MULTICENTRE RANDOMISED CONTROLLED TRIAL OF 'ONCE-ONLY' FLEXIBLE SIGMOIDOSCOPY IN PREVENTION OF BOWEL CANCER MORBIDITY AND MORTALITY

Study Short Title: The UK Flexible Sigmoidoscopy Screening Trial (UKFSST)

Protocol Amendment 1

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1. OUTLINE OF THE TRIAL

This is a multicentre randomised controlled trial designed to evaluate the effect of a single flexible sigmoidoscopy screening at age 55-64 years in the prevention of colorectal cancer morbidity and death. 195,000 men and women will be recruited to the study in 10 centres throughout the United Kingdom and randomly allocated to either screening or control groups in the ratio of 1:2. Thus 65,000 subjects will be invited for screening and 130,000 will act as controls. Controls will not be contacted. Flexible sigmoidoscopy screening will be undertaken at a screening centre in a hospital. Small polyps will be biopsied and removed during the screening procedure. Subjects found to have either no polyps or 'low-risk' polyps (< 3 adenomas, all of size < 1 cm with tubular histology and mild or moderate dysplasia) will have no further follow-up. Subjects found to have 'high-risk' polyps (≥ 3 adenomas, size ≥ 1 cm, tubulovillous or villous histology or severe dysplasia) will be invited to undergo a baseline colonoscopy screen followed by periodic colonoscopic surveillance according to a prescribed protocol.

To increase compliance rates in the trial, a 2-stage recruitment procedure will be used. At the first stage, eligible subjects will be asked if they would have the test if invited and those who respond positively will be entered into the trial. This method of selection should ensure high attendance rates among those invited for screening. All subjects entered into the trial, including controls and those refusing screening or failing to respond to the invitation for screening will be followed up passively by periodical inspection of hospital discharge data, pathology records and using the National Health Service Central Register. The endpoints of the study are 1) diagnosis of colorectal cancer 2) death from colorectal cancer. The study has been designed to detect (with 90% power and at a 5% level of significance) a difference in the incidence of colorectal cancer at 10 years and in mortality at 15 years in each of the age-groups, 55-59 years and 60-64 years. The sample size calculations assume a 55% compliance rate and a 45% reduction in mortality/incidence among those undergoing screening leading to an overall 25% reduction in mortality/incidence. In addition, it is assumed that there will be no deaths in the first 5 years to allow for a healthy population effect and that exposure to screening, education and other factors will lead to a 5% reduction in mortality in the control group.

2. TRIAL DESIGN

2.1 AIMS

Primary Aim

To quantify the reduction in incidence and mortality from colorectal cancer resulting from a single flexible sigmoidoscopy screen at age 55-64 years with colonoscopy surveillance for those found to have high-risk polyps (≥ 3 adenomas, size ≥ 1 cm, tubulovillous or villous histology, severe dysplasia).

Secondary Aims

1. To examine the efficacy of flexible sigmoidoscopy screening in each of the specific age-bands 55-59 years and 60-64 years.
2. To quantify the reduction in incidence and mortality from *distal* colorectal cancer (rectum, sigmoid colon) resulting from a single flexible sigmoidoscopy screen at age 55-64 years.
3. To quantify the reduction in incidence and mortality from *proximal* colorectal cancer (descending colon to caecum) resulting from a policy in which colonoscopy surveillance is offered only to those found at the screening flexible sigmoidoscopy to have high-risk polyps (≥ 3 adenomas, size ≥ 1 cm, tubulovillous or villous histology, severe dysplasia)
4. To determine the duration of efficacy of a single flexible sigmoidoscopy
5. To determine the optimum age for the examination.
6 To undertake an on-going evaluation of health service research issues to permit an informed decision at the end of the trial about its suitability for implementation within a national screening programme.
   The criteria to be evaluated include:
   - uptake, acceptability and impact
   - quality control of the procedure
   - cost-effectiveness

2.2 PARTICIPATING CENTRES

The study will be undertaken in 12 centres throughout the UK. Screening will be performed in an existing endoscopy unit with sufficient available sessions to undertake 3000 examinations within 2 years i.e. at 48 examinations per week. If 12 examinations are performed per session, then four spare sessions are required in single endoscopy suite and an equivalent of one extra session for the colonoscopies which will be required for subjects found to have high risk adenomas.

