NHS Bowel Cancer Screening Programmes: Evaluation of pilot of Faecal Immunochemical Test : Final report.

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Summary

The NHS BCSP has performed a pilot study of faecal immunochemical testing (FIT) in 2 of the 5 English Hubs to study the logistics, acceptability and diagnostic performance of FIT compared to the guaiac-based test (gFOBt). This paper presents the results of the epidemiological evaluation of this pilot study;

In order to obtain estimates of outcomes for a range of cut-off concentrations of the FIT test, the pilot used a cut-off concentration of 20μg/g (equivalent to 100 ng/mL).

Overall uptake in people sent a test kit was 66.4% for FIT compared with 59.3% for gFOBt (OR 1.35, 95% CI 1.33-1.38, p<0.001). The increase in uptake was greatest in the prevalent screening round, and higher in males than females. The increase was seen across all quintiles of deprivation, but there was no significant difference in the increase between quintiles.

The time interval between the date the first kit was sent and the definitive result was significantly shorter with FIT (median 9 days for FIT vs 19 days for gFOBt).

The overall positive rate with FIT for the cut-off concentration of 20μg/g was 7.8% compared to 1.7% with gFOBt (OR 4.82, 95% CI 4.59-5.05). The increase in positivity with FIT was similar in males and females and in deprivation quintiles, but increased with increasing age.

There was no significant difference in the uptake of colonoscopy between subjects positive with FIT and those positive with gFOBt.

There was a significant increase with FIT in detection of cancers, advanced adenomas, and all neoplasms. The PPV of colonoscopy for cancer was lower with FIT, but that for advanced adenoma was similar for gFOBt, and that for all neoplasms significantly higher. Even with a cut-off concentration of 150 μg/g, giving a positivity similar to gFOBt, or of 180 μg/g (giving a similar rate of referral after allowing for the increase in uptake), FIT had a higher detection rate and PPV of advanced adenomas and a higher PPV for of all neoplasms.

Further work will include further analysis of the effect of different cut-off concentrations for FIT, and the potential for using a variable cut-off concentration according to subject characteristics.

Background

Randomised trials have shown screening using guaiac-based faecal occult blood tests (gFOBt) to be effective in reducing mortality from bowel cancer(1). The NHS Bowel Cancer Screening Programme (NHSBCSP) in England currently uses gFOBt, and invites men and women aged 60-74 (inclusive) every two years. The alternative faecal immunochemical test for haemoglobin (FIT) has the potential advantages of being easier to use, requiring a single stool sample (three are used for gFOBt), of being analytically more specific and being sensitive for human blood. It also has the advantage of being quantitative, allowing the use of different faecal haemoglobin cut-off concentrations to determine referral for colonoscopy. However the costs of using FIT will be greater than for gFOBt.

The NHSBCSP has performed a pilot study of FIT to study the logistics, acceptability and diagnostic performance of FIT compared to gFOBt. This paper presents the results of the epidemiological evaluation of this pilot study.

Pilot study

The pilot took place in two of the five English NHSBCSP Hubs; Midlands & North West Hub (BCS01), and Southern Hub (BCS02). Each Hub currently invites 1.1 – 1.2 million subjects each year. Over a 6 month invitation period, each Hub invited 1 in 28 subjects at random to complete a FIT instead of a gFOBt. The details of this process at the Hubs are explained in Appendix 1. The first FIT invitations were sent on 07.04.2014, and the last invitations on 06.10.2014. Subjects are sent a pre-invitation letter 7 days prior to being sent a test kit; the pre-invitation letters for gFOBt and FIT were similar but the FIT group also received an additional single sheet explaining the rationale for the FIT Pilot. The denominator for uptake was based on the number of subjects sent a pre-invitation.

The NHSBCSP, unlike other population screening programmes, uses a protocol whereby only subjects with 5 or 6 positive windows out of the 6 windows on the gFOBt kit are designated as definitive positives and referred directly to colonoscopy. Those with 1-4 positive windows (‘weak positive’ kits) are sent a further kit, and are designated as definitively positive if one or more windows on this kit is positive, or if all are negative but any on a further kit is positive.

The FIT system used for the Pilot was the OC-SENSOR (Eiken Chemical Co. Ltd., Japan, supplied by Mast Diagnostics, UK). Laboratory analysis of faecal samples using the OC-SENSOR DIANA analyser provided a measure of the haemoglobin (Hb) concentration of faecal samples in ng Hb per mL of buffer. The volume of buffer and sample used in different FIT products varies, and to facilitate future comparison of performance between OC-SENSOR and other FIT systems, Hb concentrations are quoted in this report as µg Hb/g faeces (also standardised and provided as ng Hb/mL buffer).. The pilot used a cut-off Hb concentration of 20 µg Hb/g faeces (equivalent to 100 ng Hb/mL buffer) to determine a positive test result and referral to colonoscopy.

The aims of this evaluation were to compare FIT and gFOBt in terms of uptake, the proportion of positive tests (positivity), the uptake of colonoscopy in test-positive subjects, and detection rates and positive predictive value (PPV) for cancer, adenoma and advanced adenoma. A separate economic evaluation will be reported elsewhere.

The use of a relatively low cut-off to determine a positive FIT and referral for colonoscopy enabled the evaluation to assess the effect on screening outcomes of using a range of cut-off concentrations at and above that used in the pilot.

Data collection

All data required for the epidemiological evaluation were recorded on the Bowel Cancer Screening System (BCSS) database. Individual anonymised data were downloaded to the Centre for Cancer Prevention, QMUL. Data were downloaded at intervals during the pilot; the final download was extracted at the beginning of April 2015.

Data downloaded also included those on people invited to perform gFOBt during the pilot period, enabling uptake, positivity and detection rates to be compared between test kits.

Data for each subject included age (in years) at invitation, gender, type of screening episode and details of the previous screening episode, together with results of each test returned.. Level of deprivation was measured using the Index of Multiple Deprivation (IMD) 2010 and associated with the lower super output areas (LSOA) derived from the subjects' postcode of residence. The indices of deprivation are derived from aggregated measures of income, employment, health, disability, education, crime, barriers to housing and services and living environment from the UK 2010 census(2). IMD score was supplied by the BCSP.

IMD quintiles were based on the recorded IMD scores for all participants associated with either Hub. The IMD quintiles were Q1: 0.61- 7.38; Q2: 7.39-11.77; Q3: 11.78-17.41; Q 4: 17.42-27.97; Q5: 27.98- 83.33.

The data also included results of colonoscopies following positive test results. Data on attendance at and results of colonoscopy included size, histology and location of each polyp, and histology, location and stage of cancers detected.

