Rationale and design of the European Polyp Surveillance (EPoS) trials

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Background: Current guidelines recommend surveillance colonoscopies after polyp removal depending on the number and characteristics of polyps, but there is a lack of evidence supporting the recommendations. This report outlines the rationale and design of two randomized trials and one observational study investigating evidence-based surveillance strategies following polyp removal.

Study design and endpoints: The EPoS studies started to recruit patients in April 2015. EPoS study I randomizes 13 746 patients with low-risk adenomas (1–2 tubular adenomas size < 10 mm, low-grade dysplasia) to surveillance after 5 and 10 years, or 10 years only. EPoS study II randomizes 13 704 patients with high-risk adenomas (3–10 adenomas or adenoma ≥ 10 mm in diameter, or adenoma with high-grade dysplasia, or > 25 % villous features) to surveillance after 3, 5, and 10 years, or 5 and 10 years only. EPoS study III offers surveillance after 5 and 10 years to patients with serrated polyps ≥ 10 mm in diameter at any location, or serrated polyps ≥ 5 mm in diameter proximal to the splenic flexure. All polyps are removed before patients enter the trials. The primary end point is colorectal cancer incidence after 10 years. We assume a colorectal cancer risk of 1 % for patients in EPoS I, and 2 % for patients in EPoS II. Using a noninferiority hypothesis with an equivalence interval of 0.5 % for EPoS I and 0.7 % for EPoS II, the trials are 90 % powered to uncover differences larger than the equivalence intervals. For EPoS III, no power analyses have been performed.

Conclusions: The present trials aim to develop evidence-based strategies for polyp surveillance, thereby maximizing effectiveness and minimizing resources.

Trial registration:
ClinicalTrials.gov (NCT02319928).

Introduction

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Colorectal cancer (CRC) is a major global disease burden with more than 1.2 million people diagnosed each year and a high mortality rate [1]. Most CRCs derive from benign polyps through a series of genetic and epigenetic changes over a period of 10–15 years [2]. Until recently, it was believed that only adenomas had malignant potential, but increasing evidence suggests that 15 %–30 % of CRC cases develop from serrated polyps [3]. The prevalence of adenomas and serrated polyps is high in the general population, compared with the lifetime risk of CRC: 50 % of healthy, asymptomatic 60-year-olds have polyps, whereas the CRC lifetime risk is approximately 5 % in Western countries [4]. Thus, only a small fraction of all adenomas and serrated polyps progress to cancer.

To tackle the public health burden of CRC, most Western countries have introduced, or are considering introducing, population-based screening programs for CRC. The primary aim of such programs is to reduce CRC incidence and mortality. The predominant screening tools for CRC are fecal occult blood testing (FOBT), fecal immunochemical testing (FIT), flexible sigmoidoscopy, and colonoscopy [2]. Because colonoscopy has the highest sensitivity, it is the gold standard for detection of polyps and CRC, and the examination of choice after a positive screening test other than colonoscopy, as well as for surveillance of individuals considered at high risk for CRC due to previous adenomas or cancer, or a family history of CRC.

An efficient screening intervention requires optimal surveillance intervals [5]. However, there is currently a lack of scientific knowledge regarding the exact risk of patients with adenomas to develop CRC during follow-up. Therefore, an evidence-based risk-stratification algorithm cannot be es-

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tablished. Although some studies suggest a protective effect of colonoscopy among patients with adenomas, no studies have indeed convincingly demonstrated that post-polypectomy surveillance reduces CRC incidence or mortality [6, 7]. Recently, a large, nationwide study in an environment with limited surveillance showed no excess risk of CRC after removal of low-risk adenomas, but a small excess risk after removal of high-risk adenomas [8].

