Impact of general practice endorsement on the social gradient in uptake in bowel cancer screening

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Background: There is a socioeconomic gradient in the uptake of screening in the English NHS Bowel Cancer Screening Programme (BCSP), potentially leading to inequalities in outcomes. We tested whether endorsement of bowel cancer screening by an individual's general practice (GP endorsement; GPE) reduced this gradient.

Methods: A cluster-randomised controlled trial. Over 20 days, individuals eligible for screening in England from 6480 participating general practices were randomly allocated to receive a GP-endorsed or the standard invitation letter. The primary outcome was the proportion of people adequately screened and its variation by quintile of Index of Multiple Deprivation.

Results: We enrolled 265 434 individuals. Uptake was 58.2% in the intervention arm and 57.5% in the control arm. After adjusting for age, sex, hub and screening episode, GPE increased the overall odds of uptake (OR = 1.07, 95% CI 1.04–1.10), but did not affect its socioeconomic gradient. We estimated that implementing GPE could result in up to 165 more people with high or intermediate risk colorectal adenomas and 61 cancers detected, and a small one-off cost to modify the standard invitation (£78 000).

Conclusions: Although GPE did not improve its socioeconomic gradient, it offers a low-cost approach to enhancing overall screening uptake within the NHS BCSP.

Colorectal cancer (CRC) is the fourth most common cause of cancer death worldwide (Ferlay et al, 2013). In the UK it is the third most common cancer and has the second highest mortality rate (CRUK, 2014). Biennial screening using the guaiac faecal occult blood test (gFOBt) can reduce bowel cancer mortality by up to 25% among people undertaking screening (Hewitson et al, 2008; Scholefield et al, 2012). The National Health Service (NHS) Bowel Cancer Screening Programme (BCSP) introduced biennial screening in England in 2006 and now offers it to all individuals aged 60–74 years.

Screening uptake in England is 56%, varying from 61% in the least deprived to 35% in the most-deprived areas of the country (von Wagner et al, 2011).

The BCSP is delivered by five regional hubs and currently operates independently from general practices. General practitioners (GPs) are notified about their patients' screening results or if their patients did not have screening, but there is no organised GP involvement. However, data from the BCSP pilot (2000–2002) indicated that lack of GP involvement could be a significant barrier to uptake (Weller et al, 2009), confirming findings from previous studies that endorsement of the programme by a GP practice, or a named GP, may circumvent lack of recognition of the BCSP and enhance screening uptake (Cole et al, 2002; Zajac et al, 2010; Hewitson et al, 2011). No evidence exists on whether GPE can influence the differential uptake in CRC screening between socioeconomic groups. Although the inclusion of the GP's signature on the screening invitation increases gFOBt uptake, this is costly and time-consuming (Cole et al, 2002; Hewitson et al, 2011). Studies have also shown that naming the relevant general practice is almost as effective at increasing uptake as including the GP's signature (Hewitson et al, 2011).

We developed four interventions to increase uptake amongst individuals with lower socioeconomic circumstances (SEC), without compromising uptake in any socioeconomic group (Wardle et al, 2015). This paper reports the findings of a cluster-randomised controlled trial (RCT) of one of these interventions: general practitioner (GP) GP practice endorsement (GPE) of the BCSP's screening invitation, which could potentially be a simple and cheap intervention to embed in the routine BCSP invitation letter. One of the other three interventions that were developed, an enhanced reminder letter targeted at individuals who had not responded to the initial screening invitation, was evaluated at the same time as GPE using a pseudo-factorial design. Patients were only eligible for inclusion in the enhanced reminder study if they did not respond to the initial screening invitation, and those who were eligible were randomly assigned to receive the enhanced reminder or not. Hence the enhanced reminder study is unlikely to affect the evaluation of GPE.

In summary, the aims of this study were to evaluate the impact of GPE on the socioeconomic gradient in CRC screening uptake, and its cost. We also evaluated the impact of GPE on CRC screening uptake overall.

