SCREESCO – Screening of Swedish Colons

Study Protocol Version 3.0

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Summary

Colorectal cancer (CRC) is a major cause of death in Sweden. There are approximately 6000 new cases each year in Sweden and the disease specific mortality is more than 40%. The risk is about 1% to develop CRC between 60-70 years of age, making 60-year-olds a suitable target population for colorectal cancer screening.

The Swedish Ministry of Health and Social affairs has proposed a national study on the efficiency of colorectal cancer screening in the Swedish population regarding mortality, but also what screening method to be used. Thirteen participating counties of Sweden now fund the study to be launched in 2014.

Individuals 60 years of age will be randomized from the population register and invited to screening by mail. 31,140 individuals will be invited to primary colonoscopy and 60,300 individuals will be invited to high-sensitive FIT (OC Sensor®) with approximately 10% positivity rate and, if positive, to a subsequent follow-up colonoscopy. When test negative a second round of FIT will be asked for in two years. In total 186,840 randomized individuals will not be invited to screening serve as controls and will be followed in the Swedish Cancer Register. The inclusion period is set to five years (five years including the second round of FIT) generating approximately 17,000 colonoscopies at a compliance rate of 35% in the colonoscopy arm and 50% in the FIT arm.

Follow-up time is set to 15 years with the primary endpoint disease specific mortality and colorectal cancer incidence. Secondary outcomes, by others, to be studied are in short quality assurance variables of colonoscopy, participants and non-participants experiences of the invitation and the screening procedure, health economy measures of the CRC-screening study and when implemented in clinical care.

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1. Background

1.1 Colorectal cancer and screening

The primary purpose of cancer screening is to reduce mortality from the disease in the population by finding the cancer at an early and treatable stage. The cancer has to be an important health problem to be a suitable target for screening. With approximately 6 000 new cases each year in Sweden (1), colorectal cancer (CRC) is the third most common cancer in Sweden (after prostate- and breast cancer) and, hence, a relatively common disease, but it is also a major cause of death. There is a 1% risk to develop CRC between the ages 60-75 years, and the five-year survival rate is close to 60%. The prognosis is related to if the cancer is detected at an early or late stage of the disease. When detected at an early stage, there is a 90% five-year survival, as compared to only a 10% five-year survival if the cancer at detected at a late stage.

CRC is usually detected clinically by patient symptoms, either an alteration in bowel habits due to obstruction of the lumen, visual blood in the stool or symptoms due to anemia caused by a bleeding from the tumor. Both larger precursor stages – the adenomatous polyp (2, 3) – and cancers bleed and could be detected by sensitive methods to analyze blood in the stool. All patients diagnosed with colorectal cancer need treatment, but there is a significant difference in suffers and costs depending on the stage the disease at diagnosis. With screening early stages of the disease will be found before they are clinically detected.

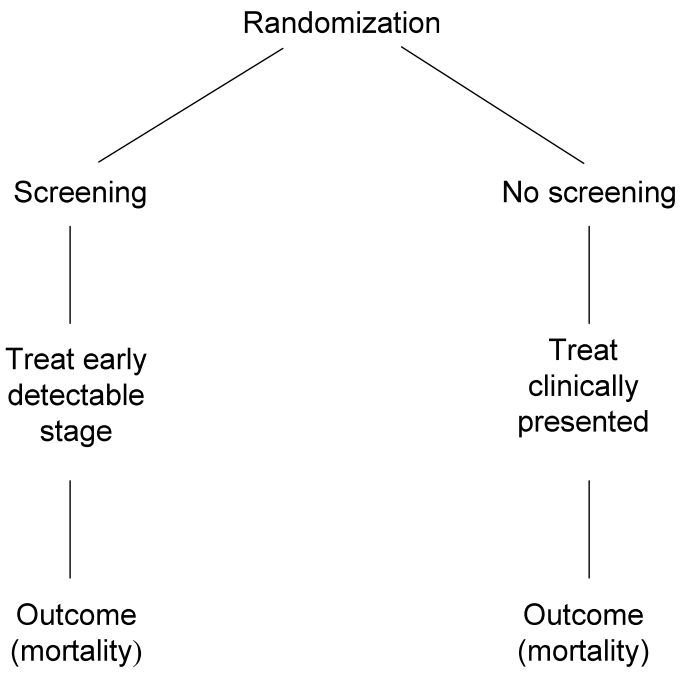
Removal of adenomatous polyps (adenomas) has a protective effect against colorectal cancer development (4, 5, 6) and, consequentially, a colorectal cancer screening program also might have the potential of decreasing the future incidence of the disease.

1.2 Evaluation of a screening program

1.2.1 Effectiveness

The effectiveness of a screening program is the ability of the program to reduce the disease specific mortality. Survival is not a valid measure of effectiveness because of the possibilities of bias; selection bias (when screened subjects and non-screened controls represent different populations), lead time bias (earlier diagnosis in screen-detected cancers adds time to the total survival time) and length biased sampling (screen-detected tumors often grow slowly and might be less malignant).

The most valid measure of effectiveness in screening is a lower mortality in the screened group, as compared to the non-screened group evaluated in a randomized controlled trial (RCT):



1.2.2 The screening test

A large majority of individuals in the general population using the screening test offered will not have colorectal cancer. Therefore the test must be free from unwanted side effects, inexpensive, but also simple to take and easy to interpret (7). Furthermore, a high sensitivity (to limit the number of missed cancers) and specificity (to limit the number of incorrect diagnosed cancers), is a prerequisite for a screening test to be used in a program of the average risk population.

