Published in final edited form as:

Colorectal Cancer. 2012 August ; 1(4): 309–319. doi:10.2217/crc.12.33.

Concerns and challenges in flexible sigmoidoscopy screening

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SUMMARY

In 1992, two well-conducted case–control studies used data from two different health maintenance organizations and demonstrated a 59–79% reduction in mortality from colorectal cancer (CRC) following exposure to sigmoidoscopy. These studies highlight the possibility of reducing mortality from CRC using population-based endoscopic screening. The development of fiber optics improved the technology, and the ease of performing flexible sigmoidoscopy (FS) with widespread adoption of this screening modality. To date, FS is the only endoscopic screening modality that has been shown to reduce mortality in randomized clinical trials. This article reviews the development of sigmoidoscopy, its use in CRC screening and the current reduced role of this proven screening modality, and explores new frontiers for population-based FS screening.

According to the International Agency for Research on Cancer, colorectal cancer (CRC) is the fourth most frequent cancer worldwide with an estimated 1,235,108 incident cases and 609,051 deaths attributable to the disease in 2008 [101]. CRC mainly develops from an adenomatous polyp through acquisition of multiple genetic changes over many years [1]. Patients diagnosed with early-stage disease have better prognoses [102]. This makes CRC a potentially preventable disease when effective screening strategies that lead to removal of precancerous lesions are employed and death from CRC can be averted when early detection of CRC is accomplished.

Unfortunately, in many developing countries of the world, there are no established population-based CRC screening programs. However, in some countries in Europe and North America, different population-based CRC screening initiatives were implemented as research projects with the goal of answering a specific population-based CRC screening question or as pilot studies to assess feasibility and guide an eventual, more broad-based, screening program or as part of routine healthcare [2].

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Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

In general, acceptable screening modalities for CRC screening that have been endorsed for population-based screening (with varying levels of evidence for effectiveness) are fecal occult blood tests (FOBTs), fecal immunochemical tests, fecal DNA tests, double-contrast barium enema, computerized tomography colonography (virtual colonoscopy), optical colonoscopy and flexible sigmoidoscopy (FS) [3,4,103].

Technological advancement of sigmoidoscopy

Sigmoidoscopy was previously performed using a rigid sigmoidoscope. This rigid tube with a light source (~25–32 cm long and 2.5 cm wide) enabled examiners to visualize the rectum up to the distal sigmoid colon. The instrument consists of a light source to allow visualization, an outer hollow plastic or metal tube, an obturator that is removed after the instrument has been inserted through the anus into the rectum, and a hand-held bellows to insufflate air into the colon to open up the bowel lumen to ensure safe advancement of the rigid instrument further in the colon.

The development of optical fibers [5] eventually enabled the development of the modern flexible sigmoidoscope, which has replaced the rigid sigmoidoscope in clinical practice. The flexible sigmoidoscope is approximately 70 cm in length and 1 cm wide, with a lighted lens system. The fiber optic bundle enables it to collect and channel light to the inside of the colorectum as well as to transmit pictures taken inside the colon to a projector (video endoscope). The flexible sigmoidoscope has a channel for insufflating air or carbon dioxide, suctioning liquids (water, stool and blood) and for passing needed adjunct instruments (e.g., biopsy forceps) during the procedure. The scope has an angle of view of approximately 100° and achieves an up and down deflection range of 180° and right and left deflection of 160°, which facilitates easy maneuvering during the examination. Noteworthy is the development of the disposable sheath flexible sigmoidoscope which is easy to set up with quick turnaround time between cases, and thereby, can facilitate FS screening in rural communities as an outreach endeavor [6–8]. Unfortunately, there has been little further development of the flexible sigmoidoscope as companies have focused their attentions to the improvement of colonoscopes with newer technologies, such as high-definition colonoscopes, confocal microscopy, autofluorescence and narrow-band imaging, which are designed to detect more polyps and improve prediction of neoplastic lesions in real time. However, colonoscopies can also be used to perform sigmoidoscopy. The additional length of the scope can make it easier for the endoscopist to reach the splenic flexure.

