PROTOCOL

Strategies to reduce the social gradient in bowel cancer screening: the ASCEND project

Funder Reference: RP-PG-0609-10106

Protocol Number: 12/0324

Version 1.0, 03/08/2012

MAIN SPONSOR: University College London

FUNDER: National Institute for Health Research

NRES reference: 12/LO/1396

Protocol authorised by:

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Prof Rosalind Raine, CI  03/08/2012
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General Information

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Sponsor

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National Institute for Health Research (RP-PG-0609-10106)
List of Abbreviations

BCSP – Bowel Cancer Screening Programme
BCSS – Bowel Cancer Screening System
CCG – Clinical Commissioning Group
CfH – Connecting for Health
DH – Department of Health
FOBt – faecal occult blood test
FS – Flexible Sigmoidoscopy
GP – General Practitioner
IDMEC – Independent Data Monitoring & Ethics Committee
IMD – Index of Multiple Deprivation
LR – Logistic Regression
LSOA – Lower Super Output Area
NAEDI – National Awareness and Early Diagnosis Initiative
NIGB – National Information Governance Board
NHS – National Health Service
OBIEE – Oracle Business Intelligence Enterprise Edition
PCRN – Primary Care Research Network
PCT – Primary Care Trust
QALY – Quality Adjusted Life Year
QARC – Quality Assurance Reference Centres
RCT – Randomised Controlled Trial
RDI – Real Digital International
SE – Socio-economic
SFT – Secure File Transfer
SFTP – Secure File Transfer Protocol
SOP – Standard Operating Procedure
SQL – Search and Query Language
Background

The NHS Bowel Cancer Screening Programme

Bowel cancer constitutes a significant public health burden in the UK. It is the third most common cancer (35,000 cases annually) and the second leading cause of cancer death (16,000 deaths annually) (1). Its incidence rises significantly with age (2). Early diagnosis is vital to improve outcomes: 93% of patients with early stage disease (Dukes A) survive five years compared with 6.6% of those with late stage (Dukes D) disease (3).

Randomised Controlled Trials (RCTs) have demonstrated that bowel cancer mortality can be reduced with screening using the guaiac-based faecal occult blood test (FOBt) (4). Reduction in mortality as a consequence of population screening is dependent on the rate of participation. Thus, the combined results of four international RCTs showed that participation rates of over 50% in biennial population screening reduced mortality by 15% (5), saving up to 2,500 lives a year (6). Further decreases in mortality could be achieved through improvements in the participation rate.

Following successful pilots, the Bowel Cancer Screening Programme (BCSP) began in England in 2006 (7). It offers the FOBt every two years to 60 to 69 year olds, and the upper age limit is currently being extended to 74 years. Five hubs covering England co-ordinate a call/recall programme and are also responsible for analysing the FOBt samples. The hub sends an invitation and leaflet about the screening programme within a few months of each individual’s birthday to all patients registered with a GP (General Practitioner) in their region. This is followed by the FOBt kit 8-10 days later. To complete the test, the individual places two small stool samples onto each of two windows and repeats this process for three separate bowel motions. The kit is returned to the hub for processing in a pre-paid envelope. If the kit is not returned within four weeks, a reminder letter is sent. A total of 13 weeks is allowed for the kit to be returned and the ‘screening episode’ is then closed. The hubs process the FOBt, and the result is sent to the individual and their GP within two weeks. Depending on the result, the individual will be offered routine FOB testing after two years (normal result), a repeat test (spoilt kit or unclear result), or referral to the local screening centre (abnormal result). Each hub works with up to 17 local screening centres which provide follow-up for individuals with abnormal test results.

The FOBt pilots reported uptake rates of 58.5% and 51.9% in the first and second rounds of screening (8). However, in both the UK Trial of FOBt screening (9) and the pilot, there were striking gradients in uptake across levels of socioeconomic (SE) deprivation. The pilot reported 61% participation in the most socially advantaged areas falling to 37% in the most deprived areas (8).

These figures are being replicated nationally as the BCSP is rolled out. Service use is not regularly monitored by socio-economic (SE) group, but we analysed national uptake rates using postcode sector, the smallest geographical unit routinely recorded by the BCSP. Each of the sectors contains on average 3,000 addresses. We found that between October 2006 and January 2009, overall screening uptake was 53%, but it varied from 61% in the least deprived quintile of postcode sectors to 35% in the most deprived quintile (10).

The low uptake and striking SE gradients are not seen for colonoscopy attendance following positive FOBt. Overall colonoscopy uptake is 84%, ranging from 86% in socially advantaged to 80% in
disadvantaged areas (11). Therefore, addressing the FOBT uptake gradient should contribute to reducing inequalities in colorectal cancer mortality.

Prior to the start of the BCSP there was evidence that more disadvantaged patients with bowel cancer tended to present as emergency admissions and at a later disease stage (12, 13). Their outcomes are also poorer. Furthermore the deprivation gap in survival is widening, reaching 7% for colon cancer and 9% for rectal cancer, between the most and least deprived individuals (14).

**Inequalities in bowel cancer screening**

There is concern about health and health care inequalities in this country. The commitment to improve health and reduce inequalities forms the cornerstone of the Government’s public health and health care policies (15, 16).

The stepwise relationship between SE group and health whereby more socio-economically advantaged individuals have better health and better uptake of health care, is well known (17). The costs of inequalities are therefore borne not only by those at the bottom of the SE hierarchy but also by those at intermediate levels. Policies that target the most disadvantaged subgroups only, or which aim to narrow the gap between the most and least disadvantaged, under-estimate the pervasive effect across the SE hierarchy and exclude those in need in the intermediate SE groups.

