EPoS
the European Polyp Surveillance trial group

PROTOCOL. Version 14, April 29th 2021.

Attachments:

Surveillance colonoscopy - practical procedures

EPoS trial variables of interest

Protocol amendments

Amendments:

February 11th 2017, Version 10

June 22nd 2017, Version 11

May 31st 2018, Version 12

Dec 6th 2019, Version 13

April 29th 2021, Version 14

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 randomise 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 randomised according to their presenting polyp characteristics

The EPoS I trial randomises patients with low-risk adenomas into 5 or 10-year surveillance; EPoS II randomises 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 thousands 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 randomised 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) randomised 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 randomised 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 randomised 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 transfusion or hospitalization, perforation, death or other colonoscopy-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.

EPoS allows 52 weeks (365 days) to achieve a colon free of polyps (time from first to final baseline colonoscopy). Patients must be randomised at the latest 26 weeks (182 days) after the final baseline colonoscopy (clean colon achieved).

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 a Boston Bowel Preparation Scale score equal or higher than 2 in all colonic segments.
* Complete excision of all polyps at baseline colonoscopy (as judged by the trial endoscopists).
* Randomisation must be performed no longer than 26 weeks (182 days) from completion date of the final baseline colonoscopy.

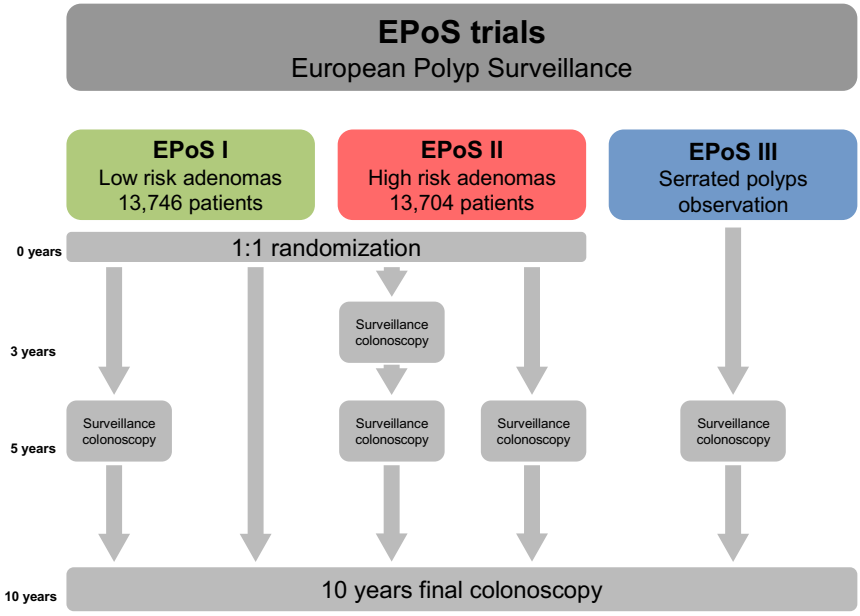
4.3 JOINT EXCLUSION CRITERIA FOR ALL EPOS TRIALS

- 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 number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis

  .
- 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 and EPoS III).
- Non retrieval of any polyp > 9 mm (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 need (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 <10 mm 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 **randomised** 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 ≥ 10 mm, or one or more adenoma with high-grade dysplasia or villous growth pattern). Individuals will be **randomised** into one of two intervention groups:

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

Group 2: Surveillance colonoscopy 5 years after final baseline colonoscopy

Individuals in both group 1 and group 2 will be subjected to a final surveillance colonoscopy after 10 years (figure 1).

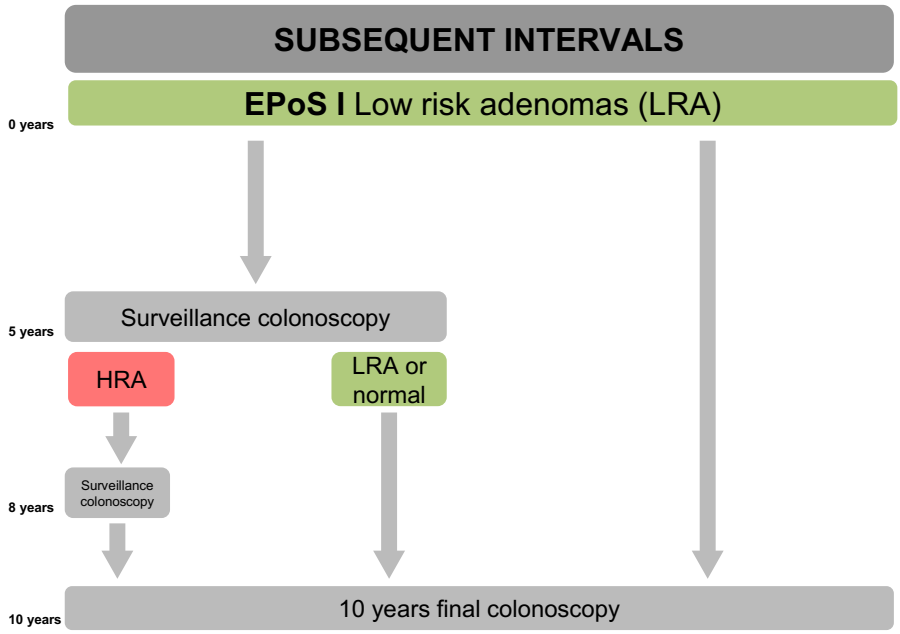
The primary and secondary endpoints will be analysed directly after the 10 year surveillance colonoscopy, (figure 1). A secondary analysis will be performed after the 5 year surveillance colonoscopy.