Approval of the local ethics committee will be obtained before commencement of the study at each centre.

A local trial coordinator (LTC) will be appointed to assume responsibility for that centre under the supervision of a centre leader. To ensure the highest standards of safety and efficacy, it is required that any endoscopist performing flexible sigmoidoscopies or colonoscopies for the trial should have acquired by the time of commencement of the 2-year screening period a minimum experience of 100 unsupervised lower GI endoscopies in addition to 50 supervised examinations; a reference will be required for each endoscopist in the trial. The trial co-ordinator will be assisted by a full-time administrator.

2.3 GP RECRUITMENT

General practitioners within the catchment area of a trial centre will be invited to participate. Each trial centre area will be divided into four quadrants and the local trial coordinator will enlist the participation of general practitioners within a particular quadrant every 6 months to ensure that information about patients is current. Larger general practices will be selected which are representative of the local population and include rural, suburban and inner city practices. Each participating practice will provide a copy of the practice headed notepaper and a specimen signature of a senior partner for use in the accompanying letters to the initial recruitment questionnaires.

2.4 SUBJECT RECRUITMENT AND INVITATION

2.4.1 Inclusion/exclusion criteria

All men and women aged between 55 and 64 years belonging to general practices which have agreed to participate in the trial will be considered for inclusion in the trial, unless they exhibit one or more of the following exclusion criteria:

(i) Incapable of providing informed consent
(ii) History of colorectal cancer or adenomas, inflammatory bowel disease
(iii) Severe or terminal disease: life expectancy < 5 years
(iv) Recent history (within previous 2 years) of sigmoidoscopy or colonoscopy.

A list of potentially eligible subjects for each of the participating general practices will be generated from the register held by the local Family Health Services Authority (FHSA). Data requested will include the full name, address and postcode, date of birth, NHS number and GP code.

Each general practitioner within each participating practice will be sent a letter (Appendix 1) asking them to scan a list of their patients and select those unsuitable for entry to the study, specifying the reason for ineligibility .

2.4.2 Initial questionnaire

Eligible subjects will be sent a short questionnaire together with an information sheet (Appendix 3), to determine whether they would be interested in undergoing bowel cancer screening if it were available. The accompanying letter is on their GP's practice headed notepaper signed by the senior partner in the practice (Appendix 2). A reminder letter (Appendix 4) and a further questionnaire will be sent to non-responders after a month.

Subjects returning a completed questionnaire and expressing an interest in having the test will be entered into the trial. Subjects who return a completed questionnaire, but indicate that they are not interested will not be contacted. Incorrect addresses will be corrected at this stage and subjects volunteering information about history of bowel cancer or previous endoscopy will be excluded.

2.4.3 Entry to the study and randomisation

Eligible subjects entered into the trial will be randomised to either invitation for screening or control in the ratio of one screenee to two controls. The unit of randomisation will be the household. Separate randomisations will be produced for each participating centre and for each general practice within each centre and for each household type (single male, single female, couples, other- where single is taken to mean only one eligible person in the

household known to us). Randomisation will be in blocks of six (4 controls, 2 screenees), matched for size of household.

2.4.4 Invitation for screening

Subjects in the intervention arm will be sent a postal invitation for screening specifying an allocated appointment time (5 weeks ahead) together with an opportunity to suggest an alternative time if not convenient (Appendix 5). An information sheet will accompany the invitation (Appendix 6). Subjects will be requested to telephone the trial centre to confirm the appointment, to change or to cancel it. It is expected that 2/3 of subjects will attend at the initially allocated appointment time, therefore to have full sessions and maximise the use of endoscopy staff, sessions will be overbooked by 50%.

