NETSCC, HTA

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PROTOCOL

Full Title: Faecal immunochemical testing (FIT) for adenoma surveillance

Short Title: FIT for Follow-up study

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SUMMARY OF PROGRAMME

The faecal immunochemical occult blood tests (FIT) are superior to the guaiac based faecal occult blood test (gFOBT) that is currently used in the NHS Bowel Cancer Screening Programme. They detect human globin in stool sample which avoids any dietary influence on positivity rates and newer versions are quantitative so that the threshold level for positivity can be varied. FITs are used in some bowel cancer screening programmes (Italy, Japan, Korea, Australia) to screen general population but in this study we propose to establish if they can be used as a safe, acceptable and cost-effective method of surveillance for people who are at increased risk of developing colorectal cancer because of a prior history of adenomas.

Our principal aim is to determine the 3-year programme sensitivity of annual faecal immunochemical test (FIT) for detection of advanced adenomas (AA) or colorectal cancer (CRC) in people who took part in the National Bowel Cancer Screening Programme and who were diagnosed with intermediate risk adenomas requiring colonoscopic surveillance.

Whilst waiting for their first surveillance colonoscopy, eligible participants will be asked to complete a FIT test once a year. Participants who are classified as being at intermediate risk of developing colorectal cancer will be asked to complete 3 annual FIT tests before undergoing their surveillance colonoscopy. If the result of the FIT test in year1 or year2 is positive their surveillance colonoscopy will be brought forward and they will not proceed to the next round of FIT testing.

Findings at surveillance colonoscopy will be used as gold standard against which we will measure the programme sensitivity and specificity of the FIT test.

Study participants, who consent to take part and complete a FIT test, will be asked to complete a questionnaire which will include general measures of quality of life and more specific instruments to monitor the psychological consequences of using the FIT.

BACKGROUND

Adenomas develop in a third of the population by age 60 [1]. Most are asymptomatic and are usually an incidental finding at colonoscopy, and most do not progress to malignancy [2]. Following adenoma removal, however, around 50% of people remain at increased risk of developing CRC or advanced adenomas (AA), which are those most likely to develop into cancer [3-5]. The risk of developing CRC and AA varies with the characteristics of previously removed adenomas [3-5]. Patients with large (≥ 1cm) or multiple adenomas removed are at intermediate or higher risk. Those with just 1-2 small adenomas are at low risk and average-risk screening is probably adequate for them. The NHS Bowel Cancer Screening Programme (BCSP) uses a modification of the UK guideline for colonoscopy surveillance after adenoma removal [6] (Figure 1) which recommends colonoscopy surveillance only for the higher-risk groups. However, there are a number of problems in the use of colonoscopy for this purpose. It is not 100% sensitive and studies suggest that most AAs and CRCs detected at surveillance exams were already present but missed at the previous colonoscopy [4, 7]. In trials comparing different intervals between exams (from 1 to 4 years), more cancers have been detected in the longer-interval groups, suggesting that some missed AA progress to malignancy during this period [8]. Moreover, the detection rate of CRC or AA at each colonoscopy is only around 3%, so 97% of colonoscopies will either be negative or only detect small adenomas of low malignant potential [5, 9]. Colonoscopy is also a very expensive procedure, and in addition all colonoscopies carry a small risk of serious complications. Therefore the negative colonoscopies are costly and risky and provide no therapeutic benefit other than reassurance. Colonoscopy should therefore be reserved for cases where the benefits outweigh the risks and costs.

Surveillance following adenoma detection currently accounts for around one fifth of colonoscopies in the UK (R. Valori, personal communication), but colonoscopy is also widely used to investigate colonic symptoms or a positive faecal occult blood screening test (FOBT) result. The use of FOBT in the Bowel Cancer Screening Programme has led to an increase in the number of colonoscopy referrals, to the point where the number of colonoscopies being undertaken is overwhelming the available endoscopy workforce. An alternative, more cost-effective method of protecting people with higher-risk adenomas is therefore urgently required.

