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# Text-message Reminders in Colorectal Cancer Screening (TRICCS): a randomised controlled trial

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**Background:** We investigated the effectiveness of a text-message reminder to improve uptake of the English Bowel Cancer Screening programme in London.

**Methods:** We performed a randomised controlled trial across 141 general practices in London. Eight thousand two hundred sixtynine screening-eligible adults (aged 60–74 years) were randomised in a 1:1 ratio to receive either a text-message reminder (n = 4134) or no text-message reminder (n = 4135) if they had not returned their faecal occult blood test kit within 8 weeks of initial invitation. The primary outcome was the proportion of adults returning a test kit at the end of an 18-week screening episode (intention-to-treat analysis). A subgroup analysis was conducted for individuals receiving an invitation for the first time.

**Results:** Uptake was 39.9% in the control group and 40.5% in the intervention group. Uptake did not differ significantly between groups for the whole study population of older adults (adjusted odds ratio (OR) 1.03, 95% confidence interval (CI) 0.94–1.12; P=0.56) but did vary between the groups for first-time invitees (uptake was 34.9% in the control and 40.5% in the intervention; adjusted OR 1.29, 95% CI 1.04–1.58; P=0.02).

**Conclusions:** Although text-message reminders did not significantly increase uptake of the overall population, the improvement among first-time invitees is encouraging.

Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of cancer death in the United Kingdom (Cancer Research UK, 2016 a, b). In England, the National Health Service (NHS) runs the Bowel Cancer Screening Programme (BCSP), an organised CRC screening programme that offers biennial guaiac faecal occult blood testing (gFOBt) to men and women aged 60–74 years. Screening is widely recommended for the early detection of CRC and repeated participation in CRC screening has been shown to reduce CRC mortality by up to 25% (Scholefield *et al*, 2002; Hewitson *et al*, 2008; Levin *et al*, 2008; Sung *et al*, 2015). However, overall uptake of CRC screening in England is low at approximately 56% (House of Commons, 2014).

Commonly reported reasons for non-participation in CRC screening include forgetting or not getting around to completing the test kit and being too busy (Janz *et al*, 2007; van Rijn *et al*, 2008; van Dam *et al*, 2013; Lo *et al*, 2015b). Previous studies have shown that various modalities of reminders are effective at improving CRC screening uptake, including telephone and postal reminders (Baron *et al*, 2008; Power *et al*, 2009; Camilloni *et al*, 2013). Telephone reminders have been found to be the most effective

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reminder modality, improving CRC screening uptake by up to 21% (Myers *et al*, 2007; Segnan *et al*, 2010; Camilloni *et al*, 2013; Davis *et al*, 2014). However, the cost of telephone reminders is often prohibitive in the context of publicly funded screening programmes due to the additional labour they require (Segnan *et al*, 2010).

In the United States, a randomised controlled trial (RCT) examining the effectiveness of a multicomponent strategy to increase uptake of gFOBt through community health centres found that text-messages (also referred to as Short Messaging Service), when used in conjunction with postal and automated telephone reminders, achieved uptake of 82%, compared with 37% in the usual care group (Baker et al, 2014). In the context of organised screening in the United Kingdom, two recent studies found that preappointment text-message reminders were effective at increasing attendance at routine breast screening appointments (Icheku and Arowobusoye, 2015; Kerrison et al, 2015). The effectiveness of text-message reminders to promote uptake of gFOBt in the NHS BCSP, however, has not been examined (Senore et al, 2015). Unlike preappointment reminders for the NHS Breast Screening Programme, a reminder for CRC screening in the BCSP would act as an additional prompt to complete and return a gFOBt kit beyond the standard 4-week postal reminder (Halloran, 2009).

Text-messages are often considered to be the next best alternative to telephone reminders, as they have the advantage of providing instant and direct transmission at a low cost (Gurol-Urganci et al, 2013). They also have an advantage over postal reminders, as the direct transmission of text-messages to a person's mobile phone means they are unlikely to be misplaced as items sent through the post (Kaplan, 2006). The effectiveness of delivering text-messages is likely to be influenced by mobile phone coverage and the accuracy of mobile phone records in the clinical systems. Mobile technology has the potential to provide outreach and access to people regardless of socioeconomic status, race, ethnicity, or location, with 93% of the UK population personally owning or using a mobile phone (Ofcom, 2016). However, challenges with integrating mobile technology with primary care remain, as a recent study reported that only 39.8% of the eligible population had a registered mobile on their GP's clinical system (Kerrison et al, 2015).

