NCCHTA

30th April 2007

DOH Research & Development Health Technology Assessment Programme
Proposal for Research Project

Part II Detailed Project Description

1 Project title

HTA 04/33 Frequency of follow-up for patients with intermediate grade adenomas

2 How has the project changed since the outline proposal was submitted.

N/A

3 PLANNED INVESTIGATION

3.1 Research objectives

Overall objectives:

- To examine the optimum frequency of surveillance in people found to have intermediate grade 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.

3.1.1 Aims of the statistical analysis

The aim of the proposed 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 according to baseline characteristics and interval to first follow-up colonoscopy?
- If so, is there a subgroup of the intermediate adenoma group 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 colorectal cancer in those with intermediate adenomas at baseline after final endoscopic examination?

3.1.2 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?

3.1.3 Aims of the economic analysis

The aims of the economic analysis are threefold:

- To estimate the incremental cost-effectiveness of alternative adenoma follow-up strategies, including a policy of no follow-up, for individuals who have intermediate grade 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.

3.2 Existing research

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

It is now widely accepted that most colorectal cancers develop from adenomas and, by extension, that the detection and removal of adenomas will lead to a reduction in the incidence of colorectal cancer. 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 colorectal cancer 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 FS Screening trial, is examining the efficacy of FS screening with removal of all adenomas detected in reducing colorectal cancer 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 colorectal cancer 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 colorectal cancer 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 colorectal cancer 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.

3.2.2 Evidence of heterogeneity of risk among patients with adenomas

The strongest evidence that colorectal cancers arise from adenomas is derived from the observation that remnants of adenomatous tissue are often seen in colorectal cancers 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 colorectal cancer 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 National Polyp Study (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 colorectal cancer 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.

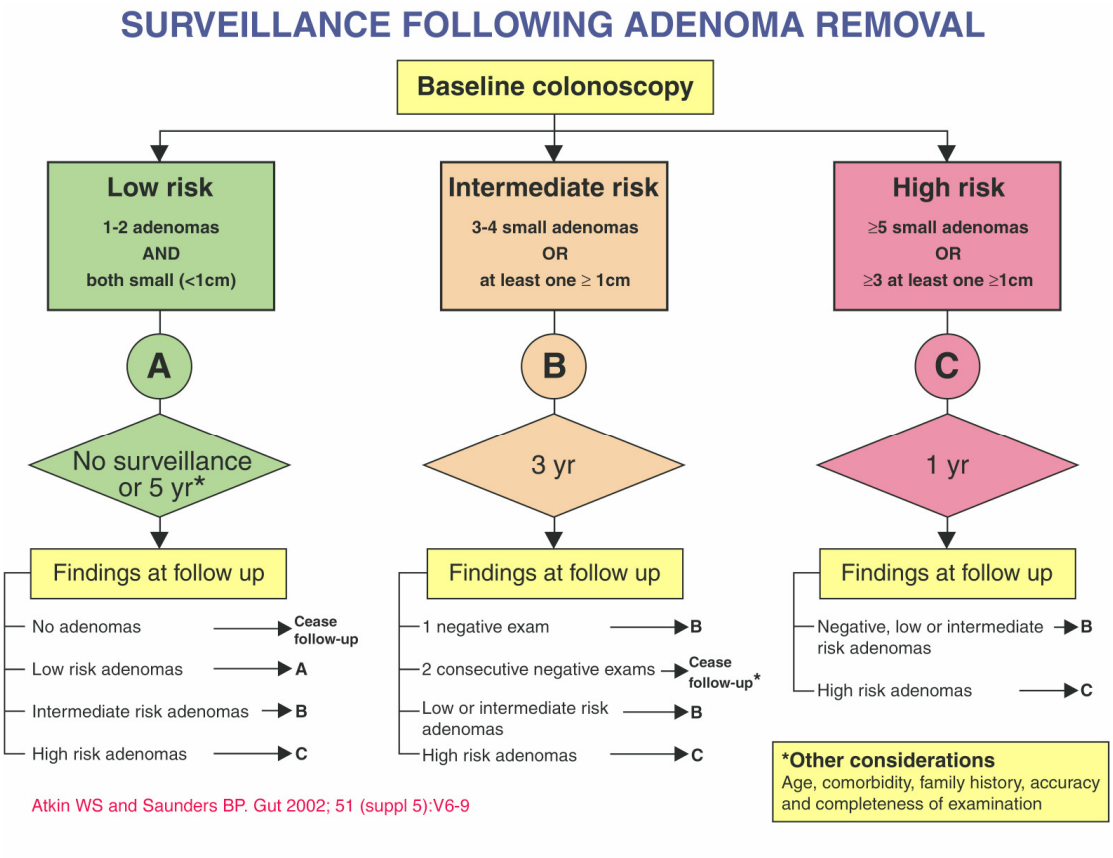
3.2.3 Studies examining the frequency of follow-up for patients with colorectal adenomas

