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A national cluster-randomised controlled trial to examine the effect of enhanced reminders on the socioeconomic gradient in uptake in bowel cancer screening

Rosalind Raine*[,1], Sue M Moss[2,24], Christian von Wagner[3], Wendy Atkin[4], Ines Kralj Hans[5], Rosemary Howe[6], Francesca Solmi[7], Stephen Morris[8], Nicholas Counsell[9], Allan Hackshaw[9], Stephen Halloran[10], Graham Handley[11], Richard F Logan[12], Sandra Rainbow[13], Steve Smith[14], Julia Snowball[15], Helen Seaman[16], Mary Thomas[17], Samuel G Smith[18,19], Lesley M McGregor[20], Gemma Vart[21], Jane Wardle[22,*] and Stephen W Duffy[23,24]

Background: The NHS Bowel Cancer Screening Programme in England offers biennial guaiac faecal occult blood testing (gFOBt). There is a socioeconomic gradient in participation and socioeconomically disadvantaged groups have worse colorectal cancer survival than more advantaged groups. We compared the effectiveness and cost of an enhanced reminder letter with the usual reminder letter on overall uptake of gFOBt and the socioeconomic gradient in uptake.

Methods: We enhanced the usual reminder by including a heading 'A reminder to you' and a short paragraph restating the offer of screening in simple language. We undertook a cluster-randomised trial of all 168 480 individuals who were due to receive a reminder over 20 days in 2013. Randomisation was based on the day of invitation. Blinding of individuals was not possible, but the possibility of bias was minimal owing to the lack of direct contact with participants. The enhanced reminder was sent to 78 067 individuals and 90 413 received the usual reminder. The primary outcome was the proportion of people adequately screened and its variation by quintile of Index of Multiple Deprivation. Data were analysed by logistic regression with conservative variance estimates to take account of cluster randomisation.

Results: There was a small but statistically significant ($P = 0.001$) increase in participation with the enhanced reminder (25.8% *vs* 25.1%). There was significant ($P = 0.005$) heterogeneity of the effect by socioeconomic status with an 11% increase in the odds of participation in the most deprived quintile (from 13.3 to 14.1%) and no increase in the least deprived. We estimated that implementing the enhanced reminder nationally could result in up to 80 more people with high or intermediate risk colorectal adenomas and up to 30 more cancers detected each year if it were implemented nationally. The intervention incurred a small one-off cost of £78 000 to modify the reminder letter.

Conclusions: The enhanced reminder increases overall uptake and reduces the socioeconomic gradient in bowel cancer screening participation at little additional cost.

*Correspondence: Professor R Raine; E-mail: r.raine@ucl.ac.uk
[24]These authors contributed equally to this work.
*Deceased.

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Colorectal cancer is a major public health problem internationally and in the United Kingdom, where it is the third most common cancer and the second leading cause of cancer death. (Ferlay *et al*, 2012; Cancer Research UK, 2014) Randomised trials have shown that screening using guaiac faecal occult blood testing (gFOBt) significantly reduces mortality from colorectal cancer. (Hewitson *et al*, 2008) In 2006 the English NHS Bowel Cancer Screening Programme (BCSP) introduced two-yearly gFOBT screening and now offers it to all individuals aged 60–74 years.

For population cancer screening to achieve its intended public health impact, high levels of participation are necessary. National variations in screening uptake, examined between 2006 and 2009 found that uptake overall was 54% and that this varied from 61% in the least deprived to 35% in the most deprived areas of the country. (von Wagner *et al*, 2011) The stepwise relationship between socioeconomic group and health whereby more socioeconomically advantaged individuals have better health and better access to health care is well known. (Graham, 2004) The costs of inequalities are therefore borne not only by those at the bottom of the socioeconomic hierarchy but at every level. Interventions that target the most disadvantaged subgroups only, or which aim to narrow the gap between the most and least disadvantaged, underestimate the pervasive effect across the socioeconomic hierarchy and exclude those in need in the intermediate socioeconomic groups.

