CANADIAN PARTNERSHIP AGAINST CANCER
PARTENARIAT CANADIEN CONTRE LE CANCER

Flexible Sigmoidoscopy Watching Brief

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Purpose of this Document

This document provides a concise synthesis of the status of four randomized controlled trials (RCTs) of flexible sigmoidoscopy (FS) for colorectal cancer (CRC) screening.

The NORCCAP trial was the first to publish results for CRC mortality, in June 2009. The U.K. FS trial reported results in April 2010. The remaining two trials are likely to publish results over the next 12 to 24 months.

This “watching brief” is intended to provide background information and, when they become available, to put trial results into perspective with respect to the extent of the benefits and adverse effects of FS CRC screening. This brief will also discuss the quality and limitations of the evidence. Health policy advisors involved in cancer control can use the information that the brief contains to respond to the results of the ongoing trials as they are published.

This document is not intended to provide definitive answers or clinical and policy recommendations.

The Expert Panel will continue to monitor and review trial evidence as it becomes available, and will provide updates to this document.

Summary

The U.K. FS trial provides the strongest evidence to date that screening with a single FS examination results in a significant 31% reduction in CRC mortality and a 23% reduction in CRC incidence. Both FOBT- and FS-based screening are now supported by the strongest level of evidence (from RCTs). However, the CRC mortality and incidence reductions observed in the U.K. FS trial are greater than those reported in the RCTs that evaluated unrehydrated fecal occult blood tests (FOBT).

With these significant results from the U.K. FS trial now available, the role of FS in organized CRC screening programs will need to be examined.

Introduction

Several colorectal cancer (CRC) screening procedures exist. These options include the fecal occult blood test (FOBT), flexible sigmoidoscopy (FS) and colonoscopy. Our main focus in this document is on new evidence for FS. However, to give this information context, we begin with a brief review of the existing (older) body of evidence on FOBT. Most established population-based CRC screening programs currently include a type of FOBT as the initial test.

In addition, it is anticipated that irrespective of the results of randomized controlled trials (RCTs) of FS, FOBT will continue to have a role in population-based CRC screening for the near future. Thus, when considering the incorporation of FS into population-based CRC screening, it will be important to also consider the advantages, magnitude of benefit and limitations of FOBT for CRC screening.

1.0 Summary of Evidence: FOBT

Before the publication of the results of FS RCTs, of all the tests available for CRC screening, fecal occult blood testing has shown the strongest evidence for efficacy.

1.1 Hemoccult FOBT

Several published RCTs used earlier versions of the Hemoccult FOBT (Hemoccult or Hemoccult II).[1,2,3,4] Hemoccult tests rely on the pseudo-peroxidase activity of hemoglobin in stool. They are referred to as guaiac FOBTs (gFOBTs).

The results of the gFOBT RCTs were pooled and summarized in a Cochrane review in 2008 (Tables 1 and 2).[5]

- The pooled results indicated that a CRC screening program with biennial gFOBT can lead to a 15% reduction in CRC mortality after 12 to 18 years.
- There was a 25% CRC mortality reduction (RR 0.75, 95% CI: 0.66–0.84) for those attending at least one round of gFOBT screening.
- The uptake/compliance for gFOBT in the RCTs was high, with approximately two-thirds of study participants attending for at least one round; a high uptake may be challenging to sustain over repeated rounds of screening, however.

It has been estimated that if a biennial gFOBT screening program was offered to 10,000 people, and if two-thirds had at least one gFOBT, 8.5 deaths (95% CI: 3.6–13.5) from CRC would be prevented over 10 years.[6]

Use of annual (rather than biennial) FOBT has been evaluated in only one RCT – the study from the U.S.[7] Based on this RCT and several modelling studies,[8,9] it has been suggested that annual FOBT screening can lead to more life-years gained than biennial screening can; however, the resources required for annual screening are greater than for biennial screening.

1.2 Newer FOBTs and FIT

- Hemoccult Sensa, a gFOBT, was developed to improve the sensitivity of Hemoccult FOBT. The fecal immunochemical test (FIT) detects human globin.
- The accuracy of the newer FOBTs was the subject of a recent systematic review for the U.S. Preventive Services Task Force (USPSTF).[10] The review concluded that Hemoccult II was less sensitive than FIT for cancer detection and that FIT had sensitivity similar to, or less than, that of Hemoccult Sensa.
- The specificity of Hemoccult Sensa was reported to be less than that of FIT, which had specificity similar to that of Hemoccult II. The review noted, however, that there are few studies directly comparing different FITs with each other or with regular or high-sensitivity Hemoccult tests (Hemoccult Sensa).
- An earlier review by the U.S. Multi-Society Task Force on Colorectal Cancer had concluded that there were no clear patterns of difference in sensitivity and specificity between Hemoccult Sensa and FITs.[11]
- There are no data on the impact of screening with Hemoccult Sensa or FITs on CRC mortality or incidence, but a decision analysis conducted for the USPSTF estimated that given better test characteristics, Hemoccult Sensa and FIT could potentially demonstrate better CRC mortality reduction than the earlier versions of gFOBT.[9]
- Two recent RCTs in the Netherlands reported that the uptake of FIT (OC Sensor) was more than 10% higher than that of Hemoccult II and that specificity may be as high as with gFOBT at a positivity threshold of 200 ng/ml.[12,13]
- Target-population uptake of Hemoccult Sensa is lower than for the FITs because of the greater number of stool specimens required, method of specimen collection and dietary restrictions prior to and during sample collection.[14]