MATERIALS AND METHODS

Intervention. We convened 18 focus groups in London and Yorkshire to explore reasons for non-uptake of bowel cancer screening amongst 128 individuals, sampled to encompass socially advantaged and disadvantaged groups (Palmer et al, 2014). They reported that lack of GP involvement attenuated the perceived relevance of the BCSP and that GP support for the BCSP carried considerable power ('If the letter had come from my GP…I would have taken it more seriously.' (FG18P6)) (Palmer et al, 2014).

We established a Primary Care Advisory Group to develop GPE text that could be easily incorporated into the standard BCSP invitation. The resulting GPE statement appeared as a banner across

the invitation letter, linking it to each individual's registered practice, i.e., 'Your GP Practice [GP practice name] supports the Bowel Cancer Screening Programme' (Supplementary Appendix A).

We sought consent from all General Practices in England (N = 8142) to add their practice name to the standard BCSP invitation. Letters to practices emphasised that endorsing the BCSP would involve little or no extra work for the practice and were sent on BCSP Hub headed paper, signed by Hub Directors. We sent up to three reminder letters to practices at approximately monthly intervals. The final reminder included an additional message for practices in deprived areas, stating we were 'particularly keen to include practices that look after patients from more deprived areas because those people are less likely to take part in screening'. In total, 80% of practices (N = 6480) granted permission to be part of the study.

Randomisation and masking. Randomisation was undertaken through the Bowel Cancer Screening System (BCSS), which identifies the population eligible for screening in each hub. The BCSS was modified to enable selection of invitees belonging to general practices, which had agreed to endorse the BCSP before creation of each invitation letter. Individual randomisation was not feasible for logistical reasons: invitation letters are produced in batches so it was not possible to vary them by individual screening invitee, but it was possible to vary them by day. Therefore, cluster randomisation was used based on day of invitation, with 'day-within-hub' constituting the randomisation unit (hub-day). Randomisation ran over 20 consecutive days in June 2013, resulting in 10 clusters of invitees receiving an endorsed invitation letter and 10 control clusters in each of the five hubs (100 clusters in total). Two weeks before the start of each intervention, a random number sequence was generated with a continuous random number for each hub-day. Hub-days above the median random number were allocated to intervention; hub-days below to control. This enabled the BCSS to take account of the dates when GPE invitations needed to be produced by any of the five hubs. Hubs were not aware of the randomisation schedule and confirmed whether the intervention was included on the standard BCSP invitation letter every day, which the Trial Office checked against the randomisation schedule. Although blinding of hubs was not possible, there was no direct contact with participants. Participants were unaware of the comparator unless a household member received an invitation during the study period that contained different information materials or if they had been invited on a previous occasion and recalled the content of that invitation.

Inclusion/exclusion criteria. Individuals were eligible for inclusion in the GPE trial if registered with practices that had previously agreed to endorse the BCSP. If the practice consent was not obtained, individuals from that practice were excluded from the trial.

Outcome measures and costs. Participants were considered to have been adequately screened if they had returned a gFOBt kit within 18 weeks of being sent an invitation, which led to a definitive 'normal' (no further investigation required) or 'abnormal' (requiring referral for further investigation, usually colonoscopy) test result. The 18-week time limit coincided with the date on which the BCSS closes a screening episode to a non-responder. Socioeconomic status was measured using the English Index of Multiple Deprivation (IMD) 2010 (Indices of deprivation 2010, 2011), which comprises 38 indicators, combined into seven domains (Income, Employment, Health and Disability, Education Skills and Training, Barriers to Housing and Other Services, Crime and Living Environment). This provides an overall measure of deprivation experienced by people living in a small area (Lower layer Super Output Area, LSOA). Each LSOA covers ~1500 individuals. Each individual's postcode was linked to the relevant LSOA. Age and sex were obtained from the BCSP database, which also contained information on the type of screening episode:

whether individuals were being invited for the first time (first-time invitee), being sent a biennial invitation having previously not responded (previous non-responder), or being sent a biennial invitation having been screened before (previous responder). We used the results to estimate the impact of GPE on the detection of colorectal adenomas and cancer in the BCSP.