The effect of a text-message reminder for CRC screening is likely to be different based on an individual's history with the screening programme, specifically whether they are first-time or repeat invitees in a given screening round. Uptake at first-time invitation is the strongest predictor of repeat uptake in the second round of invitations. A recent population-based study showed that uptake of the second round of invitations was 87% among people who previously participated in the first round (Lo et al, 2015a). In comparison, uptake among people invited for CRC screening for the first time is only around 54% (von Wagner et al, 2011). Furthermore, a recent series of trials piloting interventions to improve uptake of the BCSP in England found that interventions had a significantly stronger impact among first-time invitees compared with those who had previously been invited (White *et al*, 2015). Thus there is greater opportunity to promote uptake among first-time invitees, which would lead to greater future adherence among screening-eligible adults.

The primary aim of this RCT was to test the effectiveness of a text-message reminder to increase gFOBt uptake. The outcome measure was the total proportion of invitees adequately screened 18 weeks after the initial invitation was sent. Our secondary aims were to examine whether or not a text-message reminder is more effective in improving uptake among first-time invitees than repeat invitees and to establish the efficacy of the text-messages by testing the effectiveness among the non-responders who also had a registered mobile number. The findings will be important to show the impact of the intervention on the overall population and also

the subgroups who are of interest of the text-message reminder intervention.

## METHODS AND MATERIALS

**Study design and setting.** We performed a two-arm RCT in London across six Clinical Commissioning Groups ((CCGs): NHS organisations that manage patient care in GPs in defined geographical areas): Croydon, Greenwich, Hammersmith and Fulham, Hounslow, Lewisham, and West London. The study was carried out in collaboration with the NHS Bowel Cancer Screening Hub in London (hereafter referred to as 'the hub'), who were responsible for creating and maintaining the study database, and iPlato (iPlato, 2013), who were responsible for randomising eligible adults and delivering the text-message reminders. iPlato is an NHS Information Governance approved mobile health (m-health) organization, which provides patient care messaging services to primary and secondary health care in England.

From age 60 and up to age 74 years, the NHS BCSP biennially invites all men and women take part in CRC screening using the gFOBt kit. The gFOBt pathway includes a baseline invitation to initiate a screening episode, which is characterised as an 18-weeklong period for the adequate completion of a gFOBt kit. A week after the initial invite, the kit is dispatched, and a reminder is sent out on the fifth week of the initial invite if the kit had not been returned. Unless the results are abnormal, CRC screening does not include further investigations beyond the gFOBt pathway.

In this two-arm trial, individuals who were randomly allocated to the control group were invited to take part in the BCSP as per the usual care pathway, while individuals randomly allocated to the intervention group were additionally sent a text-message reminder if they had not returned their test kit 7 weeks into their screening episode and had a mobile number stored on their GP's clinical system (see Figure 1).

Further details of the intervention design and procedures for this RCT are available in the published protocol (Hirst *et al*, 2016).

**GP recruitment.** All GPs situated within the six CCGs were emailed and invited to participate in this study between November and December 2015. This invitation was followed by weekly email reminders. Practices were eligible if they already had an existing patient messaging service, which ensured patient consent for text-messages. In order to facilitate automated text-messages, all practices had to connect to the study-specific iPlato server, irrespective of their routine m-health provider in use for textmessages. In total, 144 out of 295 practices (48.8%) agreed to take part and returned their consent forms. Owing to technical difficulties, only 141 out of 144 GPs were successfully connected to iPlato. Low response rate was considered to be an outcome of the eligibility criteria (Hirst *et al*, 2016).

#### Trial procedures

*Identification.* Between January and March 2016, the hub retrospectively identified all men and women aged 60–74 years from all 141 practices to be included in the study based on the start date of their gFOBt screening episode. Each week, everyone who had been invited 7 weeks back were included, irrespective of whether or not they had already completed and returned their faecal occult blood test kit.

The Hub then transferred the list of the screening adults to iPlato. The weekly file contained relevant data to the individuals' screening statuses, including their unique identifier used within the NHS, referred to as the 'NHS Number', the kit return status (Yes/No), the date of screening invitation (Date/Month/Year) used to calculate the date of a text-reminder, and GP code for tailored text-messages (a unique GP identifier).