- Many FITs also have the advantage of automated analysis, which removes the inter-observer variation in test interpretation.
- There are more extensive data for FIT than for Hemoccult Sensa.[15]

1.3 Limitations of FOBTs

FOBTs have demonstrated no direct harms, but have the following limitations:

- False positive tests lead to further testing with colonoscopy, which brings the potential of associated complications.
- FOBTs have lower sensitivity (< 50%) for advanced adenomas than for CRC.[16,17] Likely because of the lower sensitivity, CRC incidence reduction (20%) has been demonstrated in only one RCT using rehydrated gFOBT and after 18 years of follow-up.[18]

1.4 Published Randomized Controlled Trials of FOBT

Table 1: Key Features of gFOBT Randomized Controlled Trials

	Minnesota[18]	U.K.[4]	Denmark[3]	Sweden[1]
Study population (N)	46,445	152,850	61,933	68,308
Ages (years)	50–80	45–74	45–75	60–64
Screening cycles	Annual, biennial	Biennial	Biennial	Biennial
Screening rounds (N)	11 (annual) 6 (biennial)	6	9	2
Follow-up (years)	18	11.7	17	15.5
Compliance, first screening (%)	Not reported	53	67	63
Compliance, at least one round (%)	75 (annual) 78 (biennial)	60	Not reported	70
Completion of all rounds (%)	46 (annual) 60 (biennial)	38	46	Not reported

Note: European trials randomly allocated subjects to invitation or no invitation for screening. Minnesota study included only those who had agreed to participate.

Rehydrated FOBT, as was used in the Minnesota trial, is not routinely used in clinical laboratories and is not recommended by any CRC screening clinical practice guideline.

The sensitivity for CRC given in Table 2 is for a program of annual or biennial testing and not for a single episode of testing. The sensitivity of a single set of unrehydrated FOBTs compared with colonoscopy has been reported to be as low as 13%.[19]

Table 2: Results of gFOBT Randomized Controlled Trials

		Minnesota[7,18]	U.K.[4]	Denmark[3]	Sweden[1]	Cochrane Meta-analysis[5]
Test positivity (%)	**Unrehydrated**	1.4–5.3	1.2–2.7	0.8–3.8	1.9	—
	Rehydrated	3.9–15.4	—	—	1.7–14.3	—
Cumulative colonoscopy rate (%)	**Annual**	38	—	—	—	—
	Biennial	28	2.6	5.3	6.4	—
Sensitivity for colorectal cancer (%)	**Unrehydrated**	80.8	57.2	55	NR	—
	Rehydrated	90.2	—	—	82	—
PPV for colorectal cancer (%)	**Unrehydrated**	5.6	9.9–11.9	5.2–18.7	NR	—
	Rehydrated	0.9–6.1	—	—	NR	—
PPV for adenomas (%)	**Unrehydrated**	6.0–11.0	42.8–54.5	14.6–38.3	NR	—
	Rehydrated	NR	—	—	NR	—
Cumulative incidence ratio screening to control (95% CI)	**Annual**	0.80 (0.70–0.90)	—	—	—	—
	Biennial	0.83 (0.73–0.94)	—	—	—	—
Colorectal cancer mortality – RR (95% CI)	**Annual**	0.67 (0.51–0.83)	—	—	—	—
	Biennial	0.79 (0.62–0.97)	0.87 (0.77–0.97)	0.84 (0.73–0.96)	0.84 (0.71–0.99)	0.84 (0.78–0.90)
All-cause mortality – RR (95% CI)		1.0 (0.97–1.02)	1.0 (0.99–1.02)	1.0 (0.98–1.02)	1.02 (0.99–1.04)	—

NR = Not reported; PPV = Positive predictive value

2.0 Randomized Controlled Trials of Flexible Sigmoidoscopy

There have been four RCTs of FS as a CRC screening test; Table 3 shows the key features of each. Two trials have now published reports on outcomes. The U.K. FS trial investigators published the results of the study's primary outcomes (11-year mortality and incidence) in April 2010.[20] The NORCCAP investigators published a preliminary analysis of cumulative CRC incidence after seven years and CRC mortality and all-cause mortality after six years of follow-up (Table 4).[21]