Research into improving uptake of cancer screening has focused primarily on factors such as ways of establishing contact (18). While this approach can help reach screening targets, it is unlikely to reduce inequalities and may even increase them if more advantaged individuals are more responsive.

A few studies have specifically addressed SE inequalities in uptake, but often by focusing specifically on under-served groups (e.g. by providing community support workers (19)). Even when successful, these initiatives serve only one group in the population and do not address the gradient per se. In addition, they are often highly intensive initiatives and therefore impractical for wide-scale implementation. Strategies focusing specifically on lower SE groups require careful evaluation of the extra costs and benefits that they produce. The benefits of increasing screening uptake may be greater among low SE groups, but the costs may also be higher.

Composite, area-based measures such as the Index of Multiple Deprivation (IMD) 2007 have been widely used as proxy indicators of individuals’ SE circumstances (20). However not all residents conform to the area’s socioeconomic profile. We cannot therefore assume that all individuals defined by the IMD as the most socially disadvantaged groups have low FOBT uptake. Through our research in Workstreams 1 and 2 of the ASCEND programme we have identified strategies that can have progressively greater impact on FOBT uptake in individuals most likely not to take up an offer of screening. They include individuals with low literacy, poor self-capability, minority ethnic groups and men. We have developed an in depth understanding of the psycho-social and cultural determinants of poor response to the BCSP. We are now ready to proceed to the next stage of the study and conduct a series of trials of individual interventions that will tackle these barriers to non-response in lower SE groups. This phase will ultimately lead to a major trial of a combined complex intervention that will reduce the SE gradient in screening uptake.
Aims and Objectives
The aim of this study is to reduce SE inequalities in bowel cancer screening uptake but not compromise uptake in any of the SE groups.

Our principal objective is to examine the effectiveness, cost and cost effectiveness of individual interventions that can reduce the SE gradient in uptake and can be easily built into current BCSP delivery system.

If we achieve an increase in average uptake rate of 3% this would lead to 35,000 more people being screened every year and result in improvements in survival and reduced inequalities.

ASCEND is a programme of 4 independent randomised controlled trials (RCTs):
- Intervention 1 (using a summary leaflet in simple language)
- Intervention 2 (using a narrative leaflet containing quotes from people who have been screened)
- Interventions 3 (using GP endorsement on invitation letters)
- Intervention 4 (using enhancement of the reminder letters)

The control (comparison) group for Interventions 1 - 4 for all 4 RCTs is usual practice (invitation from the screening programme with a standard reminder letter for those not responding to the initial invitation).

Study Design
In the last year (in Workstreams 1 and 2) we have developed four different strategies (Interventions) which now need to be tested in randomised controlled trials (Workstream 3). Two of these strategies involve addition of information leaflets to the screening invitations. The other two strategies involve modifications to current letters produced by the Bowel Cancer Screening System: the invitation for screening (or the S1 letter) and the reminder letter (S10) as shown in Figure 1 below.

Figure 1:
Planned Interventions

Intervention 1: ‘Gist’ Information Leaflet
There is evidence that some text in the current BCSP information sheet is misunderstood because of complex sentence structure (21). It is known that health literacy is closely linked with SE group and that lower HL is associated with poorer understanding of written health-related information and lower interest in reading it (22). Lower health literacy is associated with slower reading and poorer retention of the content of the FOBt leaflet (21). Individuals in lower SE groups are less able to identify the ‘gist’ (i.e. the overall, non-literal meaning) of written information which is most likely to encourage people to respond positively to the offer of screening (23). During Workstreams 1 and 2 we developed a novel information leaflet which offers two different layers of information about the screening programme beginning with four brief statements encapsulating the main aims of bowel cancer screening programme, followed by two pages offering additional details in simple language. This leaflet contains clear signposting to allow respondents to select the information style that suits them, including a reference to the “Facts” booklet which contains more detailed information.

The rationale, development and user-testing processes for this leaflet were considered and ethically approved by the UCL Research Ethics Committee (ref: 2247/002) and the Proportionate Review Subcommittee of the NRES Committee Yorkshire & The Humber - Leeds West, on 7 February 2012. REC reference: 12/YH/0106, Protocol number: 12/0012.

The final version of the Gist information leaflet to be used in the trial in Workstream 3 is shown in Appendix 1.

This leaflet will be pre-printed and included with all the S1 letters on predetermined randomisation dates. We plan to run this trial in all 5 hubs in the period between 5th and 16th November 2012. The trial will take place on 10 working days in that period with an assumption that all the hubs will be sending S1 letter to their population every day of that period. At the end of the trial we should have 50 day/hub clusters across England. Cluster size and the overall sample size calculations are described in detail on page 14.

Intervention 2: ‘Narrative’ Information Leaflet
Cancer prevention information is usually presented didactically in the form of ‘health information’ (24). The drawback of this approach is that it is more compelling and persuasive to those with higher levels of education and can therefore increase inequalities. One alternative is to use narrative forms of communication, which have been shown to promote attention and active information-processing, particularly among individuals with lower levels of education or those who use ‘emotional’ rather than ‘rational’ information processing. These approaches have the potential to reduce inequalities in response to health information. Perceived similarity with the ‘messenger’ in the narrative can increase the credibility and perceived value of the message when prior knowledge is low (25), and identification with the messenger can result in acknowledgement of susceptibility to cancer and higher perceived social norms for the recommended cancer-related behaviours (25, 26). Messengers are also credible insofar as they appear to be trustworthy or to have expertise in the area, which can be established by a messenger’s lived experience and not just their professional credentials. We recently demonstrated that women with more ‘emotional’ processing styles (which was associated with lower SE group) reported being more influenced in their cervical screening intentions by the publicity surrounding Jade Goody’s illness than those with more ‘rational’ processing styles (27).
have therefore developed narratives involving messengers with whom lower SE individuals are more likely to identify.