Use of flexible sigmoidoscopy in clinical practice

FS is typically performed as an outpatient procedure. The preparation for the procedure is simple. Patients are asked to avoid food and drinks from midnight preceding the procedure. FS is typically performed after self-application of one or two enemas approximately 2–4 h before the procedure. In the EU guidelines [103], a single enema that is self-administered at home 2 h before the endoscopy is the preferred bowel preparation option, but it is acceptable for the patient to administer the enema on-site at the endoscopy suite if feasible to the organization where the examination is taking place. No sedation is required and patients are allowed to present for the procedure without any requirement for an adult companion and

can return back to work after the procedure. Although not routinely indicated, endoscopists typically perform a digital rectal examination with a lubricated gloved finger. Then, the well-lubricated sigmoidoscope is inserted through the anal verge into the rectum and advanced into the colon up to a depth of approximately 60 cm and may reach the splenic flexure. The exact reach of the sigmoidoscope is highly variable even though a straight insertion is assumed. In a study by Painter *et al.*, in which magnetic endoscopic imaging was used to determine the exact location within the colon achieved by the endoscopist, the sigmoidoscope reached the splenic flexure in only 29% of cases and did not get past the sigmoid-descending colon junction in over 60% of the examinations [9]. Detailed examination is usually undertaken during the withdrawal phase of the examination. The procedure is usually completed within 10 min. The time commitment for FS on the part of the patient was reported to be as low as 3–4 h compared with at least 48 h for colonoscopy [10]. FS is often performed by gastroenterologists and colorectal surgeons, but primary care physicians, nurses and physician assistants can be trained to perform the procedure efficiently, thereby increasing the capacity for population-based screening programs [11–17]. The proficiency in performing the procedure is directly related to the number of procedures performed [16]. Studies have reported wide variability in the performance of endoscopists but adenoma detection rates of nonphysicians were comparable with that achieved by physicians [14,18–20].

Safety of FS in clinical practice

FS is generally safe and serious complications are rare when performed by skilled personnel. Complications that have been reported in the literature include pain, cardiac arrhythmias, hemorrhage, bacteremia and bowel perforation [21]. Among 107,704 patients who underwent 109,534 FS screenings in the Kaiser Permanente's Colorectal Cancer Prevention program (1994–1996), only 24 patients developed important complications for a complication rate of 21.9 out of 100,000 [22]. Of these, seven complications (6.4 out of 100,000) were serious (two perforations, two lower gastrointestinal bleeding, two diverticulitis and one unexplained colitis). The risk of myocardial infarction was not elevated.

Low risk of complications from FS screening was also reported from large randomized trials that evaluated the effect of FS screening on CRC incidence and mortality. In the Prostate Lung Colorectal and Ovarian (PLCO) cancer screening trial there were three perforations in 107,236 FS screening examinations (2.8 perforations per 100,000 FS screenings) but 19 bowel perforations occurred during 17,672 diagnostic colonoscopy examinations performed for evaluation of a positive FS screening (1.1 perforations per 1000 diagnostic colonoscopies) [23]. In the United Kingdom Flexible Sigmoidoscopy Screening Trial (UKFSST), there were five perforations: one in the 40,332 people who underwent FS screening and four in the 2377 people who underwent colonoscopy [24]. This further underscores the safety of FS as a screening modality.

Cost-effectiveness of population screening

Cost-effectiveness studies that have modeled different modalities for CRC screening have produced results that vary based on the assumptions in the models such as the starting age of

CRC screening, frequencies of screening in the life span, percentages of expected abnormal findings, requirements for further testing and transitional probabilities of progression of disease. O'Leary *et al.* reported FS as the most cost-effective modality [25] while Frazier *et al.* reported that the combination of FS with FOBT was the most cost-effective strategy [26]. However, colonoscopy was reported by Sonnenberg *et al.* to be more cost effective than FS [27]. However, in a randomized clinical trial that also assessed costs associated with CRC screening modalities among 232 subjects in New Zealand, the authors reported that the cost of FS was lower by at least 20% even when the cost of diagnostic colonoscopy for abnormal FS was considered [28]. Participation in screening is another factor that affects cost-effectiveness. However, Hol *et al.* demonstrated a higher diagnostic yield of FS even at a lower participation rate when compared with guaiac-based FOBT and fecal immunochemical test with higher participation rates [29].