The U.K. FS trial demonstrated an overall 23% reduction in CRC incidence and a 31% reduction in CRC mortality. In a secondary analysis, when the investigators examined the effect of screening in participants (those who do not participate are included in the analysis to adjust for self-selection bias), the incidence was reduced by 33% and CRC mortality by 43%. The incidence of distal CRC (rectum and sigmoid) was reduced by 50%. There was no reduction in the incidence of proximal cancers. The investigators did not provide mortality reductions for proximal and distal CRC. The investigators estimated that 191 people needed to be screened to prevent one CRC diagnosis. To prevent one CRC death, 489 people would need to be screened. The all-cause mortality was also reduced (3%) in the intervention group, barely below statistical significance ($p < 0.052$).

In the NORCCAP trial, there was no difference in the seven-year cumulative CRC incidence between the screening and control groups (134.5 vs. 131.9 cases per 100,000 person years).[21] There was no statistical difference in CRC mortality or all-cause mortality between the screened group and control group. However, this should not be interpreted as a conclusion that contradicts the U.K. FS trial outcomes. The results of the two trials are compatible. The U.K. FS trial shows that cumulative CRC incidence in the intervention group fell below that of the control group starting in the sixth year of follow-up because of the high yield of prevalent CRCs diagnosed in the screenees.

There was a statistical difference in all CRC mortality and rectosigmoid cancer mortality between those who attended screening and the control group. This analysis did not adjust for self-selection bias, which is a serious concern in this type of analysis. Those attending screening may differ from those who did not and from the controls. Those who attended screening may be at lower risk of CRC than the control population ("healthy screenee" effect). For example, they may be of higher socioeconomic status, live healthier lifestyles or be more vigilant about their health.

The CRC mortality reduction of 27% reported in the NORCCAP trial is quite similar to that found in the U.K. FS trial. The available data do not allow for the individual contributions of FS and FIT to be determined. This mortality reduction

is greater than reductions seen in published RCTs of unrehydrated gFOBT (Table 2).

Most clinical practice guidelines recommend FS screening every five years. The European trials are all evaluating a single FS at age 55–64 years. A once-in-a-lifetime FS strategy would significantly reduce the resource needs of an FS-based screening program.

Acceptability and anticipated uptake of FS in a population-based CRC screening program in Canada is difficult to anticipate. Very high participation rates were observed in the NORCCAP trial. However, screening attendance rates were much lower in two other FS trials (see Uptake in Table 3) and in a Dutch study that compared participation among those offered FS and those offered FIT (32% for FS vs. 62% for FIT).[13]

Table 3: Key Features of Flexible Sigmoidoscopy Randomized Controlled Trials

	NORCCAP[21]	U.K. FS[20,22]	SCORE[23]	PLCO[24]
STUDY				
Country	Norway	U.K.	Italy	U.S.
Lead investigator	Hoff, G.	Atkin, W.S.	Segnan, N.	Weissfeld, J.
Recruitment period	1999–2000	1996–1999	1995–1999	1993–2001
POPULATION				
Number randomized	55,736	170,432	34,292	154,000.0
Setting	2 areas: 1 city, 1 county	14 centres	5 areas: Arezzo, Biella, Genova, Rimini, Torino	10 cities
Source	Population registry	General practice registry	**1.** General practice patient registry (Arezzo, Rimini, Torino) **2.** Health services registry (Genova, Biella)	Public, commercial, screening centre mailing lists
Age (years)	55–64	55–64	55–64	55–74
STUDY GROUPS				
Randomization	Before invitation	After invitation	After invitation	After invitation
Study arms	**1.** FS **2.** FS & FIT **3.** No screening	**1**. FS **2.** No screening	**1.** FS **2.** No screening	1. FS 2. No screening
POWER CALCULATION ASSUMPTIONS				
Screening arm(s) (n)	7,000 FS 7,000 FS & FIT	65,000	20,000	74,000
Control arm (n)	42,000	130,000	20,000	74,000
Compliance (%)	70	55 (5% contamination in control arm)	70	85
CRC incidence reduction (intent to treat) (%)	30	20 between study arms, 40 in each subgroup: < 60 years, ≥ 60 years	21	NA
CRC mortality reduction (intent to treat) (%)	NA	20 between study arms, 40 in each subgroup: < 60years, ≥ 60 years	NA	20
Follow-up (incidence) (years)	5	10	6	NA
Follow-up (mortality) (years)	5	15	11	10
Significance level (%)	5 (two-sided)	5 (two-sided)	5 (one-sided)	5 (one-sided)
Power (%)	90	90	80	90

