening to have no adenomas or only 1-2 small, tubular adenomas with only mild or moderate dysplasia are not offered colonoscopic surveillance, but are flagged for future occurrence of malignancy.
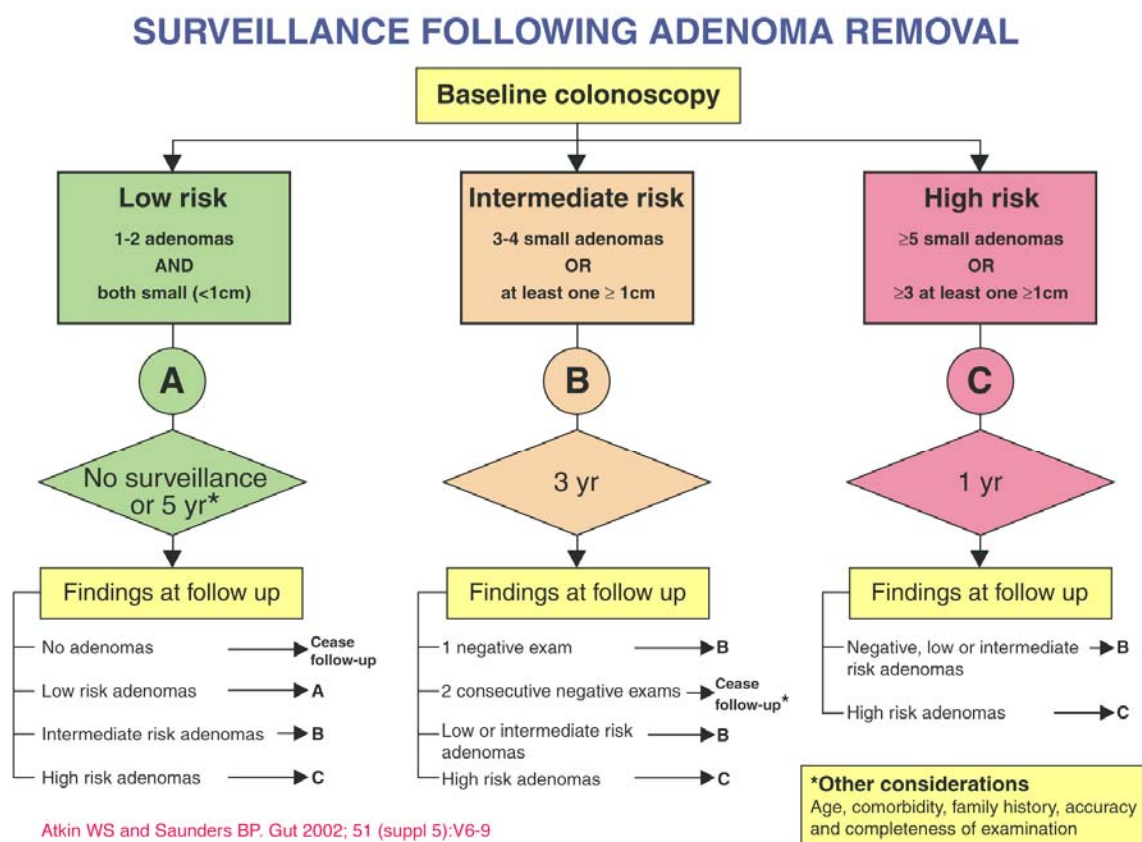
2.2.3 Studies examining the frequency of follow-up for patients with colorectal adenomas
Three randomised trials have compared the frequency of follow-up in patients with adenomas removed at colonoscopy [12, 24, 30]. The US NPS [12] was a randomised comparison of different surveillance intervals in 1418 patients with newly diagnosed adenomas removed at colonoscopy. In this study the cumulative detection rate of advanced adenomas or cancer was 3% in the groups having either 1 or 2 examinations within 3 years, suggesting that a single examination at 3 years might be sufficient. The Funen Adenoma Follow-up Study [24] found that the incidence of advanced neoplasia was higher in patients examined at four years compared with two (8.6 vs 5.2%), although the difference was not significant. However, on balance, the authors concluded that the 50% reduction in the number of examinations and the probable reduction in complications might justify the longer interval. The St Mark's Adenoma Follow-up Study [30] compared the effectiveness of annual vs. 3-yearly follow-up intervals in high-risk patients and 3-yearly vs. 5-yearly intervals in low-risk patients in preventing the

development of large adenomas or cancer. The high-risk group, defined according to a previous pilot observational study undertaken on St Mark's patients, included patients with any of the following: 1) at least 5 adenomas; 2) a malignant adenoma not requiring surgical removal; 3) age over 54 years with more than one adenoma, and 4) age over 59 years. The remaining patients constituted the low-risk group. The results of this long-term follow-up study are currently being analysed. These studies are unable to distinguish between the few high-risk and the majority of low-risk patients since even with the longest intervals examined, very few newly detected adenomas exceed 1 cm in size.

2.2.4 Current UK recommendations

In 2000, Wendy Atkin and Brian Saunders at St Mark's Hospital were invited to undertake a review of the literature and to develop guidelines for the colonoscopic surveillance following adenoma detection (see figure below). We identified a low-risk group for which it was suggested that colonoscopic surveillance might not be necessary and a high-risk group for which surveillance is definitely indicated, at least 3 yearly and maybe more frequently initially. This latter group includes people with 5 or more adenomas or 3-4 adenomas at least one of which is advanced; this group comprises only around 5% of people with adenomas. This left an intermediate risk group for which there is no evidence to indicate that it is safe not to offer surveillance. The available evidence suggested that it might be safe to stop surveillance after two negative exams, depending on the age of the patient and the quality of the examinations. However, it is possible that patients with intermediate adenomas are a heterogeneous group with respect to their risk of developing CRC and that longer intervals might suffice for a subgroup. It is also possible that it is not necessary to have two negative follow-up colonoscopies before stopping surveillance and that a single negative exam might be sufficient.

