Norwegian Colorectal Cancer Prevention (NORCCAP)
(Norwegian version approved by the project committee 19th February 1998)

Protocol
Geir Hoff
Erik Carlsen
Tor Jac Eide
Tom Grotmol
Eva Skovlund
Kjell Magne Tveit
Morten Vatn
Mandate of the project working party

The Norwegian Gastrointestinal Cancer Group (NGICG) established a working party in April 1997 «to present a protocol by September this year to describe, with cost estimates, a large scale screening study for detection of colorectal neoplasia». This working party has consisted of:

- Erik Carlsen, MD dr.med., Dept. of Surgery, Ullevål Hospital, Oslo
- Tor Jac Eide, Prof. dr.med., Dept. of Pathology, Norwegian National Hospital, Oslo
- Tom Grotmol, MD dr.med., Norwegian Cancer Registry, Oslo
- Geir Hoff (chairman), MBChB dr.med., Dept. of Medicine, Telemark Central Hospital, Skien
- Eva Skovlund, Prof. dr.phil, University of Oslo
- Kjell Magne Tveit, MD dr.med., Dept. of Oncology, Ullevål Hospital, Oslo
- Morten Vatn, MD dr.med., Dept. of Medicine, Norwegian National Hospital, Oslo

Brief outline

A prospective, controlled study with randomisation from the national population registry of men and women aged 55-64 years living in the counties of Oslo and Telemark in the south of Norway. Randomisation to intervention (screening) and control groups will be in the ratio of 1:1 in Telemark and 1:5 in Oslo. In addition there will be two distant control groups in epidemiologically matched populations outside the screening area, presumably less prone to colonoscopic contamination. Screening will be completed during two years of endoscopic screening. The screening groups in Oslo and Telemark will be randomised (ratio 1:1) to either flexible sigmoidoscopy only or a combination of flexible sigmoidoscopy and a test for faecal contents (faecal occult blood test and frozen specimens stored for future trials on test kits to be developed). 3500 individuals will be offered either one of these two screening options in each screening area, i.e. altogether 7000 in each arm of the screening group. Altogether 14,000 individuals will be offered screening examination. Polyps will be removed at flexible sigmoidoscopic screening examination (flex-sig). Histologically verified adenoma at flex-sig or a positive faecal test will qualify for a full colonoscopic examination. A positive FOBT will also qualify for a full colonoscopic examination. The choice of FOBT kit is not definite as yet (although FlexSure® OBT has been named as the most probable choice throughout this protocol). End points for the study will be a diagnosis of colorectal carcinoma (CRC) and death. End points will be followed through the National Cancer registry and National Population Registry.

Background

- Colorectal cancer (CRC) carries the highest incidence rate of all cancers in Norway for men and women collectively.
- Norway is expected to take a lead among the Nordic countries in CRC incidence rate already at the millennium, mainly due to a dramatic increase in incidence of carcinoma of the rectum.
- Symptoms are often a late manifestation and the 5 year survival rate is no more than 50%.
- Most cases of CRC develop from adenomatous polyps that can be discovered and removed during flexible sigmoidoscopy (flex-sig) or full colonoscopy.
It is not yet clear which is the optimal screening method or combination of screening modalities (e.g. flex-sig alone or flex-sig in combination with immunochemical tests for faecal occult blood).

It is still a matter of dispute what findings at flex-sig should trigger a full colonoscopy. According to the Telemark Polyp Study no. 1 (TPS-1) and an on-going multicenter study in Britain the relationship between various colonoscopic scenarios around the age of 60 may be as follows depending on definition of threshold findings:

- Any polyp found at flex-sig (TPS-1): 35% go to full colonoscopy
- Any adenoma found at flex-sig: 20% go to full colonoscopy
- «High risk adenomas» at flex-sig (U.K.): 5% go to full colonoscopy

Also, it is not clear to which extent this type of screening examination may have any untoward psychosocial effects or influence on lifestyle and lifestyle related morbidity. In the Telemark Polyp Study no.1 (TPS-1) there were less complaints consistent with irritable bowel syndrome 13 years after a flex-sig screening examination compared to controls. There was also a lower score for anxiety and depression amongst screenees than controls and this apparently beneficial «anxiolytic and anti-depressive» effect of screening was shown to last for at least one year. However, the screening group appeared to have more deaths due to lifestyle related morbidity than the control group. This apparent difference in mortality may reflect an educational and motivating problem since some degree of anxiety is an essential motivating factor for improving lifestyle. This hypothesis ought to be tested in a large scale study.

«Spontaneous endoscopic screening» activity, i.e. referral to endoscopic examination with no relevant symptoms or familial predisposition, is believed to be on a rapid increase and it is inadvertently being paid by the National Health Service (NHS). Extent and effects of this are unknown.

The gloomy prospects of increasing problems with rectal carcinoma in the population will further encourage spontaneous endoscopic screening activity.

Long term experience from controlled endoscopic population screening has so far been restricted to the small Norwegian TPS-1 study which achieved an 81% attendance rate among 400 individuals invited to have a flex-sig examination at the age of 50-59 years in 1983. During the following 13 years no CRC was observed among those attending compared to 10 cases in the control group of 399 individuals who had not been offered endoscopic screening examination and polypectomy.

