ASCEND2

PROTOCOL

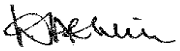
General practice endorsement in the Bowel Cancer Screening Programme: the ASCEND2 project

Version 1.0, 11/11/2015

MAIN SPONSOR: Imperial College London

FUNDER: *Cancer Research UK*

Protocol authorised by:

Name & Role	Date	Signature
Prof Wendy Atkin, Chief Investigator	**11/11/15**	

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General Information

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Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the ICL Sponsor Representative:

Mr Gary Roper, Head of Regulatory Compliance, Joint Research Office, Faculty of Medicine, Imperial College London.

Funder

Cancer Research UK – Population Research Committee Programme Award

List of Abbreviations

BCSP – Bowel Cancer Screening Programme

BCSS – Bowel Cancer Screening System

CAG – Confidentiality Advisory Group

FOBt – faecal occult blood test

GP – General Practitioner

HSCIC – Health & Social Care Information Centre (formerly Connecting for Health)

IMD – Index of Multiple Deprivation

LR – Logistic Regression

LSOA – Lower Super Output Area

NHS – National Health Service

OBIEE – Oracle Business Intelligence Enterprise Edition

RCT – Randomised Controlled Trial

SE – Socio-economic

SFT – Secure File Transfer

SFTP – Secure File Transfer Protocol

SOP – Standard Operating Procedure

SQL – Structured Query Language

Background

Strategies to reduce the social gradient in uptake of bowel cancer screening: the ASCEND Study

Bowel cancer is the third most common cancer in the UK, and the second most common cause of cancer death. This significant public health burden can be diminished by screening using the guaiac faecal occult blood test (gFOBt), which randomised controlled trials (RCTs) have demonstrated can reduce bowel cancer mortality (1). The National Health Service (NHS) Bowel Cancer Screening Programme (BCSP) commenced biennial screening in 2006 and now offers gFOBt to 60-74-year-olds in England.

There is a strong socio-economic status (SES) gradient in uptake of gFOBt screening in the BCSP which will ultimately create inequalities in bowel cancer outcomes. Previous research to tackle socio-economic inequalities in uptake has focused on specific under-served groups, rather than reducing the gradient in uptake across the entire population.

The ASCEND Study was funded by an NIHR Programme Grant for Applied Research that culminated in four national, cluster-randomised trials, embedded in the English Bowel Cancer Screening Programme. The trials compared 'usual care' with usual care plus different supplementary materials designed to reduce the SES gradient through more effective communication of the screening offer. Interventions were selected on the basis of prior evidence of their efficacy to improve understanding or screening uptake among low SES groups.

Four interventions were tested: i) a supplementary 'Gist' leaflet summarising key information in simple language ii) a supplementary 'Narrative' leaflet describing people's stories , iii) General Practitioner (GP) endorsement on the invitation letter and iv) an Enhanced Reminder letter that reiterated the screening offer. The SES marker was the Index of Multiple Deprivation (IMD) score for each home address. The primary endpoint was the gradient in uptake across IMD quintiles.

The Gist and Narrative trials showed no effect on the SES gradient in uptake or overall uptake (p ≥0·1). The GP endorsement trial showed no effect on the SES gradient, but increased overall uptake (adjusted Odds Ratio (adj OR) =1·07, 95% CI 1·04-1·10, p<0·0001). The Enhanced Reminder trial showed a significantly increased uptake with decreasing SES (p=0·005), as well as higher overall uptake (adj OR=1·07, 95% CI 1·03-1·11, p=0·001). Therefore, of the plausible interventions, only the Enhanced Reminder reduced the SES gradient, but both the GP endorsement of the screening offer and the Enhanced Reminder had an effect in increasing uptake.

In the ASCEND trials, the supplementary leaflets and GP endorsement were added to the pre-screening invitation letter, designated S1 in the Bowel Cancer Screening System (BCSS), which is sent out a week before the FOBt kit. ASCEND2 has been designed as follow-on to assess the effectiveness of a GP endorsement (GPE) banner on the S9 kit invitation letter which is sent with the FOBt kit. The underlying rationale in undertaking this additional trial is that the recipient of the test may be more susceptible to a GP endorsement in the letter sent at the same time as the FOBt rather than a week earlier as in the ASCEND trial (intervention 3).