Patients' perception

In general, patients prefer the easier bowel preparation process of FS [28] and the logistic challenges associated with the procedure are easier to overcome since sedation is not required. This lack of sedation makes FS easy to use in population-based screening but patients may remember any unfavorable experiences associated with the procedure and have reported the procedure as being more uncomfortable and embarrassing when compared with colonoscopy [28]. However, in a study by Senore *et al.* in which only 31% of colonoscopies were performed with sedation, the authors reported that patients were equally as likely to be embarrassed by colonoscopy and FS, but were more likely to complain of severe pain following colonoscopy than after FS [10]. Among 1224 average-risk patients who were overdue for CRC screening in a large multispecialty primary care practice, Hawley *et al.* reported that the preference of screening modality expressed by the patients during a telephone survey was 41.1% for colonoscopy, 35% for FOBT, 5.7% for barium enema and 12.7% for FS [30].

Care providers' perception & practice

Montaño *et al.* reported their results of a survey of 60 family physicians in which they examined factors that are associated with the provision of FS screening in the physicians' practices [31]. The authors reported that the care providers had higher sigmoidoscopy rates if they had postresidency sigmoidoscopy training and had strong support systems including office reminder systems. Medical school or residency training in sigmoidoscopy did not correlate with sigmoidoscopy performance rates.

The perception and practice of primary care physicians has changed in the last two decades. This was aptly demonstrated by Klabunde *et al.* in two large surveys of primary care physicians [15,32]. In their 1999–2000 national survey (1235 respondents, 72% response rate), the authors reported FOBT as the modality that was recommended by most physicians (95%), followed by sigmoidoscopy (78%), colonoscopy (38%) and barium enema (14%). However, in a comparable survey in 2006–2007 (1266 respondents, 75% response rate), colonoscopy screening was routinely recommended by most physicians (95%), followed by FOBT (80%), sigmoidoscopy (26%), barium enema (9%), CT colonography (5%) and fecal DNA testing (5%). This rapid decline in FS recommendation parallels a significant change

in the perception of the care providers in the effectiveness of FS as a screening modality and in the actual performance of FS by the physicians. In the 1999–2000 survey, 86% of physicians perceived colonoscopy to be very effective, while FOBT was perceived as very effective by 28%, and FS by 49% of respondents. By contrast, in the 2006–2007 survey, FS was perceived as being effective by 16%, FOBT by 12% and colonoscopy by 95%. The number of primary care physicians that performed FS also declined dramatically from 29% in the 1999–2000 survey to 4% in the 2006–2007 survey. Office systems to support CRC screening are lacking in a substantial percentage of physicians' practices and only 61.5% reported that their practice had implemented guidelines for CRC screening. This highlights the importance of primary care-based interventions to improve CRC screening and reduce CRC mortality. It is noteworthy that low reimbursement for FS by third-party payers also contributed to the decline in the use of FS in the USA [33].