Three randomised trials have compared the frequency of follow-up in patients with adenomas removed at colonoscopy 12, 24, 30. The US National Polyp Study 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.

3.2.4 Current UK recommendations

In 2000, Wendy Atkin and Brian Saunders at St Marks' 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 colorectal cancer 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.



3.3 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 propose to undertake a (mainly) retrospective cohort study using several large datasets collected in screening trials and from hospital endoscopy databases; some prospective data will become available during 2005.

3.3.1 Analysis of risk of cancer or advanced adenomas with varying frequency of colonoscopy surveillance

The aim of the proposed 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 according to baseline characteristics and interval to first follow-up colonoscopy?

If so, is there a subgroup of the intermediate adenoma group 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 colorectal cancer in those with intermediate adenomas at baseline after final endoscopic examination?

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 colorectal cancer 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.

3.3.2 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 UK FS Screening Trial, 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 (Sutton, Bickler, Sancho-Aldridge, & Saidi, 1994)*.
- *Anxiety* was measured using the 6-item version of the Spielberger Stait Trait Anxiety Inventory (STAI)(Marteau & Bekker, 1992)**. The responses were totaled 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) (Cockburn, De Luise, Hurley, & Clover, 1992)*** 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.

3.3.3 **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 grade 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.

Proposed 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 colorectal cancer 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 3.9.

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 colorectal cancer (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 modeling described in Section 3.9, using data on long-term follow-up of patients with intermediate-grade 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.

3.4 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.

3.5 Planned inclusion/exclusion criteria

Inclusion criteria
Men and women at any age with intermediate adenomas who have undergone a baseline colonoscopy.

Intermediate adenomas are defined as 3 or more adenomas, or at least one adenoma which is large (? 1 cm), has tubulovillous or villous histology, or severe dysplasia

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

3.6 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 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.

3.6.1 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 intend to apply for the Patient Information Advisory Group (PIAG) to request exemption from the Health and Social Care Act.

3.6.2 Retention of study documentation

We shall retain the data for 10 years.

3.6.3 Proposed action to comply with EU Directive 2001/2

N/A

3.7 Proposed 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 or with severe dysplasia.
- 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

3.8 Proposed 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 31, 32. 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 λ2, the rate of progression to clinical colorectal cancer, 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 λ2. 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 33 and Wong et al 34 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 colorectal cancers.

Stryker et al 35 found rates of progression in untreated adenomas suggestive of a λ2 of around 0.01 for progression to colorectal cancer. Atkin et al 27 studied a wide casemix 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 colorectal cancer 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.

3.8.1 Proposed 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 UK FS Screening Trial 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 colorectal cancer 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 colorectal cancer and has accrued an average of 7 years of follow-up No specific funding is required to obtain this data which is held on our own database.

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 colorectal cancer incidence after termination of follow-up. This study has accrued an average of 12 years of follow-up. No specific funding is required to obtain this data which is held on our own database.

The Nottingham Faecal Occult Blood test (FOBT) Trial cohort
This RCT examined the efficacy of biennial FOBT screening in reducing colorectal cancer 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 36. The cohort has been flagged at ONS to determine cancer incidence and has accrued an average of 13 years of follow-up 37. £500 funding will be required to collect data on follow-up exams.

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. Data is already available on the baseline colonoscopies, but £1,000 funding will be required to obtain the results of the follow-up colonoscopies.

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. Professor Lieberman who conducted this important study, which was published in the New England Journal of Medicine, has indicated that they require $10,000 to extract and clean the data.

