Screening of Swedish Colons SCREESCO

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Statistical Analysis Plan 3.0

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The randomized controlled trial

Screening of Swedish Colons (SCREESCO)

About the Statistical Analysis Plan version 3.0

This charter defines the main analyses on which conclusions regarding main study aims 1-3 as defined in the protocol February 19 2012. Compliance as a secondary endpoint is included here since compliance is an indicator of feasibility to report to the health authorities as soon as data are informative.

Motivation for version 3.0

On February 8 2024, the SCREESCO scientific committee assessed the impact of choice of calendar time of end of follow-up on the trade-off between timeliness of reporting results and statistical precision in the analysis of primary endpoints.

Key changes

- Added details and clarifications regarding the initial and modified power calculations.
- An assessment of optimal time for evaluation of the primary endpoints based on new thorough power calculations.

Study design

SCREESCO is a randomized screening trial for colorectal cancer with three arms: Invitation to direct colonoscopy, invitation to FIT test, or control. All counties and regions in Sweden except the Stockholm region and Västernorrland's county enroll participants. Eligible are persons in the Swedish Population register for the calendar year they turn 60. Follow-up is at least 15 years.

Interventions

The three study arms are: written invitation to direct colonoscopy and within 8 weeks an offer to participate with a booked appointment; invitation to FIT test and test equipment sent for sampling at home at inclusion and at 2 years after inclusion, offering a colonoscopy after a positive test; control group with standard diagnostic work-up and care for colorectal cancer.

Study aims concerned in the statistical analysis plan

Main aims

1/Analyze the effect of invitation to colorectal cancer screening on colorectal cancer mortality.

2/ Analyze the effect of invitation to colorectal cancer screening on colorectal cancer incidence.

3/ To supply evidence if either direct invitation to colonoscopy or invitation to FIT test should be the method of choice for colorectal cancer screening in Sweden, should a national screening program be initiated.

Secondary aims

Describe and quantify compliance to screening by study arm.

Dimensioning of the study

Assumptions

SCREESCO assumes 1% cumulative colorectal cancer mortality for a follow-up between 60 and 75 years of age. This estimate was based on publicly available historical data (until 2012) on causes of death (1). In accordance with earlier international literature on fecal occult-blood testing (2, 3, 4, 5), a 30% relative reduction in colorectal cancer mortality following screening with FIT and colonoscopy when FIT is positive was expected. A 50% relative reduction in colorectal cancer mortality following screening with direct colonoscopy was similarly expected based on previous trials on sigmoidoscopy (6, 7, 8).

Initially, compliance was expected to be 50% in the FIT arm, and 10% were expected to have a positive test and 90% of those were expected to undergo colonoscopy. Compliance was expected to be 50% in the direct colonoscopy arm. Screening in the control group was assumed to be negligible.

Initial calculation of study size

For an 80% power at a two-sided significance level of 2.5% for each pairwise comparison with the control group, 20 100 persons should be randomized to be invited to direct colonoscopy, 60 186 to be invited to FIT and 120 372 to control in an analysis at 15 years after randomization. Each of the intervention arms will be compared to the control group. Table 1 shows the association between study precision and compliance.

FIT vs control: For FIT vs control, 60 300 were randomized to FIT and 120 600 to control in order to obtain 80% power. We used alpha = 0.025, assumed 1 % mortality rate in arm C after 15 years, a ratio of 1:2, 50 % compliance, hazard ratio = 0.85 (15 % reduced mortality vs control: 30% effect and 50% compliance).

STATA command**:** stpower logrank 0.990, alpha(0.025) power(0.8) hratio(0.85) nratio(0.5)

PCOL vs control: For direct colonoscopy vs control, we used alpha = 0.025, 1 % mortality rate in the control arm after 15 years, a ratio 1:6 vs control, and 50 % compliance, hazard ratio = 0.75 (25% reduced mortality vs control: 50% effect and 50% compliance), and size of control arm of 120 600. Randomizing 1/3 of the size of the FIT arm to the direct colonoscopy arm, i.e. 20 100, gave power above 80 % (approximately 86%) when comparing to the control arm.

