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School of Health And Related Research.

Optimising Bowel Cancer Screening
Phase 1: Optimising the cost effectiveness of repeated FIT screening and screening strategies combining bowel scope and FIT screening

Sophie Whyte, Chloe Thomas, Ben Kearns, Mark Webster, Jim Chilcott

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Contents

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- Wendy Atkin and Kate Wooldrage provided input on: data informing adenoma prevalence, data available to inform the calibration process, the cost of a flexible sigmoidoscopy procedure; change in bowel scope uptake will increase over time due to normalisation of the procedure.
- Matt Rutter and Neil Hawkes provided input on: endoscopist training and future endoscopy capacity.
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- Stephen Duffy supplied advice on screening modelling issues.

1 Short Summary

ScHARR has been commissioned by the UK National Screening Committee (NSC) to consider the cost-effectiveness and endoscopy capacity requirements of a variety of different screening options incorporating faecal immunochemical testing (FIT) and bowel scope (BS) within the Bowel Cancer Screening Programme (BCSP).

An existing cost-effectiveness model was used. The model was refined considerably, new data included and model validation was undertaken. All FIT thresholds between 20 and 180 µg/ml were modelled. Analyses were undertaken to determine which screening strategies involving repeated FIT screening and/or bowel scope are most cost-effective given endoscopy constraints.

Note that the conclusions reached are based on optimising cost-effectiveness where effectiveness is measured in terms of QALYs gained. If the aim was to optimise QALY gains or CRC incidence/mortality reduction then conclusions would be different.

The analysis without endoscopy constraints indicates that the most cost effective screening strategy is the one which delivers the most intensive screening. Regardless of capacity constraints the current screening strategies (gFOBT 2-yearly 60-74 with or without bowel scope age 55) are dominated by a FIT screening strategy (i.e. a FIT strategy exists which is more effective and less expensive).

For repeated FIT screening it is recommended that the screening interval is kept to 2-yearly screening. However, increased benefits may be obtained by re-inviting non-attenders after a 1 year interval. The optimal starting age for a repeated FIT screening strategy is 50 or 51 hence it is suggested that the screening start age is reduced compared to what is currently used in the BCSP. The optimal upper screening age varies between 65 and 74, depending on the capacity constraint used. The optimal FIT threshold depends on the available capacity for screening referral colonoscopies. With 50,000 screening referral colonoscopies (current capacity) then we recommend a strategy of ***2-yearly, age 51-65, FIT161*** (8 screens). With 70,000 screening referral colonoscopies (current capacity) then we recommend a strategy of: ***2-yearly, age 50-70, FIT153*** (11 screens). If 90,000 screening referral colonoscopies is considered feasible to achieve in the future then we recommend a strategy of ***2-yearly, age 50-74, FIT124*** (13 screens).

In terms of bowel scope screening the model found uncertainty in whether it is cost effective to replace one FIT screen with a one-off bowel scope at age 58/59. However, a repeated FIT screening strategy requiring 125k screening referral colonoscopies annually would be far more effective and cost effective than a one-off bowel scope at age 59. Such strategies could be considered to have equivalent 'endoscopy capacity' (assuming that 10 bowel scopes and 4 screening referral colonoscopies are equivalent).Hence, if bowel scope capacity could be used for undertaking screening referral colonoscopies this would result in higher effectiveness and cost-effectiveness.

2 Executive Summary

Aim

ScHARR has been commissioned by the UK National Screening Committee (NSC) to consider the cost-effectiveness and endoscopy capacity requirements of a variety of different screening options incorporating faecal immunochemical testing (FIT) and bowel scope (BS) within the Bowel Cancer Screening Programme (BCSP).

New data review

Data was obtained from the BCSP in July 2016 which describes screening outcomes (uptake, positivity rates, false positivity rates, detection rates) for both guaiac faecal occult blood test (gFOBT) screening and bowel scope (BS) [1]. In addition data on computerised tomography colonography (CTC) usage was obtained. This data was analysed to explore changes over time and variations by demographic factors.

Data was obtained from the FIT pilot [2]. FIT sensitivity and specificity data were incorporated within the model but unfortunately could not be incorporated within the model calibration as no age breakdown was available. BCSP and Office for Data Release (ODR) approval, a lengthy process, is required to obtain the data broken down by age so it is suggested that this data be incorporated within phase 2 of the work programme.

Data on long term follow-up from the Nottingham gFOBT trial and the UK flexible sigmoidoscopy screening trial (UKFSST) is available and was used for model validation [3].

Data on endoscopy capacity was obtained from the BCSP, published literature and via discussions with experts (Matt Rutter and Neil Hawkes).

Modelling Approach

These phase 1 analyses utilise the existing ScHARR bowel cancer screening model from 2011. Although several model refinements have been made in the last 5 years the model had not been fully revised since 2011. Hence, the data informing all model parameters was reviewed and updated where appropriate including: cost data, utility data, screening test data (uptake, compliance, repeat testing) and mortality data.

In addition to model updates several model refinements were also implemented:

- Treatment costs in the model vary by age to represent differences in treatment pathways by age.
- Utilities vary by age and cancer stage, to better incorporate quality of life differences between screening strategies targeted at different age groups.
- Utility decrements for colonoscopy adverse events (bleeding and perforation) are included.
- Follow up with CTC has been added to the screening pathways modelled, along with appropriate costs and referrals.
- The incorporation of FIT screening for all test thresholds from 20-180 μg/ml. (Estimates of FIT screening characteristics were derived by fitting curves to data from the FIT pilot.)
- The incorporation of FIT sensitivity which varies by screening round.

The review and analysis of available data has confirmed the potential to produce a more sophisticated patient level model of bowel cancer screening with the currently available data. Phase 2 proposes a patient level model structure that will allow improved estimates of model outcomes to be generated. Exploratory analyses were undertaken to attempt to quantify the limitations of the existing modelling approach.

Model Calibration

A process of model calibration is used to estimate adenoma/cancer development and progression rates and screening test characteristics. The data available to inform this process was reviewed following input from Prof Wendy Atkin. New data from the BCSP on gFOBT screening is available but is unsuitable for inclusion as the prevalent and incident data available does not include complete screening history information. New data from the BCSP on bowel scope screening in persons aged 55 is available to supplement the data from the flexible sigmoidoscopy screening trial. This data was used to estimate the bowel scope screening test characteristics. The data informing adenoma prevalence was reviewed with clinical input sought from Prof Wendy Atkin. Based on the available data the model calibration was not updated.

Model validation

The model was validated against several different studies as part of this project.

This study produces predictions for FIT screening similar to those reported by Murphy & Gray (2015) [4].

Validation against screening data with long term follow-up was undertaken using (1) long term follow up data from the Nottingham FOBT trial [3] and (2) 17 year follow-up from the flexible sigmoidoscopy trial results [5]. This concluded that model CRC incidence estimates are fairly accurate, whilst the accuracy of CRC mortality estimates is highly sensitive to the mortality data used in the model, due to a high level of change in CRC and other cause mortality rates over the past 30 years.

Validation of surveillance colonoscopies found a significant discrepancy between model predictions and data from the BCSP. The surveillance model parameters are associated with significant uncertainty; specifically: 'adenoma recurrence rate following polypectomy' and 'proportion of adenomas referred for annual/3-yearly surveillance'. The impact of these uncertainties was explored by varying these parameter values however this uncertainty could not entirely explain differences between model predictions and BCSP data. This issue will be examined as part of more detailed surveillance modelling in Phase 2. As a result the model predicted surveillance colonoscopy estimates presented here should be treated with caution.

Key challenges of validating against long term follow up data were identified. In addition to the characteristics of the study population changes in other cause mortality, colorectal cancer mortality, and colorectal cancer incidence over the follow up period are important. We note that the ScHARR model performed well in validation when compared to the recent validation of the CISNET model to the FS trial data.[6]

Future Research: Phase 2 Aims

Phase 2 will develop a more sophisticated patient level model to allow evaluation of further screening options such as alternative surveillance criteria and modalities, targeted screening uptake interventions, and patient level screening strategies. This phase will have two key aims:

- To deliver a patient level model structure that is compatible with addressing anticipated future research questions.
- To undertake an evaluation of different surveillance strategies including FIT for follow up and alternative surveillance stopping criteria

Analyses undertaken

Cost effectiveness was evaluated by considering a cohort in who the proposed screening strategy is fully rolled out. Model predictions for expected cost-effectiveness were generated for a lifetime horizon for a cohort of 50 year olds (corresponding to 2016 population). Model predictions for expected resource use were generated for a cross sections of ages by running a series of cohorts to comprise the whole 2016 population. The whole population was modelled to receive the current screening strategy (gFOBT 60-74 2-yearly) for previous years (pre 2016) then changing to the proposed screening strategy for future years (post 2016). We note that resource use will change over time as more rounds of the proposed screening strategy are completed.

Analyses were undertaken to address the following question:

- What screening strategies involving FIT and/or bowel scope are most cost-effective given endoscopy constraints?

Endoscopy capacity within the BCSP comprises: screening referral colonoscopy, bowel scope and surveillance colonoscopy. There is considerable uncertainty in the model predictions of surveillance colonoscopy (see validation) and capacity for bowel scope and colonoscopy are different so this analysis focused on the number of screening referral colonoscopies. Three different constraints on the number of screening referral colonoscopies were considered:(1) no capacity constraints, (2) existing capacity constraints observed in the NHS BCSP (approx.. 50,000); (3) an optimistic estimate of the future capacity constraints for the NHS BCSP (approx. 90,000). Strategies involving bowel scope, gFOBT or FIT were considered, as were strategies involving both bowel scope and FIT. To identify the most cost-effective strategy a willingness to pay of £20,000 per QALY was used.

The impact of several model uncertainties were explored though sensitivity analyses including: discount rates; costs and utility values (e.g. cancer treatment costs); screening uptake rates; screening test characteristics; symptomatic presentation rates; and varying cancer risk by gender.

Results

It is essential for the reader to understand that the optimal screening strategy will vary depending on what outcome measure you consider. For example, the optimal screening strategy will vary depending on whether you choose to maximise NMB (cost effectiveness), QALYs (effectiveness), CRC incidence reduction or CRC mortality reduction. For example, QALY gains tend to be maximised by screening younger ages (as lives saved are associated with a longer life expectancy) whereas CRC incidence and mortality tend to see the maximum reductions when screening older ages (as disease is more prevalent in older ages). In this report we focus the results on screening strategies which optimise cost-effectiveness.

The optimal age in terms of cost-effectiveness for a one-off bowel scope screen is 59. (Note that QALY gain is optimised at a younger age and incidence and mortality reduction is maximised at an older age.) The optimal age (in terms of cost-effectiveness) for a one-off FIT120 screen is 57 regardless of FIT threshold (20-180 μg/ml were considered). Comparing a one-off FIT20 and a one-off bowel scope, we see that bowel scope is the most effective but FIT20 is the most cost effective. However under analyses in which bowel scope uptake and/or sensitivity is increased (in line with the trial data), bowel scope was associated with much higher effectiveness and cost effectiveness than FIT20

With no constraints on the number of screening referral colonoscopies the optimal repeated FIT screening strategy is: FIT20 annual ages 50-74. For a screening referral colonoscopy capacity of 50,000 (current)-90,000(optimistic future) 2-yearly screening from age 50/51 is optimal. For higher levels of screening referral

colonoscopy capacity screening with a lower FIT threshold and a wider age range is optimal. With 50,000 screening referral colonoscopies (current capacity) then we recommend a strategy of ***2-yearly, age 51-65, FIT161*** (8 screens). With 70,000 screening referral colonoscopies (current capacity) then we recommend a strategy of: ***2-yearly, age 50-70, FIT153*** (11 screens). If 90,000 screening referral colonoscopies is considered feasible to achieve in the future then we recommend a strategy of ***2-yearly, age 50-74, FIT124*** (13 screens).

Screening strategies combining bowel scope and FIT were considered. For a repeated FIT screening strategy, whether it is cost effective to replace one FIT screen with one-off bowel scope at age 58 is very uncertain. It depends on the level of screening referral colonoscopies and also varies in sensitivity analyses.

We consider an assumption that 10 bowel scopes and 4 screening referral colonoscopies are equivalent (based on procedure time). A repeated FIT screening strategy with 125k screening referral colonoscopies would be considerably more effective (over 3 times) and cost effective (over 4 times) than a one-off bowel scope at age 59 (290k bowel scopes, 9k screening referral colonoscopies).

Conclusions

Note that these conclusions are based on optimising cost-effectiveness. If the aim was to optimise QALY gains or CRC incidence/mortality reduction then conclusions would be different.

The analysis without endoscopy constraints indicates that the most cost effective screening is intensive FIT screening (annual screening with FIT20, ages 50-74). However, the most cost-effective feasible screening strategy differs according to the endoscopy capacity available.

Regardless of capacity constraints the current screening strategies (gFOBT 2-yearly 60-74 with or without bowel scope age 55) are dominated by a FIT screening strategy (i.e. a FIT strategy exists which is more effective and less expensive). So, compared to the current gFOBT screening programme increased benefits could be gained(QALYs) by switching to a screening programme involving repeated FIT screening.

For repeated FIT screening it is recommended that the screening interval is kept to 2-yearly screening. However, increased benefits may be obtained my re-inviting non-attenders after a 1 year interval. The optimal starting age for a repeated FIT screening strategy is 50/51 hence it is suggested that the screening start age is reduced compared to what is currently used in the BCSP. The optimal upper screening age varies between 65 and 74, depending on the endoscopy capacity constraint used. The optimal FIT threshold depends on the available capacity for screening referral colonoscopies. With 50,000 screening referral colonoscopies (current capacity) then we recommend a strategy of ***2-yearly, age 51-65, FIT161*** (8 screening episodes). With 70,000 screening referral colonoscopies (current capacity) then we recommend a strategy of: ***2-yearly, age 50-70, FIT153*** (11 screens). If 90,000 screening referral colonoscopies is considered feasible to achieve in the future then we recommend a strategy of ***2-yearly, age 50-74, FIT124*** (13 screening episodes).

In terms of bowel scope screening the model found there is some uncertainty in whether it is cost effective to replace one FIT screen with a one-off bowel scope at age 58/59. However, a one-off bowel scope at age 59 (290k bowel scopes, 9k screening referral colonoscopies) is considerably less effective and a cost effective than a repeated FIT screening strategy associated with 125k screening referral colonoscopies. Such strategies could be considered to have equivalent endoscopy capacity. Hence, if bowel scope capacity could be converted to screening referral colonoscopy capacity instead, it would result in far higher effectiveness and cost-effectiveness to undertake repeated FIT only screening strategies.

3 Background

Colorectal cancer (CRC) is the fourth most common form of cancer in the UK. According to Cancer Research UK (CRUK), 41,112 new cases were diagnosed in 2013 and there were 15,903 deaths in 2014; the most recent years for which data is available [7]. Screening for CRC has been carried out over the past decade through the Bowel Cancer Screening Programme (BCSP). Current screening practice is to invite all individuals aged 55 to a single bowel scope (BS) screen, followed by screening using the guaiac faecal occult blood test (gFOBT) every two years between the ages of 60 and 74 [8]. Bowel scope is a recent addition to the screening programme and is not yet fully available everywhere across the country. Individuals testing positive are referred to colonoscopy services for follow-up investigation.

ScHARR has previously been involved in appraising CRC screening options using the ScHARR Bowel Cancer Screening Model. Previous work has included evaluating cost-effectiveness, cost-utility and resource impact of gFOBT and BS screening in different age groups [9], work which informed the Department of Health's policy on bowel cancer screening in England. A reappraisal of screening options, commissioned by the NHS Cancer Screening Programme was undertaken in 2011 using data from the BCSP and other sources to update the model and evaluate a range of screening strategies including gFOBT and the faecal immunochemical test (FIT), together with determination of the optimal age for once-only BS screening [10, 11].

FIT is a more sensitive and reliable, but also more expensive test for CRC than gFOBT, which produces a quantitative read-out of cancer risk depending upon the amount of blood detected. A cost-effectiveness evaluation of FIT versus gFOBT based on the ScHARR model has been recently carried out for the UK National Screening Committee [4]. This has concluded that FIT screening should produce health benefits and cost-savings, and be highly cost-effective compared with gFOBT screening. However, it is unclear what the optimum strategy for FIT screening might be in the context of the BCSP in terms of targeted age, follow-up cut-off score and use of BS, particularly since there are constraints on endoscopy capacity that may prevent the most cost-effective option from being utilised.

The NSC has commissioned from ScHARR a piece of research to consider the cost effectiveness and endoscopy capacity requirements of a variety of different screening options incorporating FIT. This work uses an updated version of the existing ScHARR model to produce results and predictions specifically targeted to inform policy making, and aims to answer the following questions:

- What combination strategies involving Bowel Scope and FIT are most cost-effective?
- What FIT roll-out strategies are feasible considering endoscopy capacity constraints?

This report also contains summaries of recent data from the BCSP and other sources containing information used in the modelling including:

- Data from the BCSP on gFOBT uptake, positivity and cancer detection rates; changes over time and prevalent versus incident screening.
- Data on CT colonography use within the BCSP.
- Data on bowel scope uptake and outcomes within the BCSP.
- Comparison of data from the recent English FIT pilot with Italian FIT screening data used in previous analyses.
- Estimates of current endoscopy capacity based on data from the BCSP and the Cancer Research UK 2015 report.

4 Data Review

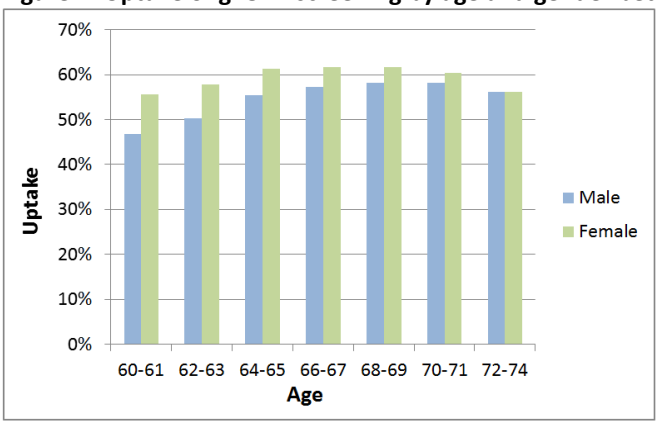
4.1 gFOBT data from the BCSP

Data from the BCSP was obtained for gFOBT screening between 2011 and 2015 [1]. During this time period almost 20 million screening invitations were sent, of which over 11 million resulted in an adequate sample. Data was obtained by gender, age and whether prevalent (first time screened; may be first or subsequent screening invitation) or incident (screening episodes subsequent to first taking up a screening invitation). Data on age was combined into two year age groups, as normally individuals are invited for screening in even age years meaning that the numbers of individuals screened at odd ages is very small.

gFOBT screening uptake

Screening uptake has remained fairly constant over the past five years at an average of 57% of those invited. Uptake is lower amongst men than women with only 54% of men taking up an invitation versus 59% of women. Uptake tends to rise with age, peaking at age 68-69 then falling in individuals aged over 70, (Figure 1). The gender difference in uptake is more marked in the younger age groups, dwindling to zero in the 72-74 year old group.

Figure 1: Uptake of gFOBT screening by age and gender between 2011 and 2015



Screening uptake is far higher in individuals who have previously been screened (86%) than those who have never been screened (29%). Mean prevalent uptake has slightly fallen between 2011 and 2015, whereas incident uptake has stayed roughly the same (Figure 2). This is unsurprising given that as the screening programme has progressed there have been increasing numbers of individuals who have turned down multiple screening invitations and are highly unlikely to agree to ever being screened. It is expected that prevalent screening uptake would reach a steady state if the screening programme were to carry-on with the same screening test for 14 years and there is a cohort of individuals who have been invited every two years between the ages of 60 and 74. Currently the programme has been going on for 10 years, but only four rounds of prevalent screening data are available out of the 7-8 total expected rounds over an individual's lifetime.

Prevalent uptake by screening session for year 2014/15 is shown in Figure 3. The first time individuals are sent an invitation to screening, uptake is almost 50%. However, amongst individuals who did not attend their first screen, uptake is lower than 20%, and is reduced further to around 10% for individuals who are being invited to their third round of screening, having not taken up screening in either of the previous two rounds. At the end of four screening rounds there remain 34% of invited individuals who have never been screened, although this number is likely to diminish slightly following all 7-8 screening rounds that an individual is likely to experience in their lifetime. These findings confirm and extend the results of a published analysis of the first three BCSP screening rounds [12].