We calculated the costs of modifying the BCSP IT system to incorporate the GPE as part of the standard invitation. This was based on the actual cost charged to the study to modify the invitation letter. We divided this figure by the number of participants in the intervention arm of the trial to calculate the cost per participant. No additional intervention costs were incurred.

Statistical considerations. The sample size was based on increasing uptake by five percentage points in the lowest IMD quintile (most deprived group) falling to one percentage point increase in the highest quintile; giving an overall 5-4-3-2-1 percentage point difference by quintile. This estimate was based on outcomes considered feasible in research to increase screening uptake (Halloran *et al*, 2010). Sample size was calculated for each hub separately, assuming a similar proportional effect in each hub. For 90% power to detect a statistical significant change as described above, the estimated numbers required per group (intervention and control) overall were 13 500, 12 200, 11 700, 5400 and 4500, assuming that all participants had the composition of Midlands and North West, London, North East, Eastern and Southern Hubs, respectively. We used the maximum of the calculated sample sizes (Midlands and North West Hub). Three further adjustments ensured high statistical power. First, on average each hub sends ∼3000 letters per day. The number of invitations per day varies, so we applied an inflation factor of 1.7 to account for this. Second, we initially predicted that 30% of practices would agree to endorse the BCSP so we increased our sample size by a factor of 100/30, which meant running the trial for 15 days to reach our target sample size of 76 500. Third, we actually conducted the trial for 20 days.

We ran several logistic regression models, based on participant level data with a binary outcome variable indicating whether or not the participant was adequately screened (1 = yes, 0 = no). We ran a univariable model on all participants regressing the outcome against treatment group (1 = GPE intervention, 0 = control) (model 1). Model (2) was a multivariable model on all participants, adjusting for sex, age, hub and screening episode. Models 1 and 2 were then performed stratifying participants by IMD quintile. Model 1 was also performed stratifying participants by sex, age, hub and screening episode, including an interaction term between treatment group and IMD score (as a continuous variable). We investigated whether GPE changed the socioeconomic gradient in uptake (both univariable and multivariable models) by testing for significant differences in the odds ratios (OR) for the treatment group variable in each IMD quintile using Wald tests. Conservative variance estimation was used to allow for correlation of individuals within randomisation clusters but not between clusters, and we used the Huber–White information sandwich method for variance estimation (Huber, 1967; White, 1980).

We calculated average marginal effects and used these to predict the impact of GPE on the detection of colorectal adenomas and cancer in the BCSP.

Analyses were performed on an intention-to-treat basis using SAS v9.3 (SAS Institute Inc., 2011) and Stata v12.1 (StataCorp, 2011).

Study approvals. Individual consent was not required because the intervention took place as part of usual communication from the BCSP. The activities of BCSP are covered by National Information Governance Board approval with regard to the handling of patient-identifiable data (Ref: PIAG 1–08(a)/2003). Ethical approval was obtained from the UK National Research Ethics Service, London-Harrow Ethics Committee, Reference number 12/LO/1396. This study is registered at the ISRCTN (registration number: 74121020).

RESULTS

The trial included 265 434 individuals from 98 instead of 100 planned clusters (a protocol violation occurred in two clusters, whereby incorrect randomisation was applied twice). Baseline characteristics were well balanced between the two trial groups and representative of the BCSP population (Table 1) (Logan *et al*, 2012). Bowel cancer screening uptake was 58.2 and 57.5% in the GPE intervention and control groups, respectively (Table 2). This increase of 0.7 percentage points (7 per 1000 screened individuals) was statistically significant ($P < 0.001$).

As expected, the absolute proportion of individuals participating in screening decreased with increasing deprivation level: 65.2% of individuals (average across both groups) in IMD quintile 1 (least deprived) participated in screening, compared with 43.3% in IMD quintile 5 (most deprived). Uptake was 0.8 percentage points lower in the intervention group in the least deprived quintile and 1.4 percentage points higher in the most deprived quintile (Table 2).

