Moving from guaiac faecal occult blood test (gFOBT) to a faecal immunochemical test for haemoglobin (FIT) in the bowel screening programme: A consultation

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Proposal for consultation:

That the bowel screening programme adopt FIT (faecal immunochemical test for haemoglobin) as a replacement for gFOBT (guaiac faecal occult blood test) in the bowel cancer screening programme.

There is no proposal to change other aspects of the programme such as bowel scope or follow up diagnosis, treatment or surveillance.

Summary

Colorectal cancer (CRC) is the third most common cancer in the UK accounting for 13% of all diagnosed cancers and is the second most common cause of cancer death (10% of all cancer deaths).[1] The average lifetime risk of CRC in the UK is significantly higher in men (1 in 14) than women (1 in 19)[1], with 95% of cases being diagnosed in people aged 50 years and over.[1]

Recent data records a 5-6% increase in CRC incidence over the last decade as well as a fall in mortality of 14% over the same period.[1]

Screening for bowel cancer

The natural history of CRC makes it suitable for CRC screening. Bowel polyps are common but, because around 1 in 10 progresses to potentially metastatic cancer and that process appears to take about 10 years[2], there is a window of opportunity for screening and early detection. Early detection can improve the 7% 5-year survival rate of a metastatic cancer to 93% by down-staging to a Dukes' stage A (Where cancer is only in the innermost lining of the colon or rectum or slightly growing into the muscle layer) at diagnosis.[1] Whilst high quality colonoscopy (invasive procedure where a flexible, slim, telescopic camera is used to look at the lining of the large bowel) with specialist histopathology is the definitive diagnostic investigation, it is not feasible or practical for population screening. Colonoscopy carries a small but significant risk of perforation and mortality[3], needs to be carried out by specially trained clinical staff and for many subjects colonoscopy is unlikely to prove an attractive primary screening modality.

The unexplained presence of blood in stool is a well-recognised symptom of colorectal pathology. The presence of blood in faeces, whether hidden (occult) or overt, is an indicator for referral and further investigation[4]. Whilst loss of a small volume of blood (perhaps up to 1.5 mL /day) into the faeces is normal,[5] increasing amounts are indicative of inflammatory disease and particularly of advanced adenomas (pre-cancers) and cancer. There is a loose relationship between the stage of cancer, number of lesions and degree of blood loss but, although most cancers will bleed, the degree and frequency of bleeding is unpredictable.

The aim of screening is to lower the burden of cancer in the population by discovering disease in its early latent stages. This permits more effective treatment than if diagnosed later when symptoms occur. Early treatment of invasive lesions, for example by endoscopic resection of early CRC, can be generally less detrimental for quality of life. The endoscopic removal of pre-malignant lesions also reduces the incidence of CRC by stopping the progression to cancer. Randomised trials in people of average risk invited to attend screening have shown a reduction in CRC mortality[6,7,8,9] and incidence[10].

Current screening strategies

Each UK country uses gFOBT as the screening test:

England
All men and women between 60 and 74 are offered screening for bowel cancer every two years. http://www.cancerscreening.nhs.uk/bowel/

England is also rolling out flexible sigmoidoscopy for 55 year olds (the bowel scope programme) as an addition to gFOBT. NHS bowel scope screening

Scotland
All men and women between the ages of 50-74 are invited to participate in the bowel screening programme. Screening Scotland - Bowel screening | NHS inform. As part of the Scottish Bowel Screening Programme, bowel scope screening (flexisigmoidoscopy) is being offered to some men and women aged around 60 in Scotland. Screening Scotland - Bowel screening - Bowel scope screening | NHS inform Scotland is rolling FIT testing out.

Northern Ireland
All women and men aged 60 to 74 are offered screening very two years Bowel cancer screening | HSC Public Health Agency

Wales
Bowel Screening Wales invites all men and women aged 60-74 for bowel screening every two years. http://www.bowelscreening.wales.nhs.uk/

The current test:

gFOBT

There is good evidence that gFOBT screening reduces CRC mortality by 14%–16% in people of appropriate age invited to attend screening[11]
The NHS Bowel Cancer Screening Programme (BCSP) in England uses the Hema-Screen gFOBT card that was used in the UK CRC screening pilot of 2000-2004[12, 13, 14] . The test card has three pairs of application windows, each pair for a different stool sample. The screening programme in England uses 5 or 6 positive windows on the first test to designate the screen 'abnormal'. The gFOBT screening algorithm is illustrated in appendix 1. This three-test screening algorithm results in 5.1% and 4.7% loss of subjects at the second and

third invitation respectively (ScHARR, publication pending). Each subject lost had 1-4 positive windows on their first test card, but failed to provide a repeat test to reach a definitive test result.