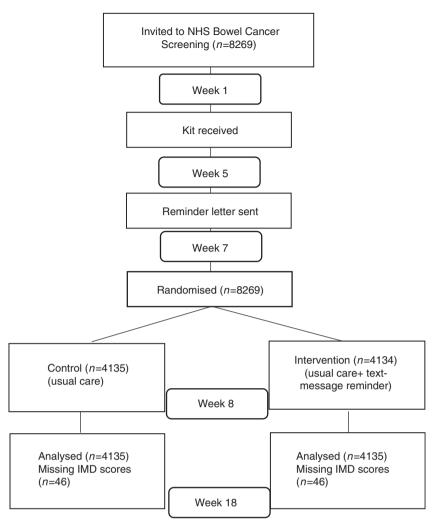


Figure 1. Study consort diagram.

*Data processing and generation.* On receipt of the data at iPlato, individuals were randomised each week in a 1:1 ratio to either the intervention or control condition. Randomisation was conducted using Mersenne Twister: a computerised, pseudorandom number generator (Matsumoto and Nishimura, 1998).

After randomisation, registered mobile number status (Yes/No) was added to the weekly data file, as well as delivery status of the text-message reminder (Yes/No) if the person was in the intervention group and eligible to receive a text-message. The last text-message reminder was sent on the 18 March 2016. When the last of the individual screening episodes were closed 18 weeks after the delivery of the baseline FOBt invitation, a complete data set was returned via secure email transfer to the Hub.

Data merge and anonymisation. The Hub made a record of whether or not a gFOBt had been adequately completed by the individual within the study database and then added individuallevel data on age, gender, the name of the CCG, the screening episode sequence number (i.e., the number of screening test kits received by the eligible individual), and area-level of deprivation (i.e., derived from the 'Index of Multiple Deprivation' (IMD) score) to the data set. The IMD uses census-derived indicators of income, education, employment, living environment, health and disability, barriers to housing and services, and crime at small-area level to generate a scale from 0 (least deprived) to 80 (most deprived). For the purposes of our analysis, IMD scores were categorised into quintiles of the national distribution to enable comparisons between individuals living in the most and least deprived groups

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of areas to be made. Prior to transferring to the research team for analysis, the Hub additionally removed identifiable data (e.g., NHS number, GP code, and postcode), which had been used to facilitate the research.

**Trial registration and ethics.** The study was approved by the East Midlands National Research Ethics Service (15/EM/0159) and is registered with the International Standard Randomised Controlled Trial Number (ISRCTN) registry for transparency (ISRCTN70904476 (18/09/2015)). The study has also been reviewed by the Confidentiality Advisory Group (CAG) and granted full approval (15/CAG/0156), permitting iPlato to process identifiable information for the purposes of this study to be able to send automated text-messages from participating GPs.

Statistical analysis. The characteristics of the screening-eligible population were demonstrated using descriptive statistics. The primary study outcome, the proportion of invitees who returned a test kit within 18 weeks, was assessed on an intention-to-treat basis. A subgroup analysis using interaction terms were included to test the intervention by invitation status (first-time invitee = 0; repeat invitee = 1). The invitation status variable was computed by dichotomising the screening episode sequence number. A secondary analysis was also performed, restricting the sample to individuals who had not returned their kit within 8 weeks and had a registered mobile number on their GP's clinical system. Analyses were conducted using multivariable logistic regression models adjusting for sociodemographic factors (age bands, gender, IMD quintiles, and CCG). Univariable logistic regression results

were reported (Supplementary Table S7). An exploratory analysis was conducted to identify the predictors of having a registered mobile number. All results are presented using odds ratios (ORs), 95% confidence intervals (CIs), and *P*-values. *P*-values < 0.05 were considered as statistically significant.

## RESULTS

**Population characteristics.** In total, 8269 men and women were eligible for CRC screening and subsequently invited to the NHS BCSP during the study identification period. Of these, 4135 were randomised to the control group and 4134 were randomised to the intervention group. Baseline characteristics are shown in Table 1: Individuals invited to screening had a median age of 66 (range 65–69) years, just over half were women (52.0%), and most had been invited to the NHS BCSP more than once (81.4%). Less than one-tenth were from the least deprived IMD quintile (8.6%), and about one-fifth were from the most deprived IMD quintile (21.1%). The proportion of invitees was highest in Croydon (21.7%), followed by Greenwich (20.7%), Hounslow (19.9%), Lewisham (16.3%), and West London (14.5%) and lowest in Hammersmith and Fulham (7.0%).