The yield of FS screening

The finding of a polyp (particularly an adenoma) or mass lesion at FS should be followed by a diagnostic colonoscopy to examine the entire colorectum. The presumed yield of FS screening relative to colonoscopy and FOBT has been estimated mainly from FOBT and colonoscopy-based studies [34–36]. In a study that evaluated the yield of FS with and without FOBT, Lieberman *et al.* reported that FOBT alone identified 23.9% of advanced adenoma, FS alone identified 70.3% and combined FOBT and FS identified 75.8% of advanced adenoma [34]. However, FS was defined as examination of the rectum and sigmoid colon during colonoscopy in this study. In another study, Imperiale *et al.* reported a prevalence of advanced proximal neoplasia including cancer among 23 out of 1564 (1.5%) patients without distal colon polyps who underwent screening colonoscopy [35]. In the VA 380 study, Lieberman *et al.* also reported that 48 out of 1765 (2.7%) patients without distal colon polyps had advanced proximal neoplasia [36]. Overall, these studies suggest a small absolute increased yield of significant neoplasia with colonoscopy over FS as a first-line screening test and minimal improvement in detection of significant neoplasia when FOBT is combined with FS [34,37]. However, in PLCO where the primary screening was performed with FS and abnormal studies were followed with colonoscopy, Schoen *et al.* reported that 977 cases of CRC were diagnosed over a mean follow-up of 11.5 years [38]. Only 97 out of 977 (9.9%) cancers were adjudged as being beyond the reach of a sigmoidoscope over this extended follow-up period. The authors estimated that if colonoscopy had been used instead of FS for screening, an additional 15.6% of cancers may have been screen-detected. Although the increased rate of cancer detection favors colonoscopy over FS, no clinical trial has demonstrated that the incremental cost and possible complications from colonoscopy makes it a more cost-effective population-based screening test. Furthermore, the efficacy of colonoscopy in reducing incidence [39–41] and mortality [42,43] from proximal colon cancer has been questioned in recent observational studies. Although a recent population-based case–control study [44] reported an overall 77% reduction on the risk of CRC with prior exposure to colonoscopy in Germany, the protection in the proximal colon was much lower than in the distal colon (56 vs 84%). Patients' factors such as inadequate bowel preparation and endoscopists' factors such as lack of adequate detection of flat and depressed lesions may reduce the efficacy of colonoscopy in the proximal colon [45,46]. However, it is also possible that the biology of colon cancer differs by tumor location

[47-49]. It is noteworthy that protection from proximal CRC supposed to be the major advantage of colonoscopy over FS. Nonetheless, colonoscopy is fast becoming the dominant screening modality for CRC screening in the USA [50,51]. Two randomized controlled trials of screening colonoscopy are currently underway in Europe (Clinical Trials database identifiers NCT00906997 and NCT00883792 [104]), but the final results are not expected until at least 2021 and 2026 respectively. Unfortunately, none of these studies compare FS with colonoscopy.

Evidence of the effectiveness of FS screening

Observational studies

Selby *et al.* compared the use of rigid sigmoidoscopy among 261 members of Kaiser Permanente who died of CRC in the distal colorectum with 868 controls [52]. The authors reported the use of rigid sigmoidoscopy for screening within 10 years prior to cancer diagnosis among 8.8% of cases versus 24.2% among controls. The adjusted OR was 0.41 (95% CI: 0.25–0.69), suggesting a 59% reduction in mortality from distal CRC. However, there was no effect of sigmoidoscopy screening among 268 patients who died of proximal CRC. In another study, Newcomb *et al.* reported 10.6% exposure to sigmoidoscopy among 66 patients enrolled in a health plan who died of CRC compared with 29.1% sigmoidoscopy exposure among 196 controls (adjusted OR: 0.21; 95% CI: 0.08–0.52) [53]. A nonsignificant reduction was reported for proximal colon (adjusted OR: 0.36; 95% CI: 0.11–1.20). In another case–control study, Newcomb *et al.* reported a significant reduction in the risk of incident distal CRC following exposure to sigmoidoscopy (OR: 0.24; 95% CI: 0.17–0.33) and noted that the effect was sustained for up to 16 years [54].