STATA command: stpower logrank 0.990, alpha(0.025) n(140700) hratio(0.75) nratio(0.1666)

Modified study size (2016)

In 2016, an analysis found that compliance was 35% in the direct colonoscopy arm implying that the power dropped to 53%. To increase power for the comparison of the direct colonoscopy arm vs control, the size of these arms were increased by extending the study to include birthyears 1957-1958. The ratio was fixed to 1:6, so that adding 10 000 extra individuals to the direct colonoscopy arm would result in approximately the same number of performed colonoscopies as originally planned, which was a tolerable amount for the colonoscopy sites to handle.

PCOL vs control: With an additional 60 000 to the control arm, hazard ratio = 0.825 (17.5 % reduced mortality vs control: 50% effect and 35% compliance), and n=120 600 + 60 000 + 20 100 + 10 000=210 700, then the power became 73%.

STATA command: stpower logrank 0.990, alpha(0.025) n(210700) hratio(0.825) nratio(0.16667)

Definition of study population

A population sample was drawn from the Swedish Population Register for the participating counties in 2014, 2015 and 2016 for persons born 1954, 1955 and 1956 respectively. In each sample 6 700 were allocated to direct colonoscopy, for each of those three persons matched on county and gender were allocated to FIT, and six persons likewise matched on county and gender were allocated to control. All individuals within each block defined by calendar year, county and gender were sampled and individually allocated to one of the three arms simultaneously. In 2016 we decided to randomize additional individuals born 1957 and 1958 to the direct colonoscopy arm and to the control arm during 2017 and 2018 using the same principles (**Table 2**).

Each sample was matched to the Swedish Cancer Register and individuals with a colorectal and/or anal cancer before or at the date the sample was drawn were excluded. In regions participating in the NordiCC trial, study subjects of NordiCC were excluded.

Follow-up starts at date of randomization. A study participant is lost to follow-up at date of emigration or at date of actively withdrawing consent to be followed through registers.

Definition of exposure, covariates and endpoints

Follow-up

Follow-up for the main endpoints is register-based. The following registers will be used: The National Cancer Register, the National In-patient Register, the National Out-patient Register, The National Clinical database for Colorectal cancer, the National Causes of Death register.

Compliance is registered by the study log of invitations and procedures undertaken. Currently there is no full register coverage of use of FIT or colonoscopy in the general population and thus not for the control group. The colonoscopy activity in the control arm and the intervention arm outside the study will be estimated by using data from The National Patient Registry.

Exposure

The exposure of interest is *invitation* to either screening arm; the control group serves as comparator separately for each arm.

Endpoints

For study main aim 1 as above, death from colorectal cancer as defined in the Swedish Cause of Death Register as cause of death or as contributing cause of death is the endpoint of interest. Deaths due to complications of diagnostic or therapeutic interventions directed to colorectal cancer will be counted as deaths from colorectal cancer.

For study main aim 2 as above, stage-specific colorectal cancer incidence is the endpoint of interest. Stage at diagnosis in the Swedish Cancer Register and/or the national Swedish colorectal cancer quality register will be reported.

For study main aim 3 as above, the study will provide a broad spectrum of data for a cost-effectiveness analysis with reduction of colon cancer mortality as the measure of effect.

Compliance is defined as being adherent to colonoscopy either by performing a screening colonoscopy after invitation (colonoscopy arm) or returning a FIT test (FIT arm), and has been assessed previously (9, 10).

Covariates

For the main analyses (intention-to-screen) no covariates will be adjusted for. A subgroup analysis in men and women will be performed.

Validation of endpoints

It was initially planned to perform a validation of death certificates using medical records. It is not clear however, that the effort to obtain medical records would be worthwhile given ethical, GDPR and administrative aspects. The scientific committee has instead decided to perform a register-based validation of colorectal cancer deaths as registered as the underlying cause of death in the cause of death register. We will assess evidence for (e.g. a diagnosis of advanced colorectal cancer close to date of death) and against death by colorectal cancer (e.g. low stage or no colorectal cancer diagnosis and high comorbidity) using data from other Swedish healthcare registries.

Statistical methods

All main analyses to address the aims 1-3 above will be based on random allocation to study arm, i.e. an intention to screen analysis. Other analyses are subsidiary.

Mortality

As the main analysis, net probability of death from colorectal cancer (in absence of competing causes) will be estimated using 1 minus the estimated survival curve when censoring for other causes of death, and presented with corresponding 95% confidence interval. The events of interest will be death from colorectal cancer or by complications to the screening procedure and/or treatment of colorectal cancer.