For centers with current guidelines for 1 year surveillance for multiple or large (>20 mm) 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)**.

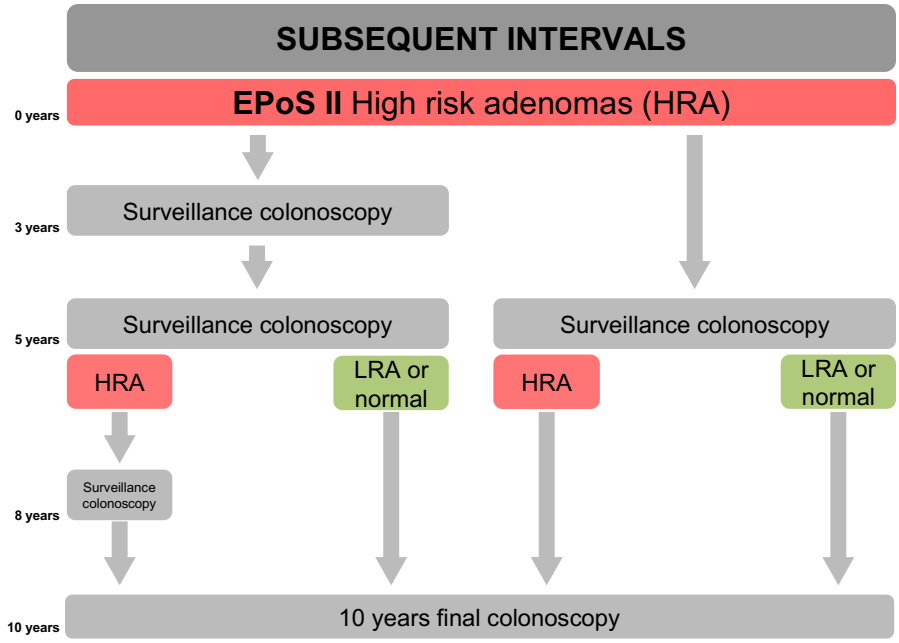
Figure 2. Surveillance intervals after first follow-up colonoscopy in EPoS I and II

Figure 2A: EPoS I



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

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	≥10 mm SP and/or SSA with dysplasia and/or TSA	≥5 mm SP in the proximal colon	<10 mm SP with no dysplasia in the distal colon	<5 mm 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 <10 mm 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 ≥10 mm	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 (TSA)) ≥ 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 (including all TSA), irrespective of size or location.

Patients with adenomas eligible for EPoS I and

1) serrated polyps with dysplasia (including any TSA) or

2) serrated polyps 10 mm or larger in any location or

3) serrated polyps 5 mm or larger proximal to the splenic flexure will be included in EPoS III. 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. RANDOMISATION

Randomisation 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 the final baseline colonoscopy. Central randomisation 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, see "Surveillance colonoscopy - practical procedures" attached. 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 centres 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 according 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.

10.3 Stable participant ID

- A **"stable" ID number** (an individual ID that we strongly believe will be there throughout the entire duration of the study, such as national ID, social security number, hospital patient ID etc) needs to be in the EPoS database from all patients
- This can be different in the different countries. Every solutions shall be approved by the EPoS Board in each case before enrolment can start at a centre
- These requirements are in place because EPoS is a very long study, it is running in many countries and many more centres, is dependent on local support and consistency, and will protect the integrity of the trial. The EPoS study group regards these requirements as necessary, and ethically, scientifically, economically, legally sound, and reasonable.

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 differences for each endpoint between the groups by calculating risk differences and applying the log-rank test. 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 randomised 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 randomised 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 randomised 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 Frontier 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

FRONTIER 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. Joint 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 Løberg, Øyvind 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 randomisation arms will be designed in coming weeks

REFERENCES

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Surveillance colonoscopy - practical procedures

The following procedures are recommended when patients are invited for surveillance colonoscopies in the EPoS trials:

1. **Notification of centres by Frontier Science**
    a. Centres are notified by Frontier Science of all patients who are due for surveillance colonoscopy according to their respective randomisation arm well in advance of the due date.
    b. Notifications are sent out by email to the local study nurse and local PI at the clinical centre on a regular basis (monthly), starting 6 months ahead of the recommended date of surveillance.
    c. Patients will only be removed from the list when their final surveillance colonoscopy is entered into the EPoS data management system in Open Clinica or their time is overdue (6 months after the originally proposed surveillance date).

2. Procedures at centres
    a. Local study PIs and study nurses at the clinical centres are requested to schedule patients for surveillance colonoscopy within the assigned time window as indicated by Frontier Science.
    b. The clinical centres should follow their ordinary clinical routines for scheduling colonoscopies and their routines for patient information.
    c. Centres are encouraged to contact patients directly by telephone or other means as appropriate locally to schedule surveillance colonoscopies (provided that this is covered by ethics committee approval).
    d. It is recommended that a brief letter is included in the invitation for colonoscopy explaining that the scheduled colonoscopy is part of the EpoS study. A text example follows below (please translate into your language, and adjust if necessary):

“Dear (PATIENT NAME),
Attached you will find an invitation to your next colonoscopy for polyp control. This colonoscopy is scheduled due to your need for follow-up after the polyp removal at your last colonoscopy and your participation in the EPoS trial.
If you have any questions related to the scheduled examination, please do not hesitate to contact us. We are looking forward to seeing you soon.
Your EpoS study team (NAME, CONTACT INFORMATION LOCAL PI or STUDY NURSE). “

3. **Registration of surveillance colonoscopies**
    a. All surveillance colonoscopies shall be registered in the EPoS data management system (Open Clinica).
    b. The surveillance colonoscopy module has been established in the software and is ready to be used.

