

# NordICC

## The Nordic-European Initiative on Colorectal Cancer

### NordICC Study Protocol

Version MB 251110, with amendments as of Oct 29, 2014

#### Summary

Colorectal cancer (CRC) is a major burden in western countries. The disease develops from precursor lesions during a long time-interval. Colonoscopy can detect and remove CRC precursor lesions and may thus be effective for CRC prevention. According to WHO and European Union guidelines, evidence from randomised trials to reduce incidence or mortality of the target disease is a prerequisite before advocating population-wide cancer screening. However, while colonoscopy screening for the prevention of colorectal cancer is established in several European countries and the United States, no randomised trials exist to quantify the possible benefit of colonoscopy screening.

NordICC is a multicentre, randomised trial in Nordic countries, the Netherlands and Poland. A minimum of 66 000 individuals, age 55-64 years, are drawn randomly from the population registries in the participating countries. 22 000 are invited for once-only colonoscopy (2:1 randomisation). Expected work-load with 50% compliance will be 11,000 colonoscopies. At the screening examination, all detected lesions are biopsied and removed whenever possible. The remaining 44 000 individuals (control group) are not offered any screening examination (care as usual). The primary study aims are CRC incidence and CRC mortality after 15 years of follow-up. The study is powered to show a risk reduction of CRC mortality of 25% in the colonoscopy screening group compared to the control group in an intention-to-treat approach, estimating 50% compliance in the screening group.

The administrative and scientific lead of the NordICC trial including the study database is situated at the Cancer Registry of Norway, Oslo, Norway. Grants from the Polish and Dutch governments cover 7,500 colonoscopies performed in these respective countries starting in May 2009. Additional grant proposals are submitted to finance the additionally needed colonoscopies to be performed.

NordICC is the first randomised trial to investigate the effect of colonoscopy on CRC incidence and mortality. The NordICC groups comprise world-leading experts in the fields of gastroenterology, oncology, medical screening, epidemiology and biostatistics who have committed themselves to this cutting-edge research project that has the potential to open up new horizons and opportunities for research on the highest possible level for many years to come. The aim of the trial is to finally address the efficacy of colonoscopy screening. It will thus open for the establishment of evidence-based guidelines for CRC screening in Europe and the world, to be able to tailor our efforts to prevent CRC in the general population

## Background

### **Incidence, risk and prognosis**

Colorectal cancer (CRC) is the second most frequent cancer regarding both incidence and mortality in Europe and the Nordic countries, both sexes combined (1). More than 85% of CRC cases are so-called “sporadic cancers”, i.e. the patient does not belong to any identified high-risk group. Symptoms often emerge at a late stage of the disease and are non-specific. The prognosis of CRC diagnosed at a symptomatic stage is poor and does not exceed a 5-year survival of 50%. Early diagnosis is crucial since treatment in an early stage is the only option for cure and a major reason for recommending CRC screening in an increasing number of countries (2-4).

### **Precursor lesions**

Most cases of CRC (60-90%) develop from wart-like outgrowths of the colonic mucosa (adenomas or adenomatous polyps). It is estimated that it takes on average 10 years from a detectable adenoma until it has evolved into cancer. Thus, the removal of adenomas may prevent cancer. Adenomas are common in the Nordic and European average-risk population (15-25% of healthy 50-year-olds and 30-50% of healthy 70-year-olds). For this reason, many health providers considering CRC screening focus not only on screening methods that can detect CRC but adenomas.

### **CRC screening tools**

Three CRC screening methods are of particular interest:

Faecal occult blood testing (FOBT): This means chemical detection of occult blood. The sensitivity for strictly asymptomatic CRC is < 30% for a single screening round with Hemoccult-II, the most commonly used FOBT. With repetition every year or every second year, the CRC sensitivity of FOBT is estimated to be >60% (5). FOBT has a much lower sensitivity for adenomas. FOBT is the only screening method with follow-up results from randomised studies (5-7). The relative reduction in CRC mortality was about 16% in the two European population studies (6,7).

Flexible sigmoidoscopy (FS): FS is an examination of the distal 50-60 cm of the large intestine with a flexible endoscope. If a positive test, defined by detection of “any adenoma” (regardless of size, but histologically verified), is followed up by a full colonoscopy, then the test sensitivity is 70% for CRC and advanced adenomas for the whole colon. The sensitivity within the reach of the FS endoscope is >90% (8). FS may, in contrast to FOBT, prevent cancer development by removal of adenomas. Four randomised studies on FS screening are ongoing (9-12). Long-term follow-up results from a small randomized FS screening study, the Telemark Polyp Study no. I (TPS-I), showed a significant reduction of CRC incidence after 13 years follow-up (13). The study did not have the statistical power to show any effect on CRC mortality. There was a statistically significant difference in overall deaths in the TPS-I study with a higher total death rate in the screening group (14).

Colonoscopy: This is the “gold standard” for examination of the colon (3). The sensitivity is > 90% for CRC and advanced adenomas. A recent case-control study from Toronto, however, has demonstrated a CRC mortality reduction only for left-sided (OR 0.33) compared to right-sided lesions (OR 0.99) suggesting that the sensitivity for detecting right-sided pre-cancerous lesions may be poorer than for left-sided during colonoscopy –or that the carcinogenesis may differ markedly between left- and right-sided lesions (15). A case-control study, the US National Polyp Study has shown a significant reduction of CRC deaths and CRC incidence after colonoscopy with polypectomy, but the control groups consisted of historical data from the USA and historical data from another continent (UK) (16).