In the main analysis the two screening arms will each separately be compared to the control arm. The date of randomization will be used as start of follow-up and the log rank test will be used as the test of significance at a 2.5% level (two-sided).

As a subsidiary analysis, probability of mortality of all causes will be estimated.

Incidence

As the main analysis, cumulative incidence of colorectal cancer will be estimated, treating death from any cause as a competing event. The date of randomization will be used as start of follow-up. We will estimate the cumulative incidence of colorectal cancer and death from other causes in the primary colonoscopy arm vs control arm and in the FIT arm vs control arm non-parametrically, with 95% confidence intervals.

The log-rank test, as initially described, will not be used since we will compare cumulative incidence functions in a competing risk setting. We will also report absolute differences in cumulative incidence functions with 95% confidence intervals (11, 12).

A subsidiary analysis will similarly estimate the competing risk cumulative incidence of colorectal cancer by stage.

Use of colonoscopy outside of the study

Usage of colonoscopy (any purpose) in the control arm and in the intervention arms outside the study protocol will be estimated as described under follow-up and will be presented with the main analysis.

Supporting a choice of screening method

As for study main aim 3 as above, the analyses will be based on data from both arms on mortality, incidence, compliance, participant's experience, side-effects and further supported by health economics analyses and modelling. Thus, provision of evidence for the health authorities' future recommendation will be based on a broad set of criteria of health effects and public health considerations.

Timing of the analyses

SCREESCO was initially powered for a main analysis 15 years after randomization. Development of serious adverse events will be followed continuously, but will also be summarized at 15 years. The previous versions of the SAP and Study Protocol did not however specify when in calendar time the analysis should be performed.

Last date of follow-up for evaluation of primary endpoint

The Scientific Committee assessed 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. A conservative choice of date of end of follow-up is 15 years after the last invitation to screening (up to and including 2033-05-24). Statistical power did not meaningfully decrease by ending the follow-up somewhat earlier, already at 2030-12-31, so scientific committee propose this date as the last date of follow-up. We briefly describe the calculations underlying this decision in the following:

Aggregated and publicly available data from the National Board of Health and Welfare (Socialstyrelsen; SoS) and Statistics Sweden (SCB) between 2010 and 2014 (1, 13), before SCREESCO could have had any meaningful impact on mortality, was used to estimate separately for men and women the competing risk cumulative incidence functions of death by colorectal cancer and of other causes from age 60 to 80 years. These were computed using estimates of the competing risk hazard functions for time steps equal to 1 day. The hazard functions were used in combination with the assumed hazard ratios to define cumulative incidence functions for the direct colonoscopy and FIT arms.

The expected net risk of death from colorectal cancer in the control arm according to the model was 0.766% (0.877% in men and 0.654% in women) after 15 years of follow-up. This is lower than the 1% that was originally assumed for the power calculations. The risk of death from colorectal cancer has decreased over calendar time, both before and during SCREESCO, and the 1% estimate was based on more historical data than the new estimate. The corresponding risk of death from any cause was 16.1% (19.1% in men and 13.0% in women).

We therefore performed a sensitivity analysis (**Sensitivity Analysis 1**) where we increased the competing risk of death from colorectal cancer to obtain an expected net risk of death from colorectal cancer of 1.002% (1.148% in men and 0.856% in women) and corresponding risk of death from any cause of 16.3% (19.3% in men and 13.2% in women).

We simulated time until death and cause of death for all randomized individuals in SCREESCO. Individuals were right censored at the first of 15 years from date of randomization, date of death from other causes and a date **X** indicating the last date of follow-up in calendar time. The dates **X** considered were 31st of December between 2024 and 2032, and in addition also the 24th of May from 2025 to 2033. In a second sensitivity analysis (**Sensitivity Analysis 2**), we instead allowed all individuals to contribute with follow-up until the end of the study, meaning that some may have been followed for more than 15 years.