SURVEILLANCE FOLLOWING ADENOMA REMOVAL

Baseline colonoscopy

Low risk — 1-2 adenomas AND both small (<1cm)

A — No surveillance or 5 yr*

Findings at follow up
- No adenomas → Cease follow-up
- Low risk adenomas → A
- Intermediate risk adenomas → B
- High risk adenomas → C

Intermediate risk — 3-4 small adenomas OR at least one ≥ 1cm

B — 3 yr

Findings at follow up
- 1 negative exam → B
- 2 consecutive negative exams → Cease follow-up*
- Low or intermediate risk adenomas → B
- High risk adenomas → C

High risk — ≥5 small adenomas OR ≥3 at least one ≥1cm

C — 1 yr

Findings at follow up
- Negative, low or intermediate risk adenomas → B
- High risk adenomas → C

*Other considerations
Age, comorbidity, family history, accuracy and completeness of examination

Atkin WS and Saunders BP. Gut 2002; 51 (suppl 5):V6-9

Since the 2002 UK-adenoma surveillance guidelines were published [31], the lack of new

evidence has meant that the recommendations have not changed [32, 33]. The lack of good quality evidence to support risk-group definitions and the number and frequency of follow-up colonoscopies, also means that national guidelines within different countries vary in their recommendations [31, 34, 35]. Most evidence that was used to define surveillance guidelines was based on advanced adenoma findings at colonoscopy as a surrogate for CRC risk, and on data that pre-dates the era of better quality colonoscopies (since the implementation of modern high-definition endoscopes and national colonoscopy quality audits). The impact of better quality baseline colonoscopies on subsequent CRC risk is not known, nor is the impact of surveillance.

With the introduction of the NHS Bowel Cancer Screening Programme (BCSP), the increased incidental detection of adenomas requiring surveillance is putting enormous pressure on endoscopy resources. Currently, adenoma surveillance accounts for ~20% of colonoscopies, and this figure will inevitably rise as more people remain under surveillance [36, 37]. We hypothesise that adequate protection against CRC could now be achieved with less colonoscopic surveillance than is currently recommended in the UK-adenoma surveillance guidelines.

By looking at evidence based on future CRC risk (rather than advanced adenomas), and on baseline colonoscopies conducted within the last 15 years since standards of endoscopy procedures have improved, we hypothesise that:
- A substantial proportion of patients with adenomas have a future risk of CRC that is no higher than the general population. These patients may not warrant colonoscopic surveillance.
- There are subgroups within the intermediate- and high-risk subgroups who require less surveillance than is currently recommended.

2.3   Research Methods
Observational study, mainly retrospective, from existing datasets.

Rationale
Since a randomised trial would take several years to achieve a result, it is suggested that this is delayed until the national screening programme has achieved roll-out in most of the country. The trial can then be undertaken at relatively low cost in individuals found to have intermediate adenomas as a result of colonoscopic investigation of a positive faecal occult blood test. In the meantime we will undertake a (mainly) retrospective cohort study using several large datasets collected in screening trials and from hospital endoscopy databases.

We will use this established cohort to collect additional follow-up data on colonoscopy procedures, cancer incidence and deaths to examine surveillance in the low-risk and high-risk adenoma groups, as well as re-examine the intermediate-risk group with longer follow-up.

2.3.1   Analysis of risk of cancer or advanced adenomas with varying frequency of colonoscopy surveillance
The aim of the statistical analysis is to answer the following questions:
1. Is there substantial heterogeneity of results at subsequent examination in terms of detection rates of advanced adenomas or CRC according to baseline characteristics and interval to first follow-up colonoscopy?
2. If so, is there a subgroup that does not need subsequent examination identifiable at baseline, and is the magnitude of this subgroup meaningful?
3. For those who do need follow-up can we identify a group for whom an interval of 3 years is too long? Similarly is there a group for whom 3 years is too short?
4. For the latter group, how long can the interval safely be extended to?
5. Is there a subgroup who needs a second examination but no further follow-up thereafter, and if so, how is the group identified from the baseline and first follow-up examination results?
6. What is the risk of CRC in each adenoma risk-group defined according to current UK-

adenoma surveillance guidelines:
   a) What is the long-term CRC risk in those who have no surveillance?
   b) What is the long-term CRC risk in those who do have at least one, or two or more surveillance exam(s)?
   c) Are there sub-groups in which CRC risk is low enough not to warrant surveillance?
   d) Among those whose risk is determined high enough to require surveillance, when would CRC risk become sufficiently low to safely stop surveillance?
7. Should risk-groups be redefined based on long-term CRC risk such that some patients might be reclassified as lower risk?
8. What are appropriate surveillance intervals within defined risk groups to warrant colonoscopy but not result in unacceptably high interval cancers?
9. What are the health and economic impacts of refined risk groups and surveillance intervals?

For questions 1-4 the analysis will draw on data on the baseline examination and the first follow-up examination, in particular how the findings at the latter relate to those at the former. For question 5, we will relate the findings at second and subsequent follow-up examinations to those at baseline and first follow-up examination.

The statistical analysis strategy will be split into three stages: (1) analysis of first follow-up findings in relation to baseline findings; (2) analysis of second and subsequent follow-up findings in relation to baseline and first follow-up findings, and (3) analysis of rates of symptomatic CRC in the years after final endoscopic examination.

Analyses will be performed both including and excluding those with first follow-up less than 3 years after baseline, as this may be a reflection of clinical opinion of extra high risk. Results of all analyses will be confirmed by internal cross-validation.

For questions 6 – 8 our statistical analyses will focus on the long-term CRC incidence after baseline. To assess the effect of surveillance on CRC risk, we will compare the incidence of CRC both in the absence and presence of surveillance, and compare CRC risk with that expected in the general population. Cox proportional hazard models will be used to assess the relationship between baseline characteristics and CRC risk to identify subgroups in which CRC risk is low enough to justify less intensive surveillance and reclassification of risk. In those who benefit from surveillance, the CRC risk will be examined after multiple exams to estimate when surveillance could safely stop, or multiple intervals to estimate the appropriate interval length between surveillance exams.

Additional health economic analyses will be conducted to estimate the cost implications of alternative surveillance strategies (question 9).

2.3.2   Examination of anxiety levels
It is unrealistic to expect to identify existing datasets that have examined the psychological impact of offering different intervals between surveillance colonoscopies. However we can compare the impact on patients undergoing endoscopic screening who are informed that they have adenomas but who are or are not offered surveillance colonoscopy. In the UKFSST, individuals from whom 1-2 small tubular adenomas were removed at screening were considered to be a 'lower risk' group and were not offered surveillance, whilst those with more numerous and/or advanced adenomas were offered surveillance according to a prescribed protocol which is similar to the BSG guidelines and were considered a 'higher risk' group. Around 2,000 patients were offered surveillance and a similar number were discharged. Both groups completed a detailed questionnaire 6 months before and 3 months after screening. At the time they received their post-screening questionnaire they had been told whether or not they needed colonoscopic surveillance. Thus this dataset will be used to estimate the likely psychological impact of informing people with adenomas that they do not need surveillance through comparing our lower risk (no surveillance) and higher risk (surveillance) groups.