Figure 2: Uptake of prevalent and incident gFOBT screening over time

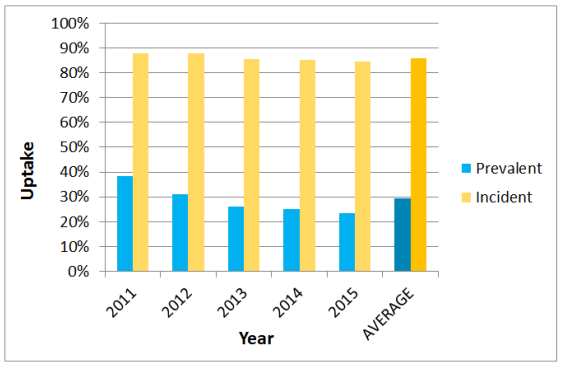
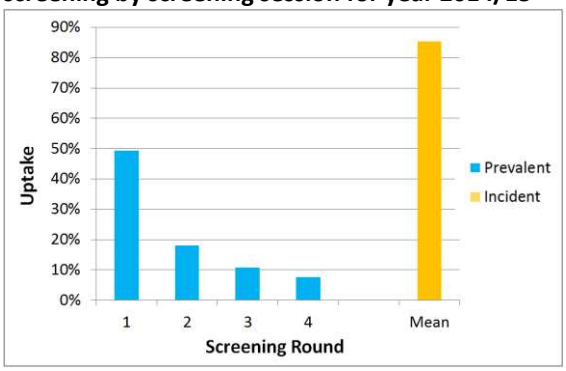


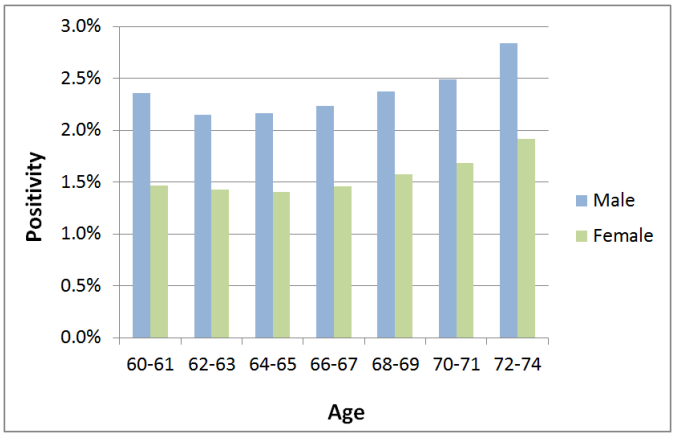
Figure 3: Uptake of prevalent and incident gFOBT screening by screening session for year 2014/15



gFOBT positivity

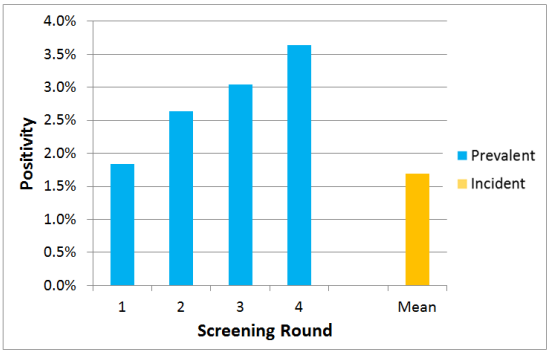
The proportion of screening samples showing abnormality (positivity) has remained fairly constant over the past five years at an average of 1.9%. Positivity is higher amongst men at 2.3% than women in whom positivity is only 1.5%, and this difference is fairly consistent with age (Figure 4).

Figure 4: Positivity of gFOBT screening by age and gender between 2011 and 2015



Individuals who have never been screened before are more likely to show a positive result than those with a screening history, and this increases with prevalent screening round (Figure 5). This is likely to be partly explained by the correlation between age and abnormality (Figure 4). However, given the evidence that those at higher risk of CRC including men and individuals from socioeconomically deprived backgrounds are less likely to attend screening [2, 13], it is possible that they may be over-represented in subsequent prevalent screening rounds compared with the first screening round. Generally, there is a trend for positivity to have reduced slightly over time in both males and females, with a slight exception for 2015 (Figure 6). This trend is unsurprising as the screening programme is increasingly screening individuals who have been previously screened and therefore are at lower risk of cancer.

Figure 5: Positivity of prevalent and incident gFOBT screening by screening session for year 2014/15



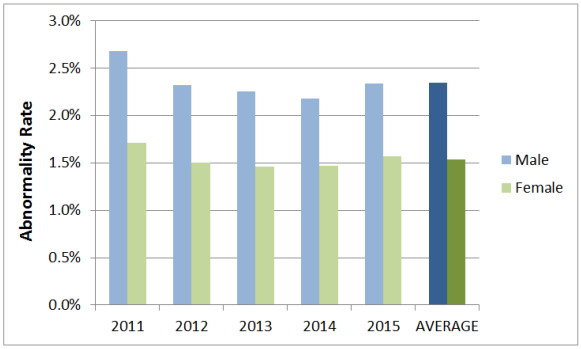
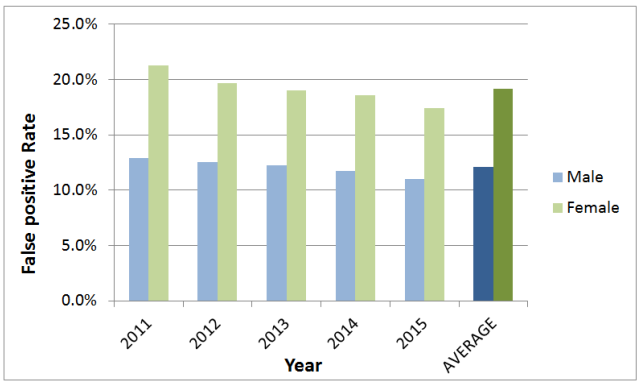


Figure 6: Positivity of gFOBT screening by gender over time

gFOBT false positives

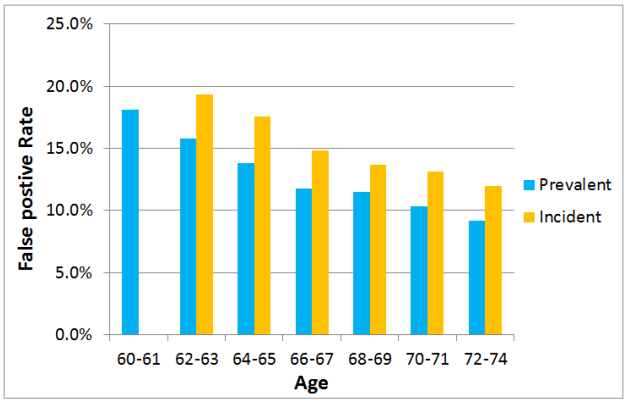
Around 15% of individuals with positive gFOBT samples turn out to have no abnormality upon further investigation. In women the false positive rate is 19%, whereas in men only 12% of positive samples are later found to have no abnormality. In general false positive rates have been decreasing slightly over time (Figure 7).

Figure 7: False positive rate for gFOBT screening by gender over time



In general false positive rates diminish slightly with increasing age (Figure 8). False positives are also lower for prevalent screening rounds than incident rounds at each given age. The inverse correlation with the proportion of abnormalities in these groups is likely to occur due to differences in case-mix as after the prevalent screen true positives (part of denominator) will be removed but false positives will remain and be more likely to be picked up in subsequent incident screens.

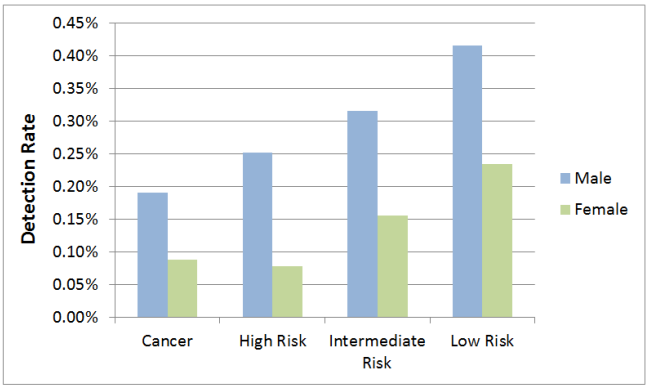
Figure 8: False positive rate for prevalent and incident gFOBT screening by age between 2011 and 2015



gFOBT detection rates

Over the past five years of screening CRC has been detected in 0.12% of adequately screened samples after follow-up investigation, with high risk adenomas accounting for a further 0.14%. A higher proportion of all adenomas are detected in men compared with women, with men around twice as likely to be diagnosed with an adenoma after follow-up investigation (Figure 9). Detection rates have changed little over time, but have reduced slightly for CRC (not shown).

Figure 9: Detection rate after gFOBT screening and follow-up investigation for colorectal cancer and adenomas of different risk levels by gender between 2011 and 2015.



The detection of CRC and all risk categories for adenomas generally increase with age (Figure 10). The age 60-61 group is anomalous with higher detection rates due to being composed of first time screened individuals only - prevalent screening rounds detect higher proportions of adenomas than incident rounds (Figure 11). This is unsurprising as following detection of an adenoma individuals will enter the surveillance programme and will no longer be invited to screening.

Figure 10: Detection rate after gFOBT screening and follow-up investigation for colorectal cancer and adenomas of different risk levels by age between 2011 and 2015

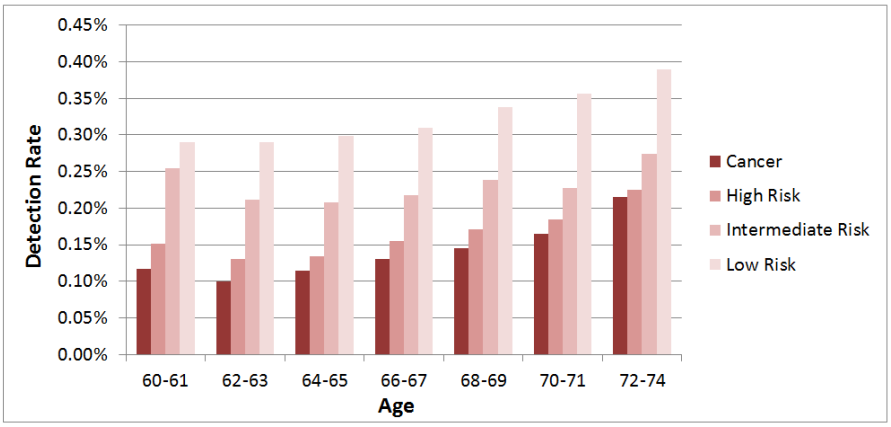
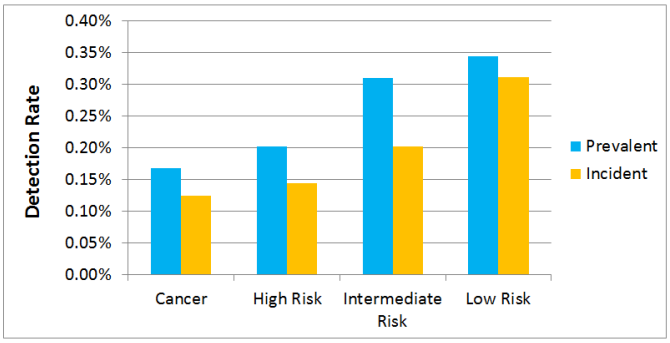


Figure 11: Detection rate after gFOBT screening and follow-up investigation for colorectal cancer and adenomas of different risk levels by prevalent or incident screening round



gFOBT data from other sources

Kronborg 2004 [14]: The 17 year follow up following a programme of biennial gFOBT screening for ages 45-75 in Denmark is presented in this study. A mortality reduction was seen however an incidence reduction was not observed. It is difficult to use this study as calibration or validation data because the gFOBT protocol used differs from the BCSP in England.

Scholefield 2012 [3]: This study presents the Nottingham trial of faecal occult blood testing for CRC 20-year follow-up. At a median follow-up of 19.5 years there was a 13% reduction in CRC mortality (95% CI 3% to 22%) in the intervention arm despite an uptake at first invitation of approximately 57%. The CRC mortality reduction in those accepting the first screening test, adjusted for the rate of non-compliers, was 18%. Despite removing 615 adenomas >10 mm in size from the intervention arm, there was no significant difference in CRC incidence between the two arms (Screened 3.0%, 2,279, N=76,059 vs. Control 3.1% 2,354, N=75,919). Note that a median of 19.5 years of follow-up would provide over 90% power to detect a 10% reduction in the intervention arm. Hence it may be plausible that a reduction in incidence of less than 10% occurred. A non-significant reduction in incidence of 6% was found after adjusting for non-acceptance of the 1st test (without adjustment the reduction was 3%). The majority of subjects were offered 3-5 tests compared to 8 in the BCSP. It seems plausible that gFOBT screening could have an impact on CRC incidence as FU colonoscopy removes adenomas. This study has been used for model validation (see section 4.4)

Mandel 1999 [15]: This trial from Minnesota reports 18 years of follow up of biennial gFOBT screening (>=1 spot referred to colonoscopy) finding a 21% lower CRC mortality rate than the control group (rate ratio, 0.79; 95% CI = 0.62–0.97) and a marked reduction in the incidence of Dukes' stage D cancers in screened groups in comparison with the control group. Again it is difficult to use this study as calibration or validation data because the gFOBT protocol used differs from the BCSP in England.

4.2 Bowel scope data

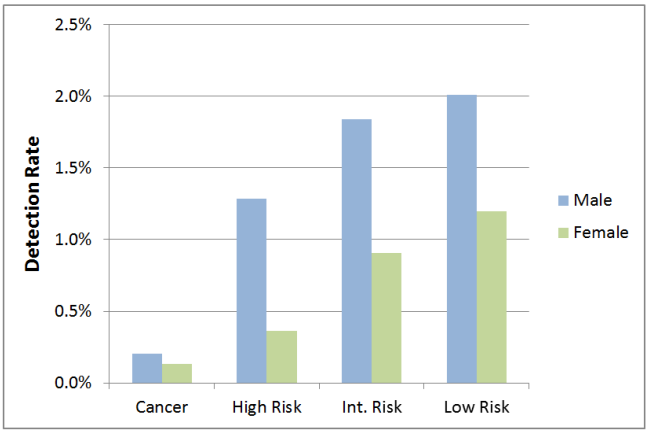
BCSP Bowel Scope Data

Bowel scope is currently being rolled out in the BCSP but roll out is very slow due to endoscopy capacity issues. Currently 65% of centres have started rollout with 100% expected to start by December 2016. However complete roll out to a centre can take over 3 years due to issue in both capacity and capacity training.

Data from the NHS BCSP on bowel scope detection rates, completion rates and uptake was obtained [1]. This includes outcomes of the 108,390 bowel scope procedures adequately carried out up to 30 April 2016. Uptake has improved slightly since the McGregor report, and is now at 44% (45% of men versus 43% of women). Of those that undergo the procedure, 4.4% require further investigation with colonoscopy. Data from 2014/15 indicates that twice as many men (6.0%) require follow-up than women (2.9%).

Detection rates for cancer and other abnormalities are much higher than seen with gFOBT screening, ranging from 0.14% with CRC to 1.4% with low risk adenomas. Data from 2014/15 shows that diagnostic rates for all abnormalities are higher in men than women, although the difference is less marked for cancer than for other abnormalities (Figure 12).

Figure 12: Detection rates for colorectal cancer and adenomas of different risk levels following BS, by gender for 2014/15



A report from McGregor and others analysed data from the first 14 months of the programme [16]. In this time, 21,187 invitations were sent with an uptake of 43.1%, which was lower than the uptake seen in the pilot (55%) and for the gFOBT screening programme (54%). A small but statistically significant gender difference in uptake was observed (45% of men versus 42% of women), together with a significant socioeconomic gradient ranging from 33% in the most deprived quintile, to 53% in the least deprived.

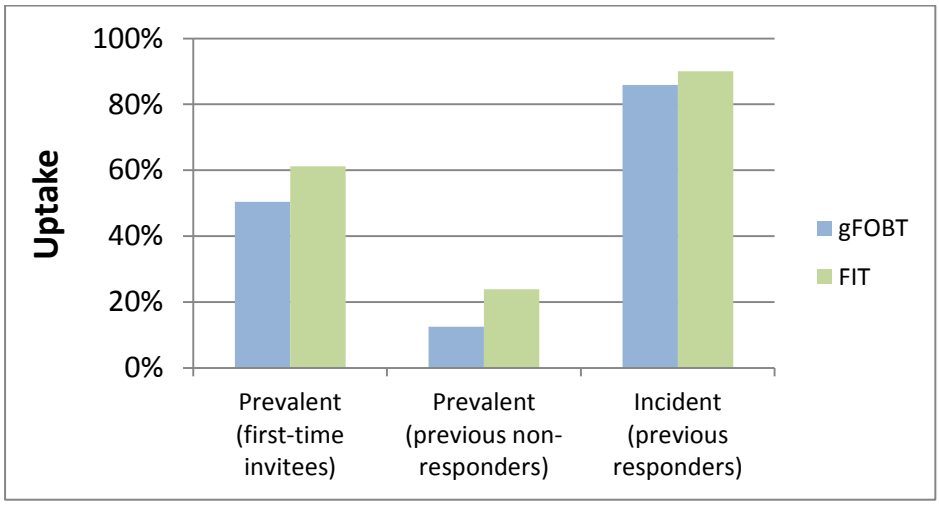
4.3 FIT screening data

FIT has several advantages over the current gFOBT test [17]. The gFOBT test requires manual subjective visual analysis of test cards, making it vulnerable to errors and to backlogs caused by unexpected loss of staff, whereas FIT uses an automated process. Sensitivity of the gFOBT test is not only lower than that of the FIT test, due to its inability to detect very small concentrations of blood, but also varies according to the quality of the manufactured guaiac reagent. Furthermore, FOBT testing cannot distinguish between human blood and certain dietary components including animal blood and antioxidants, whereas the FIT test is highly specific for human blood. The FIT test also has the advantage of providing a quantitative read-out of cancer risk, dependent upon the amount of blood detected, whereas gFOBT testing provides only a positive or negative response. The low sensitivity and specificity of gFOBT testing has led to the NHS BCSP currently using a complex three step screening process, each requiring six samples from three separate stools for a definitive positive result. This screening process results in poor uptake; particularly amongst disadvantaged groups, with high drop-out of individuals at each step, thus potentially missing high risk individuals [18]. In contrast, screening with FIT can be achieved using only one stool sample, which is easier to collect than when using gFOBT.

Previous iterations of the model have used data from Italy to estimate the sensitivity and specificity of FIT. FIT screening has been carried out in some regions of Italy for several years. The programme varies between region, but in general a cut-off of 100ng/ml is used and screening starts at age 50 [19]. An Italian ecological study found that areas where FIT screening programmes were active showed a 22% reduction in CRC- specific mortality [20]. The impact of FIT programmes on mortality was greater and took place earlier compared with available evidence on gFOBT-based screening programmes.

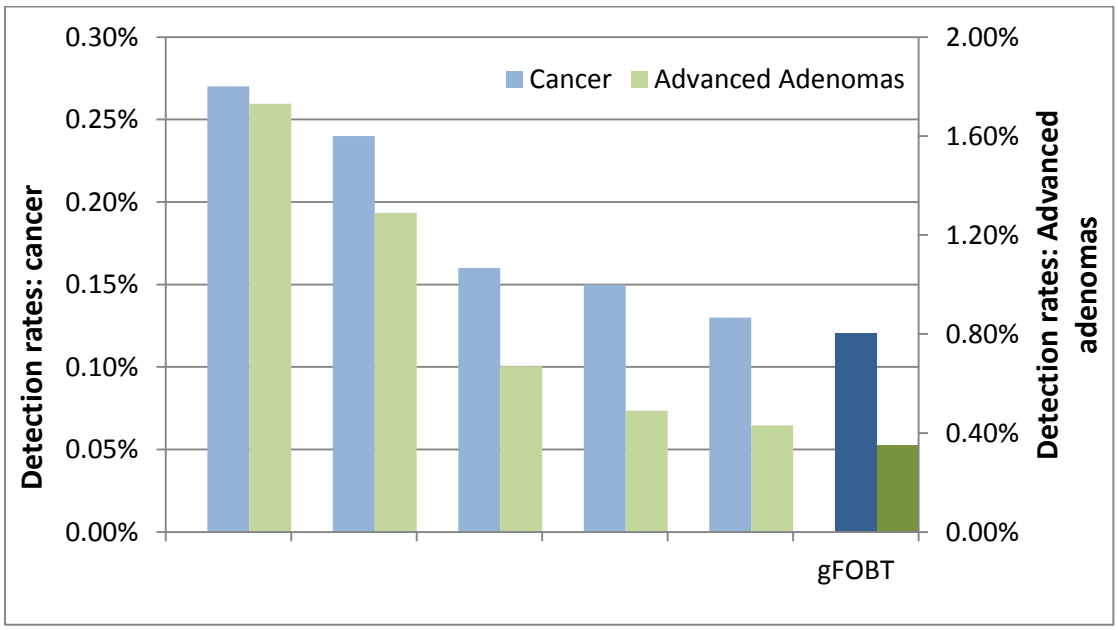
A FIT pilot took place in two of the five English screening hubs between April 2014 and October 2014 (40,930 FIT invitations) [2]. The pilot observed higher uptake with FIT compared to gFOBT (66.4% vs. 59.3%, OR 1.35, 95% CI 1.33-1.38). The FIT Pilot showed improved engagement amongst sub-populations that have hitherto been resistant to screening including males, those from lower socioeconomic groups, and those who were previous non-responders. Overall, the odds ratio for uptake of a screening invitation was 1.35 (95% confidence interval 1.33 to 1.38), with values above one indicating a higher uptake amongst people offered screening with FIT. Amongst the most deprived quintile of people, the odds ratio for uptake was 1.37 (1.31 to 1.43), whilst for males it was 1.41 (1.36 to 1.45). Uptake by screening history is displayed in Figure 13; the largest increase in uptake was observed for previous non-responders, for whom uptake increased from 12.50% with gFOBT to 23.87% with FIT; odds ratio 2.20 (2.10 to 2.29).

Figure 13 Uptake for gFOBt and FIT by screening history.



The pilot observed a higher positivity rate with FIT (cut-off of 20 µg/ml) compared to gFOBT (7.83% vs. 1.73%). At this cut-off (the lowest used), the cancer detection rate was 0.27% with FIT and 0.12% with FOBT, giving an OR of 2.20 (95% CI 1.73-2.79). When considering all neoplasms the odds ratio for detection rates increased to 5.05 (95% CI 4.72-5.41). Five different FIT cut-offs were considered in the FIT pilot. Cancer detection rates were always higher with FIT than for gFOBT: the detection rate at the highest cut-off of 180 µg/ml was 0.13%. The positivity at this cut-off was 1.52%. The next largest cut-off was 150 µg/ml, with a positivity of 1.78%; similar to that for gFOBT. At this threshold FIT had a higher detection rate and positive predictive value (PPV) of advanced adenomas and of all neoplasms. Detection rates for cancer and advanced adenomas for the cut-offs considered, and for gFOBT, are displayed in Figure 14. In conclusion, FIT is likely to offer advantages over gFOBT due to higher uptake and increased detection rates.