Professor Lieberman is also Director of the Clinical Outcomes Research Initiative (CORI), which his funded by NIH and collects endoscopy data from over 100 practice sites in the US into a data repository with the primary goal of measuring outcomes. Professor Lieberman thinks that that CORI might also be able to provide data for this project. However, considerable data mining will be necessary and we have not have time to assess the costs before the HTA deadline, so we have not included this dataset in our estimations of how we will accrue the sample size.

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 that his willingness to collaborate. He has estimates that he requires $50,000 to extract and clean the data from 100,000 people screened by FS. 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. It is estimated that each hospital will require around £400 funding to provide us with data from the endoscopy and pathology departments, and to respond to our requests for clarification on follow-up or findings.

3.8.2 Total sample size

Patients with intermediate adenomas (n)Baseline ? 1 follow-up colonoscopy? 2 follow-up colonoscopiesEndpointColorectal cancerAdvanced adenomaAdvanced adenomaTotal number of endpoints required6019836Total number of cases required10,0006,6001,200UK FS Screening trial*19251453484St Mark's Adenoma Follow-up trial603359124Nottingham FOBT trial*582483279UK Pilot of FOBT screening*1139850 (by 2005)0Kaiser Permanente FS screening service*2000+1500+500+VA Colonoscopy screening study*-3880St Mark's hospital endoscopy database900250100 (estimate)20 other UK endoscopy databases6,0001,000400 (estimate)Total11,1494,787*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.

3.9 Statistical analysis

3.9.1. 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 (ie 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 subsite 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:

Any adenoma
Multiple adenomas
Single advanced adenoma
Multiple and advanced adenoma

The logistic regressions will be of the form

where x1 represents time since last examination, x2 size of polyp at last examination, x3 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 $\beta 1$ 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 $\lambda 1$ and $\lambda 2$ are the rates of incidence of new intermediate risk adenomas and of progression of these to colorectal cancer 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 PO of negative results at baseline and the test sensitivity S:

Thus for a cohort of intermediate grade 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, $\lambda 1$ and $\lambda 2$.

The estimates of P, $\lambda 1$, $\lambda 2$ 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

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

3.9.2 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 x1 represents time since last examination, x2 size of polyp at last examination, x3 multiplicity of polyps at last examination, x4 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.

3.9.3 Analysis of colorectal cancer occurrence after endoscopic examination

The analyses above will be complemented by analyses of subsequent clinical colorectal cancers 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 modeling to formal multistate models.

Additional considerations following from comments of reviewers

How do results translate into policy?
This is best demonstrated using hypothetical examples.

Example 1. Suppose for a particular group, the logistic regression for presence of intermediate risk (IR) adenoma or worse at subsequent examination gives

where p is the probability of intermediate adenoma or worse at subsequent examination and t is time to subsequent examination. Multistate model parameters which are consistent with this might be ?0=0.06 and ?1=0.07, where ?0 is the rate of incidence of new intermediate risk adenomas and ?1 is the rate of transition from such adenomas to carcinoma (this corresponds to a mean time of progression of around 14 years). These estimates would give the results in Table 1.

Table 1. Implications of results in example 1 for interval between examinationsTime since first examination (years)Probability (as %) of IR adenoma or worse at subsequent examinationProbability (as %) of progression to carcinoma in the interval020140.3291.03182.04333.35524.7

The results therefore suggest that at three years almost one in five examinations result in detection of IR adenomas, and an interval of more than three years would mean 3% or more subjects progressing to colorectal carcinoma in the interval. The results therefore suggest a 3-year interval for this group. They also suggest a lack of sensitivity, as evidenced by the 2% with adenomas at time zero.

Example 2. Suppose we observe

and ?0=0.01, ?1=0.07. This would imply the figures in Table 2. In this case, a five-year interval or even longer might be reasonable.

Table 2. Implications of results in example 2 for interval between examinationsTime since first examination (years)Probability (as %) of IR adenoma or worse at subsequent examinationProbability (as %) of progression to carcinoma in the interval00.7011.00.0721.50.232.20.443.20.754.71.0
Thus, the implications for policy do involve a judgement in addition to the process of estimation. The estimates, however, do significantly inform that judgement.