The impact of the intervention. Overall, 40.2% of individuals were adequately screened; there was no significant difference in the proportion adequately screened between the intervention (40.5%) and control groups (39.9%; OR = 1.03; 95% CI: 0.94–1.12; P = 0.56) (Table 2).

Factors associated with CRC screening uptake. CRC screening uptake was lower among men than women (37.4% *vs* 42.8%; OR = 0.80; 95% CI: 0.73–0.88; P=0.001), higher among people aged 70–74 years than those aged 60–64 years (38.2% *vs* 42.8%; OR = 1.26; 95% CI: 1.11–1.43; P<0.001), and lower among the most deprived IMD quintile *vs* least deprived quintile (34.0% *vs* 51.5%; OR = 0.53; 95% CI: 0.44–0.64; P<0.001). Uptake also varied significantly across the six London CCGs (range from 30.5% to 47.1%). Having a registered mobile number at the GP predicted greater uptake than not having a registered mobile number 43.6%

	% (n)
Overall	100 (n = 8269)
ge, years	
60–64	44.5 (3682)
65–69	29.8 (2466)
70–74	25.7 (2121)
iender	
Male	48.0 (3973)
Female	52.0 (4296)
dex of Multiple Deprivation	
Quintile 1 (least deprived)	8.6 (705)
Quintile 2	14.1 (1157)
Quintile 3	25.0 (2044)
Quintile 4	31.1 (2544)
Quintile 5 (most deprived)	21.1 (1727)
linical Commissioning Group	
Croydon	21.7 (1791)
Greenwich	20.7 (1712)
Hammersmith and Fulham	7.0 (577)
Hounslow	19.9 (1645)
Lewisham	16.3 (1349)
West London	14.5 (1195)
vitation status	
First-time invitees	18.6 (1542)
Repeat invitees	81.4 (6727)

*vs* 36.9%; OR = 1.31; 95% CI: 1.19–1.44 P < 0.001). Limiting the analysis to invitees with a registered mobile who did not return their test kit by the eighth week also showed no significant difference between the intervention (n = 1393, 16.6%) and the control group (n = 1346; 15.9%; OR = 1.05; 95% CI: 0.85–1.28–1.52 P = 0.67).

The impact on the intervention by invitation status. Although there was no main intervention effect, a test of interaction showed a significant effect of the intervention according to invitation status (P = 0.02). There was a 5.6 percentage point difference between uptake of the first-time invitees between the intervention (40.5%) and the control groups (34.9%; OR = 1.29; 95% CI: 1.04–1.58; P = 0.02) (Table 3). Among those who had been previously invited to the screening programme at least once before this study, there was no significant difference in uptake between the intervention (41.1%) and the control group (40.5%; OR = 0.98; 95% CI: 0.89–1.08, P = 0.66). A further exploratory analysis showed no effect of the intervention on uptake when stratified by IMD quintiles, age groups, CCGs, or gender (Supplementary Table S5).

Mobile phone coverage and delivery of text-messages. Mobile phone coverage was assessed in the screening-eligible population. Coverage varied according to age, gender, IMD score, and CCG (Table 4). Compared with those aged 60-64 years, men and women aged 65-69 years (OR = 0.85; 95% CI: 0.77-0.95; P = 0.004) and 70-74 years (OR = 0.67; 95% CI: 0.59-0.75; P < 0.001) were less likely to have a registered mobile number. The proportion of people with a registered mobile number increased with area-level deprivation, with mobile registration being 53.3% in the most deprived IMD quintile, compared with 42.7% in the least deprived IMD quintile (OR = 1.67; 95% CI: 1.39–2.02; P < 0.001). Mobile registration at GPs also varied by CCG. The largest proportion of individuals with registered mobile phone numbers was observed at Croydon CCG, where coverage was 61.9% (n = 1109 out of 1791). The lowest was observed in Hammersmith and Fulham CCG, where coverage was 32.2% (n = 186 out of 577; OR = 0.29; 95% CI: 0.24-0.36 P < 0.001).

Despite differences in GP mobile phone registration, we found no statistically significant difference in the successful delivery of text-messages by participating CCG (P=0.08), age group (P=0.09), gender (P=0.45), IMD quintile (P=0.41), or invitation status (P=0.07). Among 1393 people in the intervention group with a registered mobile and no returned kit, 73.4% (n=1023) successfully received their reminders on the eighth week of their screening episode. Further details of the delivery of text-messages can be found in online Supplementary Materials (Supplementary Table S6).