Figure 14 Cancer and advanced adenoma detection rates for gFOBT and by FIT cut-off.



FIT risk scoring systems

Screening with FIT results in a quantitative result. Hence there is the potential to personalise FIT screening by varying the threshold for defining a positive result, dependent upon the individual's characteristics (such as age, gender and ethnicity). There is an ongoing systematic review, the primary objective of which is to identify risk scoring systems which combine the FIT result for colorectal cancer (CRC) screening with other personal characteristics to decide who should be referred for follow-up, and to determine whether this performs better than regular screening using the FIT [21].

An existing study by Stegeman *et al* developed a multivariable risk model with the following factors: total calcium intake, family history, age and FIT result [22]. Adding risk based stratification increases the accuracy of FIT-based CRC screening and could be used in preselection for colonoscopy in CRC screening programmes. The analysis indicates that if colonoscopy was offered to the top 10% of high risk patients according to the risk score (risk positivity threshold of 0.19), rather than the top 10% according to the FIT test (FIT positivity threshold of 50ng/ml), then an extra 5 cases of colon cancer would be detected per 100 high risk individuals.

4.4 Endoscopy Capacity

Current and Projected Endoscopy Usage

A study commissioned by CRUK reports that endoscopy activity in 2013/14 was 1.7million of which 1.37m was due to symptoms requiring diagnosis or treatment, 260,000 was part of surveillance programmes and 60,000 was part of the BCSP) [23]. The CRUK model forecasts 2.4 million procedures in 2019/20. This is a growth of 44% or 6.5% per annum. By 2019/20 it is expected that screening will account for around 330,000 of the 2.4 million total procedures.

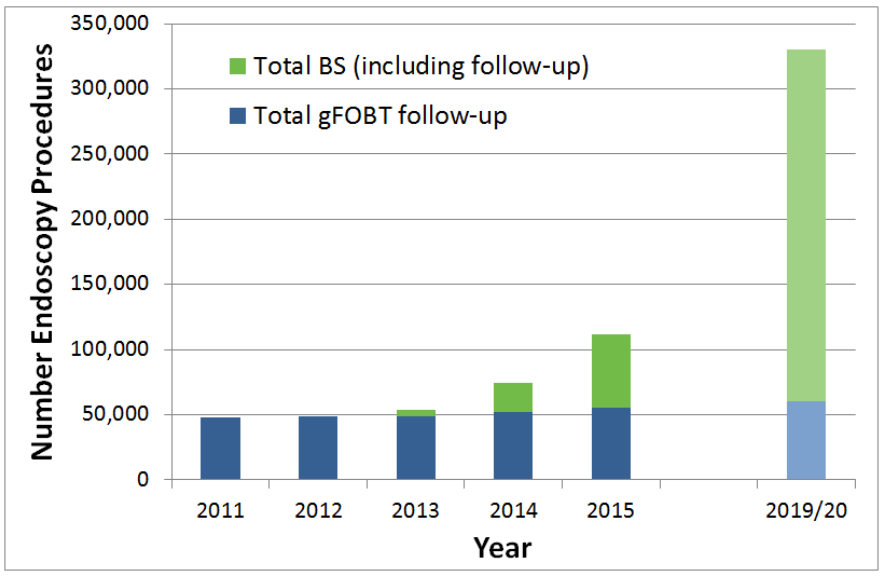
The most recent data from the BCSP indicates that endoscopy activity has already significantly increased within the screening programme, and that currently the capacity exists to perform 165,000 procedures annually, comprising 106,000 BS screening procedures, 47,000 gFOBT and BS follow-up procedures, and 13,000 surveillance procedures (Table 1).

Table 1: Estimate of the number and type of endoscopy procedures currently performed annually within the BCSP. Surveillance data from 2015/16, gFOBT data from 2015, BS data extrapolated from September 2016 data.

Type of Procedures	Number of Procedures
gFOBT screening referral colonoscopy	39,783
gFOBT follow-up BS	1,896
gFOBT follow-up partial colon.	475
Total gFOBT follow-up	**42,154**
BS screening	106,020
BS screening referral colonoscopy	4,530
Total BS	**110,550**
Surveillance colonoscopy	12,642
Surveillance BS	208
Total Surveillance	**12,850**
TOTAL COLONOSCOPY PROCEDURES	57,430
TOTAL BOWEL SCOPE PROCEDURES	108,124
TOTAL ENDOSCOPY PROCEDURES	**165,554**

The increase from the 2013/14 figure of 60,000 procedures reported by CRUK is almost entirely due to the continuing roll-out of BS and this is projected to continue to 2019/20, but there has also been a small but steady increase in gFOBT follow-up procedures in the past few years, projected to reach about 60,000 in total by 2019/20 (Figure 15). This is partly due to changes in demographics, but CRUK have also taken into account using FIT instead of gFOBT in the BCSP. FIT roll-out would be projected to increase the number of follow-up endoscopies by 102,000 if a low positivity threshold was used. However, CRUK have estimated that increasing the FIT positivity threshold to detect a comparable number of individuals to that currently identified by gFOBT would bring this down by 96,000 to only 6,000 extra follow-up procedures, thus minimising the impact of changes to the screening programme.

Figure 15: Endoscopy procedures performed within the BCSP between 2011 and 2015, with projected figures for 2019/20 from CRUK.



It is important to note that increases in screening will also lead to increases in surveillance colonoscopy if the current criteria for surveillance are maintained. CRUK estimates that screening will also lead to an increase in surveillance procedures of 37,000 by 2019/20, over one third of the 105,000 extra surveillance procedures predicted. This suggests that of the 700,000 extra procedures predicted for 2019/20 compared with 2013/14, the BCSP will be responsible for over 300,000 (270,000 through screening - predominantly BS, and 37,000 through surveillance), with changing demographics and population health responsible for a further quarter of extra procedures and changes to referral guidelines and public awareness responsible for the rest. This may be an underestimate. Currently, BS coverage is 31% (personal communication from John Davy, October 2016), suggesting that when fully rolled out there could be as many as 342,000 BS procedures annually. Added together with the CRUK estimates for FIT follow-up and surveillance procedures, this could take the total number of endoscopy procedures within the BCSP to 440,000 per year.

The CRUK estimates do not take into account potential reductions in symptomatic referrals due to screening programmes, as there is currently no evidence to support this, although in theory it would be expected to have some impact. There has also been suggestion that some capacity could be freed up by using FIT testing as a first line tool to help decide who to send for endoscopy following symptomatic presentation. This has not yet been approved by NICE and it is unclear how much it would alleviate capacity issues. However, both these factors could result in future demand outside of the BCSP being lower than predicted by CRUK.

Predicted Increases in Endoscopy Capacity

Rising demand has put pressures on endoscopy units and this projected increase in endoscopy usage assumes ability to meet future demands. However, without significant increase in capacity this seems unlikely. The CRUK report indicates that staff shortages are the biggest problem; lack of physical space used to be an issue but has been addressed in most places in recent years [23]. There is also an issue in some units with aging equipment whose replacement has been hampered by financial constraints. This suggests that endoscopy is already at full capacity and that any increase in procedures in the future, whether from the BCSP, from surveillance or from symptomatic pathways will require additional investment above and beyond the standard cost of endoscopic procedures. It is essential to take this into consideration when estimating the cost-effectiveness of different screening strategies.

Staff shortages seem to be caused by a variety of different problems including problems with staff training, recruitment and retention. Staff trained to perform procedures may be either consultant gastroenterologists or non-medical endoscopists (nurses). There is a limit to the number of endoscopies that can be performed as repetitive strain injury is common, so a reasonable maximum is considered to be 5 lists per week,

corresponding to 40-48 points of activity. BS takes only 20 minutes and is one activity point, whereas diagnostic colonoscopy at 40 minutes is worth two points, with therapeutic colonoscopy corresponding to between 3 and 6 points depending upon complexity (personal communication from Neil Hawkes). This means that a trained staff member could in theory perform up to 2,000 BS or 1,000 diagnostic colonoscopies per year. However, in reality many staff perform far fewer, particularly consultants who may only do two lists a week because of other commitments.

Traditional endoscopist training takes 12-18 months during which time 150-200 training scopes must be carried out and the list numbers of the consultant trainer reduced by one third (personal communication from Matt Rutter). A pilot of a more rapid training programme for non-medical endoscopists has recently been carried out (personal communication from Neil Hawkes). In this programme, nurses are trained over a six month period in either BS or gastroscopy (an endoscopic procedure of the upper GI tract). So far 40 new trainees have been produced and if evaluation of the pilot is positive, another 160 training positions could be available over the next two years. According to Neil Hawkes it is unlikely that any significant increase in capacity will come from consultant trainees, therefore increases in diagnostic endoscopy are likely to come largely from the non-medical endoscopist trainees.

In theory, 200 new trainees could provide an additional 400,000 BS procedures annually (Table 2), although some will train in gastroscopy instead, it is not known what proportion of the total this may be. Colonoscopy requires further experience and training, which some of the trainees (perhaps up to one third) would be expected to acquire. However, the reality is likely to be far less optimistic according to Neil Hawkes as it is unclear how large the pool of recruits may be, whether quality of recruits will diminish beyond the pilot and whether trainees are successfully retained in the workforce. Trainees are usually nurses already working in the field of endoscopy; widening the recruitment pool may mean that extra training is necessary to get staff to the required standard. Furthermore, increasing the number of endoscopists alone is not sufficient to increase staff capacity, as nurse and administration support is also needed, together with additional consultant support for complex therapeutic colonoscopies that will increase as a result of BS screening.

Table 2: Maximum estimates of increase in endoscopy capacity over the next two years.

	By end 2016	**By end 2018**
INCREASES IN CAPACITY		
Max. Number new trainees	40	200
Max. Number additional BS procedures	80,000	400,000
If one third trainees go on to train further in colonoscopy:		
Max. Number additional BS procedures	53,333	266,667
Max. Number additional diagnostic colonoscopies	13,333	66,667
TOTAL PREDICTED CAPACITY		
If all trainees recruited, trained in BS and retained		
Number BS procedures	161,457	374,791
Number diagnostic colonoscopies	70,763	124,097
If only 50% trainees recruited, trained in BS and retained		
Number BS procedures	134,791	241,458
Number diagnostic colonoscopies	64,097	90,763

To conclude, currently about 60,000 diagnostic colonoscopies are performed each year as part of the NHS BCSP; about 47,000 due to follow-up and 13,000 due to surveillance. In the most optimistic scenario 124,000 diagnostic colonoscopies could be performed per year by the end of 2018. It was assumed that the ratio of follow-up to surveillance colonoscopies would be the same as currently observed in the BCSP (72% of colonoscopies are for follow-up,). Hence it is estimated that by 2018 there will be capacity to perform about 90,000 follow-up diagnostic colonoscopies.

Colonoscopy quality

Post-colonoscopy CRC (PCCRC) rates have been proposed as a key quality indicator of a colonoscopy service. Several methods of calculating PCCRC rates have been published, with reported rates varying between 2.1% and 7.5%. In their study, Morris and others propose a standardised methodology which demonstrates a PCCRC rate within 3 years of colonoscopy of 8.6% in the English NHS between 2001 and 2007 [24]. PCCRC rates have fallen over time, with the three year rate dropping from 10.2% in 2001, to 7.3% in 2007. It is essential to have a standardised methodology in order for service quality to be measured. It is estimated that at least 75% of PCCRCs are missed or preventable, and therefore, together with improvements that have occurred since 2007, a rate as low as 1% should be achievable. Remaining PCCRCs may represent rare fast growing cancers and therefore be unavoidable.

4.5 CT colonography

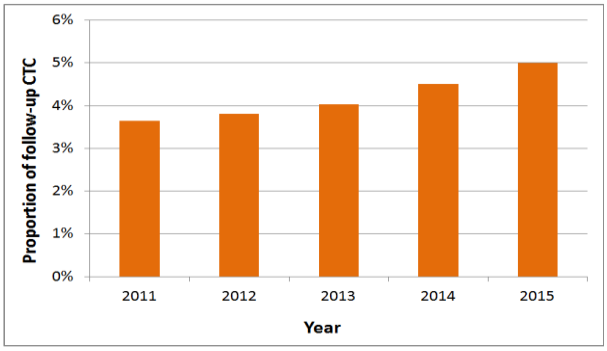
CT colonography (CTC) is recommended for patients who require further investigation, either following gFOBT/FIT screening or symptomatic presentation, but who are unsuitable for colonoscopy. Contraindications for colonoscopy include a having significant cardiovascular or respiratory condition, being too frail to undergo standard laxative preparation, or previously having an incomplete colonoscopy [25], although the latter is not relevant to screening follow-up. There may also be some additional cases where CTC is preferred over colonoscopy. If cancer or abnormality is detected during an examination, then patients are often referred to colonoscopy for more in depth investigation and potentially therapeutic benefit. This is because patients considered too frail to undergo colonoscopy for follow-up screening may be offered it if cancer or high risk abnormality is suspected, as the risks may now be considered acceptable. If patients are identified with CRC and are too frail for colonoscopy, then contrast-enhanced CTC may be carried out to enable staging of the cancer, and a CT chest exam is recommended to check for potential spread of cancer into the lungs. It is important to note that patients who are extremely frail or unwell may not undergo any further investigation at all, particularly if the abnormality is deemed low risk.

CTC use within the BCSP

Data from the BCSP about CTC usage is available for 2011 to 2015 [1]. Published data indicates that within the BCSP, CTC was used following 2.3% of positive FOBT tests between 2006 and 2012 [26]. CTC usage has increased over time as a proportion of all follow-up investigation in the BCSP from 3.6% in 2011 to 5.0% in 2015 (

Figure 16). This represents about 2,500 referrals a year. The proportion of individuals referred to CTC increases with age (Figure 17). This is as expected given that the likelihood of an individual having contraindications or being too frail to undergo colonoscopy increases with age.

Figure 16: The proportion of all follow-up investigations in the BCSP that use CTC, over time



2014/15

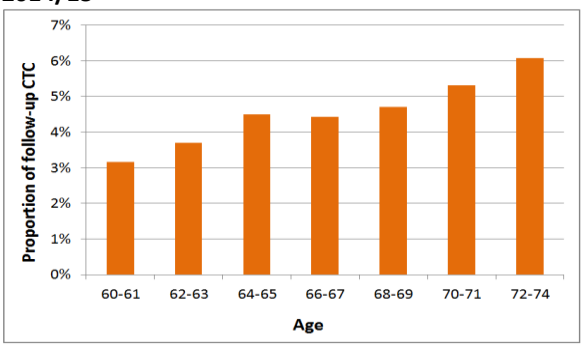
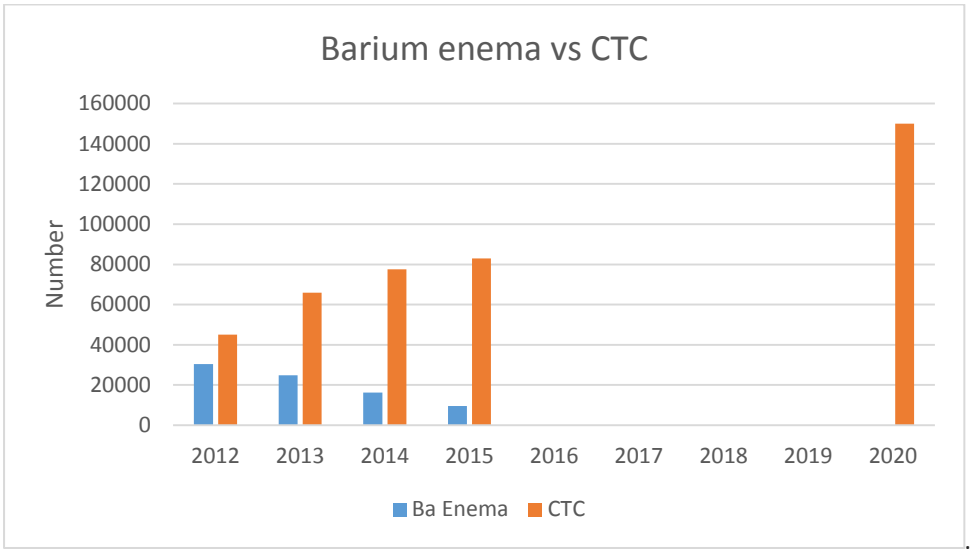


Figure 17: The proportion of all follow-up investigations in the BCSP that use CTC, by age for

The BCSP has only just started to record radiology outcomes therefore the false positive and detection rates for CRC and other abnormalities after CTC follow-up cannot currently be assessed.

The use of CTC as a tool of further investigation following screening is expected to stay roughly where it currently is at around 5% (personal communication from Dominic Blunt), although actual numbers of individuals referred is likely to increase due to an increase in population size of the screen eligible cohort, and potentially due to use of different screening strategies that detect more individuals (i.e. use of FIT instead of gFOBT). In 2015 there were a total of 83,000 procedures carried out following screening and symptomatic presentation, but 150,000 are predicted for 2020 by Cancer Research UK (Figure 18) [23]. This is partly because CTC is now recommended instead of barium enema; a less effective imaging procedure with a fourfold higher false negative rate. BCSP cases therefore only represent a small proportion of these. However, within the BCSP CTC use varies considerably by screening centre (0.039%–9.7%, IQR 0.80–3.1% for 2006-2012 [26]), with some units still not offering it, and others referring almost 10% of patients requiring further investigation, partly due to pressure on endoscopy units but also due to local clinicians' attitudes to risk with frail patients.

Figure 18: Actual and projected numbers of patients undergoing barium enema vs CTC. Figure obtained from Dominic Blunt



5 Methods

These analyses utilise the existing ScHARR bowel cancer screening model from 2011 [10, 11]. For this analysis the data informing all the model parameters has been updated where appropriate. Several refinements to the 2011 model were also implemented:

- Treatment costs in the updated model now vary by age to represent differences in treatment pathways by age.
- Follow up with CTC has been added to the screening pathways modelled, along with appropriate costs and referrals.
- The model now incorporates FIT screening with different test thresholds.
- The model now incorporates the variation of gFOBT sensitivity by screening round.

5.1 Modelling perspective and population

The modelling approach and data sources follow the NICE guidelines for technology appraisal [27]. Costs and QALYs were inflated to the current year and were discounted by 3.5%. A willingness-to-pay threshold of £13,000 is used. This threshold was chosen as recent research has suggested that this is the most appropriate threshold for the NHS to use [28].

In order to determine the most cost effective screening strategy a single cohort is model over a lifetime. This cohort has the same size at age 50 as the 2016 England population. When modelling this single cohort, to allow a fair comparison between screening interventions which commence at different ages, discounting starts at age 50, which is the youngest age at which screening intervention may be first offered. Using this approach we compare the relative expected lifetime costs and benefits of screening strategies when they are fully rolled out i.e. each individual is offered all screening rounds available in the strategy.

We generate estimated endoscopy capacity for years 1-5 of the introduction of the new screening programme. In order to generate estimates of endoscopy capacity requirement for the screening strategies it is necessary for the model to make predictions which relate to the current and future population of England. Endoscopy capacity requirements in years one to five will be affected by (1) the changing age distribution over time. For example, there will be more 55 year olds in future years than in 2016 and (2) lower disease prevalence in subsequent years due to more cancers and adenomas being screen-detected in initial years. Hence we model a population of persons aged 45-80 with an age distribution of the 2016 England population for the remainder of their lifetime. This is implemented by generating predictions for a series of cohorts for ages 45,46,…,75. For the cohort of age 'a' modelling starts from age 30 but the number of persons in the cohort at age ‘a’ matches that of the 2016 England population. For the years before age ‘a’ we model the current screening strategy (biennial gFOBT 60-74) to represent past screening and for the years for age ‘a’ onward we model the proposed new screening strategy to represent the future. We note that the current screening programme is bowel scope age 55 and biennial gFOBT ages 60-74 with the bowel scope currently rolled out to approximately 30% of the population. When estimating expected resource use in years 1-5 we consider that we are changing from a strategy of gFOBT biennial ages 60-74 to the proposed strategy.

Endoscopy capacity within the BCSP comprises: screening referral colonoscopy, bowel scope and surveillance colonoscopy. There is considerable uncertainty in the model predictions of surveillance colonoscopy (see validation) and capacity for bowel scope and colonoscopy are different so this analysis focused on the number of screening referral colonoscopies.

To summarise to generate estimates of expected lifetime costs, benefits and Net Monetary Benefit (NMB) for a single cohort of age 50. We generate estimates of year 1 endoscopy capacity requirements using the whole population model run for the 2016 England population receiving the current screening in the past and the

proposed strategy in the future. To determine the optimal strategy we consider expected costs, benefits and screening referral colonoscopy requirements in year 1.