Randomized clinical trials

Four randomized control trials have recently reported the results of their evaluation of the effectiveness of FS screening on CRC incidence and mortality. These are the Norwegian (NORCCAP) [55], Italian (SCORE) [56] and UK (UKFSST) trials [57], and the FS screening arm of the PLCO cancer screening trial in the USA [58]. Each trial has distinct characteristics (Table 1). In the NORCCAP trial, participants were drawn by individual randomization from the population registry and invited directly to once-only FS screening. This was a one-step invitation process that mimicked invitation procedures for national screening programs. In the PLCO trial, study subjects were recruited by mailing informational brochures and letters of invitation to age-eligible individuals identified on public, commercial or screening center-specific mailing lists whereas, in the Italian SCORE and UKFSST studies, a two-step process was used. An interest-in-screening questionnaire that was designed to ascertain the eligibility and willingness to participate in screening was first mailed to potential subjects. The exclusion criteria were then applied to subjects who responded to the mailings before randomization assignment was performed.

Unlike the PLCO trial, which evaluated the two rounds of screening that FS performed 3 or 5 years apart depending on the date of entry to the study [23], the Europe-based trials evaluated the effect of a single FS screening. In all the trials, adherence to the screening protocol was less than perfect. The uptake of one screening FS in the intervention arm

ranged from 57.8% in the Italian SCORE trial to 86.6% in the PLCO trial. The colonoscopy rate was also higher in the PLCO trial. In the UKFSST, screening with FS was associated with a significant 23% reduction in the overall incidence of CRC and 31% reduction in CRC-specific mortality. The reported protection was confined to the distal colorectum [57]. In the Italian SCORE, screening with FS was associated with a significant 18% reduction in the overall incidence of CRC but a nonstatistically significant 22% reduction in CRC-specific mortality was reported [56]. However, there was no effect of FS on CRC incidence over 7 years of follow-up in the Norwegian NORCCAP trial and a nonstatistically significant reduction in CRC specific mortality was found in over 6 years of follow-up [55]. In the PLCO trial, FS screening reduced the overall incidence of CRC by 21%. In this study, a significant reduction in CRC of 29 and 14% were demonstrated in both distal and proximal colon, respectively. This was the only study to show that FS screening can reduce the incidence of proximal CRC. A significant 26% reduction in mortality was achieved with FS screening in this study. By colon subsite, a 50% reduction in mortality was demonstrated in the distal colon. However, FS screening did not affect mortality from proximal colon cancer [58].

The challenges after FS examinations

Multiple rounds of FS screening

Although Selby *et al.* reported mortality benefit for up to 10 years from rigid sigmoidoscopy [52] and the UKFSST demonstrated a significant mortality benefit with a once-in-a-lifetime FS [57], patients are expected to undergo repeat FS in 5 years following a negative FS according to the current screening guidelines [4]. It is unclear whether patients do actually adhere to FS at the recommended intervals in community-based practice. However, in PLCO (the only RCT with multiple rounds of screening per protocol), there were racial and socioeconomic disparities in attendance to repeat FS. Black study subjects, unmarried persons and those with less than a high school education were less likely to return for repeat examinations [59]. Those with inadequate FS at baseline were also less likely to return for a repeat examination when compared with those with adequate baseline FS (65.3 vs 81.6%; $p < 0.001$) [60].

Inadequate FS

The inadequate FS is typically defined as depth of insertion less than 50 cm or visual inspection that is less than 90% of the mucosal surface due to suboptimal bowel preparation, without detection of polyp or mass. These patients are usually rescheduled for a repeat examination in usual clinical practice. Factors that have been identified as associated with an increased risk of inadequate FS include advancing age, female sex and cigarette smoking, but obesity was associated with a reduced risk [60-62]. Inadequate FS dampens the enthusiasm of patients for further endoscopic screening. In PLCO, those with inadequate FS were less likely to return for repeat examinations at years 3 or 5 [59,60]. Furthermore, those with inadequate FS (particularly if due to discomfort) were more likely to have inadequate FS at repeat examination (OR: 6.24; 95% CI: 5.77-6.75), underscoring the importance of offering sedation to the patient or switching to another screening modality. Inadequate FS

has also been associated with subsequent CRC [63]. It is important for patients and providers to strive to ensure an adequate FS at the first screening attempt.