Participants with a positive gFOBt result are invited for further investigation (usually colonoscopy). Fortunately, the low uptake and striking socioeconomic gradients are not seen in attendance at colonoscopy. Overall colonoscopy uptake is 83% with little variation between socially advantaged and disadvantaged areas (86–80%). (Morris *et al*, 2012) The high follow-up and low socioeconomic gradient in uptake of colonoscopy indicates that addressing the gFOBt uptake gradient should improve subsequent uptake of effective treatment and therefore contribute to reducing inequalities in survival. (Coleman *et al*, 2004).

In order to address the UK Government's commitment to reduce health inequalities, (Health, 2012) we undertook the ASCEND-randomised controlled trials research programme. In ASCEND we designed four interventions aimed at reducing the socioeconomic gradient in bowel screening participation without compromising uptake overall. The interventions were: a simplified version of the information leaflet aimed at individuals with low literacy or numeracy skills; a narrative information leaflet including experiences of people who had participated in the BCSP; general practitioner endorsement (GPE) of the invitation to participate (80% of GP practices nationally agreed to endorse the programme using the statement 'your GP practice, name of practicę supports the Bowel Cancer Screening Programme' on invitation letters); and an enhanced reminder letter (ER), replacing the usual reminder sent to those who had not returned a kit within 4 weeks.

The summary results of the four national cluster-randomised controlled trials (RCTs) of these interventions are provided elsewhere. (Wardle *et al*, 2016) In this paper, we report details of the impact of the national cluster-RCT of the enhanced reminder on the socioeconomic gradient in BCSP uptake and its cost.

MATERIALS AND METHODS

Intervention. The value of sending reminders to improve screening uptake is well established (Camilloni *et al*, 2013) and all individuals who are sent a bowel cancer screening kit as part of the BCSP are sent a reminder letter if the kit is not returned within 4 weeks. Research on breast screening attendance suggests that reminders maybe helpful in increasing uptake in low-income women, (Chambers *et al*, 2014) particularly if the content of the reminder addresses barriers to screening participation, which are known to be socially graded. Evidence has demonstrated that low awareness of bowel cancer is significantly more prevalent among more deprived groups and that individuals from lower socioeconomic groups tend to perceive the barriers to screening to be higher and the benefits of screening to be lower than high socioeconomic groups. (Power *et al*, 2011; Whitaker *et al*, 2011) One particular barrier to screening that has been extensively studied and found to be an important predictor of colorectal cancer screening uptake is perceived risk (Vernon, 1997; Vernon *et al*, 2001; Robb *et al*, 2004). We therefore developed an enhanced reminder letter, which aimed to target low awareness of bowel cancer and, in addition, specifically addressed inaccurate risk perceptions. Increasing age is a risk factor and pertinent characteristic of all screening invitees, regardless of their socioeconomic group and one that could be simply and directly stated. We designed the enhanced reminder letter in collaboration with the Health & Social Care Information Centre (HSCIC) to ensure that the enhancement we developed would fit into the usual letter without disrupting the format and thus without incurring any additional costs to BCSP. We also obtained feedback from focus group participants who had been convened to explore reasons for non-uptake of bowel cancer screening. (Palmer *et al*, 2014) The final version of the enhanced reminder included two additions to the usual letter: a banner reading 'A reminder to you' at the start of the letter and a brief restatement of the screening offer at the end of the letter.

The control intervention was the usual reminder letter. The text of both reminder letters is given in the web appendix. (Supplementary files 1 and 2).

Randomisation and blinding. The study was carried out within the routine activity of the BCSP. The BCSP in England is organised within five regional hubs (Midlands and Northwest; Southern; London; Northeast; and Eastern), all of which participated in this trial. The intervention period of this study overlapped with our trial of GPE of the offer of screening, so a proportion of individuals were in both trials (see results below).

The invitation and reminder system of the Programme did not permit randomisation of individual invitees. Instead, we randomised days within hubs. That is, for a given date within a given hub, all individuals who were due to be sent a reminder on that date were randomised to the same trial arm, either the usual reminder or enhanced reminder.

Blinding of individuals was not possible, but the possibility of biasing participation was minimal owing to the lack of direct contact with participants. Individuals were unaware of a comparator condition unless a member of their household received a reminder letter during the study period that contained different information materials. Hubs however were effectively 'blind' to the randomisation schedule, which was sent only to HSCIC. To assure quality, Hubs reported back to the Trial Office whether the intervention was included and this was checked against the randomisation schedule by the research team.