The following measures were used:
   Bowel cancer worry was assessed before and after screening with the following

question: 'How worried are you about getting bowel cancer?' with response options on a 4 point Likert scale: 'not worried at all, a bit worried, quite worried, very worried'. This has been used in previous studies of breast cancer screening and in the pilot centres of the FS trial [38].

Anxiety was measured using the 6-item version of the Spielberger Stait Trait Anxiety Inventory (STAI) [39]. The responses were totalled giving a score of between 6 and 24, with higher scores indicating higher anxiety.

Bowel symptoms were assessed with the stem question: 'Because we are studying bowel screening, we would like to know how often people get these bowel symptoms. 'In the LAST THREE MONTHS have you', followed by seven symptoms: 'been constipated? had haemorrhoids (piles)? been troubled with wind? had pains in the abdomen (gut)? had bowel incontinence? noticed blood in your stools? Response options were: 'no, occasionally, frequently'. Scores were calculated by counting a response of 'occasionally' or 'frequently' as indicating the presence of bowel symptoms. People were categorized into whether they had 'one or more' bowel symptoms or 'none'.

GP attendance was measured using one question: 'About how many times have you been to see your GP in the last 3 months?' Response options were: 'Haven't been, once, twice, three or more times'.

Positive psychological consequences of screening were assessed using three items from the positive emotional subscale of the Psychological Consequences of screening Questionnaire (PCQ) [40] were used to assess reactions to screening. These were: 'Do you think that your experience of having the Flexi-Scope test has …' 'Made you feel more hopeful about the future?' 'Made you feel less anxious about bowel cancer?' 'Given you a greater sense of well being?' Response options on 4 point Likert scale: 'not at all, a little bit, quite a bit, a great deal'. Cronbach's alpha in the present study for the emotional items was 0.81, which is similar to the value of 0.89 reported for the full 10 item scale (containing positive and negative emotional items).

We will therefore be able to establish the psychological impact of colonoscopic surveillance by looking at its effect on bowel cancer worry, state anxiety and positive emotional reactions to screening. We will also be able to assess the potential impact of colonoscopic surveillance on additional factors such as the use of health care resources and concern about colorectal health following colonoscopy through looking at GP attendance and self-reported bowel symptoms.

We also have additional measures in the surveillance group on the anxiety-inducing effects of having a colonoscopy in the form of retrospective reports of anxiety felt at various stages throughout the screening process: anxiety during the initial FS test, anxiety when a polyp was found, anxiety on being told they needed to return for a colonoscopy, anxiety experienced waiting for the colonoscopy, anxiety when waiting for the results, and anxiety following the results of the colonoscopy). We will evaluate the level of anxiety associated with each of these stages to get an estimate of the emotional impact of surveillance.

2.3.3 Economic analyses
A full economic analysis will be carried out with three key aims: -

To estimate the incremental cost-effectiveness of alternative adenoma follow-up strategies, including a policy of no follow-up, for individuals who have intermediate-risk colorectal adenomas;
To estimate the impact of alternative adenoma follow-up strategies on colonoscopy services in England and Wales, in terms of the total number of colonoscopies required and the associated impact upon staffing and clinic requirements;
To estimate the total cost impact of alternative adenoma follow-up strategies in England and Wales.

Economic outcomes
The analysis will take the form of an incremental cost-effectiveness analysis using two key

health economic outcomes:
1. Cost per cancer avoided, and
2. Cost per life year saved.

Subject to the availability of evidence, additional analysis will be undertaken to consider the cost-utility of adenoma follow-up on health-related quality of life.

Health economic methods (subject to availability of data)
The economic analysis will take the form of a state transition model to describe the progression of individuals identified as intermediate risk at baseline through to high risk to CRC and subsequent death, in the absence of any follow-up (an example of this is given in the diagram below). A follow-up mechanism will then be superimposed upon this natural history model in order to estimate the effectiveness of alternative follow-up policies in terms of the number of cancers avoided and the life-years gained. Progressions through the health states within the model will be described by instantaneous hazard rates. It is anticipated that test sensitivity and progression rates will be jointly estimated within the formal multistate modelling described in Section 2.9.

Natural history model schematic

The health benefits of each follow-up strategy will then be linked to the economic analysis. It is envisaged that the economic analysis will include two cost components: the cost of colonoscopic investigation, and the lifetime cost associated with treating CRC (which would include all treatment and follow-up costs including costs of recurrence). Incremental costs and effects for each follow-up policy will be estimated over the lifetime of the cohort and synthesised to produce cost-effectiveness estimates in terms of cost per cancer avoided and cost per life-year saved.

Model parameters
It is anticipated that the model parameters will fall into three broad categories: -

1. State transition rates;
2. Test characteristics (sensitivity, specificity);
3. Costs.

Transition rates and test characteristics will be jointly estimated through the multi-state modelling described in Section 2.9, using data on long-term follow-up of patients with intermediate-risk adenomas, while data on costs of diagnosis and cancer management will be drawn from published literature and existing modelling studies.

Subgroup analysis
The economic evaluation of adenoma follow-up strategies for specific subgroups of patients will be informed by the statistical analysis.

Sensitivity analysis
Multivariate sensitivity analysis will be undertaken to explore the impact of uncertainty on costs and effects of different adenoma follow-up policies. This involves the assignment of a statistical distribution to each model parameter which reflects the degree of uncertainty in the true value of the parameter. Monte-Carlo sampling methods will be used to generate cost-effectiveness planes, demonstrating the impact of uncertainty surrounding mean model parameter estimates. Cost-effectiveness acceptability curves (CEAC) will be produced to generate information on the likelihood that a given follow-up policy results in the greatest expected net benefit* over a range of willingness-to-pay thresholds (the net benefit measures the additional health gains following adjustment for any cost consequences).