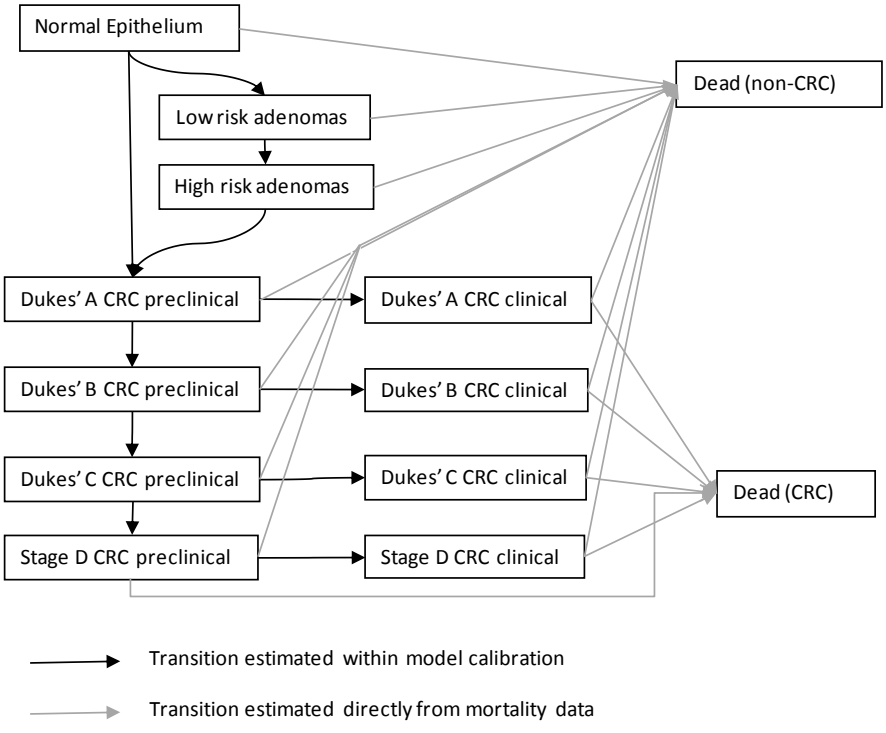
5.2 Colorectal cancer natural history model

The ScHARR model simulates colorectal cancer natural history using a set of calibrated parameters. Parameters were not recalibrated for this analysis and have not changed since the 2011 reappraisal therefore the methods behind calibration are described here in brief only. Further details can be found in Appendix A.

Health States

The existing ScHARR bowel cancer screening model is a state transition model that simulates the life experience of a cohort of 30 year old individuals in the general population of England with normal epithelium through to the development of adenomas and CRC and subsequent death. The model is composed of a series of health states defined according to an individual's true underlying histological state. CRC is divided into eight health states which describe the Dukes' stages A-D and whether or not the CRC has been clinically diagnosed: preclinical/clinical, whilst health states for low-risk and intermediate/high-risk adenomas as defined by the current British Society of Gastroenterology (BSG) guidelines for endoscopic surveillance following adenoma removal [29] are also included. The "high risk adenomas" health state includes persons with at least 3 small adenomas or at least one adenoma of size >1cm. The "low-risk adenomas" health state includes persons with 1-2 small (<1cm) adenomas. These health states correspond to those used to determine an individual's surveillance strategy, so this approach eases the modelling of surveillance. The health states and transitions included within the natural history model are shown in Figure 19.

Figure 19: Diagram of Model Structure



Natural history model calibration method

The probability of transition from one health state to another cannot be directly measured in the population and therefore must be calibrated against known data about CRC incidence, adenoma prevalence and screening outcomes. Model calibration uses the Metropolis Hastings (MH) algorithm in the methods described by Whyte et al [30]. The aim of the calibration is to obtain parameter sets whose predictions are close to the observed data.

Some new data relating to screening outcomes has come available since the 2011 screening options reappraisal. However, for a variety of different reasons this was unsuitable to use for recalibration purposes. A description of the new data, how it compares to the old data and the reasons for not using it to update the model calibration are described in full in Appendix B.

It is reasonable to assume that the rates of adenoma development and progression will not change over time. However, it is possible that symptomatic presentation rates may change over time (with increasing symptom awareness and access to diagnostics). This possibility was explored in a sensitivity analysis.

A full list of parameters obtained through the 2011 calibration and used in the current analysis is shown in Table 3.

Table 3: Model calibration results: best fitting parameter set and 95% percentiles

Parameter	Maximum a posteriori estimate, (95% percentiles)
Annual transition probabilities	
Normal epithelium to LR adenomas - age 30	0.021 (0.020, 0.022)
Normal epithelium to LR adenomas - age 50	0.020 (0.019, 0.021)
Normal epithelium to LR adenomas - age 70	0.045 (0.029, 0.047)
Normal epithelium to LR adenomas - age 100	0.011 (0.005, 0.031)
LR adenomas to high risk adenomas - age 30	0.009 (0.007, 0.014)
LR adenomas to high risk adenomas - age 50	0.008 (0.006, 0.008)
LR adenomas to high risk adenomas - age 70	0.008 (0.008, 0.010)
LR adenomas to HR adenomas - age 100	0.004 (0.003, 0.010)
HR adenomas to Dukes A CRC - age 30	0.029 (0.004, 0.031)
HR adenomas to Dukes A CRC - age 50	0.025 (0.022, 0.026)
HR adenomas to Dukes A CRC - age 70	0.054 (0.050, 0.058)
HR adenomas to Dukes A CRC - age 100	0.115 (0.084, 0.118)
Normal epithelium to CRC Dukes A	0.00004 (0.00003, 0.00008)
Preclinical CRC: Dukes A to Dukes B	0.51 (0.50, 0.89)
Preclinical CRC: Dukes B to Dukes' C	0.69 (0.50, 0.70)
Preclinical CRC: Dukes C to Stage D	0.71 (0.59, 0.73)
Symptomatic presention with CRC Dukes A	0.04 (0.04, 0.07)
Symptomatic presention with CRC Dukes B	0.18 (0.12, 0.18)
Symptomatic presention with CRC Dukes C	0.37 (0.30, 0.39)
Symptomatic presention with CRC Dukes D	0.74 (0.65, 0.92)
Screening test characteristics	
gFOBT Sensitivity for LR adenomas	0.009 (0.009, 0.010)
gFOBT Sensitivity for HR adenomas	0.124 (0.121, 0.125)
gFOBT Sensitivity for CRC	0.242 (0.233, 0.253)
gFOBT Specificity age 50	0.994 (0.991, 0.995)
gFOBT Specificity age 70	0.973 (0.972, 0.978)
FS Sensitivity for LR adenomas	0.219 (0.212, 0.229)
FS Sensitivity for HR adenomas	0.710 (0.685, 0.742)
FS Sensitivity for CRC	0.617 (0.612, 0.741)

Mortality

As CRC survival rates have been observed to increase over time the CRC survival data was updated for this analysis. CRC mortality at one and three years by age and stage of diagnosis was obtained from the International Cancer Benchmarking Partnership [31], which provides survival data for a range of cancer types in several different countries including the UK. Previously, this was combined with estimates of three and five year survival by stage from the National Cancer Intelligence Network (NCIN) [32]. However, NCIN estimates have not been updated, therefore more recent estimates of one and five year survival by stage from CRUK were used [7]. Five year survival by age and stage was estimated from one year data by assuming that the ratio of five to one year survival would not change by age.

It was assumed that all those surviving for five years would no longer be at risk from CRC mortality. In the model, those diagnosed with CRC are split into fatal and non-fatal CRC health states according to the proportions given by the five year survival data. Those with non-fatal CRC are assumed to die only from other causes, whereas those with fatal CRC die at an age and stage-dependent rate calculated from the survival data.

To model deaths from causes other than CRC, all-cause mortality rates were obtained from the interim life tables for the UK 2012-2014 from the Office of National Statistics [33]. These include deaths from CRC, and therefore other-cause mortality rates were calculated by subtracting the proportion of deaths due to CRC at

each age from all-cause mortality. Data on the proportion of deaths due to CRC was obtained from the Office of National Statistics (ONS), deaths by age, sex and underlying cause of mortality, 2014 [34]. Deaths due to ICD code C18 (malignant neoplasm of the colon) and C19-21 (Malignant neoplasm of rectosigmoid junction, rectum and anus) were included in the total for CRC deaths. This slightly overestimates the total numbers of deaths due to CRC as it includes anal cancer; however, this is a rare cancer accounting for only 1% of total cancer cases. Deaths due to CRC cancer were divided by the total number of death registrations in this period to obtain the proportion of deaths due to CRC and thereby other cause mortality rates.

There is some mismatch between the data used to calculate mortality, as the CRC survival data, ONS death certificate data, life tables and the CRC incidence data used in the model all come from different years. CRC survival has improved dramatically in recent years due to treatment improvements, whilst CRC incidence has also changed, in part due to the BCSP. This means that there is some uncertainty in the estimates of current and particularly future CRC mortality. Further investigation of this issue was carried out as part of model validation and is reported in the following section.

5.3 Model Parameters

5.3.1 Costs

Cost of screening programme

Screening programme costs were taken from the existing ScHARR bowel cancer screening model, which used costings from the Southern screening hub [10]. Composite screening costs were inflated from 2008/09 values to 2014/15 values using the Hospital and Community Health Services (HCHS) pay and prices index [35].

The FIT cost-effectiveness analysis recently commissioned by the NSC uses an estimate of gFOBT and FIT screening costs derived from a more recent analysis of Southern screening hub costs from Katy Reed [4, 36]. These estimates are considerably lower than the ScHARR values, but it is unclear how the differences have arisen. Some extra costs were included in the ScHARR analysis such as costs of the telephone helpline and appointments for follow-up of positive results. A sensitivity analysis was performed in which the Reed values were used in place of the ScHARR values. Separate costs for normal or positive results were not stated in the FIT cost-effectiveness study and so were assumed to be the same.

Table 4: Screening Costs derived from the Southern screening hub

Procedure	ScHARR Costing Analysis [10]		Reed Costing Analysis [4]
	Previous Cost (2008/9)	Inflated Cost (2014/15)	Inflated Cost (2014/15) for sensitivity analysis
Cost of gFOBT screen (non-compliers)	£2.03	£2.23	£0.83
Cost of gFOBT screen (normal result)	£3.36	£3.69	£2.03
Cost of gFOBT screen (positive result)	£6.41	£7.04	£2.03
Cost of FIT screen (non-compliers)	£6.43	£7.06	£1.66
Cost of FIT screen (normal result)	£7.37	£8.09	£5.14
Cost of FIT screen (positive	£10.67	£11.71	£5.14

result)			
Cost of specialised screening practitioner appointment for positive results (gFOBT & FIT)	£5.53	£6.07	£10.59
Cost of BS screen excl. BS exam (non-compliers)	£5.02	£5.51	NA
Cost of BS screen excl. BS exam (not referred to COL)	£6.01	£6.60	NA
Cost of BS screen excl. BS exam (referred to COL)	£14.84	£16.29	NA

Cost of colonoscopy, bowel scope and CTC

Evidence on the costs of colonoscopy and BS, with and without polypectomy is available from the 2014/15 NHS reference costs [37]. Endoscopic procedures may be carried out as outpatient appointments or as day case appointments, but the ratio of outpatient procedures to day case procedures for screening follow-up is unknown. For cost purposes it is assumed that all endoscopic procedures are carried out as day cases, given that the total number of recorded outpatient procedures in the NHS reference costs is small.

Table 5: Endoscopy Costs

Procedure	Cost	Code	Source
Specialised Screening Practitioner following gFOBT of FIT	£32.50	10.4	Unit Costs of Health and Social Care 2014/15 [35]
Specialised Screening Practitioner following BS	£16.25	10.4	Unit Costs of Health and Social Care 2014/15 [35]
Diagnostic Colonoscopy	£518	FZ51Z	NHS Reference Costs 2014/15 [37]
Diagnostic Colonoscopy with Biopsy	£600	FZ52Z	NHS Reference Costs 2014/15 [37]
Diagnostic Bowel Scope	£430	FZ54Z	NHS Reference Costs 2014/15 [37]
Diagnostic Bowel Scope with Biopsy	£484	FZ55Z	NHS Reference Costs 2014/15 [37]
Histopathology and Histology	£29	DAPS02	NHS Reference Costs 2014/15 [37]

Polypectomy will always involve a biopsy. It is unclear whether the NHS reference costs for endoscopy include the pathology costs associated with biopsy. For the purposes of this analysis we assume that pathology cost will be incurred on top of the procedure costs. The NHS reference cost for histopathology is £29 and this cost has been used in the model for both cancer and adenoma. The mean number of adenomas requiring pathology is assumed to be 1.9 based on data reported from the National Polyp Study by Winawer et al [38].

In 2014 ScHARR updated the reappraisal using current endoscopy costs. The study concluded that costs were in fact similar but it is important to differentiate between: 'Bowel scope cost', 'Total screening costs' and 'Screening cost per screening attendee' [39].

Data from the BCSP for 2014/15 indicates that CT colonography is used instead of colonoscopy as a first line follow up for on average 4.5% of screening patients testing positive in the initial screen [1]. The proportion of individuals referred for CTC increases with age from 3.2% of individuals aged 60-61 to 6.1% of individuals aged between 72 and 74. The age-dependent proportion of individuals referred to CTC was incorporated into the model as shown in Table 6.

Table 6: Age-dependent referral to CTC as a proportion of total referrals for 2014/15 from the BCSP

Age	Total Diagnostic Test Referrals	Total CTC Referrals	Proportion CTC Referrals
60-61	8,087	255	3.2%

62-63	8,222	304	3.7%
64-65	8,877	399	4.5%
66-67	9,380	415	4.4%
68-69	8,106	381	4.7%
70-71	6,668	354	5.3%
72-74	6,819	414	6.1%
TOTAL	**56,159**	**2,522**	**4.5%**

NHS Reference Costs 2014/15 state the costs of Computerised Tomography scanning of one, two, three or more than three areas [37]. In line with a recent Health Technology Assessment [40], a cost of £135 relating to CT scan of more than three areas has been used in the model.

Cost of treating screening complications

The cost of treating a perforation due to colonoscopy, BS or CTC was assumed to be £1,273 from 2014/15 NHS reference costs (weighted mean of major large intestine procedures, 19 years and over) [37]. The cost of treating hospitalised bleeding following flexible sigmoidoscopy or colonoscopy was assumed to be £475 (weighted mean of gastrointestinal bleed with multiple interventions, single intervention or without interventions). Both complications were assumed to be treated as non-elective short stay procedures.

Lifetime costs of treating colorectal cancer

The lifetime costs of treating CRC by age and Dukes' stage at diagnosis were taken from the EEPRU report on early awareness interventions for CRC [41], which estimated costs using a CRC whole disease model [42]. Costs were inflated from 2012/13 to 2014/15 using the Hospital and Community Health Services (HCHS) pay and prices index [35]. Costs are shown in Table 7.

Table 7: Costs of treating colorectal cancer by age and Dukes' stage of diagnosis (2014/15)

Age at diagnosis	Dukes' A	Dukes' B	Dukes' C	Dukes' D
40-49	£8,865	£8,851	£14,672	£11,853
50-59	£5,784	£7,104	£9,814	£8,550
60-69	£4,682	£5,419	£7,351	£6,591
70-79	£3,218	£3,498	£4,542	£4,420
80-100	£1,397	£1,566	£1,580	£818

The costs reported above were chosen to be the base case in the analysis due to being relatively recently estimated (thereby incorporating recent developments in treatment) and due to their stratification of costs by age as well as stage. Including age stratification is particularly important when assessing the differential cost-effectiveness of screening strategies that differ between age groups.

There are several other sources of CRC treatment costs. Firstly, the FIT cost-effectiveness analysis recently performed by Murphy & Gray uses a set of much higher, stage but not age-specific costs that are inflated from the ScHARR 2011 screening options reappraisal [10, 11]. These costs were originally produced for a 2009 report on the costs and benefits of bowel cancer service developments [43] (Table 8). These costs are much higher than the costs reported in Table 7.

A second set of costs were derived from the recent INCISIVE report [44], which estimates costs of treating a range of different cancers. Composite costs of CRC treatment by stage were estimated assuming costs excluded diagnostic costs (which are costed separately in the model), but included costs of treatment for relapse. The incisive report does not state the sources and years from which its unit costs are derived, so it was

assumed that all costs were from 2012/13. For the model analysis, costs were inflated to 2014/15 using the HCHS pay and prices index [35]. These costs are fairly close in value to the age and stage dependent costs shown in Table 7. A third set of CRC treatment costs are reported in a recent costing analysis from Hall et al (2015) [45]. This study recorded costs for 15 months following diagnosis of 145 patients with Dukes' A, B or C stage CRC. These costings were not used in sensitivity analysis as no Dukes' D costing was reported and individuals were not representative of CRC patients as those who died or relapsed were excluded from the analysis. They fall between the INCISIVE and Murphy & Gray costs in magnitude.

Finally, Laudicella and others have recently published a costing study using population based, patient level data to estimate the costs of treating four different types of cancer, including colorectal cancer, in each year following diagnosis [46]. The study is limited in that it groups early stage (Dukes A & B) and later stage (Dukes C & D), and groups individuals aged 18-64 or 65+, rather than providing data on a wider range of ages. However it has the advantage in that it reports costs for up to nine years following diagnosis which should include most costs of relapse. These costs differ from the others presented above in that they include all healthcare costs incurred by individuals and not those specifically incurred through colorectal cancer treatment. This has the advantage that healthcare costs indirectly attributed to cancer are included (for example extra care required to treat unrelated conditions in individuals with cancer), but the disadvantage that completely unrelated healthcare costs that would also be incurred in individuals without cancer are also included. The study does not estimate healthcare costs in individuals without cancer as comparison, but does estimate healthcare costs for the three years prior to cancer diagnosis. This means that cancer-related healthcare costs over the nine years following diagnosis could be estimated by subtracting the three-years pre-diagnosis costs from the costs for each year post-diagnosis (Table 8). It was assumed that all diagnostic costs would be incurred in the year prior to diagnosis and therefore would not be included in the estimates. Year 2-9 costs were discounted by 3.5% and the total over years 1-9 was inflated to 2014/15 values. Overall, year one only costs are slightly less than Murphy & Gray costs, whilst year 1-9 costs are much higher than any of those discussed previously, which is likely to be due to including indirect costs over the nine year time horizon. It is also notable that the reduction in CRC treatment costs in older age groups in the EEPRU cost estimates is less evident in the Laudicella year 1-9 estimates, particularly for early stages, which may indicate that whilst older individuals incur fewer direct treatment costs than younger individuals, they may incur more indirect cancer costs.

Table 8: Alternative sources of costs of treating colorectal cancer by Dukes' stage of diagnosis, all inflated to 2014/15 values.

	Dukes' A	Dukes' B	Dukes' C	Dukes' D
Murphy & Gray Costs	£13,469	£18,532	£25,416	£27,796
INCISIVE Costs	£3,768	£8,357	£13,554	£12,089
Hall Costs	£9,303	£12,373	£16,969	Not Supplied
Laudicella Costs (<65 Yr1)	£15,577		£20,115	
Laudicella Costs (65+ Yr1)	£14,556		£15,885	
Laudicella Costs (<65 Yr1-9)	£31,218		£44,086	
Laudicella Costs (65+ Yr1-9)	£32,377		£37,371	

Given the large variation between CRC treatment costs estimates from different studies, sensitivity analysis was performed using the INCISIVE costs. Note that for simplicity the model implements all CRC treatment costs in the first year following diagnosis.

5.3.2 Screening test characteristics

Screening test characteristics (sensitivity and specificity) were calculated from screening detection rates and estimated underlying disease prevalence. Estimates of test sensitivity and specificity were assumed to not vary by age..

In phase 2, this method will be updated to incorporate age, gender, location and cohort differences where data allows. Adenoma prevalence varies by gender and there is also evidence that screening test characteristics also vary by gender.[47]

For consistency it is important that the populations for the screening data are the same with respect to age distribution, gender, and screening history. In this analysis detection rates and test characteristics were estimated for persons aged 60 who had not been previously screened.

It is important that the adenoma classification definitions used are the same. In this analysis 'high risk adenomas' are defined to be those defined as intermediate/high risk in the BCSP: high-risk adenomas: (≥5 adenomas or ≥3 adenomas at least one of which was ≥1 cm) or intermediate-risk adenomas: (3–4 small adenomas or at least one ≥1 cm). In this analysis 'low risk adenomas' are defined as persons with 1-2 small (<1cm) adenomas.

It is important that the populations considered are from the same setting (i.e. trial or pilot) as trial/observational populations may have different underlying prevalence and/or detection rates. For this analysis data from the NHS BCSP was considered for gFOBT, FIT and BS. In addition, these data were compared to other data from the literature including the UKFSST, and the Italian flexible sigmoidoscopy trial.

Estimated disease prevalence

Estimates of underlying disease prevalence were taken from the ScHARR model calibration. [30]

Table 9: Disease prevalence estimates from the model calibration

Disease prevalence from model calibration				
Age	Low risk adenomas	High risk adenomas (intermediate of high risk BCSP classification)	Undiagnosed CRC	No adenomas or CRC
55	34%	3.0%	0.3%	63%
60	37%	3.7%	0.5%	58%
65	39%	4.0%	0.7%	56%

As colonoscopy has a very high sensitivity colonoscopy screening data is also useful to estimate disease prevalence. Data from the German colonoscopy screening programme (over 1.2 million persons in the 55-64 age group) found similar disease prevalence to the above estimates). [47]

Table 10: Detection rates in the German colonoscopy screening programme

Sex, Age, and Birth Cohort Effects in Colorectal Neoplasms. A Cohort Analysis, 2010				
	Detection rates (mean and 95%Cis)			
Ages 55-64	Colorectal Cancer	Any Advanced Neoplasm (	Advanced adenomas	HR adenomas (estimated)
Men	0.77% (0.75%,0.79%)	8.07% (8.00%,8.14%)	7.30% (7.23%,7.37%)	5.45% (5.39%,5.51%)
Women	0.39% (0.37%,0.40%)	4.35% (4.30%,4.39%)	3.96% (3.92%,4.01%)	2.96% (2.92%,3.00%)
Men and Women	0.55% (0.53%,0.56%)	5.91% (5.86%,5.95%)	5.36% (5.32%,5.40%)	4.00% (3.97%,4.03%)

FIT and gFOBT data

For FIT the analysis used the subgroup "Prevalent round of first time invitees only" from the FIT pilot. This subgroup is assumed to consist of persons aged 60 who have not previously been screened.

Data was available for five FIT thresholds (20, 40, 100, 150, 180). A power curve was fitted to the detection rates to allow estimation of detection rates for all FIT thresholds between 20 and 180. The power curve had the best fit of several models considered for both HR adenoma detection rate and false positive rate for both the subgroup and the whole FIT pilot population. There is a large degree of uncertainty in the FIT CRC detection rates, as the number of persons with cancer is just 6. (Note even when considering the whole FIT pilot data set there is still considerable uncertainty with just 73 cancer cases.) Figure 20 shows the data and fitted curves for the detection rates.