A large scale, randomised flex-sig screening study of 55-64 year old individuals has recently been launched in UK. In this study individuals are being randomised to screening or control groups after having accepted to participate. The acceptance rate is about 55-60% and 70-75% of these attend for examination (45% of all invited). This study will be able to say something about the beneficial effects of early diagnosis of CRC and polypectomy of adenomas. It is less able to say something about the effectiveness of endoscopic screening as a service to the normal population unless it is taken for granted that those rejecting a request to be randomised are the same as those who would reject an actual offer of a screening examination.

A multidiciplinary panel in USA have, after a very thorough survey of the literature, concluded with highly recommending screening for CRC (2). All available screening strategies for CRC are cost affective and they are at least as cost effective as screening mammography. They also conclude that there is a number of questions that need to be answered through further research, including quality of life years gained, the relative benefits of various screening modalities and what findings at flex-sig are the optimal threshold for a full colonoscopic follow-up.
From a professional point of view it would be unwise not to take responsibility and keep as much as possible of the expanding endoscopy service within a controlled framework to learn more about its consequences.

From a socioeconomic aspect it would be essential to learn more about cost effectiveness of «high tech» cancer prevention methods through a controlled study.

In one of the Official Investigations of Norway this year (NOU 1997:20, «Norwegian Strategy against Cancer»), it is suggested that «research/testing (of screening for large bowel neoplasia) should start in an area with sufficient knowledge and capacity in endoscopy».

Study organisation

Management
There are two main areas to be taken care of:
1. Advance planning, coordination and clinical supervision with responsibility for teaching medical staff and endoscopists. This is estimated to require full time engagement of one person if planning shall take less than one year. It may possibly be reduced to 50% post after this for the 2 years of screening.
2. Central registration at the Norwegian Cancer Registry. Establishment and maintenance of a separate central register with continuous update and evaluation of the quality of screening examinations. Estimated to require 50% post for an M.D./epidemiologist for a period of 3 years starting one year or less before the screening gets started.

Governing board
The study management consists of project leader (Geir Hoff) and registry leader (Tom Grotmol), both as from 1st January 1999. The management reports to a governing board appointed by the Department of Health and Social Affairs. Differences of opinion are to be settled by a simple majority vote amongst the total number of members appointed to the governing board which is the highest body for decisions in the NORCCAP study. A reference group will also be appointed by the Dept. of Health.

Funding
Grants from the Health Department and Norwegian Cancer Society will be used for the screening examination and overhead costs. When adenomas are found, individual participants are to be considered as patients requiring full colonoscopy to be covered by the National Health Insurance.

The immediate follow-up (baseline colonoscopy when adenomas are found at flex-sig) is to be performed by the screening team, but regular NHS fees for treatment of patients will be applied. Any need for further follow-ups (usually after 5 or 10 years if ever) must be performed at the local hospital according to national guidelines for polyp surveillance (1).

Minimum requirements
Local hospitals have no spare capacity to serve the project. Many hospitals use their endoscopy labs, equipment and staff for evening sessions just to keep up with the present volume of referrals. To be able to offer screening to an invited cohort of 3500 individuals per year, the following requirements have to be met for each screening team (provided a 70% attendance rate):
Premises:
Two endoscopy suites equipped with suction/air (may be portable), one enema room with access to toilet, one technical room with endoscopy washing machine, one secretarial office, possibly a waiting room (not an absolute must).

Technical equipment:
One washing machine for endoscopes, 6 videocolonoscopes, 2 complete videoracks, 2 diathermy units, fluoroscopy in one of the endoscopy rooms, 2 scaled probes for measuring the size of polyps, polypectomy snares, biopsy forceps, flasks and pump for CO₂ insufflation to be used at flex-sig.

Staff:
Two doctors (at least one experienced colonoscopist), one secretary, 4 nurses/nurse assistants. An agreement with pathologists to evaluate polypectomy specimens and biopsy material.

Capacity:
Two flex-sigs per hour in one of the two endoscopy rooms will give 2x6=12 flex-sigs per day (only 6 effective working hours since each day will have to start with enemas before flex.sig can be performed after about ½ hour and because of lunch break). This will give a working capacity of up to 60 flex-sigs per week or 2570 in 42 effective weeks per year. Colonoscopies will be performed in the second endoscopy room which will allow some 7 colonoscopies per day, i.e. 35 colonoscopic examinations per week or 1470 in the course of 42 working weeks per year.

Financial needs
Applications for funding will be put forward to the Norwegian Cancer Society, Dept. of Health and Social Affairs and the National Health Insurance (Rikstrygdeverket). The Dept. of Health is the owner of the project and will guarantee funding for the main project (ref. «primary aims» below) together with the Norwegian Cancer Society. Participants are not expected to pay for the screening examination itself. Substudies not fulfilling the requirements of «primary aims» are requested to seek financial support outside the financial frame of NORCCAP.