There are no randomised studies performed for colonoscopy with CRC mortality or incidence as the primary end-point. Still, colonoscopy is recommended as screening method in the USA, and has been launched as a national free-of-charge offer for everyone over the age of 50 in Italy, Germany and Poland.

## **Impact and significance**

Biennial FOBT screening has shown an average CRC mortality reduction of 16% in randomised studies. Colonoscopy has a potentially larger yield and is able, in contrast to FOBT, to detect premalignant disease. Therefore, colonoscopy used as a CRC screening tool may *prevent* the disease rather than early-detect it.

According to WHO and European Union guidelines, evidence from randomised trials to reduce incidence or mortality of the target disease is a prerequisite before advocating population-wide cancer screening (17). Colonoscopy as a screening tool has not been tested in randomised studies. It is unknown if colonoscopy screening has any significant effect on the incidence and mortality of CRC, and if any, how large it is. Despite this, several EU countries have introduced colonoscopy as a primary screening tool for the general population. Large amounts of money and resources are spent without any possibility to evaluate the effect of screening. Furthermore, as colonoscopy is an invasive procedure, individuals may suffer harm from screening or follow-up with a tool that never has been subjected to proper randomized trials addressing its efficacy. Recently, several researchers have expressed their concern about the striking lack of evidence in colonoscopy screening (18,19). When the International Digestive Cancer Alliance, a non-for-profit worldwide umbrella organization learned about the plans for the NordICC trial, it expressed in a letter to the NordICC groups that “a randomized trial on colonoscopy screening is desperately needed”.

NordICC is the first randomised trial to investigate the effect of colonoscopy on CRC incidence and mortality. The NordICC groups comprise world-leading experts in the fields of gastroenterology, oncology, medical screening, epidemiology and biostatistics who have committed themselves to this cutting-edge research project that has the potential to open up new horizons and opportunities for research on the highest possible level for many years to come. The aim of the trial is to finally address the efficacy of colonoscopy screening. It will thus open for the establishment of evidence-based guidelines for CRC screening in Europe and the world, to be able to tailor our efforts to prevent CRC in the general population.

## **Study aims**

### **Primary endpoints**

Comparison of the screening group vs. the control group in an intention-to-treat model after 10-15 years of follow-up with regard to:

- CRC mortality
- CRC incidence.

### **Secondary endpoints**

- CRC mortality and CRC incidence of screening attendees compared to the control group and non-attendees after 10-15 years of follow-up
- Mortality from all causes after 10-15 years of follow-up
- Differences in change of lifestyle between screening group and control group and non-compliers (add-on study, separate protocol)
- Colonoscopy yield, compliance, performance, complications and adverse events (30 days)

A first analysis evaluating the primary and secondary endpoints is planned after 10 years of follow-up.

## Patient selection

### Entry criteria

This study is a population-based randomised controlled trial, with randomisation of individuals age 55-64 years living in the screening areas directly from the Population Registries to either screening group or control group. Eligible persons with the same home address will be randomised to the same group (household randomisation).

### Exclusion criteria for colonoscopy

- Individuals with previous colorectal surgery (resections, enterostomies)
- Individuals in need of long-lasting attention and nursing services (somatic or psychosocial, mental retardation).
- On-going cytotoxic treatment or radiotherapy for malignant disease
- Severe chronic (longer than trial duration) cardiac (NYHA III-IV) or lung disease
- Lifelong anticoagulant therapy with Warfarin
- A coronary event requiring hospitalization during the last 3 months
- A cerebrovascular event during the last 3 months
- Resident abroad
- Return of unopened letter of invitation and/or reminder (address unknown)
- Message from neighbour/family/post office on death of screenee (not updated in Population Registry).

Individuals that meet one or several exclusion criteria are not offered any screening, but excluded persons with suspicious symptoms will be advised to consult their physician for further investigations.

### Invitation procedures

A centrally located body in each of the participating countries will mail a personal letter of invitation containing date and hour of appointment to every individual randomised to the screening group. The control group will not be approached and will not be actively informed about their status as controls. A letter of invitation will be mailed to eligible individuals 6-7 weeks prior to appointment. The letter also provides a prescription for the bowel cleansing regimen, to be picked up at the nearest pharmacy or bowel cleansing regimen will be mailed in response to written acceptance to attend or picked up at the screening center.

The personal invitation letter also contains a reply form and a telephone number to the screening centre for discussing medication or diseases that may be relevant for bowel cleansing, endoscopy or polypectomy. On the reply form, screenees are asked to provide their telephone number and hours of the day when the screenee can be contacted for additional information. It will be applied for permission to contact by phone those individuals who have either declined an offer of colonoscopy in their reply form or have failed to respond altogether. These will be phoned three days prior to suggested appointment to clarify if the appointment will be used or can be used by others. For those declining a screening offer due to the bowel cleansing regimen, they will be offered a simpler, modified cleansing regimen (see below).

All participants in the screening group provide written informed consent before inclusion in the trial.