NEED FOR RESEARCH IN THIS AREA

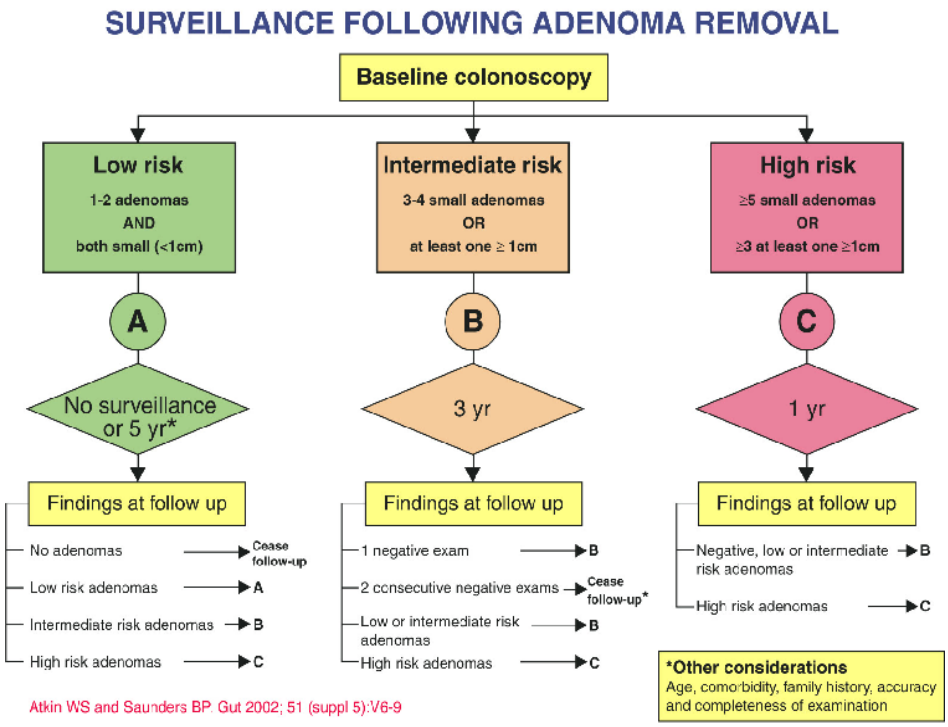
Most screening programmes use the guaiac-based faecal occult blood test (gFOBT), which has been shown to reduce CRC mortality rates in trials by up to 20% [10]. However, immunochemical faecal occult blood tests (FITs) incorporate several features that make them more suited for diagnosis of colorectal neoplasia in higher-risk groups. FITs use antibodies raised against the human globin component of haemoglobin and are not subject to interference from animal blood in the diet. They have higher sensitivity for CRC and AA than gFOBT [11-13], with higher positivity (recall) rates but similar positive predictive values. Some immunochemical tests can be automated and the cut-off level for positivity adjusted to change the sensitivity and specificity in different clinical settings. Several studies (involving a total of 108,804 people) have examined the performance of the FIT test in the screening context [12, 14-20]. The majority use the latex agglutination test (LAT) with a cut-off of 100ng haemoglobin/ml sample solution (as we propose) and achieve a positivity rate of 4%-6% using 1 or 2 samples per patient. The positive predictive value at first screen is around 10% for cancer and 20% for AA. Sensitivity for AA is around 25-30% but does not appear to decrease with repeated screening [21] and therefore programme sensitivity over 3 screenings should approach that of colonoscopy at 3 years. Therefore, annual FIT should detect most important lesions in people who would normally undergo 3-yearly colonoscopy surveillance and would result in fewer colonoscopies being undertaken overall.

Evidence on the use of immunochemical occult blood testing in higher-risk groups is limited to 3 studies [22-24]. In the first two studies (n = 252 and 169 respectively), patients with a familial risk of colorectal cancer used the FIT before colonoscopy, and sensitivities of 75% and 85% for AA were reported. In the third study, in which 611 patients with previously resected cancer used the FIT before colonoscopy, the FIT detected all 9 recurrent or metachronous cancers. There is no evidence on the programme sensitivity of FIT over more than one screening in higher-risk groups.

AIMS AND OBJECTIVES

The overall objective is to test the hypothesis that annual immunochemical faecal occult blood testing (iFOBT or FIT) is a feasible, safe, acceptable and cost-saving alternative to colonoscopy surveillance for the diagnosis of advanced adenomas (AA) and early stage colorectal cancer (CRC) in patients with intermediate risk colorectal adenomas as defined by national guidelines (see Figure 1).

Figure 1: Surveillance Guidelines



Primary aim

- To determine the 3-year programme sensitivity of annual FIT for detection of AAs or CRCs compared with colonoscopy undertaken at 3 years in patients with intermediate-risk adenomas detected following a positive faecal occult blood test (gFOBT) completed as part of the Bowel Cancer Screening Programme (BCSP) in England.