The rationale and development processes for this leaflet was considered and ethically approved by the Proportionate Review Sub-Committee of the NRES Committee North East - Northern and Yorkshire on February 10\textsuperscript{th} 2012. The REC reference number is: 12/NE/0058, and the Protocol Number is 12/0010.

The final version of this information leaflet is shown in Appendix 2.

This leaflet will be pre-printed and included with all the S1 letters on predetermined randomisation dates. We plan to run this trial in all 5 hubs in the period between 4\textsuperscript{th} and 15\textsuperscript{th} March 2013. At the end of the trial we should have 25 clusters of people who received this intervention and 25 clusters who received the usual invites across England. Cluster size and the overall sample size calculations are described in detail on page 14.

**Intervention 3: GP Endorsement of Invitation (S1) Letter**

A screening invitation from a credible and trusted source such as a GP is more likely to be taken up (28, 29), and may have a specific role in addressing low-uptake issues in disadvantaged populations (30). Active participation by GPs is costly and time-consuming, but more limited forms of endorsement, such as a statement in the invitation to the effect that the named practice supports the offer, has been shown to increase FOBt uptake (31). Australian research has shown that naming the practice is almost as good as having the letter signed by the GP (32). Reports from the bowel cancer screening pilots indicate that the anonymity of the current invitation and the lack of involvement of the GP are significant issues (33). Adding the practice name to the invitation letters is likely to have minimal cost once the GPs have agreed, and could significantly reduce the SE gradient in uptake. Some PCTs (Primary Care Trusts) are introducing unevaluated GP interventions as part of their strategy to achieve the DH (Department of Health) target for cancer mortality and demonstrating the effect of simple practice endorsement is likely to be welcomed by users and commissioners.

In order to evaluate this strategy we will first contact all the GP practices in England associated with Bowel Cancer Screening Programme. They will be asked to agree that their practice name is used in a statement of support of the screening programme on the BCSP invitation letter sent to eligible people registered with the practice. See Appendix 3 for an example of a GP endorsed invitation letter.

The recruitment of GP practices will last 12 weeks and will be run from Imperial College London. It is expected to be complete at least a month before Intervention 3 is scheduled to take place. It is likely that only a subset of GP practices (about 30%) across all IMD quintiles will give us permission to use their names in screening invitations. Therefore, screening eligible individuals registered with practices that do not respond to our request and with those that actively express their disapproval will not be randomised to receive this intervention as shown in Figure 2 below.
We have worked extensively with Connecting for Health (CfH), the organisation responsible for the design and maintenance of the Bowel Cancer Screening System (BCSS). The system is responsible for identifying the population eligible for screening in each of the five hubs and creating all the letters that are sent to the screening participants and their GPs. For the purpose of our study CfH modified the BCSS to enable selection of invitees belonging to GP practices that endorse the BCSP prior to creation of each invitation letter (S1). In addition, the BCSS will be enabled to take into account the dates when GP endorsed invitations need to be produced in any of the five hubs. The schema of processes involved within the BCSS and the hubs are shown below in Figure 3.

The length of this trial is 20 working days in each hub which will result in 10 clusters of invitees receiving an endorsed invitation letter and 10 control clusters in each hub. We plan that this intervention will take place in all hubs between 3rd and 28th June 2013 and will be combined with Intervention 4.

**Intervention 4: Enhanced Reminder Letter**

Each hub routinely sends reminder letters if a kit has not been returned after 4 weeks. Reminders are known to increase uptake among non-responders (34). Interview data from the FS Screening Trial found that practical reasons for non-response include being pre-occupied or away from home when the original invitation was sent. Other barriers may include the need for further practical guidance on completing the test or information on how to contact the local hub for a replacement kit, translated versions of the instruction materials, etc. During Workstreams 1 and 2 we have developed an enhanced reminder that briefly addresses specific concerns that inhibit test completion and could influence the SE gradient.

The enhanced reminder letter is shown in Appendix 4. It includes a reminder banner and three lines of text written to address pertinent issues based on possible reasons for non-response. The text was developed based on feedback from focus group and interview data collected during Workstreams 1 and 2, transcribed and analysed to identify themes from a ‘realist’ perspective.

Connecting for Health worked with us in order to enable BCSS to print additional text on reminder letters when required. The processes within the BCSS and the hubs to enable this intervention are shown in Figure 4.
The length of this trial is 20 working days in each hub, resulting in 10 clusters of invitees receiving the enhanced reminder on random days within the trial period. However, since this intervention takes place about five weeks after Intervention 3 in all the hubs we should achieve factorial design as shown in Figure 5.

Figure 3:
The effect of the two trials being tested in succession is that one quarter of invitees who are patients of GP practices that endorse the BCSP will receive two interventions if they do not return their kits within the four weeks’ time window. Intervention 4 is a planned intervention to take place in all hubs between 8th July and 2nd August 2013.

Comparators
Intervention 1 and 2 will compare the effectiveness of an additional leaflet added to the S1 letter (gist or narrative) against usual practice in the BCSP.

Intervention 3 and 4 will compare the effectiveness of a GP practice endorsement banner on the S1 letter and the enhanced text on the S10 letter against usual practice, both in combination and individually (as illustrated in Figure 5).