Outcome measures and costs. The outcome measure (adequately screened) was defined as the return of a gFOBt kit within 18 weeks of the initial invitation that led to a 'definitive' test result of either 'normal' (i.e., no further investigation required) or 'abnormal' (i.e., requiring referral for further testing, usually colonoscopy) by the date of data extraction. The 18-week time limit coincided with the date on which the BCSP closes a screening episode to a non-responder. The primary analysis addressed heterogeneity of the effect of the enhanced reminder by socioeconomic status quintile.

Socioeconomic status was measured using the Index of Multiple Deprivation (IMD) 2010 score associated with each individual's home address (Department for Communities and Local

Government, 2011) IMD, a well validated marker of socioeconomic status, comprises 38 separate indicators, organised across seven distinct domains (Income, Employment, Health and Disability, Education Skills and Training, Barriers to Housing and Other Services, Crime and Living Environment). These are combined, using appropriate weights, to calculate the IMD for every Lower Layer Super Output Area (LSOA) in England. Each LSOA covers ~1500 individuals. Each individual's postcode was linked to the relevant LSOA. The IMD can be used to rank every LSOA in England according to their relative level of deprivation. IMD was classified in five categories based on national quintiles, (Wardle *et al*, 2016) with 1 representing the least deprived and 5 the most deprived. In addition we estimated the overall effect of the enhanced reminder intervention on participation rates.

We calculated the costs of modifying the BCSP IT system to incorporate the enhanced reminder. This was based on the actual cost charged to the study to modify the reminder letter.

Statistical considerations. Data were analysed by logistic regression with conservative variance estimates to take account of randomisation by hub-day clusters. (Huber, 1967; White, 1980) including interaction tests for heterogeneity of effect by IMD quintile. We further adjusted for age, sex, hub and screening episode type (first ever screening episode, prevalent episode in previous non-participant or incident episode in previous participant). In formal testing for heterogeneity of effects of age, sex, hub and screening episode type by socioeconomic status, we used the continuous IMD score to increase statistical power.

We calculated average marginal effects (which give the effect on absolute percentage uptake adjusted for other factors) and used these to predict the impact of the enhanced reminder on the detection of colorectal adenomas and cancer in the NHS BCSP.

Sample size was calculated using the method of Brentnall *et al*, (2012) to give 90% power to detect as significant at the 5% level a heterogeneity of the effect of the intervention by IMD quintile such that the absolute increase in participation in the most deprived quintile was 5 percentage points and the increase in the least deprived was 1 percentage point. This indicated that 46 000 individuals would be required. With ~1500 reminders sent per hub per working day, this would have required 31 hub-day clusters. To take account of the additional variation generated by the cluster randomisation, we randomised 100 hub-days, the 20 working days from Monday 8th July 2013 to Friday 2nd August 2013, in each of the five hubs. Owing to a protocol deviation, data from one hub on one day (8th July) could not be used. This gave a total of 99 randomisation units and 168 480 individuals randomised, 78 067 to enhanced reminder and 90 413 to the usual reminder.

Study approvals. Consent forms were not required in this study because the interventions took place as part of individuals' usual communication from the BCSP.

Ethical Approval was obtained from the UK National Research Ethics Service, London—Harrow Ethics Committee, Reference number 12/LO/1396 prior to commencement of the study. Local Ethics Committee approval was not required as this was a national trial incorporated within the BCSP. Site approval was obtained at each of the Bowel Cancer Screening Programme Hubs.

Patient involvement. Patient and third sector representatives were involved in the planning and development of all four interventions examined in the ASCEND trials and a bowel cancer patient was a co-applicant on the study. The research team also undertook patient and public engagement activities, presenting information about the study at conferences and to other groups. (Supplementary file 3).

RESULTS

The RCT included 168 480 individuals from 99 clusters.