Note for FIT20-FIT100 and bowel scope the sensitivity for HR adenomas is higher than sensitivity for CRC. This was also observed for the bowel scope both in the UKFSST and the BCSP data sets. Clinical opinion may find this observation to be implausible; however, it is consistently supported by the data.

Figure 20: Detection rates and false positives from the FIT pilot: fitted curves

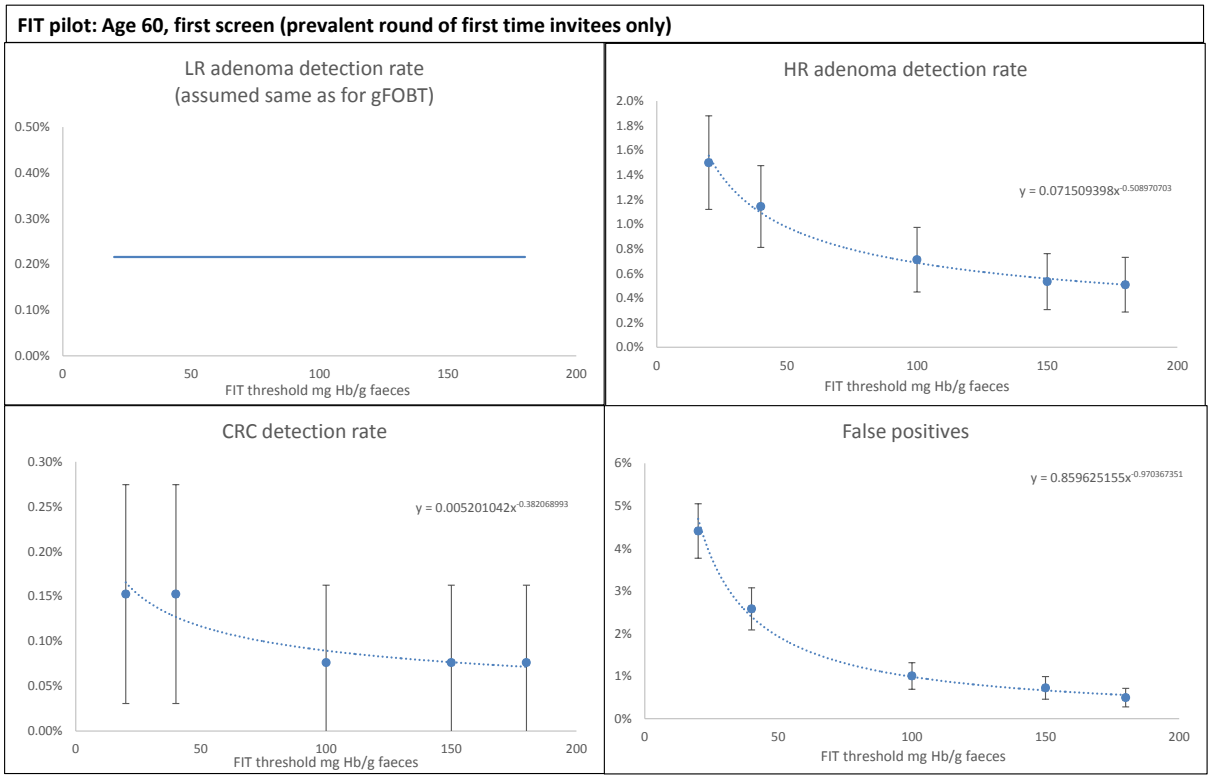


Table 11: Estimated detection rates and test characteristics from the FIT pilot by FIT threshold

FIT pilot: Age 60, first screen								
FIT threshold	**LR adenoma detection rate**	**LR adenoma sensitivity**	**HR adenoma detection rate**	**HR adenoma sensitivity**	**CRC detection rate**	**CRC sensitivity**	**False positives**	**Specificity**
20	**0.22%**	**0.01**	**1.56%**	**0.42**	**0.17%**	**0.33**	**4.70%**	**0.920**
25	0.22%	0.01	1.39%	0.38	0.15%	0.30	3.78%	0.935
30	0.22%	0.01	1.27%	0.34	0.14%	0.28	3.17%	0.946
35	0.22%	0.01	1.17%	0.32	0.13%	0.27	2.73%	0.953
40	**0.22%**	**0.01**	**1.09%**	**0.30**	**0.13%**	**0.25**	**2.40%**	**0.959**
45	0.22%	0.01	1.03%	0.28	0.12%	0.24	2.14%	0.963
50	0.22%	0.01	0.98%	0.27	0.12%	0.23	1.93%	0.967
55	0.22%	0.01	0.93%	0.25	0.11%	0.22	1.76%	0.970
60	0.22%	0.01	0.89%	0.24	0.11%	0.22	1.62%	0.972
65	0.22%	0.01	0.85%	0.23	0.11%	0.21	1.50%	0.974
70	0.22%	0.01	0.82%	0.22	0.10%	0.20	1.39%	0.976
75	0.22%	0.01	0.79%	0.22	0.10%	0.20	1.30%	0.978
80	0.22%	0.01	0.77%	0.21	0.10%	0.19	1.22%	0.979
85	0.22%	0.01	0.75%	0.20	0.10%	0.19	1.15%	0.980
90	0.22%	0.01	0.72%	0.20	0.09%	0.19	1.09%	0.981
95	0.22%	0.01	0.70%	0.19	0.09%	0.18	1.04%	0.982
100	**0.22%**	**0.01**	**0.69%**	**0.19**	**0.09%**	**0.18**	**0.99%**	**0.983**
105	0.22%	0.01	0.67%	0.18	0.09%	0.18	0.94%	0.984
110	0.22%	0.01	0.65%	0.18	0.09%	0.17	0.90%	0.985
115	0.22%	0.01	0.64%	0.17	0.08%	0.17	0.86%	0.985
120	0.22%	0.01	0.63%	0.17	0.08%	0.17	0.83%	0.986
125	0.22%	0.01	0.61%	0.17	0.08%	0.16	0.79%	0.986
130	0.22%	0.01	0.60%	0.16	0.08%	0.16	0.76%	0.987
135	0.22%	0.01	0.59%	0.16	0.08%	0.16	0.74%	0.987
140	0.22%	0.01	0.58%	0.16	0.08%	0.16	0.71%	0.988
145	0.22%	0.01	0.57%	0.15	0.08%	0.16	0.69%	0.988
150	**0.22%**	**0.01**	**0.56%**	**0.15**	**0.08%**	**0.15**	**0.66%**	**0.989**
155	0.22%	0.01	0.55%	0.15	0.08%	0.15	0.64%	0.989
160	0.22%	0.01	0.54%	0.15	0.07%	0.15	0.62%	0.989
165	0.22%	0.01	0.53%	0.14	0.07%	0.15	0.61%	0.990
170	0.22%	0.01	0.52%	0.14	0.07%	0.15	0.59%	0.990
175	0.22%	0.01	0.52%	0.14	0.07%	0.14	0.57%	0.990
180	0.22%	0.01	0.51%	0.14	0.07%	0.14	0.56%	0.990
gFOBT	0.22%	0.01	0.4%	0.11	0.11%	0.21	1.01%	0.983

The definition of False positives includes positives with no LR/HR adenomas or CRC
LR adenoma detection rate assumed same as for gFOBT as no data available from FIT pilot.
HR adenomas are those which receive surveillance within the BCSP (classified as intermediate or high risk).

Data on gFOBT screening is also available from the BCSP. This data set consists of over 445,000 adequately screened 60 year olds.

BCSP gFOBT: round 1, age 60	
LR adenoma detection rate	0.2% (0.2%,0.2%)
LR adenoma sensitivity	0.6% (0.5%,0.6%)
HR adenomas detection rate	0.4% (0.3%,0.4%)
HR adenoma sensitivity	9.7% (9.3%,10.2%)
CRC detection rate	0.1% (0.1%,0.1%)
CRC sensitivity	16.8% (15.1%,18.5%)
False positives	0.7% (0.6%,0.7%)
1-specificity	1.1% (1.1%,1.2%)

We note that specificity calculations relate to persons without LR/HR adenomas or CRC.

Persons without adenomas of CRC may have other conditions which may explain why 1-specificity is higher the and LR adenomas sensitivity.

In the 2011 screening options appraisal [10, 11] only one FIT threshold was modelled through calibration (20µg/g), due to a lack of data on other thresholds. However, results from the English pilot allow for the incorporation of multiple thresholds within the economic evaluation. In the recent FIT cost-effectiveness analysis by Murphy & Gray (2015) [4], which used data from the FIT pilot [2] to calculate FIT sensitivity and specificity at each FIT screening cut-off. We note that our method results in much lower estimates for test

sensitivity to cancer compared to values reported by Murphy & Gray (2015) [4] which ranged from 57.5% for FIT 20 μg/ml to 29.5% for FIT 180 μg/ml.

BCSP Bowel Scope

For the bowel scope analysis, data from the NHS BCSP was used. This data includes approximately 240,000 bowel scope procedures undertaken in persons aged 55. The detection rates for age 60 were estimated from this data using the relative detection rates observed in the UKFSST for which we have age categorised data for persons of ages 55-65. For bowel scope screening LR adenomas may be identified at BS or at referral colonoscopy. The NHS BCSP data only contains information about those persons detected with LR adenomas at colonoscopy hence the more detailed UKFSST data was used to supplement this. In both the UKFSST data and the BCSP data the detection rate for LR adenomas at colonoscopy was just over 1% however, the UKFSST data suggests a significant number of LR adenomas (approximately 8%) are also detected at BS (in persons not referred on to colonoscopy). We note that the test characteristics for bowel scope relate to the entire screening episode i.e. 'bowel scope plus index colonoscopy for those who are referred and attend'.

The UKFSST is also included here for comparative purposes. For the model base case the BCSP BS data was used as it includes a higher number of bowel scope procedures and is more likely to reflect how the bowel scope screening programme performs in practice. Improvements in bowel scope quality could result in higher HR adenoma and CRC sensitivity as observed in the UKFSST and this was explored within a scenario analysis.

For persons aged 60 we know approximately that: (1) 69% of CRC incidence is distal; (2) 70% of persons with adenomas have some distal adenomas; (3) 10% of the CRC detected within the UKFSST was proximal. If BS detected 95-98% of distal CRC (colonoscopy sensitivity) then BS may be expected to detect 72-74% of all CRC (68% distal + 6% proximal). Hence we hypothesise that 72-74% is an upper bound on BS sensitivity to CRC. This is just slightly higher than the sensitivity estimate from the UKFSST.

Table 12: Bowel Scope screening test characteristics estimates

	BCSP Bowel Scope **Age 60 (estimated using UKFSST data)**	**UKFSST** **Age 60, first screen**
LR adenomas detection rate LR adenomas sensitivity	9.0% (8.6%,9.4%) 24.1% (23.0%,25.1%)	9.0% (8.6%,9.4%) 24.1% (23.0%,25.1%)
HR adenomas detection rate HR adenomas sensitivity	2.5% (2.4%,2.5%) 67.7% (66.0%,69.4%)	2.9% (2.6%,3.1%) 78.1% (71.9%,84.4%)
CRC detection rate CRC sensitivity	0.2% (0.2%,0.2%) 43.7% (40.0%,47.5%)	0.3% (0.3%,0.4%) 67.9% (52.0%,83.8%)
False positives rate Specificity	NA assumed 100%	NA assumed 100%

Other data sources

Literature reviews were undertaken to identify other data sources for test characteristics. Rapid searches were undertaken around key words for for FIT or gFOBT together with filters for colon cancer, diagnostics and reviews. In total, 19 reviews were found for FIT and 77 for gFOBT. Most of these were not relevant, however several systematic reviews were identified which examined the sensitivity and specificity of screening tests, from clinical trials comparing each test against the standard of colonoscopy. FIT20 screening was estimated to have an average sensitivity for CRC of about 78%, which is much higher than that estimated from the FIT pilot, and an average sensitivity for advanced adenomas ranging between 22% and 34%. Note that advanced adenomas make up only a subset of high risk adenomas so it is unsurprising that this figure is lower than that estimated from the FIT pilot for high risk adenomas. Less data was found to inform gFOBT test characteristics, with only one small, fairly representative trial finding sensitivity to CRC of 31% and sensitivity to advanced adenomas of 14%, both of which are considerably higher than was estimated from BCSP data. The review indicates that in general, trials give higher estimates of screening sensitivity compared to estimates derived

from screening pilots or programmes. This is unsurprising as trial populations are likely to be unrepresentative of the general population.

Summary

Table 13 summarises the screening test characteristics estimates used within the model for FIT, BS and gFOBT.

Table 13: Summary of screening test characteristic estimates

	FIT pilot threshold 120 mg Hb/g faeces Age 60, first screen	**BCSP Bowel Scope Age 60 (estimated using UKFSST data)**	**UKFSST Age 60, first screen**	**BCSP gFOBT Age 60, first screen**
LR adenomas detection rate	0.2% (0.1%,0.4%)	9.0% (8.6%,9.4%)	9.0% (8.6%,9.4%)	0.2% (0.2%,0.2%)
LR adenomas sensitivity	0.6% (0.3%,1.0%)	24.1% (23.0%,25.1%)	24.1% (23.0%,25.1%)	0.6% (0.5%,0.6%)
HR adenomas detection rate	0.6% (0.4%,0.9%)	2.5% (2.4%,2.5%)	2.9% (2.6%,3.1%)	0.4% (0.3%,0.4%)
HR adenomas sensitivity	17% (11%,24%)	67.7% (66.0%,69.4%)	78.1% (71.9%,84.4%)	9.7% (9.3%,10.2%)
CRC detection rate	0.1% (0.0%,0.2%)	0.2% (0.2%,0.2%)	0.3% (0.3%,0.4%)	0.1% (0.1%,0.1%)
CRC sensitivity	17% (4%,39%)	43.7% (40.0%,47.5%)	67.9% (52.0%,83.8%)	16.8% (15.1%,18.5%)
False positives rate	0.8% (0.6%,1.1%)	NA	NA	0.7% (0.6%,0.7%)
1-Specificity	1.4% (1.0%,1.9%)	assumed 100% specific	assumed 100% specific	1.1% (1.1%,1.2%)

Colonoscopy characteristics

Colonoscopy characteristics were estimated using a systematic review of studies of tandem colonoscopies was undertaken by Van Rijn et al [48]. For adenomas of size <10mm, 167 out of 711 were missed, and for adenomas of size >10mm, 2 out of 96 were missed. A study by Bressler et al estimated that out of 12,496 cases of CRC, 430 were missed at colonoscopy (2%) [49]. Based on these studies, sensitivity to low risk adenomas was assumed to be 77%, sensitivity to high risk adenomas or CRC 98%, and specificity was assumed to be 100%.

CTC characteristics

Data on difference in detection rates for gFOBT positives receiving CTC compared to colonoscopy is available however this cannot be used to derive CTC test characteristics as the screen positive cohort who are offered CTC are older and more frail.

The SIGGAR1 study comprised two multicentre, randomised trials comparing CTC with barium enema (BE) and colonoscopy in patients with symptoms suggestive of CRC [50, 51]. The main objective was to establish how CTC compares with BE and colonoscopy for the investigation of patients with symptoms of CRC. Data from the SIGGAR1 trial was used to define CTC characteristics in the model. Published data from the trial indicates that the relative risk of CRC detection with CTC compared to colonoscopy is 0.98, the relative risk of detection of a polyp ≥ 10mm is 0.82, and the combined relative risk (cancer or polyp ≥ 10mm) is 0.89 [50]. In the absence of further data it was assumed that the relative risk of detection of low risk adenomas was the same as that of high risk adenomas (0.82). These relative risks were combined with the colonoscopy sensitivities described above to provide estimates of CTC sensitivity (48% for low risk adenomas, 80% for high risk adenomas, 96% for CRC and 87% for combined cancer or high risk adenoma).

A systematic review of the effectiveness, diagnostic accuracy and harms of CRC screening was recently carried out to inform the US Preventive Services Task Force [52]. The review included seven studies, none from the UK, which estimated the sensitivity and specificity of CTC screening. The weighted mean sensitivity was calculated as 80% for adenomas ≥ 6mm, or 87% for adenomas ≥ 10mm, whereas the weighted mean

specificity was calculated as 88% for adenomas ≥ 6mm, or 91% for adenomas ≥ 10mm. CTC specificity in the model was assumed to be 88%.

Table 14: Diagnostic test characteristics

Characteristic	Value	Source
Colonoscopy Sensitivity (low risk adenomas)	77%	Van Rijn et al 2006 [48]
Colonoscopy Sensitivity (high risk adenomas)	98%	Van Rijn et al 2006 [48]
Colonoscopy Sensitivity (colorectal cancer)	98%	Bresler et al 2007 [49]
Colonoscopy Specificity	100%	Assumption
CTC Sensitivity (low risk adenomas)	48%	Based on relative risk from Atkin et al 2013 [50]
CTC Sensitivity (high risk adenomas)	80%	Based on relative risk from Atkin et al 2013 [50]
CTC Sensitivity (colorectal cancer)	96%	Based on relative risk from Atkin et al 2013 [50]
CTC Specificity	88%	Lin et al 2016 [52]

Test completion rates

The bowel cancer screening pilot 2nd round evaluation reported that 5% of initial FOBTs had 1-4 positive spots (weak positive) so require repeat testing per the NHS BCSP referral algorithm [53]. The study also reported that 0.4% of returned kits were inadequate. 66,264 gFOBTs were completed in phase 1, 2,972 in phase 2 and 2,236 in phase 3 hence the mean number of tests completed per person was 1.08.

Repeat testing will be required for FIT kits which are not returned within a certain period. The period of time in which a test must be returned is unclear, but we assume that a test must be returned within 7-10 days. Approximately 97% of gFOBTs are returned within 7 days and 95% within 5 days, hence the retest rate for FIT was assumed to be 3%. The Italian screening programme reported that 0.6% of persons had an inadequate test (due to incorrect sampling by the subject) [19].

The bowel scope screening trial reported that out of 40621 examinations undertaken, 2145 (5%) required repeating, and out of these 1306 (3%) were repeated on the same day and 839 (2%) were repeated on a later day [54]. It was assumed that BS examinations repeated on the same day incurred no additional costs and that if the examination was repeated on a later day then the cost of an additional BS examination would be incurred.

Out of a total of 32,213 screening referral colonoscopies undertaken from Aug 2006 to Aug 2008 in the NHS BCSP, in 1,481 (4.6%) the caecum was not reached, which could be due to pathology encountered, inadequate bowel preparation or patient discomfort. One can assume that majority of the 1,481 will have required a subsequent test which would usually be undertaken on a later day (personal communication from Tom Lee, ERFUHoNT). Persons requiring a subsequent test will receive a colonoscopy, a CT colonography or a barium enema. Data from the NHS BCSP reports that out of 78,311 colonoscopy examinations, 5,453 people (7%) who return within an episode to have another procedure, which could be to remove more adenomas, to complete an incomplete test, or to check an adenoma removal site [1]. Hence a repeat colonoscopy rate of 7% is assumed here.

A study of BCSP data collected between 2006 and 2012 reports that of 1027 suspected polyp or cancer cases detected using CTC, 911 (88.7%) were referred for further investigation before diagnosis could be reached [26]. Further investigation may comprise colonoscopy, or if the patient is unsuitable for colonoscopy (perhaps

due to obstruction of the bowel), then surgery may be performed. A repeat investigation rate of 89% was applied to CTC in the model. It was assumed that all repeat investigations used colonoscopy.

Table 15: Test completion

Test	Mean Number Tests Completed	Source
gFOBT	1.08	Weller et al 2007 [53]
FIT	1.01	Zorzi et al 2009 [19]
	Proportion Incomplete/Repeated	
Bowel scope	2.1%	Atkin et al 2002 [54]
Colonoscopy	7.0%	BCSP [1]
CTC	88.7%	Plumb et al 2013 [26]

5.3.3 Screening attendance and compliance with follow-up and surveillance

Uptake of gFOBT

Uptake is defined as the proportion of individuals invited for screening who give an adequate sample. A small proportion of people opt out from screening for clinical reasons or informed dissent after receiving an invitation, and do not receive a test kit. These individuals are not invited for further screening rounds unless they later opt back in. The number of individuals opting out is not recorded by the BCSP. The majority of individuals who fail to take up screening are sent a test kit but do not return it. The overall uptake rate for financial year 2014/15 is 58.24% according to the BCSP [1]. This includes both prevalent (first time participation) and incident (subsequent invites following a first participation) screening rounds.

When modelling just one round of screening, varying the uptake rate has little effect on cost-effectiveness. This is because costs for non-attenders are very low, so an increase in uptake would lead to a proportional increase in both costs incurred and QALYs gained. In reality, however, the situation is more complex. For example, if we consider two scenarios both associated with 50% uptake: all persons attend 50% of screening rounds; and 50% of persons attend all screening rounds; we see that it is likely that these two scenarios will be associated with differing QALY gains.

The modelling approach taken here partitions the population into subgroups according to their preference for screening: “sometimes attend” and “never attend”. To date, BCSP data includes the entire first four rounds of screening [1], which is insufficient to accurately define the proportion of “never attenders”, given that an individual is likely to be eligible for up to eight screening rounds between the ages of 60 and 74. Within the four rounds of screening performed so far, 66% of invited individuals have been screened at least once and 34% never screened. With each subsequent round of invitations, a diminishing proportion of individuals who have never been previously screened complete an adequate screening test (Table 16).