Methods

Only subjects invited for screening in Hubs BCS01 and BCS02 were included in the analysis. (This association is determined by BCSP from the postcode of the subject's registered GP at the time of invitation). A total of 82 subjects outside the age range 59-75 were excluded. Subjects aged 59 and 75 at the date of pre-invitation were included because they can be selected for routine invitation according to their year of birth.

Episode type and sequence number were used to classify screening episodes as first invitations, prevalent (previous non responders) and incident (previously screened).

For subjects in whom one or more adenoma (but not cancer) were detected, adenomas were classified as high, intermediate or low risk (HR, IR or LR) using the same criteria as used in the NHSBCSP (see Appendix 2).

Outcomes have been analysed by gender and age, screening episode type, and by deprivation. Definitions of the relevant variables used are given in Appendix 2.

Uptake was calculated as the proportion of subjects sent the pre-invitation letter who were adequately screened. (see Appendix 2).

Positivity was calculated as the proportion of adequately screened subjects who had a definitive positive result.

Colonoscopy uptake was calculated as the proportion of subjects with a positive kit result who had a colonoscopy outcome/episode outcome. This will include a small number of subjects who had alternative diagnostic tests such as flexible sigmoidoscopy or CT.

Detection rates were calculated as

Number of cancers diagnosed / number of subjects adequately screened

Number of Advanced Adenoma (HR + IR Adenoma) / number of subjects adequately screened

Number of neoplasms (Cancer + HR + IR + LR Adenoma) / number of subjects adequately screened

PPV of colonoscopy was calculated as

PPV for cancer: cancer diagnosed / definitive colonoscopy outcome
PPV for advanced adenoma: Advanced Adenoma (HR + IR Adenoma) / definitive colonoscopy outcome
PPV for all neoplasms: (Cancer + HR + IR + LR Adenoma) / definitive colonoscopy outcome

Logistic regression was used to calculate odds ratios for univariate and multivariate analyses (adjusted for Hub, age, gender, and screening episode type), and to study interactions of these factors with type of test kit.

Results in terms of cancer/adenoma detection and PPVs have been calculated for a range of FIT concentration cut-offs, including a concentration of 150 µg Hb/g faeces, which results in a similar overall positive rate to that of gFOBt, and a concentration of 180 µg Hb/g faeces, which would give a similar proportion of subjects invited referred to colonoscopy, taking into account the increased uptake with FIT.

Results

Overall a total of 40,930 subjects were invited to complete a FIT during the pilot study period and 1,126,087 subjects were invited to complete a gFOBt during the same period. Table 1 gives the breakdown of subjects invited by screening episode type, age group, gender, Hub and IMD quintile.

The last returned kits were received on 02.04.2015. At the time of the data download (05.04.2015), 2.4% of subjects invited during the six-month pilot study period with a positive test result had open screening episodes (1.9% for FIT and 2.5% for gFOBt). The difference may be explained by the longer time taken to obtain a definitive test result with gFOBt due to the need for three stool samples and the repeat testing of 'weak positives'. Of the 333 open episodes, only 79 subjects had not attended a colonoscopy. The remaining 254 had attended at least once for colonoscopy, and results have been based on the most serious outcome. Data on size, histology and location of polyps were available for all polyps detected. Data on cancer stage was only available for 24 % of cancers; 10% had Dukes stage and 19 % had TNM stage recorded.

Uptake

Overall uptake was 66.4% for FIT compared with 59.3% for gFOBt (OR 1.35,95% CI 1.33-1.38, p<0.001). A total of 25,312 subjects declined invitation to screening before a testkit was sent (2.15% of those sent FIT invitations and 2.17% of those sent gFOBt invitations).

Table 2 shows uptake of FIT and gFOBt by screening round, age group, gender, Hub and IMD quintile.

Compared with gFOBt, FIT was associated with a significant increase in uptake in all screening episode types (p<0.001); the most marked difference was seen in prevalent (previous non-responder) episodes (FIT 23.9% vs gFOBt 12.5%; OR 2.19, 95% CI 2.10-2.29), compared with prevalent (first time invitees) (61.2% vs 50.4%; OR 1.55, 95% CI 1.48-1.63) and incident (90.1 vs 85.8%; OR 1.50, 95% CI 1.43-1.57) episodes (Table 2a); the variation in the increase in uptake with FIT between screening episode types was significant (p<0.001).

Whilst the uptake was higher in females then males for both FIT and gFOBt, FIT reduced the difference between genders; the increase in uptake was significantly higher in males (difference 8.1%; FIT 64.5% vs gFOBt 56.4%; OR 1.41, 95% CI 1.36-1.45) than females (difference 6.0%; FIT 68.1 % vs gFOBt 62.1; OR 1.31, 95% CI 1.27-1.34) (Table 2c. There was a significant interaction of test kit with age, with a lower increase at older ages, but this was not significant when adjusted for screening episode type. Uptake of both FIT and gFOBt was slightly higher in Hub BCS02 than in Hub BCS01, but the increase with FIT was similar in the two Hubs.

Uptake with both FIT and gFOBt showed the expected decreasing trend with increasing level of deprivation. The increase in uptake with FIT in IMD quintile 5 (the

most deprived quintile) was 54.3% vs 46.5%, (OR1.37, 95% CI 1.31-1.43) and in quintile 1(the least deprived quintile) 73.5% vs 66.9% (OR 1.37, 95% CI 1.30-1.44); the variation in the increase in uptake across quintiles was not significant, (either unadjusted or adjusted for all other variables).

Table 3 shows the results of the multivariate analysis; the effect of all variables on uptake remained highly significant ($p<0.0001$). The increased odds ratio for FIT in this analysis (1.74, 95% CI 1.70-1.79) is mainly due to the inclusion of screening episode type, with the largest increase in uptake observed in prevalent episodes which have the lowest uptake.

If IMD score - as a continuous variable - was considered, the interaction with type of kit was not significant in a univariate analysis, but became significant ($p =0.011$) in a multivariate analysis including age, gender, Hub and screening episode.

Positivity

The overall positive rate was 7.8% for FIT with the chosen 20µg/g cut-off concentration, and 1.7% with gFOBt (OR 4.82, 95% CI 4.59-5.05). Table 4 shows positivity by screening episode type, age group, gender, Hub and IMD quintile. The positive rate of FIT and the increase compared with gFOBt were significantly higher in Hub BCS01 (8.7% positive with FIT vs 1.6% with gFOBt, OR 5.68, 95% CI 5.30-6.08) than in Hub BCS02 (7.1% positive with FIT vs 1.8% with gFOBt, OR 4.16, 95% CI 3.89-4.45), whereas the positivity with gFOBt was higher in BCS02.

Positive rates for both FIT and gFOBt were highest in prevalent (previous non-responder) screening episodes, but the increase with FIT was highest in the incidence round (OR 5.06, 95% CI 4.79-5.35) (Table 4a). Positivity for both tests was higher in males than females, but the increase with FIT was similar (Table 4b). However the effect of FIT on positivity increased significantly with increasing age. The increase in positivity was similar across IMD quintile (both overall and in the individual Hubs) (Table 4c).