Study design

Primary aims
1. Evaluate the effect on CRC mortality and morbidity by screen detection of CRC and removal of precursor lesions (polypectomy of adenomatous polyps). (Problem 1)
2. Evaluation of cost/effectiveness of screening for CRC and significant, benign lesions using flex-sig only compared to flex-sig in combination with faecal tests (Problem 2).
3. To evaluate to which extent (and in which direction) the study may influence overall endoscopic activity in the general population in the screening areas and in areas where controlled screening is not established (Problem 3).

Problems to be addressed other than those listed as primary aims must be subject to separate budget applications, e.g. through regular application of grants from the Norwegian Cancer Society.
Secondary aims
Apart from the primary aims expressed as problems 1-3 above, there are several secondary aims that may be added in due time to this «core project» and described in separate protocols. These will be presented to regional ethics committees as they become described in adequate detail and will be accepted as candidate projects for inclusion in NORCCAP. The most imminent of these are:

1. Determine the prevalence of known types familial CRC in a general population and try to define other groups with intermediate increased risk. *(Problem 4)*
2. Evaluate the feasibility of teaching technical/nursing staff to perform endoscopic screening examinations. *(Problem 5)*
3. Clarify possible psychosocial effects of endoscopic screening and how it may influence lifestyle and lifestyle related morbidity and overall mortality *(Problem 6)*

Duration of study
Two years of inclusion (screening). First evaluation of primary aim after 5 years observation. Hence, a study time frame of minimum 7 years is required.

Choice of study design
Prospective, controlled with randomisation from the population registry. Randomisation to screening and control groups (local control group) at the age of 55-64 years. Randomisation will be done within each year of age in the cohort born 1935-45 provided that screening will start in January 1999 *(appendix 1)*. Randomisation will be on household level to avoid separate group allocation for spouses. In addition to a randomised local control group, control groups will also be drawn in distant, epidemiologically suited areas (distant controls) where the risk of spontaneous endoscopic screening and colonoscopic contamination of the control groups may be less.

Estimated no. of individuals required
The sensitivity of flex-sig examination in identifying adenoma bearers is uncertain and dependent on age since the prevalence of proximal adenomas outside the reach of the flexible sigmoidoscope increases with increasing age. Unpublished data from a Norwegian autopsy material (3) showed that at age 50-59 years proximal adenomas could be found in 10% of individuals with no polyp in the rectum or sigmoid colon. A colonoscopic material of age 24-85 (mean age 64) gave support to this finding (7). Also, Norwegian studies indicate that 2/3 of adenomas stop growing or regress during an observation period of 2-3 years (4,5). Most estimates, apparently not considering this phenomenon of regression, conclude with an expected reduction of CRC incidence in the order of 35-40% in a population offered flex-sig screening. A Dutch publication (6) based on a Norwegian autopsy material (3) has given an estimated CRC lifetime reduction of 50% after flex-sig screening at the age of 60 years. In the small TPS-1 study the difference between screening and control groups was 2 vs/10 cases of CRC, i.e. 80% reduction, but then the threshold for a baseline colonoscopy was a finding of any kind of polyp (not only adenomas) at flex-sig.

Based on data from the Norwegian Cancer Registry, we expect an accumulated CRC incidence of 1% during a 5 years period (180 cases per 100,000 person years) in the 60-69 years age group. A CRC incidence reduction of 50% (from 1% to 0.5%) is considered to be a substantial beneficial effect. An effect of this magnitude is expected. Amongst those attending, endoscopic screening examination (with polypectomy) is believed to reduce the
incidence of CRC in the inspected segments of the bowel with nearly 100%. Since flex-sig (and not full colonoscopy) is being used as a screening modality the estimated 100% reduction has to be modified due to the possible development of proximal CRC without a screen-detected distal index adenoma. With an estimated attendance rate of 70%, the CRC incidence reduction is expected to be at least 50% for the screening group as a whole. The minimum no. required in the screening group is estimated to be 6250 individuals with an equally large control group. With 5% significance level this gives a statistical power of 90% in showing an effect on CRC morbidity and mortality. If endoscopic screening should be offered to a larger group, then the statistical power will be increased, thus making it possible to disclose a beneficial effect of screening even if the the estimated impact on CRC morbidity should be less or attendance rate poorer than expected, or if there should be a high degree of endoscopic contamination of the control groups. There is considerable uncertainty about these 3 factors, especially the degree of spontaneous screening of controls, and it is advisable to randomise a much higher number of individuals than the estimated minimum figure. With 14,000 individuals in the screening group we retain a test strength of 90% at a RR of 0.7 (30% reduction).

**Choice of screening areas**

Two separate areas have been chosen:
1. Oslo. As the capital of Norway it has a large population and it represents a high risk area with a yearly incidence of 55-60 per 100,000 (European standard population).
2. The county of Telemark: Telemark Central Hospital has practical experience in endoscopic population screening and obtained a very high attendance rate (81%) in the TPS-1 pilot study. The CRC risk in Telemark is equal to the average risk for Norway. Yearly incidence 45-50 per 100,000.