The results of the simulation study are summarised in Table 3. For the comparison FITx2 vs CONTROL the power increased rapidly with later dates for the end of follow-up, from 35.4% when using 2024-12-31, to 64.4% at 2030-12-31, and remained around this percentage from this date onward, and the number of CRC deaths increased correspondingly from 641 to 1204. For the comparison of PCOL vs CONTROL the power was 28% and increased to 54.9% at the corresponding dates, and increased further to 58.7% at 2033-05-24. The corresponding number of CRC deaths were 692, 1392 and 1501.

Although the power in **Sensitivity Analysis 1** was higher, e.g. 77.5% at 2030-12-31 for FITx2 vs CONTROL and 67.8% for PCOL vs CONTROL, it only increased slightly after this date. The subgroup analyses had in all analyses much lower power (<40%) but the effect of choice of last date of follow-up was similar to that in the primary analysis.

In **Sensitivity Analysis 2** the power was comparable to the primary analysis at 2029-05-24 and was increasingly higher compared to in the primary analysis at later dates. At 2030-12-31 it increased to 68.4% for FITx2 vs CONTROL and 57.6% for PCOL vs CONTROL, and at 2033-05-24 it was 79.1% and 70.1% respectively.

Our estimates of power based on a lower net risk of death from colorectal cancer (0.766%) compared to previous power calculations (1%) produced slightly lower power but as a function of last date of follow-up the power did not materially change after 2030-12-31. This date allows almost all individuals to be followed for 15 years in the FITx2 arm, and the number of CRC deaths after this date is negligible in all arms. If follow-up may extend beyond 15 years from date of randomization, as in **Sensitivity Analysis 2**, there is a potential to gain additional some power at 2030-12-31 and even more at later dates.

The choice of date must balance the decrease in power against the potential value of providing evidence from the study and the potential impact of the findings on clinical practice. For this reason, we propose 2030-12-31 as the last date of follow-up rather than 2033-05-24, allowing publication of the primary endpoint almost 2.5 years earlier than 2033-05-24 with minimal impact on power.

Interim analysis

An interim analysis of the main outcome colorectal cancer mortality was previously specified to be performed at 10 years of follow-up using the O'Brien-Fleming alpha spending function in order to keep the overall type I error for each of the comparisons of the screening arms to the control arm at 2.5% (see also below under Safety). Based on the above calculations and the low power at 10 years, the scientific committee decided that this interim analysis should not be performed.

Presentation in main report

The following data will be presented in the main analysis: CONSORT diagram of study design; baseline characteristics by study arm; estimate of colonoscopies in control arm; serious adverse

events; cumulative incidence of colorectal cancer (in total and by stage) in all three study arms; net probability of death from colorectal cancer and overall mortality in all three study arms.

Safety

In February 2024 it was obvious that the scientific committee has ensured the quality of the study regarding the database, and the adherence to the study protocol as well as the statistical analysis plan. Due to the long study time, the conditions have slightly changed and therefor updates have been required. The work of a Data Monitoring and Safety Committee has been performed by the study secretariat and scientific committee, taking responsibility for integrity and safety during the intervention phase of SCREESCO (between 2014 and 2020). Serious adverse events have been reported continuously and analyses have been undertaken of safety as well as participant experiences (9, 14). The study secretariat has with support from the sponsoring part – the Council of Regional Cancer Centers in Sweden – continuously updated the study database and checked it for accuracy. The integrity of the database has been checked in analyses of early aspects of the study (15, 16). The Scientific committee is not aware of and cannot access main outcomes by study arm. Only the study statistician can access the entire study database.

From 2020 and onward follow-up data are only based on registers, i.e., without any contact with or intervention directed to any randomized individuals. As a step towards transparency, the Study Protocol and the Statistical Analysis Plan will be published on clinicaltrials.gov, where the SCREESCO study is registered.

Table 1, association between study precision and compliance

Arm A (colonoscopy N=20 100) (assumed CRC mortality reduction at 100% compliance = 50%)				**Arm B (FIT N=60 186) (assumed CRC mortality reduction at 100% compliance = 30%)**		
Compliance (%)	Efficacy (%)	Power (%) at α=2.5%		Compliance (%)	Efficacy (%)	Power (%) at α=2.5%
60%	30.0%	96.3%		60%	18.0%	93.0%
55%	27.5%	92.5%		55%	16.5%	87.7%
50%	25.0%	86.4%		**50%**	**15.0%**	**80.0%**
45%	22.5%	77.6%		45%	13.5%	70.1%
40%	20.0%	66.3%		40%	12.0%	58.4%
35%	17.5%	53.4%		35%	10.5%	46.0%
30%	15.0%	40.1%		30%	9.0%	34.1%
25%	12.5%	27.9%		25%	7.5%	23.6%
20%	10.0%	17.9%		20%	6.0%	15.2%

Table 1 shows efficacy in an intention to screen analysis and the corresponding power for different levels of compliance by study arm. The power is calculated based on the study design to compare each arm separately to the control group (N=120 372).