Before adjustment, the GPE intervention had a non-significant effect on the odds of screening uptake among all participants (OR 1.03, 95% confidence interval (CI) 0.95–1.11, $P = 0.49$; Table 3). Stratification by sub-group suggested there were differences in the odds of screening uptake by screening history: a 9% increase in the odds of uptake among first-time invitees

Table 1. Baseline sample characteristics		
	Standard BCSP invitation + GPE *N* = 131 423	Standard BCSP invitation *N* = 134 011
	Median (range)	**Median (range)**
Age (years)[a]	65 (59–74)	65 (59–74)
IMD deprivation score	14.7 (0.5–87.8)	14.6 (0.5–87.8)
	% (n)	**% (n)**
Sex		
Female	51.0 (66 986)	51.2 (68 591)
Male	49.0 (64 437)	48.8 (65 420)
IMD quintile[b]		
1 (Least deprived)	23.1 (30 350)	23.3 (31 381)
2	23.6 (30 952)	23.4 (31 340)
3	21.3 (27 950)	21.0 (28 181)
4	17.1 (22 450)	17.2 (23 007)
5 (Most deprived)	14.6 (19 174)	14.6 (19 540)
Missing	547	562
Hub		
BCS01	27.4 (35 993)	25.8 (34 598)
BCS02	24.2 (31 760)	30.3 (40 550)
BCS03	9.0 (11 818)	9.9 (13 255)
BCS04	16.2 (21 272)	16.0 (21 439)
BCS05	23.3 (30 580)	18.0 (24 169)
Screening episode		
Incident	52.3 (68 695)	52.3 (70 134)
Prevalent first time invitees	17.0 (22 287)	17.6 (23 582)
Prevalent previous non-responders	30.8 (40 441)	30.1 (40 295)

Abbreviations: BCSP = Bowel Cancer Screening Programme; GPE = GP endorsement; IMD = Index of Multiple Deprivation.
[a]Some subjects were invited just before their 60th birthday.
[b]Quintile based on national distributions using pre-defined national cut-offs.

Table 2. Proportion of people who were adequately screened by age, sex, IMD quintile, hub and screening episode

	Standard BCSP invitation + GPE	Standard BCSP invitation
	% (n)	% (n)
All participants	58.2 (76 520)	57.5 (77 122)
Age (years)		
60–64	55.9 (33 331)	54.8 (33 480)
65–69	61.0 (27 382)	60.5 (27 466)
70 +	58.7 (15 807)	58.8 (16 176)
Sex		
Female	60.7 (40 707)	60.2 (41 290)
Male	55.5 (35 813)	54.8 (35 832)
IMD quintile		
1 (Least deprived)	65.2 (19 792)	66.0 (20 716)
2	63.1 (19 530)	62.6 (19 604)
3	59.3 (16 571)	58.0 (16 336)
4	53.0 (11 902)	51.5 (11 839)
5 (Most deprived)	44.0 (8433)	42.6 (8324)
Hub		
BCS01	55.2 (19 869)	55.4 (19 150)
BCS02	62.7 (19 915)	60.3 (24 437)
BCS03	49.5 (5850)	48.2 (6385)
BCS04	59.8 (12 710)	58.9 (12 631)
BCS05	59.4 (18 176)	60.1 (14 519)
Screening episode		
Incident	86.4 (59 380)	85.7 (60 119)
Prevalent first time invitees	51.4 (11 465)	49.4 (11 646)
Prevalent previous non-responders	14.0 (5675)	13.3 (5357)

Abbreviations: BCSP = Bowel Cancer Screening Programme; GPE = GP endorsement; IMD = Index of Multiple Deprivation. A total of 1109 (547 Standard BCSP invitation + GPE and 562 Standard BCSP invitation) individuals had missing socioeconomic circumstances, 595 of these were adequately screened (292 Standard BCSP invitation + GPE and 303 Standard BCSP invitation).