Randomisation
Cluster randomisation will be used in all four trials. Individuals who are routinely invited for screening in the NHS BCSP in England will be allocated to receive an intervention on randomly selected days within a pre-specified time-period. In consultation with all BCSP hubs we have identified several periods in the calendar which will enable us to run our trials outside major public holidays and also to allow temporal separation of the interventions, where necessary. Prior to the start of the trials each of the BCSP hubs will receive a table with dates on which their population is due to receive additional leaflets or modified letters (Interventions). These tables with randomisation dates will also be given to Connecting for Health (CfH), the organisation responsible for the Bowel Cancer Screening System (BCSS) and to Real Digital International (RDI), the company that distributes four of the high volume letters from the programme for three of the BCSP hubs. The other two hubs are set up to do their own in-house printing of all the correspondence within their population.
**Eligible population**

Men and women aged between 60-74 years who have a registered GP are eligible to be screened for bowel cancer in England and are therefore eligible to be included in our trials. Invited subjects may contact their BCSP hub and opt-out of the current screening episode and others for reasons of informed choice or poor health can choose to be ceased from the screening programme. ‘Ceased’ subjects, if ceased prior to their screening due date will not be invited to be screened.

Because the screening programme started in 2006 many members of the eligible population will have been invited and/or participated in previous rounds of screening.

**Consent**

Consent forms are not applicable in this study as the interventions are taking place as part of the participant’s usual involvement with the NHS Bowel Cancer Screening Programme. The activities of NHS Bowel Cancer Screening Programme are covered by National Information Governance Board (NIGB) approval with regard to the handling of patient-identifiable data (Ref: PIAG 1-08(a)/2003).

**Exclusion criteria**

In Intervention 3 (GP endorsed invitation letters) we will only be able to randomise eligible people to receive this intervention if they are registered with practices that have agreed to endorse the BCSP (as shown in Figure 2 on page 12). We estimate that only about 30% of all GP practices in England will consent to their name being used on BCSP invitation letters so the majority of eligible people will not be entered into the randomisation and will receive the usual invitation letters.

**Outcomes**

**Primary Outcome**

The primary outcome of this study is the proportion of people in each Index of Multiple Deprivation (IMD) quintile returning an adequate faecal occult blood test (FOBt) within 18 weeks of being sent an invitation. An adequate FOBt in this study is defined as reaching a definitive FOBt outcome of either a ‘Normal’ (not further clinical investigation required) or ‘Abnormal’ (referral for prospective colonoscopy).

We will use IMD quintile here because of its demonstrated ability to explain area-level variation in bowel cancer screening uptake (10). IMD is freely available and widely accepted and used, enabling direct comparison of our results with other studies. IMD will be applied using the geographic unit of Lower Super Output Area (LSOA) level.

We have chosen to assess the proportion of FOB tests returned at 18 weeks of invitation to coincide with when the Bowel Cancer Screening System (BCSS) closes an episode to a non-responder.
Secondary outcomes

i) Time taken to return FOBt by IMD quintile

ii) Proportion of spoilt kits and their relationship to IMD quintile

iii) Proportion of non-delivered kits by IMD quintile

iv) Incremental cost per screening invitation

v) Incremental cost per screening invitation, both by IMD quintile and overall

vi) All of the above outcomes analysed using other socioeconomic (SE) variables

Statistics

Sample Size Calculations

The sample size calculations are based on achieving a reduction in the socioeconomic (SE) gradient measured as an increasingly larger percentage increase in uptake in increasingly more deprived quintiles. We anticipate that this will be accompanied by an improvement in mean overall uptake of screening, although this is not necessary to the sample size calculation.

Randomised controlled trials (RCTs) of each intervention are powered assuming there is a similar proportional effect in each BCSP hub. Instead of positing an absolute effect (which may differ across hubs, given their different demographic characteristics), we will assume a fixed proportional effect. Because different hubs have different underlying uptake rates, we do not assume generalisability of absolute uptake rates or of absolute effects of the intervention on uptake rates as is common in clinical trial interpretation. Instead, we make the less sweeping assumption that proportional effects of interventions on uptake rates within specific Index of Multiple Deprivation (IMD) quintiles will be comparable across hubs.

For Interventions 1 and 2

We estimate an average increase of 3 percentage points, based on increasing uptake by 5 percentage points in the lowest IMD quintile (most socially disadvantaged group) and 1 percentage point in the highest. This estimate is drawn from the outcomes that are considered feasible in research aiming to increase screening uptake (35). It would result in 35,175 more people being screened per year (11,366 in the lowest IMD quintile and 1,932 in the highest). These numbers would be expected to increase as the upper age limit of screening is extended to 74 years.

We base our sample size calculations on the ability to detect a difference in the parameter b, where the logit of the overall participation rate = a+bx (participation in each IMD quintile). This can be re-expressed as a comparison of two proportions where each proportion is a weighted average of the within-quintile uptake rates (36). The analytic results of the sample size calculations have been confirmed by computer simulations.

Because the BCSP hubs vary in the size of the population they serve, baseline uptake rates, and socioeconomic (SE) profile, we calculate the required sample size for each hub separately. Thus for 90% power to detect as significant a change in the gradient conferring a 5 percentage point increase
in lowest quintile uptake versus a 1 percentage point increase in the highest quintile, the estimated
numbers required per group (intervention and control) overall in all hubs combined are 13500,
12200, 11700, 5400 and 4500 if we assumed that all participants had the composition of North West 
& Midlands, London, North East, Eastern and Southern hubs respectively. We will use the maximum
of the calculated sample sizes as a failsafe option. This means that whatever the SE composition and
underlying uptake rate of the hub or combination of hubs in any given RCT, the study size will be
adequate. Thus each RCT would need a total of 13,500 participants per arm across all hubs.
However, since we are randomising by day, with an average of roughly 3000 per hub per day, we
need to increase this by the variance inflation factor

\[ ViF = 1 + (3000(1 + c^2) - 1)r \]

Where c is the coefficient of variation between days with respect to number of invitations and r is
the intra-class correlation coefficient of uptake levels by day. From data kindly supplied by the hubs
c was estimated as 0.42 and r as 0.0002 provided the duration is of the order of a month, so that
there is no serious seasonal variation. Thus we need to multiply the study sizes by 1.7. We therefore
propose 23,000 per arm or 46,000 in total for each RCT.