4. **Surveillance episode**
    a. Surveillance episode is defined as all interventions belonging to one protocol-defined surveillance intervention

5. **Additional surveillance colonoscopies**
    a. Subsequent colonoscopies required due to findings at surveillance colonoscopies (for complete polyp removal etc) shall be performed within 1 year from the first surveillance colonoscopy in that episode.
    b. Additional surveillance colonoscopies belong technically and analyses-wise to the first one in the same protocol-defined surveillance episode

6. **Colonoscopies outside the surveillance time window**
    a. All colonoscopies performed outside of the protocol-defined surveillance windows are unscheduled colonoscopies.
    b. All unscheduled colonoscopies need to be registered in the “unscheduled colonoscopy” module in the EPoS data management system (Open Clinica).

7. **Patient non-compliance**
    a. Patients who do not attend their scheduled surveillance colonoscopy shall be recalled for their next protocol-scheduled colonoscopy.
    b. Patients who do not attend their scheduled surveillance colonoscopy and actively withdraw from the study shall be referred for surveillance according to local procedures for clinical patients.

EPoS
the European Polyp Surveillance trial group

EPoS trial variables

Last update:31-MAY-2018

Variables of interest

The following data will be collected for all participants (EPoS I-III)

Baseline data (for patients with more than one colonoscopies until “clean colon”, add findings from all colonoscopies into one record, collect the relevant demographic and history data, and use the data for last colonoscopy for the rest of the data)

Randomisation and Eligibility Data

Inclusion Criteria:

- Signed informed consent
- Aged 40 – 74 years at time of the final baseline colonoscopy
- Cecal intubation achieved at baseline
- Adequate bowel cleansing (≥2 Boston Bowel Prep in all segments)
- Complete excision of all polyps at baseline
- Randomised within 26 weeks (183 days) from date of the final baseline colonoscopy

Exclusion Criteria

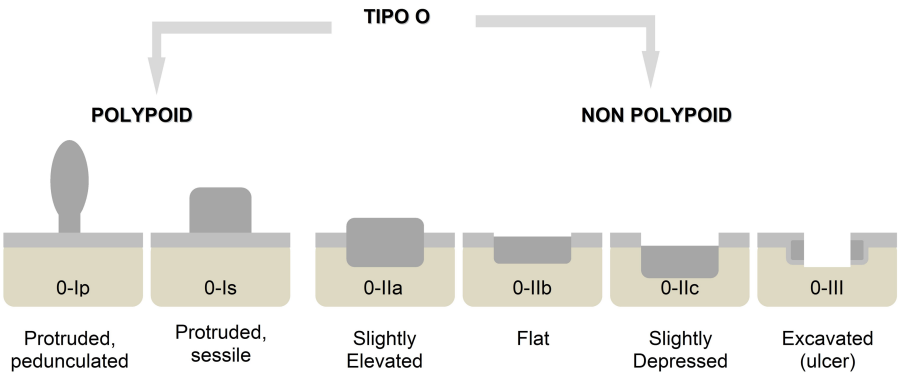
- History of, or existing surveillance for CRC or adenomas
- History of serrated polyps ≥ 10 mm in diameter at any colorectal location or ≥ 5 mm if located proximal to splenic flexure
- More than 10 adenomas detected in total at baseline
- Genetic cancer syndrome (adenomatous or serrated polyposis syndrome; 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)
- Ongoing cytotoxic treatment or radiotherapy for malignant disease
- Requirement for long-lasting attention and nursing services
- Serrated polyposis syndrome
- Non retrieval of any polyp (for EPOS I/EPOS III) or non retrieval of any polyp >9 mm (for EPoS II)

- Demographics:
    - Patient identifier
    - Date informed consent signed
    - Date of randomisation
    - Date of birth, age
    - National ID number
    - Gender,
    - Trial enrolled
        - I /II / III
    - Trial Arm
        - A /B/Observational
- Lifestyle:
    - Height
    - Weight
- Family history of CRC
    - No. of first degree relatives with CRC
        - No. of first degree relatives with CRC before age 60
- Indication for baseline colonoscopy
    - Primary colonoscopy screening
    - Colonoscopy after positive screening test (FIT, FOBT, flexible sigmoidoscopy)
    - Symptoms
    - Other

BASELINE COLONOSCOPY

- Endoscopist name
- Date of colonoscopy completion
- Bowel cleansing quality (Boston Bowel Prep Scale)
    - Score segment 1 (proximal colon)
    - Score segment 2 (transverse colon)
    - Score segment 3: (distal colon)
- Complete cecal intubation achieved? Y/N
    - Level reached

- Complete excision of all polyps at baseline? Y/N
- Number of baseline colonoscopies needed for complete resection of all polyps?
- For each polyp at baseline:
    - Colonoscopy number
    - Date of colonoscopy
- Total number of polyps:
- Polyp characteristics
    - Polyp number
    - Detected in previous colonoscopy
    - Location (colonic segment)
        - Cecum
        - Ascending colon
        - Hepatic flexure
        - Transverse colon
        - Splenic flexure
        - Descending colon
        - Sigmoid
        - Rectum
    - Size (mm):
    - Shape
    - Morphology:
        - Pedunculated (I-p)
        - Sessile (I-s)
        - Flat/depressed
            - Slightly elevated (II-a)
            - Flat (II-b)
            - Depressed (II-c/III)