Persons failing to respond to the postal invitation after 2 weeks will be sent a reminder. If the original appointment time remains unfilled, it is reoffered (Appendix 7a), otherwise a new time is offered for 6 weeks ahead (Appendix 7b). Subjects failing to respond to the reminder within one week will be considered non-responders and their appointment slots reallocated to new subjects.

An 24 hour advice telephone line will be available for any participant with problems about any aspect of the screening procedure

2.4.5 Bowel preparation

Subjects accepting their invitation for screening will be sent a reminder of the appointment time (Appendix 8), a map of the hospital and a single phosphate enema (Fletchers - Pharmax) with instructions two weeks before their appointment (Appendix 9).

2.5 THE SCREENING PROCEDURE

2.5.1 Pre-screening

On arrival in the unit, subjects will given an information sheet about the test (Appendix 10) to read in the waiting room and will be asked to complete a form requesting information about history of illnesses and operations, current medication and, specifically, whether they are taking aspirin or anticoagulants. This form includes questions about their family history of cancer (Appendix 11).

Written consent for flexible sigmoidoscopy and polypectomy, if required, will be obtained in the endoscopy suite after a full verbal explanation of the screening procedure by the examining endoscopist(Appendix 12).

2.5.2 The examination procedure

The patient will be examined in the left lateral position. The examination will begin with a digital rectal examination.

The aim of the flexible sigmoidoscopy examination will be to advance the scope as far as can be achieved without producing pain or stress to the patient; this will normally be to just beyond the sigmoid colon - descending colon junction to view the distal descending colon. An examination will not normally be expected to last more than 5 minutes. Sedatives and muscle relaxants will only rarely be used.

The examination will be undertaken by a clinical endoscopist using a 65 cm flexible sigmoidoscope connected to colour VDU monitor.

A video recording of each examination will be made and a single endoscopist at the trial co-ordinating centre will undertake quality control assessments.

2.5.3 Management of polyps detected

Small polyps (< 1 cm in diameter) detected during the examination will be removed using hot-biopsy or snare technique as appropriate and sent for histopathological assessment. Polyps of size 1 cm or larger will be removed at colonoscopy. Subjects with suspected cancer or with polyps too large to be removed endoscopically will be referred for surgery.

To avoid the possibility of explosion during electrocoagulation, use of carbon dioxide for insufflation is mandatory. If the carbon dioxide fails or is temporarily unavailable, the bowel gas should be evacuated five times and reinflated before electrosurgery.

Where possible all polyps above the distal rectum should be destroyed. Examiners should use their clinical discretion, but small hyperplastic polyps in the lower half of the rectum will usually be ignored.

2.5.4 Recording the results of flexible sigmoidoscopy

The following will be recorded on a standard form (Appendix 13)

Duration

The start and stop time of the examination (from the video recorder).

Overall assessment of the examination

Very easy, quite easy, quite difficult, very difficult

Adequacy of the bowel preparation

Excellent: no stool or fluid present

Good: residual liquid or stool present but removable by suction

Adequate; the examination accomplished, but with difficulty due to residual stool.

Poor: the examination could not be performed satisfactorily due to the presence of excess faeces.

Reasons for premature termination of the procedure

If the reason is inadequate bowel preparation, whether an extra enema was given in the unit and whether the examination was repeated.

The length (cm) of instrument inserted and the estimated anatomical location of the tip at the furthest depth of insertion.

Abnormalities detected

Cancer, polyps, haemorrhoids, diverticulosis, inflammatory bowel disease, other.

Polyps

Total number of polyps detected and for each polyp:

Anatomical site within the large bowel

Site of polyps in cm from the anal verge

Size (mm), either in situ by comparison with the size of open biopsy forceps or by measuring with callipers after removal.

Shape: stalked, narrow (base < 5mm), stalked wide, sessile, flat/depressed.

Removal: complete, biopsied only

Treatment: cold biopsy, hot biopsy, cold snare, hot snare, no treatment.