Table 3. Impact on uptake of GPE + standard BCSP invitation vs standard BCSP invitation alone: results for all participants combined and sub-groups of participants stratified by IMD quintile

	Univariate		Multivariate[a]	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
All participants	1.03 (0.95–1.11)	0.49	1.07 (1.04–1.10)	<0.0001
Participants stratified by IMD quintile				
1 (Least deprived)	0.97 (0.88–1.05)	0.43	1.04 (0.99–1.08)	0.08
2	1.02 (0.95–1.10)	0.54	1.06 (1.02–1.10)	0.004
3	1.06 (0.98–1.14)	0.16	1.08 (1.03–1.13)	0.001
4	1.06 (0.98–1.16)	0.15	1.09 (1.04–1.15)	0.001
5 (Most deprived)	1.06 (0.97–1.15)	0.19	1.07 (1.01–1.13)	0.02
Test for equal ORs in each IMD quintile (P-value)	0.27		0.49	

Abbreviations: CI = confidence interval; IMD = Index of Multiple Deprivation.
[a]Adjusting for age, sex, hub and screening episode.

Table 4. Impact on uptake of GPE + standard BCSP invitation versus standard BCSP invitation alone: univariate results for all participants combined and sub-groups of participants stratified by age, sex, hub and screening episode, plus including an interaction term between treatment group and IMD score (included as a continuous variable)

	Odds ratio (95%CI)	P-value	P-value for significant interaction with IMD score
All participants	1.03 (0.95–1.11)	0.49	0.11
Participants stratified by sub-group			
Age (years)			
60–64	1.05 (0.98–1.12)	0.2	0.06
65–69	1.02 (0.92–1.13)	0.66	0.55
70 +	0.99 (0.89–1.10)	0.9	0.32
Sex			
Female	1.02 (0.94–1.12)	0.58	0.22
Male	1.03 (0.96–1.12)	0.4	0.13
Hub			
BCS01	0.99 (0.90–1.10)	0.91	0.42
BCS02	1.11 (0.99–1.24)	0.07	0.01
BCS03	1.05 (0.88–1.26)	0.56	0.95
BCS04	1.04 (0.94–1.14)	0.47	0.31
BCS05	0.97 (0.84–1.13)	0.73	0.25
Screening episode			
Incident	1.06 (1.00–1.13)	0.045	0.68
Prevalent first time invitees	1.09 (1.01–1.16)	0.02	0.44
Prevalent previous non-responders	1.06 (1.00–1.13)	0.055	0.22

Abbreviations: CI = confidence interval; IMD = Index of Multiple Deprivation.

(OR: 1.09; $P = 0.02$) and a 6% increase in the odds of uptake among previous non-responders (OR: 1.06; $P = 0.055$); and in the odds of uptake amongst previous responders (OR: 1.06; $P = 0.045$) (Table 4). When the data were stratified by deprivation level, the ORs in each IMD quintile were not significantly different from one another (unadjusted ORs: 0.97, 1.02, 1.06, 1.06, 1.06 for the least to most deprived IMD quintiles, respectively; $P = 0.27$; Table 3).

Interactions between treatment group and IMD score were non-significant for all participants combined ($P = 0.11$), and were largely non-significant in every sub-group (Table 4).

After adjusting for age, sex, hub and screening episode, the odds of screening uptake were significantly higher in the intervention arm (adjusted OR = 1.07, 95% CI 1.04–1.10, $P < 0.0001$; Table 3), i.e., a 7% increase in the odds of screening. A similar increase was seen within each IMD quintile. However, the adjusted ORs in each IMD quintile were not significantly different from one another ($P = 0.49$); although the GPE intervention significantly increased the overall screening uptake, it did not significantly affect the socioeconomic gradient in screening uptake.

A 7% increase in the odds of screening (all participants) in the multivariable model, was associated with predictive margins (adjusted average probabilities of uptake) of 0.584 (95% CI 0.581–0.586) in the intervention group and 0.574 (95% CI 0.571–0.577) in the control group. This translates into a 1.7% relative increase in the probability of screening among all participants (0.584/0.574) and a one percentage point absolute increase (0.584–0.574; the average marginal effect). Although this appears to be a relatively small effect, in absolute terms the impact would be large if it was rolled out nationally given the population size. In the 2013/14 fiscal year, the number invited for screening in

the BCSP in England was 3 976 616 (BCSSN, 2015). An average marginal effect of one percentage point (0.010) suggests that if GPE were implemented nationally, then 39 766 extra people each year would 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 (Logan *et al*, 2012), 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 medium or high risk requiring further investigation (Logan *et al*, 2012). Hence, if GPE

were implemented nationally this could detect up to an additional 165 people ($39\,766 \times 0.0184 \times 0.83 \times 0.272$) with polyps classed as high or intermediate risk, and 61 people ($39\,766 \times 0.0184 \times 0.83 \times 0.101$) with a colorectal cancer each year.