Table 2, randomization

	Birthyear	**Date of randomization**	**Arms**
Initial randomization	1954 1955 1956	2014-02-11 2015-03-31 2016-03-01	All
Extra randomization	1957 1957 1958	2017-05-30* 2017-06-29** 2018-05-25	Primary colonoscopy and control

Table 2 shows the dates of randomization per year and which arms individuals were randomized to.

* All regions except Gävleborg ** Gävleborg only

Table 3, power and last date of follow-up

		Primary analysis		Sensitivity analysis 1		Sensitivity analysis 2	
Comparison	**Date**	**Deaths from CRC**	**Power (%)**	**Deaths from CRC**	**Power (%)**	**Deaths from CRC**	**Power (%)**
Direct colonoscopy vs control	2024-12-31	692	28.0	900	35.7	-	-
	2025-05-24	735	29.6	956	37.7	-	-
	2025-12-31	804	32.2	1044	41.6	-	-
	2026-05-24	850	34.3	1104	44.1	-	-
	2026-12-31	923	36.7	1199	47.9	-	-
	2027-05-24	973	38.2	1264	50.5	-	-
	2027-12-31	1051	41.6	1365	53.9	-	-
	2028-05-24	1105	43.6	1435	56.1	-	-
	2028-12-31	1188	46.3	1543	59.4	-	-
	2029-05-24	1234	48.1	1603	62.2	1244	49.1
	2029-12-31	1302	51.5	1690	65.0	1332	52.8
	2030-05-24	1342	52.8	1742	66.3	1391	54.4
	2030-12-31	1392	54.9	1807	67.8	1482	57.6
	2031-05-24	1420	55.8	1844	68.6	1543	60.1
	2031-12-31	1452	57.4	1885	69.7	1638	63.3
	2032-05-24	1473	57.7	1913	70.6	1701	64.9
	2032-12-31	1490	58.4	1935	70.8	1798	67.6
	2033-05-24	1501	58.7	1949	71.3	1861	70.1
FIT vs control	2024-12-31	641	35.4	832	46.5	-	-
	2025-05-24	678	37.3	881	49.4	-	-
	2025-12-31	737	40.7	958	53.4	-	-
	2026-05-24	777	42.9	1010	55.6	-	-
	2026-12-31	840	47.0	1092	59.8	-	-
	2027-05-24	883	50.2	1147	61.8	-	-
	2027-12-31	951	53.0	1235	65.5	-	-
	2028-05-24	997	54.6	1294	67.7	-	-
	2028-12-31	1068	58.2	1387	71.5	-	-
	2029-05-24	1104	59.8	1433	73.4	1116	60.3
	2029-12-31	1152	61.9	1496	74.9	1190	63.5
	2030-05-24	1179	63.7	1530	76.6	1240	65.8
	2030-12-31	1204	64.4	1563	77.5	1317	68.4
	2031-05-24	1214	64.8	1576	77.8	1368	70.3
	2031-12-31	1214	64.8	1576	77.8	1447	72.6
	2032-05-24	1214	64.8	1576	77.8	1500	74.6
	2032-12-31	1214	64.8	1576	77.8	1579	77.6
	2033-05-24	1214	64.8	1576	77.8	1631	79.1

Table 3 shows the power and number of deaths from colorectal cancer (CRC) as a function of the last date of follow-up in the primary analysis and two sensitivity analyses. Results were based on 5000 simulations and the Monte-Carlo Standard Error was between 0.57-0.71%. In the first sensitivity analysis the risk of death from CRC was higher in all arms (HR=1.31 compared to primary analysis), and in the second sensitivity analysis the follow-up extended until the date of end of follow-up or death from other causes (i.e. potentially extending beyond 15 years from date of randomization).

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