Endoscopist

Name of endoscopist performing the flexible sigmoidoscopy.

2.5.5 Results of screening

Subjects will be told the results of the test at the end of the examination and will take home a letter with a further explanation of the results. A similar version of the letter will be sent to GPs (Appendix 14). There are four types of result:

Finding	Action
1. Normal: no significant polyps	Discharge
2. Small (< 1cm) polyps	Wait for pathology results
3. Large (≥ 1cm) polyp(s)	Colonoscopy appointment
4. Polyp requiring surgery or cancer	Refer to surgeon

Subjects who need to be see a surgeon or to undergo colonoscopy should, if at all possible, be given an appointment before leaving the unit. Patients requiring colonoscopy will be given an appropriate bowel preparation to take home.

We wish to examine participants' experiences of the test. Subjects will be asked to complete a short questionnaire on the morning after the test and return it in a prepaid envelope. A reminder letter and a further copy of the "morning after" questionnaire will be mailed to those who do not return a completed questionnaire within 4 days of the test (Appendix 15).

2.6 HISTOPATHOLOGICAL ASSESSMENT OF POLYPS

2.6.1 Handling of specimens

Single biopsy specimens (≥ 5mm) will be placed in a pot clearly marked with the subject's name. Polyps of metaplastic appearance (< 3mm and pearly-white) removed from the rectum should not be sent to local pathology department, but stored in formalin for later histological assessment at St Mark's Hospital. All other polyps will be examined locally.

Multiple specimens of size < 5mm will be transported to Histopathology in a single pot using a Millipore filter strip marked with a grid as described in Appendix 16. The multiple biopsy specimens are placed serially on the grid with the most distal furthest from the marked corner. The specimens, which should be placed serially along the straight line by the endoscopist, remain on the filter throughout processing.

2.6.3 Histopathological assessment

The following will be recorded by a single pathologist at each centre:

Polyp type:
adenomatous, metaplastic, inflammatory, other
Diameter of each specimen:
maximum, measured after fixation.
Histology:
classified using WHO criteria (1) as:

tubular	1- <20% villous
tubulovillous	20-<80% villous
villous	80-< 100% villous

Grade of dysplasia: categorised according to WHO criteria (1) as mild, moderate or severe.

The residual specimen remaining after making the required slides will be stored in the histopathology department of the local trial hospital. If storage becomes a problem it can be sent to a repository at the Imperial Cancer Research Fund. Stored material will be kept for future genetic research and for independent assessment of histopathology by a panel of pathology experts.

1. Jass J, Sobin L. World Health Organisation, Histological Typing of Intestinal Tumours. 2nd Edition.Springer-Verlag, 1989:pp127.

2.7 FOLLOW-UP OF SUBJECTS WITH NEOPLASIA

2.7.1 Classification into low and high risk

Subjects will be categorised by the *endocopist* as high risk or low risk according to the number, type and histopathology of their polyps as follows:

Low Risk	**High risk**
all of the following:	any of the following:
1-2 adenomas	≥ 3 adenomas
small (< 1cm)	large (≥ 1cm)
tubular	tubulovillous or villous
mildly or moderately dysplastic	severely dysplastic

2.7.2 Baseline colonoscopy

Patients found to have high risk polyps will be referred for a baseline colonoscopy screening examination.

The proportion of subjects requiring colonoscopy is not expected to exceed 5%. Thus for a centre screening 48 subjects per week, there will be a maximum of three colonoscopies generated by the trial per week.

2.7.3 Pre-colonoscopy counselling

This may be conducted by telephone. Its purpose is to:

Explain the nature of a polyp and its potentially cancerous nature. Its removal will be recommended and colonoscopy and polypectomy will be explained as well as the rare possible complications.

If a patient is felt to be at risk for polypectomy, this will be explained and discussed.

Minimise the risk of bleeding at polypectomy. Aspirin products will be discontinued for one week before colonoscopy and, if polypectomy is undertaken, for one week afterwards.

