

Clinical imaging: colorectal cancer screening and diagnosis

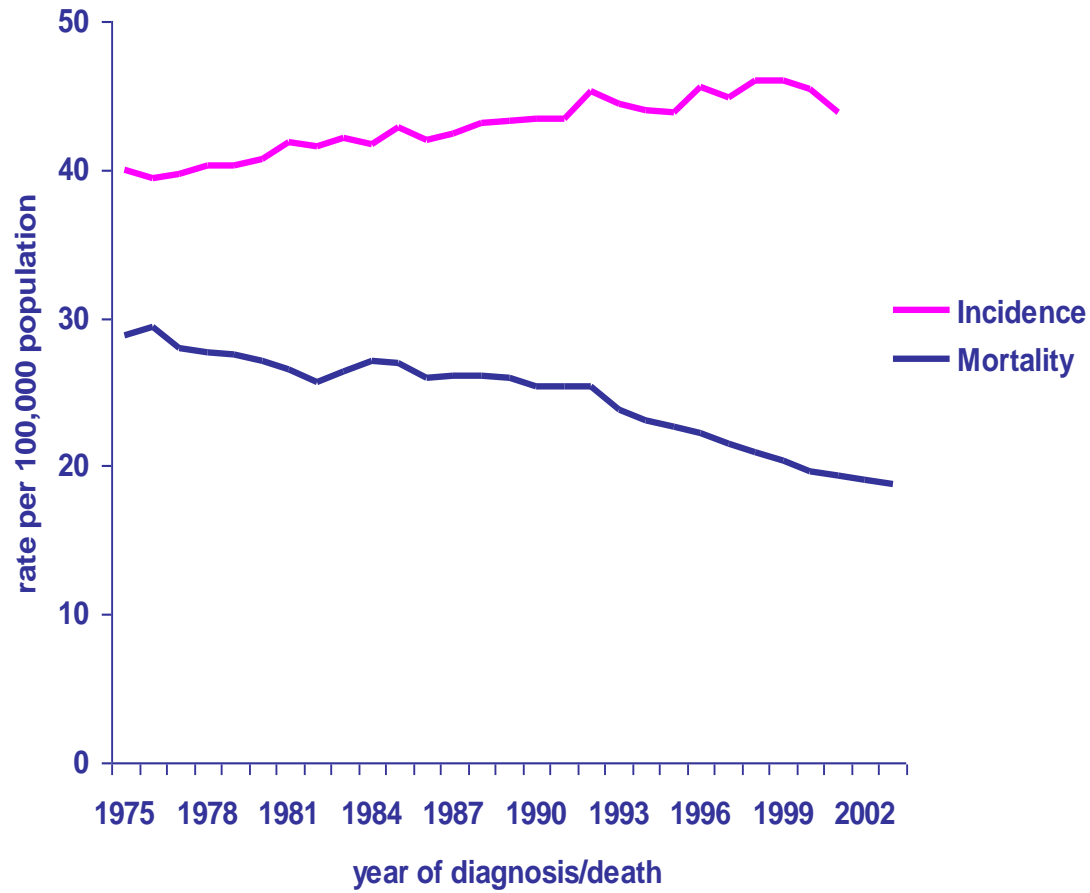
Wendy Atkin

Professor in Gastrointestinal Epidemiology, Department of Surgery and Cancer

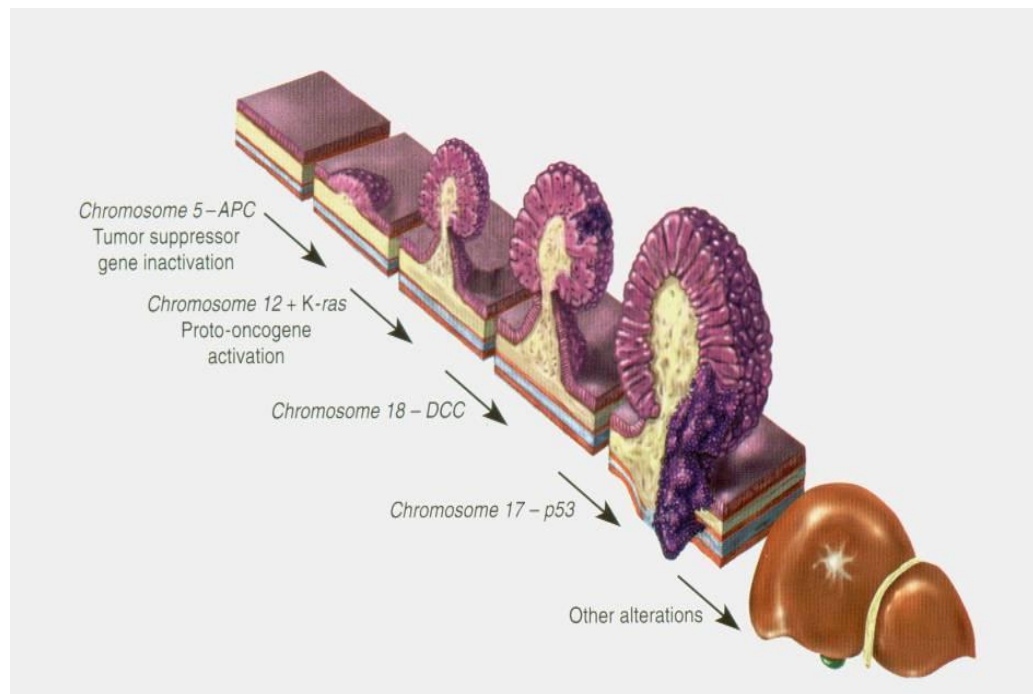
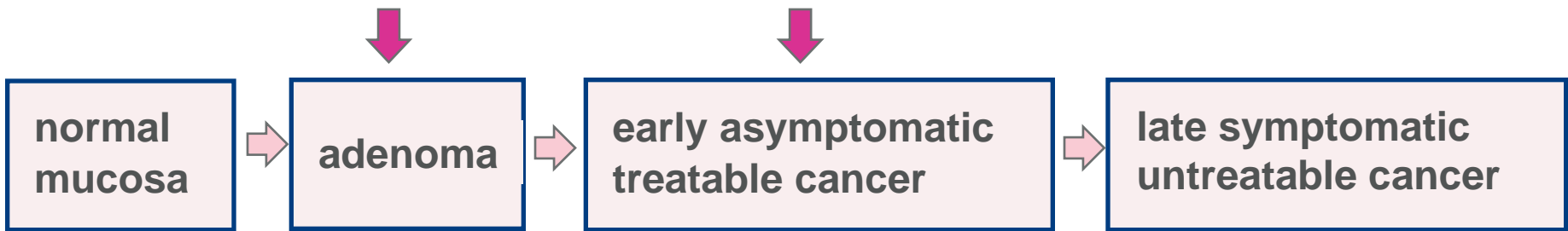
Rationale for screening for colorectal cancer in UK

