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

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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.

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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 BCSP); early invitation letters (4 weeks). 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-respondent. 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

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 higher 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 economic 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 4-week 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-respondent. 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 socio-economic 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 socio-economic 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.
(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 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 Victoria’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

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

| Factor                        | Usual reminder | Enhanced reminder | Total          |
|-------------------------------|----------------|-------------------|----------------|
|                               | 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             | 16,972         | 20.6             | 34,378         | 20.4             |
| 4                             | 16,853         | 18.6             | 16,679         | 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        |                  |                |                  |

aPrevalent 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.

bSome individuals were invited just before their 60th birthday.

Index of multiple Deprivation: quintile based on national distributions using pre-defined national cut-offs.
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 under-estimation 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 |
|-------------------------------------------------|-------------------------------------------------|---------------------------------|-----------------|
| **Multivariate logistic regression results**  |
| **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 North West | 1.00 | |
| Southern | 1.03 (0.99–1.08) | P = 0.123 |
| London | 0.88 (0.83–0.93) | P<0.001 |
| North East | 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 |

*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 | 5378 (25.4) | 3739 (25.8) | 9117 (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 (21.9) | 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

| IMD quintile       | % Adequately screened | Adjusted logistic regression* | 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|

*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* |
|-----------------------------|-----------------------------------------|------------------------|------------------------------|
| **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                     |

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

Enhanced reminders to increase bowel cancer screening uptake

The data showed that the enhanced reminder had a significant effect on increasing uptake, particularly in more deprived populations. The proportion of individuals who responded to the screening invitation increased by 11% in the most deprived quintile compared with the least deprived quintile.

In conclusion, this large national trial demonstrated that a simple, brief message to enhance awareness of bowel cancer can be effective in increasing uptake of bowel cancer screening. By targeting more deprived populations, the enhanced reminder 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, SMorriss, 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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