## Intervention

### Screening tool

Colonoscopy is the screening tool used in this trial. All individuals in the screening group will be offered a full colonoscopy. At colonoscopy, all detected CRC precursor lesions will be removed, whenever possible. The colonoscopy procedure and the bowel cleansing are free of charge for the

screenees. Post-screening follow-up or surveillance after closing recruitment in NordICC is to be taken care of by the local health service according to national guidelines. A standard protocol for follow-up of screenees with neoplasia is incorporated in the endoscopy and pathology software to be used by all participating centres (ColoReg IT module developed for this purpose). Divergence from program recommendations (e.g. due to local guidelines, co-morbidity etc) must be explained.

### **Bowel preparation**

Two tablets of bisacodyl 5mg two days before and 2-litres of PEG (Polyethylene glycole) on the day before colonoscopy is the standard bowel cleansing regime used in the trial. However, alternative regimens can be designed for individual participants, after agreement with the local screening centre. In Norway, 3l of PEG solution (Endofalk®, Falk Pharma, Freiburg, Germany), as split dose for some of the individuals, is used for preparation. Individuals who may not be willing to undergo a bowel cleansing regimen designed for full colonoscopy or for other reasons wish to only undergo flexible sigmoidoscopy may also be offered a limited regimen to only clean the distal colon, to be able to perform limited endoscopic procedures. The primary aim of the present trial, however, is to achieve full colonoscopy (not FS), even if the bowel cleansing regimen is limited.

### **Endoscopic examination**

Ordinary 130-cm or 160- cm video colonoscopes are used for the examinations. CO<sub>2</sub> as insufflation gas is to be used and a magnetic endoscope imaging system (MEI) is recommended for orientation of the endoscope in the abdomen. Any polyp or other pathological findings are either biopsied or removed during the screening exam, as indicated.

The participant's experience of discomfort or expressed wish to discontinue guides the decision to stop insertion of the endoscope before reaching the caecum. Special caution is warranted when using diathermy in the ascending colon and the caecum. The risk of high-grade dysplasia shall be balanced against the risk of perforation when using diathermy for removal of a sessile polyp on a thin bowel wall.

### **Intervention in the control group and ethical considerations.**

The control group will not be offered any screening or intervention within the trial, but follow usual care in the participating countries. Usual care will, for the time being, mean no screening in Sweden, Denmark, Iceland, Poland, the Netherlands and Norway.

FOBT screening has been shown to reduce CRC mortality and is advocated by many CRC screening guidelines. However, recent US guidelines declare incidence reduction as the primary aim for screening (17). In spite of this, FOBT, not a first choice for adenoma detection, is still a recommended screening modality. A new screening tool should be tested against current practice. In the area of the trial, current practice will be provided for the control group and the design of the trial is therefore regarded as ethical and in accordance to the Declaration of Helsinki.

Individuals assigned to the control group will not be informed about their status as controls in the present trial. This approach facilitates a truly population-based study, which will be used to estimate the effect of the screening intervention in the general population, mimicking national CRC screening programs. The design, with regard to this detail, follows the previous NORCCAP-I study (11).

All ethics committees at the participating centres have approved the study protocol before recruiting individuals to the trial. In Sweden, the national ethics committee particularly reviewed the non-information of the control group and found it ethically acceptable. No data will emerge from the study enabling identification of individual patients in either group.



## Follow-up and analyses

Participants are followed up regarding the primary endpoints (incidence and mortality of CRC) until death. The primary analysis is performed 15 years after randomisation through national or regional registries. For the primary endpoints, a first analysis is planned at 10 years post – screening. No specific stopping rule exists.

All randomised participants shall be followed up according to the protocol, regardless of attendance or completion of work-up of screen-positives or recommended intervention (intention-to-screen).

## Statistics

### Power calculation

CRC mortality is the variable used for power calculation. All persons randomized will form the group for analysis (intention-to-screen analysis Follow-up after screening/inclusion in the trial is planned for 15 years for the main analyses.

The CRC mortality-reducing effect of the colonoscopy intervention is estimated to 50% (17). Compliance to the screening examination is estimated to be 50%. Thus, the effect on CRC mortality would be 25%. Assuming 80% power and a two sided alpha level of 0.05, using a 2:1 randomisation (control group vs. screening group), 22,000 individuals would have to be invited to colonoscopy. This gives (with 50% compliance) an estimated workload of 11,000 colonoscopies. 44,000 individuals have to be randomised to the control group (first row in table below).

The estimate of efficacy of the intervention is somewhat uncertain, as it is based on non-randomised studies and expert opinion. Our estimated efficacy of 50% is a conservative estimate, as some trials have shown mortality risk reductions after endoscopy of up to 80% (5,13,16). Also, there is considerable uncertainty regarding possible FOBT screening contamination in the trial areas during the follow-up period. FOBT screening in the control group would dilute the effect of the intervention. The table below shows adequate power also for different scenarios of efficacy of the intervention, attendance rates to screening in the trial and contamination in the control group.

Presently (January 2009) the Netherlands, Poland and Iceland have obtained funding for altogether 9,500 colonoscopies, but there are good prospects of funding of an additional 5,000 colonoscopies in Sweden and further colonoscopy contributions from the Netherlands, Poland and Norway.

Table: Power of the trial with different scenarios of effect, attendance and contamination. Numbers from bootstrap models by M. van Ballegoijen and CWN Looman, Rotterdam.