Flexible sigmoidoscopy (FS)

The English bowel screening programme is currently rolling out flexible sigmoidoscopy (FS) to all 55 years olds (FS). Scotland offers FS to some people around the age of 60. This followed the publication of an RCT that demonstrated the effectiveness of a once-in-a-lifetime FS to reduce CRC incidence by 23% and mortality by 31% in those invited to FS[15]. Their observations were largely confirmed by studies in Italy[16], Norway[17,18] and the US[19]. Whilst gFOBT screens for the presence of CRC (its impact on adenomas and polyps], whilst important, is largely fortuitous), FS screens for the presence of adenomas and polyps in the sigmoid colon, rectum and anus, and therefore has a preventative role.

Immunochemical FOBT (FIT)

Direct evidence of mortality and morbidity benefits of using FIT

There has been one RCT evaluating the efficacy of FIT screening. In this study, 94 423 individuals were offered a once-only FIT screen. After 8 years, the investigators found a statistically significant 32% reduction in rectal cancer mortality, but no reduction in colonic or overall CRC mortality[20]. There are two caveats concerning this study: Firstly, follow-up of positive FIT was performed by flexible sigmoidoscopy, which may explain the lack of effectiveness in the entire colon. Furthermore, randomisation was based on townships and not on individuals[11].
In addition, three Japanese case–control studies evaluated the efficacy of FIT[21,22,23]. All three studies found a significant reduction in CRC mortality from FIT screening, ranging from 23% to 81%, depending on the study and years since last FIT.

Comparisons with gFOBT

There have been 13 population-based screening studies comparing performance characteristics of gFOBT and FIT[24,25,26,27,28,29,30,31,32,33,34;35,36]. Although the studies used different tests and slightly different protocols, the results of all studies consistently showed that FIT has significantly higher sensitivity for advanced adenomas and cancer than the gFOBT. For some cut off levels for referral, FIT was also more specific[11]

Quantitative FIT performance in average-risk asymptomatic individuals: sensitivity and specificity for CRC.

Study	FIT product	Population (n)	Cut-off*	Sensitivity (95% CI)	Specificity (95% CI)
Park *et al*[37]	OC-Micro**	770 invited for screening	20	92.3% (64.0%,99.8%)	90.1% (87.7%,82.1%)

		colonoscopy			
de Wijkerslooth *et al*[38]	OC-Micro	1,256 invited for screening colonoscopy	20	75% (36%,96%)	95% (93%,96%)
de Wijkerslooth *et al*[38]	OC-Micro	1,256 invited for screening colonoscopy	10	88% (47%,99%)	91% (89%,92%)
Brenner & Tao[39]	OC-Micro	2,235 invited for screening colonoscopy	6.1	73.3% (45%,92%)	95.5% (95%,96%)
Hol *et al*[40]	OC-SENSOR	5,007 invited for FIT screening	20	Not available	95.8%*** (93.2%,97.5%)

*Cut-off for positivity (µg Hb/g faeces); **OC-Micro is another product from Eiken Chemical Co. Ltd., Japan; the analyser is smaller than OC-SENSOR DIANA; *** Estimated under the rare disease assumption.[40]

Costs

Economic modelling of FIT has been undertaken by ScHARR for gFOBT, FIT and FS[41] and found that all options reduced the long-term economic burden from CRC with cost-effectiveness increasing in succession from gFOBT to FIT to FIT combined with FS. In the Netherlands Wilschut.[42, 43] examined the economics of using either gFOBT or FIT with different thresholds; modelling demonstrated that all options brought long-term economic savings, gFOBT was the least cost-effective and FIT became increasingly cost-effective as the threshold fell from 40 µg Hb/g faeces to 10 µg Hb/g faeces.
In a companion paper to this commissioned to examine the cost effectiveness of FIT compared to gFOBT[44] , Murphy and Gray concluded that FIT is cost-effective under base case assumptions and across various sensitivity analyses at a range of FIT cut-off values. The results also suggest that FIT is cost-saving compared to gFOBT for all FIT cut-off values using base case model assumptions.

Staffing

Endoscopy

FIT is sensitive to much lower concentrations of blood than gFOBT and therefore can detect cancers more reliably and at an earlier stage. FIT is also substantially better at detecting advanced adenomas. This means that FIT can find many more cancers. As the follow up to a positive FIT is a colonoscopy depending where the cut off (level of blood in stool detected to denote a positive screening test) is set this could put even more pressure on an already stretched colonoscopy service.