Table 1 describes the characteristics of the study individuals by trial arm. The arms were well balanced with respect to sex. For other variables, there were slight imbalances between trial arms, presumably induced by between-hub between-day differences in individuals sent reminders. The proportion of individuals decreased as deprivation increased in both arms. This is because individuals were categorised by IMD quintiles based on the national distribution of scores, rather than by the distribution of scores in our sample (i.e., not 20% in each quintile). The enhanced reminder arm was characterised by older individuals, a higher proportion of prevalence screens in previous non-participants and fewer first ever screening episodes.

Table 2 shows the percentages and absolute numbers adequately screened by trial arm, stratified in turn by sex, age, screening episode type, hub and IMD quintile. Overall, there was 0.7 percentage point higher participation rate with the enhanced reminder (25.8% compared with 25.1% uptake after the usual reminder). This was not significant in the univariate analysis, but was significant when adjusted for age, sex, hub and screening episode type (adjusted OR = 1.07, 95% CI 1.03–1.11, $P = 0.001$, Table 3), from 25.1 to 25.8% uptake. In both trial arms and overall, higher participation rates were observed for females, younger individuals, incident screens (i.e., in persons who had previously participated), the Southern hub and the less-deprived quintiles.

In terms of the relationship of this trial to the GPE trial, the unadjusted OR for uptake associated with the enhanced reminder in those not in the GPE trial was 1.06, higher than the overall unadjusted OR of 1.04. Furthermore, the OR associated with receiving the enhanced reminder adjusted for GPE trial status was 1.04, identical to the unadjusted OR.

There was a significant interaction between trial arm and IMD quintile after adjustment ($P = 0.005$). Table 4 shows the adjusted ORs from multivariate analysis stratified by IMD quintile. Within the most deprived quintile, the odds of returning a completed kit were 11% higher in the enhanced reminder arm (absolute increase from 13.3 to 14.1%). There was no difference in the odds of returning a completed kit within the least deprived quintile. Odds ratios were similar across the three most deprived quintiles, ranging from 1.09 to 1.13 and in each case were significantly higher in the enhanced reminder group compared with the usual reminder group.

Table 3 shows the multivariate adjusted effects of trial arm, sex, age, screening episode type, hub and IMD quintile, with each factor adjusted for all others in the logistic regression. The differences in participation by trial arm, sex, screening episode type, hub and IMD quintile were all statistically significant.

Table 5 gives the effect of the enhanced reminder within subgroups of sex, age, hub and screening episode type, and the test for interaction of the intervention with IMD quintile. The effect of the enhanced reminder was stronger in the London and Northeast hubs (although the effect was not significant), and the interaction between trial arm and IMD quintile was strongest in the Southern hub.

A 7% increase in the odds of screening across all individuals in the adjusted model was associated with predictive margins (adjusted average probabilities of uptake) of 0.259 (95% CI 0.255–0.265) in the enhanced reminder group and 0.250 (95% CI 0.248– 0.253) in the usual reminder group. This implies a 3.6% relative increase in the probability of screening (0.259/0.250) and a 0.9 percentage point absolute increase (0.259–0.250; the average marginal effect). The adjusted effect was larger than the unadjusted (see discussion below). In the 2013/14 fiscal year the number of reminder letters sent in the BCSP in England was 2 144 277.

Table 1. Distributions of the study population in each arm of the trial by sex, age, screening episode type, hub and IMD quintile

	Usual reminder		Enhanced reminder		Total	
Factor	**No.**	**%**	**No.**	**%**	**No.**	**%**
Sex						
Male	46 839	51.8	40 320	51.7	87 159	51.7
Female	43 574	48.2	37 747	48.4	81 321	48.3
Age (years)[a]						
<65	46 771	51.7	38 390	49.2	85 161	50.6
65–69	27.781	30.7	24 870	31.9	52 651	31.2
70–74	15 861	17.5	14 807	19.0	30 668	18.2
Screening episode type						
Prevalent first time	21 271	23.5	14 483	18.5	35 754	21.2
Incident	25 813	28.5	23 722	30.4	49 535	29.4
Prevalent previous non responder	43 329	47.9	39 862	51.1	83 191	49.4
Hub						
Midlands and NorthWest	25 490	28.2	22 051	28.2	47 541	28.2
Southern	23 107	25.6	19 131	24.5	42 238	24.5
London	10 385	11.5	10 809	13.8	21 194	13.8
North East	12 796	14.1	12 291	15.7	25 087	15.7
Eastern	18 635	20.6	13 785	17.7	32 420	17.7
IMD quintile[b]						
1 (least deprived)	18 928	20.9	15 933	20.4	34 861	20.7
2	19 446	21.5	16 594	21.3	36 040	21.4
3	18 286	20.2	16 092	20.6	34 378	20.4
4	16 853	18.6	14 679	18.8	31 532	18.7
5 (most deprived)	16 489	18.2	14 441	18.5	30 930	18.4
Not known	411	0.4	328	0.4	739	0.4
Total	90 413		78 067		168 480	