There are a number of screening tests and methods to examine the colorectum in order to find CRC and/or adenomatous polyps:

Indirect tests: The most commonly used screening test has been the guaiac based fecal occult blood test (FOBT) (Hemoccult®). Four larger RCTs have demonstrated a 16% decreased in CRC mortality with the test in screening (8, 9, 10, 11). The degree of mortality reduction with Hemoccult® depends on the compliance with the test and the dietary restrictions, the sensitivity of the test, the screening frequency (annual or biennial), the number of screening rounds the subjects participate in and, also, the compliance with the diagnostic follow-up colonoscopy after a positive test. More advanced fecal immunological tests (FITs) with higher sensitivity, but only a marginally increase in the false positive rate (specificity), are now available. FIT demonstrates presence of human blood only, as opposed to the guaiac test that also can be positive due to animal hemoglobin. Moreover, no dietary restrictions are needed with FIT.

Direct tests: The main advantages with endoscopy (*e.g.* colonoscopy and sigmoidoscopy) are the direct visualization of the colorectum and the possibility of obtaining tissue samples from suspected cancer lesions for histopathology and/or removing adenomatous polyps during the procedure. The bowel can be examined with sigmoidoscopy and a subsequent colonoscopy in case of

pathological finding within the reach of the sigmoidoscope (approximately 60 cm) or with a complete colonoscopy as primary test (when 1/3 of tumors will appear in the right part of the colon). Recently, three randomized controlled trials with sigmoidoscopy as the primary screening test have demonstrated both a reduced disease specific mortality of around 30%, but also a reduced incidence of CRC of as much as 40% (12, 13, 14).

Up to now, there are no larger randomized controlled studies of the average risk population published demonstrating a disease specific mortality reduction with colonoscopy as the primary screening test.

1.2.3 Compliance

The proportion of individuals offered a screening test who take the test is referred to as compliance (7). The compliance to a screening program is a major determinant of the program's effectiveness and there has to be a rigid organization with a call- recall system and quality assurance in a screening program to be effective (15).

Instead of number needed to treat (NNT) used to estimate the efficacy in interventional RCTs evaluating medication, the number needed to screen (NNS) is used in the evaluation of RCTs of screening. The NNS is the number of individuals who need to be invited (offered) screening to prevent one death (intention-to-screen). The results then reflect the efficacy of the screening program to reduce mortality among those *invited* to screening. With NNS there is often an underestimation of the efficacy of the screening test in those people who actually participate – are being screened. The NNS for most screening programs are usually much higher than the number of people who have to participate to prevent one death (16). It is only the participants that can contribute to the mortality reduction achieved by the screening program and with low compliance the number of deaths prevented will be few, and consequently the NNS will be large (16). Therefore, a high participation rate in a screening program is important to be able to evaluate its effectiveness on mortality.

1.2.4 Cost-effectiveness

There are a large variety of variables involved when measuring the cost-effectiveness of a colorectal cancer screening program and focus cannot only be on the eventual incidence and mortality reduction of the disease. Firstly, one has to make assumptions about the duration of the early, asymptomatic and curable stage of the disease. Secondly, one has to estimate the effectiveness and negative effects of the screening procedure, such as morbidity due to complications and costs. A low compliance in a screening program will both effect the incidence and mortality reduction achieved and the cost-effectiveness of the program.

1.3 Challenges in colorectal cancer screening

1.3.1 Colonoscopy quality assurance

There are some outstanding challenges in implementing colorectal cancer screening for the average risk population. One important issue is the quality assurance of the endoscopic examinations and the follow-up of eventual findings. If the quality of the examinations is not excellent, but with frequent practical mistakes and neglect to find adenomas and or cancers, the positive effect of the screening procedure for that particular individual and of the program as a whole is both diminished and unethical (17, 18, 19, 20, 21).

Colonoscopy resources and quality will be a key issue in the present study. Currently in Sweden, about 65 000 procedures are carried out outside the Stockholm area yearly, while approximately 30 000 are carried out in Stockholm. A crude estimate is that a future national screening program will need a substantial number of colonoscopies, and, thus, much work is needed to both increase the number of colonoscopies performed nationally and also increase and secure the quality of the investigations.

Adenomatous polyps should be removed in order to prevent the occurrence of CRC. The removal of adenomas is a sometimes difficult and dangerous procedure, since it may cause bleeding and perforation of the bowel wall. It is important that the adenoma is completely removed and correctly diagnosed. Thus, both a skillful endoscopists and high-quality histopathology are extremely important.

1.3.2 Lack of pathologists

Another problem when implementing a screening program is the created increased burden for pathologists. There is a need for standardization of the use of the diagnostic criteria and the possibility to have a group of pathologists to evaluate the sections. In order to do so, it would be of great advantage if the histological sections could be stained and digitally processed and evaluated electronically.

1.3.3 Compliance and emotional effects

Another important factor, in need of further studies, is the actual adherence rate or compliance discussed above and the emotional effects of the inclusion of healthy persons from the general population in colorectal cancer screening (22, 23, 24, 25).