Bearing in mind that a total of 60-70,000 invitations are sent out nationally in a typical working
week, this would mean that the required sample size could be obtained within a working week (five
days). However, the number of clusters would be small. We therefore propose to use two weeks (10
days) invitations for each of the narrative and gist interventions. This will be overpowered, but will
give 40-50 day/hub clusters, which confers confidence of avoiding inadvertent bias, for example, due
to one large but aberrant day/hub cluster.

For Interventions 3 and 4

The same fundamental assumptions are made as above. In addition:

For the GP endorsement, with all the hubs participating and all GP’s participating, we would require
the same period and study size as for the narrative and the gist interventions. However, assuming
30% GP participation, in order to recruit 46,000, we should need close to three weeks (15 days). We
therefore propose to allow four full working weeks (20 days), to achieve approximately 40,000
subjects per arm and a total of 100 day/hub clusters.

For the enhanced reminder, to be conservative, we will double the time required, assuming around
50% need reminders and that the enhanced reminder has only the same effect on those receiving it
as any other intervention applied to the entire invited population. This could theoretically be
achieved in two weeks, but as a failsafe, we propose four weeks, which will give approximately
60,000 reminders and a total of 50 day/hub clusters per arm.

If the enhanced reminder study begins exactly five weeks after the GP endorsement study, we would
expect approximately 20,000 subjects in the intervention arm of both studies. With 50% requiring a
reminder, this would give 10,000 subjects receiving both the GP endorsement and the enhanced
reminder. These figures will give a very precise estimate of the response rate to the combination of
the two interventions. If it is substantially higher than would be expected from the effect of each in
isolation, it will be formally assessed for significance as a specific trial arm in Workstream 4.
Below is a summary of how each RCT will therefore run:

<table>
<thead>
<tr>
<th>Clustering and Randomisation</th>
<th>Total approx. number randomised nationally (intervention + control)</th>
<th>Proposed Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster randomisation nationally by hub and day: Eastern, London, North East, North West &amp; Midlands and Southern</td>
<td>120,000-140,000 (50 clusters)</td>
<td><strong>5th-16th November 2012</strong></td>
</tr>
<tr>
<td>Intervention 1. Gist Leaflet</td>
<td>120,000-140,000 (50 clusters)</td>
<td><strong>4th-15th March 2013</strong></td>
</tr>
<tr>
<td>Intervention 2. Narrative Leaflet</td>
<td>72,000-84,000 (100 clusters)</td>
<td><strong>3rd June 28th June 2013</strong></td>
</tr>
<tr>
<td>Intervention 3. GP Endorsed Invitation Letter</td>
<td>120,000-140,000 (100 clusters)</td>
<td><strong>8th July - 2nd August 2013</strong></td>
</tr>
</tbody>
</table>

### Data Analyses

We will undertake a descriptive analysis of socio-demographic characteristics in the two arms across each intervention and analyse uptake differences by logistic regression (LR). Although randomisation should ensure comparability, the analysis will be performed with and without adjustment for age, sex, screening round and hub (37). The question of whether the intervention has a greater impact on uptake in the lower SE groups will be assessed by a test of interaction between trial arm and IMD quintile in the LR analysis. We will also use hierarchical LR to account for heterogeneities (i.e. due to varying policies and procedures in PCTs). We will adjust for incident (2nd) round versus prevalent (1st) round status and check for heterogeneity of effects between incident and prevalent screens. The use of the maximum sample size from the calculation above will also enable subgroup analyses by sex, age, hub and incident versus prevalent screening round.

A secondary analysis of time taken to return the FOBt by IMD quintile will be examined using the log rank method (38). When comparing the intervention against usual practice, we will in the first instance compare all interventions to all controls on an intention-to-treat basis.

Finally, we will also examine effectiveness in terms of the SE variables identified in Workstream 1.

### Local and Concurrent Initiatives

Promoting FOBt uptake has been part of the strategy to achieve the Department of Health’s (DH) target for cancer mortality reduction in some Primary Care Trusts (PCTs). Interventions vary across PCTs/Clinical Commissioning Groups (CCGs) and include local research programmes and initiatives, awareness-raising campaigns, and additional mailings about the BCSP.

We will carry out a survey to identify national and local initiatives aiming to increase uptake of FOBt screening during the period leading up to, and during our trials. These interventions may increase uptake rates in specific regions and affect the analyses of the results of the trials; however we would not expect concurrent initiatives to act as confounders of the interventions because it is unlikely that concurrent interventions would also occur on alternate days. We will therefore aim to contact and re-contact all the individuals/groups below on a three/six-monthly basis during the time period September 2012 – September 2013, and collate all research activities and health promotion activities.
initiatives into a database. This information will be made available to the wider research team, who will be alerted three/six-monthly when the database is updated.

We will contact TJ Day (NHS Bowel Cancer Screening Programmes) to obtain details of all research approved by the NHS Bowel Cancer Screening Programme Research Committee in England and all BCSP Hub Directors/Managers and QARC Directors, who will provide us with details of any other initiatives taking place in their regions.

In addition we will identify and contact Cancer Target Leads (usually in health promotion/public health) in CCGs to ensure that we do not miss activities that BCSP Hubs may not be aware of. We also plan to contact Quality Assurance Reference Centres (QARCs), Primary Care Research Networks (PCRN), our charity partner Beating Bowel Cancer, colleagues in other Research Institutions and Universities, and the National Awareness and Early Diagnosis Initiatives (NAEDIs). Due to restructuring in PCTs, these contacts may need to be revised regularly. We will aim to approach this information seeking exercise from as many angles as possible in order to ensure we have a clear view of all concurrent initiatives that are taking place.