Table 16: Prevalent gFOBT screening uptake and proportion of individuals never screened in subsequent screening rounds (BCSP 2014/15 [1])

Screening Episode	Prevalent Uptake	Proportion Never Screened	Proportion Screened at least Once
Round 1	49%	51%	49%
Round 2	18%	41%	59%
Round 3	11%	37%	63%
Round 4	8%	34%	66%

The proportion of persons who sometimes attend and the attendance rate for this group was chosen so that the number of persons attending one or more of the first four rounds matches that seen in the current gFOBT screening programme. If someone has previously taken up a screening invitation, then the probability that

they will take up subsequent invitations is much higher than if they have not previously taken up a screening invite. Over the past four screening rounds, the figure for incident screening uptake i.e. the attendance rate for "sometimes attenders" is 85.36%. The proportion of persons who sometimes attend is estimated as the mean overall uptake rate divided by the mean incident uptake rate (0.85/0.58 = 68%). As expected, this is slightly higher than the proportion screened at least once following four rounds of screening shown in Table 16.

Table 17: Participation rates for screening

Test	Parameter	Value	Source
gFOBT	Mean overall uptake rate	58%	BCSP 2014/15 [1]
	Mean incident uptake rate	85%	BCSP 2014/15 [1]
	Proportion screened at least once over all rounds	68%	Estimated from above values
FIT	Mean overall uptake rate	65%	RR compared with gFOBT from Moss et al 2016 [2]
	Mean incident uptake rate	90%	RR compared with gFOBT from Moss et al 2016 [2]
	Proportion sometimes attenders	73%	Estimated from above values
FS	Screening compliance	44%	BCSP 2014/15 [1]
Colonoscopy	Compliance following FOBT	87%	BCSP 2014/15 [1]
	Compliance following FS	96%	Atkin et al 2002 [54]
	Surveillance compliance	82%	BCSP [1]

Uptake varies by gender and age (see section 3.1) but the modelling approach does not currently allow this to be incorporated. This simplification could be considered a limitation of the modelling approach. Further analysis of uptake data would allow a more sophisticated model of uptake to be considered in the future.

Uptake of FIT

Data for uptake of FIT was obtained from the recent UK FIT pilot study [2]. The study compared gFOBT and FIT screening and found that uptake of FIT is consistently higher than uptake of gFOBT, likely due to the ease of use of the FIT test kit. This result is particularly marked in groups that are less responsive to screening but at higher risk of CRC, including men and those who are socioeconomically deprived. Uptake values for gFOBT reported in the study differ slightly from those described above due to the model using more recent BCSP data. To standardise the FIT data from the pilot study to the current BCSP data, relative risks for total uptake compared with gFOBT and incident screening rate compared with gFOBT were calculated and multiplied with the BCSP gFOBT data to derive a total uptake of 65% and an incident screening rate of 90% for use in the model (see calculation example for total uptake in Table 18). As with gFOBT, an estimate of the proportion of "sometimes attenders" has been calculated at 73% (Table 17).

Table 18: Example of FIT total uptake calculation using FIT pilot [2] and BCSP data [1]

a: gFOBT total uptake in FIT pilot	**0.59**
b: FIT total uptake in FIT pilot	**0.66**
c: Relative Risk for uptake of FIT compared with gFOBT in FIT pilot (=b/a)	**1.12**
d: Total uptake gFOBT in BCSP	**0.58**
e: Estimate of FIT total uptake (=c*d)	**0.65**

Uptake of bowel scope

Data on uptake of BS was obtained from the BCSP for the financial year 2014/15 [1]. In total 77,149 individuals were invited for BS screening, of which 40,974 responded but only 34,265 attended, resulting in an uptake rate

of 44.41%. Given that BS is a one-off screen at age 55 that has been introduced fairly recently, it was not relevant to model incident or prevalent uptake.

Compliance with follow-up and surveillance colonoscopy

Data from the NHS BCSP reports compliance rates of 87.2% for screening referral colonoscopy or CTC following gFOBT [1]. It was assumed that this would be the same for FIT. Data for follow-up compliance following BS screening was not available from the BCSP and instead was taken from the BS screening trial [54]. This is higher than compliance following FOBT screening at 96.3%, likely due to these individuals already having consented to and undergone a fairly invasive screening procedure. Compliance was assumed to be 82.4% for persons invited for surveillance colonoscopy, in line with data from the BCSP [1]. Compliance for follow-up CTC was assumed to be 99% in line with estimates presented in a study of data from the BCSP.

Complications following endoscopy/CTC

Colonoscopy, bowel scope and CTC procedures are associated with a small risk of bleeding or perforation; and perforation may lead to death. Incidence of hospitalisation for bleeding and perforation following flexible sigmoidoscopy with or without polypectomy are taken from the flexible sigmoidoscopy trial [54]. This trial also reported the rate of perforation for colonoscopy, which were used in previous versions of the model. However these values have been updated in the current version of the model using data from a more recent study of 130,831 patients undergoing colonoscopy in the BCSP [55]. This reports a colonoscopy perforation rate of 0.031% without polypectomy, and 0.091% with polypectomy, with an average of 2.3 polypectomies per patient. The rate of bleeding requiring transfusion (represented in the model as hospitalisation) was 0.04%.

Gatto et al report that the incidence of death subsequent to a perforation within 14 days of a procedure was 4 out of 77 colonoscopic perforations (5.2%) and 2 out of 31 sigmoidoscopic perforations (6.5%) [56]. This study refers to a Medicare population, so the cases may be older and in worse health than the proposed English screening population; however, no alternative reference was identified. Gatto et al also reported that the risk of perforation from BS increased in association with increasing age, but this association has not been modelled here [56].

Risk of perforation following CTC is even lower than for colonoscopy. A rate of 0.02% is assumed, in line with results from a systematic review and meta-analysis of the data [57]. No individuals died following perforation in any of the included studies, so mortality rate following CTC is assumed to be 0%.

Risks of CTC are fairly low and tend to occur in patients with contributing conditions such as inflammatory bowel disease [58]. There is a small risk of bowel perforation, estimated in a recent meta-analysis of 100,000 individuals to be only 0.02% in screening subjects (0.04% if all patients are considered) [57]. Only 0.008% of patients will require surgery due to the CTC process and no deaths were recorded [57]. This is considerably lower than the risk of perforation from colonography. Lifetime risk of radiation-related cancer due to a single CTC scan has been estimated at around 0.05% at age 60, doubled if a chest or abdominal/pelvic scan is also performed. Risk varies by age, being higher in younger people due to their longer lifespan.

Table 19: Complications following Endoscopy/CTC

Complication	Cost	Source
Colonoscopy (without Biopsy) Perforation Rate	0.031%	BCSP (Rutter 2014 [55])
Colonoscopy (with Biopsy) Perforation Rate	0.091%	BCSP (Rutter 2014 [55])
Colonoscopy Probability of Death following Perforation	5.2%	Gatto et al 2003 [56]
Colonoscopy Probability of Hospitalisation for Bleeding	0.04%	BCSP (Rutter 2014 [55])
BS (without Biopsy) Perforation Rate	0.0%	BS UK Screening Trial, 2002 [54]
BS (with Biopsy) Perforation Rate	0.0%	BS UK Screening Trial, 2002 [54]

BS Probability of Death following Perforation	6.5%	Gatto et al 2003 [56]
BS Probability of Hospitalisation for Bleeding	0.03%	BS UK Screening Trial, 2002 [54]
CTC Perforation Rate	0.02%	Bellini et al 2014 [57]
CTC Probability of Death following Perforation	0.0%	Bellini et al 2014 [57]

5.3.4 Utility values

A utility value is a preference weight reflecting the relative value that individuals place on different health states. Here different utility values are used for persons with CRC and for persons without CRC. NICE recommends that utilities should be based upon public preferences (e.g. EQ-5D values) and valued by patients [27]. Given that the focus of the model is comparison of screening strategies at different ages, and that screening may result in earlier detection of CRC (which may also be at an earlier stage) it is also particularly important that age and stage dependent utilities are included in the model. As one of the screening strategies considered is that of not screening, it is also important that a comparison with the health-related quality of life of the general population is considered.

For this study, *de novo* utility estimates were generated, based on a subject's age, whether or not they have CRC, and for those with CRC, whether or not it was at an advanced stage (stage D). The sub-division of CRC into advanced and non-advanced cancers is used as there is a paucity of evidence to derive more refined stage-specific values for CRC. The utility values used for this study are presented in Table 20.

Table 20: Utilities used in the model for the basecase scenario

Age Group	Without CRC	With CRC – stage A-C	With CRC – stage D
30-34	0.9111	0.8679	0.6692
35-39	0.8974	0.8533	0.6579
40-44	0.8835	0.8384	0.6465
45-49	0.8675	0.8216	0.6335
50-54	0.8508	0.8045	0.6204
55-59	0.8326	0.7855	0.6057
60-64	0.8130	0.7653	0.5901
65-69	0.7919	0.7436	0.5734
70-74	0.7696	0.7199	0.5551
75-79	0.7441	0.6943	0.5354
80-84	0.7193	0.6669	0.5142
85+	0.6846	0.6295	0.4854

The evidence sources used to derive these utility values were:

- Pooled data from the Health Survey for England for the years 2003 to 2014 inclusive (excluding years 2007, 2009 and 2013 as no data were collected for these) [59]. This provided age-specific data on health-related quality of life for people with and without cancer, measured using the EQ-5D-3L. It was assumed that the utility values observed for people with cancer would be applicable to people with CRC.
- Results from a systematic review and meta-analysis for CRC studies [60], which enabled results for CRC patients to be broken down into advanced (stage D) and non-advanced (stage A-C) stages.

Full details of the analysis methods undertaken are provided in Appendix D.

There may be a small utility decrement associated with undergoing a screening test; however, such a decrement is likely to only last a short period of time. There is no data available for utility values during a screening test, so no utility decrement due to screening test was included within the modelling.

Disutility values were sought for patients who experience adverse events during polypectomy such as bowel perforation or bleeding. However, we were not able to identify values for disutilities for these events from the literature. As an alternative we estimated values for disutility for bleeding by assuming they would be similar to a major gastrointestinal bleed and used the value from Dorian and colleagues of 0.1511 for two weeks, i.e. a total QALY loss of 0.006 [61]. Values for perforation were assumed to be the same as for stomach ulcer/abdominal hernia/rupture taken from Ara and Brazier [62]. The disutility value was 0.118 for one month, i.e. total QALY loss of 0.010.

5.4 Modelling subgroup risk of CRC incidence and mortality

A subgroup with a higher risk of CRC than the general population (e.g. males) will have a different cancer disease natural history to the general population. The exact way in which the disease natural history model will vary between subgroups with different CRC risk is not known. For example, whether difference is in the rate at which precancerous conditions develop, the rate at which precancerous conditions transition to cancer, or both of these.

Data from the NHS BCSP 2014/2015 shows that compared to the general population males have a higher proportion of both adenomas and CRC detected suggesting a higher rate of adenoma development.

In the absence of other data we make the assumption here that for subgroups with higher CRC incidence the rate of adenoma development is higher but the rate of progression from adenomas to CRC remains unchanged. This was implemented by adjusting the rate of transition from normal epithelium to LR (by the same multiplier for all ages) so that the expected incidence changes. Firstly the model was run applying a range of different relative risk to the 'Normal->low risk adenomas' transition probabilities and the relative change in incidence was recorded in each case. These value were then stored in a table so that the appropriate transition probabilities multiplier could be looked up for the required incidence relative risk.

If the incidence and mortality relative risks were similar this would imply that differences in mortality were as a direct result of differences in incidence (assuming a similar stage distribution of incidence). The mortality relative risks for deprivation are greater than the incidence relative risks so in addition to having higher incidence these subgroups are also associated with poorer survival. The ratio of incidence and mortality relative risks was applied to the mortality rates in the model.

5.5 Repeated and combination screening strategies

A key benefit of economic modelling over and above trial data is the ability to simulate the results for a number of screening strategies for which there are no trial evidence. Several analyses were undertaken to determine what repeated screening strategies are optimal. Analyses were undertaken comparing screening strategies which had the same endoscopy capacity.

For repeated FIT screening strategies the maximum age range we considered was 50-74 years. We restricted the screening strategies considered to those which used the same FIT threshold across all screening ages and those which had a constant screening interval. Strategies which relax these two constraints will be considered as part of phase 2. Screening strategies considered included those with: starting ages between 50 and 60; screening intervals of 1, 2, 3, 4, 5 or 6 years; 3 or more screens; any FIT threshold between 20 and 180.

Strategies which included a one-off bowel scope screen and repeated FIT screening were also considered.

5.6 Model validation

The model was validated in several different ways to check different aspects of the model against other CRC models, trial data and population data to help identify errors and explain any differences. Full details of model validation can be found in Appendix E, but a summary of validations performed and results obtained is given here.

Recent CRC incidence statistics

Model predictions of CRC incidence and mortality were compared against the most recent CRC incidence statistics [7] and ONS death certificate data [34] from 2014. These validations indicated that the model predicts recent CRC incidence fairly accurately. CRC mortality from death certificate data is slightly over-estimated by simulating a no screening scenario and slightly under-estimated by simulating steady state gFOBT roll-out, thereby fairly accurately representing the 2014 status of screening had been taking place for approximately 6 years (BCSP was introduced in 2006-2009).

Previous economic analysis including FIT

Model results were validated against those obtained in the FIT versus gFOBT cost-effectiveness analysis performed by Jacqueline Murphy and Alastair Gray in order to check for inconsistencies between the two models and determine the effect of updating parameters [4]. Whilst the two models are broadly similar, ScHARR model updates have a significant impact on cost-effectiveness results such that comparison of FIT with gFOBT testing in the ScHARR model is highly cost-effective but not cost-saving as found in the Murphy & Gray analysis. This difference arises predominantly due to updates in CRC treatment costs, which are much lower in the ScHARR model, meaning that the reduction in cancer cases seen with FIT screening compared to gFOBT screening saves insufficient incremental costs to outweigh the additional costs of screening. The ScHARR model uses updated data for CRC survival which results in lower expected incremental life years and QALYs.

Long term follow up screening trial data

CRC incidence and mortality results were compared with the 20 year follow-up of the Nottingham randomised controlled trial of gFOBT screening vs no screening to check how closely the model reproduces long-term results [3]. The validation suggests that the model accurately estimates CRC mortality reduction due to screening, but is slightly overestimating gFOBT effectiveness in reduction of cancer incidence, although model findings are within the trial 95% confidence intervals. Mortality estimates were highly dependent upon the year from which mortality data and life tables were taken, indicating the importance of adjusting mortality parameters to reflect the study setting when performing validations.

Secondly, FS model results were validated against the FS trial 11 year and 17 year follow-up data [5]. Model predictions of CRC incidence reductions due to screening were very close to FS data, whilst CRC mortality was slightly over-estimated by the model and the benefits of screening on mortality were underestimated (albeit within 95% confidence intervals). Once again, mortality estimates were highly dependent upon the mortality parameters used. We note that the ScHARR model performed well in validation when compared to the recent validation of the CISNET model to the FS trial data.[6]

Surveillance

Data from the BCSP on number of surveillance colonoscopies carried out was compared with estimates of surveillance colonoscopy usage in the model. The model overestimates surveillance colonoscopy by around two-fold which is a significant discrepancy. The data informing the surveillance model parameters are associated with significant uncertainty. The uncertain parameters include ‘adenoma recurrence rate following polypectomy’ and ‘proportion of adenomas referred for annual/3-yearly surveillance’. The impact of these uncertainties was explored by varying these parameter values however this uncertainty could not entirely explain differences between model predictions and BCSP data. Further validation is required to explore these differences however data from the BCSP to enable this was not available within the timescale of this project.

This issue will be examined as part of more detailed surveillance modelling in Phase 2. As a result of the differences between the ScHARR model predictions and BCSP data the model predicted surveillance colonoscopy estimates presented here should be treated with caution.

5.7 Sensitivity analyses

A series of sensitivity analyses were undertaken to explore the impact of specific uncertainties (both parameter values and modelling assumptions) on model results. For each sensitivity analysis, only the range of screening options defined in the final results tables were analysed.

Discount rate

A scenario analysis in which discount rates for costs and utilities were both set to 1.5% was undertaken.

Costs

A sensitivity analysis around CRC treatment costs was undertaken in which lower treatment costs were applied (obtained from the INCISIVE report). A sensitivity analysis around the cost of bowel scope was undertaken with cost of £150 and £450.

Screening uptake

Sensitivity analyses were undertaken which explored different screening uptake rates. An analysis in which the uptake of FIT was assumed to be the same as the current gFOBT uptake was undertaken. Expert opinion suggested that it is likely that bowel scope uptake will increase over time due to normalisation of the procedure (Personal communication from Wendy Atkin). Current bowel scope uptake is 44%; an analysis with higher bowel scope uptake (55%) was undertaken.

Screening test characteristics

For the model base case the BCSP BS data was used as it includes a higher number of bowel scope procedures and is more likely to reflect how the bowel scope screening programme performs in practice. Improvements in bowel scope quality could result in higher HR adenoma and CRC sensitivity as observed in the UKFSST and this was explored within a scenario analysis. In this scenario analysis bowel scope test sensitivity was higher based on data from UKFSST, and a higher uptake of 55% was also applied.

The base case assumes that screening tests will be independent when used in combination (e.g. FS followed by FIT) or as a repeated test (e.g. biennial FIT). However, it is possible that sensitivity and specificity are reduced in subsequent tests [18]. As the structure of the model makes it difficult to assign different characteristics to repeat tests, a sensitivity analysis was carried out where it was assumed that sensitivity of FIT and gFOBT was 25% lower. A second sensitivity analysis was carried out where in addition to the reduced sensitivity, specificity was also reduced in line with the findings from Kearns et al (2014) [18].

Colorectal cancer natural history model

Symptomatic presentation rates may be changing over time with increased symptom awareness. The model currently uses presentation rates based on pre-screening data (as this data is not confounded by screening). To explore this uncertainty, scenario analyses in which the rates of symptomatic presentation were increased by 5% or by 10% from baseline estimates was undertaken.

Population subgroups

It is known that screening uptake and cancer incidence vary for certain population subgroups. Screening strategies which vary by population characteristics will be explored in Phase 2 of this work programme. An exploratory scenario analysis which considered either an entirely male or entirely female population was

undertaken here to demonstrate the importance of such subgroup differences. Male/female screening uptake rates and colorectal cancer risk were applied for these analyses.

6 Results

6.1 Optimising Cost-effectiveness

The following analyses focus on maximising cost effectiveness which we measure as Net Monetary Benefit (NMB) which is defined as:

incremental QALYs WTP threshold – incremental costs*

We set the WTP threshold to £20,000 per QALY. Results presented are the discounted lifetime total costs (screening, treatment and surveillance costs) and QALYs for the population of England.

It is essential for the reader to understand that the optimal screening strategy will vary depending on what outcome measure you consider. For example, the optimal screening strategy will vary depending on whether you choose to maximise NMB (cost effectiveness), QALYs (effectiveness), CRC incidence reduction or CRC mortality reduction. For example, QALY gains tend to be maximised by screening younger ages (as lives saved are associated with a longer life expectancy) whereas CRC incidence and mortality tend to see the maximum reductions when screening older ages (as disease is more prevalent in older ages). In this report we focus the results on screening strategies which optimise cost-effectiveness.

Outcomes presented are lifetime costs and effects (discounted) for a cohort of 50 year old corresponding to the 2016 population of England. Endoscopy use estimates are annual estimates for the first year of the new screening strategy for the whole population. The economic results for FIT and bowel scope strategies are considered first. Optimal and feasible strategies are then compared, including comparison with the existing gFOBT based strategy. Results of sensitivity analyses are described here but the tables are provided in the appendix.

6.2 Optimal age for a one of bowel scope or FIT screen

What is the optimal age for a one-off Bowel Scope screen?

For a one-off bowel scope, 59 was the optimal age to maximise cost effectiveness, see Table 21. The maximum QALY gain occurs at age 56, the maximum CRC incidence reduction at age 64/65 and the maximum CRC mortality reduction at age 66. A one off bowel scope is associated with both costs and QALY gains. Compared to no screening the ICER for a one-off bowel scope at age 59 was approximately £3,000 per QALY.

Under the sensitivity analysis which used lower CRC treatment costs the ICER was £8,000 per QALY compared to no screening. Under the scenario analysis with higher bowel scope test sensitivity from UKFSST, and higher uptake of 55% the ICER was under £2,000 per QALY and the optimal age was 58. Under a scenario analysis where the cost of bowel scope was £150 one-off bowel scope was cost saving.

Table 21: Optimal age for a one-off bowel scope screen

Screening strategy	Incremental compared to no screening			Lifetime reduction	
	Costs (£m)	QALYs	NMB (£m)	CRC incidence	CRC mortality
Bowel Scope age 55	£41.5m	9,654	£151.5m	7.3%	8.3%
Bowel Scope age 56	£37.1m	**9,655**	£156.0m	7.6%	8.7%
Bowel Scope age 57	£33.0m	9,602	£159.0m	7.9%	9.1%
Bowel Scope age 58	£29.4m	9,497	£160.6m	8.2%	9.5%
Bowel Scope age 59	£26.2m	9,341	**£160.7m**	8.4%	9.8%
Bowel Scope age 60	£22.9m	9,139	£159.9m	8.6%	10.1%
Bowel Scope age 61	£20.3m	8,892	£157.5m	8.8%	10.3%
Bowel Scope age 62	£18.0m	8,605	£154.1m	8.9%	10.5%
Bowel Scope age 63	£16.2m	8,283	£149.5m	9.0%	10.7%
Bowel Scope age 64	£14.6m	7,928	£143.9m	**9.1%**	10.8%
Bowel Scope age 65	£13.4m	7,544	£137.5m	**9.1%**	10.9%
Bowel Scope age 66	£12.5m	7,140	£130.3m	9.1%	**11.0%**
Bowel Scope age 67	£11.8m	6,716	£122.5m	9.0%	10.9%
Bowel Scope age 68	£11.3m	6,277	£114.3m	8.9%	10.8%
Bowel Scope age 69	£11.1m	5,833	£105.5m	8.7%	10.7%
Bowel Scope age 70	**£10.5m**	5,385	£97.2m	8.5%	10.5%

What is the optimal age for a one-off FIT? Does this vary by FIT threshold?