1.4 Colorectal cancer screening in Sweden

The National Board of Health and Welfare has not been recommending CRC screening due to lack of experiences of screening in routine health care and refer CRC screening to the Research and Development list waiting for studies outside Sweden to generate results. Based on the results from the four RCTs with a net CRC-mortality reduction of 16% (8, 9, 10, 11) the Council of the European Union in 2003 recommended CRC-screening with guaiac-based fecal occult blood test (FOBT) in the average risk population aged 55-74 years old. The recommendations have recently been updated in the European Guidelines of

Quality Assurance in CRC-screening (26) and as a result, national CRC-screening programs with guaiac-based FOBT have started around Europe, *e.g.* United Kingdom, Finland, France, Italy and shortly in Denmark and Norway. In Sweden, only the counties of Stockholm/Gotland have an organized colorectal cancer screening program of the 60-69 years old general population using guaiac-based FOBT as the primary screening test.

1.5 A call for a population-based Swedish CRC-screening study

The Swedish minister of Health and Social affairs, Göran Hägglund, funded a task force in 2011 in order to design a study of the effectiveness of colorectal cancer screening of the average risk population of Sweden. The Swedish Association of Local Authorities and Regions (SALAR) organized the task force in cooperation with the newly started Regional Cancer Centers of Sweden. A committee was formed with one committee member from each national center and professor Rolf Hultcrantz, the Principal Investigator of the present study, has been the chairman of the committee. The present study was designed based on what data was needed to get better outcome of colorectal cancer screening. The study design was submitted in January 2012 to the Ministry of Health and Social affairs and, since then, a thorough work has been carried out in order to get all counties in Sweden to fund the study. Eighteen counties in Sweden achieved the funding in March 2013 covering the actual screening procedures. The counties of Stockholm and Gotland cannot take part in the study due to the already implemented CRC-screening program with Hemoccult®.

2. Study aims

2.1 Primary endpoints

1. To investigate if colorectal cancer screening has an effect on the mortality from colorectal cancer in the Swedish population.
2. To investigate if colorectal cancer screening has an effect on the incidence of colorectal cancer in the Swedish population.
3. To investigate what method should be used in Sweden regarding the effect according to 1 and 2.

2.2 Secondary endpoints

- To study associations of DNA in blood with findings at colonoscopy

- To study the FIT microbiome profile in CRC patients and controls to identify microbial biomarkers that are associated with colonoscopy findings

3. Material and Methods

3.1 Study population

In total 278,280 individuals, residents of Sweden will be randomized from the population register maintained by Swedish tax agency (Skatteverket) (27). The randomized individuals will turn 60-years old the calendar year of randomization. 31,140 individuals will be invited to a primary screening colonoscopy, 60,300 individuals will be invited to high-sensitive FIT and, if positive, to a subsequent colonoscopy and 186,840 persons will serve as controls (11. Figure 1 and 2). The inclusion period is set to three years with a repeated test after two years in the FIT arm.

3.1.1 Inclusion criteria

All individuals 60 years old and living in Sweden and randomized and identified through the Register of the total population.

3.1.2 Exclusion criteria

Residents of the counties of Stockholm and Gotland, individuals with a diagnosis of colorectal cancer and/or anal cancer in the continuous updated cancer registers run by the local Regional Cancer Centers, individuals randomized to be included in the ongoing NordICC-trial (28) and individuals living in Västernorrland County – the only county (region) in Sweden except for Stockholm/Gotland not participating in the study.

3.1.3 Randomization

From the Swedish tax agency three sets of individuals by random from the population register (27) will be asked for, approximately 67 000 individuals each born in 1954, 1955 and 1956. The randomization process will then be performed at the Head secretariat in the beginning of 2014, 2015 and 2016 and in the colonoscopy arm 2017, 2018):

- 6,700 individuals born 1954, 1955, 1956 will randomized, by county (region) in proportion to the population, to be invited to primary colonoscopy (3.2.1 Colonoscopy) and 5,250 born in 1957 and1958.
- Three individuals per primary colonoscopy individual will be matched according to year of birth, gender and county (region) of residence and invited to FIT (3.2.2 FIT).
- Six individuals per primary colonoscopy individual will be matched according to year of birth, gender and county (region) of residence and serve as controls.

3.2 Invitation procedures

3.2.1 Colonoscopy arm

All individuals randomized to the colonoscopy arm will receive an invitation letter by regular mail including the brochure with information about the incentives of the study. The invitee will be informed that they shortly by mail will receive an appointment for colonoscopy within 8 weeks, sent from the endoscopy clinic in their area of residency.

3.2.2 FIT arm
All individuals randomized to FIT as primary screening test will by regular mail receive an invitation to participate in the study. The invitation includes a brochure with information about the incentives of the study and the need for a follow-up colonoscopy in case of a positive test. The invitation contains a FIT-kit for two separate test samples and instructions on how to take the test. With the invitation is a pre-paid return-envelope for submitting the two tests together directly to the analyzing laboratory. The returned FIT will be stored in Bio bank after analysis.

3.2.3 Controls
The individuals randomized to the control arm will not be contacted and informed about participation as controls in the study. If any individuals would contact the Head secretariat to ask about if they are controls, information will be given.

3.2.4 Undelivered invitations
All invitations will be sent by the Regional Cancer Center, Uppsala/Örebro, where the Head secretariat of SCREESCO is located. Undelivered and returned invitations will be sent out a second time. Since allocation to intervention is by random, we believe the number of undelivered invitations will be approximately the same in both intervention arms.

3.3 Interventions

3.3.1 Colonoscopy arm
A primary screening colonoscopy will be carried out once and with an estimated adherence of about 35%, approximately 10,000 colonoscopies will be carried out. The examination will be performed with or without sedation following a standard bowel cleaning preparation. The endoscopy centers will be accredited and the performance of the examiners will be investigated. All requirements will follow the European guidelines (26). If the colonoscopy is not complete the participant is offered to be examined again with colonoscopy or CT colonoscopy.