Table 3 gives the results of the multivariate analysis. The adjusted OR for FIT was 4.70 (95% CI 4.48-4.94). Even in a multivariate analysis the difference in the increase in positive rate between Hubs remained significant.

Uptake of colonoscopy

Overall colonoscopy uptake was 85.3% in subjects positive with FIT, and 84.9% in those positive with gFOBt (Table 5). The difference was not significant. There was a slightly greater increase in colonoscopy uptake with FIT in females than males, but the difference in the increase between genders was not significant. There was some variation with IMD but no clear trend.

Detection rates

Table 6 shows detection rates by screening episode type, age group, gender, and Hub.

There was a significant 2 fold increase in detection of cancers, a 4 fold increase in advanced adenomas, and a 5 fold increase in all neoplasms. The cancer detection rate was 0.27% with FIT and 0.12% with gFOBt (OR 2.20, 95% CI 1.73-2.79, p<0.001).

Detection rates of advanced adenoma were 1.73% and 0.35% respectively (OR 4.97, 95% CI 4.50-5.49), p<0.001), and of all neoplasms 3.74% and 0.76% (OR 5.05, 95% CI 4.72-5.41, p< 0.001).

For advanced adenomas and all neoplasms there was a significant difference in the increased detection with FIT between screening episode types, with the greatest increase observed in incident screens. There were no significant differences in the increase in detection with other variables, but Hub BCS01 (with higher positivity) had higher detection rates of advanced adenomas and all neoplasms than Hub BCS02.

PPV

Table 6 also shows PPVs by screening episode type, age group, gender, and Hub.

The PPV of colonoscopy for cancer was significantly lower for FIT than for gFOBt (4.0% vs 8.3%, OR 0.46, 95% CI 0.36-0.59, p<0.001), but the PPVs for advanced adenoma were similar between tests (26.0% vs 24.1%, OR 1.10, 95% CI 0.98-1.23, p=0.1).

For all neoplasms the PPV was higher for FIT; 55.6% vs 51.8% (OR 1.17, 95% CI 1.06-1.29, p=0.003).There were no significant differences in the increase between episode types, gender or Hub.

FIT cut-off concentrations

Table 6 also shows FIT positivity with different faecal Hb cut-off concentrations. Even with a cut-off concentration of 180 µg Hb/g faeces (900 ng Hb/mL buffer), which would result in a similar number of people attending colonoscopy to gFOBt after accounting for the increased uptake, FIT had a significantly higher detection rate and higher PPV for advanced adenomas and a higher PPV for all neoplasms.

Table 6b and 6c and Figures 1 and 2 give the detection rates and PPVs using different FIT cut-off concentrations by gender and screening episode type.

Number of kits sent

A total of 4.8% of gFOBt subjects received more than one kit compared with 2.2% of FIT subjects (Table 7). Those receiving more than one FOBt kit were primarily those with a weak positive result from the first test; for FIT the main reason for repeat testing was a missing date on the returned kit.

Time to definitive result and colonoscopy

Figure 3 shows the number of days from the date the first kit was sent to the date a definitive result was recorded, and Figure 4 the number of days to the date of first diagnostic test, by type of test; for both there was a significantly shorter interval with FIT than gFOBt. For days to definitive results the median intervals were 9 days with FIT and 19 days with gFOBt, explained by both the need for three stool samples with gfOBt, and the protocol for repeat testing of 'weak positives'. Although the median time from a positive result to colonoscopy was the same with FIT and gFOBt (24 and 25 days respectively), the longer time from date kit sent to a positive result with gFOBt (10 days with FIT vs 35 days with gFOBT) resulted in a longer time from date kit sent to diagnostic test (median 39 days with FIT and 64 days for gFOBt).

Inadequate responses and spoilt kits

There were fewer FIT episodes with an inadequate response (0.3%) than gFOBt episodes (0.5%). although there was a higher number of FIT kits that were returned spoilt, 1.1% for FIT and 0.8% for gFOBt. The protocol for repeat testing increases the probability of a subject having at least one spoilt kit.

Discussion

The results demonstrate a considerable and significant increase in uptake with FIT, together with a reduced time interval both to obtaining a definitive result and to diagnostic test in those positive. The increase in uptake results both from more subjects returning the initial kit, and the requirement for only a single FIT test to be returned ; 1387 (4.6%) of the 30324 subjects returning a 'weak positive' first FOBt, do not subsequently have an adequate overall response.

The detection of both cancers and advanced adenomas is greatly increased using the relatively low concentration cut-off used in the pilot. The slightly higher proportion of open episodes in subjects with positive test results with gFOBt would reduce the differences only slightly (and would have no effect on PPVs, which are calculated based on those with a definitive diagnostic outcome). Even at a higher cut off which may be required due to the constraint of colonoscopy workload the detection rate and PPV of advanced adenomas are increased. It should be noted that the use of a single cut off concentration may result in different positive rates in different Hubs due to differences in demographic variables. It is likely that with repeat screening the positive rate will fall as subjects with adenomas are removed from the population.

Further work will focus on the effect of different cut-off concentrations for FIT, and the potential for using a variable cut-off concentration according to subject characteristics. The location of adenomas according to cut off concentrations will be explored. In addition it is planned to collect more complete data on the stage of cancers detected in the FIT cohort. There is scope for modelling work to examine both cut off concentrations and potential to increase the screening interval at low cut offs.

Table 1 Breakdown of Invitees by Hub and Test Kit

	FIT						gFOBt					
	BCS01		BCS02		Total		BCS01		BCS02		Total	
Invitees	19,289	47.13%	21,641	52.87%	40,930	3.51%	537,770	47.76%	588,317	52.24%	1,126,087	96.49%
Female	9874	51.19%	11190	51.71%	21064	51.46%	273949	50.94%	303098	51.52%	577047	51.24%
Male	9415	48.81%	10451	48.29%	19866	48.54%	263821	49.06%	285219	48.48%	549040	48.76%
59-64	8223	42.63%	9208	42.55%	17431	42.59%	228544	42.50%	246486	41.90%	475030	42.18%
65-69	6733	34.91%	7303	33.75%	14036	34.29%	187777	34.92%	201935	34.32%	389712	34.61%
70-75	4333	22.46%	5130	23.71%	9463	23.12%	121449	22.58%	139896	23.78%	261345	23.21%
IMD 1	2699	13.99%	5488	25.36%	8187	20.00%	74640	13.88%	148950	25.32%	223590	19.86%
IMD 2	3517	18.23%	4789	22.13%	8306	20.29%	95683	17.79%	127793	21.72%	223476	19.85%
IMD 3	3501	18.15%	4617	21.33%	8118	19.83%	96466	17.94%	127360	21.65%	223826	19.88%
IMD 4	3782	19.61%	4328	20.00%	8110	19.81%	105771	19.67%	117979	20.05%	223750	19.87%
IMD 5	5715	29.63%	2247	10.38%	7962	19.45%	162920	30.30%	61340	10.43%	224260	19.91%
IMD n/k	75	0.39%	172	0.79%	247	0.60%	2290	0.43%	4895	0.83%	7185	0.64%
First	3007	15.59%	3418	15.79%	6425	15.70%	84010	15.62%	90713	15.42%	174723	15.52%
Prevalent	5864	30.40%	5994	27.70%	11858	28.97%	160222	29.79%	162617	27.64%	322839	28.67%
Incident	10418	54.01%	12229	56.51%	22647	55.33%	293538	54.58%	334987	56.94%	628525	55.81%

