EPoS
the European Polyp Surveillance trial group

PROTOCOL. Version Feb 11 2017

Amendments:

February 11th 2017

PROTOCOL SUMMARY AND SIGNIFICANCE

This protocol describes the epos (ancient Greek (Επος) for “story”) of a group of related clinical trials aiming at addressing one of the most important unsolved challenges in the prevention of colorectal cancer (one of our major cancer killers); the surveillance of patients with premalignant polyps in the large bowel.

This project is timely because large scale colorectal cancer screening programmes are currently rolled out in most Western countries. These programmes are diagnosing large numbers of individuals with premalignant polyps (adenomas and serrated polyps). This creates both a diagnostic and resource dilemma, because the optimal surveillance strategy for these individuals to reduce future cancer risk is currently unknown.

The EPoS trials will randomize or register more than 27,500 individuals in different European countries to different surveillance colonoscopy intervals to disentangle the most effective and cost-effective surveillance strategy for the population. Subjects will be randomized according to their presenting polyp characteristics

The EPoS I trial randomizes patients with low-risk adenomas into 5 or 10-year surveillance; EPoS II randomizes patients with high-risk adenomas into 3 or 5-yearly surveillance; EPoS III will include patients with serrated polyps in a one-arm study with surveillance after 5 and 10 years. The primary endpoint for all three trials is incidence of colorectal cancer after 10 years of follow-up.

This EPoS trials are the largest in polyp surveillance ever conducted. They address a clinical problem affecting hundreds of thousand individuals in Europe and the US each year, it has a large size, and should thus provide definitive results.

1. BACKGROUND

Colorectal cancer (CRC) is a major global disease burden with more than 1.2 million people diagnosed each year. The mortality rate is high, making colorectal cancer one of the major cancer killers worldwide (1).

To attack this public health problem most Western countries have introduced or are about to introduce population screening programmes for CRC. The primary aim of such programmes is the reduction of CRC incidence and mortality in an average risk population. The predominant screening tools for CRC are fecal occult blood testing (FOBT or FIT), flexible sigmoidoscopy and colonoscopy (2). The latter two have the potential to prevent cancer by removing precursor lesions (adenomas). Colonoscopy is the gold standard for detection for polyps and CRC as it has highest sensitivity. It is the examination of choice after a positive screening test other than colonoscopy, as well as for surveillance of high-risk individuals for CRC, e.g. persons with previous adenomas or cancer, or persons with a hereditary risk for CRC.

Due to the increasing use of screening for CRC, more and more people are diagnosed with adenomas. These individuals are in need for surveillance strategies to prevent future CRC and death from CRC. In order for the screening intervention to be efficient, an optimal surveillance interval is of paramount importance (3). However, today, there is a striking lack of scientific knowledge about the risk magnitude of adenoma patients developing CRC in the future. Therefore, no evidence-based risk stratification algorithm has been established (2,4). No studies have convincingly demonstrated that post-polypectomy surveillance reduces CRC incidence or mortality. Some studies have suggested that surveillance colonoscopy may be effective in reducing the risk of colorectal cancer among patients with adenomas (5,6). Recently, a large, nationwide study in an environment of limited surveillance showed no excess risk of colorectal cancer after adenoma removal for low-risk adenomas but a small excess for high-risk patients (7). Thus, the proper surveillance strategy and interval after adenoma removal is currently unknown.

Consequently, although guidelines on polyp surveillance do exist in Europe and the US, they are (due to the lack of adequate scientific evidence) based on

“expert opinion” and low quality data, and they differ in their recommendations (2,4). In fact, all guidelines specifically emphasise the need for large-scale clinical trials to close the knowledge gap in polyp surveillance (2,4).

Because colonoscopy is an expensive and invasive procedure with a certain risk of adverse events and complications, surveillance colonoscopy should be targeted at those individuals who are most likely to benefit. Also, surveillance colonoscopies should be offered at a frequency required to provide adequate protection against development of cancer yet be cost-effective for providers and caregivers (2). Today, surveillance colonoscopy is one of the main indications for colonoscopy, accounting for more than 20% of all colonoscopies performed in patients older than 55 years in the U.S. (8). In many countries, surveillance colonoscopies are filling colonoscopy lists and large amounts of money are spent without knowing whether this is an effective strategy.