**Target population**

The target population is the general population at age 55-64 years. 10-15% of these individuals are expected to be able to document having at least one first degree relative with CRC, ovarian, endometrial or other potentially HNPCC-related cancer. These participants will be offered an evaluation at the regional genetics department *if they are interested in evaluation and information* about their individual CRC risk and possible benefit of surveillance. A proportion of these individuals and their relatives may in turn be referred by the genetics department to have a colonoscopic examination which should be performed by the screening team.

**Exclusion criteriae**

1. Patients with previous open colorectal surgery (resections, enterostomies)
2. Individuals in need of long lasting attention and nursing services (somatic or psychosocial reasons, mental retardation)
3. On-going cytotoxic treatment or radiotherapy for malignant disease
4. Severe chronic cardiac or lung disease (NYHA III-IV)
5. Patients with heart valve replacement on life long anticoagulant therapy
6. A coronary event during the last 3 months if having lead to hospitalisation
7. Cerebrovascular accident during the last 3 months
8. Resident abroad
**Procedures for individual invitations**

Ref. «randomisation» (appendix 1). Individuals in the screening group will receive a letter of invitation to have an appointment for either flex-sig alone or a combination of flex-sig and faecal tests. A reply form will accompany the letter of invitation asking about medication in use possibly relevant to the endoscopic examination and polypectomy. Kits for faecal tests will be included for this arm of the study. An expressed wish from invited individuals *not to participate* will terminate all future notification and reminding letters. A reminding letter will be sent to individuals who fail to respond to the initial letter of invitation. We also ask for phone number and which are the most convenient hours of contact if needed.

The letter of invitation will suggest a time for appointment and be mailed 4-5 weeks in advance with a request for those invited either to verify their willingness to attend, phone to have the appointment changed or reject the offer. A reminding letter will be mailed if no reply has been received within 3 weeks before the suggested time for an appointment.

**Screening method**

Participants will be offered a flexible sigmoidoscopic examination only or a combination of flex-sig and faecal test (FOBT test (FlexSure®) and a specimen to be kept frozen for future use). Faecal samples are to be collected at home before attending for sorbitol enema cleansing (Klyx®) and flex-sig examination. FlexSure® is expected to give a positivity rate of 2%. Ref. «logistics», appendix 4.

**On arrival**

Participants are to be received by nurse/nurse assistant who will explain the procedure and go through previous history (including possible exclusion criteriae, present and past medication and family history of cancer).

**Endoscopic screening examination**

A colonoscope is to be used for flexible sigmoidoscopy immediately after cleansing of the rectum and distal colon using a 240 ml Sorbitol enema (Klyx®). CO₂ insufflation is to be used to allow polypectomy to be performed in spite of inadequate bowel cleansing. In case of technical failure with the CO₂ system, polypectomy may be performed after insufflation and suction of air five times. (Ref. Addendum: Procedure for endoscopy). Those presenting a polyp ≥10 mm (most likely an adenoma) will be offered a full colonoscopic examination without prior biopsy or polypectomy at flex-sig. Polyps of this size will be removed at o colonoscopy. The flex-sig examination is to be video taped to allow a second opinion as part of quality assurance/supervision. Other findings than polyps are to be biopsied according to the judgement of the endoscopist.

«Baseline colonoscopy»

The threshold criteriae for colonoscopy after flex-sig are:
1) a histologically verified adenoma <10 mm in diameter at flex-sig.
2) any polyp ≥10 mm in diameter at flex-sig.

If coecum is not reached at colonoscopy, it is left to the endoscopist to decide if another attempt should be made to visualise the remaining colon. Relevant symptoms or a positive FOBT are considered as absolute indications for another attempt at colonoscopy or DCBE. All polyps are to be removed either at flex-sig or baseline colonoscopy In the case of positive FOBT but normal findings at colonoscopy, FOBT is to be repeated. If FOBT remains positive,
the participant is to be referred for gastroscopy and possibly other examinations at the local hospital. Doctors employed in the NORCCAP study will be offered to handle this on behalf of the local hospital.

Examinations added to flex-sig
In addition to flex-sig half the participants will be supplied with test kits for faecal sampling to be returned at attendance for flex-sig (FlexSure® and sample to be frozen for research purposes). The sigmoidoscopist is not to know the result of the FOBT until after completion of the flex-sig examination. A positive FOBT will qualify for a full colonoscopic examination. Those having polyps $\geq 10$ mm discovered at flex-sig will may be asked to participate in a study involving separate collection of stool samples prior to colonoscopy for analysis of genetic markers.

Tissue samples
Tissue samples from each polyp removed or submitted to biopsy will be placed in a separate vial of its own containing formalin. A small tissue sample from polypectomised polyps will be stored in liquid nitrogen for genetic molecular analysis, the remaining bulk of the polyp will be pinned to a piece of filter paper and immersed in formalin. Histopathological diagnosis is to be performed on paraffin imbedded material. Biopsies from normal appearing mucosa will be taken at baseline colonoscopy of adenoma bearers.

Faeces «bank»
This will store frozen faeces samples in 20 ml NUNC tubes and dried smears on «FlexSure® collection cards» (one card for each participant, each with windows for 3 samples). There will be only one NUNC stored sample for each participant. frozen samples will be tested for calprotectin (PhiCal® test kit), molecular markers and other test kits to be developed. NORCCAP owns all rights to future use of the faeces bank.