3.3.2. Primary colonoscopy appointment
With the colonoscopy appointment (within 8 weeks) sent after the initial invitation letter are instructions to call and confirm the appointment, following the same procedure as the participants with a positive FIT (3.3.9 Bowel preparation for follow-up colonoscopy). A difference, though, is that in the group randomized to primary colonoscopy screening, a reminder will be sent out from the CIS-S if no confirmation of the colonoscopy appointment has been performed within 8 weeks. The endoscopy site will then send a new colonoscopy appointment (within 8 weeks) to be confirmed as previously described.

3.3.3 FIT arm and the positivity rate
A high-sensitive FIT (OC-Sensor®) with about 10% positivity rate will be used. The screening method of FIT is well known and established with an adjustable positivity rate from about 2% up to almost 10% (with an opposed effect on

specificity). Almost all individuals have traces of blood and hereby hemoglobin in their feces, why the level of sensitivity of the test is an important balance of not missing any lesions, but at the same time minimizing the total number of false positive tests. In SCREESCO people are regarded as having a positive test result if at least one out of the two test samples are positive, i.e. above the set cut off level of 50 µg Hb/L (50 ng Hb/mL). With the used OC-Sensor® 1 µg Hb/L buffer = 0,2 µg Hb/g feces, *i.e.* 50 µg Hb/L buffer equals 10 µg Hb/g feces.

3.3.4 Two rounds of FIT

We plan two rounds of FIT – one the first year and one the third year. All individuals randomized to the FIT-arm will have new test-kits sent home after two years, regardless of compliance with the invitation to the first round. Previous studies have been performed with FOBT every second year for ten years and we will follow the findings and perform interim analyses and suggest that further rounds of FIT are carried out if the scientific committee deems it necessary. Two tests per round will be asked for without dietary restrictions. If 50% of the invitees comply and send their FIT test to the laboratory (experiences from the ongoing screening program in the counties of Stockholm and Gotland) and 10% are positive, this will generate approximately 1,200 colonoscopies for each year in the FIT-arm except for year four when the number of generated colonoscopies is estimated to 2,400 due to the second round re-testing.

3.3.5 Information of FIT-result

All participating individuals in the FIT-arm will be informed about their test result by mail within 4 weeks after the test was sent in. People with a negative test result will in the same mail be informed that a new test-kit will be sent after two years. People with positive test will be informed by mail that they within one week will get a colonoscopy appointment (within 4 weeks instead of 8 weeks as in primary endoscopy arm [3.3.1] due to positive test) by mail sent by the endoscopy site in their area of residency.

3.3.6 Reminder and default returned FIT

People with no tests sent in will get a reminder by mail after 8 weeks and with instructions to call to receive new test kits if they are missing. People with default FITs sent in will receive new test kits with instructions.

3.3.7 FIT returned after 6 months

FIT returned after 6 months will be scientifically handled as non-compliers. The test results are expected un-valid due to expiring date of the test.

3.3.8 Follow-up colonoscopy appointment of individuals with positive FIT

The endoscopy site in the participants geographical area of residency will electronically within the Central IT-Support System – Study (CIS-S) (6. Data management) simultaneously receive the information about the participant who needs an appointment for colonoscopy and book one.

3.3.9 Bowel preparation for colonoscopy
Instructions to call and confirm the colonoscopy appointment within the 4 weeks is included with the mailed colonoscopy appointment and after confirmation the participant with a positive FIT will receive bowel preparation (Laxabon®) by mail without charge. Split dose is highly recommended (26).

3.3.10 Medical history taken at telephone confirmation of appointment
At confirmation of the colonoscopy appointment the study nurse will ask a few specific questions about the health status of the invitee, including medications (*e.g.* Warfarin®) and check with the responsible physician in doubt of colonoscopy risks. The invitee will also at the telephone conversation be able to ask questions about the colonoscopy.

3.3.11 Reminder of follow-up colonoscopy
Without confirmation by telephone a reminder together with a new colonoscopy appointment time is sent out from the corresponding endoscopy site, following the same confirmation procedure as above.

3.3.12 Follow-up after positive FIT follow-up colonoscopy
Individuals with no pathological finding at colonoscopy will be invited to a second FIT after two years and individuals with a pathological finding will be followed regarding to the specific clinical guidelines.

3.3.13 Positive FIT and asking for a new FIT replacing colonoscopy
Individuals asking for a new FIT instead of a follow-up colonoscopy after a positive test will not have this option. In the study, all positive FIT will be followed by a colonoscopy. All individuals invited to the FIT-arm will have a second round of FIT sent home after two years (except those who had a cancer diagnosis or polyp findings requiring surveillance)

3.3.14 Weight and height measurement and nurse questionnaire
At both primary colonoscopy and follow-up colonoscopy after a positive FIT, the nurse will weigh and measure height (not only asked for) and ask up to ten health questions regarding *e.g.* smoking, alcohol and use of non-steroid anti-inflammatory drugs to be registered in the CIS-S. The questions will be asked *before* the colonoscopy to limit re-call bias.

3.3.15 Blood sample at colonoscopy
At colonoscopy the participant will be asked to leave two blood samples (EDTA®) to be stored in Biobank for future analyses after signing an informed consent (3.4 Informed consent). The individual can decline leaving blood samples for the study, but participate with colonoscopy.