'Prevalent first time': people being invited for the first time. 'Incident': invitations to people who have participated in screening previously. 'Prevalent previous non responder': people invited to be screened at least once previously, who have never responded.
[a]Some individuals were invited just before their 60th birthday
[b]Index of multiple Deprivation: quintile based on national distributions using pre-defined national cut-offs.

(BCSSN, 2015) An average marginal effect of 0.9 percentage points (0.009) suggests that if the enhanced reminder were implemented nationally, then 19 298 extra people each year might be screened. In 2013/14 the positivity rate among the screened population was 1.84%. (BCSSN, 2015) Evidence suggests that 83% of people with a positive test result attend a specialist screening practitioner clinic and undergo further investigation, and among those who go on to have further investigations, 10.1% will have a colorectal cancer and 27.2% will have colorectal adenomatous polyps classed as intermediate or high risk requiring further investigation. (Logan *et al*, 2012) Hence, if the enhanced reminder were implemented nationally it might detect up to an additional 80 people (19 298*0.0184*0.83*0.272) with polyps classed as high or intermediate risk, and 30 people (19 298*0.0184*0.83*0.101) with a colorectal cancer in England each year.

The enhanced reminder incurred a one-off cost of £78000 to modify the usual reminder within the NHS BCSP. This would not need to be incurred again if the enhanced reminder were implemented. No additional costs were incurred per person invited to screening, hence the average marginal cost per additional enhanced reminder was zero.

DISCUSSION

The addition of simple, brief messages to the usual BCSP reminder letter increased the odds of participation in the Programme by 11% among those living in the most deprived areas (in absolute terms from 13.3 to 14.1% uptake) and by 7% (from 25.1 to 25.8% uptake) overall. As a result of our research design, whereby the intervention was embedded within the BCSP's usual practice, these benefits can be realised immediately, with no operational changes required and at no additional cost. We estimate the enhanced reminder can result in up to 80 more people with high or intermediate risk polyps and 30 additional colorectal cancers detected in England each year. The stronger effect of the enhanced reminder in low socioeconomic status groups is reflected in the corresponding stronger effect suggested in London and the Northeast.

A major strength of our trial is its national coverage and the large sample size yielding substantial statistical power to detect small differences in uptake between subgroups. The trial was specifically powered to detect socioeconomic differences in the effect on uptake, allowing us to draw conclusions about the demonstrated differences between IMD quintiles, but not about the relevance of the other statistically significant differences found. This is, to our knowledge the first trial specifically designed to examine effects across the entire socioeconomic gradient and the first intervention to result in a slightly greater proportional effect in more deprived populations. Our results could be argued to satisfy Victora's 'inverse equity' hypothesis, which predicts that newly implemented public health interventions initially reach those of higher socioeconomic status and only later affect the poor when the affluent have achieved new minimum achievable levels for morbidity, a hypothesis that has been confirmed internationally. (Victoria *et al*, 2000).

Until recently, studies that addressed socioeconomic inequalities in uptake tended to focus specifically on under-served groups. (Ahmed *et al*, 2010) Even if they are successful, these initiatives do not benefit the larger population in need outside the targeted group. In addition, they are often highly intensive (e.g., by providing community support workers) and are therefore impractical for wide-scale implementation. More recently less-resource-intensive interventions such as text message reminders

have been found to increase attendance at breast screening appointments (Kerrison *et al*, 2015) and their effectiveness in improving uptake of gFOBT screening in the BCSP is currently being examined. (Hirst *et al*, 2015).