Active follow-up, i.e. involving contact with individual participants
Familial disposition for CRC
The project will expose a no. of individuals with possible familial disposition for CRC. The project must take care of this group and offer adequate medical genetic counselling.

Guidelines for endoscopic follow-up after flex-sig and baseline colonoscopy.
Only some individuals with adenoma discovered at screening endoscopy are qualified for polyp surveillance. The following guidelines are a concentrated version of the Norwegian guidelines for polyp surveillance (1). A prerequisite for these guidelines is that all polyps $\geq 5$ mm have been removed, that general health and life expectancy of the patient is reasonable, that there is no suspicion of FAP or HNPCC, no methodological flaws (e.g. inadequate endoscopic examination, incomplete polypectomy, inadequate histopathology report) and interval symptoms must be given credit and an evaluation independent of the surveillance program. Individuals with HNPCC and FAP qualifies for follow-up recommended for these groups within the National Health Service.

The following are to be recommended colonoscopic follow-up after 5 years:
- Individuals with 3 or more adenomas removed
- Individuals with only biopsy of adenoma (i.e. inadequate removal)
- Individuals having had adenoma(s) removed and having a history of gynaecological cancer
- Individuals having had adenoma(s) removed and having a first degree relative with CRC

The following are to be recommended colonoscopic follow-up after 10 years on the condition that the above mentioned criteria for 5-yearly controls have not been met and there has been:
- Villous components and < 3 adenomas
- Severe dysplasia and < 3 adenomas. If there is any doubt about adequate resection or possibly presence of a carcinoma, then this patient is to be regarded as «patient with carcinoma» and treated accordingly.
- 1-2 adequately removed adenomas ≥ 10 mm in diameter.

No colonoscopic follow-up is to be recommended if the criteria for 5 and 10 year controls are not met and there is:
- 1-2 resected, small (<10 mm) adenomas
- Resected hyperplastic polyps (± 1-2 small adenomas)
- No known adenomas left in situ, adenoma remnants or remaining polyps with unknown histology.

If these guidelines had been applied in the TPS-1 study, then flex-sig screening of the general population at age 50-59 would result in 5 or 10 year follow-ups for 9 individuals (3%) of 324 attending for screening and for 65 (14%) of 451 screened at 63-75 years of age.

**Passive follow-up, i.e. register based follow-up**
CRC morbidity and mortality will be followed through registries at 5, 10 and 15 years. The same applies for overall mortality with specification of cause of death. Spontaneous screening activity will be looked into through a central registry of pathology reports (polypectomy activity), endoscopic activity registered in local endoscopy labs. (split into defined age groups in screening and control populations).

### Information and collaboration

#### Pathology labs
All pathology labs serving populations recruiting screening or control groups should consent to report findings of all colorectal polyps to the National Cancer Registry.

#### Gastroenterology labs
Public and private endoscopy centres must agree to report their colonoscopic and flex-sig activity each year, again to provide an estimate of spontaneous endoscopic screening activity.

#### GPs in the screening area
All GPs will be informed about the project and the importance of endoscopic screening to be kept within the framework of a controlled study. Also, they will be given advice on how to handle patients who wish to participate but who have not been invited.

#### Mass media
A press conference will be held in the screening area immediately before the start of the study and also later during the study. The extent of this must be a compromise between the need to maintain a high attendance rate and at the same time avoid to encourage a high degree of spontaneous screening and endoscopic contamination of control groups.

**Individuals in the screening group**
Information about the study will be part of the written invitation to participate.

**Individuals in the control group**
Controls will not be informed about being enrolled as controls.

## Evaluation

### Continuous evaluation

Apart from evaluation of «primary aims» there must be continuous evaluation of:

- **Attendance**: The project management must continuously evaluate the need for information through mass media. This includes a balance between a need to maintain a high attendance rate and an unintended influence on spontaneous endoscopic screening in the population.
- **Quality assurance**: For each participating centre and each endoscopist a record will be made of the no. of polyps discovered, complications, level reached at endoscopy, the use of sedation etc. The reported experience of each participant will be followed continuously.

### Ownership of data

Several substudies are expected to be added to the «core» study. These are to be regarded as parts of the NORCCAP study and subject to decisions made by the governing board and project management. The core study through the project leader must have access to the use of all data that may be obtained to maintain an overall view for management and quality assurance and secure an adequate volume of data in future publications. For each substudy to be included it must be specified in its protocol and application for inclusion which data (if any) there may be reasons for not allowing NORCCAP to use.

## Primary aim no.1, CRC reduction

Primary aim 1: «Evaluate the effect on CRC mortality and morbidity by screen detection of CRC and removal of precursor lesions (polypectomy of adenomatous polyps). *(Problem 1)*

**Hypothesis**: a) Detection and removal of adenomas will prevent CRC  
b) Detection of asymptomatic/early CRC will reduce CRC mortality

### Material:

<table>
<thead>
<tr>
<th></th>
<th>Offered screening</th>
<th>Local controls</th>
<th>Distant controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oslo (high risk)</td>
<td>7000</td>
<td>35000</td>
<td>7000 (Bergen)</td>
</tr>
<tr>
<td>Telemark (intermediate risk)</td>
<td>7000</td>
<td>7000</td>
<td>7000 (Vest-Agder)</td>
</tr>
<tr>
<td>Total</td>
<td>14000</td>
<td>42000</td>
<td>14000</td>
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**Method**: Flex-sig to be offered to half of the screening group in each screening area, flex-sig combined with faecal tests to the other half. The test groups in each area will primarily be compared with local controls.