Table 2a Uptake of FIT and gFOBt by screening round and hub

		Prevalent (first time invitees)		Prevalent (previous non-responders)		Incident (previous responders)		Total	
		Invited	Adequately Participated	Invited	Adequately Participated	Invited	Adequately Participated	Invited	Adequately Participated
FIT	HUB1	3,007	1,814	5,864	1,315	10,418	9,340	19,289	12,469
			60.33%		22.42%		89.65%		64.64%
	HUB2	3,418	2,119	5,994	1,516	12,229	11,063	21,641	14,698
			62.00%		25.29%		90.47%		67.92%
	Total	6,425	3,933	11,858	2,831	22,647	20,403	40,930	27,167
			61.21%		23.87%		90.09%		66.37%
gFOBt	HUB1	84,010	40,556	160,222	18,088	293,538	250,398	537,770	309,042
			48.28%		11.29%		85.30%		57.47%
	HUB2	90,713	47,515	162,617	22,251	334,987	289,137	588,317	358,903
			52.38%		13.68%		86.31%		61.01%
	Total	174,723	88,071	322,839	40,339	628,525	539,535	1,126,087	667,945
			50.41%		12.50%		85.84%		59.32%

Odds ratios (95% CI)

(FIT vs gFOBt) ; Prevalent (first time invitees) 1.55 (95% CI 1.48- 1.63) ,
Prevalent (previous non-responder) 2.19 (95% CI 2.10-2.29)) , Incident (previous responder) 1.50 (95% CI 1.43-1.57)

Table 2b Uptake of FIT and gFOBt by age group and gender

	59-64				65-69			
	Female		Male		Female		Male	
FIT	8,669	5,786	8,762	5,319	7,392	5,193	6,644	4,475
		66.74%		60.71%		70.25%		67.35%
gFOBt	238,797	140,490	236,233	118,385	201,103	132,170	188,609	115,851
		58.83%		50.11%		65.72%		61.42%

	70-75				Total			
	Female		Male		Female		Male	
FIT	5,003	3,375	4,460	3,019	21,064	14,354	19,866	12,813
		67.46%		67.69%		68.14%		64.50%
gFOBt	137,147	85,689	124,198	75,360	577,047	358,349	549,040	309,596
		62.48%		60.68%		62.10%		56.39%

Odds ratios (95% CI)

(FIT vs gFOBt) ; Females 1.31 (95% CI 1.27-1.34), Males 1.41 (95% CI 1.56-1.45)

Table 2c Uptake of FIT and gFOBt by IMD quintile*

		IMD1		IMD2		IMD3		IMD4		IMD5		n/k		Total	
		Invited	Adequately Participated	Invited	Adequately Participated	Invited	Adequately Participated	Invited	Adequately Participated	Invited	Adequately Participated	Invited	Adequately Participated	Invited	Adequately Participated
FIT	HUB1	2,699	1,968	3,517	2,489	3,501	2,422	3,782	2,470	5,715	3,072	75	48	19,289	12,469
			72.92%		70.77%		69.18%		65.31%		53.75%		64.00%		64.64%
	HUB2	5,488	4,047	4,789	3,357	4,617	3,148	4,328	2,778	2,247	1,252	172	116	21,641	14,698
			73.74%		70.10%		68.18%		64.19%		55.72%		67.44%		67.92%
	Total	8,187	6,015	8,306	5,846	8,118	5,570	8,110	5,248	7,962	4,324	247	164	40,930	27,167
			73.47%		70.38%		68.61%		64.71%		54.31%		66.40%		66.37%
gFOBt	HUB1	74,640	50,371	95,683	62,115	96,466	59,978	105,771	60,453	162,920	74,809	2,290	1,316	537,770	309,042
			67.49%		64.92%		62.18%		57.15%		45.92%		57.47%		57.47%
	HUB2	148,950	99,166	127,793	81,756	127,360	78,668	117,979	66,884	61,340	29,469	4,895	2,960	588,317	358,903
			66.58%		63.98%		61.77%		56.69%		48.04%		60.47%		61.01%
	Total	223,590	149,537	223,476	143,871	223,826	138,646	223,750	127,337	224,260	104,278	7,185	4,276	1,126,087	667,945
			66.88%		64.38%		61.94%		56.91%		46.50%		59.51%		59.32%

***IMD1 is least deprived quintile**

Odds ratios (95% CI) (FIT vs gFOBt) ;

IMD1 1.37 (95% CI 1.30-1.44), IMD2 1.31 (95% CI 1.25-1.38) ,IMD3 1.34 (95% CI 1.28-1.41) , IMD4 1.39 (95% CI 1.33-1.45), IMD5 1.37 (95% CI 1.31-1.43)

Table 3 Results of multivariate analysis for uptake and positivity

	Uptake				Positivity			
	OR (univariate)	95% CI	OR (multivariate)	95% CI	OR (univariate)	95% CI	OR (multivariate)	95% CI
FIT	1.35	1.33-1.38	1.74	1.70-1.79	4.82	4.59-5.05	4.70	4.48-4.94
Male			1.00				1.00	
Female			1.15	1.14-1.16			0.68	0.65-0.70
First invitation			1.00				1.00	
Prevalent			0.17	0.17-0.17			1.35	1.25-1.46
Incident			7.09	6.98-7.21			0.80	0.75-0.85
Age (years)			0.97	0.97-0.97			1.03	1.03-1.04
IMD quintile 1			1.00				1.00	
2			0.93	0.91-0.94			1.07	1.01-1.13
3			0.86	0.85-0.88			1.20	1.13-1.26
4			0.75	0.73-0.76			1.39	1.32-1.47
5			0.55	0.54-0.55			1.72	1.63-1.82
BCS01			1.00				1.00	
BCS02			1.02	1.01-1.04			1.16	1.12-1.1.20