- 2nd biggest cancer killer
- NHS spends £1.6 billion per year
- No effective Rx of advanced disease
- Survival only 50%
- No effective primary prevention
- 75% cases CRC have no known risk factors

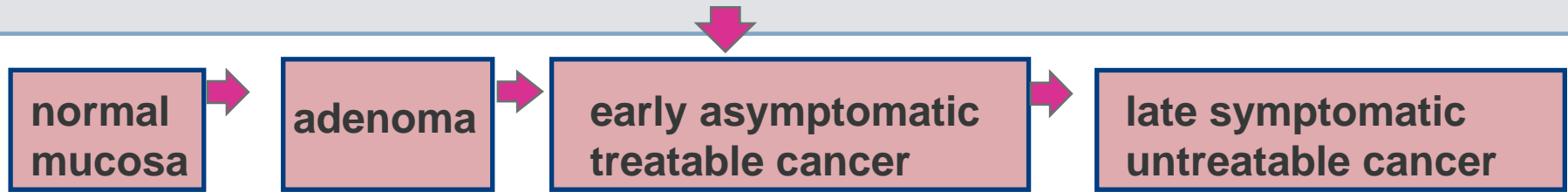
Bowel cancer incidence and mortality: UK 1975-2003



Reducing CRC incidence and mortality by screening

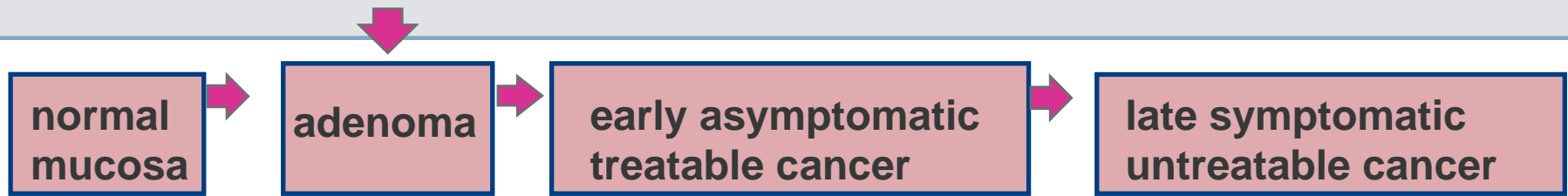


Target for screening – cancer



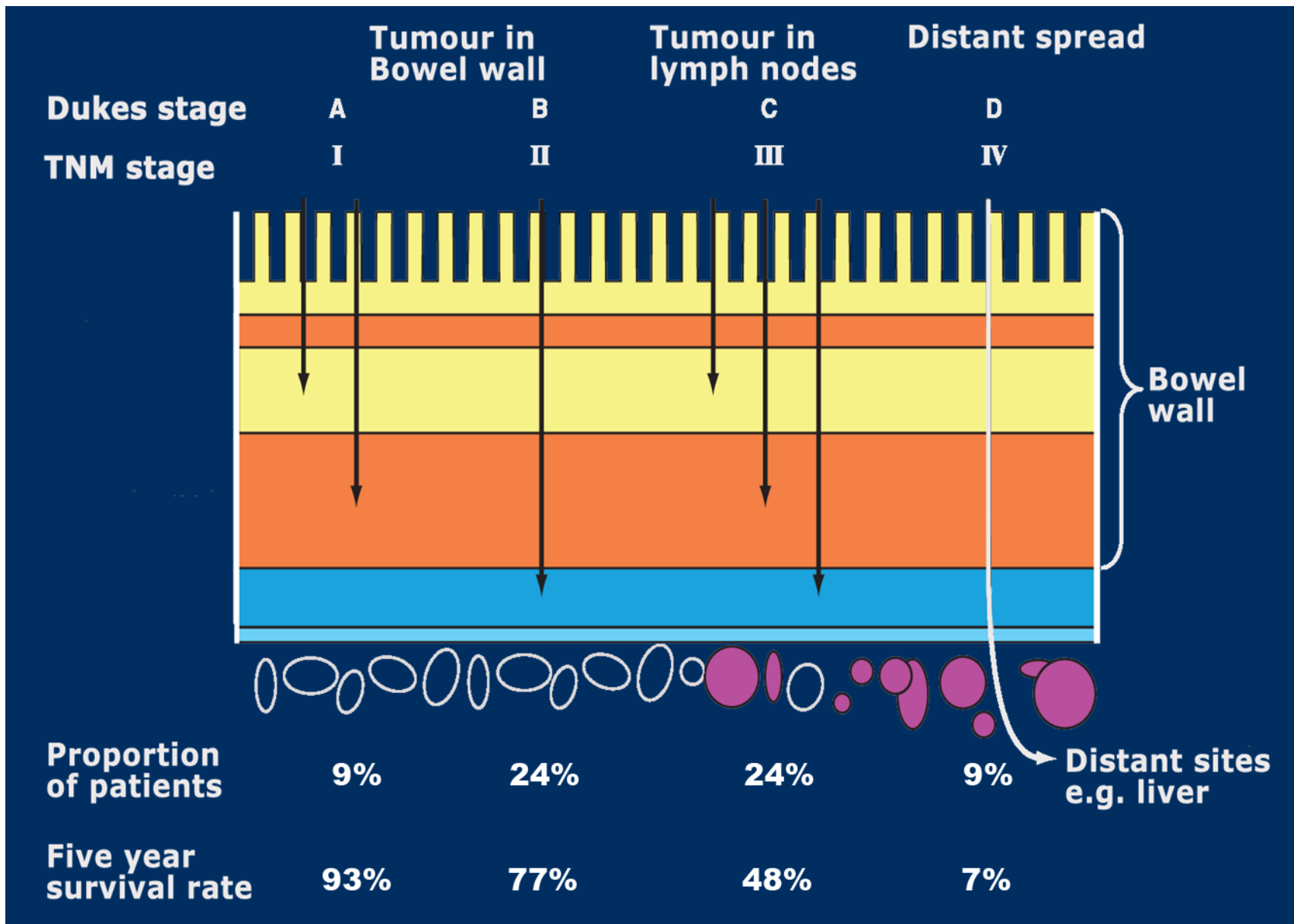
- Reduction in mortality rate
- No reduction in incidence rates
- No reduction in morbidity rates
- Short lead time - frequent testing
- Costly - screening costs added to Rx
- High anxiety levels in test positives