	NORCCAP[21]	U.K. FS[20,22]	SCORE[23]	PLCO[24]
UPTAKE				
Interested in screening (invited)* (%)	Not applicable	55	16	Not available
Attended screening (randomized)† (%)	67	71	58	83
Attended screening (invited)‡ (%)	67	39	9	Not available
SIGMOIDOSCOPY				
Instrument	140 cm colonoscope	60 cm videoscope	4 centres: 140 cm colonoscope 1 centre: "sigmoidoscope"	60 cm flexible sigmoidoscope
Endoscopist	Not given	Registrar-level gastroenterologists & surgeons	Gastroenterologist	Physicians, nurse practitioners
Screen frequency	Once only	Once only	Once only	Baseline, year 5
Criteria for colonoscopy	**1.** Any polyp ≥ 1 cm **2.** Any neoplasia	**1.** Any polyp ≥ 1 cm **2.** ≥ 3 adenomas **3.** Any polyp with villous component or severe dysplasia **4.** Any cancer **5.** ≥ 20 hyperplastic polyps above distal rectum	**1.** Any polyp > 5 mm **2.** Any polyp + inadequate bowel prep **3.** ≥ 3 adenomas **4.** Any polyp with villous component or severe dysplasia **5.** Any cancer **6.** Clinical judgment of endoscopist	Any polypoid lesion or mass
Proportion requiring colonoscopy (%)	20.4	5.2	8.4	23.4

FS = flexible sigmoidoscopy; FIT = immunochemical fecal occult blood test

*Proportion of individuals interested in screening from those with a delivered invitation.

†Proportion of those with a delivered invitation who were interested in screening and attended for FS.

‡Proportion of those with a delivered invitation who were interested in screening and attended for FS (Product of Interested in Screening and Attended Screening – Randomized).

Table 4: Mortality Outcomes: U.K.[20] and NORCCAP[21] Flexible Sigmoidoscopy Trials

	Intervention vs. control group (intent-to-treat analysis), hazard ratio (95% CI)	**Screening vs. non-screening*** (intervention analysis), hazard ratio (95% CI)
All CRC mortality		
NORCCAP[†]	0.73 (0.47–1.13)	0.41 (0.21–0.82)[‡]
U.K.	0.69 (0.59–0.82)	0.57 (0.45–0.72)
Rectosigmoid CRC mortality		
NORCCAP[†]	0.63 (0.34–1.18)	0.24 (0.08–0.76)[‡]
U.K.	Not reported	Not reported
All-cause mortality		
NORCCAP[†]	1.02 (0.98–01.07)	Not reported
U.K.	0.97 (0.94–1.00)	0.95 (0.91–1.00)

*Subanalysis of the effect of screening in participants.

[†]Results are for FS and FS + FIT groups combined.

[‡]Note that the NORCCAP screening vs. non-screening analysis does not adjust for self-selection bias; therefore, caution is advised when using these results since this approach raises serious concerns (see text).

3.0 How Does Flexible Sigmoidoscopy Screening Compare with Colonoscopy?

The key features of four published studies of colonoscopy screening are summarized in Table 5.

Table 5: Key Features of Colonoscopy Cohort Studies

		Leiberman[25]	Imperiale[26]	Schoenfeld[27]	Regula[28]
Publication year		2000	2000	2005	2006
Country		U.S.	U.S.	U.S.	Poland
Design		Cohort study	Cross-sectional study	Cohort study	Cross-sectional study
Population	**Number**	3,196 of 17,732 screened	1,994 of 2,686 eligible	1,483 of 1,593 eligible	50,148
	Setting	Veterans Affairs study	Eli Lilly employee screening program	Veterans Affairs study	National Screening Program database evaluation
	Sex (%)	Male: 96.8	Male: 58.8	Female: 100	Female: 64.1
	Age (years)	50–75	≥ 50	40–79	40–66
	Family history (%)	13.9	Not reported	15.7	≈20
	Complete colonoscopy (%)	97.9	97.0	98.7	91.1

The baseline colorectal adenoma and CRC detection rates from publication of the baseline findings of the four FS trials are shown in Table 6, alongside comparable data from four colonoscopy screening studies, to aid the comparison.

- Not all comparison data were presented or could be calculated from the published reports (shown as “Not reported”).

- Adenomas are divided by location and presence of advanced histology. Proximal lesions are those found in the cecum, ascending colon or transverse colon. Distal lesions are those found in the descending and sigmoid colon and the rectum. Advanced adenomas are those with features placing them at high risk for progressing to cancer (size > 1 cm, villous histology or high-grade dysplasia).
- In the FS trials, the proportion of screened individuals requiring colonoscopy varied from 5% to 23% depending on the permissiveness or restrictiveness of the criteria for colonoscopy (see Table 3). The highest colonoscopy rate was in the PLCO study and the lowest was in the U.K. FS trial. Whether the presence of any neoplasia on FS was an indication for colonoscopy appears to be a major factor in determining the subsequent colonoscopy rate, as can be seen when comparing the NORCCAP and U.K. FS trials.
- FS can lead to the detection of proximal adenomas and cancers if there are distal adenomas that lead to a complete colonoscopy.
- The data in Table 6 suggest that in the colonoscopy studies, advanced lesions were more equally distributed between the distal and proximal colon than previously believed.
- The colonoscopy cohort studies suggest that an FS screening strategy would fail to detect 21% to 65% of proximal advanced neoplasia.