We were unable, for logistical reasons, to use individual randomisation and this led us to implement cluster randomisation as the strongest alternative. If anything, this led to an underestimation of the effect. This can be seen if one considers the overall absolute difference in participation between the enhanced and usual reminder arms (0.7%) along with the differences observed within individual hubs, of 0.6% (Midlands and North-west), 0.9% (Southern), 1.5% (London), 1.5% (Northeast) and 0.4% (Eastern). The average of the latter, weighted by study population in each hub is 0.9%, larger than the overall unadjusted effect. This probably reflects a greater and more systematic variation between clusters than was anticipated when the trial was designed. This is also almost certainly the reason for a larger and more significant multivariate adjusted effect than the unadjusted. Ideally, future studies should be randomised at individual level, and if this is not possible, stratified analyses, conditional on hub and possibly other covariates should be planned *a priori*.

Although we used an area-based measure of deprivation, which may underestimate individual effects, IMD quintile has been demonstrated ability to explain socioeconomic variations in bowel cancer screening uptake at the LSOA level. (von Wagner *et al*, 2011) IMD is widely used, enabling direct comparison of our results with other studies.

There may have been some individuals who received the usual or enhanced reminder after sending in a kit. This would have the tendency to underestimate the effect of the enhanced reminder. It is also worth noting that the enhanced reminder arm of the study had older individuals and a greater proportion of prevalent screening invitations. These would be likely to attenuate the effect of the enhanced reminder because the enhanced reminder arm

Table 3. Adjusted odds ratios and 95% confidence intervals or the effect of each variable on participation

	Mulitivariate logistic regression results[a]	
Factor	**Odds ratio (95%CI)**	***P*-value**
Trial arm		
Usual reminder	1.00	
Enhanced reminder	1.07 (1.03–1.11)	$P<0.001$
Screening episode type		
Prevalent first time	1.00	
Incident	4.55 (4.39–4.71)	$P<0.001$
Prevalent previous non responder	0.20 (0.19–0.21)	$P<0.001$
Sex		
Male	1.0	
Female	1.03 (1.00–1.06)	$P=0.024$
Age		
59–64	1.0	
65–69	0.85 (0.82–0.88)	$P<0.001$
70–74	0.66 (0.64–0.68)	$P<0.001$
Hub		
Midlands and NorthWest	1.00	
Southern	1.03 (0.99–1.08)	$P=0.123$
London	0.88 (0.83–0.93)	$P<0.001$
NorthEast	0.96 (0.91–1.00)	$P=0.062$
Eastern	0.98 (0.92–1.04)	$P=0.451$
IMD quintile		
1 (least deprived)	1.00	
2	0.84 (0.81–0.88)	$P<0.001$
3	0.71 (0.68–0.74)	$P<0.001$
4	0.58 (0.55–0.61)	$P<0.001$
5 (most deprived)	0.38 (0.36–0.40)	$P<0.001$

[a]Adjusted for sex, age, screening episode type, IMD quintile, trial arm and hub.

Table 2. Numbers and percentages of individuals adequately screened, by trial arm and sex, age, screening episode type, hub and IMD quintile

	Number (%) adequately screened		
Factor	**Usual reminder**	**Enhanced reminder**	**Total**
Sex			
Male	11 201 (23.9)	9 899 (24.6)	21 100 (24.2)
Female	11 511 (26.4)	10 267 (27.2)	21 778 (26.8)
Age			
<65	12 229 (26.1)	10 251 (26.7)	22 480 (26.4)
65–69	6898 (24.8)	6674 (26.8)	13 572 (25.8)
70–74	3585 (22.6)	3241 (21.9)	6826 (22.3)
Screening episode type			
Prevalent first time	5398 (25.4)	3739 (25.8)	9137 (25.6)
Incident	14 985 (58.0)	14 033(59.2)	29 018 (58.6)
Prevalent previous non responder	2329 (5.4)	2394 (6.0)	4723 (5.7)
Hub			
Midlands and North-West	5899 (23.1)	5231 (23.7)	11 130 (23.4)
Southern	6795 (29.4)	5827 (30.5)	12 622 (29.9)
London	2196 (21.1)	2444 (22.6)	4640 (21.9)
North East	2836 (22.2)	2911 (23.7)	5747 (22.9)
Eastern	4986 (26.8)	3753 (27.2)	8739 (27.0)
IMD quintile			
1 (least deprived)	6601 (34.9)	5522 (34.7)	12 123(34.8)
2	5782 (29.7)	5107 (30.8)	10 889 (30.2)
3	4578 (25.0)	4316 (26.8)	8894 (25.9)
4	3436 (20.4)	3104 (21.1)	6540 (20.7)
5 (most deprived)	2198 (13.3)	2040 (14.1)	4238 (13.7)
Total	22 712 (25.1)	20 166 (25.8)	42 878 (25.4)