On the basis of adenomas characteristics at screening, patients can be stratified into different risk groups for subsequent development of CRC. Usually, patients are classified into low risk and high risk (some guidelines additionally define an intermediate risk group). The most commonly used characteristics are polyp size and number, as well as histologic type (villous or tubular growth pattern), and grade of dysplasia (low grade or high grade dysplasia) (2,4). The low risk group usually includes people with 1-2 tubular adenomas smaller than 10 mm in diameter; and the high-risk group includes individuals with 3 or more adenomas; or any adenoma larger than 9 mm in diameter, or any adenoma with high grade dysplasia or villous growth pattern.

More recently, a new polyp type, the serrated polyp, has been identified as a risk factor and a precursor for CRC (4). In the past, serrated polyps were considered to have no malignant potential, but recent studies indicate that individuals with serrated polyps are at higher risk for CRC than the average population (4). Due to the lack of proper studies, however, there is great uncertainty on the natural course of serrated polyps, the speed of progression and the quantification of subsequent risk for cancer, and thus surveillance intervals for these patients.

Reflecting this, current surveillance recommendations for all groups differ between guidelines (see table 1) and are mostly classified as of low or very low evidence quality (9).

Table 1: Current guideline recommendations for polyp surveillance

	Low-risk adenoma patients	High-risk adenoma patients	Serrated polyp patients
European Union Guidelines (2)	**10 years/none**	**1-3 years**	**No recommendation**
European Society for Gastrointestinal Endoscopy (10)	**10 years**	**3 years**	**3 or 10 years**
United States Multi-Society Task Force (4)	**5 years**	**3 years**	**3-5 years**

Recommended intervals are arbitrary because of the lack of clinical trials with adequate statistical power and long-term follow-up. Thus, it is possible that longer intervals have the same utility in prevention of CRC, with improved cost-effectiveness.

There are only two high-quality randomized clinical trials comparing different intervals in surveillance colonoscopy (11,12). In the US study (11), after baseline colonoscopy with excision of adenomas, follow-up colonoscopy at 1 and 3 years was compared with one colonoscopy at 3 years. There were no differences in the rate of advanced adenomas between the two groups, concluding that a surveillance interval of 3 years may be recommended. The results of this study are the main basis for recommendation of 3 years intervals after removal of high-risk adenomas. The other study (from Denmark) (12) randomized individuals into multiple comparison groups by adenoma characteristics. The study was too small to uncover clinically significant differences between the groups, although there was a trend of CRC being more common in the 4-year surveillance group compared to a 2-year surveillance group.

However, the confidence intervals were very wide (RR 6.2; 95% CI 1.0-117) and thus the results are not conclusive.

In summary, surveillance recommendations after polyp removal are based on low quality evidence, due to the lack of large-scale clinical trials. The aim of this protocol is to address the optimal surveillance intervals for persons with different risks of CRC based on findings at screening colonoscopy in order to reduce the future risk of CRC. We plan to perform two large multinational randomized trials comparing different surveillance intervals in patients with low-risk and high-risk adenomas, and a registration trial to observe the natural history of serrated polyps.

2. OBJECTIVES

The EPoS trials aim to investigate the optimal time intervals for colonoscopy surveillance of patients with polyps of the large bowel. The EPoS trials constitute two parallel-group randomized controlled trials; **EPoS I**; for patients with low-risk adenomas; **EPoS II**; for patients with high-risk adenomas. **EPoS III** is an observational study focusing on serrated polyps.

3. TRIAL ENDPOINTS

3.1 PRIMARY ENDPOINT

The primary endpoint in EPoS I, II and III is CRC incidence. CRC incidence will be compared in the different arms in EPoS I and II, and in EPoS III.

3.2 SECONDARY ENDPOINTS

The following endpoints will also be compared in the different arms in EPoS I and II, and in EPoS III

- Colorectal cancer mortality
- Cost-effectiveness
- Yield of advanced adenomas, adenomas and serrated polyps
- Adverse events within 30 days of colonoscopy (defined as bleeding requiring tranfusion or hospitaization, perforation, death or other colonoscpy-related events)
- Differences regarding indication of baseline colonoscopy

3.3 PREDEFINED SUBGROUP ANALYSES

Subgroups defined by variables which may be associated with the risk of CRC and adenoma yield during follow-up will be analysed. These include: patient age and gender, reason for first colonoscopy (colonoscopy screening; colonoscopy after a positive screening test (FIT, FOBT, sigmoidoscopy;); clinical symptoms; other indications) and the following polyp characteristics: type of polyp, size of polyp, in case of adenoma: growth pattern (tubular, tubulovillous or villous), grade of dysplasia (high vs. low); multiplicity and location of polyps (proximal vs distal colon).

