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ABSTRACT

OBJECTIVES: In 2016, it was announced that the faecal immunochemical test(FIT) would replace the guaiac faecal occult blood test in the UK Bowel Cancer Screening Programme(BCSP). England has limited endoscopy capacity. This study informed decision making by determining the most cost-effective FIT screening strategy (age range, frequency and FIT threshold) under a constrained endoscopy capacity.

METHODS: An economic model with a colorectal cancer (CRC) natural history component was used to model 60,221 screening strategies with: first screen at age 50-60; screening interval 1-6 years; 3+ screening episodes; FIT integer threshold 20-180 µgHb/g faeces. Screening strategies requiring the same endoscopy capacity were compared to determine the characteristics of the most cost-effective strategies.

RESULTS: With 50,000 annual screening referral colonoscopies the 20 most cost-effective strategies had: starting age 50-53, 2-yearly screening, 7/8 rounds of screening, and FIT threshold 127-166. Compared to a 2-yearly screening interval, screening less frequently (3,4,5,6-yearly) with a more sensitive FIT was less cost-effective.

CONCLUSIONS: The UK BCSP should use a two-yearly FIT screening interval. When endoscopy capacity increases the screening starting age should be reduced first followed by reducing the FIT threshold. These findings are relevant for other CRC screening programmes with constrained endoscopy capacity.

KEYWORDS faecal immunochemical test; colorectal cancer; cost-effectiveness

INTRODUCTION

In England, population screening for colorectal cancer (CRC) has been offered since 2006 through the Bowel Cancer Screening Programme (BCSP). In 2016, screening practice in the English Bowel Cancer Screening Programme (BCSP) was to invite 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. Individuals testing positive were referred to colonoscopy or CT colongraphy services for follow-up investigation. BS screening roll out was slow due to capacity issues. The faecal immunochemical test (FIT) is an alternative to gFOBT which is more sensitive and more expensive. The FIT produces a quantitative score depending upon the amount of blood detected. The FIT threshold (or FIT cut-off) is the score above which referral to colonoscopy/CT colonography occurs. FIT has the advantages of being specific for human blood and detecting blood at a much lower concentration with a single faecal sample, with many EU countries using, or intending to use FIT.(1) In 2016, the Public Health Minister for England announced that FIT would replace gFOBT in the English BCSP ,(2) and this was eventually implemented in 2019.

A previous cost-effectiveness evaluation concluded that FIT screening is highly cost-effective compared with gFOBT screening. (3) This manuscript reports on work conducted to assist the UK National Screening Committee (NSC) in deciding how FIT could best be used within the BCSP, whilst considering constraints on endoscopy capacity. The aim was to determine the optimal strategy in terms of screening age range, screening frequency and FIT threshold to inform policy making. The focus was to determine which FIT screening strategy was optimal if FIT is the sole screening modality within the BCSP. The NSC were interested in understanding (1) what the optimal FIT screening strategy is with the currently available endoscopy capacity, (2) what FIT screening strategy would be optimal to aim for if endoscopy capacity increases in the future, and (3) how best to transition from (1) to (2).

METHODS

In the UK the choice of screening strategy is restricted by the available endoscopy capacity to follow up persons with a positive screening test result. Analyses were undertaken comparing screening strategies that had the same screening referral colonoscopy requirements. For a fixed screening referral colonoscopy capacity, the aim was to determine:

(1) What is the optimal screening age range?
(2) What is the optimal screening interval?
(3) 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?
(4) Is it preferable to screen a narrower age range more intensively (short interval, low FIT threshold) or a wider age range less intensively.

ScHARR Bowel Cancer Screening Economic Model

An existing School of Health and Related Research (ScHARR) state-transition bowel cancer screening model was updated.(4, 5) Full details of the model structure, data, updates, and refinements are described within Appendix 1.