Table 4a Positivity of FIT and gFOBt by screening round and hub

		Prevalent (first time invitees)		Prevalent (previous non-responders)		Incident (previous responders)		Total	
		Adequately Participated	Positive	Adequately Participated	Positive	Adequately Participated	Positive	Adequately Participated	Positive
FIT	HUB1	1,814	122	1,315	150	9,340	807	12,469	1,079
			6.73%		11.41%		8.64%		8.65%
	HUB2	2,119	125	1,516	141	11,063	782	14,698	1,048
			5.90%		9.30%		7.07%		7.13%
	Total	3,933	247	2,831	291	20,403	1,589	27,167	2,127
			6.28%		10.28%		7.79%		7.83%
gFOBt	HUB1	40,556	709	18,088	518	250,398	3,845	309,042	5,072
			1.75%		2.86%		1.54%		1.64%
	HUB2	47,515	813	22,251	684	289,137	5,006	358,903	6,503
			1.71%		3.07%		1.73%		1.81%
	Total	88,071	1,522	40,339	1,202	539,535	8,851	667,945	11,575
			1.73%		2.98%		1.64%		1.73%

Odds ratios (95% CI)

(FIT vs gFOBt) ; Prevalent (first time invitees) 3.81 (95% CI 3.32-4.38) , Prevalent (previous non-responders)3.73 (95% CI 3.26-4.27), Incident (previous responders) 5.06 (95% CI 4.79-5.35)

Table 4b Positivity of FIT and gFOBt by age and gender

	59-64				65-69			
	Female		Male		Female		Male	
FIT	5,786	329	5,319	436	5,193	336	4,475	411
		5.69%		8.20%		6.47%		9.18%
gFOBt	140,490	1,882	118,385	2,403	132,170	1,732	115,851	2,332
		1.34%		2.03%		1.31%		2.01%

	70-75				Total			
	Female		Male		Female		Male	
FIT	3,375	279	3,019	336	14,354	944	12,813	1,183
		8.27%		11.13%		6.58%		9.23%
gFOBt	85,689	1,432	75,360	1,794	358,349	5,046	309,596	6,529
		1.67%		2.38%		1.41%		2.11%

Odds ratios (95% CI)

(FIT vs gFOBt) ; Females 4.93 (4.59-5.29), Males 4.72 (4.43-5.04)

Table 4c Positivity of FIT and gFOBt by IMD quintile

		IMD1		IMD2		IMD3		IMD4		IMD5		n/k		Total	
		Adequately Participated	Positive	Adequately Participated	Positive	Adequately Participated	Positive	Adequately Participated	Positive	Adequately Participated	Positive	Adequately Participated	Positive	Adequately Participated	Positive
FIT	HUB1	1,968	146	2,489	190	2,422	184	2,470	225	3,072	330	48	4	12,469	1,079
			7.42%		7.63%		7.60%		9.11%		10.74%		8.33%		8.65%
	HUB2	4,047	238	3,357	211	3,148	234	2,778	231	1,252	127	116	7	14,698	1,048
			5.88%		6.29%		7.43%		8.32%		10.14%		6.03%		7.13%
	Total	6,015	384	5,846	401	5,570	418	5,248	456	4,324	457	164	11	27,167	2,127
			6.38%		6.86%		7.50%		8.69%		10.57%		6.71%		7.83%
gFOBt	HUB1	50,371	614	62,115	823	59,978	862	60,453	1,066	74,809	1,686	1,316	21	309,042	5,072
			1.22%		1.32%		1.44%		1.76%		2.25%		1.60%		1.64%
	HUB2	99,166	1,511	81,756	1,334	78,668	1,466	66,884	1,408	29,469	729	2,960	55	358,903	6,503
			1.52%		1.63%		1.86%		2.11%		2.47%		1.86%		1.81%
	Total	149,537	2,125	143,871	2,157	138,646	2,328	127,337	2,474	104,278	2,415	4,276	76	667,945	11,575
			1.42%		1.50%		1.68%		1.94%		2.32%		1.78%		1.73%

***IMD1 is least deprived quintile**

Odds ratios (95% CI)

(FIT vs gFOBt) ; IMD1 4.73 (95% CI 4.23-5.29), IMD2 4.84 (95% CI 4.33-5.40) ,IMD3 4.75(95% CI 4.27—5.29) , IMD4 4.80 (95% CI 4.33-5.33), IMD5 4.98 (95% CI 4.49-5.54)

Table 5a Uptake of diagnostic tests by screening round

	Prevalent (first time invitees)		Prevalent (previous non-responders)		Incident (previous responders)		Total	
	Positive Kit Result	Uptake of Diagnostic Test	Positive Kit Result	Uptake of Diagnostic Test	Positive Kit Result	Uptake of Diagnostic Test	Positive Kit Result	Uptake of Diagnostic Test
FIT	247	216 87.45%	291	227 78.01%	1589	1381 86.91%	2127	1824 85.75%
gFOBt	1522	1300 85.41%	1202	913 75.96%	8851	7622 86.11%	11575	9835 84.97%

Table 5b Uptake of diagnostic tests by gender

	Female		Male		Total	
	Positive Kit Result	Uptake of Diagnostic Test	Positive Kit Result	Uptake of Diagnostic Test	Positive Kit Result	Uptake of Diagnostic Test
FIT	944	826 87.50%	1183	998 84.36%	2127	1824 85.75%
gFOBt	5046	4269 44.60%	6529	5566 85.25%	11580	9835 84.97%

Table 6a PPVs and detection rates with different FIT cut-off concentrations

	gFOBt			FIT 20µg			FIT			
	BCS01	BCS02	Total	BCS01	BCS02	Total	40µg	100µg	150µg	180µg
Invited	537770	588317	1126087	19289	21641	40930	40930	40930	40930	40930
Adequately Participated	309042	358903	667945	12469	14698	27167	27167	27167	27167	27167
Positive Screening	5072	6503	11575	1079	1048	2127	1415	656	483	412
Positivity	1.64%	1.81%	1.73%	8.65%	7.13%	7.83%	5.21%	2.41%	1.78%	1.52%
Attended Diagnostic Test	4296	5539	9835	913	911	1824	1202	546	400	339
Uptake of Diagnostic Test	84.70%	85.18%	84.97%	84.62%	86.93%	85.75%	84.95%	83.23%	82.82%	82.28%
Cancer	383	435	818	34	39	73	65	44	40	36
High-risk Adenoma	471	521	992	103	109	212	165	88	67	56
Intermediate-risk Adenoma	609	763	1372	131	128	259	186	95	66	60
Low-risk Adenoma	794	1119	1913	240	231	471	298	124	81	63
Abnormal	1267	1751	3018	277	265	542	322	135	101	83
Normal (No Abnormalities Found)	772	950	1722	128	139	267	166	60	45	41
Cancer PPV	8.92%	7.85%	8.32%	3.72%	4.28%	4.00%	5.41%	8.06%	10.00%	10.62%
Advanced Adenoma (HR and IR) PPV	25.14%	23.18%	24.04%	25.63%	26.02%	25.82%	29.20%	33.52%	33.25%	34.22%
All Neoplasms PPV	52.54%	51.24%	51.80%	55.64%	55.65%	55.65%	59.40%	64.29%	63.50%	63.42%
Cancer Detection Rate	0.12%	0.12%	0.122%	0.27%	0.27%	0.27%	0.24%	0.16%	0.15%	0.133%
Advanced Adenoma (HR and IR) Detection Rate	0.35%	0.36%	0.354%	1.88%	1.61%	1.73%	1.29%	0.67%	0.49%	0.427%
All Neoplasms Detection Rate	0.73%	0.79%	0.763%	4.07%	3.45%	3.74%	2.63%	1.29%	0.93%	0.791%