**Test strength**: This has been dealt with in a previous chapter of this protocol. Based on an estimated 50% reduction in CRC morbidity and mortality the minimum no. of individuals that will have to be offered flex-sig screening will be 6250. This will give a test strength of 90%
for detection of a reduced CRC morbidity and mortality with a 5% significance level. This will be reduced if the reduction in CRC should prove to be less than anticipated, or if the attendance rate should be lower than expected or if there will be a high degree of colonoscopic contamination (spontaneous endoscopic screening) in the control groups. There is much uncertainty concerning these three factors, and we have therefore included a considerably higher no. of individuals than the required minimum. A test strength of 90% will be maintained with 14000 included in the screening group in spite of a RR of 0.70 (30% reduction instead of 50%).

Responsible: Project coordinator (Geir Hoff), NN in Oslo (experienced endoscopist), NN in Telemark (experienced endoscopist)

Primary aim no. 2, addition of faecal tests

Primary aim 2: «Evaluation of cost/effectiveness of screening for CRC and *significant, benign lesions using flex-sig only compared to flex-sig in combination with faecal tests» (Problem 2).

*Individual with significant benign lesion is defined as person with adenoma ≥ 10 mm in diameter, with villous components in adenoma, with severe dysplasia in adenoma or bearer of 3 or more adenomas.

Hypothesis: Screening for significant colorectal lesions by means of a combination of flex-sig and faecal tests is more cost/effective than the application of only one of these screening modalities.

Questions:
In this cost/effectiveness analysis it will also be possible to evaluate the gain of baseline colonoscopy on all adenoma bearers.

■ Should the threshold for baseline colonoscopy have been higher/lower? (Ref. the UK study where only bearers of significant lesions are qualified for a baseline colonoscopy.

■ Sensitivity and specificity of faecal tests for detection of proximal lesions will be estimated and compared with findings at «gold standard» baseline colonoscopy after finding of distal adenomas.

■ The gain from adding faecal tests to flex-sig will be evaluated and weighed against possible loss in attendance rate.

■ The gain (finding of proximal significant lesions) will be evaluated for each of the added faecal tests.

Material:

<table>
<thead>
<tr>
<th>Offered flex-sig</th>
<th>Offered flex-sig and faecal tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>7000</td>
<td>7000</td>
</tr>
</tbody>
</table>

Method:
1. An immunochemical test for human blood in faeces (FlexSure® OBT) is the most likely FOBT to be used. It is more sensitive than Hemoccult II® and more specific for bleeding from the distal GI tract. It is therefore not expected to have more than a 2% positivity rate, i.e. about the same as Hemoccult II®. The test can be read bedside within 5 minutes.
2. Individuals with a positive FlexSure® OBT are to be offered a full colonoscopy regardless of findings at flex-sig. FOBT is to be repeated if colonoscopy reveals no pathology before considering referral for further examination at the local hospital (gastroscopy etc.). A doctor employed in NORCCAP may act on behalf of the local hospital if the local gastroenterologist has a preference for this.

3. Results of analyses on samples from the faeces bank that may be revealed at a later date as part of test kit research shall not trigger any action, advice or contact towards the individual participant.

4. Flex-sig to half of the participants in each screening area and flex-sig combined with FOBT and faecal sampling for a faeces «bank» to the other half.

5. Dried frozen faecal samples (remainder of sample on FlexSure® OBT collection card) are to be stored for future testing of test kits to be developed.

6. Individuals with polyps ≥ 10 mm detected at flex-sig (expected to be 490 individuals) will have a baseline colonoscopy without prior polypectomy or biopsy. These individuals may be asked to supply a separate sample of faeces prior to colonoscopy for analysis of faecal molecular tumor markers.

**Expected gain regarding significant lesions:**

<table>
<thead>
<tr>
<th></th>
<th>Combined Flex-sig and FlexSure</th>
<th>Flex-sig only: Signif. lesion</th>
<th>Non-signif. lesion</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Signif. lesion</td>
<td>5% of 4900</td>
<td>5% of 4900</td>
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<td>245</td>
</tr>
<tr>
<td>Non-signif. adenoma</td>
<td>*0.5% of 4900</td>
<td>**15% of 4900</td>
<td>24</td>
<td>735</td>
</tr>
<tr>
<td>Total</td>
<td>269</td>
<td>735</td>
<td>1004</td>
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</tbody>
</table>

*70% attendance of 7000 offered either flex-sig alone or in combination with faecal tests give 4900 screenees in each arm of this part of the study. In the combined arm up to 20% will have proximal neoplastic lesions without distal index lesion (i.e. «missed cases» at flex-sig). 5% of these 20% (i.e. 1% of all 4900=49) will have a significant lesion proximally without a distal index lesion to trigger an offer of baseline colonoscopy. Since most of these isolated proximal significant lesion after all will be benign adenomas, one can not expect that more than 50% of them will be able to test positive for a FOBT (unfortunately, there are no hard data on this). With discovery of significant lesion as a defined aim, there will not be 1%, but 0.5%(=24 individuals) that may be expected to benefit from faecal tests being added to flex-sig. A 95% confidence interval for additional findings due to the use of FOBT is expected to have a span of 1-2%. If the added benefit should be 0.024 (as estimated), then a 95% CI will be 0.016-0.032).