- Method of polyp removal
  - Cold snare:
    - in toto/ piecemeal
  - Hot snare: lifting:
    - Yes/no
    - in toto/piecemeal
  - ESD
  - Surgery
- Endoscopically complete (yes/no)
- Histopathology
    - Non –epithelial/Non neo-plastic Polyp
    - Hyperplastic polyp
    - Sessile serrated adenoma/polyp
    - Tubular adenoma
    - Tubulovillious adenoma
    - Villous adenoma
    - Not retrieved

- Baseline Colonoscopy adverse events (≤ 30 days from baseline colonoscopy)
  - Bleeding requiring blood transfusion or hospitalization
  - Perforation
  - Late perforation (<30 days)
  - Death (<30 days) - Cause

- Other, specify
- For each AE:
  - start date
  - severity (mild, moderate, severe)

CDISC Controlled Terminology SDTM - 2012-03-23
C66769 - AESEV - Severity/Intensity Scale for Adverse Events

NCI Code	CDISC Submission Value	CDISC Synonym	CDISC Definition	NCI Preferred Term
C41338	MILD	Grade 1; 1	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Mild Adverse Event
C41339	MODERATE	Grade 2; 2	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.	Moderate Adverse Event
C41340	SEVERE	Grade 3; 3	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Severe Adverse Event

Previous baseline Colonoscopies

- Baseline Colonoscopy number
- Date of colonoscopy
- Why was this colonoscopy inadequate
  - Incomplete polypectomy
  - Polyps left in situ
  - Incomplete colonoscopy
  - Poor bowel prep
  - Piecemeal resection of polyps
  - Anticoagulant/antiplatelet therapy
  - Other

- Endoscopist name
- Complete cecal intubation achieved? Y/N
- Bowel cleansing quality (Boston Bowel Prep Scale)
  - Score segment 1 (proximal colon)
  - Score segment 2 (transverse colon)
  - Score segment 3: (distal colon)
- Complete excision of all polyps? Y/N
- Total number of polyps (excluding that already detected in previous baseline colonoscopy):

- For each polyp:
    - Detected in previous colonoscopy: yes/no
    - Location (colonic segment)
        - Cecum
        - Ascending colon
        - Hepatic flexure
        - Transverse colon
        - Splenic flexure
        - Descending colon
        - Sigmoid
        - Rectum
    - Size (mm):
    - Shape
    - Morphology:
        - Pedunculated (I-p)
        - Sessile (I-s)
        - Flat/depressed
            - Slightly elevated (II-a)
            - Flat (II-b)
            - Depressed (II-c/III)
    - Method of polyp removal
        - Cold snare:
            - in toto/ piecemeal
        - Hot snare: lifting:
            - Yes/no
            - in toto/piecemeal
        - Biopsy forceps
        - ESD
        - Surgery
    - Endoscopically complete (yes/no)
    - Histopathology
        - Polyp type
            - Non –epithelial/Non neo-plastic Polyp
            - Hyperplastic polyp

- Sessile serrated adenoma/polyp
- Tubular adenoma
- Tubulovillious adenoma
- Villous adenoma
- Not retrieved

- Baseline Colonoscopy adverse events (≤ 30 days from baseline colonoscopy)
    - Bleeding requiring blood transfusion or hospitalization
    - Perforation
    - Late perforation (<30 days)
    - Death (<30 days) - Cause
    - Other, specify
- For each AE:
    - start date
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C41340	SEVERE	Grade 3; 3	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Severe Adverse Event

Previous Surveillance colonoscopies

- Baseline Colonoscopy number
- Date of colonoscopy
- Why was this colonoscopy inadequate
    - Incomplete polypectomy
    - Polyps left in situ
    - Incomplete colonoscopy
    - Poor bowel prep

    - Piecemeal resection of polyps
    - Anticoagulant/antiplatelet therapy
    - Other
- Endoscopist name
- Complete cecal intubation achieved? Y/N
- Bowel cleansing quality (Boston Bowel Prep Scale)
    - Score segment 1 (proximal colon)
    - Score segment 2 (transverse colon)
    - Score segment 3: (distal colon)
- Complete excision of all polyps? Y/N
- Total number of polyps (excluding that already detected in previous baseline colonoscopy):
- For each polyp:
    - Detected in previous colonoscopy: yes/no
    - Location (colonic segment)
        - Cecum
        - Ascending colon
        - Hepatic flexure
        - Transverse colon
        - Splenic flexure
        - Descending colon
        - Sigmoid
        - Rectum
    - Size (mm):
    - Shape
    - Morphology:
        - Pedunculated (I-p)
        - Sessile (I-s)
        - Flat/depressed
            - Slightly elevated (II-a)
            - Flat (II-b)
            - Depressed (II-c/III)
    - Method of polyp removal
        - Cold snare:

- in toto/ piecemeal
- Hot snare: lifting:
  - Yes/no
  - in toto/piecemeal
- Biopsy forceps
- ESD
- Surgery

- Endoscopically complete (yes/no)
- Histopathology
  - Polyp type
    - Non –epithelial/Non neo-plastic Polyp
    - Hyperplastic polyp
    - Sessile serrated adenoma/polyp
    - Tubular adenoma
    - Tubulovillious ad
    - Villous adenoma
    - Not retrieved