Efficacy of intervention	Effect reduction in control group due to contamination	Attendance rate	Colonoscopies	No. Invited	Power
50%	0%	50%	11000	22000	81%
70%	5%	50%	6000	12000	81%
70%	15%	50%	7500	15000	81%
50%	5%	50%	13000	26000	81%
50%	15%	50%	20000	40000	82%
50%	0%	25%	23000	92000	81%

## Statistical Analysis Plan

Participants are followed up regarding the primary endpoints (incidence and mortality of CRC) until death/incidence of CRC or 15 years from baseline, whichever happens first. All randomised participants shall be followed up through national or regional registries, regardless of attendance. The primary analytic approach of the trial will follow the intention-to-screen (ITS) principle. We will compare the average rate of each primary endpoint between the screening and control arms by fitting a Cox proportional hazards model. If the distribution of any baseline characteristics is found to be imbalanced between the arms, we will conduct a sensitivity analysis in which those characteristics will be included as covariates in the model. The primary analysis will be performed 10 years after randomization.

As explained above, we do not expect full adherence to screening in the intervention arm and we expect that some individuals in the control group will be screened. In the presence of substantial misclassification, the ITS analysis will only be able to detect moderate to large causal effects of screening. Even if an effect is detected by the ITS analysis, its magnitude is likely to be underestimated. We will therefore conduct secondary analyses to estimate the causal effect that would have been observed if all individuals in the intervention arm had been screened and none of the individuals in the control arm had been screened at baseline. We will refer to these analyses as “adherence-adjusted” analyses.

We will use two different analytic approaches to obtain “adherence-adjusted” estimates: instrumental variables methods and inverse probability weighting. For comparability, we will translate the estimates from both approaches into a common metric: adjusted (CRC-free) survival curves. To implement instrumental variables methods (with the indicator for treatment arm as the instrument), we will use g-estimation of nested structural models. To implement inverse probability weighted estimation, we will estimate the weights and the parameters of a marginal structural Cox model. The estimation of inverse probability weights in the intervention arm requires the measurement of variables that jointly predict compliance with the baseline intervention and the endpoint. These variables include age, sex, family history of colorectal cancer, smoking status, use of aspirin, NSAIDs, and hormone replacement therapy. Some of these variables are measured at baseline for all trial participants (age, sex), some may only be available for screening attendees. However, efforts will be made to also collect these variables for non-adherent individuals. These efforts include tracking information from existing registries and direct approach of samples of non-adherents and controls. Further adjustment for “spontaneous” screening in the control group would similarly require measurement of joint time-varying predictors of screening and the endpoint in members of the control group.

## Pathology

Histopathology findings are integrated with an endoscopy report

All tissue samples (biopsies and diathermy loop resected specimens) are registered in a network IT-module where the colonoscopy report has already been entered by the endoscopist. In this IT-module, the polyp/tumour findings at colonoscopy are tabulated as follows:

Polyp no.	Segment	Level	Phase measured	Diameter	Character	Procedure	Completely removed (endoscopist's judgement)	<i>Specimen (glass)no.</i>	<b>Histo-pathology</b>
								<i>1</i>	
								<i>2</i>	
								<i>3</i>	
Options	Rectum Sigmoid Descending Transverse Ascending	Cm from anus	1)At withdrawal (straightened endoscope) 2)During insertion	mm	1)pedunculated 2) sessile 2)flat	1)Biopsy 2)Hot biopsy 3)Snare resection	1)Yes 2)No		(See text)

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Local pathology labs will serve the respective centres and analyse the tissue samples histopathologically.

All histopathology reporting follows WHO guidelines and classification and grading (17,18). For benign lesions (polyps) the following must be available for subsequent entry in the endoscopy/pathology IT-module: type of polyp, grade of dysplasia, growth pattern and invasiveness. For surgical specimens of malignant lesions, the following must be provided: Size of specimen, size of tumour, resection margins, histological type, dedifferentiation, total number of lymph nodes with number invaded by cancer, TNM (16) and Dukes' staging (19).

Online reporting from the pathology labs are to be integrated with the endoscopy IT module. The endoscopy/pathology IT-module must at all times be able to display pending histopathology reports, showing the oldest at the top of the list. Also, there must be a display of patients not having been given adequate advice on follow-up or appointment (adequacy to be defined).

### Secretariat and data management

The NordICC head secretariat is situated in Oslo, Norway. This centre co-ordinates all administrative work, coordination of screening activity, planning and data monitoring. At the Oslo centre, a joint database is established, connected electronically to all participating screening centres. The screening centres use the same electronic reporting system ("ColoReg") for both endoscopy and histopathology reports. The IT-module "ColoReg" is developed for a colonoscopy screening trial in Norway by the Cancer Registry of Norway and KeyMind Computing Ltd (property of the Cancer Registry of Norway). "ColoReg" is modified for use in NordICC and distributed free of charge to participating NordICC centres. A central server provides continuous registration of all data generated at the screening centres. Continuous quality control programmes for endoscopy, histopathology, patient satisfaction and microbiological surveillance of equipment are an integrated part of the screening activity.

### Main study publications

- Methods and rationale paper
- Study participants' characteristics, randomization, side effects etc.
- 10 year follow-up (primary endpoints)
- 15-year follow-up (primary endpoints)

### Quality assurance

Continuous quality control and improvement is considered to be an important part of the present study.