*Where Net Benefit = (Programme life years gained * willingness to pay threshold) –*

programme cost

In addition, value of information analysis will be carried out as a means of quantifying the level of uncertainty within the model, and to estimate the impact on the expected net benefit of the alternative strategies of obtaining perfect information on model parameters. Value of information analysis can be used to assess the value of additional information on all parameters concurrently, or on specific parameter groups or individual parameters, enabling the prioritisation of further research through pursuing research projects whose additional information is expected to yield the greatest payoff in terms of expected net benefit. Uncertainty in model parameters indicates that there is a possibility of selecting a sub-optimal strategy, and hence the value of information is high in situations where the additional information gained from further research would alter the strategy adopted. Similarly, if further research on a specific parameter would not alter the adoption decision, there is no value in conducting such research. Value of information analysis can therefore be considered as a useful tool in placing a monetary ceiling upon further research, whilst also providing a basis for the design of clinical trials.

Additional Health Economic Analysis
An additional Health Economic analysis will be conducted on all adenoma risk groups, using the long-term follow-up of the all adenomas group.

There are two objectives (question 9):
1) To evaluate the within-study (up to ~10 years of follow-up) health-related resource use, costs and outcomes (in terms of CRC incidence), and to estimate incremental cost-effectiveness of each surveillance strategy identified in the statistical analyses (including no surveillance and surveillance according to existing guidelines).

2) To extrapolate the economic findings to a lifetime time horizon (100 years of age) using economic modelling, in order to evaluate long-term incremental resource use, costs, outcomes (in terms of CRC incidence, and life years/quality-adjusted life years gained), and cost-effectiveness of each surveillance strategy identified in the statistical analyses (including no surveillance and surveillance according to existing guidelines).

2.4   Planned interventions
None, most of the data is retrospective. For the prospective data only patients already undergoing routine surveillance colonoscopy will be included. No change to their current management will be made for purposes of this project.

2.5   Inclusion/exclusion criteria
Inclusion criteria
- Men and women at any age with adenomas who have undergone a baseline colonoscopy.
- People with low-risk adenomas are defined as those with 1 or 2 adenomas, both of which are small (< 1 cm).
- People with intermediate-risk adenomas are defined as those with 3 or 4 small (<1cm) adenomas, or 1 or 2 adenomas, at least one which is large (≥ 1 cm).
- People with high-risk adenomas are defined as those with 5 or more small (< 1 cm) adenomas or those with 3 or more adenomas, at least one of which is large (≥ 1 cm).

Exclusion criteria
- Strong family history or dominantly inherited condition
- Inflammatory bowel disease
- Previous colorectal cancer

2.6   Ethical arrangements
This is an observational study which will have no impact on the study participants. It will benefit society since at present there is an inadequate evidence base for the current

recommendations for colonoscopic surveillance in patients with intermediate-risk adenomas. It is possible that for some patients the intervals recommended in current guidelines are too long, putting them at increased risk. For others the intervals may be too short putting them at unnecessary risk of harm arising from potential complications from unnecessary colonoscopies.

2.6.1 Informed consent
Fully informed consent to use the patient data in this study will not be possible, due to its retrospective nature, although many programmes obtain consent from subjects for use of their results for audit and improvement of the service. For much of the analyses it will be possible to anonymise the data, but where the study researchers will have to match data from different databases to provide adequate information for the statistical analysis anonymisation will not be possible. Such matching will be carried out prior to the statistical analysis and the data re-anonymised so that those charged with the analysis do not have identified data. Identified data will need to be supplied to ONS if the cohort is to be followed using the national cancer registries as we would like to do.

We will amend our Patient Information Advisory Group (PIAG) section 60 approval, now section 251 approval, to request permission to collect additional data to the end of 2016 where available and include the analysis of the data to include the low- and high-risk adenoma groups.

2.6.2 Retention of study documentation
We will retain the data for 10 years after the end of the study, in accordance with Imperial College London's retention policy.

2.7 Outcome measures

- Colorectal cancer diagnosed symptomatically or at follow-up colonoscopy.

- Multiple or advanced adenomas detected at follow-up colonoscopy. Advanced adenomas are defined as adenomas larger than 1 cm, with severe dysplasia or with tubulovillous or villous histology.

- The subsite of adenomas which will inform about whether or not flexible sigmoidoscopy is adequate for surveillance.

- For the psychological impact analysis: anxiety, bowel cancer worry, number of GP visits and bowel symptoms.

- For the economic analyses: cost per cancer avoided and cost per life year saved

2.8 Sample size
For simplicity, we base our sample size requirements on the comparison of the rates of detection at first follow-up at two different intervals, using the heterogeneity in practice with respect to follow-up intervals. A reasonable possibility might be 5% of subjects with an intermediate or high risk lesion at first follow-up at 4-6 years and 3% at 2-4years [41, 42]. For 90% power to detect this at 5% significance level in a two-sided test, we would need a total of 4,400 subjects with at least one follow-up examination. For second or subsequent follow-up, we might stipulate the more relaxed criterion of wishing to estimate the detection rate within 1% in either direction. If we anticipate 3% of subjects to have intermediate or high-risk lesions at second or subsequent follow-up, this would require 1,200 subjects with at least two follow-up endoscopies.

We might also stipulate a sample size to give relatively low coefficients of variation of S, the test sensitivity, and λ_2, the rate of progression to clinical CRC, in order to compare different intervals between follow-up with respect to rates of cancers that would accrue. In order to use these with confidence to predict effects of different follow-up policies, we require a high degree of precision in estimation of S and λ_2. We therefore stipulate that both have

coefficients of variation of no more than 30% (i.e. the standard error of each estimate has magnitude no larger than 30% of the value of the estimate).

Closed form estimation is not possible for these quantities and it is difficult to predict the variability of our estimates. Work by Chen et al [43] and Wong et al [44] suggest that with around 30 events, CV's of 30% or less can be achieved if the rate of progression is small (0.2 per annum or less). However, we would be likely to wish to stratify or at least introduce covariates, which would reduce the precision. We therefore aim to recruit cohorts with a total of 60 CRCs.

Stryker et al [45] found rates of progression in untreated adenomas suggestive of a λ_2 of around 0.01 for progression to CRC. Atkin et al [27] studied a wide case mix of treated polyps at entry (corresponding to the situation in this project), and suggests a rate of around 2 per thousand per year after colonoscopy overall and around 4.5 per thousand per year for the high-risk subgroup. Thus, in the literature, the rate ranges from 2 to 10 per thousand per year.