4. METHODS

4.1 JOINT DESIGN SETTING

EPoS I and II are randomised controlled trials without drugs. EPoS III is a one-arm observational study. Eligible for all trials are individuals with no history of CRC or adenomas between 40 and 74 years who have undergone colonoscopy with removal of one or more adenomas or serrated polyps at one of the study centres (hospitals in the participating countries, approved for trial participation). The indication for colonoscopy is not restricted in any way, and includes screening as well as clinical symptoms or other indications. At the baseline colonoscopy and before study entry, all polyps have to be completely removed, the colon fully investigated with adequate quality of bowel preparation, and the colonoscopy needs to be performed under high quality standards.

~~Patients can be included at any point in time between the baseline colonoscopy and the date of first surveillance colonoscopy.~~

4.1.1 Surveillance colonoscopies

Surveillance colonoscopy is the intervention tool used in all trials. At surveillance colonoscopy, all detected polyps will be registered and described, removed whenever possible and subjected to histopathology. Standard video-colonoscopes are used for the examinations. All required data from endoscopy reports, quality-data used for quality monitoring and histopathologic results must be registered in the central study database. Local pathology labs will serve the participating centres and perform

histopathological analysis of the tissue samples. All histopathology reporting follows WHO guidelines for classification and grading (13). Serrated polyp classifications are according to recent guidelines (13).

4.1.2. Time of surveillance colonoscopies

Surveillance colonoscopies are scheduled at the participating centres according to the time slots defined in the protocol for the different study groups and arms (see below). For all participating patients, a reminder will be sent by the EPoS database management team to the national coordinators and the study-administration of the participating centres approx. 4-6 months before the surveillance colonoscopy is scheduled.

Surveillance colonoscopies are to be performed within a 6-month time interval from the protocol-defined date. Surveillance colonoscopies which are performed earlier than 6 months before or later than 6 months after the protocol-defined date are recorded as a protocol deviation (but results as well as reason for deviation are to be recorded in the trial database).

4.2 JOINT INCLUSION CRITERIA FOR ALL EPOS TRIALS AT BASELINE COLONOSCOPY

* Men and women age 40-74 years
* Cecal intubation (preferably documented by images/video of the appendiceal orifice and the ileocecal valve; but not required).
* Adequate colonic cleansing, with Boston Bowel Cleansing Score equal or higher than 2 points in all colonic segments.
* Complete excision of all polyps at baseline colonoscopy findings (as judged by the trial endoscopists)
* Randomisation must be performed no longer than 26 weeks (182 days) from completion date of baseline colonoscopy

4.3 JOINT EXCLUSION CRITERIA FOR ALL EPOS TRIALS

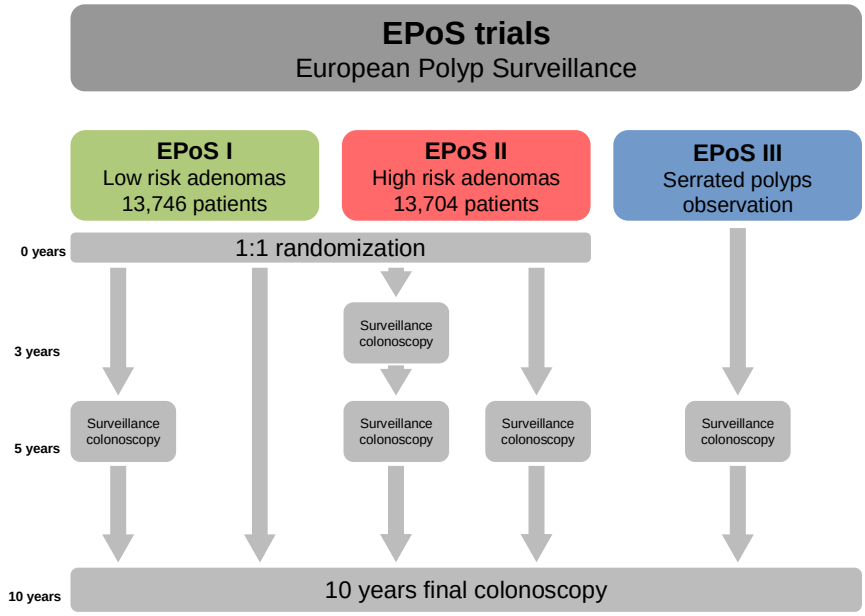
- Lack of consent
- History of CRC or adenomas
- More than 10 adenomas