3 year surveillance colonoscopy

- Did patient attend 3 year surveillance colonoscopy
- Reason surveillance was not done
  - An unscheduled colonoscopy was performed outside the 6 month window instead
  - Study endpoint reached (death or CRC)
  - Comorbidity
  - Patient refused
  - Site administration error
  - Other
- Should the patient be invited for subsequent colonoscopy
- Date of final colonoscopy
- Endoscopist name
- Bowel cleansing quality (Boston Bowel Prep Scale)
  - Score segment 1 (proximal colon)
  - Score segment 2 (transverse colon)

    - Score segment 3: (distal colon)
- Complete cecal intubation achieved? Y/N
    - Level reached
- Complete excision of all polyps at baseline? Y/N
- Number of baseline colonoscopies needed for complete resection of all polyps?
- For each polyp at baseline:
    - Colonoscopy number
    - Date of colonoscopy
- Total number of polyps:
- Polyp characteristics
    - Polyp number
    - Detected in previous colonoscopy
    - Location (colonic segment)
        - Cecum
        - Ascending colon
        - Hepatic flexure
        - Transverse colon
        - Splenic flexure
        - Descending colon
        - Sigmoid
        - Rectum
    - Size (mm):
    - Shape
    - Morphology:
        - Pedunculated (I-p)
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            - Flat (II-b)
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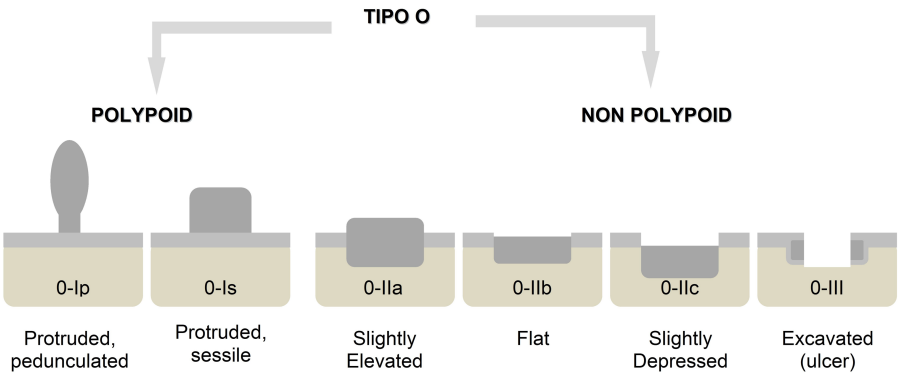

- Polyp Characteristics
  - Polyp number
  - Location
  - Size
  - Shape
  - Morphology
- Method of polyp removal
  - Cold snare:
    - in toto/ piecemeal
  - Hot snare: lifting:
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- Endoscopically complete (yes/no)
- Histopathology
    - Non –epithelial/Non neo-plastic Polyp
    - Hyperplastic polyp
    - Sessile serrated adenoma/polyp
    - Tubular adenoma
    - Tubulovillious adenoma
    - Villous adenoma
    - Not retrieved
  - Total Number of cancer detected

- Cancer number
- Location
- Histology
    - Adenocarcinoma
    - Neuroendocrine tumour
    - Squamous cell carcinoma
    - Metastasis
    - Other
- Grade of differentiation
    - High-grade
    - Low-grade
    - Other
    - Unknown
- Stage
- MSI stage

UNSCHEDULED COLONOSCOPY

(6 months out of the scheduled surveillance colonoscopy)

- Date of endoscopy
- Study centre
- Endoscopist name
- Cleansing quality of colon
- Intubation depth
- Indication for endoscopy
- Reason for schedule deviation
- Findings at unscheduled visit:
- For each removed polyp and each tumor detected at unscheduled visit:
    - A. Polyps: same variables as at baseline, see above.
- B: Number of Cancers detected

  For each cancer:
    - Location
        - Cecum
        - Ascending colon
        - Hepatic flexure
        - Transverse colon

        - Splenic flexure
        - Descending colon
        - Sigmoid
        - Rectum

    - Histology
        - Adenocarcinoma
        - Neuroendocrine tumour
        - Squamous cell carcinoma
        - Metastasis
        - Other (free-text)
        - Grade of differentiation

    - Stage
        - I
        - II
        - III
        - IV
        - TNM
        - MSI Stage

Survival / Endpoint Data

- Diagnosis of CRC - Y/N
    - Date of Diagnosis
- **Death – Y/N**
    - Date of Death
    - Cause of Death
    - Was death related to CRC

- **Study completion status:**
    - Completed study and full follow up
    - Early termination – reason:
        - Withdrawal of consent – date
        - Lost to Follow Up – date of last contact
        - Enrollment violation
        - Enrollment violation
        - CRC diagnosis
        - Death
        - Other (specify)

EPoS protocol amendments

EPoS protocol amendment, February 11th 2017

1. Exclusion criteria (section 4.3)

Current protocol: Serrated polyposis syndrome (SPS) was not mentioned

Change: SPS was added as an exclusion criterion. SPS is defined as

I. Five or more serrated polyps proximal to the rectosigmoid junction, of whom at least 2 have a diameter 10 mm or larger.
II. ≥ 20 serrated polyps, or
III. any serrated polyp proximal to the sigmoid colon in a first degree relative with SPS.