If we assume that the underlying risk of CRC in our cohorts is considerably higher than the population risk, but that the relative risk might be brought down by the protection of endoscopic examination to between one and two times the population risk in males aged 50 or over, we would have a figure of between 2.5 and 5 endpoints per thousand per year. In total, therefore, we would require between 12,000 and 24,000 person-years of follow-up after endoscopy episodes. Assuming an average of four years observation, this would require recruiting cohorts to a total of 6,000 subjects. We propose as a failsafe strategy to recruit 10,000.

Updated sample-size calculations for all adenomas risk groups' analysis
As stipulated above, we required an intermediate-risk cohort with a total of at least 60 CRCs for the initial analysis of the intermediate-risk adenoma group. This stipulation would also hold for each of the low-risk and high-risk groups. In the current data with 6 years of follow-up we have approximately 120, 170 and 50 CRCs diagnosed in these groups respectively. With an expected accrual of an additional 195 CRCs in the total cohort, this will provide sufficient precision within each of the three risk groups.

2.8.1   Datasets to achieve required sample sizes
To address these questions a large sample size and relatively long period of follow-up is required. No single dataset is adequate although the UKFSST cohort of 1,925 patients with intermediate adenomas is the largest that we know of. This cohort was recruited between 1996 and 1998 and 1,453 have had at least one follow-up colonoscopy and 484 have had at least two follow-ups. Four other screening derived cohorts with a total sample size of approximately 2,000 individuals with intermediate adenomas who have had at least one follow-up will supplement this high quality dataset. In addition, we shall obtain datasets from several UK hospital endoscopy units which routinely record the date and type of examination, indication for colonoscopy and diagnosis, and the size and location of any polyps detected. It will then be necessary to search the hospital pathology databases for records with the SNOMED codes for adenomas. The datasets derived from the endoscopy and pathology databases will then be matched to identify patients with intermediate adenomas who have undergone baseline and surveillance colonoscopies. Since this is a study of intermediate adenomas detected in average risk individuals who are likely to undergo population screening, patients with the dominantly inherited syndromes (FAP, HNPCC, etc) or inflammatory bowel disease will be excluded. We have estimated that we will need to extract data from 20 hospitals to achieve the required sample size.

UK Flexible Sigmoidoscopy Screening Trial
As part of this randomised trial to examine the efficacy of a single FS screening in reducing CRC incidence and mortality rates, 40,674 men and women aged between 55 and 64 years attended for FS screening. FS screening was performed by an experienced doctor in endoscopy units in 13 UK centres. A single endoscopist in each of 13 UK centres performed around 3,000 procedures during the trial. Endoscopists were encouraged to remove all small polyps during screening. Larger polyps seen in the distal colon at FS were later removed at colonoscopy. Individuals found to have 3 or more adenomas or one or more large (≥ 1 cm),

tubulovillous, villous or severely dysplastic adenomas were offered a baseline colonoscopy and surveillance according to a prescribed protocol (similar to the BSG guidelines). 1925 patients had a baseline colonoscopy, 1,453 have had at least one follow-up and 484 have had at least two follow-up colonoscopies. In addition the cohort is being followed up using the records held by ONS and Cancer Registries for incidence of CRC and has accrued an average of 7 years of follow-up.

St Mark's Adenoma Follow-up Study
The St Mark's Adenoma Follow-up Study [30] compared the effectiveness of annual vs. 3-yearly follow-up intervals in high-risk patients and 3-yearly vs. 5-yearly intervals in low-risk patients in preventing the development of large adenomas or cancer. This dataset includes 359 patients with intermediate adenomas who had a baseline and at least one follow-up colonoscopy. In addition the cohort has been flagged at ONS to determine CRC incidence after termination of follow-up. This study has accrued an average of 12 years of follow-up.

The Nottingham Faecal Occult Blood test (FOBT) Trial cohort
This RCT examined the efficacy of biennial FOBT screening in reducing CRC mortality. Individuals who tested positive were investigated by colonoscopy. A total of 582 individuals had an intermediate adenoma detected and the results of follow-up were published [46]. The cohort has been flagged at ONS to determine cancer incidence and has accrued an average of 13 years of follow-up [47].

The UK National Pilot of FOBT screening.
This pilot study, commissioned by the Department of Health and included two regions in Scotland and England, each with around 1 million population. A total of 1139 individuals were found to have intermediate adenomas as a result of colonoscopic investigation of a positive FOBT. The first round of screening was undertaken between 2000 and 2002, therefore only a proportion will have had a follow-up colonoscopy so far, although all will be due by 2005. Professor David Weller, who undertook the pilot evaluation, has indicated his willingness to collaborate.

Veterans Affairs Colonoscopy Screening Study
The VA study has the following groups which had a baseline screening colonoscopy exam and at least one follow-up surveillance exam within 5 years which meet the criteria for an intermediate lesion: A total of 388 individuals meet these criteria.

Kaiser Permanente
In this study around half a million people aged over 50 years have undergone an FS screen and, as with the UK study, those with intermediate or high risk adenomas are offered a colonoscopy. Dr T.R. Levin, who has published results of this study, has indicated his willingness to collaborate. This population was screened between 1994 and 1996 so it will have accrued considerable years of follow-up and is an important dataset.

UK Hospital Endoscopy and Pathology databases
We shall obtain datasets from several UK hospital endoscopy units which routinely record the date and type of examination, indication for colonoscopy and diagnosis, and the size and location of any polyps detected. It will then be necessary to search the hospital pathology databases for records with the SNOMED codes for adenomas. The datasets so derived will then be matched to identify patients with intermediate adenomas who have undergone baseline and surveillance colonoscopies. Since this is a study of intermediate adenomas detected in average risk individuals who are likely to undergo population screening, patients with the dominantly inherited syndromes (FAP, HNPCC, etc) or inflammatory bowel disease will be excluded.

We have undertaken a preliminary investigation to determine how many people with intermediate adenomas can be obtained by searching databases in hospitals which have used an endoscopy database for at least 5 years. We performed a pilot study using the St Mark's Hospital endoscopy database, which has been operational since 1995, and identified around 900 patients with an intermediate adenoma and a baseline colonoscopy, and around 150 who have had at least one follow-up colonoscopy (this data needs more cleaning but is

approximately correct). We have not yet completed our investigations but so far we estimate that we need to contact 20 hospitals to achieve the required sample size.