- History of serrated polyps ≥ 10 mm in diameter at any colorectal location or ≥ 5 mm if located proximal to the splenic flexure

- Serrated polyposis syndrome (SPS)
  defines as:
    - ≥20 serrated polyps, or
    - At least 5 serrated polyps proximal to the sigmoid colon, of which at least two are >10 mm in size, or
    - Any serrated polyp proximal to the sigmoid colon in a first degree relative with SPS.

  .
- Incomplete colonoscopy
- Incomplete endoscopic excision of polyps (exception: In consistence with current guidelines (2, 4, 10), small (1-4 mm in diameter), whitish polyps in the rectum are considered insignificant for future colorectal cancer risk and are therefore not included in evaluation of patients for the EPoS trials)
- Non retrieval of any polyp (for EPoS I) or non retrieval of any polyp > 9 mm and the patient could be consistently classified as high-risk (for EPoS II)
- Genetic cancer syndrome (adenomatous or serrated polyposis syndrome; Lynch or Lynch-like syndrome)
- Inflammatory bowel disease
- History of surgical colon resection for any reason
- Severe co-morbidity with reduced life expectancy (NYHA 3-4)
- On-going cytotoxic treatment or radiotherapy for malignant disease
- Long-lasting attention and nursing services (somatic or psychosocial, mental retardation).

Figure 1: EPOS trials overview



4.3 SPECIFIC DESIGNS AND SETTINGS

4.3.1. EPoS I

Eligible individuals are persons with low-risk adenomas removed at baseline colonoscopy (1-2 tubular adenomas size <10mm with low-grade dysplasia) and no serrated polyps with dysplasia, with diameter 10 mm or larger at any location or with diameter 5 mm or larger proximal to the splenic flexure.

Individuals will be **randomized** into one of two intervention groups:

Group 1: Surveillance colonoscopy at 5 and 10 years after baseline colonoscopy.

Group 2: Surveillance colonoscopy at 10 years after baseline colonoscopy.

The primary and secondary endpoints will be analyzed directly after the 10 year surveillance colonoscopy, (figure 1).

4.3.2 EPoS II

Eligible individuals are persons with high-risk adenomas removed at baseline colonoscopy (three to ten adenomas; or one or more adenoma w/size ≥ 10mm, or one or more adenoma with high-grade dysplasia or villous growth pattern).

Individuals will be **randomized** into one of two intervention groups:

Group 1: Surveillance colonoscopy 3 and 5 years after baseline colonoscopy

Group 2: Surveillance colonoscopy 5 years after baseline colonoscopy

Individuals in both group 1 and group 2 will be subjected to a final colonoscopy surveillance after 10 years (figure 1).
The primary and secondary endpoints will be analysed directly after the 10 year surveillance colonoscopy, (figure 1). A secondary analysis will be performed after the 5 year colonoscopy.
For centers with current guidelines for 1 year surveillance for multiple or large (>20mm) adenomas; they may exclude those patients.

In both EPoS I and EPoS II, surveillance intervals after the first surveillance colonoscopy take into account findings at the first surveillance colonoscopy. Surveillance intervals after first surveillance colonoscopy are shown in **Figure 2A (EPoS I) and-B (EPoS II)**.