References to the methodology for multistate models
The seminal work in this area is by Zelen and Feinleib (1969) and by Day and Walter (1984). Methodological enhancements and applications to breast disease have been developed by our group (Chen et al, 1997a,b; Duffy et al, 1997; Myles et al, 2003). We and our colleagues in Taiwan have also applied these to large bowel cancer (Launoy et al, 1997; Prevost et al, 1998; Chen et al, 2003).

What if logistic regression and multistate model results disagree?
The first task in this circumstance will be to seek the source of the disagreement. Is it, for example, due to the effects of a small number of 'outlier' studies giving atypical results? Are the hierarchical models used for pooling inappropriate- for example, do we get better agreement by changing the assumed distribution of a random effect? If the disagreement cannot be resolved methodologically, we will have to choose between the two. A major criterion in such a choice will be which model gives the best fit to the raw data on the basis of a formal goodness-of-fit test.

Issues of pooling
We shall be using state-of-the art hierarchical models (Spiegelhalter et al, 2000). In terms of application to disease progression and screening, some of these have been developed in-house (Myles et al, 2003).We will check carefully for heterogeneity of population characteristics and of estimated effects. We also propose to estimate both fixed and random centre effects and to analyse centre-level covariates. We will perform repeat analyses under different pooling assumptions by way of sensitivity analysis. Our main target will be to estimate underlying rates of incidence of new adenomas, allowing for population differences and differences in sensitivity of examination between centres.

'The observational methodology is not strong'
A considerable amount can be learnt from non-randomised studies with respect to lead times, incidence of subclinical conditions, test sensitivity and disease progression (Chen et al, 1997a,b; Duffy et al,1997;Prevost et al, 1998; Chen et al, 2003).

Completeness and accuracy of databases
A number of internal consistency checks within each database will be performed and any substantial heterogeneity among centres will be thoroughly investigated. Shortcomings of particular databases will be taken account of in analysis, interpretation and reporting.

Sample size
There is no readily available technology for power/efficiency estimation in potentially complex multistate models. Because of this, our estimates depend on a strong element of anticipation of what is likely from standard error estimates from similar exercises in the past. Consequently, there is considerable uncertainty around our required sample size estimates, which must therefore be regarded as minimal. We are likely, however, to have numbers of events substantially in excess of these sample size estimates. We provide letters of support from the collaborators as requested. Some, for example, the National Taiwan University project, have already provided the data.

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3.10 Research Governance

This is not a trial, therefore a DMEC is not appropriate, however we intend to convene an independent steering committee, which, in addition to reporting to HTA 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.

3.11 Independent supervision of the study

We will have an independent steering group. We are currently approaching investigators with the relevant expertise and will inform the commissioners of names if we are successful.

4 Project timetable and milestones

0-3 months	Seek ethics approval from COREC and exemption from Health and Social Care Act from PIAG Advertise for project manager and data clerk Ask providers of datasets to begin to examine the quality of the data
3-15 months	Once ethical and PIAG approval is obtained, extract data from datasets, match endoscopy and pathology data from hospitals. Data clerk will code data on characteristics of adenomas and request missing data. Health psychologist will perform analyses on anxiety data from UK FS Screening Trial dataset. At 6 months, statistician will begin preliminary analyses
15-21 months	Statistician will perform statistical analysis on cleaned datasets.
21-27 months	Health economist will perform economic analyses
27-30 months	Write final reports

5 Expertise: roles and responsibilities; supervision of junior staff

Prof. Wendy Atkin:
Epidemiologist/statistician with expertise in colorectal cancer screening, gastrointestinal endoscopy and study design. Principal investigator in UK FS Screening Trial. Designed BSG guidelines for colonoscopic surveillance for colorectal adenomas. She will have overall responsibility for the validity of the datasets, and for data acquisition and cleaning. She will supervise the project manager and maintain overall legal, financial, and ethical responsibility for the study. She will also ensure that the timetable and milestones are adhered to.

Prof. Stephen Duffy

Stephen Duffy is the study statistician on the Swedish Two-County Trial of Mammographic Screening, the UK Breast Screening Frequency Trial and the Gothenburg Breast Screening Trial. He has worked in cancer prevention and screening research for the last 20 years and currently heads the Cancer Screening and Aetiology Group in the Wolfson Institute of Preventive Medicine, with particular emphasis on evaluation of early detection programmes in the health service setting rather than the research environment. He will be responsible for the statistical analysis and supervise the statistician.