2.8.2 Total sample size

	Patients with intermediate adenomas (n)		
	Baseline	≥ 1 follow-up colonoscopy	≥ 2 follow-up colonoscopies
Endpoint	Colorectal cancer	Advanced adenoma	Advanced adenoma
Total number of endpoints required	60	198	36
Total number of cases required	10,000	6,600	1,200
UK FS Screening trial*	1925	1453	484
St Mark's Adenoma Follow-up trial	603	359	124
Nottingham FOBT trial*	582	483	279
UK Pilot of FOBT screening*	1139	850 (by 2005)	0
Kaiser Permanente FS screening service*	2000+	1500+	500+
VA Colonoscopy screening study*	-	388	0
St Mark's hospital endoscopy database	900	250	100 (estimate)
20 other UK endoscopy databases	6,000	1,000	400 (estimate)
Total	11,149	4,787*	1287

* screening derived datasets. The dataset from Kaiser Permanente is likely to be a large under-estimate since 250,000 people have received an FS screen compared with 40,000 in the UK.

2.9   Statistical analysis

2.9.1.   Baseline and first follow-up screen analyses
a. Simple analysis of rates of events since last examination
In the first instance we will use simple descriptive statistics to summarise findings at first follow-up colonoscopy in relation to time since baseline examination, and consider the detection rates of advanced adenomas at subsequent examination stratified by findings at baseline examination, interval since baseline examination, age and sex. There is particular a priori interest in comparing intervals of less than 4 years (i.e. roughly 3 years) with intervals of 4-6 years (roughly 5 years). The stratification by baseline findings is particularly important, as there is likely to be heterogeneity, which in turn should inform policy.

We will be dealing with the detection of adenomas in the large bowel at first follow-up examination. These will be relatively common premalignant conditions (in a population all of whom have already had at least one such lesion). Practice in terms of interval to follow-up examination is not standard, and we will use this variability in practice to deduce the relative effects of different policies. If there are larger prevalences observed with longer intervals, this would suggest a suitable interval at which a sufficiently large harvest of polyps will result to render the practice effective and economical. On the other hand, a constant detection rate with time since last examination might lead us to suspect that de novo lesions were relatively rare and the constant harvest is of lesions missed at the baseline examination.

The above approach is attractive because of its simple, empirical nature. We would, however, wish to quantify our qualitative conclusions, and to extrapolate to intervals other than those for which we have data, for example to almost immediately after baseline examination, in relation to the issue of missed lesions. For this, more formal statistical analyses would be necessary.

b. Logistic regression to relate findings at first follow-up with findings at baseline and to the interval between the two
The goal here is to formally estimate the combined effects of findings at baseline and time since baseline on the findings at subsequent examination. In the first instance we shall

consider the findings at subsequent endoscopic examination by time since previous examination and the size, multiplicity, grade and sub site of polyps found at baseline examination. To study different outcomes at subsequent examination, we shall fit a number of logistic regressions with different outcomes, including:

1. Any adenoma
2. Multiple adenomas
3. Single advanced adenoma
4. Multiple and advanced adenoma

The logistic regressions will be of the form

where x_1 represents time since last examination, x_2 size of polyp at last examination, x_3 multiplicity of polyps at last examination, and so on. Host factors such as age, gender and any personal or family history data available can also be built into these analyses. The results of these can be used to determine subgroups which, for example, have very low rates of polyps at subsequent examination and may not need further surveillance beyond the baseline, and to determine optimal interval times for those who do need further surveillance.

In addition, we shall estimate any modifiers of the effect of time since last examination. For example, there may be a subgroup with β_1 close to zero, despite a non-negligible harvest of polyps at subsequent examination. This would suggest that the polyps were present but missed at the baseline examination, and may point to a group that only needs a single subsequent examination. This can be verified by using data on those subjects with more than one repeat examination. In addition, all analyses with implications for policy beyond the baseline examination will be subject to cross-validation across cohorts and between randomly chosen sets within cohorts.

The attraction of the above method is that it gives quantitative results with implications for whether subsequent examinations are needed and if so, at what intervals, without making parametric assumptions about the distribution of progression rates or explicitly estimating test sensitivity. However, it is worthwhile to carry out some parametric multistate modelling, partly for internal consistency checking and partly for further interpretation. For example, for those for whom there is evidence of an increasing chance of polyps according time to subsequent examination, an estimate of the test sensitivity would indicate what proportion of these might be detected and treated by improved performance of the baseline examination, and what proportion occur de novo and therefore need repeat examinations to detect them.

c. Formal multistate models
We propose exponential distributions for incidence and progression of adenomas. This means that at a subsequent examination t years after the baseline, the proportion observed with at least one polyp would be

where λ_1 and λ_2 are the rates of incidence of new intermediate risk adenomas and of progression of these to CRC respectively. P is the proportion of polyps newly observed at subsequent examination which were not there at baseline. It is estimable by its relationship to the observed proportion P_O of negative results at baseline and the test sensitivity S:

Thus for a cohort of intermediate-risk adenomas at baseline examination we also need to know the numbers with negative results at baseline in order to estimate the relevant parameters. The variation in practice in terms of t, the time between examinations, gives the necessary degrees of freedom to estimate all three parameters S, λ_1 and λ_2.

The estimates of P, λ_1, λ_2 and S can then be made from the observed data, and subsequently used to estimate the proportions picked up at examination before progression to malignancy.

It will give a third and most formal criterion for choosing suitable intervals between examinations. The analysis will be augmented with further analyses as follows

1. Covariate adjustment for age, sex and where available family history
2. Subgroup analysis, such as by sex and polyp class
3. More detailed models, such as the five state: no disease- small polyp- large polyps- preclinical cancer- clinical cancer
4. Sensitivity analyses for a range of plausible underlying incidence rates

2.9.2 Second and subsequent follow-up

Analysis of findings at second and subsequent follow-up will closely parallel those of first follow-up with the slight complication of the need to consider their joint association with both baseline and first follow-up results. As for part (a) of the analytic strategy, simple analysis of rates of polyps by time since last examination, the major difference will be stratification by the two previous examinations.

For part (b), the logistic regression, the endpoint (y-) variable will be the finding at second or subsequent follow-up and the x-variables studied will be firstly as before the time since last examination and baseline. Then we will augment the model with findings at first follow-up examination to see if these significantly improve prediction of findings at second and subsequent follow-up. The logistic regression model would now be

where x_1 represents time since last examination, x_2 size of polyp at last examination, x_3 multiplicity of polyps at last examination, x_4 presence of polyps at first follow-up examination etc.