Table 4. Adjusted odds ratios and 95% confidence intervals for the effect of the enhanced reminder within each IMD quintile

	% Adequately screened		Adjusted logistic regression[a]	
IMD quintile	Usual reminder	Enhanced reminder	Odds ratio enhanced *vs* usual reminder (95%CI)	*P*-value
1 (least deprived)	34.9	34.9	1.00 (0.94–1.06)	$P=0.98$
2	29.7	30.8	1.04 (0.98–1.11)	$P=0.2$
3	25.0	26.8	1.13 (1.06–1.20)	$P<0.001$
4	20.4	21.1	1.09 (1.02–1.17)	$P=0.009$
5 (most deprived)	13.3	14.1	1.11 (1.04–1.20)	$P=0.003$

[a]Adjusted for sex, age screening episode type and hub.

Table 5. Effect of the enhanced reminder within subgroups

Variable	OR (95% CI), enhanced *vs* usual reminder,	Significance of effect	Significance of interaction[a]
Sex			
Male	1.04 (0.95–1.14)	$P=0.41$	$P=0.37$
Female	1.04 (0.95–1.13)	$P=0.45$	$P=0.24$
Age			
<65	1.03 (0.96–1.11)	$P=0.44$	$P=0.06$
65–69	1.11 (0.99–1.25)	$P=0.08$	$P=0.62$
70–74	0.96 (0.83–1.10)	$P=0.56$	$P=0.79$
Hub			
Midlands and NorthWest	1.03 (0.96–1.11)	$P=0.38$	$P=0.99$
Southern	1.05 (0.92–1.20)	$P=0.44$	$P=0.001$
London	1.09 (0.93–1.28)	$P=0.29$	$P=0.90$
NorthEast	1.09 (0.97–1.22)	$P=0.14$	$P=0.73$
Eastern	1.02 (0.84–1.25)	$P=0.81$	$P=0.98$
Screening episode type			
Prevalent first time	1.02 (0.95–1.10)	$P=0.51$	$P=0.12$
Incident	1.05 (0.97–1.12)	$P=0.21$	$P=0.05$
Prevalent previous non responder	1.12 (1.03–1.23)	$P=0.008$	$P=0.43$

[a]*P*-value for heterogeneity of effect of enhanced reminder by IMD expressed as a continuous score within each subgroup.

contained a higher proportion of previous non-responders who are much less likely to respond to a screening invitation compared with first timers and people who have already participated in a previous round. (Steele *et al*, 2010; Lo *et al*, 2015) As can be seen from Table 2, the previous non-responders had an overall participation rate of 6% compared with 59% in previous responders. Thus the true increase in participation with the enhanced reminder is likely to be greater than reported here.

We used published data from 2013/14 to estimate the additional number of colorectal cancers and high or intermediate risk polyps detected annually by implementing the enhanced reminder. These figures vary between geographical regions and change over time. For example, in common with all successful population screening programmes, the proportion of cases identified by the Programme falls as the proportion of individuals in the population who have been repeatedly screened increases.

Contamination between study groups could have occurred if, for example, household members were randomised to different arms of the trial during the 4-week study period. Although this limitation is noted, it would also have applied to a parallel randomised trial. It is also possible that concurrent initiatives affected uptake. We therefore surveyed the number and location of interventions occurring during the four national trials (of which enhanced reminder was one) and identified nine research studies and 27 health promotion activities focusing on bowel cancer screening occurring within the time frame of the trials. However, it is unlikely that they influenced our results because the chance of these initiatives occurring on the same alternate days as enhanced reminder would be negligible.