The following quality control programmes will be included as part of the NordICC trial:

- *Continuous registration of performance, for both centres and individual endoscopists and staff*
  - Pathological findings (polyps, adenomas, cancers)
  - Satisfaction of screenees with endoscopists/personnel/logistics
  - Pain and discomfort during and after the screening examination
  - Complications and adverse effects
  - Video taping of all endoscopies performed for subsequent analyses of quality



- *Continuous evaluation of cleansing processes*
  - Periodic microbiological swab samples from all endoscopes used
- *IT systems to secure logistics and quality*
  - Continuous central registration with notification of sub-standard performance variables (to be defined together with the participating centres)
  - Notification of all complications
  - Notification of screen-positives who have not been appointed for adequate (to be defined) follow-up
  - Notification of screenees who have not been sent a printout of results
  - Notification of missing, inadequate or illogical registration of histological findings

A questionnaire will be handed out to all participants after the screening examination. The questionnaire is to be filled in the day after the exam at home, and is to be mailed back to the particular screening centre in a pre-paid attached envelope. The questionnaire provides questions on

- general satisfaction with participation in the study
- pain and discomfort during and in the hours after the colonoscopy
- discomfort due to the bowel preparation
- complications or side-effects (known to the participant)

The same questionnaire will be mailed to screenees subjected to biopsy or polypectomy 4 weeks after the procedure, primarily to pick up hemorrhagic complications after therapeutic procedures (polypectomy which may cause bleeding after 2-3 weeks).

Alternative to the use of a questionnaire on paper, the use of a web- and/or telephone-based interphase will be evaluated (see chapter 11).

### Patient's costs

The study covers the initial screening examination and any follow-up colonoscopies scheduled during the trial screening period. Expenses for bowel cleansing and the endoscopic examinations performed at the screening centres are free of charge. Travel expenses are not covered. Any subsequent colonoscopies are scheduled at the patient's local hospital in accordance with national guidelines, and must be covered, as any routine clinical examination, partly by the patient and partly by the national health insurance.

### Minimal requirements at the screening centres

#### Space

- endoscopy suites with suction equipment
- toilet
- room for technical equipment
- office
- waiting area

#### Equipment

- automatic endoscope washing machine
- video colonoscopes
- diathermy units
- ScopeGuide<sup>®</sup> (or equivalent 3D imaging system),
- CO<sub>2</sub> insufflator.
- Disposable biopsy forceps and snares

#### Manpower

- colonoscopists

- secretary
- endoscopy assistants.
- pathologists

### Participating centres and local investigators

One or more centres in each of the participating countries. The screening period is planned to last approximately 2 years, with a workload of between 500 and 5,000 colonoscopies per centre. Quality of the endoscopies has to be proved beforehand for each eligible centre. CO<sub>2</sub> insufflation is required for the screening examinations, and the use of endoscopic imaging systems (e.g. scope guide) are encouraged.

### Participating countries and invited individuals in the screening group (April 2009)

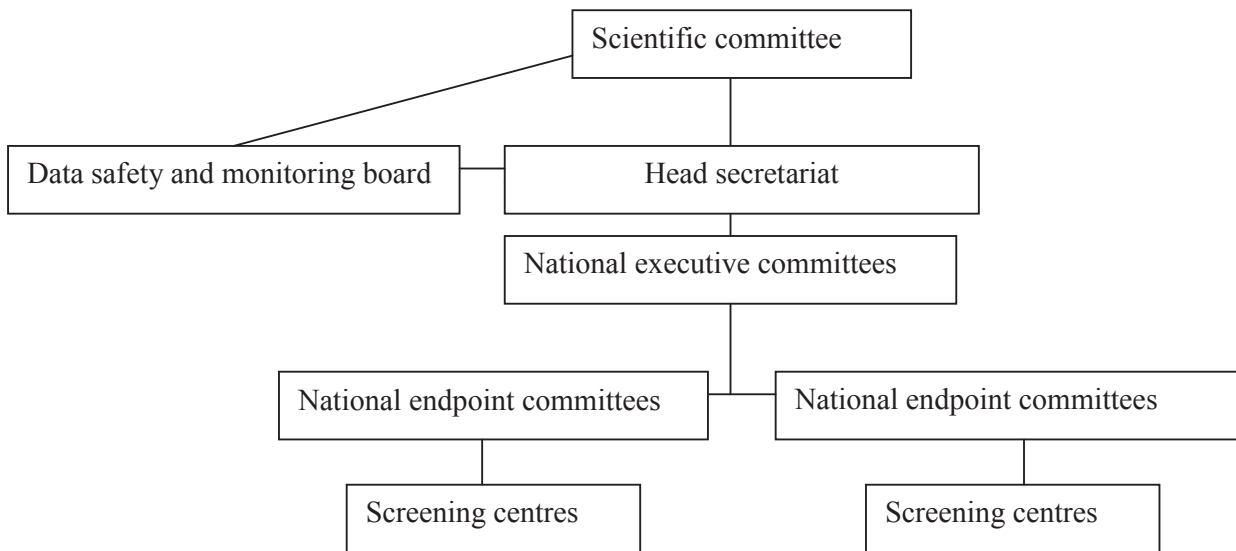
	<b>Funded</b>	<b>Pending for funding</b>	<b>TOTAL</b>
<b>Poland</b>	<b>10,000</b>		
<b>The Netherlands</b>	<b>5,000</b>		
<b>Sweden</b>		<b>5,000</b>	
<b>Norway</b>	<b>5,000</b>		
<b>Iceland</b>		<b>1,000</b>	
<b>Total no. of invited to screening group</b>			<b>26,000</b>

Additionally, the following countries are willing to participating in the trial, but have at the current time no funding for active participation: Latvia, Hungary, Czech Republic, Denmark, Finland