There is no current literature published on the English BCSP that makes a distinction between the role of the S1 and S9 invitation letters. Intervention 3 had to be incorporated into the S1 pre-invitation letters due to space constraints in adding additional text to the S9 kit invitation letter. The space issue has since been resolved and now there are no barriers to assessing the effect of moving the GPE banner to S9 letter. This will require a minimal amount of cost and effort to implement as the necessary changes have already been programmed into the BCSS.

We surmise that receiving an endorsement from the GP when you receive a kit is likely to be more effective than the modest increase in uptake that was seen with the Enhanced Reminder intervention. If we can achieve a 3% increase in uptake this would lead to 35,000 more people being screened every year and result in improvements in survival and reduced inequalities.

Aims and Objectives

The aim of this study is to increase uptake in the BCSP and to reduce SE inequalities in bowel cancer screening uptake but not compromise uptake in any of the SE groups.

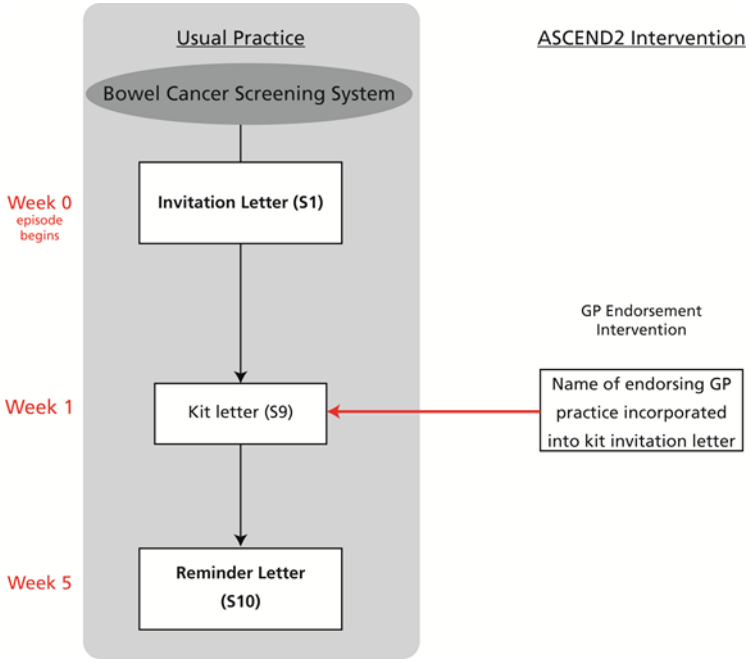
Our principal objective is therefore to: examine the effectiveness, cost and cost effectiveness of an individual intervention at the invitation stage that can reduce the SE gradient in uptake and can be easily built into the current BCSP delivery system.

The control (comparison) group for this RCT is usual practice.

Study Design

ASCEND2 is a follow-on study to the ASCEND research programme and designed as a randomised controlled trial (RCT) using a general practice endorsement (GPE) on the BCSP kit invitation letters. As part of the ASCEND programme four different strategies (interventions) were developed and then tested in independent RCTs. Interventions 3 and 4 involved modifications to current letters produced by the Bowel Cancer Screening System: the invitation for screening (the S1 letter) and the reminder letter (S10). The invitation process is described in Figure 1 below.