The model simulates the life experience of a cohort of 50-year-old individuals in the general population of England with normal epithelium through to the development of adenomas (low-risk and intermediate/high-risk), CRC (by Duke's stage) and subsequent death. CRC health states are further divided by if the cancer has been clinically diagnosed. Adenoma definitions are based on the British Society of Gastroenterology (BSG) (6). Both age and stage at diagnosis influence subsequent CRC survival, with age-specific other cause mortality also included. Transition probabilities were obtained via calibration.(7) The ScHARR model has undergone an extensive series of validations including: internal validation as part of model development, check on face validity by clinical experts, cross validity via comparison with another model and external validation against long term follow up screening trial data.(8, 9)

The model simulates screening by tracking screening invitations sent, FIT tests completed, FIT tests requiring repeating, FIT outcomes (modelled according to underlying disease state and FIT sensitivity/specificity), referrals to colonoscopy, attendance at colonoscopy (with/without polypectomy), colonoscopy complications and screen detected CRC (by stage). Surveillance is modelled according to the BSG guidelines (6). Key input parameters are presented in

, and reflect the evidence used at the time of performing the analysis to inform the deliberations of the UK NSC.

Repeated FIT screening strategies modelled

A wide range of screening strategies (60,221) were modelled. Screening strategies with the same endoscopy capacity requirement (screening referral colonoscopies) were compared. Screening strategies considered included those with: starting ages between 50 and 60; max screening age up to 74; screening intervals of 1, 2, 3, 4, 5 or 6 years; 3 or more screening episodes; any FIT integer threshold between 20 and 180 μg Hb/g faeces.

Generally, screening strategies utilising more colonoscopy capacity are more intensive and therefore more cost-effective. To robustly determine the most cost-effective screening strategy for a given capacity level it is essential to compare strategies with the same required capacity. It is for this reason that all integer FIT threshold increments were considered so that several strategies with very similar capacity requirements could be compared.

Model outcomes and Decision perspective

The modelling approach and data sources follow the NICE guidelines for technology appraisal (10). Costs were inflated to the most recently available year (2014/15 at the time of analysis) and were discounted by 3.5%, with a perspective of the NHS and personal social services (11). To identify the -strategy with the greatest Net Monetary Benefit (NMB) a willingness to pay of £20,000 per quality adjusted life years (QALY) was used. (10)

When deciding on an optimal screening programme possible outcome measures to consider are: NMB (cost effectiveness), QALYs (effectiveness), CRC incidence reduction or CRC mortality reduction. Factors influencing the choice of outcome measures for optimising the screening programme are

illustrated in **Figure 1**. The optimal screening strategy will vary according to the choice of outcome measure. For example, QALY gains tend to be maximised by screening younger ages (as lives saved are associated with a longer life expectancy) whereas CRC mortality tends to see the maximum reductions when screening older ages (as disease is more prevalent in older ages).(8) This analysis focused on screening strategies that optimise cost-effectiveness (NMB) as this was considered to be the most comprehensive outcome measure incorporating costs, quality of life and quantity of life.

Cost effectiveness was evaluated by comparing the lifetime expected costs and effects (QALYs) for a cohort receiving the proposed screening strategy compared to a cohort receiving no screening. Model predictions were generated for a lifetime horizon for a cohort of 50 year olds (N=785,955 corresponding to the 2016 population) in whom the proposed screening strategy is fully rolled out. Full roll out means that all persons are invited to screening from the screening start age (in practice many persons has previously received gFOBT so would receive their first FIT invite at an older age).

Endoscopy capacity

Endoscopy capacity within the BCSP comprises screening referral colonoscopy, bowel scope and surveillance colonoscopy. Evidence from the BCSP indicated that the capacity existed to perform 165,000 procedures annually at the time of analysis, comprising approximately 47,000 gFOBT/BS follow-up colonoscopy procedures, 106,000 BS screening procedures, and 13,000 surveillance colonoscopy procedures.(12) Bowel scope and colonoscopy capacity are not simply transferable due to differences in time, resource, training, and accreditation requirements. At the time of these analyses, the revision of the surveillance guidelines was imminent but it was not known how the guidelines would change. Hence, these analyses focussed on the number of screening referral colonoscopies only. As the NHS were aiming to increase endoscopy capacity, the base case for current capacity was considered to be 50,000 screening referral colonoscopies, with an optimistic alternative estimate of 90,000. Alternative endoscopy capacity constraints between 30,000 and 150,000 were also considered.

The endoscopy capacity associated with a screening strategy can be measured in two ways: (1) the capacity required in year 1 to deliver the FIT screening strategy to a population previously screened with gFOBT, (2) the colonoscopy capacity required when the screening strategy is fully rolled out, for example measured as total lifetime colonoscopies (for screening or screening and surveillance) for a given population. In this analysis we focus on (1) as this was requested by the decision maker. Model predictions for expected resource use were generated for a cross section 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) before changing to the proposed screening strategy for future years (post 2016). Model results were generated to show how colonoscopy capacity changes over time as the screening programme is rolled out.