The formal multistate modelling in (c) will be carried out to model sensitivity, incidence and progression after the first follow-up. The results will give a further indication of the desirability or otherwise of subsequent follow-up beyond the first one and of changing the frequency of examination after the first follow-up.

2.9.3 Analysis of colorectal cancer occurrence after endoscopic examination

The analyses above will be complemented by analyses of subsequent clinical CRCs in the follow-up period where available. Such events are rare and estimates will therefore be imprecise, but the analysis will add some value to the exercise, by enabling us to assess the trade-off between harvest of polyps at subsequent examination and expected number of cancers occurring before the subsequent examination. Again the analysis will proceed in steps of increasing complexity, beginning with simple description of rates of cancers by time since and findings at last examination, through regression modelling to formal multistate models.

We will assess the absolute risk of CRC using Kaplan-Meier curves and will compare the incidence of CRC to that expected in the general population, both in the absence and in the presence of surveillance. We will use Cox proportional hazards models to assess the effect of surveillance on the risk of CRC, with the number of follow-up visits included as a time-varying covariate.

The models will also be used to assess the relationship between patient, polyp and procedural characteristics at baseline and CRC risk. We will use univariable models to estimate unadjusted hazard ratios and will use multivariable models to estimate the effect of surveillance adjusted for patient, polyp and procedural characteristics and to identify independent predictors of future CRC risk. The risk factors identified in the multivariable models will then be used to aid in the creation of distinct subgroups. These subgroups will then be scrutinised to determine whether in any subgroup the CRC risk after baseline is low enough relative to the general population to not warrant surveillance. Conversely, in subgroups that do appear to benefit from surveillance, the results will be examined to see whether the risk of CRC becomes low enough after a certain number of exams in order for surveillance to safely cease.

In order to examine appropriate surveillance interval lengths, we will analyse the yield of advanced adenomas and CRC at surveillance visits by interval in patients who attended follow-up after baseline. In the high-risk group we will also examine the effect of a short vs a longer surveillance interval (one year as recommended vs longer than one year) on long-term CRC incidence. In order to investigate this, we will create crude groupings based on the interval to first follow-up exam and the incidence of CRC between groups will be compared.

2.10   Research Governance

An ndependent Trial Steering Committee has been established, which, in addition to reporting to the funders on the progress of the study, will also consider ethics and governance issues as they arise. The study will be undertaken in full compliance with the Research Governance Framework. We anticipate that the major governance issue relates to data protection and we intend to seek exemption under Section 60 from the Health and Social Care Act through PIAG.

3. REFERENCES

1. Winawer S, Zauber A, O'Brien M, Ho M, Gottlieb L, Sternberg S. Prevention of colorectal cancer by colonoscopic polypectomy. New Engl J Med 1993;329:1977-81.
2. Selby J, Friedman G, Jr CQ, Weiss N. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med 1992;326:653-7.
3. Muller A, Sonnenberg A. Prevention of colorectal cancer by flexible endoscopy and polypectomy. A case-controlled study of 32,702 veterans. Ann Intern Med 1995;123:904-10.
4. Kavanagh A, Giovannucci E, Fuchs C, Colditz G. Screening endoscopy and risk of colorectal cancer in United States men. Cancer Causes Control 1998;9:455-62.
5. Newcomb P, Storer B, Morimoto L, Templeton A, Potter J. Long-term efficacy of sigmoidoscopy in the reduction of colorectal cancer incidence. J Natl Cancer Inst 2003;95:622-5.
6. Prorok P, Andriole G, Bresalier R, Buys S, Chia D, Crawford E, Fogel R, Gelmann E, Gilbert F, Hasson M, Hayes R, Johnson C, Mandel J, Oberman A, O'Brien B, Oken M, Rafla S, Reding D, Rutt W, Weissfeld J, Yokochi L, Gohagan J. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Controlled Clinical Trials 2000;21 (6 Supp):273S-309S.
7. Atkin WS, Cook CF, Cuzick J, Edwards R, Northover JM, Wardle J, UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer; baseline findings of a UK multicentre randomised trial. Lancet 2002;359:1291-300.
8. Segnan N, Senore C, Andreoni B, Aste H, Bonelli L, Crosta C, Ferraris R, Gasperoni S, Penna A, Risio M, Rossini F, Sciallero S, Zappa M, Atkin WS, the SCORE Working Group – Italy. Baseline findings of the Italian multicentre randomised controlled trial of "once-only sigmoidoscopy". J Natl Cancer Inst 2002;94:1763-72.
9. Grotmol T, Bretthauer M, Gondal G, Hofstad B, Efskind P, Huppertz-Hauss G, Thiss-Evensen E, Holmsen S. Flexible sigmoidoscopy screening: A randomised, Controlled study in the population in the south of Norway. The Norwegian colorectal cancer prevention study (NORCCAP). Gastroenterology 2001;120 supp 1:A228.
10. Pignone M, Rich M, Teutsch S, Berg A, Lohr K. Screening for colorectal cancer in adults at average risk: A summary of the evidence for the US preventative services task force. Ann Intern Med 2002;137:132-41.
11. Wegener M, Borsch G, Schmidt G. Colorectal adenomas: distribution, incidence of malignant transformation, and rate of recurrence. Dis Colon Rectum 1986;29:383-7.
12. Winawer S, Zauber A, O'Brien M, Ho M, Gottlieb L, Sternberg S. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. New Engl J Med 1993;328:901-6.
13. Neugut A, Jacobson J, Ahsan H, Santos J, Garbowski G, Forde K, Treat M, Waye J. Incidence and recurrence rates of colorectal adenomas - a prospective study. Gastroenterology 1995;108:402-8.
14. VanStolk R, Beck G, Baron J, Haile R, Summers R. Adenoma characteristics at first colonoscopy as predictors of adenoma recurrence and characteristics at follow-up. Gastroenterology 1998;115:13-8.
15. Noshirwani C, VanStolk U, Rybicki L, Beck G. Adenoma size and number are predictive of adenoma recurrence: implications for surveillance colonoscopy. Gastrointest Endosc 2000;51:433-7.
16. Martinez M, Sampliner R, Marshall J, Bhattacharyya A, Reid M, Alberts D. Adenoma characteristics at baseline colonoscopy as risk factors for recurrence of advanced adenomas. Cancer Epidemiology Biomarkers and Prevention 2001;10:157.
17. Waye J, Braunfeld S. Surveillance intervals after colonoscopic polypectomy. Endoscopy 1982;14:79-81.
18. Bond J. Polyp guideline: diagnosis, treatment and surveillance for patients with nonfamilial colorectal polyps. Ann Intern Med 1993;119:836-43.
19. Byers T, Levin B, Rothenberger D, Dodd G, Smith R. American-cancer-society guidelines for screening and surveillance for early detection of colorectal polyps and cancer - update 1997. Ca-a Cancer Journal For Clinicians 1997;47(3):154-&.
20. Bond J. For the Practice Parameters of the American College of Gastroenterology. Polyp Guideline: Diagnosis, treatment, and surveillance for patients with colorectal polyps. Am

J Gastroenterol 2000;95:3053-63.