2. EPoS trial eligibility (section 4.3)

Current protocol:

- Individuals with 1-2 tubular adenomas with diameter less than 10 mm and low-grade dysplasia is eligible for EPoS I, irrespective of the presence of serrated polyps
- Serrated polyps with dysplasia was not eligible if they are < 10mm in the distal colon or < 5 mm in the proximal colon.

Change:

- If a patient have 1-2 tubular adenomas with diameter less than 10 mm and low-grade dysplasia and 1 or more serrate polyps, the patient will be eligible for EPoS I only if the serrated polyp
  I. has no dysplasia and
  II. is less than 10 mm if located distal to the transverse colon and
  III. is less than 5 mm if located proximal to the splenic flexure

- If a patient has adenoma(s) eligible for EPoS I and at least one serrated polyp
  I. with dysplasia or
  II. with diameter 10 mm or larger in the distal colon or
  III. with diameter 5 mm or larger in the proximal colon,

  then the patient is only eligible for EPoS III (Table 1 below).

- Individuals with serrated polyps with dysplasia is eligible for EPoS III, irrespective of size.

3. Handling of patients already included in EPoS.

I. There are no patients currently enrolled in EPoS I, II or III who fulfil the criteria for SPS.
II. One patient is enrolled in EPoS I and has a serrated polyp 10 mm or larger in the distal colon
III. 29 patients are enrolled in EPoS I and have at least one serrated polyp 5 mm or larger in the proximal colon
IV. 5 patients are enrolled in EPoS I and have at least one serrated polyp with dysplasia.

The 35 patients in section 3. II-IV will be withdrawn from EPoS I and re-enrolled in EPoS III. These re-enrolments will violate the maximum 6 months period from last colonoscopy to randomization stated in the protocol.

The DSMB has approved points 1-3 above.

4. New member of the governing board (section 14)

Rune Erichsen (Denmark) and Monica Ferlitsch are new members in the EPoS Governing Board (on the condition that these countries actually start recruiting in EPoS).
Paulina Wieszczy (Poland) is a new member of the EPoS Scientific committee.

5. Adverse events (section 3.2)

Current situation: Adverse events were not defined.

Change: Adverse events defined as events within 30 days of colonoscopy (defined as bleeding requiring tranfusion or hospitalization, perforation, death or other colonoscopy-related events)

Table 1: Polyp eligibility criteria for EPoS I-III.

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

6. Statistics analysis plan (Section 11)

Current situation: Primary endpoints will be assessed using Cox proportional hazards model.

Change: Primary endpoints will be assessed by calculating risk differences with 95% confidence intervals and log-rank test.

7. Joint decision setting (section 4.1)

Current situation: The patients can be included at any time point between the baseline colonoscopy and the date of first surveillance colonoscopy.

Change: This sentence has been deleted from the protocol as the patients have to be included within 6 months of their final baseline colonoscopy.

EPoS protocol amendment, June 22nd 2017

1. Exclusion criteria (section 4.3)

Change to be applied: For EPoS III, all polyps have to be retrieved and subjected for histopathology examination.

Current protocol: 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)

New protocol: Non retrieval of any polyp (for EPoS I and III). Non retrieval of any polyp > 9 mm and the patient could be consistently classified as high-risk (for EPoS II)

EPoS protocol amendment, May 31st 2018

Approved by the EPoS Executive and Scientific committees on May 31st 2018.

1. Changes in the Surveillance Module of the EPoS data management system

Changes in the protocol or CRF implemented according are highlighted in yellow below.

Surveillance not performed according to schedule
All surveillance colonoscopies which have not been performed according to schedule have be registered in the EPoS data management system, with a specified reason.

The specified reasons in the EPoS data management system are:
Current protocol:
- An unscheduled colonoscopy was performed outside the 6 month window instead
- Patient no longer eligible for surveillance colonoscopy
- Patient refused
- Site administration error
- Other

Change implemented in this amendment ():
- An unscheduled colonoscopy was performed outside the 6 month window instead
- Study endpoint reached (death or CRC)
- Comorbidity
- Patient refused
- Site administration error
- Other

- This information has to be entered into the EPoS data management system regarding future invitation for subsequent colonoscopies according to schedule.
- If the reason for non-performance is permanent, the patient should be cancelled for future EPoS surveillance colonoscopies.
- If the reason is temporary, the patient shall be scheduled for future EPoS colonoscopies according to schedule.
- This decision should be based on the local physician's discretion and does not need to be specified further in the database.

New question/reply in the surveillance module of the EPoS data management system:

Should the patient be invited for subsequent colonoscopy?
- Yes/No

2. Surveillance colonoscopy - practical procedures

The following procedures are recommended when patients are invited for surveillance colonoscopies in the EPoS trials:

3. **Notification of centres by Frontier Science**
    a. Centres are notified by Frontier Science of all patients who are due for surveillance colonoscopy according to their respective randomization arm well in advance of the due date.
    b. Notifications are sent out by email to the local study nurse and local PI at the clinical centre on a regular basis (monthly) starting 6 months ahead of the recommended data of surveillance.
    c. Patients will only be removed from the list when their final surveillance colonoscopy is entered into the EPoS data management system in Open Clinica or their time is overdue (6 months after the originally proposed surveillance date).