3.3.16 Positive finding at colonoscopy
Individuals with pathological finding at colonoscopy, *i.e.* colorectal cancer or advanced adenomas qualifying to the adenoma surveillance program, will be

followed regarding to the specific local clinical guidelines. No further screening test will be offered within the study for this category of patients. Patients with *other* findings at colonoscopy, *e.g.* inflammatory bowel disease, will be taken care of by the performing endoscopist, but not excluded from a second round of FIT-screening within the SCREESCO-study if randomized to the FIT intervention arm.

3.3.17 Individuals with positive FIT but negative colonoscopy
Individuals with a positive FIT but with a negative colonoscopy (no adenoma or colorectal cancer) will not be investigated further within the study, except for a second round of FIT after two years if randomized to the FIT intervention arm.

3.3.18 Questionnaire after the colonoscopy
After the colonoscopy, the participant will receive a short questionnaire about their experiences of the invitation to screening, bowel preparation and colonoscopy examination, together with a pre-paid return envelope addressed to the endoscopy unit. The participant will be asked to fill out and post the questionnaire within 24 hours.

3.4 Informed consent

The SCREESCO-study has approval from the Ethical Review Board (No. 2012/2058-31/3) Stockholm, Sweden, that a returned FIT-test is to be regarded as informed consent to participate in the study. At colonoscopy, an informed consent is signed by both the study participant in the primary intervention arm, the individuals with a positive FIT and the endoscopist informing about the procedure. The informed consents will be stored at the endoscopy site.

3.5 Quality assurance of colonoscopy

A specific part of the study will be aimed at studying the outcome of the estimated 17 000 colonoscopies. The patients will be subjected to colonoscopy in 33 different centers throughout Sweden in the 18 participating regions (counties). Previous work in this field has demonstrated that a good quality endoscopist should perform more than 100 procedures/year and be able to detect adenomas in more than 20 % of the examinations. Moreover, following intubation of the instrument to the caecum, the withdrawal time should be more than six minutes.

There will be a thorough evaluation endoscopist performance according to set guidelines. This will be carried out by using a specific quality register in the CIS-S, where data on the success rate of the colonoscopist, findings and side effects will be entered from all the estimated 17 000 colonoscopies. In the study registry, adverse advents such as pain, bleeding and perforations will also be collected. The register data will continuously be cross-linked with data from the National Patient register (29) and the Swedish Causes of Death register (30) in order to find severe adverse events.

The colonoscopy performance register will contain a unique set of data, which could be used for both colonoscopy development as well as the follow-up of the safety and success in a screening setting – enabling correlation of the

performance regarding findings and adverse events of each endoscopist and the previous described quality indicators. The results will be stratified by different categories of endoscopists, those with high and medium numbers of procedures annually, with special focus on nurses performing endoscopies since involving nurses in the endoscopies may be an important step and a key to a successful CRC-screening program in the country.

An internet-based on-line system to connect one endoscopist with a set of experts will be developed within the study to deliver immediate second opinion of findings during a procedure. Criteria for the identification of adenomatous polyps as opposed to hyperplastic polyps (31) during the endoscopy will also be developed in the study. Hyperplastic polyps are unlikely to develop dysplasia and, hence, do not have to be removed. If they can be identified in the endoscope much work is saved and patient safety is improved.

Moreover, both primary screening colonoscopies and follow-up colonoscopies after a positive FIT test will be evaluated with a participant questionnaire (3.3.18 Questionnaire after the colonoscopy).

3.6 Pathology

All removed adenomatous polyps will be sent for histopathology and stored in a biobank (Biobank of the Karolinska Institute) for further analyses. Approximately 11 000 adenomas will be removed during the study. A new technique for digitalization of sections from adenomas larger than 10 mm will be developed. Digital images will be made in Aperio machines from sections of adenomas and stored. These images will be used for quality studies to develop processes for diagnostic procedures in pathology in colorectal screening. Secondary studies on correlation of evaluation between various pathologists will be performed in order to create kappa-values in collaboration with Swedish gastrointestinal pathologists in the KVAST (Kvalitets- och standardiseringskommittén [in Swedish]) Study Group of the Swedish Society for Pathology (32). The data will be used to demonstrate which type of adenomas need to be extra carefully resected and which of them are especially at risk to develop new adenomas. The purpose is to combine these results with the results from the colonoscopy investigation in order to possibly reduce the number of polyps needed to be resected generating a decreased risk for perforation of the colonic wall by the procedure and also a reduced work-load for both endoscopists and pathologists (31).

3.7 Secondary studies

The following secondary studies are planned:

- Complier and non-complier experiences
- Health-economy: intervention arms versus control arms
- Quality assurance of primary and secondary screening tests
- DNA in blood and advanced colorectal neoplasia
- Microbiome in feces

- Socio-economical inequities in screening participation and in screening-detected colorectal findings

3.8 Follow-up

Follow-up time is set at 15 years after inclusion and invitation for the primary endpoint colorectal cancer mortality and incidence. The previous versions of the Study Protocol did not however specify when in calendar time the analysis should be performed. The Scientific Committee assessed in 2024 the impact of choice of date for the end of follow-up on the statistical precision for comparing colorectal cancer specific mortality between each of the two active screening arms and the control arm and decided the last date of follow-up is 2030-12-31 (see the Statistical Analysis Plan 3.0 for details). The Scientific Committee also decided, in contrast to what was initially specified, that no interim analyses will be performed for the primary endpoint.