Secondary aims

- To examine the acceptability of FIT compared with colonoscopy as an alternative method of surveillance for people at an increased risk of CRC.
- To calculate the incremental costs and cost-effectiveness of FIT vs. colonoscopy surveillance.
- To model the potential of FIT screening to replace colonoscopic surveillance for groups at intermediate risk of developing CRC such as those with a personal or family history of CRC but not a dominantly-inherited syndrome. These groups pose a major resource problem for endoscopy units.

RESEARCH PLAN

This is a pragmatic accuracy and efficiency study to assess programme sensitivity of annual FIT using colonoscopy at 3 years in those testing negative as a reference standard. The study will also address acceptability and cost-effectiveness of annual FIT as an alternative to 3-yearly colonoscopy for adenoma surveillance.

Eligible participants

All the people aged between 60 and 71 years who were diagnosed with intermediate or high risk adenomas at colonoscopy following a positive FOBT in the National Bowel Cancer Screening Programme in England and who need colonoscopic surveillance are eligible to take part in our study.

Exclusion criteria: none

Sample Size

A range of sample-size calculations have been carried out for varying prevalence rates of CRC/AA and varying detection rates for the FIT regimen compared to the 3-year colonoscopy (see Table 1). Our sample size calculations are based on estimation of the proportional programme sensitivity of the three annual FITs compared with a three-year anniversary colonoscopy, assuming that any CRC/AA cases found as a result of the intermediate FITs would also be found at the 3-year colonoscopy. We determined the sample size required to give acceptable precision on this relative sensitivity. The statistical analysis is conditional on the total number of CRC/AA cases found, including those at the 3-year colonoscopy in those with negative FIT results. Suppose the prevalence of CRC/AA is 3% and the FIT regimen was able to diagnose 75% of cases which would otherwise be detected at the 3-year colonoscopy. To provide a 95% CI within ±10% of this, we would require 72 cases of CRC/AA and 2401 recruits. With a relative sensitivity of 80%, we would require a sample of 2048. With a 2.5% rate and 80% sensitivity, we would require 72 cases and 2881 recruits in total. With the same assumptions, if the relative sensitivity was 80%, for a 95% CI within ±10% of this we would need 61 cases of CRC/AA and 2048 patients, assuming a 3% rate of CRC/AA. With a 2.5% rate, we would require 61 cases and 2458 recruits in all.

Table 1: FIT vs. colonoscopy: Sample size calculations

CRC/AA prevalence	Relative detection rate	Width 95% CI	Cases of CRC/AA	Sample size Assuming compliance with all tests of 40%
3%	75%	20% (+/-10%)	72	6003 ± 600
	80%	20% (+/-10%)	61	5120 ± 512
2.5%	75%	20% (+/-10%)	72	7203 ± 720
	80%	20% (+/-10%)	61	6145 ± 615

Table 1 shows the range of possible case yield and sample size assuming 40% attrition. By definition, we are taking our study population from those who have complied with initial referral to colonoscopy. It is therefore likely that our population is more motivated than the population in general, and our anticipated rates of further participation are therefore likely to be conservative. If we assume that 65% of those recruited comply with the first FIT, that we lose a further 20% of those remaining at either the second or third FIT episodes, and that 80% of those remaining fully compliant attend their surveillance colonoscopy, we are left with a proportion fully compliant of 0.4 (0.65 x 0.8 x 0.8). With the most conservative assumptions on relative programme sensitivity (75%) and AA/CRC prevalence (2.5%), and allowing for a compliance rate of 40% requires a maximum sample size of 8000 (see Table 1).

Planned Interventions

Identifying eligible people

People with intermediate risk adenomas will be identified in the Bowel Cancer Screening Programme database by the Connecting for Health team in Exeter who will send us a dataset with participants' contact details. This dataset will be stored securely on servers in a data centre provided by IOKO. This company provides a secure managed hosting facility compliant with all the current regulatory requirements governing the NHS data storage and they work with around 200 NHS organisations at present. Secure access to the data centre would be provided from a few identifiable computers over a virtual private network connection (VPN). Data exchange would be encrypted and access controlled by the use of strong passwords. IOKO will provide a fully managed service, in line with industry standards including daily monitoring and backups.