Target for screening – adenoma

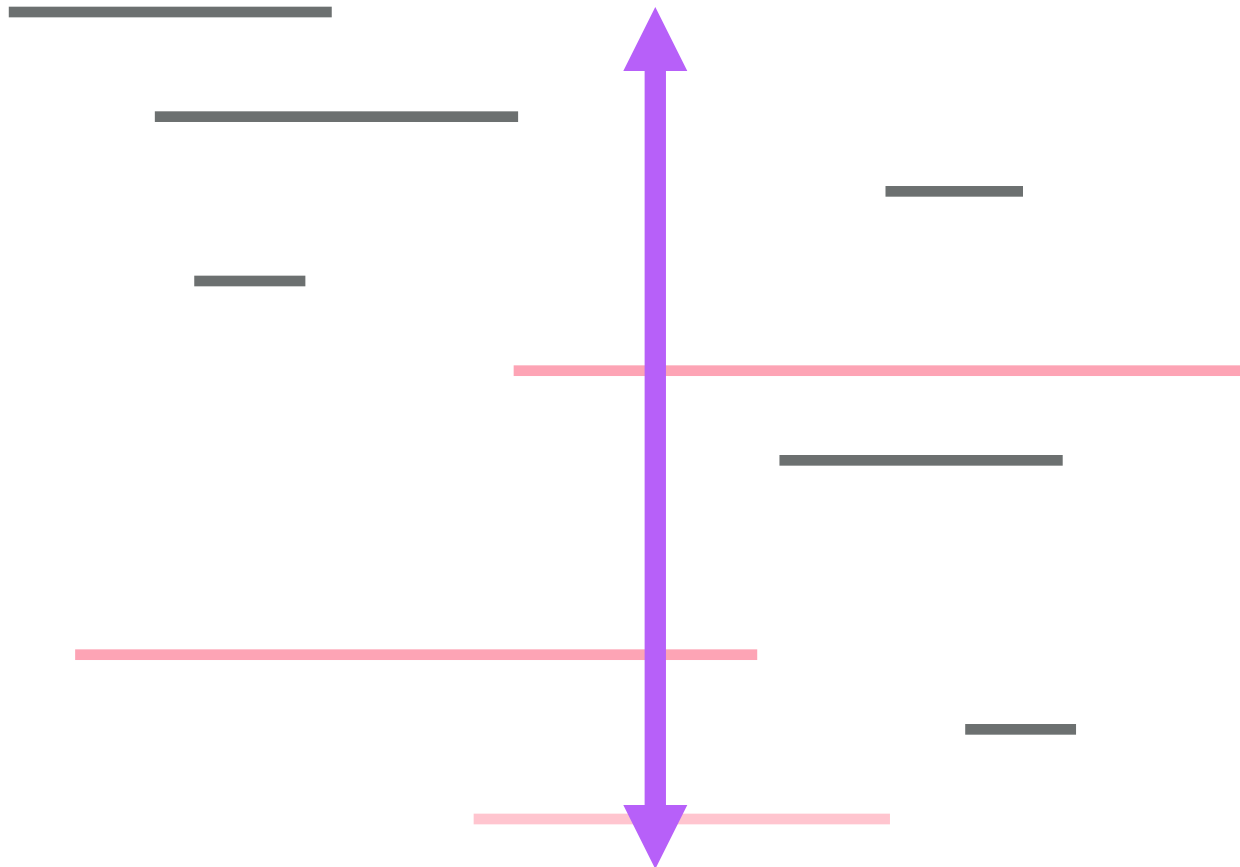


- Reduction in mortality rate
- Reduction in incidence rates
- Reduction in morbidity rates
- Long lead time - infrequent testing
- Less costly - screening costs offset v Rx
- Low anxiety levels in test positives
- Over-Rx - costs?

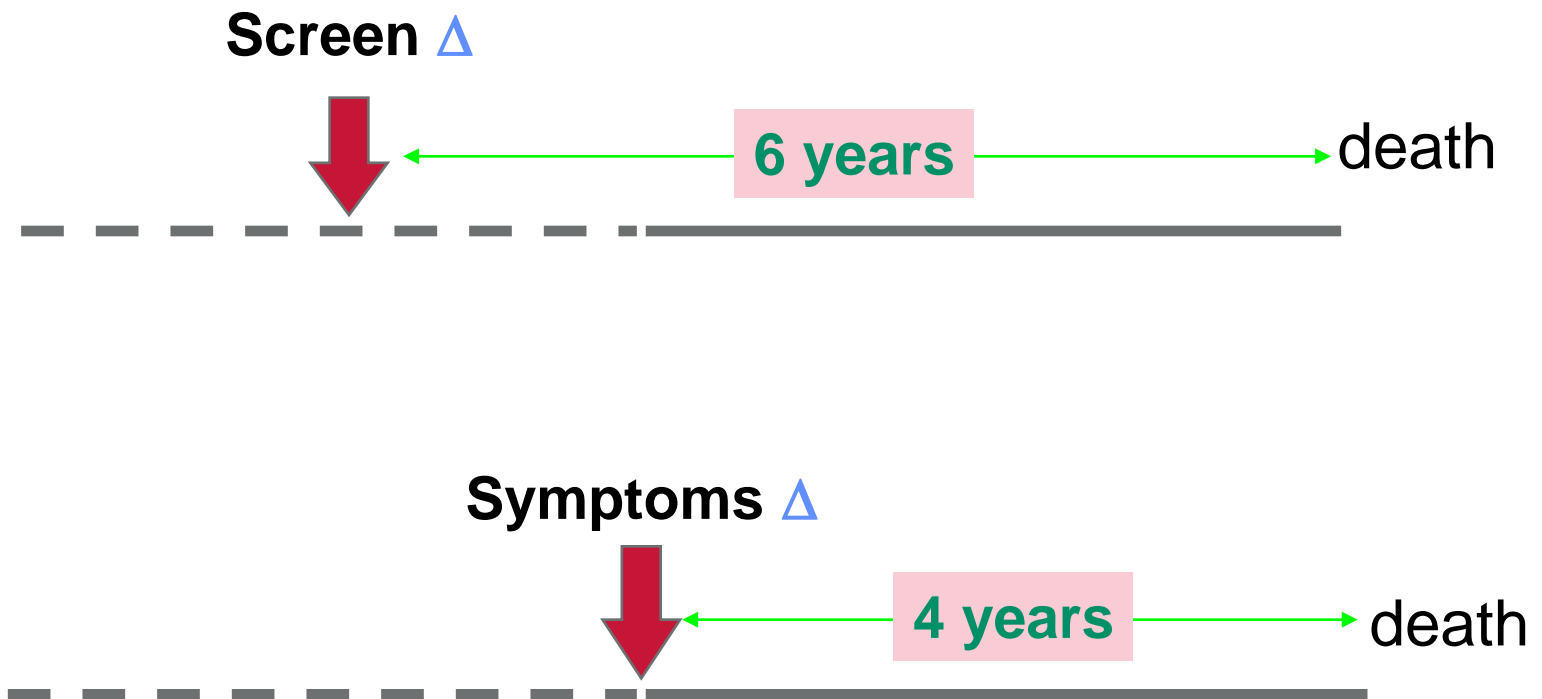
Dukes and TNM stage and 5-year survival (UK)