** The expected total no of adenomas discovered at flex-sig is 20%,- 5% significant adenomas and 15% non-significant adenomas (i.e. bearers of small adenomas without severe dysplasia or villous components and no more than 2 adenomas)

◊This will be the expected no. of baseline colonoscopies generated from findings at flex-sig screening.
Primary aim no. 3, influence on routine colonoscopies

1. Primary aim: «To evaluate to which extent (and in which direction) the study may influence overall endoscopic activity in the general population in the screening areas and in areas where controlled screening is not established (Problem 3)».

Hypothesis:

a) Organised endoscopic screening will give a temporary increase in referrals for routine colonoscopy during the first months of the screening project. Thereafter there will be a reduction in referrals for the screened age group 55-64 years old for as long as the screening project will last.

b) Organised endoscopic screening activity will give a higher detection rate and polypectomy frequency of potential CRC precursor lesions per total no. of colonoscopies compared with routine clinical colonoscopic activity.

Method:

This part of the NORCCAP study is primarily an evaluation of part of the health service that serves individuals with bowel complaints in the screening and control populations. The quality of this will be completely dependent on a close collaboration with the National Health Insurance (Rikstrygdeverket) and insight into their files registering the use of various health services for defined age cohorts in the screening and control populations (not only the 55-64 year old cohorts). If such insight into files should prove to be impossible, we will have to depend on reports from endoscopy labs and radiology departments.

Material:

Yearly reports split into age cohorts 40-49 years old, 50-54, 55-59, 60-64, 65-69 and ≥ 70 years old in the screening and distant control areas for the period 1995-2005 (i.e. before and after the start of the project). These reports should contain information on:

- The no. of colonoscopies, flex-sigs and rigid sigmoidoscopies performed
- The no. of DCBE performed
- The no. and types of lesions discovered and removed in routine clinical work
- The no. of removed/biopsied colorectal lesions in organised screening (from NORCCAP files)

Literature

2. Winawer SJ, Fletcher RH, Miller et al. Colorectal Screening: Clinical Guidelines and
Appendices

Appendix 1

Randomisation within relevant age cohorts

The following choice of cohorts is on the express condition that screening activity will start in January 1999 and that it will take 2 screening teams 2 years to examine 70% of 14,000 invited to participate (3500 invited per year per team).

Telemark
*1999, first year of project:
Intervention: ½ of each cohort born 1935(age 64), 1936(63), 1938(61), 1940(59), 1942(57), 1944(55)
Control 1: ½ of each cohort born 1935, 1936, 1938, 1940, 1942, 1944
Control 2: As for control 1 (above), but from epidemiologically suited area other than the screening county.

2000, second year of project:
Intervention: ½ of each cohort born 1937(63),1939(61),1941(59) ,1943(57), 1945(55)
Control 1 (local): ½ of each cohort born 1937, 1939,1941,1943,1945
Control 2 (distant): As for control 1 (above), but from epidemiologically suited area other than the screening county.

Oslo
*1999, first year of project:
Intervention:1/6 of each cohort born 1935(64),1936(63),1938(61),1940(59),1942(57), 1944(55)
Control 1 (local): 5/6 of each cohort born 1935, 1936, 1938, 1940, 1942, 1944
Control 2 (distant): As for control 1 (above), but from epidemiologically suited area other than the screening county.

2000, second year of project:
Intervention: 1/6 of each cohort born 1937(63),1939(61),1941(59) ,1943(57), 1945(55)
Control 1 (local): 5/6 of each cohort born 1937, 1939,1941,1943,1945
Control 2 (distant): As for control 1 (above), but from epidemiologically suited area other than the screening county.

* Choosing 10 birth cohorts for screening to be spread over 2 years of screening will give screening examination at age 63,61,59, 57 and 55 years in both years of the project. Age group 64 year old will, however, only be examined in the first year. Thus, there will be 6 age cohorts examined the first year and 5 the second year of the study (see table below for explanation). Experience from TPS-1 showed that older age groups had a poorer attendance rate than younger ones.
**NORCCAP, age for relevant birth cohorts (born 1935-45) in 1999 and 2000**

<table>
<thead>
<tr>
<th>Year 1999</th>
<th>Year 2000</th>
</tr>
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<tbody>
<tr>
<td>1935 (64)*</td>
<td>(65)</td>
</tr>
<tr>
<td>1936 (63)</td>
<td>(64)</td>
</tr>
<tr>
<td>1937 (62)</td>
<td>(63)</td>
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<td>1938 (61)</td>
<td>(62)</td>
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<td>1939 (60)</td>
<td>(61)</td>
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<td>1940 (59)</td>
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<td>1941 (58)</td>
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<td>1942 (57)</td>
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<td>1943 (56)</td>
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<td>1944 (55)</td>
<td>(56)</td>
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<tr>
<td>1945 (54)</td>
<td>(55)</td>
</tr>
</tbody>
</table>

(* Age at time of screening examination in bold letters)

**No. of birth cohorts** offered screening **at age:**

| 1 | 64 |
| 2 | 63 |
| 2 | 61 |
| 2 | 59 |
| 2 | 57 |
| 2 | 55 |
Appendix 2.