The details of all the eligible people will initially be available only to the NHS staff at South of England Bowel Cancer Screening Programme Hub. Once people consent to take part in the study, their details will become available to the research team at the Imperial College.

Materials to be used in the study

Please, see Appendix 1

FIT test

We will use the semi-quantitative immunochemical faecal occult blood test OC-SENSOR produced by Eiken Chemical Co., Tokyo, Japan and distributed by MAST group Ltd., UK. The FIT kit contains written instructions and a single sampling tube, with 2 ml haemoglobin stabilising buffer. The users are asked to collect the sample on a single occasion and to post it immediately to the processing laboratory (Bowel Cancer Screening Programme – South of England Hub, Postgraduate Medical School, University of Surrey, Daphne Jackson Road, Manor Park, Guildford GU2 7WG)

FIT testing/surveillance

Round 1 (Yr 1): All the eligible people will be sent a FLYER to alert them to our study around 1 year after the colonoscopy at which intermediate risk adenomas were detected.
A week later, an INVITATION to take part in the study will be sent, together with detailed patient information sheet, a consent form and a FIT kit.
Those who do not respond to this invitation within 3 weeks will be sent a REMINDER and a replacement kit if required.
People who give their consent and return a completed test will form our sample and will be required to complete 2 further rounds of FIT testing.
Those who test positive at the first FIT will be offered immediate colonoscopy in the Bowel Cancer Screening centre that is responsible for their surveillance and will return to point B in the BSG guideline algorithm (Figure 1). They will not receive FIT kits in years 2 and 3.

Round 2 (Yr 2): Patients who test negative in the first round will be sent another FIT one year later. Those who test positive at the second round will be offered immediate colonoscopy and will return to point B in colonoscopic surveillance programme (Figure 1).

Round 3 (Yr 3): People who test negative at years 1 and 2 together with those who did not complete their test in Round 2 will be sent another FIT at 3 years. These people will all be invited for the routine surveillance colonoscopy due at 3 years, irrespective of the FIT result,

and will return to point B in colonoscopic surveillance programme as depicted in Figure 1. All lesions detected at colonoscopy would be removed and subjected to pathological assessment, as is the usual practice. Both patients and their GPs will be informed of the results of each completed FIT test in each round.

FIT test processing

People who take part in the study will mail their used kit in prepaid, addressed envelopes to the laboratory of the Bowel Cancer Screening Programme South of England Hub. The kits will be processed as per the manufacturer's instructions and the results from the processor will be uploaded into the database. The positivity threshold will be set at 100 ng haemoglobin/ml sample solution as was used in other studies (14-20).

A proportion of tests will be spoilt either due to inappropriate handling by users or due to technical faults in the laboratory. In such cases participants will be offered a chance to repeat the test and a new kit would be sent to them.