Length bias: interval cancers



Lead time bias: 5 year survival



Colorectal cancer screening modalities

Direct imaging

- **Endoscopy**
 - colonoscopy or flexible sigmoidoscopy
- **Radiological**
 - CT colonography, barium enema

Stool/blood tests:

- **Faecal occult blood testing**
 - gFOBT: guaiac (haem) or FIT: immunochemical (globin)
- **Molecular markers in blood or stool**

Guaiac FOBT: Evidence

Cochrane systematic review included 4 randomised trials

- CRC mortality reduction
 - 16% in invited population:
 - 27% in persons using ≥ 1 test
- No CRC incidence reduction
- No reduction in all-cause mortality

English Bowel Cancer Screening Programme based on guaiac occult blood test

Started April 2006

3 years to cover whole country

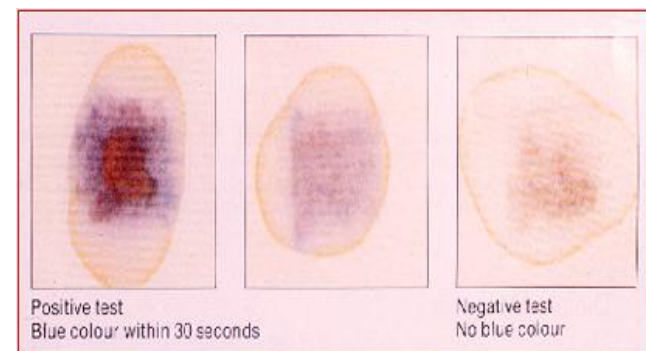
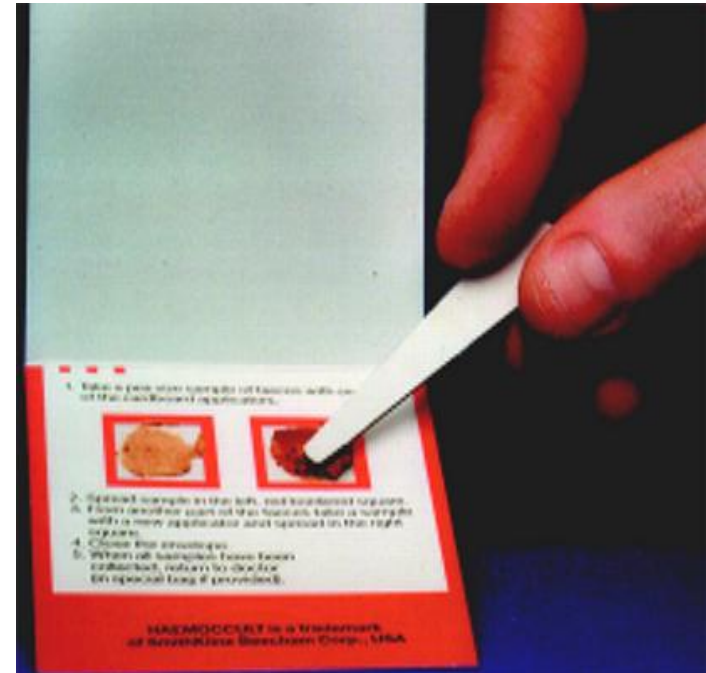
M and F, ages 60-69

Repeated 2 -yearly

2% of people test positive

1 in 10 positives have CRC

4 in 10 positives have large
adenomas



Missed colorectal cancers in 3 rounds of FOBT screening (Scotland)

	Round 1	Round 2	Round 3
Interval cancers	31 %	48%	59%

Immunochemical FOBT (FIT)

Advantages

- Single sample – simple to use
- Specific for human blood
- Quantitative test
 - Choose cut-off for positivity
- Fully automated
 - Can deal with 1000s of tests per day
 - Less manpower
 - Better standardisation
 - Strict QA