Dr Paul Tappenden: Expertise in health economic modeling and methods for value of information analysis. For ScHARR he has undertaken cost-effectiveness for NICE assessments. Recently led an options appraisal which involved modelling the cost-effectiveness and resource impact of alternative screening options for bowel cancer, and is currently working on an economic evaluation of chemotherapies for colorectal cancer on behalf of NICE. Paul will be responsible for the health economic analyses and will supervise the health economic research fellow.

Prof Jane Wardle
Long experience in examining health behaviors and adverse and beneficial psychological effects of cancer screening. Undertook psychological impact studies for UK Flexible Sigmoidoscopy Screening Trial. Will assume overall responsibility for the psychological aspects of this study.

Dr Anne Miles:
Works with Jane Wardle, performed many of the psychological impact studies for the UK Flexible Sigmoidoscopy Screening Trial. Will perform assessments of the psychological effects of colonoscopic surveillance.

Prof David Weller: Responsible for the evaluation of the UK Pilot of FOBT screening which was commissioned by the Dept of Health. He has agreed to obtain a dataset from that pilot.

Dr Sue Moss: Assistant director of the DOH Cancer Screening Evaluation Unit, performed statistical analyses on the Nottingham faecal occult blood test trial and will be responsible for providing a dataset from that trial.

Professor David Lieberman: Director of the US CORI database, 100 US institutions; principal investigator on the VA cooperative colonoscopy screening study published in the New England Journal of Medicine. He has expressed interest in providing data from that trial.

Dr T.R. Levin. GI endoscopist who has published widely on endoscopic screening, was a member of the US Preventive Services Task Force on colorectal cancer screening. Runs the Kaiser Permanente flexible sigmoidoscopy screening programme which has screened almost 1/2 million people in Northern California. He has access to the database and has published several papers on the results collected in the database and has expressed intent to collaborate on this project by supplying data from this cohort.

ProfessorJohn Northover, Director of the Cancer Research UK Colorectal Cancer Unit, has had a long interest in follow-up after surgery for colorectal cancer.

Dr Andrew Renehan, Senior Research Fellow at the Christie Hospital, Manchester, has published a meta-analysis on the benefits of follow-up following surgery for colorectal cancer.

Dr Brian Saunders, Lead Clinician for one of three National Endoscopy Training Centres is co-author with Wendy Atkin of the BSG guidelines for colonoscopic surveillance for sporadic colorectal adenomas.

Dr Roland Valori, National Lead for Endoscopy Services in England, who has played an leading role in the improvement of the delivery of gastrointestinal endoscopy, is concerned about the

potential impact of colonscopic surveillance following detection of colorectal adenomas at screening on the clinical service.

Professor Jonathan Brown, Consultant Gastroenterologist at Gloucester Hospital and Visiting Professor at Cranfield University in the Department of Information Technology and Bioscience, has agreed to assist with extraction and coding of data from legacy endoscopy reporting systems.

6 Justification for support required

Project manager
The project will be based at the Cancer Research UK Colorectal Cancer Unit at St Mark's Hospital. The role of the project manager is vital in ensuring that the data is collected in a timely manner. The PM will oversee the project, complete the required forms for the ethics committee and PIAG; manage the financial aspects, and to ensure that contacts at local hospitals are motivated to provide valid and accurate data.

Data clerk
The role of the data clerk will be to code the data which is mainly in text fields and to check the accuracy. In the pilot we undertook for this study we put our existing data clerk on to the job of checking through individual records examining where it was not possible to assess baseline status from the data provided or the results at follow-up were missing or inaccurate. The data clerk was able to find the missing data, and in the short time available we were able to assess that putting together an accurate dataset from hospital and other study databases is feasible.

Statistician
The statistician will perform the statistical analyses that form the core of the proposal. The project therefore includes a considerable commitment to statistical analysis, some of a specialist nature. A statistician will need to be dedicated full time to the descriptive analyses (estimated 30 working days), logistic regression (estimated 60 working days), multistate modeling (estimated 80 working days) and interpretation and reporting (estimated 40 working days). The last three tasks in particular, require a member of staff with a first degree in statistics, mathematics or related discipline, and a postgraduate qualification in statistics or quantitative epidemiology.