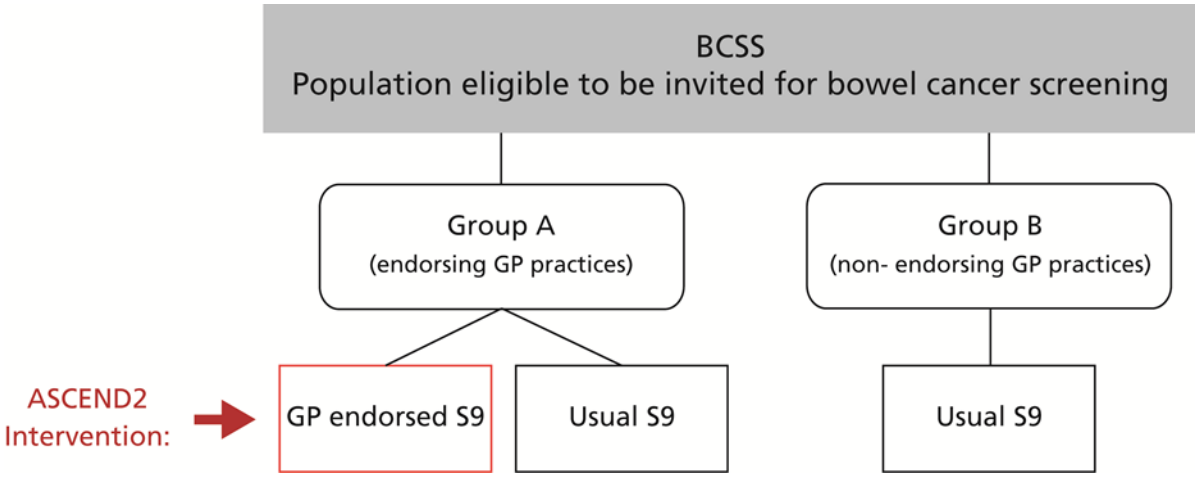
Figure 1:



The study design of ASCEND 2 (intervention 5) is identical to that of intervention 3 except that the intervention is now included at the S9 stage. The S9 kit invitation letter is sent out to screening eligible individuals one week after they have been sent their initial S1 pre-invitation letter. The kit invitation includes the FOBt kit with instructions along with a cover letter explaining what has been sent and how to return the completed kit.

General practices will have been recruited as part of the ASCEND study prior to intervention 3 and those that have consented will be included in intervention 5. Consenting practices have agreed to include their names on BCSP letters to eligible individuals for the duration of the programme and they will be informed of the plan to undertake an additional intervention via the final study results letter. Screening eligible individuals, who are registered with practices that either did not respond to our request or actively expressed their disapproval, will not be randomised to receive this intervention (see Figure 2).

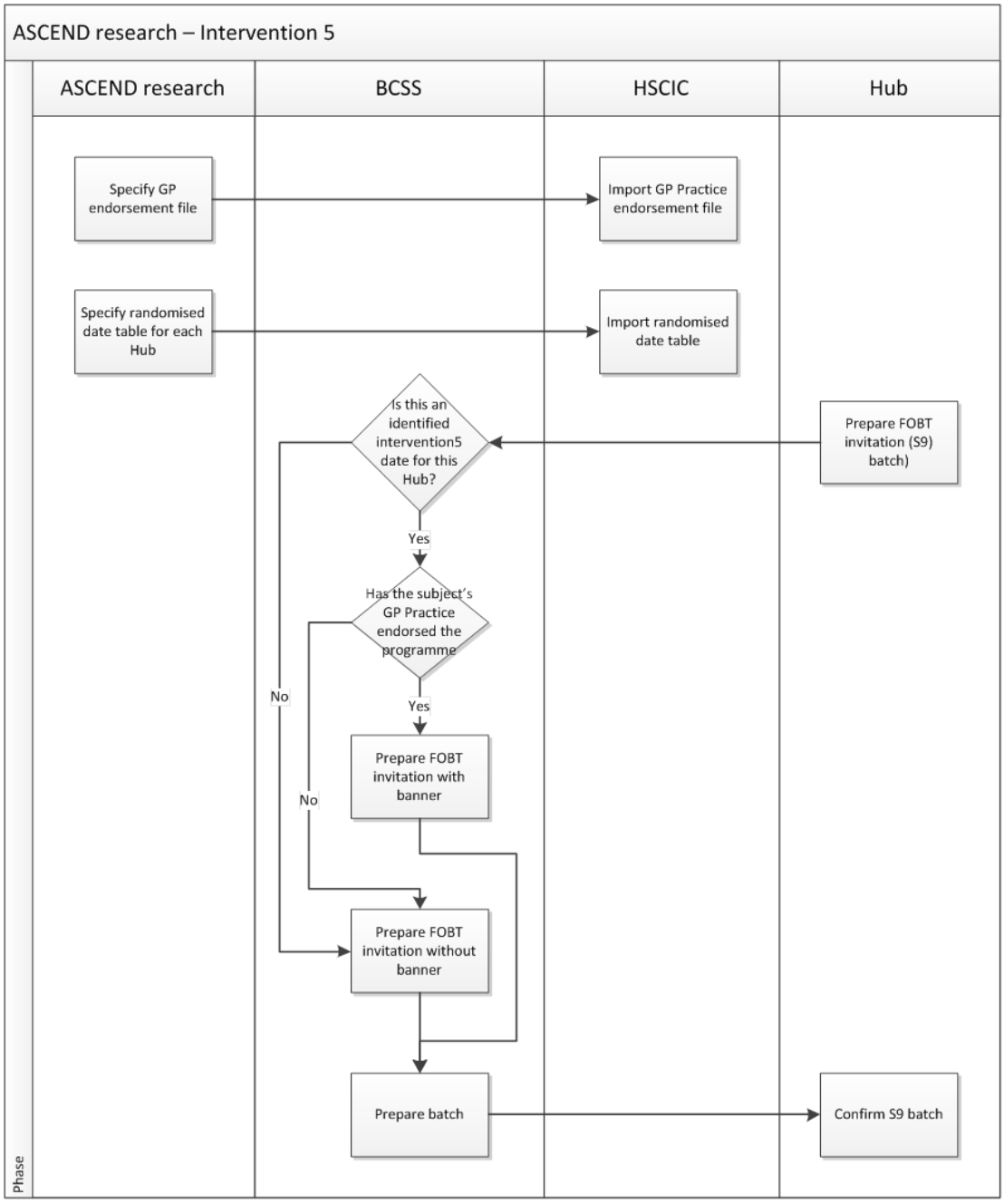
Figure 2:



We have worked extensively with the Health & Social Care Information Centre (HSCIC), 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 subjects and their GPs. For the purpose of our study the HSCIC modified the BCSS to enable selection of invitees registered with GP practices that endorse the BCSP prior to creation of each kit invitation letter (S9). 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 processes involved within the BCSS and the hubs are shown below in Figure 3.

The duration of this trial is 30 working days in each hub which will result in 15 clusters of invitees randomised to receiving an endorsed kit invitation letter and 15 control clusters in each hub. We plan that this intervention will take place in all hubs between Monday 1st Feb and Friday 11th March 2016.

Figure 3:



Comparators

Intervention 5 will provide data to compare the effectiveness of a GPE banner included on the S9 kit invitation letter against the usual S9 letter in the BCSP: it shall not involve any structural changes to the S9 letter.

Randomisation

Cluster randomisation will be used in this trial. 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 will identify trial dates which will enable us to run our intervention outside major public holidays or significant updates to the Bowel Cancer Screening System (BCSS). Prior to the start of the trial each of the BCSP hubs will receive a table with dates on which their population is due to receive GPE kit invitation letters (the intervention). These tables with randomisation dates will also be given to Health & Social (HSCIC), the organisation responsible for the BCSS.

Eligible population

Men and women aged between 60-74 years who live in England and are registered with a GP are eligible to be screened for bowel cancer in England and are therefore eligible to be included the trial. Invited subjects may contact their BCSP hub and opt-out of the current screening episode and others for reasons of choice or poor health can 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 subject's usual involvement with the NHS Bowel Cancer Screening Programme.

The intention of this trial is to amend the S9 kit invitation letter currently sent out to eligible subjects and to identify whether a GPE banner will lead to a corresponding change in uptake of screening. The design of this intervention does not represent a change to the current remit of the NHS BCSP, and as it closely supports screening activities, does not significantly deviate from the originally approved purposes. The activities of the NHS BCSP are covered under an existing Confidentiality Advisory Group (CAG) Section 251 approval with regard to the handling of patient-identifiable data (Ref: PIAG 1-08(a)/2003) All data sent from the HSCIC to the BCSP Data Analyst will be pseudo-anonymised ensuring no disclosure of identifiable information will be made to the team. Further information regarding the data management process is described on page 13.

Exclusion criteria

We will randomise eligible people to receive this intervention only if they are registered with practices that have agreed to endorse the BCSP (as shown in Figure 2). 80% of general practices consented to their name being used on BCSP invitation letters so the majority of eligible people will be included in the randomisation.