Data of all 278,280 individuals randomized from the population register (FIT-, primary colonoscopy- or control arm) will be obtained from the Causes of Death register (30) and the Cancer register (1) managed by the Swedish National Board of Health and Welfare. Regarding secondary outcomes, *e.g.* quality control of performed colonoscopies and non-steroid anti-inflammatory drugs and adenoma development, information will be retrieved from registries such as The Swedish National Patient Register (29) and The Swedish Prescribed Drug register (33).

4. Ethical considerations

To randomize people from the Total Population Register and invite them to screening colonoscopy (or not when control) is an ethical challenge. Primarily, we do have to consider possible risks for the participants*, i.e.* side effects of the primary and follow-up colonoscopies, but secondarily, we also have to consider the stress a false positive test could generate. Furthermore, we will cross link register information of individuals randomized as controls without their informed consent and the information generated must be treated rigorously and that is why the controls are de-identified and the register information gathered aggregated at group level. On a population level, it is of utter most importance that the study is performed. Most certainly, due to the increasing frequency of opportunistic screening, we only have one chance to get a solid answer to our primary endpoint - to investigate if colorectal cancer screening has an effect on the mortality from colorectal cancer in the Swedish population. The study has been processed and approved by the regional Ethics Review Board at Karolinska Institutet, Stockholm, Sweden (No. 2012/2058-31/3).

5. Statistical analyses

All individuals will be randomized and allocated to one of three arms; colonoscopy, FIT or control. Disease specific mortality is the variable used for

power analysis. Individuals registered in the national Register of the total population will be the bases for the intention to screen analysis.

Study planning including the sample size target were based on the following power calculation. The lifetime cumulative mortality in colorectal cancer in Sweden is about 1% after 15 years. With a 80% power and a 2.5% significance level according to the Bonferroni method the present study need to randomize 20,100 persons in the colonoscopy arm, 60,186 in the FIT arm and 120,372 in the control arm.

Based on previous studies, we estimate that the reduction in mortality will be about 30% for those examined with FIT and a subsequent colonoscopy if the FIT is positive and approximately 50% for individuals who are examined with a primary screening colonoscopy. The compliance is estimated to about 50% in the FIT-arm and approximately 10% of them will have a positive test and invited to follow-up colonoscopy with 80-90% adherence rate. Compliance with primary colonoscopy is estimated to 50% and there is supposed to be a low contamination from opportunistic screening.

In 2016 we prolonged the colonoscopy arm due to a lower-than-expected compliance, 35% instead of 50% and added 10, 500 participants.

See the Statistical Analysis Plan for further details regarding the power calculations and rationale for setting the last date of follow-up to 2030-12-31.

6. Data management

The Central IT-Support System – Study (CIS-S) platform will be located at the Head secretariat. All information generated by the invitation routines, laboratory tests and findings at colonoscopy, as well as individual questionnaire information, will be automatically registered in the system prospectively and available with explicit restriction to guarantee discretion of personal information of individuals.

7. Head secretariat

The Head secretariat of the study is situated at the Regional Cancer Centre in the Uppsala/Örebro region (now called Mellansverige), Uppsala, Sweden.

https://cancercentrum.se/samverkan/vara-uppdrag/prevention-och-tidig-upptackt/screening-tjock-och-andtarmscancer/screesco-studien/

https://cancercentrum.se/samverkan/regional-cancer-centres/

8. Participating centers supplement: sites and local PIs

There are 33 participating endoscopy sites distributed nationally and in the areas of residency of the invitees (and controls) of the study.

SCREESCO Principal investigators per site

Stefan Spinnell Bengt Sundbaum	Sunderby hospital
Leif-Göran Carlsson	Skellefteå hospital
Lars Almersson	Lycksele hospital
Tomas Koczkas	Östersund hospital
Åke Öberg	University hospital of Umeå
Michael Wagner	Uppsala University hospital
Lech Rademacher	Avesta hospital
Stefan Willmarsson	Karlstad hospital
Lars Strandberg	Falun hospital
Verena Voss Jörn Holm Torbjörn Sakari	Gävle hospital
Laszlo Kosztyu	Hudiksvall hospital
Gunilla von Schoultz Karin Nyborg	Lindesberg hospital Karlskoga hospital
Gunter Häselbarth	Mora hospital
Märit Larsson	Eskilstuna hospital
Daniel Nordström	Nyköping hospital
Ronald Malcher Josip Kujundzic	Västerås hospital
Rikard Svernlöv	University hospital of Linköping
Eva Adauktusson Ahmad Kassem	Värnamo hospital
Mats Persborn Jörgen Tolstrup Rasmussen Bengt Druvefors	Eksjö hospital
Roland Persson	Kalmar hospital
Hjalmar Åselius	Västervik hospital
Otto Ůberbacher Cyrus Dyarmand	Varberg hospital
Joakim Holmin Robert Kunz	Halmstad hospital
Dietrich Ahlhausen	Northern Älvsborg County hospital
Anders Lasson	Southern Älvsborg County hospital
Andreas Pischel	Sahlgrenska University hospital Gothenburg
Morteza Shafazand	Sahlgrenska University hospital /East (Eastern hospital) Gothenburg
Birgit Edin Fotios Chalkidis	Falköping hospital
Ervin Toth	University hospital of Malmö
Jörgen Torp	Kristianstad hospital
Matthias Hoeschen	Helsingborg hospital
Björn Ohlsson	Karlshamn hospital
Peter Andersson Staffan Jangmalm	Växjö hospital

9. Main study publications

Planned and published main studies of SCREESCO:

- Compliance, findings and negative effects of the screening initiative (34)
- Emotional impact of screening on participants and non-participants (35)
- Quality assurance of screening colonoscopy (36)
- Study of intervention compared to control: adverse events and incident colorectal cancers during the intervention phase
- Health economy of colorectal cancer screening implementation
- Main analysis of the primary end-point (mortality)

See Section 3.7 for a list of secondary studies.