Current guidelines recommend surveillance colonoscopies for patients after polyp removal, depending on the number and features of the removed polyps (○ Table 1) [9 – 11]. However, because of the striking lack of large-scale clinical trials, there is uncertainty regarding the effectiveness and thus cost-effectiveness of these recommendations, which are largely based on expert opinion and low-quality data. Guidelines have been developed by consensus groups, and are often influenced by a safety-first approach. This may result in too many colonoscopies for too many people, in line with the recent recognition of "too much medicine" [12]. Guideline recommendations vary, and in fact all guidelines emphasize the need for large-scale clinical trials to close the knowledge gap in postpolypectomy surveillance [9 – 11].

Colonoscopy is a resource-demanding, invasive procedure, and requires highly trained and skilled colonoscopists and assistants, and well-equipped centers. Patients may consider colonoscopy burdensome. In addition, there is a small, but not negligible, risk of complications (mainly bleeding and perforation). Thus, colonoscopy should be reserved for individuals who are likely to benefit from it, and unnecessary procedures should be avoided. However, because of the increasing use of screening for CRC, more and more people are diagnosed with adenomas and referred for surveillance programs. Therefore, the number of patients referred for polyp surveillance after colonoscopy is rapidly increasing in developed countries.

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 USA [13]. In many countries, surveillance colonoscopies are placing a huge demand upon capacity for colonoscopy, utilizing large amounts of resources without evidence of benefit. Too much surveillance may jeopardize the effectiveness and cost-effectiveness of CRC screening programs. The gastroenterological scientific community should generate new and robust evidence for the utility of surveillance after polyp resection, and appropriate surveillance intervals [14]. This report outlines the rationale, design, and methodology of a large-scale randomized controlled trial (European Polyp Surveillance [EPoS] trial), which aims to establish evidence-based surveillance intervals after removal of low-risk and high-risk adenomas and also to elucidate the natural history of serrated polyps. The hypothesis is that current surveillance guidelines recommend colonoscopy too often. The primary study end point is CRC incidence after 10 years of follow-up.

Methods

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Current evidence

On the basis of adenoma characteristics, patients will be stratified into different risk groups for subsequent development of CRC. Usually, patients are classified into low risk and high risk – although some guidelines also define an intermediate risk group – based on polyp size and number, histological type (villous or tubular growth pattern), and grade of dysplasia (low grade or high grade) [9 – 11]. The low-risk group usually includes patients with 1 – 2 tubular adenomas of < 10 mm in diameter without high-grade dysplasia, and the high-risk group includes patients with 3 or more adenomas, or an adenoma > 9 mm in diameter, or an adenoma with high-grade dysplasia or > 25 % villous growth pattern (so-called "advanced adenoma").

Only two randomized clinical trials have compared different surveillance colonoscopy intervals [15, 16]. In the US study [15], after baseline colonoscopy with excision of adenomas, follow-up colonoscopy at 1 and 3 years was compared with colonoscopy at 3 years only. There were only three outcome events (CRC) in the trial, and no differences in the rate of advanced adenomas were observed between the two groups. A surveillance interval of at least 3 years was recommended. These results are the main basis for the current recommendation of at least 3-year intervals after removal of high-risk adenomas. A study from Denmark randomized individuals into multiple comparison groups by adenoma characteristics. However, the study was too small to uncover clinically significant differences between the groups [16].

Trial design

The EPoS trials, which started to recruit patients in April 2015, 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 for patients with serrated polyps (○ Fig. 1).

Study end points

The primary end point in EPoS I, II, and III is CRC incidence over 10 years. CRC incidence will be compared in the different arms in EPoS I and II, as well as across EPoS I and II, and compared with EPoS III.

The following secondary end points will also be compared in the different arms in EPoS I and II, across EPoS I and II, and compared with EPoS III:
▶ cost-effectiveness;
▶ yield of adenomas and serrated polyps (including subtypes) during follow-up;
▶ major adverse events (perforations, bleedings) in surveillance colonoscopies.

Subgroups are defined by variables that may be associated with the risk of CRC and adenoma yield during follow-up. These include patient age and sex, indication for colonoscopy (colonosco-

Table 1 Current guideline recommendations for polyp surveillance.