Table 6: Proportion of Individuals in Whom Colorectal Adenoma or CRC Were Detected by FS or Colonoscopy Screening

		Flexible Sigmoidoscopy					Colonoscopy			
		NORCCAP[21] (Total cohort)	**NORCCAP[21] (FS only cohort)**	**U.K. FS[20]**	**SCORE[23]**	**PLCO[24]**	**Leiberman, 2000[25]**	**Imperiale, 2000[26]**	**Schoenfeld, 2005[27]**	**Regula, 2006[28]**
Country		Norway	Norway	U.K.	Italy	U.S.	U.S.	U.S.	U.S.	Poland
Study design		RCT	RCT	RCT	RCT	RCT	Cohort study	Cross-sectional study	Cohort study	Cross-sectional study
Results	**No polyps (%)**	83.0	83.0	75.0	82.0	66.0	61.0	78.0	80.0	NR
	Any adenoma (%)	17.0	NR	NR	NR	31.0	37.0	22.0	20.0	13.0
	Distal adenoma (%)	NR	NR	12.0	10.0	23.0	23.0	8.0	6.0	NR
	Any advanced lesion (%)	NR	NR	NR	NR	NR	11.0	5.0	5.0	6.0
	Distal advanced lesion (%)	NR	NR	NR	NR	NR	7.0	3.0	NR	NR
	Proximal advanced lesion (%)	NR	NR	NR	NR	NR	5.0	3.0	NR	NR
	Any cancer (%)	0.3	0.3	NR	0.5	0.4	1.0	0.6	0.1	0.8
	Distal cancer (%)	NR	NR	0.3	0.5	0.2	0.6	0.3	NR	NR
	Proximal cancer (%)	NR	NR	NR	NR	NR	0.4	0.4	NR	NR

RCT = Randomized controlled trial; NR = Not reported

4.0 Considerations for the Feasibility of Flexible Sigmoidoscopy Screening

Equipment: FS is a screening method that involves video endoscopy; it is performed using a 60 cm long sigmoidoscope or using the longer colonoscope.

Setting or Facility: FS requires an appropriate setting in which to perform the unsedated procedure. FS can be performed in an endoscopy room or an operating room in a hospital, or in an ambulatory endoscopy clinic, although this would require an appropriate funding model (see below). In the past, FS may have been performed in an office setting, but this practice would likely not meet current standards for infection control (see below).

Endoscopy Capacity: Regardless of where FS is performed, adequate capacity is required; that is, the resources must be available specifically for this purpose. FS may be perceived as displacing colonoscopy if, for example, endoscopy rooms currently dedicated to colonoscopy are used for FS. An expansion of endoscopy capacity is required; otherwise the introduction of FS could adversely affect access to colonoscopy.

Infection Control: Reprocessing (or cleaning) of used sigmoidoscopes requires the same reprocessing used for colonoscopes (manual cleaning, followed by chemical disinfection using dedicated equipment – that is, a “scope washer”). Reprocessing needs to be performed by individuals specifically trained to do this, not by casual staff who are not appropriately trained in the cleaning and disinfecting procedures. Typically, in a large hospital-based endoscopy unit, a dedicated endoscopy technician cleans the scopes.

Physician Endoscopists: FS is performed by appropriately trained physicians, such as gastroenterologists, general surgeons and family physicians (FPs), although few FPs currently perform FS or have been trained to do FS in Canada.

Non-Physician Endoscopists: Appropriately trained non-physicians, including registered nurses, can perform FS. Polyp detection rates, depth of endoscope insertion, complication rates and patient satisfaction are no different for appropriately trained non-physician and physician endoscopists performing FS.[29] Ontario is piloting nurse-performed FS (RN-FS) and has set up a formal training program to train nurses to perform FS; a small number of RNs have been trained to date. If other provinces undertake non-physician FS, formal training programs will be required.

Issues Related to Non-Physician FS: In Ontario, to implement RN-FS three key specific issues had to be addressed:

1. Malpractice coverage for physicians when serving as trainers and when serving as back-up (following training, when RNs function independently)
2. Physician reimbursement during training and back-up phases (additional fee codes were added to the schedule of benefits)
3. Medical directives allowing RNs to perform FS at each hospital.

Endoscopy Assistants: Regardless of whether a physician or non-physician endoscopist performs FS, a trained endoscopy assistant is needed to assist the endoscopist with the procedure.