4. **Procedures at centres**
    a. Local study PIs and study nurses at the clinical centres are requested to schedule patients for surveillance colonoscopy within the assigned time window as indicated by Frontier Science.
    b. The clinical centres should follow their ordinary clinical routines for scheduling colonoscopies and their routines for patient information.
    c. Centres are encouraged to contact patients directly by telephone or other means as appropriate locally to schedule surveillance colonoscopies (provided that this is covered by ethics committee approval).
    d. It is recommended that a brief letter is included in the invitation for colonoscopy explaining that the scheduled colonoscopy is part of the EpoS study. A text example follows below (please translate into your language, and adjust if necessary):

        “Dear (PATIENT NAME),
        Attached you find an invitation to your next colonoscopy for polyp control. This colonoscopy is scheduled due to your need for follow up after the polyp removal at your last colonoscopy and your participation in the EPoS trial.
        If you have any questions related to the scheduled examination, please do not hesitate to contact us. We are looking forward to seeing you soon.
        Your EpoS study team (NAME, CONTACT INFORMATION LOCAL PI or STUDY NURSE). “

8. **Registration of surveillance colonoscopies**
    a. All surveillance colonoscopies shall be registered in the EPoS data management system (Open Clinica).
    b. The surveillance colonoscopy module has been established in the software and is ready to be used.

9. **Surveillance episode**
    a. Surveillance episode is defined as all interventions belonging to one protocol-defined surveillance intervention

10. **Additional surveillance colonoscopies**
    a. Subsequent colonoscopies required due to findings at surveillance colonoscopies (for complete polyp removal etc) shall be performed within 1 year from the first surveillance colonoscopy in that episode.
    b. Additional surveillance colonoscopies belong technically and analyses-wise to the first one in the same protocol-defined surveillance episode

11. **Colonoscopies outside the surveillance time window**
    a. All colonoscopies performed outside of the protocol-defined surveillance windows are unscheduled colonoscopies.
    b. All unscheduled colonoscopies need to be registered in the "unscheduled colonoscopy" module in the EPoS data management system (Open Clinica).

12. **Patient non-compliance**
    a. Patients who do not attend their scheduled surveillance colonoscopy shall be recalled for their next protocol-scheduled colonoscopy.
    b. Patients who do not attend their scheduled surveillance colonoscopy and actively withdraw from the study shall be referred for surveillance according to local procedures for clinical patients.

3. Identification of EPoS patients

The following information is a description of standard procedures agreed on at the EPoS board meeting in Barcelona in October 2017 (Section 10.3 in the protocol).

- A **"stable" ID number** (an individual ID that we strongly believe will be there throughout the entire duration of the study, such as national ID, social security number, hospital patient ID etc) needs to be in the EPoS database from all patients
- This can be different in the different countries. All solutions shall be approved by the EPoS board in each case before enrolment can start at a centre
- These requirements are in place because EPoS is a very long study, it is running in many countries and many more centres, is dependent on local support, consistency and will protect the integrity of the trial. The EPoS study group regards these requirements as necessary, and ethically, scientifically, economically, legally sound and reasonable.

4. Time allowed for baseline colonoscopies

Section 4.1: Joint decision setting.
The following section has been added to this section:

EPoS allows 52 weeks (365 days) to achieve a colon free of polyps (time from first to final baseline colonoscopy). Patients must be randomised at the latest 26 weeks (182 days) after the final baseline colonoscopy (clean colon achieved).

EPoS protocol amendment, Dec 6th 2019

Bretthauer and Løberg for the EPoS PI group, Dec 6, 2019

Updated EPoS Sample Size Calculation, November 2019

The EPoS Board (see bullet point 5 below) has approved this document and its recommendations unanimously during an email voting process Nov 28 to Dec 3, 2019.

The EPoS DSMB has been informed about the decisions described in this document by email on Nov 28, 2019, and its members had no objection.

The document and its recommendations are implemented as of Dec 6, 2019

Summary

Based on new evidence from large-scale observational studies, the expected event rates for CRC incidence in EPoS at 10-year follow-up is lower than what was expected when the EPOS trials were designed (new expected CRC incidence 0.5% in EPoS I, and 1.4% in EPoS II). Accordingly, we recommend changing the EPoS sample size calculation to an updated sample size of 6818 patients in EPoS I, and 9652 patients in EPoS II (see green lines in tables 2 and 3 below). Allowing for a 10% rate of patients lost-to-follow up, we recommend stopping patient enrolment at 7,500 patients in EPoS I, and 10,617 patients in EPoS II, respectively. We recommend to stop recruitment for EPoS trial III at the same time, to be able to compare all trials within the same timely manner at study end.

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1. **Background and aim**

   At its meeting on October 21, 2019 in Barcelona, the EPoS Board requested the Executive committee to present an updated and realistic endpoint assessment and sample size scenario for the EPoS trials.
   EPoS PI group and topic expert EPoS investigators met on video conference on Nov 20, 2019 and agreed on a recommendation for an updated EPoS sample size calculation to be approved by the EPoS Board and the EPoS DSMB with the aim for immediate implementation upon these approvals.
   The following individuals attended the video call on Nov 20, 2019: Michael Bretthauer (meeting chair), Rodrigo Jover, Evelien Dekker, Michal Kaminski, Joaquin Cubiella, Øyvind Holme, Rune Erichsen, Monika Ferlitsch, Paulina Wieszczy, Magnus Løberg, Anita Aalby.

   This document summarizes the new evidence and scenarios for updated, realistic sample size for the EPoS trials, and the recommendation for an updated EPoS sample size calculation as derived at the Nov 20 meeting.