Follow-up after abnormal FS

When a polyp (particularly an advanced adenoma defined as an adenoma with a size ≥ 1 cm or with villous histology or high-grade dysplasia) or mass is found during FS, the patient is referred for diagnostic colonoscopy. Such diagnostic evaluations are encouraged to be performed as soon as possible. In the PLCO trial, approximately 22.9% of the screened participants underwent diagnostic colonoscopy whereas only 5.3% in UKFSST, 13.3% in NORCCAP and 7.8% in SCORE underwent colonoscopy due to the different thresholds used in the studies (Table 1). Racial disparity was reported from PLCO as black subjects were significantly 12% less likely to undergo diagnostic colonoscopy after an abnormal FS [64].

Unanswered questions for the future

The uptake of FS has been decreasing in the USA [32,51] but it is still a commonly used screening modality in the UK [24]. Given the suggestion that CRCs that occur within the recommended screening interval (interval cancers) express aggressive phenotypes [65,66] and may contribute to the observed reduced efficacy of colonoscopy in the proximal colon, the major question then becomes: ‘is it better to use a screening modality with less sensitivity more frequently (every 5 years for FS) or use higher sensitivity test less frequently (every 10 years for colonoscopy)’?

Studies that have considered colonoscopy as a cost-effective screening modality have generally modeled repeat screening every 10 years [27]. It is conceivable that this pattern of analysis may need to be revisited given the reported findings in surveys that primary care physicians [67] and gastrointestinal endoscopists [68] and actual clinical practice documentation [69,70] frequently recommend colonoscopies in excess of guidelines. Furthermore, it is conceivable that colonoscopy use for postpolypectomy surveillance would increase given the fact that adenoma detection rate is now considered a quality measure [71]. The frequency of postpolypectomy surveillance colonoscopy was reported to constitute approximately 24% of gastroenterology practice [72] and potentially diverts resources from screening.

Despite these uncertainties, it may be quite challenging to reverse the dominance of colonoscopy in the USA, but other countries using FS as the primary screening modality may await the results of the ongoing randomized clinical trials evaluating colonoscopy as a primary screening tool before making a change if needed. Given the fact that the theoretical benefit of colonoscopy over FS has not been conclusively demonstrated to outweigh the additional cost and risks associated with the procedure and the clear evidence of the benefits of FS screening, we are of the opinion that countries without population-based CRC screening, particularly those with limited resources, should consider a FS screening program because it has been proven to be effective and yet, it is less expensive, safer and more convenient for the patients than colonoscopy.

Conclusion & future perspective

In the next 5–10 years, we speculate that the dominance of FS screening in Europe would remain so. However, in the USA, the ongoing healthcare reform may lead to a substantial change in clinical practice with reduced use of colonoscopy as a screening tool, but more as a diagnostic tool and primary screening with fecal immunochemical testing and FS will increase.

Flexible sigmoidoscopy is an effective CRC screening modality. Although the use of colonoscopy is increasing in developed countries, FS remains a viable screening option. This is particularly true for resource-limited countries that lack organized screening programs. This will enable the development of an affordable screening tool that can be performed by physicians and nonphysicians with a substantial advantage that capacity can be more easily developed and sustained.

Acknowledgments

AO Laiyemo is supported by the National Cancer Institute's new faculty recruitment supplement to the Comprehensive Minority Institution/Cancer Center Partnership between Howard University Cancer Center and Sidney Kimmel Comprehensive Cancer Center of Johns Hopkins University (5U54CA091431-09 S1).