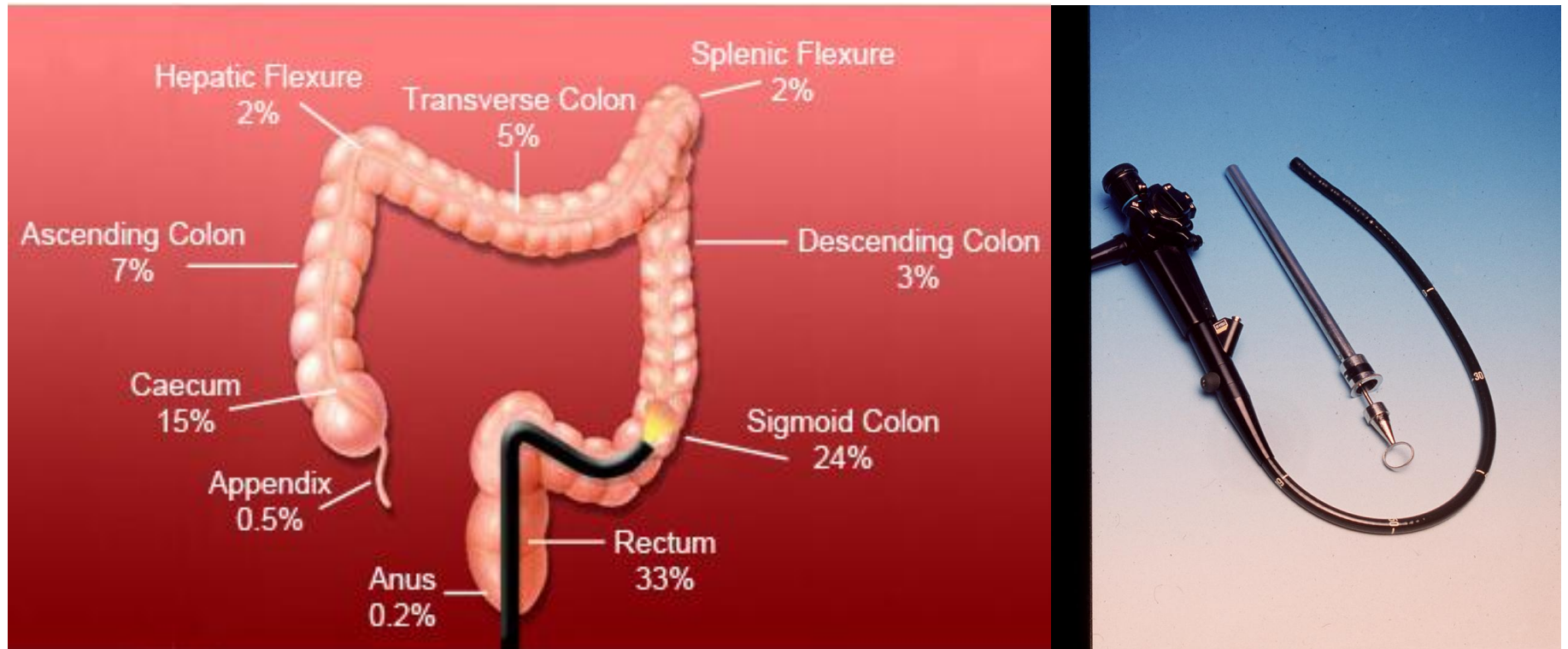
Italy: National Survey of FIT screening, 2008

Round	Uptake Rate	Positivity Rate	PPV Colorectal Cancer	PPV Advanced Adenomas
1st	46.3%	5.9%	2.7%	13.1%
Subsequent	47.5%	4.5%	1.3%	8.3%

78 programmes, using FIT 100 ng/ml



Endoscopic Screening



Acceptability and feasibility FS vs. colonoscopy

	Flex-sig	Colonoscopy
Bowel prep.	Enema	Laxative/diet
Pain	+/-	+/>++
Medication	None	Sedation/analgesia
Commitment	2-3 hours	24-36 hours
Perforations	1 in 10,000	1 in 2,500
Compliance	20-70%	6%
Cost	++	+++
Endoscopist skill	++	+++

Evidence for efficacy of FS

Case-control and cohort studies

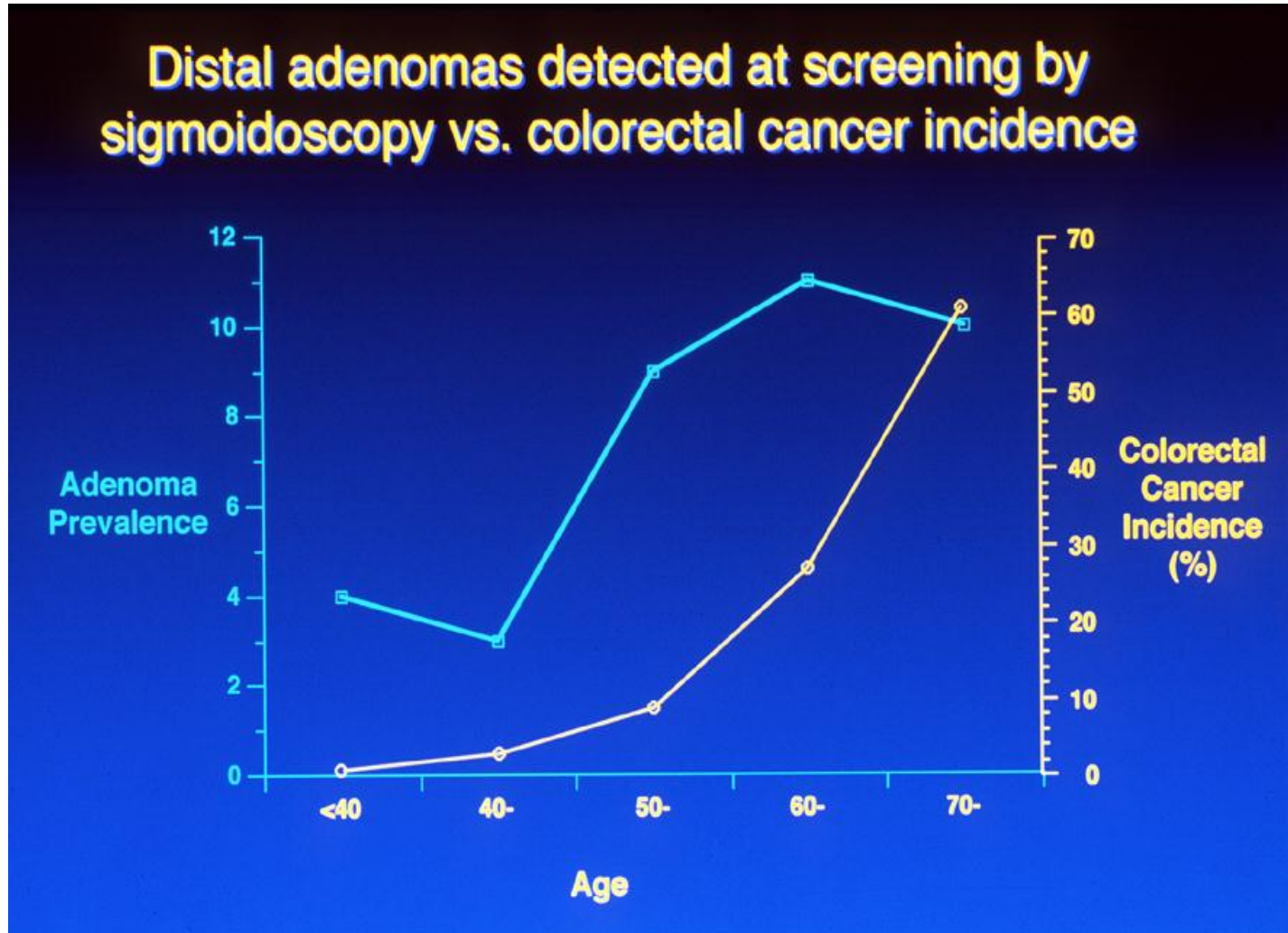
- 40-50% reduction in overall colorectal cancer incidence
- 60-80% reduction in distal cancer incidence