## DISCUSSION

This trial examined the effectiveness of adding a text-message reminder to the current NHS BCSP through the involvement of primary care. The primary analysis showed that the intervention was not effective at improving uptake of adequate gFOBt screening within six CCGs in London. Likewise, the secondary analysis, limited to individuals who had not returned their test kit within 8 weeks and had a registered mobile number at primary care, indicated that there was no significant difference between the trial arms. However, the subgroup analysis showed that the intervention increased uptake of gFOBt uptake among first-time invitees from 34.9% to 40.1%.

Overall, uptake within the six CCGs (Croydon, Greenwich, Hammersmith and Fulham, Hounslow, Lewisham, West London) was 40.2%, which is consistent with uptake in all of London (40.8%), reported for the first 2.6 million invitations in 2011 (von Wagner *et al*, 2011). The social gradient in uptake in this text-

	Intention-to-tr	Intention-to-treat (N=8269)		Secondary analysis ( $N = 2739$ )		
	% uptake ( <i>N</i> )	OR (95% CI)	P-value	% uptake ( <i>N</i> )	OR (95% CI)	P-value
Study group						
Control Intervention	39.9 (1648) 40.5 (1674)	Ref. 1.03 (0.94–1.12)	0.560	15.9 (214) 16.6 (231)	Ref. 1.05 (0.85–1.28)	0.670
Gender			4			- I
Female Male	42.8 (1837) 37.4 (1485)	Ref. 0.80 (0.73–0.88)	0.001	16.1 (224) 16.4 (221)	Ref. 0.97 (0.79–1.19)	0.750
Age, years						
60–64 65–69 70–74	38.2 (1407) 40.9 (1008) 42.8 (907)	Ref. 1.13 (1.00–1.27) 1.26 (1.11–1.43)	0.050 0.000	16.7 (233) 16.9 (132) 14.2 (80)	Ref. 1.14 (0.87–1.49) 0.97 (0.72–1.33)	0.340 0.870
Index of Multiple Depriva	tion					
Quintile 1 (least deprived) Quintile 2 Quintile 3 Quintile 4 Quintile 5 (most deprived)	51.5 (363) 41.9 (485) 43.4 (888) 38.0 (967) 34.0 (587)	Ref. 0.79 (0.65–0.95) 0.77 (0.64–0.95) 0.61 (0.51–0.73) 0.53 (0.44–0.64)	0.003 0.000 0.000 0.000	26.4 (178) 23.4 (71) 17.4 (113) 15.0 (137) 11.0 (72)	Ref. 0.93 (0.59–1.44) 0.62 (0.41–0.92) 0.52 (0.35–0.76) 0.38 (0.26–0.57)	0.740 0.020 0.001 0.000
Clinical Commissioning Gr	oups	÷				
Croydon Greenwich Hammersmith and Fulham Hounslow Lewisham West London	47.1 (843) 43.3 (742) 35.9 (207) 40.1 (660) 37.5 (506) 30.5 (364)	Ref. 0.89 (0.77–1.01) 0.68 (0.56–0.83) 0.77 (0.67–0.89) 0.73(0.63–0.85) 0.56 (0.47–0.65)	0.080 0.000 0.000 0.000 0.000	18.5 (129) 17.0 (109) 14.2 (18) 18.6 (73) 13.8 (77) 12.0 (39)	Ref. 0.93 (0.69–1.25) 0.75 (0.44–1.29) 0.95 (0.68–1.33) 0.79 (0.58–1.09) 0.65 (0.43–0.96)	0.640 0.290 0.780 0.160 0.030
Invitation status						
First-time invitee Repeat invitee	37.5 (579) 40.8 (2743)	Ref. 1.01 (0.89–1.16)	0.870	18.9 (117) 15.5 (328)	Ref. 0.74 (0.56–0.98)	0.040
Registered mobile numbe	r					
No Yes	36.9 (1541) 43.6 (1781)	Ref. 1.31 (1.19–1.44)	0.000	NA NA		

Table 3. Impact of the intervention by invitation status							
	Control ( <i>n</i> = 4135) <sup>a</sup>	Intervention (n = 4134)					
	% (N)	% (N)	OR (95% CI)	P-value			
Invitation status							
First-time invitee Repeat invitee	34.9 (282) 41.1 (1366)	40.5 (297) 40.5 (1377)	1.29 (1.04–1.58) 0.98 (89–1.08)	0.02 0.66			
Abbreviations: CI = confidence interval; OR = odds ratio.							