Economic analyses
Two health economic modellers will be involved in the project. It is envisaged that the work will involve the following key tasks:
Systematic searching and reviewing of evidence on costs and quality of life (RA1 20 days);
Costing analysis for cancer management according current clinical guidance RA1 10days);
Development of a conceptual model structure (including elicitation of expert clinical opinion) (RA1:RA2 20:10 days);
Development of a quantified health economic model (RA1:RA2 - 40:10 days);
Validation of model and checking (RA1:RA2 - 10:5 days)
Probabilistic sensitivity analysis (including value of information analysis to inform the design of the RCT) (RA2 40 days)
Interpretation and reporting of results (RA1:RA2 - 20:5 days)

Tasks 1-4 will be undertaken primarily by the RA1 level analyst under the supervision of the RA2 level analyst. Tasks 5-7, in particular undertaking Expected Value of Information analysis to inform future research, requires more specialist modelling expertise and will be undertaken by the RA2 analyst with some support from the RA1 analyst.

Travel expenses
- We have assumed that there will 40 journeys to study centres over the course of the project at a cost of £100: total £4,000.

- Travel budget for the steering committee. Assume 6 members meeting 4 times over the course of the study: £2000

Equipment
We require two computers for the project manager and data clerk.

Consumables
We require £2,000 1for stationery, discs, postage, courier for datasets, and other miscellaneous consumable items. In addition £5551 is required specifically for the psychological studies, including printing of 6,000 8 page questionnaires, stationery and postage.

Support for data collection
(see also section on Sample Size where the contribution of each data source is described)
We have had to assess this on a case by case basis. We require no support for our own in house studies (the UK FS screening study and the St Mark's adenoma follow-up study (the only UK randomised trial examining colonoscopic surveillance intervals).

The Nottingham FOBT study, although quite small, is useful since it has accrued the longest time of follow-up, comparable with that of the St Mark's adenoma follow-up study. £2,000 is required to extract from the database and update the data with more recent colonoscopy follow-up results. The UK pilot of faecal occult blood screening was undertaken during 2000-2002 during which time 240,000 people were screened and 4,800 underwent a colonoscopic investigation for a positive test. Data from the baseline colonoscopy should be easy

The two US databases are invaluable as they are very highly regarded and the collaboration of the US investigators may lead to a change in US recommendations and the end of international confusion on the issue of the correct way to manage people with a history of colorectal adenomas. Professor Lieberman requires only $10,000 to provide the VA colonoscopy screening dataset. Dr Levin requires $50,000 because much more work is involved for his data analyst. Both investigators will donate their own time at no cost to the project.

Overall costs for data collection

CostsUK FS Screening trial*0St Mark's Adenoma Follow-up trial0Nottingham FOBT trial*£2,000UK Pilot of FOBT screening*£6,000Kaiser Permanente FS screening service*£26,950$50,000VA Colonoscopy screening study*£5,400$10,000St Mark's hospital endoscopy database020 other UK endoscopy at £1000 each£20,000Total£58,340

Additionally, a data manager will be required to work with each hospital endoscopy unit in downloading the data to a spread sheet, sending to ONS and then anonymising. This will be undertaken by a colleague of Dr Jonathan Brown, who is familiar with legacy databases. This has been costed on an ad hoc basis, assuming an average of 3 days per hospital over the course of the study @£250 per day with 2 overnight stays per hospital @£100 per night or £19,000 in total.

It is expected that additional information will be required to be extracted from hospital or pathology records to supplement inadequate entries for some patients. We have estimated that each of the 20 UK hospitals will allocate a local administrator for approx 2 hours each week for 4 months @£15 hour (assuming this is done out of hours) at a total cost of £9,600.

Flagging with ONS In order to ascertain the occurrence of death or a diagnosis of colorectal cancer among the UK cohort, the UK datasets will be flagged at ONS. Each custodian of a dataset will send unanonymised patient information to ONS which will send anonymised data to us for analysis. Cases will be linked by a unique study number if further information is required. The total cost has been estimated at £5000 for list cleaning and 6 monthly outputs for 2 years, supplying cause of death and ICD coding for cancers.

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