	Low-risk adenoma patients[1]	High-risk adenoma patients[2]	Serrated polyp patients
European Union Guidelines [9]	10 years/none	1 – 3 years	No recommendation
European Society of Gastrointestinal Endoscopy [11]	10 years	3 years	3 or 10 years
United States Multi-Society Task Force [10]	5 years	3 years	3 – 5 years

[1] Low-risk adenoma patients: patients with fewer than three adenomas < 10 mm in diameter, without high-grade dysplasia, or villous or tubulovillous growth pattern.
[2] High-risk adenoma patients: patients with three or more adenomas, at least one ≥ 10 mm in diameter, high-grade dysplasia, or villous or tubulovillous growth pattern.
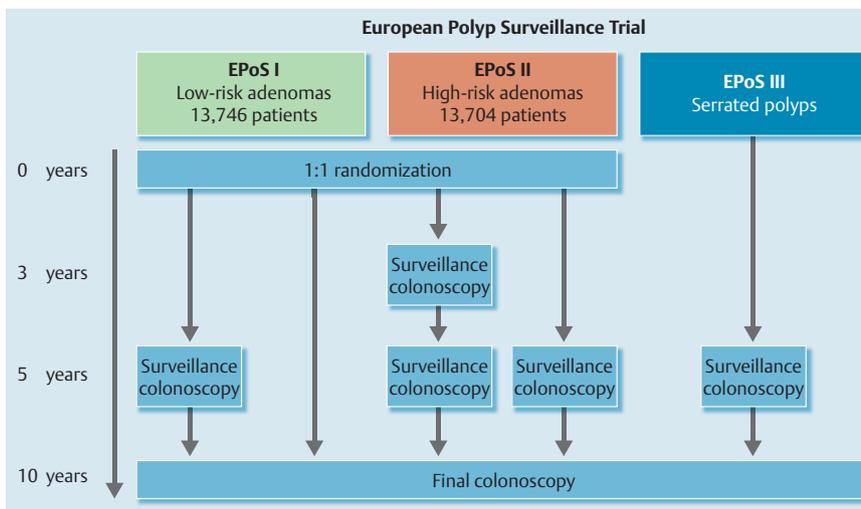
Fig. 1 European Polyp Surveillance (EPoS) trials: flow chart for initial surveillance interval.

py screening, colonoscopy after a positive CRC screening test [FIT, FOBT, sigmoidoscopy], clinical symptoms, or other indications), and the following polyp characteristics: polyp type (adenoma, serrated polyp), polyp size, adenoma growth pattern (tubular, tubulovillous or villous), grade of dysplasia (high grade vs. low), multiplicity, and location (proximal vs. distal colon), and serrated polyp subtype. New molecular markers that may develop during the course of the study will also be considered.