Finally, we will aim to collate information on national advertising campaigns/poster campaigns, and other public awareness initiatives and promotion activities (such as “bowel in town”), National Bowel Cancer Awareness Month, etc.

In collaboration with the Primary Care Advisory Group established in Workstream 2, we will design a brief telephone survey of the nature, scope and timing of initiatives planned or implemented concurrently with our trials to be carried out with BSCP Hubs, and Cancer Target Leads. This will clarify area specific ‘usual practice’ during the life of the project.

**Measuring costs**

The incremental cost per screening invitation of each intervention will be compared with usual practice. A lifetime time horizon will be used. The cost components included will be the costs of each intervention, screening costs, and costs of diagnosing and managing bowel cancer. These costs will be calculated from the perspective of the NHS and personal social services. Our cost analysis will use a similar approach and similar sources of data as previous studies (39). The costs calculated will be considered along with the ‘Primary Outcome’ described above in a cost consequences analysis framework to identify which interventions should be combined in the complex intervention (Workstream 4). We do not propose to undertake full economic evaluations in Workstream 3 (i.e. incremental cost per quality-adjusted life year (QALY) gained), because the role of the economic analysis in Workstream3 is only to aid ranking of interventions to determine which should be combined in the complex intervention. In addition, we would not want to exclude interventions with a high incremental cost per QALY gained (e.g. > £30,000) at this stage because when combined in the complex intervention they might be more cost-effective.

**Data Management**

A Data Analyst at Southern Hub working on behalf of all BCSP hubs will design and pilot the data extraction algorithms. The raw data will be extracted by Connecting for Health (CFH) from BCSS and given to the Data Analyst at Southern Hub to clean and pseudo-anonymise. The postcode variable will be replaced with Index of Multiple Deprivation (IMD) score.
The Southern Hub has specified the data to be extracted by CfH on behalf of the ASCEND research team. Data will be extracted by using direct SQL queries on the Bowel Cancer Screening System and with the possible additional use of OBIEE bespoke reports. Patient identifiable information currently specified includes practice, postcode and date of birth. During project scoping CfH will give consideration to the feasibility of anonymising these fields within CfH prior to supply to Southern hub.

Data transfer between CfH and the Southern Hub will be via encrypted network connection (NHS.NET) and/or NHS Secure File Transfer (SFT).

The raw data will be loaded into an encrypted Oracle database at the Southern Hub and algorithms written to process and anonymise the data into the format required by the ASCEND academic statisticians. Any permutations of geo-demographic variables that could lead to potentially identifiable patient information will be subject to further levels of anonymisation.

Although anonymised, data transfer between Southern Hub and the ASCEND research team will use password protected files and SFTP. The ASCEND research team will undertake to keep the data secure, and not to attempt to reverse engineer, link the data to other datasets or use the data for any purpose other than the ASCEND project. The project will adhere to the NHS Cancer Screening Programmes Confidentiality and Disclosure Policy.

The data will be extracted three times from the BCSS 18 weeks following the last intervention date for each of the interventions in March, July and November 2013.

The BCSS variables that will be extracted are listed in Appendix 5 and 6.

**Quality Control and Quality Assurance**

**Process Evaluation**

Prior to the start of any of the interventions the trial managers will visit all BCSP Hubs and conduct semi-structured interviews with hub directors and managers. The principle objective of these interviews is to identify organisational and resource related barriers to successful roll out of each intervention. There may be changes in administrative procedures, facilities and staff training and additional expertise that need to be put in place to ensure successful implementation of all the trials.

Particular note will be taken of any adverse effects (e.g. excessive extra workload) which could make future implementation of any of the interventions unfeasible. With increase in FOBt uptake we expect an increase in the workload in the hubs but also in associated screening centres. In addition, GPs may experience an increase in their workload following Intervention 3.

It is expected that screening centres and GPs will communicate their experience to the Helpline so we plan to record those inquiries and comments but in consultation with all the hubs we will explore additional opportunities to obtain a measure of the impact of our interventions on all the organisations involved with bowel cancer screening.
Evaluation of Intervention Fidelity

Interventions 1 and 2

These two interventions require inclusion of an additional information leaflet with each S1 invitation letter on pre-specified random dates. Randomisation tables will be provided to each hub and also to Real Digital International (RDI), the company that prints and distributes four of the bulk BCSP letters for the Eastern, Southern and London Hubs.

In order to ensure fidelity of the interventions the trials managers will set up and pilot quality check methods at each Hub to check whether the appropriate materials have been sent to eligible people on particular days.

Furthermore, in agreement with all the hubs we will have a standard operating procedure (SOP) in place prior to the start of the first trial.

Interventions 3 and 4

These two interventions require insertion of the name of the person’s GP practice into the S1 letter or additional text into the S10 letter. This can only be achieved by implementing changes on the BCSS. We conducted extensive consultations with CfH whose programmers will apply the necessary changes to the BCSS to ensure that GP endorsed letters and enhanced reminders can be generated on pre-specified random dates. Changes to the BCSS include addition of a variable that will indicate whether a person received an intervention or whether he/she was a part of the control cluster.

The Trial office will provide CfH with details of all the GP practices that agreed to endorse the BCSP and randomisation dates for each hub.

The process diagrams for the GP endorsement and enhanced reminder letters are detailed in Figures 2 and 5 (page 11 and 14).

A standard operating procedure (SOP) will be written for each hub to follow and will be monitored closely by the Trial Manager during the intervention periods.

Monitoring and Auditing

An Independent Data Monitoring & Ethics Committee (IDMEC) has been established to monitor the progress of the trial. Data will be supplied to the Chair and meetings will occur at least once a year after trial recruitment starts.