For a one-off FIT, 57 was the optimal age to maximise cost effectiveness regardless of FIT threshold, see Table 22. As for a one-off bowel scope the maximum QALY gain occurs at age 56, the maximum CRC incidence reduction at age 64/65 and the maximum CRC mortality reduction at age 66. A one-off FIT was found to be cost saving and therefore dominates the no screening comparison, with cost savings ranging from £10m to £35m depending on the FIT threshold. Under the sensitivity analysis with lower CRC treatment costs one-off FIT was no longer cost saving and was associated with a cost of £3m-£5m and an ICER of about £500/QALY to £1,000/QALY compared to no screening.

Table 22: Optimal age for a one-off FIT screen with FIT120

Screening strategy	Incremental compared to no screening			Lifetime reduction	
	Costs (£m)	QALYs	NMB (£m)	CRC incidence	CRC mortality
FIT120 age 55	-£12.0m	3,464	£81.2m	2.4%	2.9%
FIT120 age 56	-£12.5m	**3,471**	£81.9m	2.5%	3.1%
FIT120 age 57	-£12.9m	3,459	**£82.1m**	2.6%	3.2%
FIT120 age 58	-£13.1m	3,428	£81.7m	2.7%	3.3%
FIT120 age 59	-£13.3m	3,378	£80.8m	2.8%	3.4%
FIT120 age 60	-£13.5m	3,310	£79.7m	2.9%	3.6%
FIT120 age 61	**-£13.5m**	3,226	£78.1m	2.9%	3.6%
FIT120 age 62	-£13.4m	3,127	£76.0m	2.9%	3.7%
FIT120 age 63	-£13.2m	3,013	£73.5m	3.0%	3.8%
FIT120 age 64	-£12.9m	2,887	£70.6m	**3.0%**	3.8%
FIT120 age 65	-£12.5m	2,750	£67.5m	**3.0%**	3.9%
FIT120 age 66	-£12.0m	2,605	£64.1m	3.0%	**3.9%**
FIT120 age 67	-£11.4m	2,452	£60.5m	2.9%	3.9%
FIT120 age 68	-£10.8m	2,291	£56.6m	2.9%	3.9%
FIT120 age 69	-£10.1m	2,128	£52.6m	2.8%	3.8%
FIT120 age 70	-£9.6m	1,963	£48.9m	2.7%	3.8%

What is the comparative effectiveness of a one-off bowel scope screen compared to a one-off FIT20 screen?

To help the reader understand the relative benefits of bowel scope and FIT, we undertook a comparison of one-off bowel scope/FIT20 at optimal ages. When the analysis used uptake rates from the BCSP we see that Bowel Scope is the most effective but FIT20 is the most cost effective. However, an exploratory analysis in which 100% uptake was assumed for both bowel scope and FIT20 illustrates that bowel scope has the potential to be associated with much higher effectiveness and cost-effectiveness. Under the scenario analysis with higher bowel scope test sensitivity from UKFSST, and higher uptake of 55%, bowel scope was associated with much higher effectiveness and cost effectiveness than FIT20. See Table 23 below.

Table 23: Comparison of a single bowel scope or FIT20 screen at optimal age

Screening strategy	Incremental compared to no screening			Lifetime reduction		Screening referral colonoscopies (year 1)	Screening flexible sigmoidoscopy (year 1)
	Costs (£m)	QALYs	NMB (£m)	CRC incidence	CRC mortality		
Comparison with uptake as observed in the BCSP (BS 44%, FIT 65%)							
Bowel Scope age 59	£26.2m	**9,341**	£160.7m	8.4%	9.8%	9,197	289,081
FIT20 age 57	**-£35.5m**	8,259	**£200.7m**	6.6%	7.8%	26,333	-
Comparison assuming 100% uptake for both Bowel Scope and FIT							
Bowel Scope age 59	£55.1m	**21,033**	**£365.6m**	19.0%	22.0%	20,708	650,878
FIT20 age 57	**-£56.8m**	12,673	£310.2m	10.1%	11.9%	40,405	-
Scenario analysis with higher bowel scope test sensitivity from UKFSST, and higher uptake 55%							
Bowel Scope age 58	£25.4m	14,286	£260.3m	11.6%	14.0%	13,184	372,511

6.3 Optimising repeated FIT screening

Optimal repeated FIT screening in the absence of endoscopy capacity constraints

Without endoscopy constraints the optimal FIT screening strategy is the most intensive strategy of annual screening with FIT20 ages 50-74. This strategy is cost saving.

Under the sensitivity analysis in which repeated FIT screens have a lower sensitivity this strategy remains cost saving. Under the scenario analysis with lower CRC treatment costs 'annual FIT20 ages 50-74' is still the most cost effective but is no longer cost saving with an ICER of just under £5,000 per QALY.

Optimal repeated FIT screening with constrained number of screening referral colonoscopies

For a fixed screening referral colonoscopy capacity we are interested in the following questions:

- *What is the optimal screening age range*
- *What is the optimal screening interval*

- *For a fixed screening age range, is a higher FIT threshold at a shorter screening interval or a lower FIT threshold at longer screening interval preferable?*
- *Is it preferable to screen a small age range intensively (short interval, low FIT threshold) or a larger age range less intensively.*

Analyses were undertaken comparing screening strategies which had the same screening referral colonoscopy requirements.

The following range of screening strategies was considered:

- maximum age range was 50-74 years
- Screening starting ages between 50 and 60
- Screening intervals of 1, 2, 3, 4, 5 or 6 years (constant screening interval)
- 3 or more screening episodes
- FIT threshold between 20 and 180 (same FIT threshold across all screening ages)

We note that screening strategies which relax constraints on a constant screening interval and FIT threshold will be considered as part of phase 2.

Results were generated for three screening referral colonoscopy capacities: 50,000 (just over estimated current capacity), 70,000 and 90,000 (to reflect optimistic future capacity). Table 24 presents the 8 most cost effective screening strategies for each of 1-6 yearly screening with screening referral colonoscopies <50,0000.

- With a screening referral colonoscopy capacity of 50,000 (similar to current capacity) the optimal strategy was: ***2-yearly, age 51-65, FIT161*** (8 screening episodes)**.**

- With a screening referral colonoscopy capacity of 70,000 the optimal strategy was: ***2-yearly, age 50-70, FIT153*** (11 screening episodes).

- With a screening referral colonoscopy capacity of 90,000 (to reflect optimistic future capacity) the optimal strategy was: ***2-yearly, age 50-74, FIT124*** (13 screening episodes).

- Results for screening referral colonoscopy capacity over 140,000 suggest that at higher capacities annual screening becomes optimal.

For a screening referral colonoscopy capacity of up to 100,000 2-yearly screening was the optimal frequency. For higher capacity a lower FIT threshold and wider screening age range is recommended. The optimal screening strategies include screening of the 50-59 age group.

Under the scenario analysis in which repeat FIT screens have reduced sensitivity scenario analyses suggest that the optimal repeat FIT screening strategy remains unchanged.

Table 24: The most cost effective screening strategies with screening referral colonoscopies <50,0000.

Strategy	Costs (discounted, incremental compared to no screening)	QALYs (discounted, incremental compared to no screening)	Cancer incidence	Cancer mortality	Number of screens	NMB	Screening referral colonoscopys
Screening referral colonoscopys < 50000							
1-yearly, age 56-63, FIT156	-£60.5m	18,372	15.4%	18.9%	8	£427.9m	49,895
1-yearly, age 55-62, FIT161	-£57.9m	18,464	14.8%	18.1%	8	£427.2m	49,942
1-yearly, age 56-63, FIT157	-£60.3m	18,333	15.3%	18.8%	8	£427.0m	49,705
1-yearly, age 55-62, FIT162	-£57.8m	18,426	14.8%	18.0%	8	£426.3m	49,757
1-yearly, age 57-64, FIT151	-£62.5m	18,187	15.9%	19.6%	8	£426.3m	49,938
1-yearly, age 56-63, FIT158	-£60.1m	18,295	15.3%	18.8%	8	£426.0m	49,518
1-yearly, age 55-62, FIT163	-£57.6m	18,389	14.8%	18.0%	8	£425.4m	49,573
1-yearly, age 57-64, FIT152	-£62.3m	18,148	15.9%	19.6%	8	£425.3m	49,744
2-yearly, age 51-65, FIT161	-£59.2m	19,098	15.1%	18.4%	8	**£441.2m**	49,856
2-yearly, age 53-67, FIT155	-£64.1m	18,824	16.1%	19.9%	8	**£440.6m**	49,945
2-yearly, age 51-65, FIT162	-£59.0m	19,056	15.1%	18.4%	8	**£440.1m**	49,668
2-yearly, age 52-66, FIT160	-£61.5m	18,915	15.5%	19.1%	8	**£439.8m**	49,991
2-yearly, age 53-67, FIT156	-£63.8m	18,780	16.1%	19.8%	8	**£439.5m**	49,753
2-yearly, age 51-65, FIT163	-£58.8m	19,014	15.0%	18.3%	8	**£439.1m**	49,482
2-yearly, age 52-66, FIT161	-£61.3m	18,872	15.5%	19.0%	8	**£438.8m**	49,804
2-yearly, age 53-67, FIT157	-£63.6m	18,737	16.0%	19.8%	8	**£438.4m**	49,564
3-yearly, age 52-70, FIT122	-£67.8m	18,274	16.3%	20.3%	7	**£433.3m**	49,837
3-yearly, age 50-71, FIT154	-£62.3m	18,539	16.2%	20.2%	8	**£433.1m**	49,951
3-yearly, age 50-68, FIT130	-£62.9m	18,485	15.3%	18.9%	7	£432.6m	49,913
3-yearly, age 50-71, FIT155	-£62.1m	18,493	16.1%	20.2%	8	£431.9m	49,759
3-yearly, age 52-70, FIT123	-£67.5m	18,218	16.3%	20.2%	7	£431.8m	49,586
3-yearly, age 50-68, FIT131	-£62.7m	18,431	15.3%	18.8%	7	£431.3m	49,674
3-yearly, age 52-67, FIT100	-£68.0m	18,157	15.4%	18.9%	6	£431.1m	49,841
3-yearly, age 50-71, FIT156	-£61.8m	18,447	16.1%	20.1%	8	£430.8m	49,568
4-yearly, age 50-70, FIT98	-£66.8m	17,933	15.6%	19.3%	6	£425.5m	49,921
4-yearly, age 51-71, FIT95	-£68.9m	17,807	16.0%	19.9%	6	£425.1m	49,936
4-yearly, age 50-74, FIT115	-£66.5m	17,886	16.4%	20.7%	7	£424.2m	49,832
4-yearly, age 50-70, FIT99	-£66.5m	17,861	15.5%	19.2%	6	£423.7m	49,590
4-yearly, age 51-71, FIT96	-£68.6m	17,734	16.0%	19.8%	6	£423.2m	49,597
4-yearly, age 50-74, FIT116	-£66.2m	17,825	16.4%	20.7%	7	£422.7m	49,564
4-yearly, age 50-70, FIT100	-£66.1m	17,791	15.5%	19.1%	6	£421.9m	49,266
4-yearly, age 51-71, FIT97	-£68.2m	17,662	15.9%	19.7%	6	£421.4m	49,264
5-yearly, age 50-70, FIT74	-£68.1m	17,379	15.2%	18.7%	5	£415.7m	49,620
5-yearly, age 51-71, FIT72	-£70.1m	17,239	15.7%	19.3%	5	£414.9m	49,529
5-yearly, age 50-70, FIT75	-£67.7m	17,284	15.2%	18.6%	5	£413.4m	49,165
5-yearly, age 51-71, FIT73	-£69.6m	17,143	15.6%	19.2%	5	£412.5m	49,065
5-yearly, age 50-70, FIT76	-£67.2m	17,192	15.1%	18.5%	5	£411.1m	48,721
5-yearly, age 51-71, FIT74	-£69.1m	17,048	15.5%	19.1%	5	£410.1m	48,614
5-yearly, age 52-72, FIT71	-£70.9m	16,937	15.9%	19.8%	5	£409.7m	49,933
5-yearly, age 50-70, FIT77	-£66.8m	17,101	15.0%	18.5%	5	£408.8m	48,288
6-yearly, age 50-74, FIT70	-£67.7m	16,646	15.5%	19.4%	5	£400.6m	49,624
6-yearly, age 52-70, FIT53	-£70.5m	16,496	15.1%	18.6%	4	£400.4m	49,534
6-yearly, age 53-71, FIT51	-£72.2m	16,364	15.6%	19.2%	4	£399.5m	49,344
6-yearly, age 50-74, FIT71	-£67.2m	16,548	15.4%	19.3%	5	£398.2m	49,148
6-yearly, age 52-70, FIT54	-£69.9m	16,369	15.0%	18.4%	4	£397.3m	48,880
6-yearly, age 53-71, FIT52	-£71.6m	16,233	15.5%	19.0%	4	£396.2m	48,671
6-yearly, age 50-74, FIT72	-£66.7m	16,452	15.3%	19.2%	5	£395.8m	48,683
6-yearly, age 50-68, FIT58	-£65.5m	16,472	14.1%	17.1%	4	£394.9m	49,494

6.4 Screening strategies combining Bowel scope and FIT

Is it cost effective to replace one screening episode of a repeated FIT strategy with a bowel scope?

Whether it is cost effective to replace one screening episode of a repeated FIT strategy with a one off bowel scope depends upon the screening referral colonoscopy capacity. If we consider the replacement of the FIT screen at age 58/9 with a bowel scope then this is cost effective for the repeated strategy with 50,000 screening referral colonoscopy capacity '2-yearly, age 51-65, FIT161', but not for the other optimal strategies identified. See Table 25.

These results varied when sensitivity analyses were run. Under the sensitivity analysis where lower CRC treatment costs were used it was not cost effective to replace the FIT screen with bowel scope at age 58 in any of the tested strategies. However, under the scenario analysis with higher bowel scope test sensitivity from UKFSST, and higher uptake of 55%, it was cost-effective to replace the FIT screen at age 58 with bowel scope at any of the screening referral colonoscopy capacity levels considered. Under the sensitivity analysis where repeated FIT screens have lower sensitivity it was cost-effective to add bowel scope to each of the repeated FIT screening strategies.

Table 25: Repeated FIT screening with replacement bowel scope

Screening strategy	Incremental compared to no screening			Lifetime reduction		Screening referral colonoscopies (year1)	Screening flexible sigmoidoscopy (year 1)
	Costs (£m)	QALYs	NMB (£m)	CRC incidence	CRC mortality		
2-yearly, age 51-65, FIT161							
repeated FIT screening	-£59.2m	19,098	£441.2m	15.1%	18.4%	49,856	-
repeated FIT screen with FIT age 59 replaced by BS	-£3.6m	22,373	**£451.1m**	18.2%	21.7%	52,805	289,081
2-yearly, age 50-70, FIT153							
repeated FIT screening	-£73.7m	23,600	**£545.8m**	20.2%	24.9%	69,912	-
repeated FIT screen with FIT age 58 replaced by BS	-£12.3m	26,471	£541.7m	22.7%	27.4%	72,438	300,813
2-yearly, age 50-74, FIT124							
repeated FIT screening	-£89.7m	27,037	**£630.4m**	24.7%	30.7%	89,822	-
repeated FIT screen with FIT age 58 replaced by BS	-£25.7m	29,468	£615.0m	26.9%	32.7%	91,428	300,813
2-yearly, age 50-74, FIT105							
repeated FIT screening	-£96.9m	28,486	**£666.6m**	26.2%	32.2%	99,622	-
repeated FIT screen with FIT age 58 replaced by BS	-£31.2m	30,627	£643.7m	28.0%	34.0%	100,378	300,813

For a combination screening strategy with a one off bowel scope followed by FIT screening what is the optimal interval between bowel scope and subsequent FIT screening?

To determine the optimal interval between a bowel scope at age 59 and repeated FIT screening a strategy with 4 2-yearly screens following bowel scope was considered (for FIT20 and FIT180). The optimal interval between a bowel scope at age 59 and subsequent repeated FIT screening is 1 year (i.e. the next FIT screen at age 60). Under the scenario analysis in which data from the UKFSST was used to estimate bowel scope test sensitivity and a higher uptake rate of 55% was considered, the optimal interval was increased to 3 years with a FIT screen at age 62 being optimal.

Table 26: Optimal re-invite age for strategies with Bowel Scope

Screening strategy	Incremental compared to no screening			Lifetime reduction		Screening referral colonoscopies (year1)	Screening flexible sigmoidoscopy (year 1)
	Costs (£m)	QALYs	NMB (£m)	CRC incidence	CRC mortality		
BS age 59, 4 2-yearly FIT20 screens from age 60	-£31.0m	24,488	**£520.7m**	24.3%	28.7%	103,627	289,081
BS age 59, 4 2-yearly FIT20 screens from age 61	-£34.4m	24,212	£518.7m	24.9%	29.5%	100,259	289,081
BS age 59, 4 2-yearly FIT20 screens from age 62	-£36.8m	23,854	£513.9m	25.3%	30.1%	100,873	289,081
BS age 59, 4 2-yearly FIT20 screens from age 63	-£38.3m	23,428	£506.9m	25.7%	30.6%	100,356	289,081
BS age 59, 4 2-yearly FIT20 screens from age 64	-£39.0m	22,924	£497.5m	**25.9%**	**31.0%**	95,414	289,081
BS age 59, 4 2-yearly FIT120 screens from age 60	-£1.8m	17,287	**£347.6m**	16.4%	19.8%	36,846	289,081
BS age 59, 4 2-yearly FIT120 screens from age 61	-£3.0m	17,146	£346.0m	16.6%	20.2%	36,052	289,081
BS age 59, 4 2-yearly FIT120 screens from age 62	-£3.7m	16,960	£343.0m	16.9%	20.5%	36,805	289,081
BS age 59, 4 2-yearly FIT120 screens from age 63	-£4.0m	16,738	£338.8m	17.0%	20.8%	36,877	289,081
BS age 59, 4 2-yearly FIT120 screens from age 64	-£3.9m	16,472	£333.4m	**17.1%**	**21.0%**	35,862	289,081
BS age 59, 4 2-yearly FIT180 screens from age 60	£4.9m	16,072	**£316.5m**	15.1%	18.2%	31,132	289,081
BS age 59, 4 2-yearly FIT180 screens from age 61	£3.9m	15,954	£315.2m	15.3%	18.6%	30,555	289,081
BS age 59, 4 2-yearly FIT180 screens from age 62	£3.3m	15,797	£312.7m	15.5%	18.9%	31,248	289,081
BS age 59, 4 2-yearly FIT180 screens from age 63	£3.1m	15,610	£309.1m	15.6%	19.1%	31,366	289,081
BS age 59, 4 2-yearly FIT180 screens from age 64	£3.1m	15,385	£304.6m	**15.7%**	**19.3%**	30,627	289,081

6.5 Endoscopy capacity – bowel scope versus repeated FIT screening

A one-off bowel scope at age 59 requires approximately 290k bowel scope procedures and 9k screening referral colonoscopies. Based on procedure time one might suggest that 10 bowel scopes and 4 screening referral colonoscopies were equivalent. By this equivalence 290k bowel scope could be compared to 116k screening referral colonoscopies, hence one-off bowel scope at age 59 is associated with 125k screening referral colonoscopies. A repeated FIT screening strategy with 125k screening referral colonoscopies would be considerably more effective (over 3 times) and cost effective (over 4 times) than a one-off bowel scope at age 59. See Table 27.

Table 27: Repeated FIT screening and one-off bowel scope with similar 'total endoscopy capacity' (assuming 10 bowel scopes = 4 screening referral colonoscopies)

Screening strategy	Incremental compared to no screening			Lifetime reduction		Screening referral colonoscopies (year1)	Screening flexible sigmoidoscopy (year 1)
	Costs (£m)	QALYs	NMB (£m)	CRC incidence	CRC mortality		
Bowel Scope age 59	£26.2m	9,341	£160.7m	8.4%	9.8%	9,197	289,081
2-yearly, age 50-74, FIT74	**-£111.1m**	**31,613**	**£743.3m**	**29.3%**	**35.6%**	125,129	-

6.6 gFOBT based strategies

Table 23 presents the economic results for the key screening strategies. Biennial gFOBT screening from 60-74 years is cost saving and more effective than no screening, addition of a single bowel scope at the age of 55 years increases costs and effectiveness and is estimated to be cost effective at a threshold of £20,000 per QALY, i.e. increased NMB.

However all repeated FIT screening strategies have a NMB of over £400 million and are superior to the repeated gFOBT strategy with or without bowel scope. The repeated FIT strategies are cost saving compared to the gFOBT strategy (and therefore also no screening and gFOBT with bowel scope at 55 years) and are more effective than the gFOBT strategies where the FIT threshold is less than 160 μg/ml.

The following tables presents more detailed results for the key strategies.