Joint design settings

⊙ **Fig. 2** presents an overview of the inclusion criteria of the EPoS trials. Individuals aged between 40 and 74 years with no history of CRC or adenomas who have undergone colonoscopy with removal of one or more adenoma or serrated polyps at one of the study centers are eligible for recruitment. The indication for colonoscopy includes screening as well as clinical symptoms or other indications. At the baseline colonoscopy, the cecum must be intubated, adequate colonic cleansing achieved (Boston Bowel Preparation Score equal to or higher than 2 points in all colonic segments), and all polyps completely removed (judged by the endoscopist). Patients can be included within 6 months following the baseline colonoscopy. For patients who require multiple procedures for complete polyp removal or other reasons, the last procedure counts as the date of baseline colonoscopy. All polyps removed at each procedure will be recorded and totalled to assess eligibility for the EPoS trials. The only exception is diminutive rectal polyps (≤ 5 mm); they do not need to be removed.
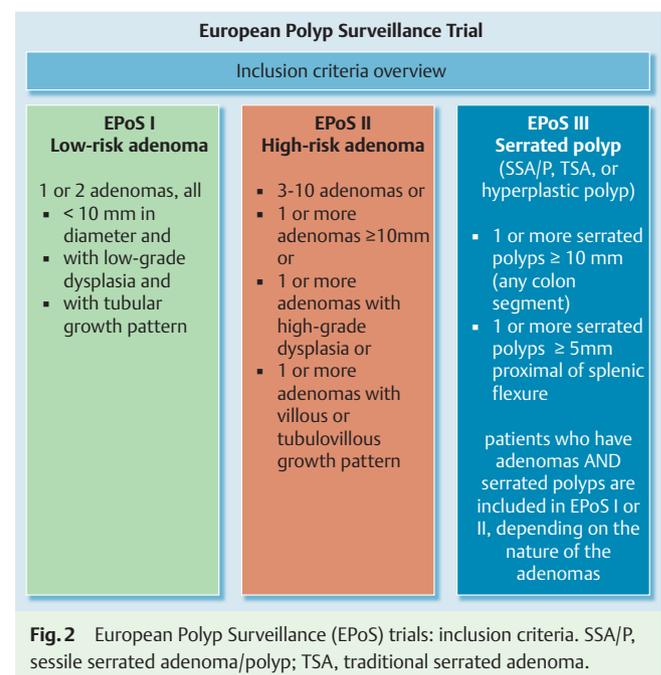
Surveillance colonoscopies

At surveillance colonoscopy, all detected polyps (except small diminutive rectal polyps, see above) will be registered and described, removed whenever possible, and subjected to histopathology. All required data from endoscopy reports, quality data used for quality monitoring, and histopathological results are registered in the central study database. Local pathology units serving the participating centers perform histopathological analysis and use World Health Organization guidelines for classification and grading of polyps [17]. Serrated polyps will be classified according to recent guidelines [17, 18]. Polyp specimen slides will be stored at the sites to facilitate re-assessment, in order to accommodate for changing classification systems in the future. Surveillance colonoscopies will be scheduled according to the time intervals defined in the protocol (see below). Surveillance colonoscopies will be performed within a 6-month time window from the protocol-defined due date. Unscheduled colonoscopies performed outside the 6-month window from (either before or after) the protocol-defined date will be recorded as a protocol deviation (results and reasons for deviation are recorded in the trial database). The trial centers will invite patients for scheduled surveillance colonoscopies. The database management team will provide centers with lists of patients due for protocol-based surveillance colonoscopy.

Exclusion criteria

The following exclusion criteria apply to all EPoS trials:
1. lack of patient consent;
2. personal history of CRC, history of adenomas before the baseline colonoscopy, personal history of serrated polyps ≥ 10 mm in diameter at any colorectal location or ≥ 5 mm if located proximal to the splenic flexure;
3. more than 10 adenomas;
4. CRC at baseline colonoscopy;

Fig. 2 European Polyp Surveillance (EPoS) trials: inclusion criteria. SSA/P, sessile serrated adenoma/polyp; TSA, traditional serrated adenoma.

5. incomplete colonoscopy;
6. incomplete endoscopic excision of polyps;
7. nonretrieval of any polyp (for EPoS I), nonretrieval of any polyp > 9 mm in diameter for patients already eligible for EPoS II;
8. genetic hereditary cancer syndrome (familial adenomatous polyposis [FAP], attenuated FAP, Mut-YH associated polyposis, Lynch or Lynch-like syndrome), or serrated polyposis syndrome;
9. inflammatory bowel disease;
10. history of surgical colon resection for any reason;
11. severe co-morbidity with reduced life expectancy;
12. ongoing cytotoxic treatment or radiotherapy for malignant disease;
13. long-lasting attention and nursing services (somatic or psychosocial, mental retardation).

Specific design and settings
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) (○ Fig. 2). Synchronous serrated polyps may have been removed as well. Individuals will be randomized in a 1:1 ratio 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 end points will be assessed at the 10-year surveillance colonoscopy (○ Fig. 1).