10. **Scientific committee**

Original list of members of the Scientific Committee

Name	**Country**	**Area of expertise**
Rolf Hultcrantz	Sweden	Gastroenterology
Lars Holmberg	Sweden	Screening, surgery
Anders Ekbom	Sweden	Epidemiology
Anna Forsberg	Sweden	Gastroenterology, endoscopy
Robert Steele	United Kingdom	Screening, Surgery
Richard Palmqvist	Sweden	Pathology
Mef Nilbert	Sweden	Molecular oncology
Andreas Pischel	Sweden	Endoscopy
Marc Buyse	Belgium	Biostatistics
Yvonne Wengström	Sweden	Qualitative research
Per Carlsson	Sweden	Health economy
Lars Engstrand	Sweden	Microbiota
Johannes Blom	Sweden	Screening, surgery

Updated list of members of the Scientific Committee (May 06, 2021)

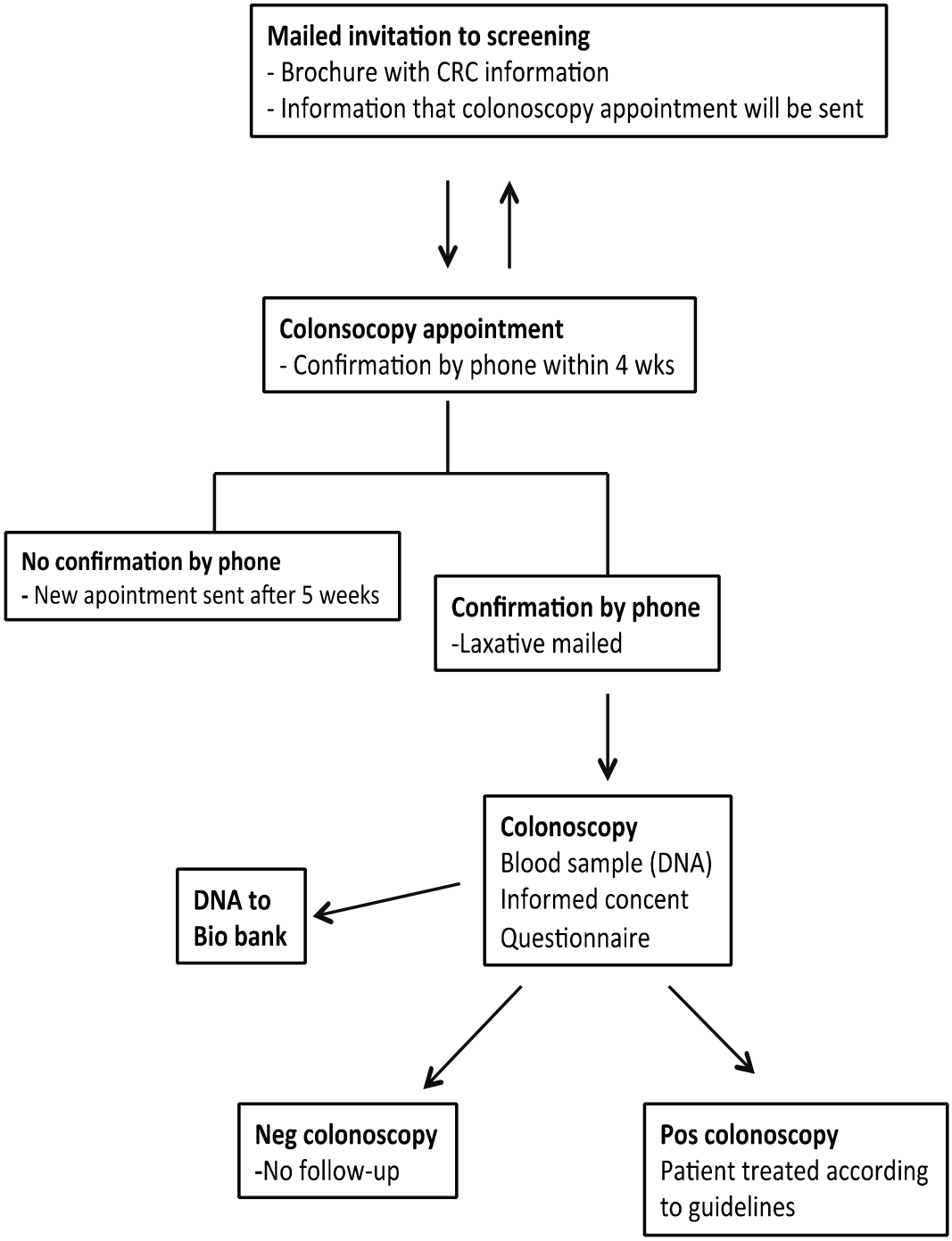
Name	**Country**	**Area of expertise**
Rolf Hultcrantz	Sweden	Gastroenterology
Lars Holmberg	Sweden	Screening, surgery
Anders Ekbom	Sweden	Epidemiology
Anna Forsberg	Sweden	Gastroenterology, endoscopy
Robert Steele	United Kingdom	Screening, Surgery
Chris Metcalfe	United Kingdom	Medical Statistics
Christian Löwbeer	Sweden	Laboratory medicine, clinical chemistry
Andreas Pischel	Sweden	Endoscopy
Yvonne Wengström	Sweden	Qualitative research
Lars-Åke Levin	Sweden	Health economy
Lars Engstrand	Sweden	Microbiota
Johannes Blom	Sweden	Screening, surgery
Mikael Hellström	Sweden	Radiology
Kaisa Fritzell	Sweden	Qualitative research
Ulf Strömberg	Sweden	Epidemiology