Subjects will be informed that they are likely to receive sedation during colonoscopy and, if so, will not be able to drive or operate heavy machinery for 24 hours afterwards.

2.7.4 Recording the results of colonoscopy

The following will be recorded on a standard form (Appendix 17):

Overall assessment of the examination

Very easy, quite easy, quite difficult, very difficult

Medication

Names and doses

Adequacy of the bowel preparation

Excellent:	no stool or fluid present
Good:	residual liquid or stool present but removable by suction
Adequate;	the examination accomplished, but with difficulty due to residual stool.
Poor:	the examination could not be performed satisfactorily due to the presence of excess faeces.

Reasons for premature termination of the procedure

Action taken if incomplete (repeat colonoscopy, refer for barium enema).

Segment reached

Estimated anatomical location of the tip at the furthest depth of insertion.

Abnormalities detected

Cancer, polyps, haemorrhoids, diverticulosis, inflammatory bowel disease, other.

Polyps

Total number of polyps detected and for each polyp:

Anatomical site within the large bowel

Site of polyps in cm from the anal verge

Size (mm), either in situ by comparison with the size of open biopsy forceps or by measuring with callipers after removal.

Shape: stalked, narrow (base < 5mm), stalked wide, sessile, flat/depressed.

Removal: complete, biopsied only

Treatment: cold biopsy, hot biopsy, cold snare, hot snare, no treatment.

Action

Surveillance colonoscopy: recall in 1 or 3 years

Wait for pathology results,

Repeat colonoscopy,

Refer for barium enema

Review polyp excision site in 2 months

Review in out-patients department.

Endoscopist

Name of endoscopist performing the colonoscopy

2.7.5 Surveillance colonoscopy

The frequency and number of follow-up colonoscopies will depend on findings at baseline colonoscopy and at each follow-up examination according to the following protocol:

All high-risk subjects will undergo at least two follow-up examinations at 3-yearly intervals.

If total colonoscopy to the caecum cannot be achieved at baseline, a double contrast barium enema (DCBE) will be performed to preclude cancer or large polyps. DCBE should not be performed after colonoscopy if polypectomy was performed.

If colonoscopy follow-up is not feasible, it can be replaced by DCBE and flexible sigmoidoscopy.

If at screening flexible sigmoidoscopy or baseline colonoscopy, ≥ 5 adenomas or an adenoma of size ≥ 2 cm are found, or if the baseline colonoscopy is technically unsatisfactory, an additional colonoscopy will be undertaken 12 months after baseline.

Subjects found to have either ≥ 3 adenomas or an advanced adenoma (≥ 1cm, villous histology, high grade dysplasia or malignant) at any single follow-up examination will be considered to be at increased risk and should be given more frequent surveillance (2-yearly colonoscopy).

2.8. STATISTICAL DESIGN AND ANALYSIS OF THE RESULTS

2.8.1 Endpoints to the trial

There are two primary endpoints to the study: 1) diagnosis of colorectal cancer 2) death from colorectal cancer.

2.8.2 Sample size

(see Appendix 18 for sample size calculations)
It has been calculated that a sample size of 195,000 will be required to demonstrate with 90% power at a 5% level of significance a 20% difference between screened and control groups in incidence at 10 years and in mortality at 15 years in the two separate age groups 55-59 years and 60-64 years. Subjects will be randomly allocated to the invitation for screening or control arms of the study in the ratio 1:2. Thus 65,000 subjects will be invited for screening and 130,000 will act as controls.

These calculations assume the following:

1. The proportions of men and women will be equal.
2. Exposure of the control group to gastrointestinal endoscopy will result in an overall 5% reduction in incidence and mortality in the control group compared to the general population.
3. 55% of subjects invited for screening will undergo the test and there will be a 45% reduction in incidence/mortality among those undergoing screening leading to an overall 20% reduction in incidence/mortality compared with the control group.
4. No difference in incidence can be detected within 2 years of screening because most symptomatic cancers which would normally be diagnosed during that time will be detected as asymptomatic cancers at entry. i.e. a lead time of 2 years is assumed.
5. No difference in mortality can be detected for the first 5 years because persons with an existing diagnosis, who would be expected to die soon after entry, will be excluded.