Table 6b PPVs and detection rates by gender, with different FIT cut-off concentrations

	20µg		100µg		150µg		180µg		gFOBt	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Adequate Response	12,813	14,354	12,813	14,354	12,813	14,354	12,813	14,354	309,596	358,349
Positive Screened	1183	944	397	259	300	183	258	154	6529	5046
Positivity	9.23%	6.58%	3.10%	1.80%	2.34%	1.27%	2.01%	1.07%	2.11%	1.41%
Attended Diagnostic test	998	826	320	226	241	159	206	133	5566	4269
Uptake of Diagnostic Tests	84.28%	87.39%	80.60%	87.26%	80.33%	86.89%	79.84%	86.36%	85.25%	84.60%
Cancer	50	23	31	13	29	11	26	10	517	301
High-risk Adenoma	145	67	59	29	47	20	40	16	738	254
Intermediate-risk Adenoma	162	97	66	29	44	22	40	20	867	505
Low-risk Adenoma	264	207	66	58	46	35	37	26	1156	757
Abnormal	256	286	69	66	56	45	45	38	1529	1489
Normal (No Abnormalities)	121	146	29	31	19	26	18	23	759	963
Cancer PPV	5.01%	2.78%	9.69%	5.75%	12.03%	6.92%	12.62%	7.52%	9.29%	7.05%
Advanced Adenoma PPV	30.76%	19.85%	39.06%	25.66%	37.76%	26.42%	38.83%	27.07%	28.84%	17.78%
All Neoplasms PPV	62.22%	47.70%	69.38%	57.08%	68.88%	55.35%	69.42%	54.14%	58.89%	42.56%
Cancer Detection Rate	0.39%	0.16%	0.24%	0.09%	0.23%	0.08%	0.20%	0.07%	0.17%	0.08%
Advanced Adenoma Detection Rate	2.40%	1.14%	0.98%	0.40%	0.71%	0.29%	0.62%	0.25%	0.52%	0.21%
All Neoplasms Detection Rate	4.85%	2.74%	1.73%	0.90%	1.30%	0.61%	1.12%	0.50%	1.06%	0.51%

Table 6c PPVs and detection rates by screening episode type , with different FIT cut-off concentrations

	20µg			100µg			150µg			180µg			gFOBt		
	Prevalent (first time invitees)	Prevalent (previous non-responders)	Incident (previous responders)	Prevalent (first time invitees)	Prevalent (previous non-responders)	Incident (previous responders)	Prevalent (first time invitees)	Prevalent (previous non-responders)	Incident (previous responders)	Prevalent (first time invitees)	Prevalent (previous non-responders)	Incident (previous responders)	Prevalent (first time invitees)	Prevalent (previous non-responders)	Incident (previous responders)
Adequate Response	3,933	2,831	20,403	3,933	2,831	20,403	3,933	2,831	20,403	3,933	2,831	20,403	88,071	40,339	539,535
Positive Screened	247	291	1589	79	101	476	61	81	341	51	70	291	1522	1202	8851
Positivity	6.28%	10.28%	7.79%	2.01%	3.57%	2.33%	1.55%	2.86%	1.67%	1.30%	2.47%	1.43%	1.73%	2.98%	1.64%
Attended Diagnostic test	216	227	1381	69	76	401	54	58	288	44	51	244	1300	913	7622
Uptake of Diagnostic Tests	87.45%	78.01%	86.91%	87.34%	75.25%	84.24%	88.52%	71.60%	84.46%	86.27%	72.86%	83.85%	85.41%	75.96%	86.11%
Cancer	6	14	53	3	9	32	3	8	29	3	8	25	93	86	639
High-risk Adenoma	27	31	154	12	15	61	9	12	46	8	10	38	137	115	740
Intermediate-risk Adenoma	32	32	195	16	14	65	12	12	42	12	11	37	209	140	1023
Low-risk Adenoma	53	59	359	18	15	91	13	9	59	9	7	47	235	189	1489
Abnormal	62	55	425	17	14	104	15	9	77	10	8	65	377	238	2403
Normal	36	36	195	3	9	48	2	8	35	2	7	32	249	145	1328
Cancer PPV	2.78%	6.17%	3.84%	4.35%	11.84%	7.98%	5.56%	13.79%	10.07%	6.82%	15.69%	10.25%	7.15%	9.42%	8.38%
Advanced Adenoma PPV	27.31%	27.75%	25.27%	40.58%	38.16%	31.42%	38.89%	41.38%	30.56%	45.45%	41.18%	30.74%	26.62%	27.93%	23.13%
All Neoplasms PPV	54.63%	59.91%	55.10%	71.01%	69.74%	62.09%	68.52%	70.69%	61.11%	72.73%	70.59%	60.25%	51.85%	58.05%	51.05%
Cancer Detection Rate	0.15%	0.49%	0.26%	0.08%	0.32%	0.16%	0.08%	0.28%	0.14%	0.08%	0.28%	0.12%	0.11%	0.21%	0.12%
Advanced Adenoma Detection Rate	1.50%	2.23%	1.71%	0.71%	1.02%	0.62%	0.53%	0.85%	0.43%	0.51%	0.74%	0.37%	0.39%	0.63%	0.33%
All Neoplasms Detection Rate	3.00%	4.80%	3.73%	1.25%	1.87%	1.22%	0.94%	1.45%	0.86%	0.81%	1.27%	0.72%	0.77%	1.31%	0.72%

Table 7 Number of test kits sent per subject

	FIT		gFOBt	
1	39160	97.78%	1048924	95.21%
2	829	2.07%	28205	2.56%
3	57	0.14%	22727	2.06%
4	2	0.00%	1617	0.15%
5	0	0.00%	157	0.01%
6	0	0.00%	24	0.00%
7	0	0.00%	4	0.00%
8	0	0.00%	2	0.00%
9	0	0.00%	0	0.00%
10	0	0.00%	2	0.00%
Total Kits Sent	40997		1180976	