FIT sensitivity and specificity

FIT sensitivity and specificity values were estimated using data from the English FIT pilot in combination with estimates of disease prevalence taken from the ScHARR model calibration. (7) Sensitivity was calculated as detection rate divided by the disease prevalence. The FIT pilot reported data on 27,167 persons. As detection rates vary by age and screening history, the subgroup "Prevalent round of first time invitees only" (N=3933) was used for this analysis which consists of

persons aged 60 who have not previously been screened (13). The model fitted to detection rates was used to generate sensitivity and specificity values for each FIT integer threshold, see **Figure 2Error! Reference source not found.** and

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The FIT pilot data used to estimate screening test characteristics relates to a single FIT screening round so results in subsequent rounds were effectively based on extrapolation. There is a paucity of data on whether FIT sensitivity and specificity may vary when a repeated screening strategy is considered and some models assume independence.(14-18) In the base case analysis we assume that subsequent tests have the same sensitivity and specificity as the initial test and that results of sequential tests are independent. With constant sensitivity, detection rates will decrease in subsequent rounds due to lower underlying disease prevalence. Two scenario analyses were undertaken. Firstly, FIT sensitivity was assumed to be 25% lower at repeat screens and secondly both sensitivity and specificity were reduced by 25% at repeat screens (14). Changes in test characteristics at repeat screens may differ by country depending on the routine follow up pathways for persons with a clear colonoscopy (e.g. no screen for 10 years versus re-invitation after 2 years).

Uncertainty analyses

The impacts of several model uncertainties were explored though sensitivity analyses including: discount rates; costs and utility values; screening uptake rates; screening test characteristics; symptomatic presentation rates; and varying cancer risk by gender. A complete description of these analyses can be found within Appendix 1. Probabilistic sensitivity analyses (PSA) were run with all uncertain parameters varied simultaneously. It was not feasible to undertake sensitivity analyses for all possible repeat FIT screening strategies due to the computation time associated with the large number of strategies evaluated. Hence, the uncertainty analyses illustrate the impact of uncertainty on model outcomes for a key set of screening strategies only.

RESULTS

Baseline results

The model predicts repeat FIT CRC screening to be highly cost effective. In the absence of any endoscopy constraints the most cost-effective screening strategy was the most intensive screening strategy considered (Annual FIT 20 ages 50-74). The optimal FIT threshold depended on the available capacity for screening referral colonoscopies. A total of 350 different screening strategies were identified with a screening referral colonoscopy capacity of 49,500-50,000 which was similar to usage in 2016. The screening strategies with more frequent screening use a less sensitive FIT (higher FIT threshold). There are numerous screening strategies with similar outcomes in terms of cost-effectiveness. **Error! Reference source not found.** presents the 8 most cost effective strategies for each screening interval to illustrate this point.

The optimal strategy was *2-yearly, age 51-65, FIT161* (8 screening episodes). As several strategies resulted in similar NMB, the characteristics of the 20 most cost-effective strategies are also

considered. With a screening referral colonoscopy capacity of up to 50,000 the 20 most cost-effective strategies had: (i) starting age 50-53, (ii) 2-yearly screening, (iii) 7/8 rounds of screening, (iv) FIT threshold of 127-166. For higher levels of endoscopy capacity, the optimal strategies involved more intensive screening. With a capacity of 90,000 screening referral colonoscopies optimal strategies involved screening 2-yearly from age 50-51 with a FIT threshold of 100-129. **Error! Reference source not found.** shows the characteristics of the optimal screening strategies with screening referral capacity ranging from 30,000 to 150,000 per year. For endoscopy capacity up to 100,000 a 2-yearly screening interval is optimal and above 105,000 yearly screening may be optimal. For higher levels of capacity, a lower FIT threshold is recommended. Compared to a 2-yearly screening interval, screening less frequently (3,4,5,6-yearly) with a more sensitive FIT was less cost-effective.