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Practice points

- Flexible sigmoidoscopy (FS) screening has been shown to decrease colorectal cancer mortality in large, high-quality randomized clinical trials.
- Physician and nonphysician endoscopists can perform the procedure with an acceptable degree of efficiency.
- Bowel preparation is accomplished with enema and sedation is not required, making the logistic challenges associated with the procedure easy to overcome.
- When patients have had inadequate FS, they often do not return for repeat examination, and inadequate FS has been associated with subsequent colorectal cancer.
- When biopsy or polypectomy is not performed during FS, some patients do not follow-up with diagnostic colonoscopy.
- Following a normal screening examination, a repeat study is typically scheduled for 5 years.
- Although FS is an acceptable option for colorectal cancer screening in most screening guidelines, the use of this proven screening modality continues to decrease.
- FS is a cost-effective modality for population-based screening, and such programs can be easily designed, developed and implemented in countries without colorectal cancer screening programs.
- FS-based population screening is ideal for countries with limited resources.

Table 1

Summary of randomized controlled trials of flexible sigmoidoscopy screening.

Characteristics	PLCO [23,58]	UKFSST [57]	NORCCAP [55]	SCORE [56]
Country	USA	UK	Norway	Italy
Number of centers	10	14	2	6
Study entry period	1993–2001	1996–1999	1999–2000	1995–1999
Age of eligibility (years)	55–74	55–64	55–64	55–64
Recruitment strategies	Two steps: mass mailings of informational brochures and letters of invitation to age-eligible individuals from public and commercial lists; randomization of consenting subjects	Two steps: an initial response to an interest-in-screening questionnaire; and eligible responders were randomized	One step: individual randomization from the population registry with direct invitation for screening	Two steps: an initial response to an interest-in-screening questionnaire; and eligible responders were randomized
Case ascertainment	Active follow-up using annual study update forms and data abstraction from medical records	Registry-based	Registry-based	Registry-based
Number in control arm	77,455	113,195	41,913	17,144
Number in the FS screening arm	77,447	57,237	13,823	17,148
Number of FS screening rounds offered	2	1	1	1
Screened with FS at least once, n (%)	67,073 (86.6)	40,674 (71)	8846 (64.8)	9911 (57.8)
Biopsy during FS screening per protocol	No	Yes	Yes	Yes
Definition of a positive FS screen	Any polyp or mass	Biopsy at screen or referral for colonoscopy or surgery	Referral for colonoscopy	Biopsy at screen or referral for colonoscopy or surgery
Positive screen in screening program (%)	32.9	27.7	21	17.6
Indication for colonoscopy referral	Per primary physician and medical care	1.0 cm polyp, three or more adenomas, tubulovillous or villous change, severe dysplasia, malignancy or 20 or more hyperplastic polyps above the distal rectum	1.0 cm polyp, any adenoma, or malignancy or positive fecal occult blood test	0.5 cm polyp, inadequate bowel preparation harboring at least one polyp, three or more adenomas, tubulovillous or villous change, severe dysplasia, malignancy
Screening-related colonoscopy performed (%)	22.9	5.3	13.3	7.8
Yield of cancer per 1000 screened	3.6	3.4	2.4	5.4
Length of follow-up (years)	11.9	11.2	7 for incidence and 6 for mortality	10.5 for incidence and 11.4 for mortality
CRC incidence in control arm per 1000	16.6	16.1	1.3	1.8
CRC incidence in intervention arm per 1000	13.1	12.4	1.3	1.4

Characteristics	PLCO [23,58]	UKFSST [57]	NORCCAP [55]	SCORE [56]
CRC mortality in control arm per 1000	4.4	4.8	2.4	0.44
CRC mortality in intervention arm per 1000	3.25	3.3	1.8	0.35
Efficacy of FS in preventing CRC incidence	RR = 0.79 (95% CI: 0.72–0.85)	HR = 0.77 (95% CI: 0.70–0.84)	Not presented	RR = 0.82 (95% CI: 0.69–0.96)
Efficacy of FS in preventing CRC mortality	RR = 0.74 (95% CI: 0.63–0.87)	HR = 0.69 (95% CI: 0.59–0.82)	HR = 0.73 (95% CI: 0.47–1.13)	RR = 0.78 (95% CI: 0.56–1.08)

CRC: Colorectal cancer; FS: Flexible sigmoidoscopy; HR: Hazard ratio; RR: Relative risk.