Figure 1 Detection rates and PPVs by gender and FIT cut-off

Figure 2 Detection rates and PPVs by screening round and FIT cut off

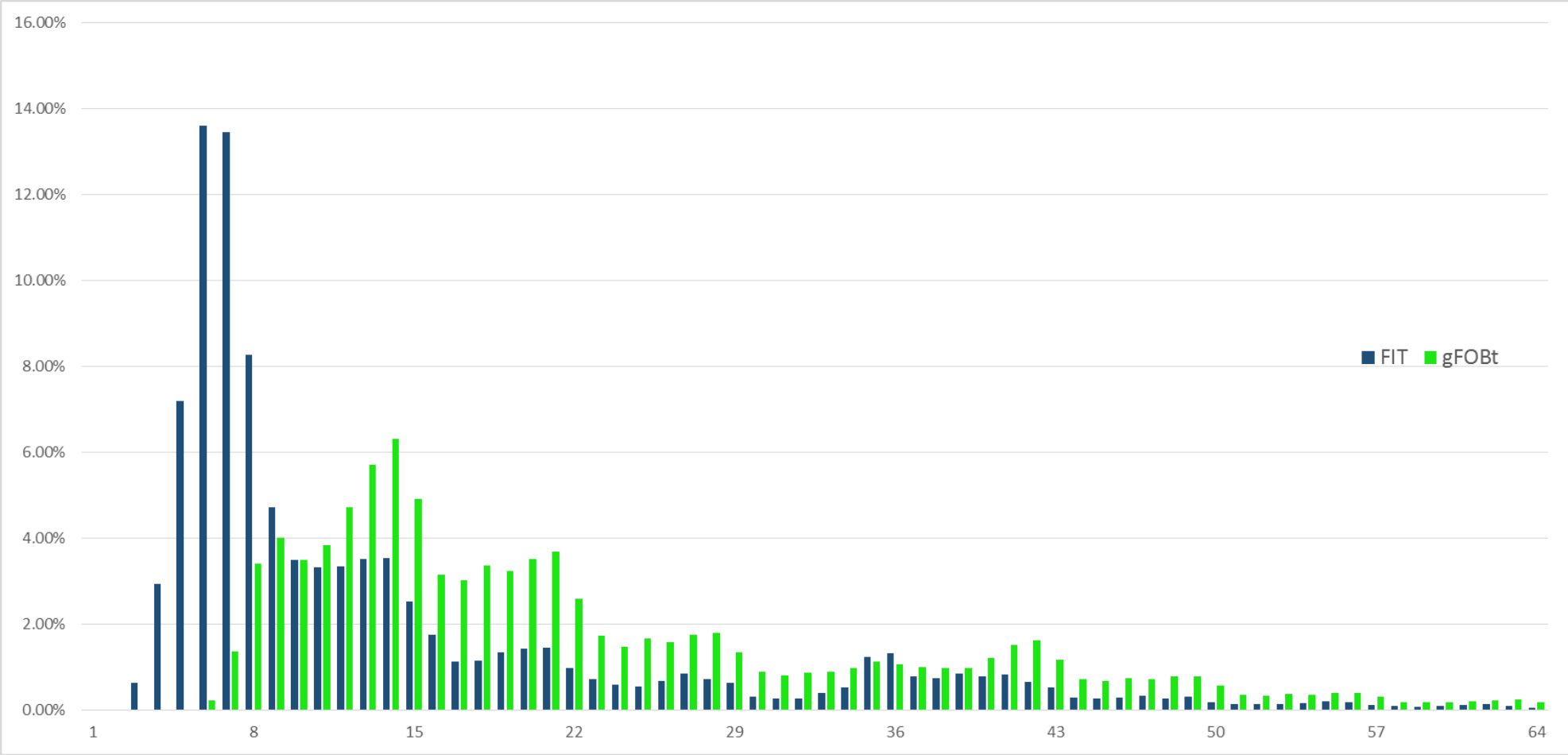

Figure 3 Time to definitive result from being sent a test kit

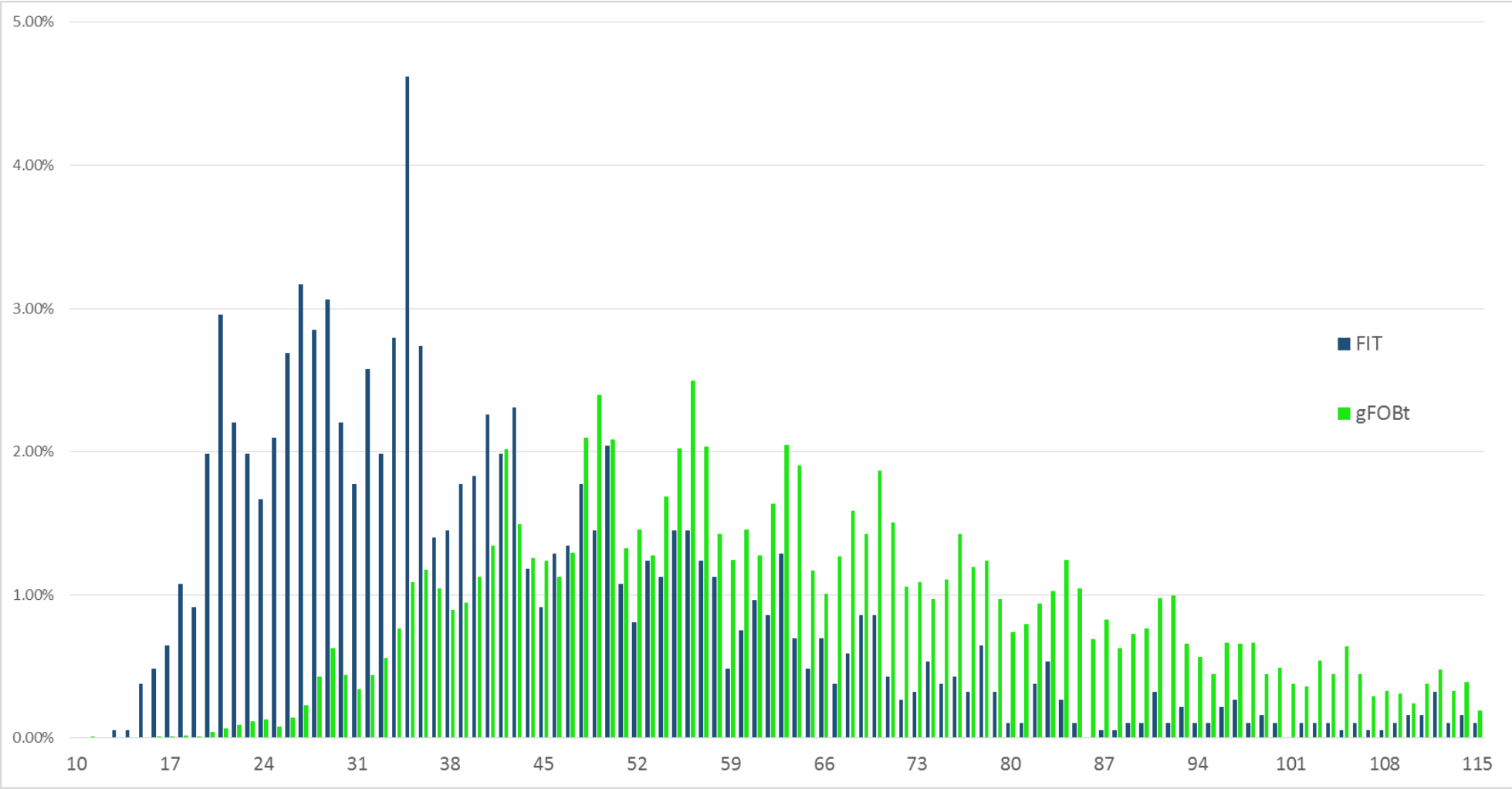

Figure 4 Time to first diagnostic test from being sent a test kit

Appendix 1

Randomisation of FIT invitations sent by the Southern and the Midlands & northwest Hubs.

An invitation to be screened can be produced once eligible individuals reach their screening due by date (SDD). You are eligible once you reach the age of 60 and you continue to be eligible until you turn 75. For the FIT pilot, invitations did not include those individuals are above the age of 74 and who opted into the programme.

The Hubs invite individuals by individual Screening Centre (18 Centres in Southern Hub, 15 Centres in the Midlands and North West Hub). Each day the Hub decide what date they will invite up to and in so doing they can see how many individuals will be invited for each Centre. The further ahead of the selected date, the larger the number of individuals invited. The invitation date is adjusted to smooth the rate of invitations for each Centre and so avoid surges of work from clusters produced by closure of screening associated with holidays etc. gFOBt and FIT invitations are treated in the same way.

The order of invitation from a Screening Centre is produced by BCSS and is not influenced by subject demographic.

HSCIC programmed BCSS to substitute a FIT invitation in place of a gFOBt on every 28th invitation (e.g. No. 1-27 gFOBt, No. 28 FIT, No. 29-55 gFOBT, No. 56 FIT etc).

This process was repeated every working day throughout the pilot and the sequence order was maintained for each Centre.

This process means that the selection of a FIT invitation is effectively random and does not reflect any personal characteristic other than they are of an age to be screened, live in an areas covered by one of the two screening Hubs and they are either being screened for the first time, it is two years since completion of their last screen or they have been returned to screening two years after completion of an episode of surveillance.

The pilot algorithm did not allow subjects to select FIT or gFOBt.
The FIT and the gFOBT cohorts will have the same mix of individuals.

The demographics of the population served by individual Centres and the two Hubs are different and their screening history will be slightly different given that Centres started screening at different times and part of the population served by the Midlands and NW Hub were part of the 2000-2006 screening pilot.

Southern Hub – Screening Centres served.

South Devon Bowel Cancer Screening Centre
Gloucestershire Bowel Cancer Screening Centre
Solent Bowel Cancer Screening Centre
Somerset Bowel Cancer Screening Centre
Dorset Bowel Cancer Screening Centre
Hampshire Bowel Cancer Screening Centre
Berkshire Bowel Cancer Screening Centre
Surrey Bowel Cancer Screening Centre
Sussex Bowel Cancer Screening Centre
Bristol and Weston Bowel Cancer Screening Centre