Figure 2. Surveillance intervals after first follow-up colonoscopy in EPoS I and II

Figure 2A: EPoS I

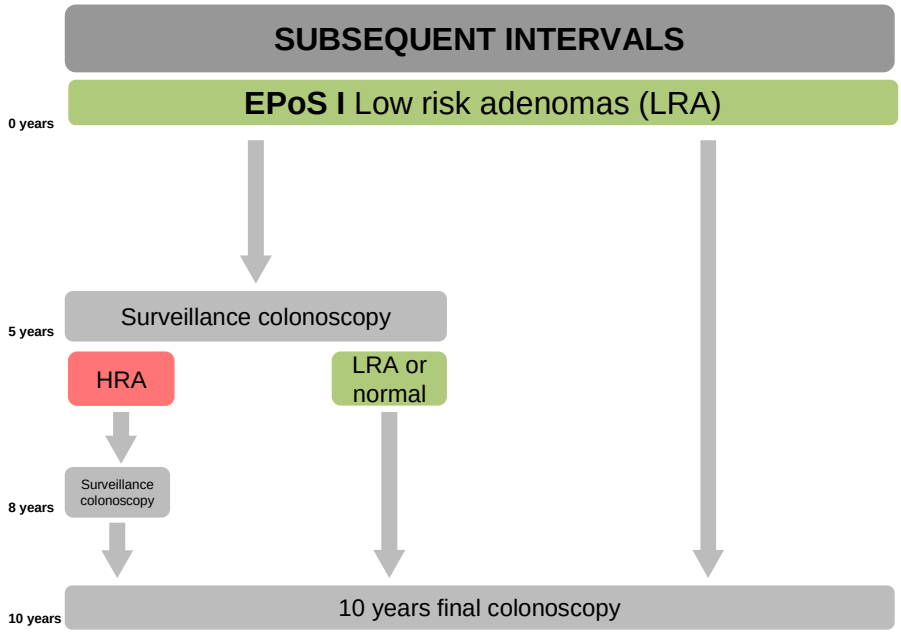
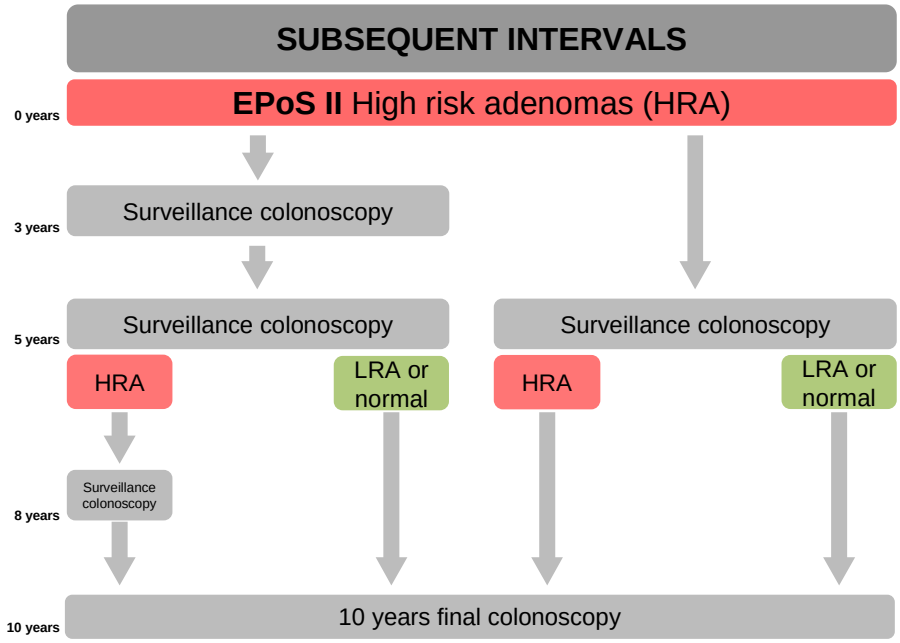


Figure 2B; EPoS II



LRA: Low risk adenoma; HRA: High-risk adenoma

Figure 2C: Polyp characteristics and eligibility in EPoS. SP: Serrated polyp, TSA: Traditional Serrated Adenoma.