EPoS II
Eligible individuals are persons with high-risk adenomas removed at baseline colonoscopy (3 – 10 adenomas, or one or more adenoma with size ≥ 10 mm in diameter, or one or more adenoma with high-grade dysplasia or > 25 % villous growth pattern) (○ Fig. 2). Synchronous serrated polyps may have been removed as well. Individuals will be randomized in a 1:1 ratio into one of two intervention groups:
▶ Group 1: surveillance colonoscopy at 3 and 5 years after baseline colonoscopy;
▶ Group 2: surveillance colonoscopy at 5 years after baseline colonoscopy.
Individuals in both Group 1 and Group 2 will be subjected to a final surveillance after 10 years (○ Fig. 1). The primary and secondary end points will be assessed at the 10-year surveillance colonoscopy. An interim analysis will be performed after the 5-year colonoscopy.
In both EPoS I and EPoS II, surveillance intervals after the first surveillance colonoscopy will take into account findings at the first surveillance colonoscopy. Surveillance intervals after first surveillance colonoscopy are shown in ○ Fig. 3.

EPoS III
Individuals are eligible if they have one or more serrated polyp (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 polyp ≥ 5 mm if located proximal to the splenic flexure removed at baseline colonoscopy (○ Fig. 2). Patients with both serrated polyps and adenomas are not eligible for EPoS III but can be included in EPoS I or II according to the characteristics of
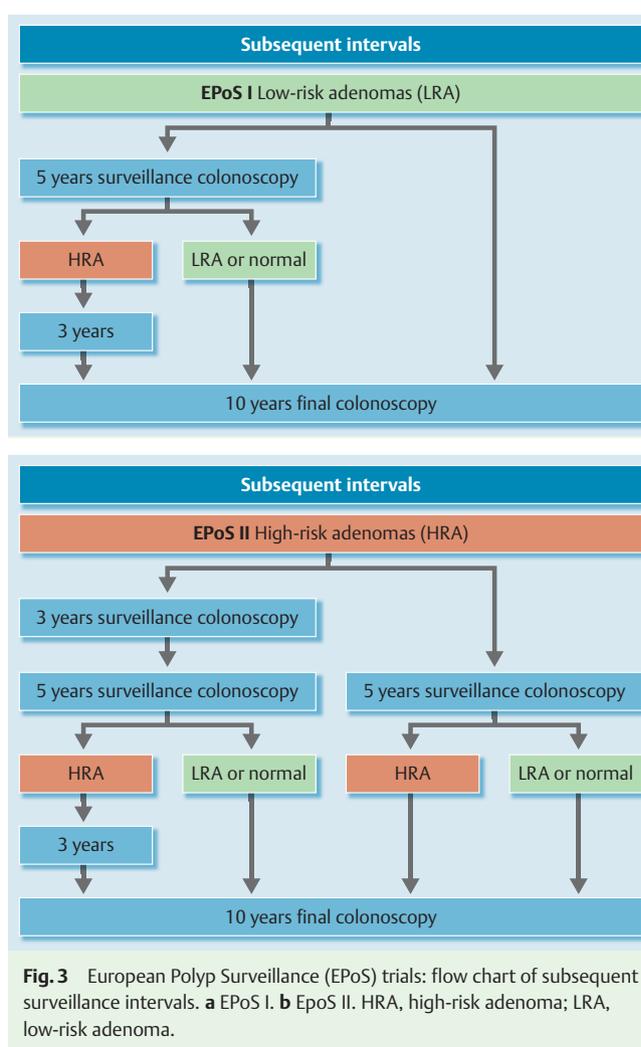
Fig. 3   European Polyp Surveillance (EPoS) trials: flow chart of subsequent surveillance intervals. **a** EPoS I. **b** EPoS II. HRA, high-risk adenoma; LRA, low-risk adenoma.

their adenomas. Colonoscopy will be repeated at 5 and 10 years in all individuals. The primary and secondary end points will be assessed at the 10-year surveillance colonoscopy. Findings at surveillance will be compared with those obtained in the EPoS I and II trials.