## References

1. [http://europa.eu.int/comm/health/ph\\_determinants/genetics/keydo\\_genetics\\_en.htm](http://europa.eu.int/comm/health/ph_determinants/genetics/keydo_genetics_en.htm)
2. Regula J, Rupinski M, Kraszewska E et al: Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia N Engl J Med 2006;355:1863-72
3. Rex DK, Johnson DA, Lieberman DA, et al. Colorectal cancer prevention 2000: Screening recommendations of the American College of Gastroenterology. Am J Gastroenterol 2000;95:868-77
4. Kronborg O. Screening for colorectal cancer in the average-risk population. Sem Colon Rect Surg 2002;13:16-30
5. Mandel JS, Bond J, Church TR et al. Reducing mortality from colorectal cancer by screening for faecal occult blood. N Engl J Med 1993;328:1365-71
6. Kronborg O, Fenger C, Olsen J, et al. Randomised study of screening for colorectal cancer with fecal occult blood test. Lancet 1996;348:1472-7
7. Hardcastle JD, Chamberlain JO, Robinson MHE et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472-7
8. Liebermann DA, Weiss DG. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. N Engl J Med 2001;345:555-60
9. Atkin, W. S., R. Edwards, J. Wardle, J. et al. Design of a multicentre randomised trial to evaluate flexible sigmoidoscopy in colorectal cancer screening. J Med Screen 2001;8: 137-44.
10. UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. Lancet 2002;359:1291.300
11. Bretthauer M., Gondal G, Larsen I, et al. Design, organization and management of a controlled population screening study for detection of colorectal neoplasia: attendance rates in the NORCCAP study (Norwegian Colorectal Cancer Prevention). *Scand J Gastroenterol* 2002; 37(5): 568-73.
12. Palitz AM, Selby JV, Grossman S, Finkler LJ, Bevc M, Kehr C, et al. The colon cancer prevention program (CoCaP): rationale, implementation, and preliminary results. HMO Pract 1997;11:5-12
13. Thiis-Evensen E, Hoff G, Sauar J, et al. Population-based surveillance by colonoscopy: Effect on the incidence of colorectal cancer. Telemark Polyp Study I. *Scand J Gastroenterol* 1999;34:414-20
14. Hoff G, Thiis-Evensen E, Grotmol T, et al. Do undesirable effects of screening affect all-cause mortality in flexible sigmoidoscopy programmes? Experience from the Telemark Polyp Study 1983-1996. *Eur J Cancer Prev.* 2001;10:131-7
15. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer: a population-based, case-control study. *Ann Intern Med* 2008;150:1-8
16. Winawer SJ, Zauber AG, Ho MN et al. Prevention of colorectal cancer by colonoscopic polypectomy. N Engl J Med 1993;329:1977-81
17. Levin B, Lieberman DA, McFarland B, et al. Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline From the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008;134:1570-95
18. Sobin LH, Wittekind CL eds. TNM classification of malignant tumors. 6th edition. New York; John Wiley & sons 2002
19. Hamilton SR, Aaltonen, LA. Pathology and Genetics. Tumours of the Digestive System WHO Classification of tumours, vol. 2. IARC WHO (DenneeClassification of tumours, No 2; 20

### NordICC organizational structure



#### **Scientific committee (SC)**

**Definiton:** The SC is the head group in the internal NordICC hierarchy. It consists of at least one member from each of the participating countries and the coordinating secretariat.

**Tasks and responsibilities:** Overall responsibility and decision authority for the trial in general, including aspects of management, screening, quality control, endpoint observation and publication activity. Reviews and summarizes reports on quality and adverse events from the secretariat and sends information to the DSMB each month during the screening period.

#### **National executive committees (NEC)**

**Definiton:** The national NEC's are the coordinating groups in the participating countries. At least one member should be from each of the national screening centres. Unless otherwise decided by the National Executive Committtee, the chair person should be its representative in the Scientific Committee.

**Tasks and responsibilities:** Overall responsibility for the national screening centres and the management of the trial in the respective country. Reports to the SC every month.

#### **Endpoint committee (EC)**

The EC group is responsible for standardisation of classification of causes of death (extraction forms for uniform classification of deaths) or other endpoints. Due to language problems during revision, there should be one committee in each country, suggestively consisting of one pathologist, one oncologist and one surgeon. The abstraction form should be identical in all participating centres.

#### **Coordinating secretariat (Cancer Registry of Norway, Oslo)**

The Oslo secretariat manages the trial together with the national screening sites and is responsible for data collection from all screening centres. The NordICC main database is situated here. The secretariat sets up and manages the NordICC trial databases, including tracking of data

and statistical service. The secretariat should have a continuous knowledge on quality issues and adverse events and report to the scientific committee every month.

### **Data safety and monitoring board (DSMB)**

DSMB is an external group; their members are not connected to the trial in any way. The DSMB gives advice to the SC on adverse event and endpoint evaluation. The DSMB advises the SC on early trial termination. The group should consist of one cancer epidemiologist, one biostatistician and one gastroenterologist.