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 their initial invitation (S1). An adequate FOBt in this study is defined as reaching a definitive FOBt outcome of either a 'Normal' (no further clinical investigation required) or 'Abnormal' (referral for colonoscopy).

We will use IMD quintile here because of its demonstrated ability to explain area-level variation in bowel cancer screening uptake (2). 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 from the pre-invitation to coincide with when the Bowel Cancer Screening System (BCSS) closes an episode due to non-response.

Secondary outcomes

i) Time taken to return FOBt by IMD quintile

ii) Proportion of spoilt kits by 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

To calculate the required study size, we need to take into account:

1. The size of the effect/interaction we wish to detect.
2. The anticipated distribution of socioeconomic status and the expected participation by socioeconomic status in the control arm and by screening round.
3. The proportion of GPs agreeing to be included in the trial.
4. A variance inflation factor to account for the cluster (hub-day) randomisation.
5. The size of the effect/interaction by screening round.

In ASCEND, the combined effect of GP endorsement with introductory letter was a 3% overall increase in participation. As a failsafe, we design the trial using the more conservative 2% overall

estimate. We posit an interaction such that in the least deprived quintile, there is a 1% increase in participation with the intervention, in the second least deprived a 1.5% increase, and so on, with a 3% increase in the most deprived quintile.

The control group from the GP endorsement trial in ASCEND had the socioeconomic status distribution and completion rates by socioeconomic status shown in Table 1. Note that the percentages per quintile are not all 20% since socioeconomic status is associated with age and place of residence (in the latter case therefore being influenced by the proportions of subjects by hub). We anticipate these rates in the control group of the proposed trial and anticipate the intervention participation rates in the final column of Table 1.

We calculated the required sample size using the method of Brentnall et al (2012). To obtain 90% power to detect the interaction as significant at 5% level with 2-sided testing, in an individually randomised study, we would require 11,714 individuals in each arm. In ASCEND, 80% of the GP's approached agreed to participate in the GP endorsement trial, giving 14,643(=11,714/0.8) subjects per trial arm. Also in ASCEND, we estimated a variance inflation factor for cluster randomisation of 1.7, but results post hoc suggest that a larger inflation would be more appropriate. We therefore use an inflation factor of 2.5, giving a total study size of 36,608 per arm, a total randomised of 73,216. Assuming approximately 3,000 kits are sent per hub-day, this indicates that we should randomise 25 hub-days. To cope with any plausible failures of our assumptions, we propose to randomise 100 hub-days to allow for subgroup analyses, completing trial accrual from the five hubs in four working weeks with a target population of 300,000.

In order to also consider subgroups by screening round, we propose a further increase to 150 hub-days. With 150 hub-days, we have a target population of 450,000. The smallest screening round subgroup in ASCEND1, prevalent screen first-time, comprised around 15% of the recruits. This would give 67,500 in this smallest subgroup. Within screening round subgroups, the variation between hub-days is around 20% lower than in the population as a whole, which in turn suggests a variance inflation factor of around 2. For 90% power for the same size of effect as expected overall, we would need 2 x 14,643 per arm, just under 30,000 per arm, 60,000 in total. Thus, the study size of 150 hub-days is likely to be more than adequate for subgroup comparisons. The trial will involve no additional costs or work on the part of hub staff if the trial size is increased as the GP endorsement and random allocation will be programmed within the Bowel Cancer Screening System.

Table 1. Expected socioeconomic status distribution, and intervention and control completion rates

Socioeconomic status (national IMD quintile)	Percentage in each quintile from ASCEND	Control group completion percent by quintile from ASCEND	Anticipated intervention group completion percent
1 (least deprived)	23.5	66.0	67.0
2	23.5	62.6	64.1
3	21.1	58.0	60.0
4	17.3	51.5	54.0
5 (most deprived)	14.6	42.6	45.6

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 (4). 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 episode versus prevalent episode 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 (5). 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 the ASCEND study.