In conclusion, this large national trial demonstrated that a simple, brief message to enhance awareness of bowel cancer and clarify the objective of cancer screening, disseminated as part of routine practice by the BCSP, achieved a greater proportional effect in more deprived populations. This enhanced reminder incurred a small cost to implement and will incur only minimal maintenance costs if rolled out into routine practice. It could identify 80 more individuals with high or intermediate risk polyps and 30 additional bowel cancers in England each year.

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CONFLICT OF INTEREST

Rosalind Raine (the manuscript's guarantor) affirms that all authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

AUTHOR CONTRIBUTION

Authors contributed to the study as follows: JW and RR were joint principal investigators. They designed the study and wrote the grant application in collaboration with WA, SD, AH, SMorris, CvW and the hub directors (GH, RL, SH, SR, SS). JW, RR, WA, CvW, IKH, SS, LMcG, GV and MT led the development and testing of the intervention. SD generated the randomisation codes. The Hub Directors (GH, RL, SH, SR, SS) were responsible for identifying individuals and delivering the intervention assisted by IKH and RH. JS and IKH led the data extraction. SMoss, SD, AH and NC analysed the primary and secondary outcomes. FS, MT and SMorris analysed the cost data. RR, MT, SMorris and FS drafted the paper and all authors contributed to the reviews and revisions. All authors have seen and approved the final version. JW and RR are guarantors.

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[1]Department of Applied Health Research, University College London, London, WC1E 7HB, UK; [2]Wolfson Institute of Preventive Medicine, Queen Mary University of London, London EC1M6BQ, UK; [3]Cancer Research UK Health Behaviour Research Centre, Department of Epidemiology and Public Health, University College London, London, WC1E 7HB, UK; [4]Cancer Screening and Prevention Group, Faculty of Medicine, Department of Surgery & Cancer, Imperial College London, London, SW7 2AZ UK; [5]Department of Biostatistics, King's Clinical Trials Unit, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [6]Department of Surgery and Cancer, Imperial College London, London, UK; [7]UCL Division of Psychiatry, 6th Floor, Wing B, Maple House, 149 Tottenham Court Road, London W1T 7NF, UK; [8]Department of Applied Health Research, University College London, London, WC1E 7HB, UK; [9]Cancer Research UK & UCL Cancer Trials Centre, Cancer Institute, University College London, 90 Tottenham Court Road, London, W1T 4TJ, UK; [10]Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey GU2 7XH, UK; [11]North East Bowel Cancer Screening Programme Hub, Biochemistry Department, Gateshead Health NHS Foundation Trust, Queen Elizabeth Hospital, Gateshead NE9 6SX, UK; [12]Eastern Bowel Cancer Screening Programme Hub, Nottingham University Hospitals, Nottingham NG7 2UH, UK; [13]London Bowel Cancer Screening Programme Hub, The Northwest London Hospitals NHS Trust, Northwick Park & St Mark's Hospitals, Watford Road, Harrow, Middlesex HA1 3UJ, UK; [14]Midlands and North West Bowel Cancer Screening Programme Hub, Hospital of St Cross, Barby Road, Rugby CV22 5PX, UK; [15]Southern Bowel Cancer Screening Programme Hub, Surrey Research Park, 20 Priestly Road, Guildford Road, Surrey GU2 7YS, UK; [16]Southern Bowel Cancer Screening Programme Hub, Surrey Research Park, 20 Priestly Road, Guildford Road, Surrey GU2 7YS, UK; [17]NIHR CLAHRC North Thames, Department of Applied Health Research, University College London, London, WC1E 7HB, UK; [18]Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London EC1M 6BQ, UK; [19]Cancer Research UK Health Behaviour Research Centre, Department of Epidemiology and Public Health, University College London, London, WC1E 7HB, UK; [20]Cancer Research UK Health Behaviour Research Centre, Department of Epidemiology and Public Health, University College London, London, WC1E 7HB, UK; [21]Research Office, University of Roehampton, London SW15 5PU UK; [22]Department of Epidemiology and Public Health, Cancer Research UK Health Behaviour Research Centre, University College London, London, WC1E 7HB, UK and [23]Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London EC1M 6BQ, UK

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