By adjusting the cut off of FIT the BCSP can ensure that test positivity and the referral rate is appropriate for the available colonoscopy resource. As colonoscopy capacity grows or demand shifts the UKNSC and programme will recommend alteration of the cut offs to maximise the number of cancers detected. As FIT is more acceptable, and has led to higher uptakes, this will also need to be taken into account when considering the cut off levels.

Laboratories

Whilst some reorganisation of laboratory space will be required and new laboratory benching, power and deionised water supplies might need to be installed, the overall analytical space requirement will be smaller than is currently required. The pre-analytical processing and refrigeration storage space is likely to need to grow and will depend on the technology used to open the FIT package. Manual opening of up to 8,000 FIT packages a day needs a technological solution. FIT allows for the use of conventional modern analytical principles (immunoassay), automated analytical systems, requires a small number of analytically trained staff and provides objective analytical results from an optical instrument measurement.

Kit transport

Packed FIT devices occupy a great deal of space. The package size is also large for bulk shipping prior to distribution by commercial organisations and the cost of on-site box construction and packaging from flat card should be considered.

Sample stability is less than that for gFOBT (acceptably <10 and probably <15 days).

QA and QC

All FIT analysers will need to be subject to daily internal QC procedures. Agreed national QA protocols should be developed and adopted by each screening Hub and the BCSS FIT software must enable QC data to be shared across Hubs and a sensitive QC monitoring system instituted at rollout.

Acceptability

FIT consistently shows better participation rates than those achieved by gFOBT[45] and it is unexpectedly high participation rates that have contributed to the endoscopy resource challenges faced by some countries adopting FIT[46]. Participants find FIT easier to use than gFOBT[47,48,49]. The insertion of the FIT sample probe back into the collection device is still likely to be a challenge but current feedback suggests it is easier than with the gFOBT card system. For most subjects the plastic serrated sampling probe is easier to use than the cardboard spatula, it is cleaner and once inserted into the device the faecal sample is hidden

from view and effectively sanitised. A single-sample FIT means that a planned approach to participation and sample collection is not necessary (*e.g.* waiting until the weekend to avoid collection at work or waiting until after returning from holiday).

The demographics of BCSP non-participants in the UK highlight first-time invitees (younger subjects), males and the deprived populations as those less likely to participate.[50] The 2014 FIT Pilot demonstrated increases in these groups from 50.2% to 61.5% (first-timers), 57.0% to 65.5% (men) and from 46.9% to 55.1% (IMD quintile 5 [most deprived]).[51],[52,] Indeed, the increase in participation rate was highest in these 'hard to reach' groups.

The single FIT brings a further advantage for participants in that the time between invitation, returned result and, for participants with a positive test result, diagnostic test, is much shorter[51,52] as participants noted this in the pilot.

IT

The way the bowel cancer screening IT system (BCSS) interfaces with the FIT analytical system should be reviewed to ensure that it is suitable. The FIT QC data collection and sharing software was part of the FIT Pilot software specification but was not completed prior to the Pilot. These data will provide a valuable tool for internal QC, particularly to determine instruments that appear as 'outliers' or for reagent batches that show bias. The software design should be reviewed by the programme and if necessary revised and QC monitoring and review procedures developed by the hubs and shared with Screening Quality Assurance Services .

The combination of FIT, bowels scope and shifting sensitivities will require an IT system that is able to accommodate data changes.

Public information

The public information will need to be updated in order to accommodate the proposed changes