Randomization and database management
Eligible individuals will be invited to participate in the study and provide written informed consent prior to randomization. A central randomization and data management center has been established for the trial. Randomization into the relevant trial is performed using a central electronic web-based randomization system provided by Frontier Science and Technology Research Foundation Inc. using a stratified permuted block algorithm [19]. Individuals included in the randomized trials (EPoS I and II) are randomly assigned to a corresponding treatment arm in a 1:1 ratio, depending on their polyp characteristics, stratified by country, age (age blocks 40 – 55 years, 56 – 65 years, and 66 – 74 years, respectively), and sex. Trial centers log into the electronic randomization and data entry system through a dedicated, secured virtual private network system provided by the data management team (Frontier Science Scotland). The data management team is responsible for implementing quality-control systems for the data collected. This includes checks on data values at the time of data entry. More complex central checks will also be conducted,

Table 2 European Polyp Surveillance trial power[1].

	Power	10-year CRC incidence (proportion)[2]		Group size	Total sample size
		P1 proportion	P2 proportion		
EPoS I	80 %	0.001	0.015	4897	9794
EPoS I	90 %	0.01	0.015	6783	13 746
EPoS II	80 %	0.02	0.027	4947	9894
EPoS II	90 %	0.02	0.027	6852	13 704

[1] P1 is the control group (shorter surveillance intervals), P2 is the intervention group (longer surveillance intervals).
[2] Sample size needed to exclude a difference between the control group and the intervention group of 0.5 % or more for EPoS I and 0.7 % or more for EPoS II

and any relevant discrepancy queries are sent to the participating centers.

End point ascertainment
The primary end point (CRC incidence) will be ascertained at the final 10-year colonoscopy in all individuals. Yield of adenomas and serrated polyps and adverse events will be ascertained for all colonoscopies performed in the trial and registered in the dedicated EPoS database. Cost-effectiveness analyses will be performed using the effectiveness estimates derived from the trials and estimated actual intervention-related costs in the participating countries. CRC mortality and CRC incidence in individuals who do not comply with surveillance recommendations will be ascertained by linkage with the national cancer and cause of death registries in the participating countries.

Ethics and oversight
The study is approved by the ethical committees at the participating centers. An independent Data Safety and Monitoring Board (DSMB) will review end point data. The members of the DSMB are appointed by the Study Investigators and must not otherwise be involved in the study. The DSMB will always have at least one member with biostatistical experience. The activities of the DSMB will be coordinated by the data management office. The study is registered at clinicaltrials.gov (NCT02319928).

Statistical analysis plan
Participants will be followed for the primary end point (incidence of CRC), until death, diagnosis of CRC, or end of follow-up, whichever happens first. The primary analysis will estimate the difference in 10-year risk of CRC between the study groups under the intention-to-treat (ITT) principle. We will conduct a one-tailed test of equivalence and will estimate a 95 % confidence interval. For each end point, we will also estimate Kaplan–Meier survival curves and the average hazard ratio by fitting a Cox model. If the distribution of any baseline characteristics is found to be imbalanced between the arms, we will conduct a sensitivity analysis in which they are included as covariates in the model.
We will also perform adherence-adjusted analyses to estimate the causal effect that would have been observed if all individuals in the study groups had adhered to the study protocol (i.e. the per-protocol effect) [20, 21]. We will use two analytic approaches to estimate the per-protocol effect: instrumental variable estimation and inverse probability weighting. For comparability, we will translate the estimates from both approaches into a common metric: adjusted survival curves, where survival means free of CRC. To implement instrumental variable estimation, we will use the indicator for treatment arm as the instrument [22]. To implement inverse probability weighted estimation, we will estimate the weights as a function of variables that jointly predict adherence

and the end point [23, 24]. These variables include age, sex, and baseline findings. Other variables, such as physical activity, family history of CRC, smoking status, use of aspirin, nonsteroidal anti-inflammatory drugs, and hormone replacement therapy, will be included if available from public registries at the study sites.