Error! Reference source not found. presents model outcomes for lifetime predictions for the optimal screening strategies (at 50,000, 70,000 and 90,000 capacity) including a breakdown of: costs, effectiveness, endoscopy use, number of persons screened, harm and long-term effect on CRC incidence and mortality. With higher endoscopy capacity a more intensive screening strategy was feasible; these are associated with increased screening costs but lower total costs due to the reduction in cancer managements costs associated with cancer prevention and early diagnosis. The more intensive screening strategies were also associated with a higher rate of harm and a greater reduction in CRC incidence and mortality. The number of screening referral colonoscopies required to prevent one case of CRC ranged from 6.3 with '2-yearly FIT161 age 51-65' to 8.2 with '2-yearly FIT105 age 50-74'. The number of screening referral colonoscopies required to prevent one CRC death ranged from 11.9 with '2-yearly FIT161 age 51-65' to 15.5 with '2-yearly FIT105 age 50-74'.

General findings

(1) What is the optimal screening age range when endoscopy capacity is constrained?

The optimal screening age range varies by endoscopy capacity but generally starts at age 50/51 and ranges to age 70, or 74 if capacity allows. With screening referral colonoscopy capacity under 65,000 the optimal upper screening age ranged between 65 and 71. However a policy of reducing the upper age only to increase it again once capacity allows would be unlikely to be acceptable to the public.

(2) What is the optimal screening interval when endoscopy capacity is constrained?

The optimal screening interval is 2-yearly FIT screening. With a high screening referral colonoscopy capacity over 105,000 annual screening may become optimal.

(3) Consider a constrained endoscopy capacity. 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?

For a feasible endoscopy capacity (50,000-100,000), the optimal screening interval is 2-yearly FIT screening. Screening strategies involving 3-yearly screening with a more sensitive FIT were less cost-effective.

(4) *Consider a constrained endoscopy capacity. Is it preferable to screen a narrower age range more intensively (short interval, low FIT threshold) or a wider age range less intensively?*

The optimal screening age range varies by endoscopy capacity, but it is generally cost effective to screen a reasonably wide age range; a minimum of 8 screening episodes equating to a 14-year age range. It is more cost-effective to increase the age range to start screening from age 50/51 at a higher FIT threshold, than to start screening at an older age, but with a lower FIT threshold.

Endoscopy use

Results were generated to demonstrate how endoscopy use changes over time with the roll out of a new FIT screening strategy (Appendix 2). There are variations in predicted numbers of screening referral colonoscopies in each year due to the age distribution of the population. For each of the screening strategies the predicted endoscopy resource use remains constant for the first six years then decreases significantly thereafter due to a decrease in disease prevalence in the screening population.

Sensitivity analyses

The results of the scenario analyses are presented in Appendix 2. Lower CRC treatment costs result in higher total incremental costs (due to less savings in treatment costs) and lower NMB. A lower discount rate for future costs and QALYs (1.5% instead of 3.5%) results in almost double NMBs. Increased rates of symptomatic presentation (+10%) results in slightly lower NMB. An assumption of reduced FIT test sensitivity in repeated screens (25% lower) results in an approximately 15% lower QALY gain and therefore lower NMB; the number of screening referral colonoscopies is also lower. If both FIT sensitivity and specificity are reduced in repeated screens (both by 25%) then the number of screening referral colonoscopies increased dramatically to an unfeasible capacity. The PSA resulted in mean costs and QALYs which only differed slightly to the deterministic results.

CONCLUSIONS

Policy Recommendations

The NSC were interested in understanding: (1) what the optimal FIT screening strategy is with the currently available endoscopy capacity; (2) what FIT screening strategy would be optimal to aim for once endoscopy capacity increases in the future; and (3) how best to transition from (1) to (2).

Our findings suggested keeping the screening interval as 2-yearly screening and retaining the upper age at 74 as in the gFOBT programme. When more colonoscopy capacity is available it was recommended to first reduce the screening start age to 50 and secondly reduce the FIT threshold. Following a consultation period the NSC published recommendations based on this research in August 2018.(19) The NSC recommendation was: “FIT offered at 50 to 74 years at as low a threshold as possible (down to FIT20); this will need to start at a manageable threshold but the aspiration would be to drive the threshold down with time.” In June 2019, FIT was implemented in England at a threshold of 120 µg Hb/g offered biennially to individuals aged 60 to 74 years.