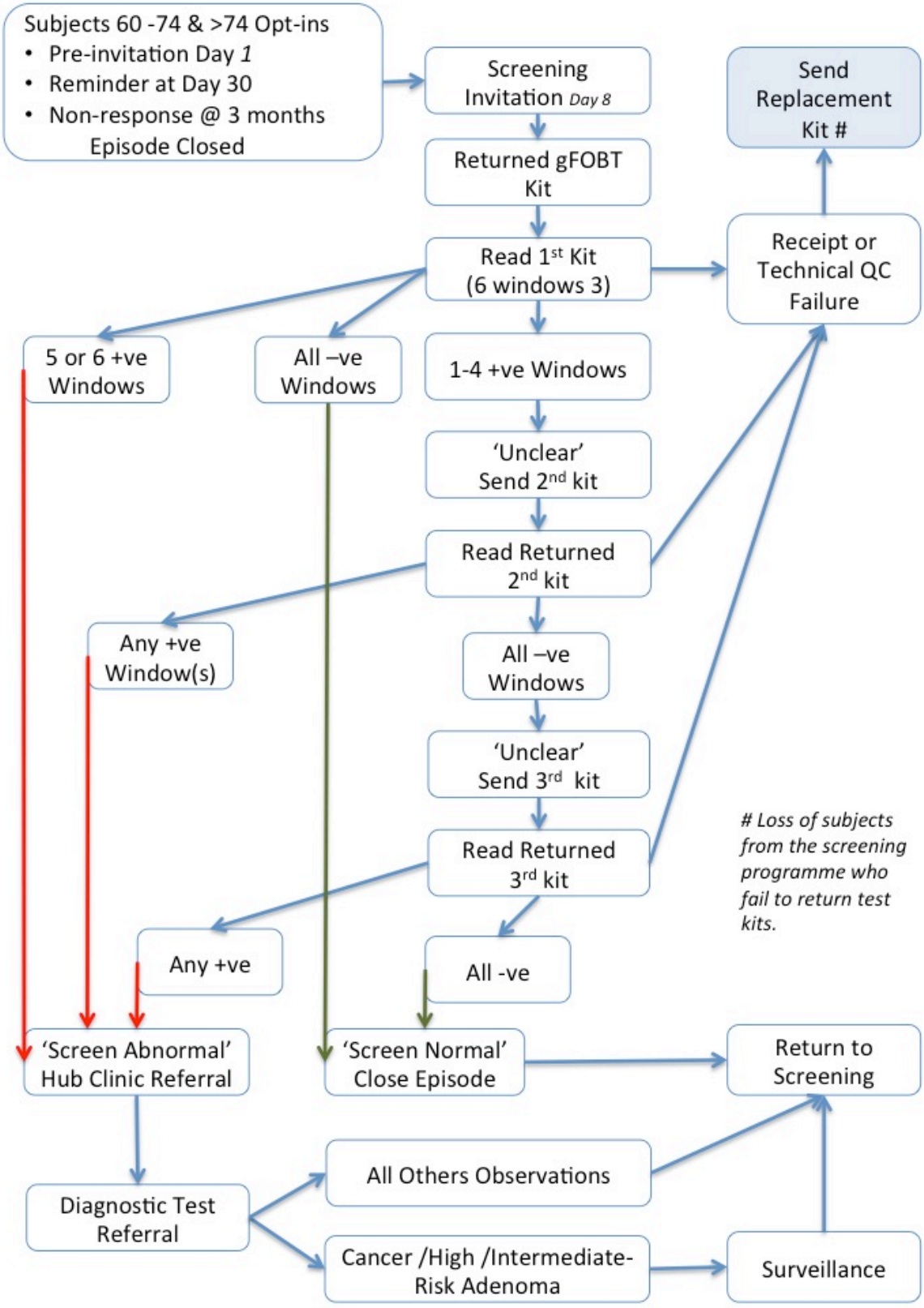
Summary comparison table

	gFOBT	**FIT**	**Comments**
Population-based Evidence	4-5 RCT	Large pop'n c.f. with gFOBT	
Analytical method	Manual colorimetic	Automated Immunoassay	gFOBT by eye
Analytical specificity	Oxidants & faecal dyes Release of oxygen from H_2O_2	Human globin only	

Analytical interference	Red meat, some vegetables, vit. C&E	None reported	
Analytical sensitivity	Low *(300 ug/g faeces)*	High *(10ug/g faeces)*	Product dependent
Analytical throughput	50/hr/person	260/hr/analyser	Analyser /person dependent
Positivity	1.5 – 3.5%	Determined by BCSP	Episode /subject dependent
Faecal Samples No.	3 – 9 /Episode	1 /Episode	Ex. spoilt kit
Anatomic specificity	All GI tract (inc. gums)	Primarily colorectum	
Sample stability	21 days	Minimum 10+ days	Cut-off dependent
Quality control	EQAS difficult IQC positivity monitoring	EQAS difficult Good analyser IQC	
Uptake (Pilot)	59%	67%	Episode age & sex dependent
Equity of Access	Poor uptake from low IMD, men, blind, less dexterous	Better uptake c,f, gFOBT, low IMD & men	Single sample better for elderly
Operator – No. /skills /banding	Many with practice and aptitude (Band 2 or 3)	Few with aptitude (mix of Band 3/6/7)	
Mailing /package	Only a special envelope	Best in a package	Meets UN3374
Procurement	Choice from about 4	Choice from about 4	FIT needs analyser with IT interface
Turn around time	1-3 working days (staff dependent)	1 working day	
Lab Staff required	25 Band 2/3	4 Band 4/6/7	Rough estimate
Kit cost	25 - 40p	£1 – 2.5	Inc. of analyser

Appendix 1

gFOBT screening



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