Serrated polyp	≥10mm SP and/or SSA with dysplasia and/or TSA	≥5mm SP in the proximal colon	<10mm SP with no dysplasia in the distal colon	<5mm SP with no dysplasia in the proximal colon	None
No adenoma	EPoS III	EPoS III	No inclusion	No inclusion	No inclusion
1-2 tubular adenoma <10mm with low-grade dysplasia	EPoS III	EPoS III	EPoS I	EPoS I	EPoS I
>2 adenoma	EPoS II	EPoS II	EPoS II	EPoS II	EPoS II
Villous histology	EPoS II	EPoS II	EPoS II	EPoS II	EPoS II
High grade dysplasia	EPoS II	EPoS II	EPoS II	EPoS II	EPoS II
Adenoma ≥10mm	EPoS II	EPoS II	EPoS II	EPoS II	EPoS II

4.3.3. EPoS III;

Individuals are eligible if they have one or more serrated polyps (defined as polyps which are non-adenomatous; including hyperplastic polyp, sessile serrated adenomas/polyps (without and with dysplasia), and traditional serrated adenomas) ≥ 10 mm in diameter at any colorectal location, or one or more serrated polyps ≥ 5 mm if located proximal to the splenic flexure removed at baseline colonoscopy. Individuals are also eligible for EPoS III if they have at least one serrated polyp with dysplasia, irrespective of size.

Patients with adenomas eligible for EPoS and

1) serrated polyps with dysplasia or

2) serrated polyps 10 mm or larger in any location

3) serrated polyps 5 mm or larger proximal to the splenic flexure will be included in EPoS III.~~I and at Patients with serrated polyps AND adenomatous polyps are NOT eligible for EPoS III but they can be randomized for EPoS I or II according to the characteristics of their adenomatous polyps.~~ Patients with adenomas eligible for EPoS II and serrated polyps will be eligible for EPoS II. The data of these patients will

also be used for the EPoS III endpoint “yield of advanced neoplasia during surveillance colonoscopy after serrated polyp excision”.
Colonoscopy will be repeated at 5 and 10 years in all individuals in order to quantify CRC incidence and the yield of surveillance colonoscopy in detecting advanced neoplasia. Findings in surveillance colonoscopies will be compared with those obtained in the EPoS I and II trials.

5. VARIABLES OF INTEREST

For the detailed list of variables gathered in the trials, see the “List of variables” document attached

6. RANDOMIZATION

Randomization and data management will be done centrally for this trial. Eligible individuals will be invited to participate in the study and provide written informed consent prior to randomisation. Randomisation must be performed within 26 weeks (182 days) from baseline colonoscopy. Central randomization into the relevant trial (EPoS I, II or III) will be done using the Frontier Science randomisation system for all subjects, depending on their polyp characteristics. Subjects in EPoS I and II will be assigned to a corresponding treatment arm in a 1:1 ratio, depending on the additional stratification factors of site, age and sex.

7. FOLLOW-UP APPOINTMENTS

Local centres will send out follow-up invitations before the scheduled surveillance colonoscopy. Each centre will schedule the surveillance colonoscopy using their own system. A second reminder should be sent if the patient does not schedule the follow-up colonoscopy within 6 months of the first invitation.

8. QUALITY ASSURANCE OF SURVEILLANCE COLONOSCOPY

All EPoS centre are required to have an established system for quality control monitoring for endoscopy and histopathology services. This may include:

- Continuous monitoring of performance for centres and endoscopists
- Detection rates (polyps, cancers)
- Cecum intubation rate, withdrawal time, procedure time
- Use of sedation

- Complications and adverse effects
- Satisfaction of screenees with endoscopists/personnel/logistics
- Pain and discomfort during and after the screening examination
- Sample studies for histopathologic review of removed polyps

9. ETHICS

The study will be submitted for approval by the ethical committees at each participating centre. All individuals will provide written informed consent before enrolment.

10. STUDY MONITORING

10.1 ROUTINE MONITORING

The central data management office will be responsible for implementing quality control systems for the data collected. This will include checks on data values at the time of data entry (or, if data is transferred in batches, at the time that the data is uploaded into the central database). More complex central checks will also be conducted and any relevant queries sent to the participating centres in a timely way.

10.2 DATA SAFETY AND MONITORING BOARD (DSMB)

In addition to the routine monitoring described in section 10.1, there will be an Independent Data Safety and Monitoring Committee (DSMB) which will review the safety data at regular intervals, and the endpoint data at the defined intervals. The DSMB will also ensure that the study is conducted to required ethical standards. The members of the DSMB will be appointed by the Study Principal Investigators and must not be involved in the Study in any way. At least one statistician will be appointed to the Board, and the activities of the Board will be coordinated by the central data management office.