The NSC decision making is restricted to screening. Endoscopy capacity is a key determinant in selecting the optimal screening programme that can be implemented. This study focussed on screening referral colonoscopies. The majority of endoscopy is due to symptomatic referrals and as part of surveillance programmes (estimated as 1.37m and 260,000 respectively in 2013/2014).(20) Changes to surveillance guidelines or symptomatic referral pathways, such as the introduction of FIT testing for symptomatic patients, have the potential to have a large impact on the available endoscopy capacity. Higher rates of screen detection will result in a decrease in the numbers of cancer presenting symptomatically. However, this may not significantly impact on the endoscopy capacity required for symptomatic referrals as many of these will not have CRC. To best share endoscopy resource between the symptomatic, screening and surveillance services it may be useful for future studies to compare CRC risk or potential to benefit (in terms of QALYs) between these services.

We note that these conclusions are based upon optimising cost-effectiveness. If the aim was to maximise QALY gains or CRC incidence/mortality reduction, then conclusions may be different.

Previous research

A study by Wilshut *et al*. compared FIT screening strategies for a Dutch population with limited colonoscopy capacity.(21) With unconstrained endoscopy capacity, the most cost-effective screening strategy was the most intensive one, which is consistent with the findings presented here.

A key difference between the two analyses is the number of screening strategies considered. In the Dutch study a total of 240 screening strategies were evaluated including 5 cut-off levels: (50, 75, 100, 150, 200 µg Hb/g), 4 start screening ages, 3 end screening ages and 4 screening intervals (1, 1.5, 2 and 3 years). In this study, 60,221 screening strategies were modelled. The higher number of strategies modelled here resulted in more robust conclusions. Other differences include the screening eligible age-range (45-80 vs 50-74), and CRC treatment costs (which vary by age at diagnosis in this analysis, but not in the Wilshut study). These differences make comparisons difficult. Recommendations from the Wilshut study were to increase the cut-off, narrow the age-range, restrict surveillance and reduce the number of screening rounds. However, it is not entirely clear how these conclusions have been reached.

Three other studies have investigated if it is more beneficial to screen at a longer interval with a more sensitive FIT, and had consistent findings to this study. (22)(23)(24)

Limitations and future research

More accurate predictions may have arisen from a more detailed model structure. For example, if adenomas types, sizes and multiplicity were explicitly modelled rather than using the low risk/high risk classifications. A cohort-level model was used, which limits the ability to incorporate patient-level evidence (for example, characteristics which influence screening uptake). (25) There is the potential to personalise FIT screening by varying the threshold for a positive result, dependent upon the individual's characteristics (such as age, gender and ethnicity). This has been shown to provide increases to FIT sensitivity and detection rates, although the impact on cost-effectiveness is unclear.

(26, 27) Risk-based screening strategies which relax constraints on a constant screening interval and FIT threshold may offer greater benefits for a fixed endoscopy capacity. (28-31)

A major source of uncertainty in this study related to the FIT sensitivity and specificity estimates. Data from the UK FIT pilot has a relatively small sample size (small number of CRC detected) which means estimates are associated with considerable uncertainty. To enable a better understanding in the future it is essential that further UK data on the CRC detection rates (in an unscreened population of known age in the BCSP) are collected at a low FIT threshold. The test characteristics estimated at initial screening round have been extrapolated to subsequent screening rounds which leads to considerable uncertainty, which could be explored in future analyses. Using country specific data is preferred as international variation in follow up practices can impact on test characteristics. For example, false positive rates may be higher if persons with 'No adenomas detected' at colonoscopy are re-invited to screening after a shorter time interval. Collectively, these uncertainties may have affected the comparative estimates; particularly when comparing lower cut-offs and longer intervals to higher cut-offs and shorter intervals.

A further limitation is the lack of full PSA for all screening options due to computational challenges. However, sensitivity analyses were undertaken to explore key model uncertainties and PSA undertaken
for a core set of screening strategies resulted in mean costs and QALYs which only differed slightly to the deterministic results. This manuscript reports the evidence and results which informed the UK NSC's decision making. Contemporary evidence may result in different results, which could limit the generalisability of these findings.

Figure 1: Choice of outcome measures for optimising a cancer screening programme

Figure 2: Detection rates and false positives from the FIT pilot: fitted curves

Appendix 1: Model description

Appendix 2: Additional Results

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