Updated list of members of the Scientific Committee (Nov 26, 2024)

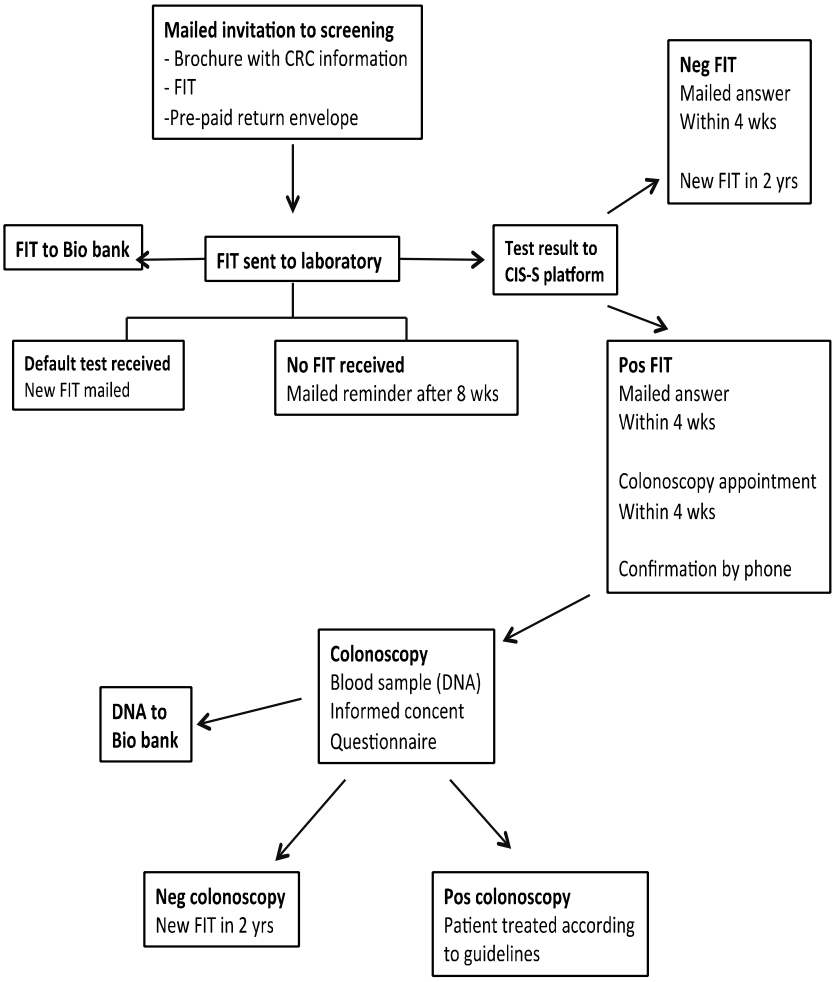
Name	Country	Area of expertise
Lars Holmberg	Sweden	Screening, surgery
Anna Forsberg	Sweden	Gastroenterology, endoscopy
Marcus Westerberg	Sweden	Medical Statistics
Jonas F Ludvigsson	Sweden	Epidemiology
Robert Steele	United Kingdom	Screening, Surgery
Chris Metcalfe	United Kingdom	Medical Statistics
Christian Löwbeer	Sweden	Lab medicine, clinical chemistry
Lars Engstrand	Sweden	Microbiota
Johannes Blom	Sweden	Screening, surgery
Mikael Hellström	Sweden	Radiology
Kaisa Fritzell	Sweden	Qualitative research
Ulf Strömberg	Sweden	Epidemiology

11. Figures

11.2 Figure 1. Flow chart of invitation procedure of individuals randomized to intervention primary colonoscopy



11.1 Figure 2. Flow chart of invitation procedure of individuals randomized to intervention FIT



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13. Summary of changes to the SCREESCO study protocol and statistical analysis plan 2013-2024

Changes in the study protocol version 2.0
Study protocol was amended after new power-calculation due to anticipated 35% participation in the colonoscopy arm. In Swedish 2017-03-10, translated to English 2021-04-29. List of members Scientific Committee was updated.

Changes in the study protocol version 3.0
Study protocol was amended after the Scientific Committee decided on a last date of follow-up based on new power calculations. It was also decided that the previously described interim analysis will not be performed. The list of main publications was updated, and so was the list of members of the Scientific Committee. A summary of changes of the protocol and statistical analysis plan was added. Weblinks under *Head Secretariat* were updated.

Changes in the statistical analysis plan 2.0
Statistical analysis plan was amended after new power-calculation due to anticipated 35% participation in the colonoscopy arm.

Changes in the statistical analysis plan 3.0
Statistical analysis plan was amended on 2024-11-04 after the Scientific Committee decided on a last date of follow-up based on new power calculations. It was also decided that the previously described interim analysis will not be performed. Details and clarifications regarding the initial and modified power calculations were added. The analysis of incidence of colorectal cancer was changed and is now based on cumulative incidence curves instead of the log-rank test.