11. STATISTICAL ANALYSIS PLAN

Participants are followed for the primary endpoint (incidence of CRC), until death/incidence of CRC or end of follow-up, whichever happens first. All randomised participants are followed up through national or regional registries, regardless of whether they continue in the study or not. The primary analytic approach of the trial will follow the intention-to-treat (ITT) principle. We will compare the ~~average rate~~

~~of~~differences for each endpoint between the intervention groups by calculating risk differences and log-rank test ~~fitting a Cox proportional hazards model~~. The limit for the statistical significance will be established in 0.05 and 95% confidence intervals will be calculated. 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.

We will also do analyses to estimate the causal effect that would have been observed if all individuals in the intervention arms had been compliant. 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 one intervention arm requires the measurement of variables that jointly predict compliance with the baseline intervention and the endpoint. These variables include age, sex, baseline findings, physical activity, family history of colorectal cancer, smoking status, use of aspirin, NSAIDs, and hormone replacement therapy (9).

11. SAMPLE SIZE CALCULATION

Assuming a risk of CRC of 1% at 10 years for patients with low risk adenoma and of 2% for patients with high-risk adenomas at baseline and using a non-inferiority hypothesis with an equivalence interval of 0.5% for patients with low risk adenomas and 0.7% for patients with high risk adenomas, we need to include 6,783 individuals in each arm of the EPoS I trial, and 6,852 in each arm of the EPoS II trial. That supposes a total of 13,566 individuals randomized in the EPoS I and 13,704 in the EPoS II trial (with a power of 90% and a one-sided alpha of 0.05, see table).

The table shows power scenarios for 80% and 90% power for EPoS I and II, respectively.

Table 2: **Power Analysis for EPoS I and EPoS II, based on non-inferiority tests of two independent proportions.**

		10 year CRC incidence (proportion)			
	Power	P1 proportion	P2 proportion	Group size	Total sample size
EPoS I	80%	0.01	0.015	4897	9794
EPoS I	90%	0.01	0.015	6783	13566
EPoS II	80%	0.02	0.027	4947	9894
EPoS II	90%	0.02	0.027	6852	13704

P1 is the control group (shorter surveillance intervals), P2 is the intervention group (longer surveillance intervals).

11.1 Power rationale and Ethical considerations

Because removal of precursor lesions is assumed to prevent development of invasive cancer, it is implausible that less intense colonoscopic surveillance following adenoma removal would entail a lower cumulative incidence of colorectal cancer than more frequent surveillance. Such an outcome would, however, arise if the preventive effect of more frequent surveillance (with removal of incident adenomas) is outweighed by overdiagnosis of invasive cancer. A similar, or even identical, cumulative incidence of colorectal cancer following more or less frequent surveillance is theoretically possible, notably if the average progression time from a detectable precursor lesion (adenoma) to invasive cancer are longer than the different surveillance intervals applied in the EPoS trials. However, trials designed to document equivalence would require unrealistically large sample sizes and are therefore unlikely to ever be undertaken.

We considered as the most plausible outcome of the EPoS trials a slightly, perhaps only marginally, higher cumulative incidence of colorectal cancer with less than with more frequent colonoscopic surveillance. As a corollary, our two studies named EPoS I and EPoS II are both designed as non-inferiority randomized trials.

There are several reasons why trials designed to test this hypothesis are considered ethically justifiable:

- Firstly, colonoscopy carries risks, chiefly caused by bleeding or perforation of the colon. Although such complications are rare, notably in high quality settings, they are severe and sometimes life threatening. Hence, complications might substantially counteract the possible survival benefit of more intense surveillance which, in absolute terms (number of lives saved per colonoscopy) is small anyway.
- Secondly, screening to detect precursor lesions and invasive cancer may entail overdiagnosis and overtreatment of lesions that would never have progressed to a lethal stage during the individual's remaining lifetime. The probability of overdiagnosis is likely to be positively correlated with the number of surveillance colonoscopies. Although the extent of overdiagnosis is poorly quantified for colonoscopic screening, it is substantial for other, more established, screening tools such as PAP-smear for cervical cancer, mammography for breast cancer and prostate-specific antigen (PSA) for prostate cancer.
- Thirdly, colonoscopy is costly and resource demanding. As a corollary, resources saved by less frequent surveillance of adenoma patients might convey greater public health benefit if used for other purposes in the health care system.
- Fourthly, the level of inferiority considered acceptable need and should not be the same in EPoS I as in EPoS II. Instead, we argue that a slightly higher absolute difference (inferiority) in cumulative incidence of colorectal cancer would be justifiable in EPoS II. This argument is based on the fact that in EPoS II, subjects randomized to less intense surveillance are spared one or probably two colonoscopies during a 5-year period compared with currently applied guidelines. In contrast, subjects enrolled in the EPoS I trial would be spared only one colonoscopy over a 10-year period.