Reimbursement/Funding Model: Funding required for endoscopy by physicians consists of physician compensation and facility funding (which covers the non-physician costs of providing the service). Physicians who perform FS are compensated per procedure by provincial and territorial health plans, as they are for other endoscopic procedures. Facility funding is provided by a hospital's global budget for procedures performed there. Currently, since provinces and territories do not provide a facility fee, or provide an insufficient one, it is not financially viable for an individual physician or group of physicians to provide FS outside the hospital setting, such as in an ambulatory endoscopy centre. If appropriately trained non-physicians were to perform FS screening, funding would be required to cover the costs of providing the equipment, endoscopy room time, endoscopy assistant, etc.

Biopsy of Lesions Detected at FS: When a polyp is detected at FS, it can be biopsied and removed as long as it is small and electrocautery is not required. If non-physicians were to perform FS screening, they will need to be able to perform these biopsies.

Criteria for Referral to Colonoscopy: Some individuals in whom abnormal lesions are detected at FS will need to be referred for colonoscopy. For those in whom masses or other lesions suspicious for cancer are identified at FS, the need for referral is straightforward; for those in whom one or more polyps are identified, criteria for referral to colonoscopy are needed. The colonoscopy capacity required will depend on the criteria; for example, in the U.K. FS trial, because of rather stringent criteria, only 5% of persons who underwent FS screening were referred for colonoscopy (Table 3).

Quality Assurance: Quality assurance is a central feature of organized cancer screening; if FS were to be integrated into provincial and territorial CRC screening programs, quality assurance programs would be needed. A program would be required for the endoscopists, facilities, etc; a detailed assessment of what processes are currently in place would inform what needs to be added.

Monitoring and Evaluation: Information technology support and data systems would need to be developed to support the addition of FS to provincial and territorial CRC screening programs.

5.0 Policy Implications

5.1 Is the Evidence Enough to Direct Policy Change?

Population screening strategies for any condition should be introduced only if certain requirements are met, as listed below.[30] Screening for CRC with gFOBT meets the requirements.

- The disease is an important public health problem.
- There is an effective treatment for localized disease.
- Facilities for further diagnosis and treatment are available.
- There is an identifiable latent or early-symptomatic stage of disease.
- The technique to be used for screening is effective.
- The test(s) are acceptable to the population.
- The natural history of the disease is known.
- There is a strategy for determining which patients should and should not be treated.
- The cost of screening is acceptable.
- Effective treatment is available and management of cases in the early stages has a favourable impact on prognosis.

Given the evidence from the FS trials of the effectiveness of FS at reducing CRC mortality, public health officials and policy-makers will need to review and consider the potential implications for population screening strategies in their jurisdictions. As with all potential population screening tests, there will need to be evaluation of how FS meets key requirements for screening (above) and how it compares with FOBT and other screening tests.

The results of the U.K. FS trial show a significant mortality benefit. Before making a decision to change current policies on CRC screening, the potential generalizability of FS trial results to the Canadian context (including uptake rates) will need to be considered.

Any policy changes adding FS as an option for CRC screening will require close monitoring and evaluation of the use of the test, best accomplished through phased implementation pilots with well-designed evaluation plans.

5.2 What Will the Impact on Endoscopy Resources Be?

Even given the substantial mortality reduction that FS screening could achieve, as reported by the U.K. FS trial, it will be a challenge for health systems to make any immediate changes to current approaches to screening. These systems may not have the capacity to accommodate immediate adoption of FS screening.

If policy decisions are made to allocate resources to FS screening, it will be necessary to ensure that adequate endoscopy capacity is maintained in the system to provide diagnostic services for symptomatic patients and for follow-up of those with positive FOBTs. This issue may be more prominent in shared endoscopy facilities, where both screening and diagnostic endoscopy is delivered.

The referral rates for colonoscopy resulting from FS screening in Canada would likely fall between rates reported from the NORCCAP trial (20.4%) and the U.K. FS trial (5.2%). For example, in an FS clinic setting in Ontario, the referral rate to colonoscopy was 13%.[31] In addition, alternative models of service delivery should be considered, including screening in publicly funded, non-hospital settings.

An unintended consequence of publication of the U.K. FS trial results could be to increase the demand for colonoscopy by the public if there is a view that FS efficacy supports the likelihood of colonoscopy efficacy – even though the trials do not evaluate colonoscopy.

If FS were integrated into existing and planned CRC screening programs, a suitable reimbursement and funding model would need to be developed.

5.3 What Perspectives Will Health-Care Providers, the Public and Patients Have?

Health-care providers, the public and patients will respond to FS recommendations based on past experience, knowledge, interpretation of the evidence and their own personal values and beliefs. Each group may pressure or lobby for their preferences.

Family Physicians: Family physicians may support FS because it provides more choice for patients. FPs may be concerned, though, that it will require more of their time to explain options, benefits and risks. FPs may view the added option of FS as providing relief on demands for colonoscopy, especially if their specialist colleagues endorse FS. FPs will likely be concerned about local access to FS, and will be influenced by the opinions of local specialists. FPs will need to be supported with clear information and direction about whether and how FS is to be introduced into CRC screening programs. Some FPs will consider whether there is a role for them in providing FS services.