<sup>a</sup>Reference group (adjusted for age, gender, Index of Multiple Deprivation, and Clinical Commissioning Group).

message reminder trial was consistent with the trends in first-time and repeat CRC uptake, specifically with men consistently having lower uptake than women, and people living in the most deprived areas of the six CCGs having poorer uptake rates than those in the least deprived areas (von Wagner *et al*, 2011; Lo *et al*, 2014; Moss *et al*, 2016).

If CRC screening-eligible people complete their gFOBt test kit when they are first invited, it is very likely that they will continue to do so following subsequent invitations (Janda *et al*, 2010; Lo *et al*, 2015b). A previous study on repeat screening participation over two rounds of screening invitations demonstrated that while 86% of previous responders completed their second invitation, only 23% of the previous non-responders returned the test kit (Lo *et al*, 2015a). Hence, the effect of this intervention on the first-time invitees has important implications for the CRC screening uptake, specifically to minimise practical barriers among individuals who have not engaged with screening before their first invitation.

	% (N)	OR (95% CI)	P-value
Overall	49.4 (N=4089)		
By gender Female Male	48.4 (n = 2079) 50.6 (n = 2010)	Ref. 1.08 (0.99–1.18)	0.09
By age (years) 60–64 65–69 70–74	53.6 (n = 1972) 49.2 (n = 1213) 42.6 (n = 904)	Ref. 0.85 (0.77–0.95) 0.67 (0.59–0.75)	0.004 <0.001
By IMD Quintile 1 (least deprived) Quintile 2 Quintile 3 Quintile 4 Quintile 5 (most deprived)	42.7 (n = 301) 40.7 (n = 471) 50.2 (n = 1026) 51.7 (n = 1316) 53.3 (n = 920)	Ref. 1.24 (1.01–1.51) 1.61 (1.34–1.93) 1.62 (1.36–1.94) 1.67 (1.39–2.02)	0.04 <0.001 <0.001 <0.001
By CCG Croydon Greenwich Hammersmith and Fulham Hounslow Lewisham West London	61.9 (n = 1109) 56.1 (n = 960) 32.2 (n = 186) 36.2 (n = 595) 58.1 (n = 784) 38.1 (n = 455)	Ref. 0.79 (0.68–0.90) 0.29 (0.24–0.36) 0.35 (0.30–0.41) 0.81 (0.70–0.95) 0.38 (0.32–0.44)	0.001 <0.001 <0.001 0.007 <0.001

**Strengths and limitations.** To our knowledge, this is the first large-scale trial examining the effectiveness of text-message reminders in the context of gFOBT-based CRC screening in a nationally organised programme. The trial was purposefully

designed to test a sustainable and a low cost (<£0.05 per text) alternative to postal reminders (second Class UK postage = £0.55), with zero workload to GPs and minimal opportunity costs to the NHS BCSP (Hirst *et al*, 2016). However, there may likely be a one-off investment cost (e.g., change in IT infrastructure) to the NHS BCSP, if text-message reminders were directly sent from the screening programme. Unlike an appointment reminder, the text-message reminders in CRC screening will be limited to non-responders, if applied within NHS BCSP. Unfortunately, possible inaccurate and out-of-date mobile numbers and low proportions of people with registered mobile phone numbers in primary care raise concerns that GP clinical records for mobile phone numbers may not be up-to-date.

It is important to note a number of potential modifications, which could improve the impact of the text-message reminder. In this study, the reminder was sent 8 weeks after the person was mailed their invitation. It is possible that at this point many people would have already misplaced or thrown out their test kit. Future research could test whether sending a text-message reminder earlier in the episode could have more impact on uptake. Relatedly, previous studies that have shown an effect of text-message reminders on CRC and breast screening uptake had informed participants at the time of initial screening invitation that they may receive a text-message reminder (Baker *et al*, 2014; Kerrison *et al*, 2015). Sending a 'note' at the start of the trial may act as a 'primer' and enhance the impact of a text-message reminder.

#### CONCLUSION

GP-endorsed text-reminders at 8 weeks past the initial invitation of CRC screening did not increase overall uptake in a socioeconomically deprived and ethnically diverse areas in London but their positive impact on first-time invitees is promising and could pay long-term dividends for the effectiveness of the programme.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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