2. **Current recruitment status (Nov 1st, 2019)**
   - EPoS I: 6,982 patients (mean age 60.9 years, 43% females)
   - EPoS II: 9,982 patients (mean age 62.1 years, 36% females)
   - EPoS III: 1,647 patients (mean age 60.7 years, 54% females)

3. New evidence for CRC incidence

New evidence from modern, high-quality colonoscopy settings, suggests that the originally expected CRC incidence (from older evidence using clinical colonoscopy settings with no quality assurance programs) at 10 years (EPoS I: 1%; EPoS II: 2%) may be too high.

Table 1

Reference	**Year of baseline colonoscopy**	**Study type**	**10-Year CRC incidence Low risk**	**10-Year CRC incidence High risk**
Lee et al, Gastroenterology 2019	2004-2010	US cohort study 64,000 patients Mean age 61.6 years, 54% females	0.5%	1%
He et al, Gastroenterology 2019	1989 →	US cohorts (NHS, PHS), 6,161 patients with conventional adenomas Mean age 59 years, 77% females	0.3%	1.7%
Wieszczy et al, Gastroenterology 2019	2000-2011	Polish cohort study 236,089 patients Mean age 56 years, 62% females	0.4%	0.8%
Click et al, JAMA 2018	1993-2001	US PLCO sigmo trial 15,935 patients w/adenomas at sigmo screening Mean age 64 years, 39% females	0.7%	1.9%

4. Updated power calculations

EPoS power calculations for lower than originally anticipated CRC incidence are presented in tables below

EPoS I

Yellow: current estimate, Green: Updated estimate

Table 2

10 year CRC incidence (P1=P2)	Acceptable increase (delta)	Power	Group size	Total sample size
0.005	0.005	90	3409	6818
0.005	0.005	80	2461	4922
0.006	0.005	90	4086	8172
0.006	0.005	80	2950	5900
0.007	0.005	90	4763	9526
0.007	0.005	80	3438	6876
0.008	0.005	90	5438	10876
0.008	0.005	80	3926	7852

0.009	0.005	90	6111	12222
0.009	0.005	80	4412	8824
0.01	0.005	90	6783	13566

EPoS II

Yellow: current estimate, Green: Updated estimate

Table 3

10 year CRC incidence (P1=P2)	Acceptable increase (delta)	Power	Group size	Total sample size
0.01	0.007	90	3461	6922
0.01	0.007	80	2499	4998
0.011	0.007	90	3803	7606
0.011	0.007	80	2746	5492
0.012	0.007	90	4145	8290
0.012	0.007	80	2992	5984
0.013	0.007	90	4486	8972
0.013	0.007	80	3238	6476
0.014	0.007	90	4826	9652
0.014	0.007	80	3484	6968
0.015	0.007	90	5165	10330
0.015	0.007	80	3729	7458
0.016	0.007	90	5504	11008
0.016	0.007	80	3973	7946
0.017	0.007	90	5842	11684
0.017	0.007	80	4218	8436
0.018	0.007	90	6179	12358
0.018	0.007	80	4461	8922
0.019	0.007	90	6516	13032
0.019	0.007	80	4704	9408
0.02	0.007	90	6852	13704

5. Updated EPoS sample size calculation

A. On the basis of new and accumulating evidence from current, large-scale observational studies (see table 1 above), the most realistic event rates for CRC incidence in EPoS at 10-year follow-up are
   a. 0.5% in EPoS I
   b. 1.4% in EPoS II

B. There is unanimous consensus to maintain the original non-inferiority margin of 0.5% in EPoS I and 0.7% in EPoS II, respectively. There is further unanimous consensus to maintain the power of the trials at 90%

C. We acknowledge the ethical imperative to avoid enrolling more patients into the EPoS trials than necessary to fulfill the main research questions.

D. On the basis of A-C, we recommend to change the EPoS sample size calculation according to points A and B above, which results in updated sample size of 6,818 patients in EPoS I, and 9,652 patients in EPoS II (see green lines in tables 2 and 3 above).

E. Allowing for a 10% rate of patients lost-to-follow up (patients where we will not be able to ascertain final status with regard to the main study endpoints), we recommend:
    a. to stop patient enrolment at 7,500 patients in EPoS I, and
    b. 10,617 patients in EPoS II, respectively.
F. With the current enrolment numbers as of November 2019 (see above), we recommend that patient recruitment stops when the target number has been achieved, which will presumably be in February or March 2020.
G. We also recommend to stop recruitment for EPoS trial III (which runs along EPoS I and II, without sample size calculation), to be able to compare the three trials at study end within the same timely manner.

EPOS AMENDMENT APRIL 29TH 2021

EPoS Board Meeting 29th April 2021.

The amendment refers to section 4.3. (see figures 2A and 2B in section 4.3.) of the main EPoS protocol and clarifies handling of polyp findings at surveillance in year 5 in EPoS I and II.

Definitions of adenomas into low-risk and high-risk follow the same criteria as at randomisation/baseline: high-risk: three to ten adenomas; or one or more adenoma ≥ 10 mm, or one or more adenoma with high-grade dysplasia or villous growth pattern.

Polyps which are not available for histopathology are categorized according to the endoscopists visual evaluation as described in the colonoscopy report:

- If they are described as most likely adenomas, they are categorized as adenomas.
- If they are described as most likely hyperplastic/non-adenomas, they are categorized as hyperplastic/non-adenomas
- If they are not described or description is insufficient to categorize to any of the two above, they are categorized as adenomas.