Gastroenterologists: Gastroenterologists may be concerned that FS will encroach on colonoscopy resources but that colonoscopy will still be preferred because it is a more complete examination. They will be concerned about how the capacity for endoscopy can be increased through non-hospital models of delivery, with appropriate reimbursement methods for technical costs and equipment. If FS provided by non-physicians is an option, specialists may be concerned about compensation, liability and the possibility that colonoscopy could also be "taken over."

The Public and Patients: FS could be seen as an attractive screening option that is "more accurate" than FOBT yet entails less inconvenience and risk than colonoscopy. Physician recommendation will continue to influence the public. Patients who have been diagnosed with CRC by colonoscopy, and advocacy groups, may support FS, but may continue to promote colonoscopy as the "more accurate" test. If wait times for FS are perceived to be shorter than for colonoscopy, FS may be preferred. Once-in-a-lifetime screening is unlikely to resonate with the public and may be viewed as an attempt to save money.

5.4. What Are Potential Effects on Planning and Implementation of Colorectal Cancer Screening Programs?

Provinces and territories developing CRC screening programs must consider whether FS should be an option, or whether it should be integrated into current screening programs. These are early days for provincial and territorial CRC screening programs; one approach is to wait to see what impact the programs will have as they are fully implemented before making a decision to change them.

Consideration may need to be given to including FS in screening programs. A determination will need to be made of the potential added value of including FS in existing screening programs with gFOBT or FIT. Such a determination will involve an assessment of the requirements for screening, specifically the following:

- The test should be suitable – accurate, acceptable, safe and relatively inexpensive. Equipment costs will be a significant factor.
- Will the public accept the test and will the test improve uptake? Would once-only FS screening appeal to the public and would there be an expectation that it be an option?
- What are the complication rates?
- How does the cost/benefit of FS compare with that of FOBT?
- There needs to be an agreed policy on whom to treat as patients and what level of abnormality will be referred for further testing. This policy will determine what percentage of the screened population will require referral

- Address issues of access to CRC screening for people in remote areas, including the option of FS.
- Provider reimbursement would need to adequately support equipment purchase, maintenance and reprocessing.

6.0 Cost-Effectiveness of Flexible Sigmoidoscopy Screening

- Cost-effectiveness is not yet established for all available screening modalities; cost-effectiveness is based on modelled estimates.
- Most models have used costs of screening and cancer care derived from U.S. data.
- A systematic review of seven cost-effectiveness analyses of CRC screening methods (including one-time or annual FOBT, FS every five years and colonoscopy every 10 years) in average-risk persons conducted for the USPSTF concluded that
    1. Screening for CRC is cost-effective compared with no screening (estimated cost between US$10,000 and $25,000 per life-year saved).
    2. A single optimal strategy could not be determined.[32]
- A recent decision analysis, also conducted for the USPSTF, did not assess costs (but used the number of colonoscopies as a proxy for resource use) and reported that assuming equally high adherence to screening, four strategies provided similar life-years gained:
    1. Annual gFOBT screening with Hemoccult SENSA
    2. Annual screening with FIT
    3. FS every five years
    4. Colonoscopy every 10 years.[9]
- Recently, two models that provide cost-effectiveness estimates for various screening modalities using Canadian costing data have been published. Only one of these models included FS.
- The Canadian Agency for Drugs and Technology in Health (CADTH) completed an economic analysis of FIT. A mid-sensitivity FIT was the most cost-effective strategy, being both less costly and more effective than a standard, low-sensitivity gFOBT and colonoscopy.[17]
- The second Canadian model included FS as one of 10 screening strategies modelled. Biennial low-sensitivity gFOBT, annual high-sensitivity gFOBT, annual FIT and colonoscopy every 10 years were the preferred strategies. FS every five years was estimated to result in fewer quality-adjusted life-years gained than did annual FIT, annual high-sensitivity FOBT or colonoscopy every 10 years. The incremental cost per quality-adjusted life-year gained compared with no screening was $6,192 for high-sensitivity FOBT, $6,237 for annual FIT and $7,892 for FS every five years.[33]

Summary

The U.K. FS trial provides the strongest evidence to date that screening based on a single FS examination results in a significant 31% reduction in CRC mortality and a 23% reduction in CRC incidence. Both FOBT- and FS-based screening are now supported by the strongest level of evidence (from RCTs). However, the mortality and incidence reductions observed in the U.K. FS trial are greater than those reported in the RCTs that evaluated unrehydrated FOBT.

With these significant results from the U.K. FS trial now available, the role of FS in organized CRC screening programs will need to be examined.

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References

[1] Lindholm E, Brevinge H, Haglind E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. Br J Surg 2008 Aug;95(8):1029–36.