### Groups and group members per April 2010

<b>Function</b>	<b>Committe/group members</b>	<b>Country/region</b>
	<b>Scientific Committee, voting members</b>	
PI	Michael Bretthauer	Norway
Co-PI	Geir Hoff	Norway
Chair, Scientific committee	Hans-Olov Adami	USA/Sweden
Polish representative	Jaroslav Regula/Michal Kaminski	Poland
Dutch representative	Ernst Kuipers/Monique van Leerdam	the Netherlands
Icelandic representative	Tryggvi Stefansson	Iceland
Swedish representative	Lars Pahlman	Sweden
Biostatistician	Ann Zauber	USA
Biostatistician	Marjolein van Ballegoijen	Netherlands
Epidemiologist	Miguel Hernan	USA
	<b>Scientific Committee, observers</b>	
Observer	Anders Ekbohm	Sweden
Observer	Louise Olsson	Sweden
Observer	Marcis Leja	Latvia
Observer	Miroslav Zavoral	Czechia
Observer	Istvan Racz	Hungary
Observer	Morten Rasmussen	Denmark
Observer	Nea Malila	Finland
	<b>National Executive Committee</b>	
	<b>Norway</b>	
	Geir Hoff	
	Michael Bretthauer	
	<b>Poland</b>	
	Michal Kaminski	
	Jaroslav Regula	
	<b>Netherlands</b>	
	Ernst Kuipers	Rotterdam
	Monique van Leerdam	Rotterdam
	<b>Iceland</b>	
	Tryggvi Stefansson	Reykjavik
	<b>Sweden</b>	
	Lars Pahlman	Uppsala county
	Georg Dafnis	Södermanlands county



Kenneth Smedh	Västmanlands county
Magnus Andersson	Örebro county
Thomas Hallgren	Värmlands county
Lars Strandberg	Dalarnas county
	Gästrik-Hälsinge county
Jörn Holm	
Louise Olsson	
<b>Latvia</b>	
Marcis Leja	
Mairita Ergle-Morica	

**Endpoint Committee  
(to be decided)**

**Coordinating Secretariat, Oslo**

Geir Hoff	Norway
Michael Bretthauer	Norway
Cecilie Krogh	Norway

**Data Safety & Monitoring Board (DSMB)**

Jean Faivre	France
Jack Mandel	Canada
Stephen Duffy	UK

## Authorship

The following principles should accommodate four overarching goals with regard to authorship of papers arising from the trial:

- Be in agreement with the Vancouver guidelines for authorship.
- Make sure that investigators receive adequate academic reward for their contributions to NordICC.
- Be completely transparent, regularly reviewed and available for open discourse at any time.
- In all scientific emanation from this project, the list with named authors will be followed by the group acronym (NordICC) and an exhaustive footnote listing all collaborators and their specific role on the project.

For specific manuscripts, the list of named authors need to accommodate both individual contributions and, in some instances, limits to the number of authors that scientific journals accept. Slightly different principles may be applied to papers reporting main findings in the entire study and to papers based on ancillary studies and projects using NordICC as a frame-work to address novel hypothesis not outlined in this protocol.

When main findings are reported, the author list should name both the scientific committee and one representative from each participating centre. One (or two) of these representatives might have taken the lead in analysis and drafting of the manuscript and appear as first (and second) author. Otherwise, they will be listed in an order determined by the number of subjects their centre has recruited to the trial. The position as last author (which can be

shared by two individuals who have contributed equally) should rotate between the participating countries. Within each country, the members of the scientific committee would be responsible for electing their representative. In publications based on ancillary studies and new projects created with NordICC as a frame-work, authorship needs to be discussed on a case-by-case basis.

# Amendment 1

(approved by the NordICC board on meeting in Oslo on Nov 6, 2014)

## 1. Study size and ratio between screening and control groups

In order to increase the statistical power of the study, we open for recruitment of more individuals to be assigned to the control group.

There is a lack of individuals in the original trial areas within the NordICC age range, as all or most of the individuals who live in the areas have been included in the original cohort. Thus, the new individuals will be ascertained from geographic areas in the participating countries which have similar baseline risks for colorectal cancer incidence and mortality as compared to the originally included trial areas. Similarity will be established by retrieving data from the national cancer and cause of death registries for the new areas of interest, and reviewed by the scientific board before approval.

After board approval of eligibility of the new control areas (comparable baseline risk as original areas), the new control subjects will be randomly drawn from the new cohorts (all men and women in the new geographic areas matched by age and sex to the original trial cohort). The number of new controls will be as high as the number of original controls. This results in a ratio of screening versus control (including new and old controls) of 1:4, instead of the original 1:2 ratio.

We will perform two endpoint analyses:

- a. The primary analysis will only include the original cohort (1:2 ratio)
- b. An additional (secondary) analysis will also include the new control cohort (1:4 ratio)

Thus, the primary endpoint analysis will still be the originally planned, as described in the protocol.

## 2. Data Safety and Monitoring Board (DSMB)

The main tasks of the DSMB have been to oversee the study enrolment, performance and quality of screening interventions. The study recruitment was concluded in June 2014. Thus, there will be no further patient interventions in the NordICC trial. Therefore, the DSMB will be discontinued and the members informed by the principal investigator and the chairman of the board. As early stopping rules don't apply to the NordICC trial after the intervention phase (as there is no consequence of early stopping), the scientific board does not find it necessary to maintain a DSMB for NordICC for the remaining trial period. Thus, the DSMB will be released from its duties with appreciation, and no new members will be assigned. The DSMB members will be acknowledged in NordICC main publications.