Data Management

A Data Analyst working on behalf of all BCSP hubs has designed and piloted the data extraction algorithms. The raw data will be extracted by Health & Social Care Information Centre (HSCIC) from BCSS and pseudo-anonymised then given to the Data Analyst to clean. The postcode variable will be substituted with Index of Multiple Deprivation (IMD) score by HSCIC.

The Data Analyst has specified the data to be extracted by HSCIC and the National Office on behalf of the ASCEND2 research team. No patient identifiable information is required. Data transfer between HSCIC/the National Office and the Data Analyst will be via encrypted network connection (NHS.NET) and/or NHS Secure File Transfer (SFT).

The pseudo-anonymised raw data will be processed and further anonymised into the format required by the ASCEND2 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 the Data Analyst and the ASCEND2 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 ASCEND2 project . The project will adhere to the NHS Cancer Screening Programmes Confidentiality and Disclosure Policy.

The data will be extracted from the BCSS 18 weeks following the last intervention date.

Quality Control and Quality Assurance

Evaluation of Intervention Fidelity

This intervention requires insertion of the name of the subject's general practice into the S9 kit invitation letter. This can only be achieved by implementing changes on the BCSS. As part of the previous ASCEND trial we conducted extensive consultations with HSCIC whose programmers applied the necessary changes to the BCSS to ensure that general practice-endorsed kit invitation letters can be generated on pre-specified random dates. Changes to the BCSS include addition of a variable that will indicate whether a subject received an intervention or whether he/she was a part of the control cluster.

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

The process diagrams for the GPE letters are detailed in Figure 3.

Monitoring and Auditing

The Imperial College Joint Research Compliance Office, on behalf of Imperial College 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, prior to commencement of this study and Local Ethics Committee approval has also been sought and obtained from the Bowel Cancer Screening Programme Research Committee.

Ethical Approval for the NIHR-funded ASCEND study was obtained from UK National Research Ethics Service, London – Harrow Ethics Committee, Reference number 12/LO/1396 prior to commencement of this study.

Risks for Trial Subjects

Risks to the subjects associated with this study are not any higher than the risks associated with usual contact with the BCSP. The ASCEND project was designed with advice from patient representatives and charities who found no cause for concern.

ASCEND2 is a follow-on trial that is identical in design to Intervention 3 from the ASCEND study, with the GPE banner simply added to a different invitation letter (the test kit or S9 letter rather than the pre-invitation or S1 letter) that is currently in use in the BCSP.

Clinical Trial Documentation

In accordance with Imperial College Retention Schedule, the Imperial College London Joint Research Compliance Office and the EU Good Clinical Practice Directive 2005/28/EC, all primary research data will be retained for a minimum period of 10 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 will have a chance to comment on draft papers for publication. 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.

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Appendix 1: General Practice Endorsed Kit Invitation letter (S9)

NHS No: 999 000 5451

25 December 2005

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

S9# 278/7/26

Dear Mrs Anne Belinda Example-Subject

Your GP practice, crewkerne, supports the Bowel Cancer Screening Programme

Following the recent letter you received inviting you to take part in the NHS Bowel Cancer Screening Programme, please find enclosed your test kit together with full instructions on how to use it. Please check that **your name** is clearly printed on the test card (call **Freephone** 0800 707 60 60 if not).

The test kit is used to detect tiny traces of blood, invisible to the naked eye, in your bowel motions. This test will identify people who may need further investigations. This could mean a repeat test and/or having a colonoscopy. Colonoscopy is an investigation looking at the inside of the large bowel with a small camera. Most people that complete a test kit do not need a colonoscopy.

Once you have completed the test kit, please return it in the **reply paid** envelope provided. No stamp is needed and the kit is safe to send through the post. Results from the test kit will normally be sent to you within two weeks. If you have not heard anything after this time, please call the **Freephone** number at the top of this letter (calls are free from UK landlines).

We do not have your medical history, and screening is not appropriate for everyone. **If you have already been referred to hospital by your GP for bowel investigations, or if you have had previous bowel surgery, then screening may not be appropriate for you. Please call us for advice using the Freephone number.**

You can also call the **Freephone** number if you have any queries about using the test kit, or if you need to request a replacement. 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.

Yours sincerely

Hub Director name here
Hub Director title here

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