Patient experience questionnaires

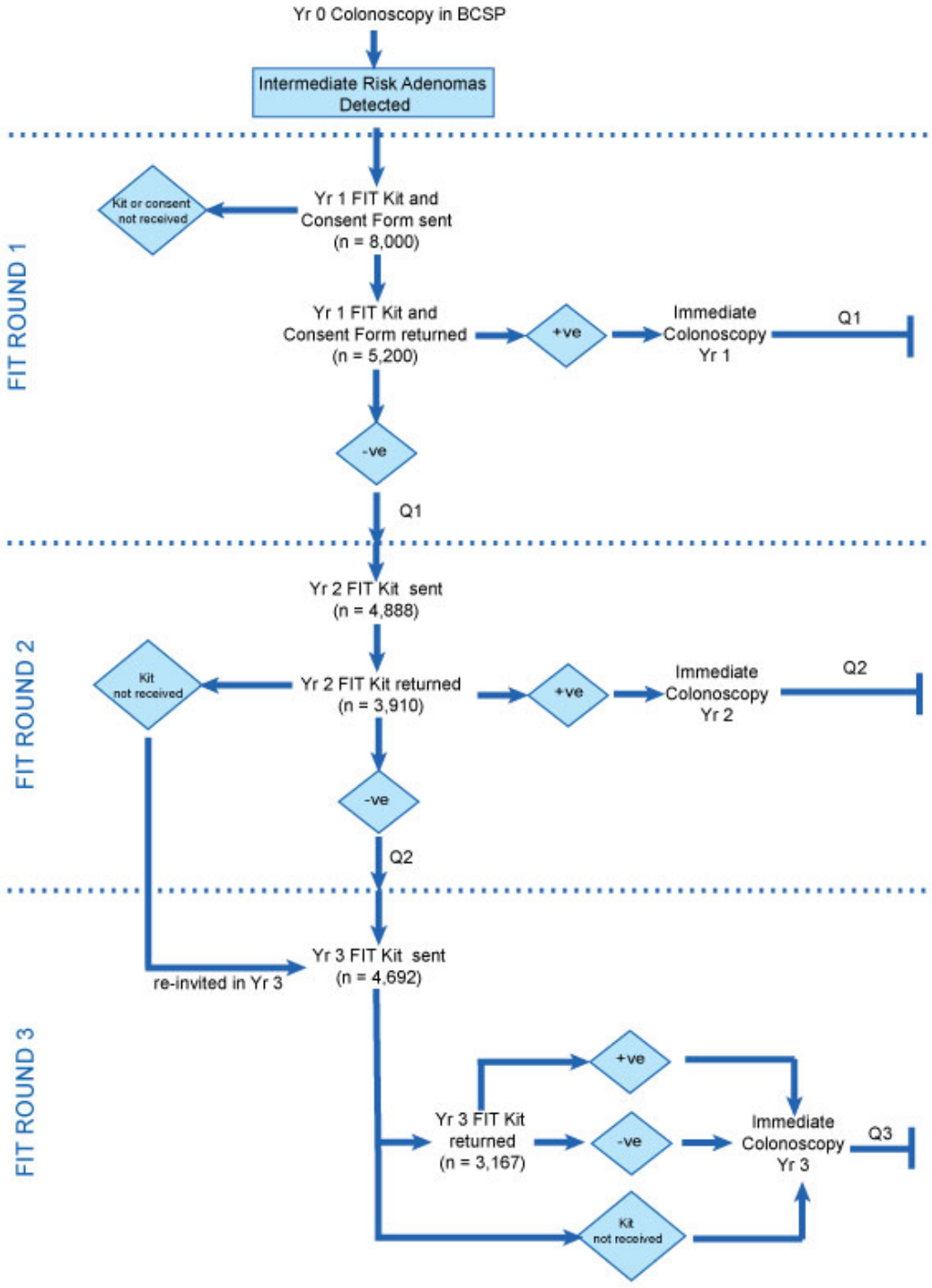
Throughout the study, we will assess various aspects of patient experience including the acceptability and psychological consequences of annual surveillance using a home-based faecal immunochemical testing.

In order to study the emotional consequences of FIT surveillance we will assess general mood before completing the first Fit test and then after each round of FIT surveillance. Our itinerary of questions to monitor emotional impact include the short version of the Spielberger State Anxiety Inventory (STAI) (27) and more specific measures of bowel-cancer related worry which has previously been used to study the psychological impact of being offered colonoscopic surveillance [26]. We also use three items from the emotional subscale of the positive psychological consequences of screening questionnaire to ascertain the degree of reassurance gained after each round of FIT surveillance (28).

In Rounds 1 and 2 questionnaires will be administered with the receipt of final testing outcomes (i.e. a negative FIT result letter or letter informing participants of the outcomes of their diagnostic colonoscopy). In order to avoid unnecessary distress we shall not mail questionnaires to those with a diagnosis of cancer. In the final round of FIT surveillance, questionnaires will be administered with the letter informing patients about the outcome of their 3-year surveillance colonoscopy.

Flow of the participants through the study and planned interventions are shown in Figure 2 below.

Figure 2: FIT study interventions plan



ETHICAL CONSIDERATIONS

Risks and anticipated benefits for trial participants and society

The anticipated benefits for society and for future patients found to have intermediate risk adenomas include avoidance of the need for regular colonoscopic surveillance, which carries a measurable risk of serious complications. In addition the alternative method of surveillance we have proposed – stool testing with a sensitive FIT - would be more convenient as it can be conducted at home, with the inconvenience of colonoscopy restricted to those who test positive (expected to be less than 20% over 3 years). There are additional anticipated benefits to society such as cost-saving and better use of endoscopy resources by replacing some of colonoscopic surveillance with FIT.