## 3. Database management

Frontier Science Scotland Ltd assumed responsibility for the NordICC database management in 2011. The partnership is further regulated by contracts between Frontier Science Scotland and the Oslo NordICC main secretariat, and with the participating countries and centres. Frontier Science will organize the follow-up of study individuals together with the PI and Co-PI's, and the national representatives. Eleanor McFadden of Frontier Scotland Ltd. is appointed a member of the scientific board.

## 4. Participating countries update

The following countries have actively recruited individuals to the trial and will thus constitute the core research group, together with scientific personnel from the USA

- Poland

- Norway
- Netherlands
- Sweden

## 5. New NordICC groups structure and members

Due to changes in participation of patients from different countries, changes in personal and responsibilities, the following changes for individuals in the NordICC groups are agreed on:

- The NordICC scientific committee constitutes of members of the group, without no distinction between voting and observing members.
  - Michal Kaminski (Poland) is appointed as new Co-PI
  - Evelien Dekker (NL) substitutes Monique van Leerdam (NL)
  - Iris Landorp-Vogelaar (NL) substitutes Marjolein van Ballegooijen (NL)
  - Kjetil Garborg (N), Mette Kalager (N), Magnus Løberg (N), Eleanor McFadden (UK), Manon van Spaander (NL), and Maciej Rupinski (PL) are appointed new members
  - Anders Ekblom, Marcis Leja, Miroslav Zavoral, Istvan Racz Morten Rasmussen, and Nea Malila leave the board
  - The National Executive Committees of Latvia and Iceland are discontinued
  - The Data Safety and Monitoring Board is discontinued

### NordICC committees as of Nov 6<sup>th</sup>, 2014:

Committee/group members	Country/region
<b>Scientific Committee members</b>	
Hans-Olov Adami (Chair)	Sweden
Michael Bretthauer (PI)	Norway
Michal Kaminski (Co-PI)	Poland
Geir Hoff (Co-PI)	Norway
Jaroslav Regula	Poland
Ernst Kuipers	the Netherlands
Evelien Dekker	The Netherlands
Lars Pahlman	Sweden
Louise Olsson	Sweden
Ann Zauber	USA
Iris Landorp-Vogelaar	Netherlands
Miguel Hernan	USA
Mette Kalager	Norway
Eleanor McFadden	UK
Manon van Spaander	Netherlands
Tryggvi Stefansson	Iceland
Magnus Løberg	Norway
Kjetil Garborg	Norway
Maciej Rupinski	Poland
<b>National Executive Committee</b>	
<b>Norway</b>	
Michael Bretthauer, Geir Hoff	Oslo
<b>Poland</b>	
Michal Kaminski, Jaroslav Regula	Warsaw
<b>Netherlands</b>	
Ernst Kuipers, Evelien Dekker	Rotterdam,

**Sweden**

Lars Pålman  
Georg Dafnis  
Kenneth Smedh  
Magnus Andersson  
Thomas Hallgren  
Lars Strandberg  
Jörn Holm

**Coordinating Secretariat, Oslo**

Michael Bretthauer  
Mette Kalager

Amsterdam

Uppsala county  
Södermanland  
Västmanland  
Örebro  
Värmland  
Dalarnas  
Gästrik-Hälsinge

Norway

Norway



# Statistical Analysis Plan

## NordICC Baseline analysis

MB 09.10.2014

### 1. Baseline Characteristics

- a. Numbers, age and sex of all randomized individuals by country and center
- b. Number, age and sex of those randomized to colonoscopy and no screening
- c. Number, age and sex of those who had the intervention (colonoscopy screening compliance rate) amongst those randomized to the intervention (screening compliance) by country and center
  - i. Number, age and sex for those who complied
- d. Number, age and sex of patients who were randomized to the intervention and consented to participate, but were excluded from the colonoscopy per country and centre
- e. Number, age and sex of patients who did not participate (non-compliers)

### 2. Baseline colonoscopy data and findings (by country, center and endoscopist where available)

Domains: (coloreg dat).

- a. Patient characteristics
  - i. Symptoms
  - ii. Lifestyle (BMI, smoking...)
  - iii. Family history of CRC
- b. Bowel regimen and cleansing quality
- c. Coecum intubation rate
- d. Time to coecum, procedure time
- e. Sedation regimens
  - i. No sedation
  - ii. Sedation from start
  - iii. Sedation after start
  - iv. If sedation:
    1. Midazolam only (median dose)
    2. Opioid only (median dose; diff. drugs)
    3. Combination Midazolam/Opioid
    4. Other (specified)
- f. Findings and therapy (split by proximal and distal colon, and overall)
  - i. Polyps
    1. High-risk adenomas, low-risk adenomas, other polyps
  - ii. Cancers
    1. Treatment method (surgery or endoscopic treatment)
    2. Stage
  - iii. Other findings (other disease, other tumours etc)
- g. Number, age and sex for patients with advanced adenomas (high-grade dysplasia, villous features, size 10 mm or above, or three or more), and non-advanced

- 3. Complications and adverse events of colonoscopy by country, center and endoscopist**
  - a. Vasavagal reactions, pain etc (Coloreg)
  - b. Perforations
  - c. Bleeding
  - d. Death and morbidity within 30 days
- 4. Pain, discomfort and satisfaction of colonoscopy by country, center and endoscopist and sedation (Gastronet data)**

Domains:

  - a. Patient pain and discomfort during and after exam
  - b. Satisfaction
  - c. Complications within 24 hours
  - d. CO2 insufflation