21. Figiel L, Figiel S, Wietersen F. Conservative management of colonic polyps. Based on roentgenographic observations of growth rate. J Mich State Med Soc 1963;62:383-8.

22. Zauber A, Winawer S, Loeve F, Boer R, Habbema D. Effect of initial polypectomy versus surveillance polypectomy on colorectal cancer incidence reduction: micro-simulation modelling of National Polyp Study data. Gastroenterology 2000;128 (supplement):1200(abstract).

23. Matek W, Guggenmoos-Holzmann I, Demling L. Follow-up of patients with colorectal adenomas. Endoscopy 1985;17:175-81.

24. Kronborg O, Fenger C. Prognostic evaluation of planned follow-up in patients with colorectal adenomas. An interim report. Int J Colorectal Dis 1987;2:203-7.

25. Gorski T, Rosen L, Riether R, Stasik J, Khubchandani I. Colorectal cancer after surveillance colonoscopy - False-negative examination or fast growth? Dis Colon Rectum 1999;42:877-80.

26. Muto T, Bussey H, Morson B. The evolution of cancer of the colon and rectum. Cancer 1975;36:2251-70.

27. Atkin W, Morson B, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med 1992;326:658-62.

28. Winawer SJ, Zauber AG, O'Brien MJ, Gottlieb LS, Sternberg SS, Stewart ET, Bond JH, Schapiro M, Panish JF, Waye JD, Kurtz RC, Shike M, Ho MN, The National Polyp Study Workgroup. The national polyp study design, methods and characteristics of patients with newly diagnosed polyps. The National Polyp Study Workgroup. Cancer 1992;70:1236-45.

29. Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, Ganiats T, Levin T, Woolf S, Johnson D, Kirk L, Litin S, Simmang C, Gastrointestinal Consortium Panel. Colorectal cancer screening and surveillance: Clinical guidelines and rationale-Update based on new evidence. Gastroenterology 2003;124:544-60.

30. Williams C, Macrae F. The St Mark's neoplastic polyp follow-up study. Front Gastrointest Res 1986;10:226-42.

31. Atkin WS, Saunders BP. Surveillance guidelines after removal of colorectal adenomatous polyps. Gut. 2002;51:V6-V9.

32. Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJW, Evans GD, Eaden JA, Rutter MD, Atkin WS, Saunders BP, Lucassen A, Jenkins P, Fairclough PD, Woodhouse CR, British Society of Gastroenterology, Association of Coloproctology for Great Britain and Ireland. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut. 2010;59(5):666-89.

33. NICE. Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas (CG118). National Institute for Health and Care Excellence; 2011.

34. Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for Colonoscopy Surveillance After Screening and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012;143(3):844-57.

35. Hassan C, Quintero E, Dumonceau JM, Regula J, Brandão C, Chaussade S, Dekker E, Dinis-Ribeiro M, Ferlitsch M, Gimeno-Garcia A, Hazewinkel Y, Jover R, Kalager M, Loberg M, Pox C, Rembacken B, Lieberman D, European Society of Gastrointestinal Endoscopy. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2013;45(10):842-51.

36. Gavin DR, Valori RM, Anderson JT, Donnelly MT, Williams JG, Swarbrick ET. The national colonoscopy audit: a nationwide assessment of the quality and safety of colonoscopy in the UK. Gut. 2013;62(2):242-9.

37. Nnoaham KE, Lines C. Modelling future capacity needs and spending on colonoscopy in the English bowel cancer screening programme. Gut. 2008;57(9):1238-45.

38. Sutton S, Bickler G, Sancho-Aldridge J, Saidi G. Prospective study of predictors of attendance for breast screening in inner London. J Epidemiol Community Health 1994;48:65-73.

39. Martean TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State—Trait Anxiety Inventory (STAI). Br J Clin Psychol 1992;31:301-306.

40. Cockburn J, De Luise T, Hurley S, Clover K. Development and validation of the PCQ: A questionnaire to measure the psychological consequences of screening mammography.

Soc Sci Med 1992;10:1129-1134.

41. Huang E, Whelan R, Gleason N, Maeda J, Terry M, Lee S, Neugut A, Forde K. Increased incidence of colorectal adenomas in follow-up evaluation of patients with newly diagnosed hyperplastic polyps. Surg Endosc 2001;15:648-8.

42. Blumberg D, Opelka F, Hicks T, Timmcke A, Beck D. Significance of a normal surveillance colonoscopy in patients with a history of adenomatous polyps. Dis Colon Rectum 2000;43:1084-91.

43. Chen T, Chiu Y, Luh D, Yen M, Wu H, Chen L, Tung T, Huang C, Chan C, Shiu M, Yeh Y, Liou H, Liao C, Lai H, Chiang C, Peng H, Tseng C, Yen M, Hsu W, Chen C. Community-based multiple screening model. Design, implementation, and analysis of 42,387 participants Taiwan community-based integrated screening group. Cancer 2004;100:1734-43.

44. Wong J, Yen M, Lai M, Duffy S, Smith R, Chen T. Progression rates of colorectal cancer by Dukes' stage in a high-risk group: analysis of selective colorectal cancer screening. Cancer J 2004;10:160-9.

45. Stryker S, Wolff B, Culp C, Libbe S, Ilstrup D, MacCarty R. Natural history of untreated colonic polyps. Gastroenterology 1987;93:1009-13.

46. Lund J, Scholefield J, Grainge M, Smith S, Bennett D, Mangham C, Armitage N, Robinson M, Logan R. Colorectal adenoma surveillance, lessons from a randomised trial. Gastroenterology 1999;116:G328-G328.

47. Scholefield J, Moss S. Faecal occult blood screening for colorectal cancer. J Med Screen 2002;9:54-5.