An Advisory Group has also been established and includes all ASCEND co-Applicants and a number of External Experts. The Advisory Group will meet formally every 12 months and give expert input on an individual basis as required.

The Chief Investigator will be responsible for the day to day monitoring and management of the study. The UCLH/UCL/Royal Free Joint Research Office, on behalf of UCL as Sponsor, will monitor and conduct random audits on a selection of studies in its clinical research portfolio. Monitoring and
auditing will be conducted in accordance with the Department of Health Research Governance Framework for Health & Social Care (April, 2005), and in accordance with the Sponsor’s monitoring and audit policies and procedures.

**Ethics**

**Ethical Approval**

Ethical Approval will be obtained from the UK National Research Ethics Service, London – Harrow Ethics Committee, Reference number 12/LO/1396 prior to commencement of this study. Local Ethics Committee approval is not required as this a national trial incorporated within the NHS Bowel Cancer Screening Programme (BCSP).

**Risks for Trial Participants**

Risks to the participants associated with this study are not any higher than the risks associated with participation in the BCSP. The ASCEND project has been developed during Workstreams 1 and 2 by patient representatives and charities providing advice on the design and approach taken by the study and the development of interventions, who have found no cause for concern.

**Clinical Trial Documentation**

In accordance with UCL Records Management Policy, the University College London Joint Research Office and the EU Good Clinical Practice Directive 2005/28/EC all primary research data will be retained for a minimum period of 20 years following completion of the study.

**Publication Policy**

All publications and presentations relating to the study will be discussed and authorised by the Chief Co-investigators. Project Co-investigators will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal’s policy. Authorship of parallel studies which are not initiated by the Chief Co-investigators will be according to the individuals involved in the project but must acknowledge the contribution of the project investigators and collaborating institutions: NHS Bowel Cancer Screening Programme, University College London, Imperial College London and Queen Mary University of London.
References

Appendices

Appendix 1: Gist Leaflet

NHS Bowel Cancer Screening Programme: The Essentials

- Bowel cancer is the third most common cancer
- The FOB test spots hidden signs of bowel cancer early
- Doing the FOB test every 2 years lowers the risk of dying from bowel cancer
- Men and women aged 60-74 are sent the FOB test to do at home

Would you like to know more? See inside for details

How does the FOB test work?

- The FOB (Faecal Occult Blood) test checks for tiny amounts of blood in stools (poo) that cannot be seen by the eye
- Blood in stools can be a sign of bowel cancer
- An FOB test kit is sent to your home
- The FOB test is easy to do
- You do the FOB test at home by putting small amounts of stool onto a test kit
- You send the test kit back to the laboratory in a special freepost envelope

How accurate is the FOB test?

- A small number of people (2 out of 100) get an abnormal result
- If you get an abnormal result, you will get an appointment to talk about further testing
- For most people, the follow-up test will show there is no bowel cancer
- If bowel cancer is found, it is likely to be at an early stage where treatment is more successful

What happens after you've done the FOB test?

- You get your FOB result through the post within 2 weeks
- Most people (98 out of 100) get a normal result
- If you have a normal result you will be sent another FOB test every 2 years up to age 74

Where can I get more information?

For more information see the enclosed leaflet:

‘Bowel Cancer Screening: The Facts’
Appendix 2: Narrative Leaflet

Screening stories

Judith's story

When the home-based test kit arrived Judith just put it to one side because she thought it was going to be too much work. However, when she did get around to doing it, she realized how quick and easy it was. Like most people, Judith got a "normal" result which she found to be very reassuring. For Judith, doing the test kit made her feel more in control of her health.

Chandula's story

Chandula did the test kit soon after it arrived through his letterbox. The results were "abnormal" so he went to have a follow-up investigation at the bowel cancer screening centre. A few small growths were found in his bowel and removed for further tests. Much to his relief, they were found to be clear of cancer. Remedying these growths was still very important because they could have turned into cancer over time. He now tells his friends that doing the test kit is simple and nothing to worry about.

The screening programme aims to find bowel cancer early

"It is just like having breast screening because it can pick up whatever is wrong before it develops into something bigger. If the doctors find something early it can be dealt with, and if they don't find anything then you're happy." (Haycroft)

Most people (98 out of 100) will get a "normal" result from the test kit

"When I got my reply to say everything was clear I was delighted. It was such a relief." (Cynthia)

A small number of people (2 out of 100) get an 'abnormal' result and are offered a follow-up investigation

"I went and spoke to a very nice lady who explained that even though people get a call back they don't often get a cancer result. I felt a lot calmer after the appointment. I had the follow-up investigation the following Monday. They found two growths, which were removed. The results were fine and everything was ok." (Monica)

Bowel cancer often has no early warning signs

"I was very lucky to have had the cancer picked up through screening. I had no symptoms at all and I would not have known anything was wrong. By the time I had got any symptoms, it would probably have been a lot more serious." (Maureen)

Bowel cancer often found through the screening programme is likely to be at an early stage and can be successfully treated

"The decision I made to complete the test kit was probably the best decision I have ever made in my life. Had I not taken that course of action, there is no doubt in my mind I would not be alive today." (Harold)

Bowel Cancer Screening
People's Stories

This leaflet tells you about other people's experiences of the English NHS Bowel Cancer Screening Programme

Developed by University College London, 2012
25 December 2005

Mrs Anne B Example-Subject
Hembury House
Cheriton
Shobrooke
Credton
Devon
YY1 5TT

Q5 278/7/26

Dear Mrs Anne Belinda Example-Subject

Cancer Screening Programmes

25 December 2005

Mrs Anne B Example-Subject
Hembury House
Cheriton
Shobrooke
Credton
Devon
YY1 5TT

Q5 278/7/26

Dear Mrs Anne Belinda Example-Subject

Your GP practice, Timbuktu General Practice, supports the Bowel Cancer Screening Programme

This is an invitation to take part in the NHS Bowel Cancer Screening Programme. The programme aims to detect bowel cancer early, when successful treatment and cure is more likely. Screening is offered every two years to people aged 60-69 who are registered with a GP in England. We are starting to extend the screening age range, so if you are aged 70-74, you are being invited as part of this process.