In conclusion, based on the arguments outlined above, and acknowledging that any defined level of inferiority can be considered arbitrary, we have accepted an equivalence level of 0.5% in absolute colorectal cancer incidence in EPoS I, and of 0.7% in EPoS II. This implies that the null hypothesis of non-inferiority would be

rejected only if the upper limit of the 95% confidence interval for the absolute difference in cumulative incidence of colorectal cancer after ten years of follow-up exceeds 0.5% in EPoS I and 0.7% in EPoS II.

12. PILOT PROJECT - COST-EFFECTIVENESS

We have performed a Markov model to compare differential cost of surveillance for advanced adenomas at 3 vs at 5 years (Zapater, unpublished data). Considering 15 years surveillance, the cost of a 3-year surveillance interval after high-risk adenoma removal would be 602.82 € per patient, whereas the cost with a 5-year surveillance interval would be 548.99 € per patient. That supposes a differential cost of 53.83 € per patient. In Europe, approximately. 6.000.000 colonoscopies are performed every year, and in approximately 5% of them high-risk adenomas are diagnosed. Thus, the estimated cost saving of 53.83€ per patient would translate to a total saving of 16.149.000 € per year in Europe. Moreover, a reduction in the number of colonoscopies performed for polyp surveillance will also avoid possible complications for patients. The colonoscopy burden that is currently being used for performing surveillance colonoscopy could be more appropriately used for CRC screening.

13. TIME PLAN

- One year is allowed for planning and set-up of the study infrastructure.
- The approximate recruitment period necessary to include a sufficient number of patients will be 2 to 3 years, or longer if the number of participating countries/centres is lower than expected.
- Surveillance colonoscopies will be performed at years 3, 5 and 10 of follow-up Main publication will be after 5 years and 10 years. The publications following analysis of the primary endpoint will be after 5 years and 10 years. A baseline manuscript documenting the quality control aspects of the colonoscopies will be prepared after all patients have been recruited.

14. **Study organisation**

PRINCIPAL INVESTIGATOR TEAM

ROLE: coordination of the study

MAIN PRINCIPAL INVESTIGATOR: Rodrigo Jover

CO-PRINCIPAL INVESTIGATOR: Michael Bretthauer

EPOS-III STUDY PI: Evelien Dekker

GOVERNING BOARD:

ROLE: Set the main rules of the trial and national coordination of the study

Reviews and summarizes reports on quality and adverse events from the secretariat and interacts with the DSMB.

COMPOSITION: 1 delegate per participant country and a representative of Frontiers Science

SPAIN: Rodrigo Jover (Chairman of the Governing Board)

NORWAY: Michael Bretthauer (Co-Chair)

NETHERLANDS: Evelien Dekker

SWEDEN: Hans-Olov Adami

POLAND: Michal Kaminski,

PORTUGAL: Mario Dinis-Ribeiro

AUSTRIA: Monika Ferlitsch

DENMARK: Rune Erichsen

FRONTIERS SCIENCE: Eleanor McFadden

SCIENTIFIC STUDY COMITEE

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. Join meetings of the Governing Board and the

Scientific Study Committee will be performed at least twice a year during the development of the study.

MEMBERS

Antoni Castells, Enrique Quintero, Pedro Zapater, Maria Pellisé, Joaquín Cubiella, Hans-Olov Adami, Miguel Hernán, Mette Kalager, Geir Hoff, Magnus Loberg, Øvind Holme, Monique van Leerdam, Iris Lansdorp-Vogelaar, Jaroslaw Regula, Paulina Wieszczy, Ann Zauber, Gerrit Meijer

DSMB: A 3-person group to investigate data after 5 years to decide on early termination of the study due to extreme differences between randomization arms will be designed in coming weeks

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