Long duration of protection against distal cancer

- Selby et al., NEJM 1992; 326:653-7
At least 10 years
- Newcombe et al., JNCI 2003; 95:623
At least 15 years
- Atkin et al., NEJM 1992; 326:658-62
Risk of rectal cancer reduced for remainder of life

Hypothesis:

Flexible sigmoidoscopy only needs to be done once!



Randomised clinical trials on flexible sigmoidoscopy

USA	PLCO	154 000	3-5 yrly
UK	 FlexiSCOPE trial	170 000	Once-only
Italy	SCORE	35 000	Once-only
Norway	NORCAPP	56 000	Once-only

Weissfeld et al., JNCI 2005;97:989-92

Segnan et al., JNCI 2002;94:1763-72.

Hoff et al., BMJ 2009;338:1846

Atkin et al., Lancet 2010, 375:1624-33

Flexible sigmoidoscopy screening regimen



- **Once-only flexible sigmoidoscopy screen between ages 55 and 64 years**
- **Remove small polyps (< 10 mm) during screening**
- **Colonoscopy only for high-risk adenomas:
≥3, ≥ 10 mm, ≥ 25% villous, high grade dysplasia**

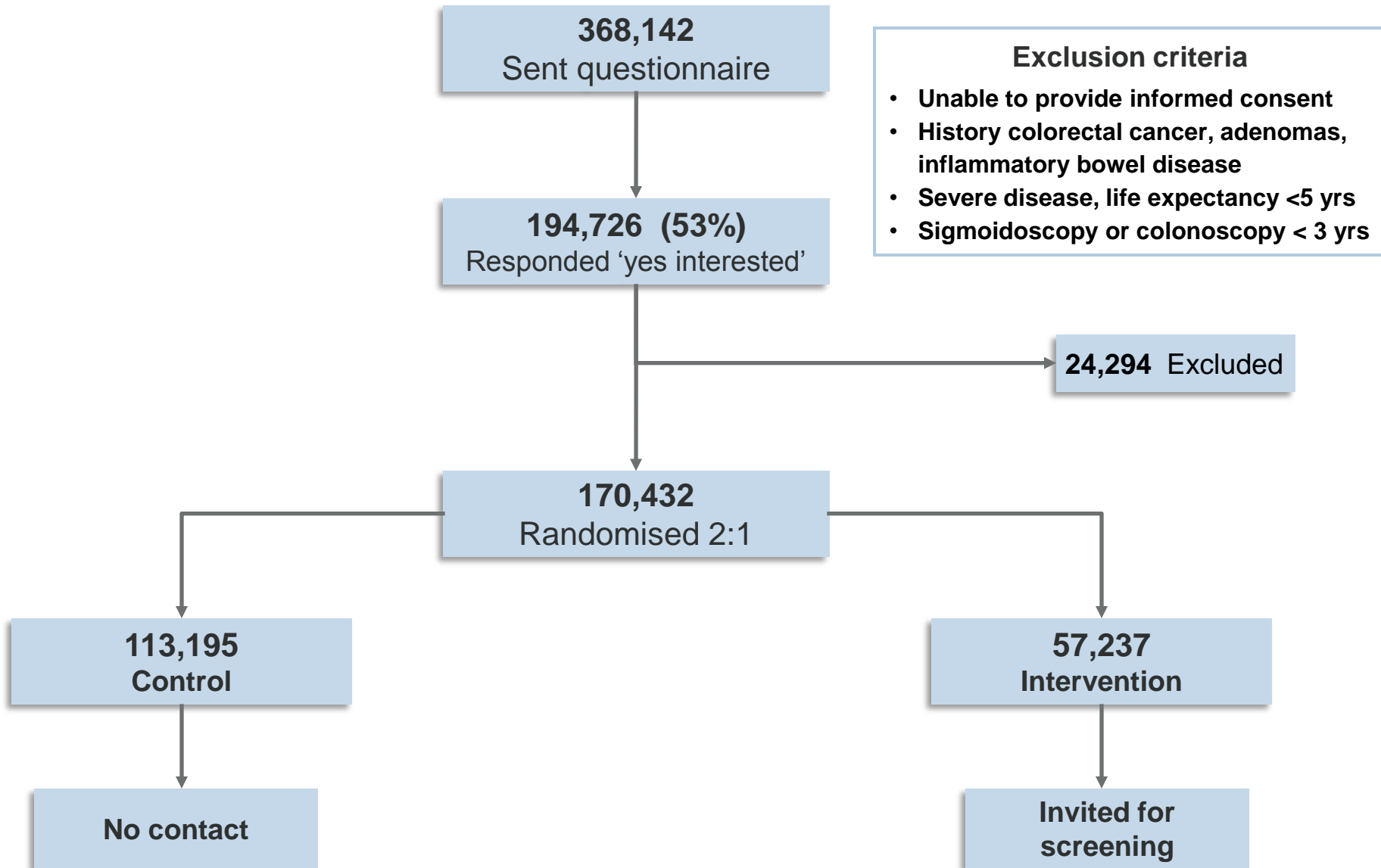


UKFSS Trial Centres

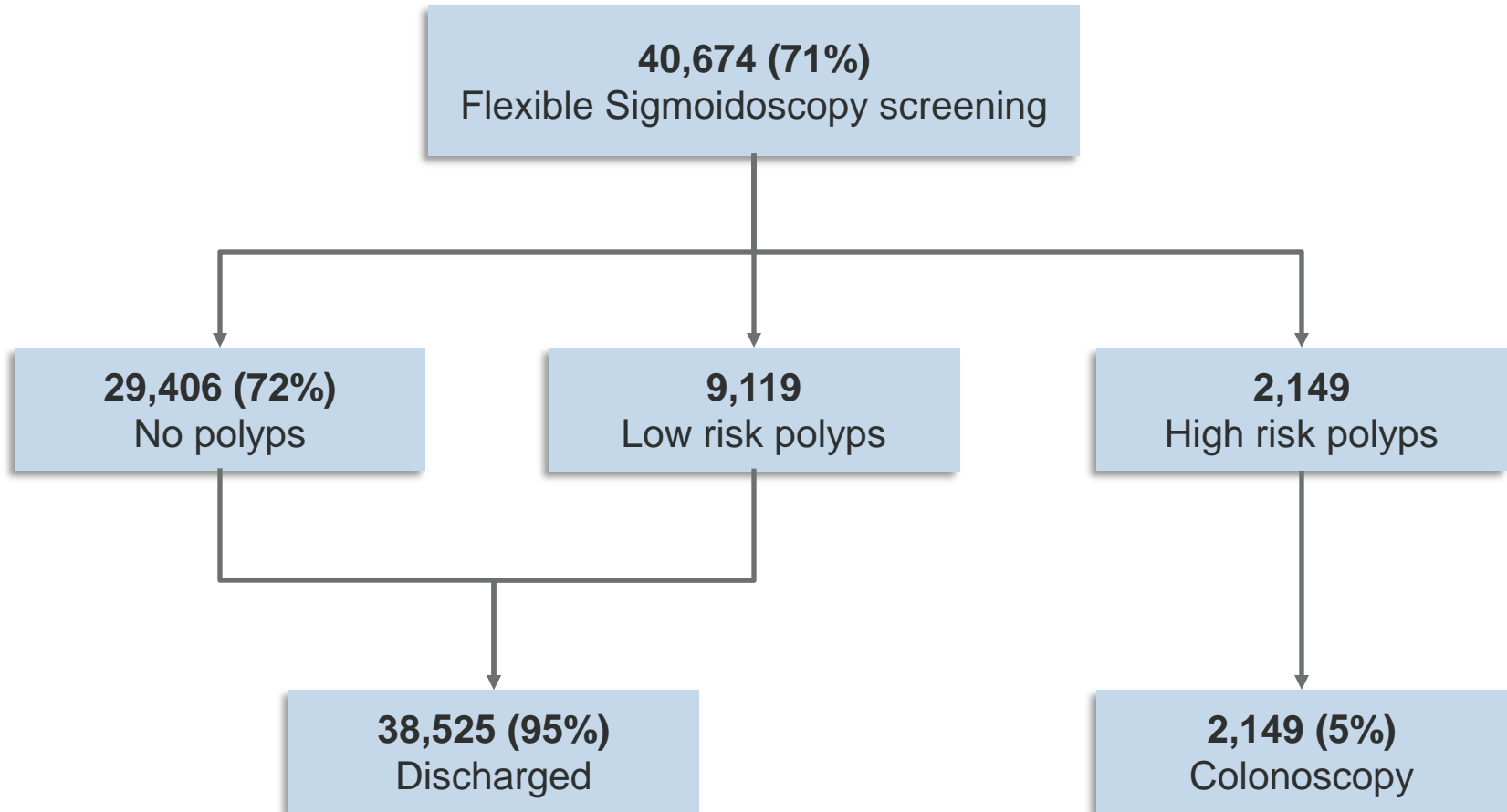


- Recruitment and screening 1996-9 in 13 centres
- Each centre: 1 endoscopist who performed ~ 3,000 FS