Table 28: Summary results for key screening strategies

Screening strategy	Incremental compared to no screening			Lifetime reduction		Screening referral colonoscopies (year1)	Screening flexible sigmoidoscopy (year 1)
	Costs (£m)	QALYs	NMB (£m)	CRC incidence	CRC mortality		
Current	£0.0m	-	£0.0m	-	-	-	-
gFOBT ages 60-74 biennial	-£37.3m	11,608	£269.4m	10.7%	16.8%	36,406	-
Bowel scope age 55, gFOBT ages 60-74 biennial	£12.9m	19,197	£371.1m	16.5%	22.5%	42,920	329,121
One off screens							
Bowel Scope age 59	£26.2m	9,341	£160.7m	8.4%	9.8%	9,197	289,081
FIT20 age 57	-£39.6m	9,093	£221.5m	7.3%	8.5%	28,995	-
Repeated FIT screening							
2-yearly, age 51-65, FIT161	-£59.2m	19,098	£441.2m	15.1%	18.4%	49,856	-
2-yearly, age 50-70, FIT153	-£73.7m	23,600	£545.8m	20.2%	24.9%	69,912	-
2-yearly, age 50-74, FIT124	-£89.7m	27,037	£630.4m	24.7%	30.7%	89,822	-
2-yearly, age 50-74, FIT74	-£111.1m	31,613	£743.3m	29.3%	35.6%	125,129	-
Bowel scope and repeated FIT screening							
Bowel scope age 59, 2-yearly, age 51-65 (excl.59), FIT161	-£3.6m	22,373	£451.1m	18.2%	21.7%	52,805	289,081
Bowel scope age 58, 2-yearly, age 50-70 (excl. 58), FIT153	-£12.3m	26,471	£541.7m	22.7%	27.4%	72,438	300,813
Bowel scope age 58, 2-yearly, age 50-74 (excl. 58), FIT124	-£25.7m	29,468	£615.0m	26.9%	32.7%	91,428	300,813

Table 29: Cost results for key screening strategies

Screening strategy	Costs								
	Cost gFOBT/FIT/BS Screening (discounted)	Cost screening referral colonoscopy/CTC (discounted)	Total Cost Surveillance colonoscopy (discounted)	Cost screening complications (discounted)	Total costs related to screening (discounted)	Cancer management (inc. pathology) costs (discounted)	Total cost (discounted)	Total life years gained (discounted)	Total QALYs gained (discounted)
Current									
No screening	£0.00m	£0.00m	£0.00m	£0.00m	£0.00m	£846.92m	£846.92m	15,225,293	12,214,213
gFOBT ages 60-74 biennial	£10.86m	£15.34m	£7.66m	£0.04m	£33.91m	£775.73m	£809.64m	15,239,965	12,225,821
Bowel scope age 55, gFOBT ages 60-74 biennial	£108.82m	£19.05m	£13.25m	£0.10m	£141.22m	£718.54m	£859.77m	15,248,630	12,233,409
One-off screens									
Bowel Scope age 59	£83.86m	£4.90m	£6.97m	£0.06m	£95.79m	£777.28m	£873.07m	15,236,387	12,223,554
FIT20 age 57	£4.93m	£14.20m	£6.39m	£0.03m	£25.54m	£781.77m	£807.32m	15,236,041	12,223,306
Repeated FIT screening									
2-yearly, age 51-65, FIT161	£36.55m	£22.93m	£13.17m	£0.06m	£72.70m	£714.99m	£787.69m	15,248,014	12,233,311
2-yearly, age 50-70, FIT153	£46.79m	£30.11m	£16.80m	£0.07m	£93.77m	£679.40m	£773.17m	15,253,507	12,237,813
2-yearly, age 50-74, FIT124	£51.30m	£37.23m	£19.53m	£0.09m	£108.15m	£649.06m	£757.21m	15,257,710	12,241,250
2-yearly, age 50-74, FIT105	£51.48m	£50.34m	£23.16m	£0.11m	£125.09m	£610.75m	£735.84m	15,263,048	12,245,826
Bowel scope and repeated FIT screening									
Bowel scope age 59, 2-yearly, age 51-65 (excl.59), FIT161	£115.08m	£23.31m	£15.80m	£0.10m	£154.30m	£689.01m	£843.31m	15,251,827	12,236,586
Bowel scope age 58, 2-yearly, age 50-70 (excl. 58), FIT153	£128.53m	£30.12m	£19.08m	£0.12m	£177.85m	£656.76m	£834.61m	15,256,799	12,240,684
Bowel scope age 58, 2-yearly, age 50-74 (excl. 58), FIT124	£132.98m	£36.79m	£21.49m	£0.13m	£191.39m	£629.87m	£821.26m	15,260,478	12,243,681

Table 30: CRC incidence and mortality for key screening strategies

Screening strategy	Cancer Incidence and mortality						
	Screen detected CRC	Surveillance detected CRC	Symptomatic presentation CRC	Total Cancer Cases	Total Cancer Deaths	CRC incidence reduction	CRC mortality reduction
Current							
No screening	-	-	52,015	52,015	22,697	0.0%	0.0%
gFOBT ages 60-74 biennial	4,146	49	42,239	46,433	18,887	10.7%	16.8%
Bowel scope age 55, gFOBT ages 60-74 biennial	3,936	69	39,421	43,426	17,579	16.5%	22.5%
One-off screens							
Bowel Scope age 59	735	35	46,860	47,630	20,474	8.4%	9.8%
FIT20 age 57	678	29	47,527	48,233	20,758	7.3%	8.5%
Repeated FIT screening							
2-yearly, age 51-65, FIT161	1,899	62	42,199	44,159	18,514	15.1%	18.4%
2-yearly, age 50-70, FIT153	2,865	84	38,581	41,530	17,049	20.2%	24.9%
2-yearly, age 50-74, FIT124	3,826	99	35,224	39,149	15,732	24.7%	30.7%
2-yearly, age 50-74, FIT105	4,004	116	32,679	36,799	14,628	29.3%	35.6%
Bowel scope and repeated FIT screening							
Bowel scope age 59, 2-yearly, age 51-65 (excl.59), FIT161	1,956	74	40,499	42,529	17,760	18.2%	21.7%
Bowel scope age 58, 2-yearly, age 50-70 (excl. 58), FIT153	2,783	94	37,326	40,202	16,472	22.7%	27.4%
Bowel scope age 58, 2-yearly, age 50-74 (excl. 58), FIT124	3,689	107	34,244	38,039	15,269	26.9%	32.7%

Table 31: Screening results for key screening strategies

Screening strategy	Screening		Harm	
	Invited for screening	Screening responders	Endoscopy harm: bleeds	Endoscopy harm: perforations
Current				
No screening	-	-	-	-
gFOBT ages 60-74 biennial	5,491,540	3,402,152	18	48
Bowel scope age 55, gFOBT ages 60-74 biennial	6,262,691	3,745,030	125	64
One-off screens				
Bowel Scope age 59	753,581	334,696	107	25
FIT20 age 57	762,675	497,041	13	26
Repeated FIT screening				
2-yearly, age 51-65, FIT161	5,995,975	3,898,626	20	54
2-yearly, age 50-70, FIT153	8,080,851	5,253,562	28	74
2-yearly, age 50-74, FIT124	9,323,799	6,060,855	36	93
2-yearly, age 50-74, FIT105	9,313,358	6,051,502	49	113
Bowel scope and repeated FIT screening				
Bowel scope age 59, 2-yearly, age 51-65 (excl.59), FIT161	5,985,014	3,734,148	122	63
Bowel scope age 58, 2-yearly, age 50-70 (excl. 58), FIT153	8,072,293	5,090,197	130	82
Bowel scope age 58, 2-yearly, age 50-74 (excl. 58), FIT124	9,318,847	5,900,870	138	99

Table 32: Endoscopy resource use for key screening strategies

Screening strategy	Annual endoscopoy resource use (for the entire 2016 population)			
	Screening referral colonoscopies (year1)	Screening flexible sigmoidoscopy (year 1)	Surveillance Endoscopy Utilisation (year 5)	CTC Usage (year 1)
Current				
No screening	-	-	-	-
gFOBT ages 60-74 biennial	36,406	-	21,264	1,637
Bowel scope age 55, gFOBT ages 60-74 biennial	42,920	329,121	32,746	1,824
One-off screens				
Bowel Scope age 59	9,197	289,081	21,264	291
FIT20 age 57	28,995	-	21,264	884
Repeated FIT screening				
2-yearly, age 51-65, FIT161	49,856	-	21,264	1,623
2-yearly, age 50-70, FIT153	69,912	-	21,264	2,520
2-yearly, age 50-74, FIT124	89,822	-	21,264	3,468
2-yearly, age 50-74, FIT105	125,129	-	21,264	4,793
Bowel scope and repeated FIT screening				
Bowel scope age 59, 2-yearly, age 51-65 (excl.59), FIT161	52,805	289,081	21,264	1,723
Bowel scope age 58, 2-yearly, age 50-70 (excl. 58), FIT153	72,438	300,813	21,264	2,608
Bowel scope age 58, 2-yearly, age 50-74 (excl. 58), FIT124	91,428	300,813	21,264	3,527

*****Note that estimated surveillance colonoscopies are presented for year 5 rather than year 1 as it takes several years for the new screening strategy to result in a change in surveillance colonoscopies. However, annual screening referral colonoscopies and bowel scope resource use is similar over years 1-5.

Table 33: Detailed cost effectiveness results for key screening strategies

Screening strategy	Incrementals compared to no screening					NMB
	Total costs related to screening (discounted)	Cancer management (inc. pathology) costs (discounted)	Total cost (discounted)	Total life years gained (discounted)	Total QALYs gained (discounted)	
Current						
No screening	£0.0m	£0.0m	£0.0m	-	-	£0.0m
gFOBT ages 60-74 biennial	£33.9m	-£71.2m	-£37.3m	14,672	11,608	£269.4m
Bowel scope age 55, gFOBT ages 60-74 biennial	£141.2m	-£128.4m	£12.9m	23,337	19,197	£371.1m
One-off screens						
Bowel Scope age 59	£95.8m	-£69.6m	£26.2m	11,094	9,341	£160.7m
FIT20 age 57	£25.5m	-£65.1m	-£39.6m	10,748	9,093	£221.5m
Repeated FIT screening						
2-yearly, age 51-65, FIT161	£72.7m	-£131.9m	-£59.2m	22,720	19,098	£441.2m
2-yearly, age 50-70, FIT153	£93.8m	-£167.5m	-£73.7m	28,214	23,600	£545.8m
2-yearly, age 50-74, FIT124	£108.2m	-£197.9m	-£89.7m	32,416	27,037	£630.4m
2-yearly, age 50-74, FIT105	£125.1m	-£236.2m	-£111.1m	37,754	31,613	£743.3m
Bowel scope and repeated FIT screening						
Bowel scope age 59, 2-yearly, age 51-65 (excl.59), FIT161	£154.3m	-£157.9m	-£3.6m	26,534	22,373	£451.1m
Bowel scope age 58, 2-yearly, age 50-70 (excl. 58), FIT153	£177.9m	-£190.2m	-£12.3m	31,506	26,471	£541.7m
Bowel scope age 58, 2-yearly, age 50-74 (excl. 58), FIT124	£191.4m	-£217.0m	-£25.7m	35,185	29,468	£615.0m

6.7 Results summary

Optimal age of one-off bowel scope or FIT screen

The optimal age (in terms of cost-effectiveness) for a one-off bowel scope screen is 59. (Note that QALY gain is optimised at a younger age and incidence and mortality reduction is maximised at an older age.)

The optimal age (in terms of cost-effectiveness) for a one-off FIT120 screen is 57 regardless of FIT threshold (all thresholds between 20-180 μg/ml were considered).

Comparing a one-off FIT20 and a one of bowel scope, we see that bowel scope is the most effective but FIT20 is the most cost effective. However under analyses in which bowel scope uptake and/or effectiveness is increased, bowel scope was associated with much higher effectiveness and cost effectiveness than FIT20

Optimising repeated FIT screening

With no constraints on the number of screening referral colonoscopies the optimal strategy is: FIT20 annual ages 50-74.

The optimal screening age range, screening interval, and FIT threshold depend on the screening referral colonoscopy capacity. For a screening referral colonoscopy capacity of 50,000 (current)-90,000(optimistic future) 2-yearly screening from age 50/51 is optimal. For higher levels of screening referral colonoscopy capacity screening with a lower FIT threshold and a wider age range is optimal.

Screening referral colonoscopy capacity	Optimal repeated FIT screening strategy
50,000 (similar to current capacity)	2-yearly, age 51-65, FIT161 (8 screens)
70000	2-yearly, age 50-70, FIT153 (11 screens)
90,000 (optimistic future capacity)	2-yearly, age 50-74, FIT124 (13 screens)
110,000	2-yearly, age 50-74, FIT90 (13 screens)
130,000	2-yearly, age 50-74, FIT70 (13 screens)
150,000	1-yearly, age 50-74, FIT159 (25 screens)

Screening strategies combining Bowel scope and FIT

It is cost effective to replace FIT screening with one-off bowel scope at age 58 in the optimal repeated FIT screening strategy identified at a capacity of 50,000 screening referral colonoscopies, but not at higher screening referral colonoscopy capacity levels. However, this conclusion varied when scenario analyses were run.

Endoscopy capacity – bowel scope versus repeated FIT screening

We consider an assumption that 10 bowel scopes and 4 screening referral colonoscopies are equivalent (based on procedure time). A repeated FIT screening strategy with 125k screening referral colonoscopies would be considerably more effective (over 3 times) and cost effective (over 4

times) than a one-off bowel scope at age 59 (290k bowel scopes, 9k screening referral colonoscopies)

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6.8 Endoscopy capacity in years 1-20

Model predictions for expected resource use were generated considering changing from gFOBT 60-74 2-yearly to the proposed screening strategy. Resource use will change over time due to (1) more rounds of the proposed screening strategy being completed (lower disease prevalence and more persons undergoing surveillance); and (2) the changing age distribution over time e.g. 55 year olds in future years than in 2016.

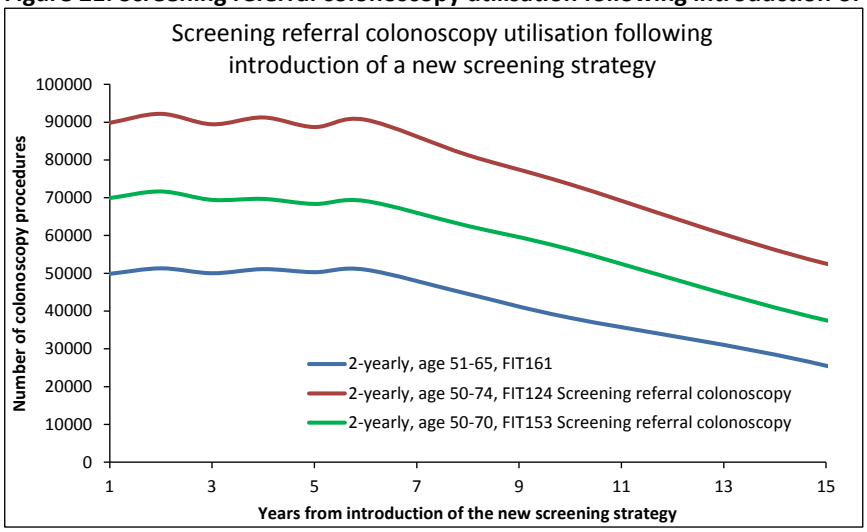
The required endoscopy requirements for the first five years are detailed in Table 34 and Figure 21. Screening referral colonoscopy capacity is similar over the first 6 years and then decreases subsequently as disease prevalence in the population decreases. This decrease more marked for screening strategy using a more sensitive test.

Surveillance colonoscopy capacity estimates are subject to considerable uncertainty as explored in the model validation section. However, current estimates suggest that surveillance colonoscopy capacity will increase over the first 8 years before then decreasing. Increases in years 2 and 4 are related to the fact that there will be no new surveillance in year 1 and more in years 2 and 4 (for annual and 3-yearly recall).

Table 34: Required capacity (screening referral colonoscopies) over the first 20 years

Strategy	Years from introduction of the new screening strategy									
	1	2	3	4	5	6	8	10	15	20
2-yearly, age 51-65, FIT161										
Screening referral colonoscopy	49,856	51,316	50,015	51,108	50,300	50,963	44,548	38,203	25,534	6,062
Surveillance colonoscopy	21,264	22,967	23,690	27,306	29,186	28,819	34,551	35,223	29,653	20,191
Total	71,120	74,283	73,705	78,414	79,486	79,782	79,099	73,426	55,187	26,253
2-yearly, age 50-70, FIT153										
Screening referral colonoscopy	69,912	71,658	69,437	69,688	68,362	69,125	62,525	56,293	37,567	25,218
Surveillance colonoscopy	21,264	24,744	25,751	33,551	36,667	36,217	46,169	46,520	41,081	31,167
Total	91,176	96,402	95,188	103,239	105,029	105,342	108,694	102,813	78,648	56,385
2-yearly, age 50-74, FIT124										
Screening referral colonoscopy	89,822	92,209	89,446	91,254	88,713	90,636	81,279	73,545	52,550	40,102
Surveillance colonoscopy	21,264	26,408	27,764	39,404	44,099	43,420	56,819	57,127	49,744	39,145
Total	111,086	118,617	117,210	130,658	132,812	134,057	138,098	130,673	102,294	79,247
2-yearly, age 50-74, FIT105										
Screening referral colonoscopy	99,622	102,247	98,811	100,790	97,748	99,847	89,199	80,450	57,019	43,314
Surveillance colonoscopy	21,264	27,070	28,561	41,672	46,938	45,949	60,895	60,982	52,554	41,114
Total	120,885	129,317	127,372	142,462	144,687	145,796	150,094	141,432	109,573	84,428

Figure 21: Screening referral colonoscopy utilisation following introduction of new screening strategy



6.9 Other Sensitivity Analyses

Cost of bowel scope

Discount rate

As expected, when discount rates are reduced, more costs and QALYs are produced with each screening strategy. Given that disproportionately more QALYs are produced in the future, which is subject to higher discounting, the reduction in discount rate reduces the ICER of the optimal strategy for each of the three capacity scenarios. There is no change in the optimal strategy amongst strategies tested.

Colorectal cancer natural history model

Increasing symptomatic presentation rates increases total costs and QALYs for all strategies, but has very little effect on the ICER, meaning that optimal strategies remain the same as in the base case.

Population gender subgroups

Total costs are estimated to be higher in males than in females, because of increased treatment costs due to higher CRC incidence rate in males. Similarly, total QALYs gained are lower in males than females. However, ICERs are much higher in women than men as incremental QALYs are much lower in females, as they have less capacity to benefit from screening.

Probabilistic sensitivity analysis

Results are provided in the appendix.

7 Conclusion

7.1 Policy implications of findings

Repeated FIT screening

1. Regardless of capacity constraints the current screening strategies (gFOBT 2-yearly 60-74 with or without bowel scope age 55) are dominated by a FIT screening strategy (i.e. a FIT strategy exists which is more effective and less expensive).
2. The optimal age for a repeated FIT screening strategy is 50/51 hence it is suggested that the screening start age is reduced compared to what is currently used in the BCSP. The upper screening age varies between 65 and 74, depending on the capacity constraint used.
3. It is recommended that the screening interval is kept to 2-yearly screening. However, increased benefits may be obtained my re-inviting non-attenders after a 1 year interval.
4. The optimal FIT threshold depends on the available capacity for screening referral colonoscopies:
    - With 50,000 screening referral colonoscopies (current capacity) then we recommend a strategy of ***2-yearly, age 51-65, FIT161*** (8 screens).
    - If 90,000 screening referral colonoscopies is considered feasible to achieve in the future then we recommend a strategy of ***2-yearly, age 50-74, FIT124*** (13 screens).

Note that these conclusions are based on optimising cost-effectiveness. If the aim was to optimise QALY gains or CRC incidence/mortality reduction then conclusions would be different.

Bowel Scope screening

1. There is some uncertainty in whether it is cost effective to replace one FIT screen with a one-off bowel scope at age 58/59.
2. A repeated FIT screening strategy with 125k screening referral colonoscopies would be considerably more effective (over 3 times) and cost effective (over 4 times) than a one-off bowel scope at age 59 (290k bowel scopes, 9k screening referral colonoscopies).Such strategies could be considered to have equivalent 'endoscopy capacity' (assuming that 10 bowel scopes and 4 screening referral colonoscopies are equivalent).
3. Hence, if bowel scope capacity could be used for undertaking screening referral colonoscopies this would result in higher cost-effectiveness.

7.2 Limitations of the analysis and future research

FIT CRC sensitivity data

There is a very large degree of uncertainty in the sensitivity to cancer of FIT due to the small sample size. However, the FIT pilot data reflects usage of FIT in a (non-trial) screening setting so we suggest it is the most appropriate data source for this analysis. The result of this is increased uncertainty in model predictions involving FIT.

Variations in CRC risk and screening uptake within the population

The approach taken here models the whole population as a series of homogenous age cohorts. As it is known that screening attendance can be lower in some subgroups with higher CRC risk (e.g. males) this cohort modelling approach will not accurately estimate the cost effectiveness of screening. This inaccuracy is however unlikely to impact on the incremental cost-effectiveness of different screening strategies. Phase 1 started to look at the differential cost –effectiveness in different population subgroups by considering males and females separately. This limitation will be addressed within the patient level model structure proposed in Phase 2. Phase 2 will aim to deliver a patient level model structure that is compatible with addressing anticipated future research questions. This will include the evaluation of targeted screening uptake interventions, and patient level screening strategies.

Uncertainty in surveillance model predictions

There is a high degree of uncertainty in the data which informs the surveillance component of the screening model. Data was not available to refine or properly validate this component of the model for this phase. Validation analyses demonstrated that the surveillance model parameters (such as adenoma recurrence rates following polypectomy) have a large impact on model predicted cancer rates. This uncertainty translates directly to uncertainty in model predictions and conclusions. As a result of the differences between the ScHARR model predictions and BCSP data the model predicted surveillance colonoscopy estimates presented here should be treated with caution.

As part of phase 2 it is proposed that (1) further data will be obtained to inform the surveillance component of the model and (2) the patient level model structure will allow evaluation of alternative surveillance criteria including FIT for follow up and alternative stopping criteria.

Screening strategies combining bowel scope and FIT

There is considerable uncertainty in how different screening modalities with work when used in combination. This is due to the lack of trial evidence to inform this part of the model. Hence the predictions in relation to combination screening strategies which include bowel scope and FIT should be treated with caution.

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