[2] Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. J Natl Cancer Inst 1999 Mar 3;91(5):434–7.

[3] Kronborg O, Jorgensen OD, Fenger C, Rasmussen M. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. Scand J Gastroenterol 2004 Sep;39(9):846–51.

[4] Scholefield JH, Moss S, Sufi F, Mangham CM, Hardcastle JD. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut 2002 Jun;50(6):840–4.

[5] Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (Hemoccult): an update. Am J Gastroenterol 2008 Jun;103(6):1541–9.

[6] Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, Hemoccult. BMJ 1998 Aug 29;317(7158):559–65.

[7] Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med 1993 May 13;328(19):1365–71

[8] Technical report for the national committee on colorectal cancer screening. Health Canada, 2002. Available from http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/ncccs-cndcc/pdf/ccstechrep_e.pdf.

[9] Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, Van BM, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2008 Nov 4;149(9):659–69.

[10] Whitlock EP, Lin JS, Liles E, Beil TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2008 Nov 4;149(9):638–58.

[11] Levin B, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS, et al. Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin 2008 May;58(3):130–60.

[12] van Rossum LG, van Rijn AF, Laheij RJ, van Oijen MG, Fockens P, van Krieken HH, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology 2008 Jul;135(1):82–90.

[13] Hol L, van Leerdam ME, Van BM, van Vuuren AJ, van DH, Reijerink JC, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. Gut 2010 Jan;59(1):62–8.

[14] Young GP, Cole SR. Which fecal occult blood test is best to screen for colorectal cancer? Nat Clin Pract Gastroenterol Hepatol 2009 Mar;6(3):140–1.

[15] Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM. American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2009 [corrected]. Am J Gastroenterol 2009 Mar;104(3):739–50.

[16] Zauber AG, Levin TR, Jaffe CC, Galen BA, Ransohoff DF, Brown ML. Implications of new colorectal cancer screening technologies for primary care practice. Med Care 2008 Sep;46(9 Suppl 1):S138–S146.

[17] Heitman S, Au F, Hilsden R, Manns B. Fecal Immunochemical Testing in Colorectal Cancer Screening of Average Risk Individuals: Economic Evaluation. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

[18] Mandel JS, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000 Nov 30;343(22):1603–7.

[19] Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med 2004 Dec 23;351(26):2704–14.

[20] Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR,Northover JMA, Parkin DM, Wardle J, Duffy SW, Cuzick J. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomized controlled trial. Lancet. Published online April 28, 2010. DOI:10.1016/S0140-6736(10)60551-X

[21] Hoff G, Grotmol T, Skovlund E, Bretthauer M. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ 2009;338:b1846.

[22] Atkin WS, Edwards R, Wardle J, Northover JM, Sutton S, Hart AR, et al. Design of a multicentre randomised trial to evaluate flexible sigmoidoscopy in colorectal cancer screening. J Med Screen 2001;8(3):137–44.

[23] Segnan N, Senore C, Andreoni B, Aste H, Bonelli L, Crosta C, et al. Baseline findings of the Italian multicenter randomized controlled trial of "once-only sigmoidoscopy" – SCORE. J Natl Cancer Inst 2002;94:1763–72.

[24] Weissfeld JL, Schoen RE, Pinsky PF, Bresalier RS, Church T, Yurgalevitch S, et al. Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial. J Natl Cancer Inst 2005;97:989–97.

[25] Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. N Engl J Med 2000;343:162–8.

[26] Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med 2000;343:169–74.

[27] Schoenfeld P, Cash B, Flood A, Dobhan R, Eastone J, Coyle W, et al. Colonoscopic screening of average-risk women for colorectal neoplasia. N Engl J Med 2005 May 19;352(20):2061–8.

[28] Regula J, Rupinski M, Kraszewska E, Polkowski M, Pachlewski J, Orlowska J, et al. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Engl J Med 2006;355(18):1863–72.

[29] Ho C, Jacobs P, Sandha G, Noorani HZ, Skidmore B. Non-physicians performing screening flexible sigmoidoscopy: clinical efficacy and cost-effectiveness [Technology report no. 60]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2006.

[30] Wilson JMG, Junger G. Principles and Practice of Screening for Disease. Geneva: WHO, 1968.

[31] Shapero TF, Hoover J, Paszat LF, Burgis E, Hsieh E, Rothwell DM, Rabeneck L. Colorectal cancer screening with nurse-performed flexible sigmoidoscopy: results from a Canadian community-based program. Gastrointest Endosc 2007;65:640–5.

[32] Pignone M, Saha S, Hoerger T, Mandelblatt J. Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the US Preventive Services Task Force. Ann Intern Med 2002;137:96–104.

[33] Telford JJ, Levy AR, Sambrook JE, Zou D, Enns RA. The cost-effectiveness of colorectal cancer screening in Canada. CMAJ (in press).