You will be sent a test kit with full instructions in about two weeks. The kit is simple to use in the privacy of your own home. If you want to be screened, wait until the kit arrives, follow the instructions, and return the kit in the Freepost envelope provided. You will get your results by letter within 2 weeks.

We do not have your medical history, and screening is not appropriate for everyone. If you have already been referred to hospital for bowel investigations by your GP, or if you have had previous bowel surgery, then screening may not be appropriate for you. Please call us for advice. If you don’t wish to be screened, then please call and let us know. The Freephone number for all calls is at the top of this letter (calls are free from UK landlines).

If you need help from family or a carer in order to use the kit, please call us (or ask them to call us) for further important information. You can also use the Freephone number if you have any questions about taking part in the programme. Finally, please take the time to read the enclosed leaflet ‘Bowel Cancer Screening - The Facts’, which may help to answer any questions you may have.

Yours sincerely
Appendix 4: Enhanced Reminder (S10)

Cancer Screening Programmes

25 December 2005
Mrs A Example-Subject
Hub address
Hembury House
Chelton
Shobrooke
Crediton
Devon
YY1 5TT

S1/27/6/7/26
NHS No: 333 333 4444

A REMINDER TO YOU

Dear Mrs Example-Subject

You were recently sent a test kit from the NHS Bowel Cancer Screening Programme. This is a simple test you can carry out at home, which checks for signs of abnormalities (such as polyps or cancers) in the bowel. The test is designed to detect tiny traces of blood not visible to the naked eye in bowel motions.

If blood is found, then a further examination called a colonoscopy is recommended. This examination looks at the inside of the bowel. Only around 2 in every 100 people completing the home test kit are advised to have a colonoscopy.

We do not appear to have received your completed test kit. If you returned your kit more than 7 days ago but have not received a result, please call the Freephone number at the top of this letter. (If you returned your kit within the last 7 days please ignore this letter).

If you have any queries or concerns about using the kit, would like a replacement kit, or do not wish to take part in the screening programme, please contact us on the Freephone number.

If we do not hear from you within 13 weeks, you will be discharged from this screening round. You will be invited to participate in screening again in 2 years’ time, unless you have reached your 75th birthday by then. People aged 75 or over are not automatically invited for screening, but can request a test kit by calling the Freephone number above.

Doing the test kit is important because the risk of bowel cancer increases as you get older. If bowel cancer is found early, treatment is more successful. It’s never too late to do the test. Call Freephone 0800 707 60 60 if you need to speak to a helpline assistant.

Yours sincerely
Appendix 5: Specification of dataset to be extracted by CfH

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All Records for all subjects in ASCEND_SUBJECT

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Communication Data

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Returned Mail Data (1 record for each episode)

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SSP Data from OBIEE (All records where FOBT result for episode was definitive abnormal)

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Diagnostic Test Data from OBIEE (All records where FOBT result for episode was definitive abnormal)

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Appendix 6: Specification of data to be extracted by CfH and provide to the research teams for analysis

One record for each control/intervention subject episode plus one record for each previous screening episode for these subjects.

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<tr>
<td>PREVALENT_INCIDENT</td>
<td>Prevalent or Incident</td>
</tr>
<tr>
<td>EPISODE_SEQ</td>
<td>Sequence number of episode (routine and late responder for same invite date will be treated as a single episode)</td>
</tr>
<tr>
<td>S1_SENT_DATE</td>
<td>Date S1 Letter Sent (Limit to at least 3 months before date of data extraction)</td>
</tr>
<tr>
<td>S9_SENT_DATE</td>
<td>Date S9 Letter Sent</td>
</tr>
<tr>
<td>REMINDER_SENT_DATE</td>
<td>Date Reminder Letter Sent</td>
</tr>
<tr>
<td>FIRST_LOGGED_KIT_DATE</td>
<td>Date of First Logged Kit</td>
</tr>
<tr>
<td>EPISODE_SUBTYPE_CODE</td>
<td>1 = Routine, 3 = Late Responder</td>
</tr>
<tr>
<td>RESPONSE_TO_INVITATION</td>
<td>1 = returned at least one kit, 0 = no kit returned</td>
</tr>
<tr>
<td>ADEQUATELY_SCREENED</td>
<td>1 = adequately screened, 0 = not adequately screened</td>
</tr>
<tr>
<td>DEFINITIVE_ABNORMAL</td>
<td>1 = definitive abnormal, 0 = definitive normal, null = no result</td>
</tr>
<tr>
<td>SPOILT_KIT_COUNT</td>
<td>Count of spoilt kits in episode</td>
</tr>
<tr>
<td>RETURNED_MAIL_COUNT</td>
<td>Returned Mail Count</td>
</tr>
<tr>
<td>ATTENDANCE_AT_SSP</td>
<td>1 = attended, 0 = not attended, null = n/a</td>
</tr>
<tr>
<td>ATTENDANCE_AT_COLONOSCOPY</td>
<td>1 = attended, 0 = not attended, null = n/a</td>
</tr>
<tr>
<td>ATTENDANCE_AT_OTHER_TEST</td>
<td>1 = attended, 0 = not attended, null = n/a</td>
</tr>
<tr>
<td>DIAGNOSTIC_OUTCOME</td>
<td>[null]'No Result'</td>
</tr>
</tbody>
</table>