2.8.3 Analysis of the trial

All subjects randomised at entry will be included in the analysis (intention to treat).

The main analysis for a significant difference in *incidence* between the two treatment groups will occur when at least 10 years has lapsed since flexible sigmoidoscopy screening in 50% of subjects randomised to the screening arm of the trial.

The main analysis for a significant difference in *mortality* between the two treatment groups will occur when at least 15 years has lapsed since flexible sigmoidoscopy screening in 50% of subjects randomised to the screening arm of the trial.

If compliance is higher than anticipated it may be possible to analyse the results earlier than above.

2.9 DATA MONITORING AND QUALITY CONTROL

The following will be monitored for each centre and where appropriate for each endoscopist for quality control purposes.

Compliance

Response rates in each centre and by general practice to the baseline questionnaire and the invitation for screening.

Attendance rates for screening.

Quality of the examination

Rates of premature termination of the procedure by centre, by endoscopist

Adequacy of the bowel preparation

Stated depth of insertion of the flexible sigmoidoscope and anatomical site reached.

Number of examinations per session

Acceptability of screening

Complication rates

Screenee assessment of the examination, the bowel preparation, the attitude of the endoscopy staff, the adequacy of the information provided before the procedure.

Waiting time in the unit before screening.

Pathological assessment of polyps

Time required to receive the results of screening.

Waiting time for baseline colonoscopy or for surgery.

Yield

Proportion of screenees with polyps, adenomas, cancer. The stage distribution of cancers. Rate of referral for colonoscopy.

Histopathology

Agreement between co-ordinating and trial centre pathologists.

Speed of relaying results to the endoscopist.

Contamination

The exposure of the controls to gastrointestinal endoscopy by scanning local gastrointestinal endoscopy databases.

2.10 ADVERSE EVENTS

Investigators will report to the trial co-ordinating centre promptly all events which are both serious (fatal, life threatening, leading to hospitalisation) and suspected (probably or definitely) of being related to *any* procedure undertaken as part of the trial (administration of bowel preparation, flexible sigmoidoscopy, polypectomy, colonoscopy, surgery or any drugs administered during these procedures).

All adverse reactions to the procedure, including those which are mild and do not require treatment, will be recorded on an adverse reactions form (Appendix 19).

An independent data monitoring committee will examine all adverse effects associated with the procedure at 6-monthly intervals.

Protocol Amendment 1

As of July 2016, the UK Flexible Sigmoidoscopy Screening Trial (UKFSST) has created a study dataset containing 16 years of median follow-up on the study cohort. In addition to the original study objectives (see 'Aims', section 2.1 of the UKFSST Protocol V5.97, January 1997, page 5), the UKFSST study team has identified the following potential questions which could be addressed by further analysis of the UKFSST dataset. These analyses will be conducted by the Cancer Screening and Prevention Research Group (CSPRG) medical statistician and published in peer reviewed journals. No additional data will be requested to meet these objectives.

- The quality of FS screening on screening outcomes and CRC incidence/mortality
- Patient and procedural factors affecting performance of FS screening
- The safety and acceptability of once-only FS
- The effect of family history of CRC on the incidence of CRC after screening
- The use of advanced stage at diagnosis of incident cancers as a surrogate for CRC mortality
- The efficacy of colonoscopy surveillance for higher-risk adenomas found at screening
- The incidence of proximal CRC after FS, by the number and type of polyp detected at FS
- The incidence of CRC according to smoking history
- The potential contamination of UKFSST by Faecal Occult Blood Tests (FOBTs) given as part of the Bowel Cancer Screening Programme (BCSP)
- Medications in relation to risk of adenomas and CRC
- The effect of prior FS on participation and outcomes of FOBTs as part of the BCSP