**Expected no. of endoscopic examinations**

Estimated workload by inviting 3500 individuals age 55-64 years of age for endoscopic screening examination:

3500 per year invited, standard screening team

- 2450 attending (70%)

Up to 2% (49)+50 1st degree relatives ≈100 referred from regional genetics department for colonoscopy

Up to 10% (245) wishing contact w/ regional genetics department

2450 for primary flex-sig. ± FOBT (capacity 2500/year)

490 with adenoma(s) at flex-sig. (20%)
60 w/pos. FOBT (5% out of 1225)

Total colonoscopies: 100+490+60=650 (capacity 1400/year)
**Appendix 3**

**Logistics at attendance for flex-sig**

Received by nurse who takes care of:
- Faecal samples (FOBT revealed after endoscopy)
- Case history form (incl. exclusion criteriae)
- Family history form.

Explain the procedure for the examination.

- Case history form checked by doctor before endoscopy

- 240 ml Klyx® (enema) before flex-sig

- Flex-sig (with care) during CO₂ insufflation

  - Polyp ≥10mm
  - Polyp <10 mm
  - No polyp

- Asked to submit sample of faeces for molecular genetic marker analysis

- Histologically verified adenoma

- Polypektomy/ biopsi

- hyperplastic polyp or mucosal tag

- Coloscopy with removal of all polyps

- After completed flex-sig evaluation by medical geneticist may be offered if the family history is suggestive any familial cancer syndromes

- Pos. FOBT

- Neg. FOBT

No endoscopy if any criteriae for exclusion
The logistics of 2 years with NORCCAP

Appendix 4 (Hatched boxes mean «no further contact to be made»)

Random invitation within cohorts born 1935-45. Oslo+Telemark: 14,000 invited and randomised 1:1 to flex-sig alone or flex-sig + FOBT

Randomised controls from cohorts in Oslo+Telemark born 1935-45 (local controls)

Cohorts born 1935-45, from matched counties constitute distant controls (Bergen and Vest-Agder)

To be followed passively (registry information) for CRC at 5, 10 and 15 years. Colonoscopic «pollution» to be followed through files of the National Insurance (Rikstrygdeverket).

- **Reply yes (65%)**
- **No reply (30%)**
- **Reply no (5%)**

Mail one reminding letter

- **Reply yes (5%)**

70% participation expected

Flex-sig after cleansing w/ 240 ml Klyx®. Use CO₂ insufflation. Polypectomy/biopsies of polyps < 10 mm

Up to 10% offered contact with regional dep. of medical genetics

- **Colonoscopy if adenoma found at flex-sig (20%)**
- **No adenomas and no referral from genetics dep. (70-80%)**

Referred to colonoscopy by regional genetics dep. (2% + 50 (?) relatives)
Appendix 5

The volume of histopathology

Estimated no of participants with polyps requiring histopathological diagnosis at each screening center each year. 70% attendance rate for flex-sig out of 3500 invited per center per year gives 2470 individuals attending. 2450=100% in the percentual table below. Polypectomy is to be performed whenever possible, in practice if the polyp measures ≥4 mm in diameter. Biopsy specimens will suffice for smaller polyps. This gives:

- 90% (2205) diagnostic flex-sigs,
- 10% (245) therapeutic flex-sigs,
- 3.5% (86) diagnostic colonoscopies,

5% (123) have polyps ≥10 mm. This qualifies for colonoscopy without obtaining tissue specimen at flex-sig. Polypectomy in all 5% at colonoscopy.

30% (735) have polyps at flex-sig.

10% (245) polypectomised at flex-sig.

3% (74) have no adenoma. No follow-up.

15% (368) to be biopsied at flex-sig.

5% (123) have polyps ≥10 mm. This qualifies for colonoscopy without obtaining tissue specimen at flex-sig. Polypectomy in all 5% at colonoscopy.

7% (172) have adenoma and will go to colonoscopy

3.5% (86) will have new polyps discovered that require polypectomy at colonoscopy

5% (123) have adenoma and will have a colonoscopy. All polyps to be removed.

10% (245) have no adenoma and will not have any follow-up
Letter of invitation
(Norwegian only)

Reply form
(Norwegian only)

Reminding letter
(Norwegian only)

Case history form
(Norwegian only)

Family history form
(Norwegian only)

Procedure for endoscopy
(Norwegian only)

Information to participants after flex-sig
(Norwegian only)

Post screening reply form (the «day after» form)
(Norwegian only)