Inviting people who have had colonoscopy and have been told they need a colonoscopy in three years' time may heighten their perception of their risk of colorectal cancer and possibly increase doubts about the effectiveness of colonoscopy in preventing colorectal cancer. During the study, they will have additional protection against development of cancer as they will undergo FIT testing annually *in addition* to their 3-year surveillance colonoscopy. However, patients need to understand that around 1 in 10 people participating in the study will require an early colonoscopy because they will have a positive FIT at Years 1 or 2. Around one half of people having an early colonoscopy will have no adenomas detected, so the early colonoscopy will not be of benefit to them. Conversely, some people will have advanced adenomas detected and for these people it will be an advantage to have important lesions found and treated earlier.

There are no additional risks since there will not be an increase in the number of recommended colonoscopies Participants, who have an early colonoscopy because of a positive FIT test at years 1 or 2, will have their next scheduled colonoscopy 3 years later. The current guideline for adenoma surveillance recommends that patients with intermediate adenomas should have two negative exams before stopping surveillance.

Obtaining informed consent from participants

We have engaged service users with the project in order to get their input in drafting clear and understandable information for participants to ensure that they are able to give fully informed consent. Their suggestions have been incorporated in the materials we submit with this application (see Appendix1). The consent form and comprehensive patient information sheet will be posted to potential participants and they will be encouraged to discuss the materials with members of their families, friends and GPs. A proportion of people may want to discuss

the study and potential implications of their taking part with a member of staff so we provided a help-line number and a half-day training course for staff manning the help-line.

Proposed time period for retention of relevant clinical trial documentation

The Imperial College Clinical Research Governance Office requires that all primary research data be retained for a minimum period of 10 years following completion of the study.
We shall endeavour to ensure that the study is conducted ethically and efficiently. We shall establish a Trial Steering Committee (TSC) which will meet bi-annually. Imperial College research governance procedures will ensure that all appropriate regulations and guidelines are followed.

DATA ANALYSES

Primary outcome

- The cumulative yield of CRC/AA in those testing positive on any one of the three annual FITs, relative to the total CRC/AA (those testing positive on any of the FITs plus additional CRC/AA cases detected at the 3-year colonoscopy in those testing negative at all three FITs). From this, we can calculate the proportion of cases which would go undetected if the FIT regimen was standard.

Secondary outcomes

- Completion and positivity rates for 1st, 2nd and 3rd annual FITs.
- Positive predictive values for the detection of CRC/AA at the 1st, 2nd and 3rd FIT screenings in patients who undergo colonoscopic investigation.
- Detection rate of CRC/AA at the 3-year colonoscopy in patients who test negative at the 1st, 2nd and 3rd FIT screening.
- Subjective physical and mental well-being following 1st, 2nd and 3rd annual FITs (e.g. the impact positive vs. negative FIT screenings, interval colonoscopies etc.)
- Preference for annual FIT vs. 3-yearly colonoscopy for surveillance and satisfaction with FIT at the 3 year assessment.
- Incremental costs and cost-effectiveness of the FIT regimen versus three-year colonoscopy surveillance.

The primary analysis will be to estimate the relative programme sensitivity of the three FIT tests compared to a colonoscopy at three years. This is calculated as:

$$P_3 = \frac{f_1 + f_2 + f_3}{T} = \frac{f_1 + f_2 + f_3}{f_1 + f_2 + f_3 + c_3}$$

where f_1, f_2 and f_3 are the numbers of CRC/AA cases found as at colonoscopy following a positive first, second or third FIT, and c_3 is the number of CRC/AA cases found at the 3-year colonoscopy in those without positive FIT results. This is calculated using those taking up all FIT tests up to a positive finding of CRC/AA or with three negative FIT results. Subsequent analyses will also performed using those who missed the second or third FIT, thus estimating the relative programme sensitivity of a single or two FIT episodes.

Conditional on T, the total number of cases CRC/AA cases, the above estimate standard error

$$s = \sqrt{\frac{P_s(1-P_s)}{T}}$$

And the 95% confidence interval on P_s expressed in percentage terms is

$$100(P_s \pm 1.96s)$$

We hypothesise that the observed P_s will be at least 75%. A positive result of the study, analogous to the logic of equivalence trials, would be a 95% confidence interval whose lower point does not fall below 65%.

The accuracy of estimation depends on the assumptions:

(1) That compliance is not strongly confounded with presence or absence in the bowel of CRC/AA;

(2) That any CRC/AA cases found at colonoscopy following a positive result at first or second FIT would have been found at the 3-year colonoscopy; and

(3) That additional CRC/AA lesions which would have been found at 3-year colonoscopy in those with positive first or second FIT results, but which were not found at colonoscopy following the positive FIT, are sufficiently small in number to have negligible effect on the estimate P_s.