GPE incurred a one-off cost to modify the standard invitation within the BCSS of £78 000. This is only 59 pence per participant in the intervention arm of the trial. This would not need to be incurred again if GPE were implemented. No additional costs were incurred per person invited to screening, hence the average marginal cost per GPE screening invitation was zero.

DISCUSSION

The addition of a simple statement of GP endorsement to the standard BCSP invitation letter increased the odds of participation in the gFOBt screening programme by 7% with only a small up-front cost. This translates into a 1.7% relative increase in the probability of screening and a 1% point absolute increase, and represents an almost cost-free approach to enhancing screening uptake, with no effort required from primary care other than agreement to have the practice name on the letters.

GPE did not have a significantly stronger effect in lower *vs* higher socioeconomic groups. This is the first study highly powered to examine effects on the socioeconomic gradient, and the size of the trial indicates that even if the non-significant differences are real, they are not substantial, at least for the format of GPE used.

The increase in overall uptake was smaller than previous studies (Camilloni *et al*, 2013), which may be because they used a more intensive intervention, with letters directly from the GP or featuring individual GPs' signatures. However, in the BCSP all invitation letters come from the hubs and keeping up to date with the names of all GPs at every practice would be costly, time consuming and subject to error, as shown previously (Hewitson *et al*, 2011). The only practical option was to include a banner noting the individual's general practice supported the programme. Although this approach may have diluted the impact, this should be balanced against the wide coverage, impact on colorectal adenoma and cancer detection, and negligible cost.

The strengths of our trial were its national coverage, the large sample size yielding substantial statistical power to detect small differences in uptake between sub-groups, and easy incorporation of the intervention into the existing BCSP.

There were several limitations. First, it was not possible to use individual randomisation for logistical reasons so a clustered design was used, which could compromise statistical efficiency and increase the required sample size (Campbell, 2014). This was addressed in our sample size calculation, and our sample size target was surpassed. Second, contamination between study groups, such that individuals in the control group were exposed to the GPE intervention, could have occurred, for example, in the unlikely event that different household members were randomised to different arms of the trial during the 4-week study period. Third, our findings may have been influenced by other factors operating within areas and affecting outcomes. For example, it is possible that local initiatives affected uptake in specific regions. This is unlikely to affect our findings because it is improbable that concurrent interventions would occur on the same alternate days as each intervention. Fourth, as part of the programme, we developed four interventions and another trial evaluating a simple enhanced reminder was conducted at the same time as this trial using a pseudo-factorial design. The enhanced reminders targeted individuals who had not responded to the initial screening invitation; individuals who had not responded to the invitation were randomly assigned to receive an enhanced reminder reiterating

the screening message or the usual reminder letter. Some participants in the GPE trial were eligible for inclusion in the enhanced reminder trial, and those who were not eligible had all responded to the first screening invitation. Those who were eligible for inclusion in the enhanced reminder study were randomly allocated to receive the enhanced reminder or not. Hence, this has not been adjusted for in our statistical analysis, though there is a chance of residual confounding.

GP endorsement increased overall screening uptake although it did not significantly affect the socioeconomic gradient in bowel cancer screening participation. This illustrates the challenge of shifting the gradient in screening participation within the context of a national screening programme.

Given the exceptionally high level of agreement by general practices to endorse the BCSP, the small one-off cost to modify the standard invitation letter, and the overall increase in uptake, we suggest that the BCSP consider adding GPE to the screening invitation letter.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

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. WA oversaw the recruitment of GP practices and had overall

responsibility for delivery of the intervention. The hubs 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. SMorris, FS, RR and MT drafted the paper and all authors contributed to the reviews and revisions. All authors have seen and approved the final version. RR is guarantor.

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