Power calculations
In the standard-care control groups, we assume a 1 % risk of CRC at 10-year follow-up for patients with low-risk adenomas at baseline, and 2 % for patients with high-risk adenomas at baseline. These numbers are based on data from cancer registries [13], and in accordance with CRC risks observed in the flexible sigmoidoscopy screening trials after comparable follow-up [22, 25–27]. The study has 90 % power to detect an absolute difference using a noninferiority hypothesis with an equivalence interval of 0.5 % for patients with low-risk adenomas and 0.7 % for patients with high-risk adenomas, with a one-sided alpha of 0.05. To achieve this, we need to include a total of 13 746 individuals in the EPoS I trial and 13 704 in the EPoS II trial. ● **Table 2** outlines sample size scenarios for 80 % and 90 % power for EPoS I and II, respectively. For patients with serrated polyps, there are no reliable surveillance data available in the literature. Thus, EPoS III is a one-arm observational study, with no power analyses performed.

Discussion
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The EPoS trials are the first large-scale randomized trials to address surveillance intervals following polypectomy. Although national and international guidelines for polyp surveillance in patients who have undergone removal of adenomas or serrated polyps are in place, they are based upon consensus opinion rather than high-quality evidence. Although guidance for clinicians is valuable also in areas where high-quality evidence is lacking, it is nonetheless vital to perform large clinical trials to fill the knowledge gap and thus subsequently revise and update guidelines using the evidence developed.

Trial end points
The primary goal of surveillance after polypectomy is to reduce future CRC risk in patients with previously removed adenomas or serrated polyps. Thus, CRC incidence is the obvious end point for a trial of comparative effectiveness of different surveillance strategies. CRC mortality is also a very important outcome and relevant end point in CRC surveillance. However, as the goal is prevention of the disease rather than reduction of mortality by early detection, we believe that incidence is the better of these two important end points. Using incidence, however, requires a design that permits comparison of groups without the risk of

overdiagnosis and lead-time bias. Overdiagnosis of CRC can occur when CRCs grow slowly and do not harm the patients in their remaining lifetime, or (if CRCs grow rapidly) the patient is older and does not live long enough to get harmed. Lead-time bias occurs if disease is detected earlier among asymptomatic individuals (e.g. through screening or surveillance colonoscopy) compared with detection in patients who become symptomatic. This bias also occurs when different surveillance strategies entail the last follow-up colonoscopy at different time intervals for the measurement of CRC incidence. To eliminate such biases, all patients enrolled in the EPoS trials undergo their last surveillance colonoscopy at the same time point–10 years after inclusion.

Based on data from cancer registries, we expect that in the standard-care arms, 1 in 100 patients in EPoS I (1%) and 2 in 100 patients in EPoS II (2%) will develop CRC during the 10-year follow-up period. This is in accordance with the absolute risks of CRC observed in the flexible sigmoidoscopy screening trials after a comparable follow-up period [22,25–27] as well as in pooled analyses [28].

Due to the low absolute risk for CRC, studies evaluating screening effects often focus on surrogate end points such as adenoma or advanced adenoma yield, or a combination of advanced adenomas and CRC. However, because there is great uncertainty regarding transition rates and transition times from adenomas to cancer, studies using surrogate end points are problematic [29–31]. Because the optimal frequency of surveillance colonoscopies after polyp removal concerns hundreds of thousands of individuals each year, a high-quality trial using a strong end point such as CRC incidence is urgently needed.