The plausibility of assumption (1) can be assessed by comparing findings in those complying with differing numbers of FIT episodes. As noted elsewhere, any bias from this is likely to be small and will be further minimised by encouraging compliance with future scheduled investigation in all participants. Assumption (2) is clearly reasonable. Assumption (3) can be checked by enumeration of the CRC/AA lesions (if any) found at the four-year colonoscopy in those with a positive first FIT.

Secondary analyses will include estimation of specificities and predictive values of the FIT episodes. These will be calculated by standard methods.

Economic analysis

An economic analysis is a vital part of this study because we expect that a small proportion of lesions will be missed by the FIT regimen, but that it will generate substantial cost savings

because fewer surveillance colonoscopies will be required. We therefore expect that the FIT regimen will fall in the bottom left hand corner of the cost-effectiveness plane (i.e., it will be less costly and either equally or, at most, marginally less effective than three-yearly colonoscopy surveillance). We will undertake an economic analysis to highlight this trade-off. A cost-minimisation analysis may be appropriate; or it will be possible to calculate the incremental cost (positive or negative; probably negative) per unit change (increase or decrease; probably decrease) in cases detected of the FIT regimen versus three-year colonoscopy surveillance.

The time horizon for the main economic analysis will be three years because this is the cycle time for colonoscopy surveillance. A full lifetime cost-effectiveness model using quality-adjusted life years as the outcome measure is not appropriate because this would require separate data describing the outcomes and the treatment pathways associated with the two options.

Outcomes in the economic analysis will be assessed using all the primary and secondary outcomes from the main study. The main outcome in the economic analysis will be the number of cases detected by the FIT regimen versus three-yearly colonoscopy surveillance.

The costs components included in the analysis will be the cost of the FIT regimen and subsequent colonoscopies where indicated, the cost of three-year colonoscopy surveillance, and the cost of dealing with the complications of colonoscopy. Costs will be measured from the perspective of the NHS and personal social services. The cost of the FIT screening test and colonoscopy will be calculated as a function of the main cost drivers, which include staff time, disposable and capital equipment, and laboratory costs. The volume of resource use will be measured directly in the study; unit costs will be taken from standard national published sources.

Our results will be subjected to comprehensive sensitivity analysis in order to investigate the stability of the results to all assumptions. If appropriate, we will also undertake a probabilistic sensitivity analysis and calculate confidence intervals around the baseline incremental cost-effectiveness ratios, cost-effectiveness acceptability curves and cost-effectiveness confidence ellipses.

We estimate that the FIT regimen will generate cost savings because fewer relatively expensive surveillance colonoscopies will be required (we estimate up to as many as 80% fewer). We will undertake a budget impact analysis to calculate the total cost to the NHS of three-yearly colonoscopy surveillance at its current levels of utilisation and the total cost to the NHS of the FIT regimen if it was used in its stead.

Our data will be used to identify the main cost drivers and important cost-effectiveness parameters of the FIT regimen versus three-yearly colonoscopy surveillance. This will inform

future economic analyses based on prospective head-to-head comparisons of the two options.

SERVICE USERS

Our research plans incorporate best practice in the involvement of users. Users have been involved in the pre-study phase in the design of information materials and psychological questionnaires sent to patients to ensure that we address their needs and concerns. They have been involved in planning the intervention, particularly with respect to the timing of invitations and results to maximise participation and minimise anxiety. We gathered users' responses about the psychological implications of receiving a false positive test result which informed our development of patient materials such that they clearly demonstrate the possibility of being a false positive.

Our partnership with users will be active and continue throughout the study. They will be involved in assessment of the pilot and on interpretation of the results of the study and future implications for the management of higher risk patients.

We consulted a range of users including those who have used the BCSP and have tested positive, those who are in an active adenoma surveillance programme, and those who have refused to attend for surveillance.

The mechanisms for involvement of users include workshops and focus groups, and three users will be members of the independent steering committee. We will pay travel and subsistence costs. Recognising that many users will be in active employment, we will try to arrange meetings in the evenings. Where possible, we will reimburse individuals for lost revenue at the rate specified by the NIHR. Users' contributions will be recognised explicitly in our publications. We are confident that active participation in our study will enable service users to learn about the research process and feel empowered to become involved with other NHS research which in turn will also benefit from their involvement.

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