Bath, Swindon and Wiltshire Bowel Cancer Screening Centre
East Kent Bowel Cancer Screening Centre
North and East Devon Bowel Cancer Screening Centre
West Kent and Medway Bowel Cancer Screening Centre
Buckinghamshire and Milton Keynes Bowel Cancer Screening Centre
Cornwall Bowel Cancer Screening Centre
Oxfordshire Bowel Cancer Screening Centre
Western Sussex Bowel Cancer Screening Centre

Midlands & NW Hub – Screening Centres served.

Bolton Bowel Cancer Screening Centre
Heart of England Bowel Cancer Screening Centre
Coventry and Warwickshire Bowel Cancer Screening Centre
Sandwell and West Birmingham Bowel Cancer Screening Centre
Cumbria and Morecambe Bay Bowel Cancer Screening Centre
North Staffordshire Bowel Cancer Screening Centre
Pennine Bowel Cancer Screening Centre
Lancashire Bowel Cancer Screening Centre
Cheshire Bowel Cancer Screening Centre
Merseyside and North Cheshire Bowel Cancer Screening Centre
Herefordshire & Worcestershire Bowel Cancer Screening Centre
Shropshire Bowel Cancer Screening Centre
Withington Bowel Cancer Screening Centre
Liverpool and Wirral Bowel Cancer Screening Centre Wolverhampton Bowel Cancer Screening Centre

Appendix 2 Definitions

Adequate participation was defined as having final kit result of Normal or Definitive Positive, using the field recorded on the NHSCBSP database. This included only subjects returning a first kit within 182 days of invitation, after which the episode was closed.

Subjects were defined as '**inadequately participation'** if they had a final kit outcome of kit 'not returned', spoilt or weak positive and with only 1 kit associated with the episode.

A definitive positive kit result for FIT was a reading of >= 100ng/mL. For gFOBt, a definitive positive was a strong positive result on kit 1, or a spoilt or weak positive result followed by any positive result in a subsequent kit (typically 2 or 3).
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A **definitive colonoscopy** is one where BCSS records the clinical outcome of colonoscopy.

IMD Quintiles were based on the recorded IMD scores for all participants associated with hubs 1 and 2. IMD score was supplied by the BCSP, based on the subjects postcode of residence.

IMD quintiles are

Qu 1 : 0.61 - 7.38

2 : 7.39 - 11.77

3 : 11.78 - 17.41

4 : 17.42 – 27.97

5 : 27.98-83.33

Age was defined as number of years of age at date of invitation. A range of 59-75 was used for age groups, defined as 59-64, 65-69, 70-75.

Screening episode type was categorised as prevalent (first time invitees), prevalent (previous non-responders) and incident (previous responders).

Low risk Adenoma:	Patients with only 1–2, small (<1 cm) adenomas.
Intermediate risk Adenoma:	Patients with 3–4 small adenomas or at least one >1 cm
High risk Adenoma:	Patients with >5 adenomas OR >3 adenomas at least one of which is >1 cm

1. Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. Am J Gastroenterol. 2008 Jun;103(6):1541-9.
2. . DfCaLGEiod. http://www.communities.gov.uk/publications/corporate/statistics/indices (accessed 11 Nov 2011). 2010.