Noninferiority

It may seem implausible that less-intense colonoscopic surveillance following adenoma removal would entail a lower cumulative incidence of CRC compared with 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 CRC following more or less frequent surveillance is theoretically possible, notably if the average progression time from a detectable precursor lesion (adenoma) to invasive cancer is 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 with less frequent compared with more frequent surveillance. As a corollary, both EPoS I and EPoS II are designed as noninferiority randomized trials.

There are several reasons why trials designed this way are considered ethically justifiable. First, colonoscopy carries risks, chiefly caused by bleeding or perforation. Although such complications are rare, they are severe and sometimes life threatening. Hence, complications might counteract the possible survival benefit of more intense surveillance which, in absolute terms (number of lives saved per colonoscopy), is small anyway. Second, 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 co-

lonoscopic screening, it is substantial for other screening tools such as the Pap-smear for cervical cancer, mammography for breast cancer, and prostate-specific antigen for prostate cancer. Third, colonoscopy is costly and resource demanding, and places a heavy burden upon patients. 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. Fourth, the level of inferiority in absolute difference considered acceptable should not be the same in EPoS I as in EPoS II. Instead, a slightly higher absolute difference (inferiority) in cumulative incidence of CRC 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.

Based on the arguments above and acknowledging the fact that any defined level of inferiority can be considered arbitrary, we have accepted an equivalence level of 0.5% in absolute CRC incidence in EPoS I, and of 0.7% in EPoS II. This implies that the null hypothesis of noninferiority would be rejected only if the upper limit of the 95% confidence interval for the absolute difference in cumulative incidence of CRC after 10 years of follow-up exceeds 0.5% in EPoS I and 0.7% in EPoS II. As in any randomized trial, defining margins for superiority or noninferiority should be based on what can be expected from the new intervention, what appears clinically relevant to detect, and what numbers of enrolled patients are feasible in relation to the number needed to reach statistical significance. After extensive discussion, we reached a consensus that the margins defined are clinically relevant, and scientifically and ethically sound and feasible to test.

Stage migration

Stage migration is a well-known phenomenon in oncology and can occur when more sensitive diagnostic tools are implemented [32]. Previously undetectable metastases may be visualized, for example, with high-resolution magnetic resonance imaging or positron emission tomography. Patients previously staged favorably may become categorized in higher, more advanced stages. Such stage migration does not reflect real changes in disease stage, but will create spurious temporal trends in stage-specific survival even in the absence of real improvements [32].

As a consequence of increased diagnostic sensitivity, the detection rates of adenomas and serrated polyps have increased during recent years. Hence, a mechanism similar to stage migration may affect the CRC risk in contemporary groups of polyp patients that were rarely detected and removed 10 or 15 years ago. However, current risk estimates, which categorize patients according to number of polyps, are derived from studies for which patients were recruited 10, 15, or even 20 years ago. Hence, risk of CRC following adenoma removal may be lower among contemporary patients. To retain adequate statistical power according to the EPoS estimates, we envision recruitment numbers higher than the minimum required according to the power calculation.

Comparison between EPoS trials

In addition to the main comparisons, we plan to compare CRC incidence rates between EPoS I, II, and III. This is important because current classification of high-risk vs. low-risk adenomas based on polyp size, number, and features of growth and dysplasia may not optimally distinguish between high- and low-risk lesions [33].

Hence, EPoS may provide evidence allowing the development of a classification that better predicts the risk of CRC. Furthermore, the comparative risk for patients with serrated polyps compared with adenoma patients is currently unclear. However, EPoS III will allow a comparison of CRC risk in different categories of polyps without lead-time bias. Furthermore, we will be able to compare the risk of CRC in patients with concomitant serrated polyps and adenomas who are enrolled in EPoS trials I and II, respectively, with other subgroups.

Conclusions

The EPoS trials are the first large-scale, long-term, randomized trials to address the topic of optimal surveillance intervals after polyp removal. We hope that these trials will bring new knowledge to the field and will change clinical practice towards more evidence-based and cost-effective surveillance recommendations.

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Competing interests: None

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