Trial Recruitment



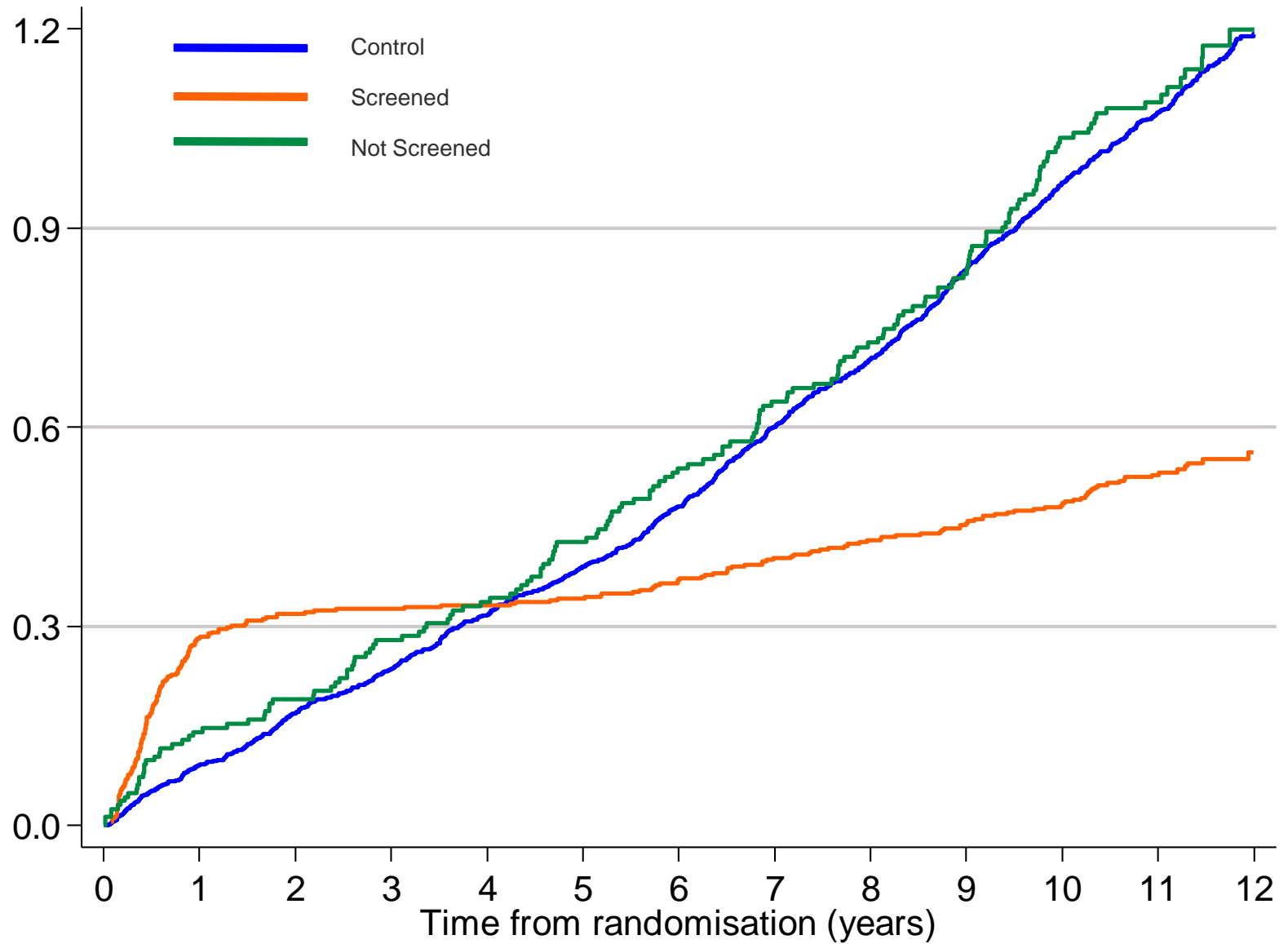
Baseline results of screening



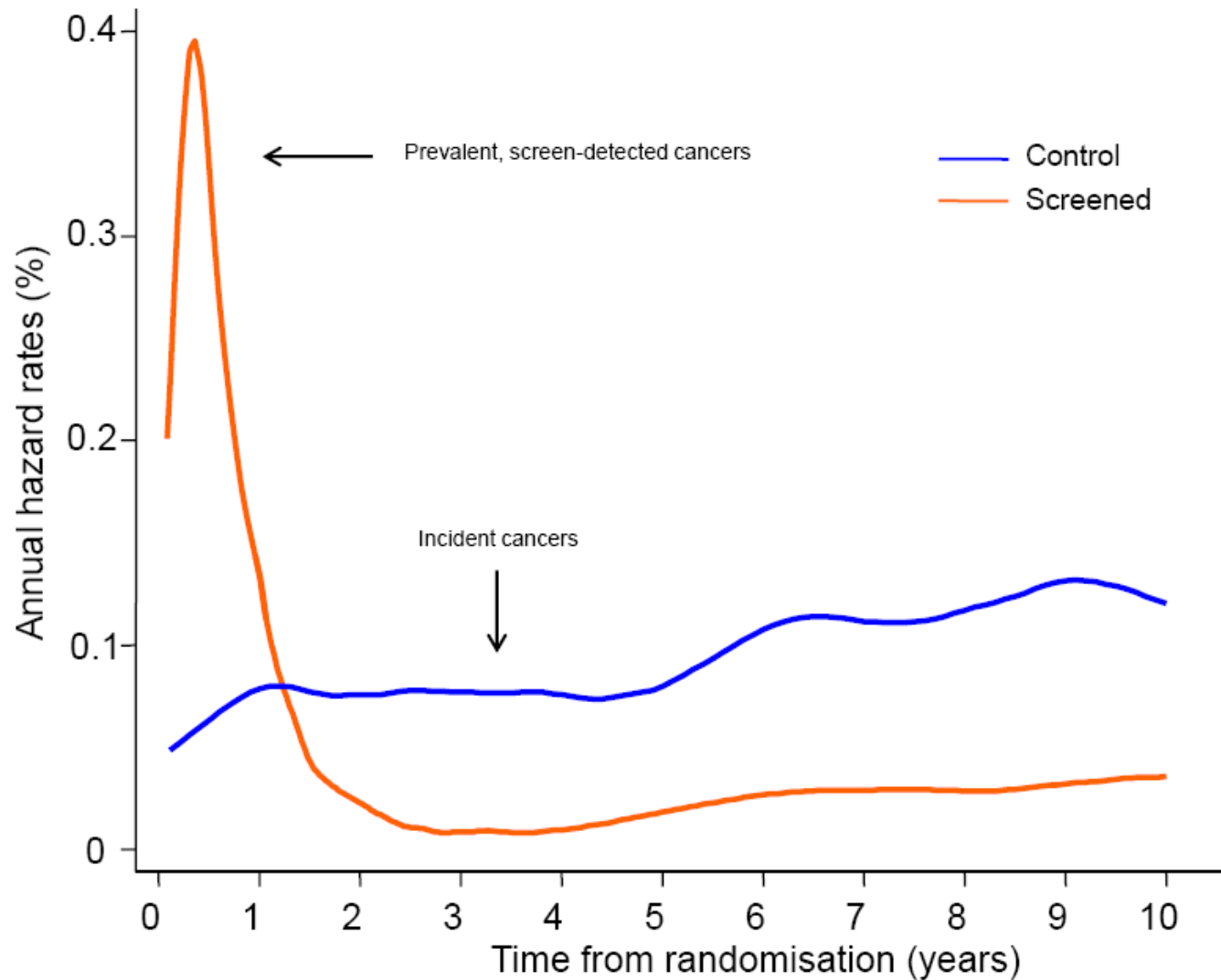
UK trial: Cumulative incidence reduction by 11 years

	Control group (n=112,939)		Screened (n=40,621)		<u>Screened vs. Control</u>
	Cases N	Rate /100,000 py	Cases N	Rate /100,000 py	Hazard ratio adjusted* (95% CI)
Incidence					
Distal	1,192	98	215	48	0.50 (0.42 - 0.59)
Proximal	628	51	224	50	0.97 (0.80 - 1.17)
Colorectal cancer all sites	1,818	149	445	100	0.67 (0.60 - 0.76)
Mortality					
Colorectal cancer	538	44	111	25	0.57 (0.45 - 0.72)

Cumulative incidence distal cancer (%)



Annual incidence rates for distal cancer (%)



Curves are truncated at 10 years of follow-up because of incomplete ascertainment of cancers in the final calendar year of the study.

Efficacy of a once-only flexible sigmoidoscopy

After 11 years of follow-up, in people who had the screening:

- Cumulative incidence, including prevalent cancers detected at screening, reduced by
 - 50% for distal cancers (rectum and sigmoid colon)
 - 33% for colorectal cancer overall
- Colorectal cancer mortality was reduced by 43%
- No sign of a waning of effect at longer follow-up times

FS in the NHS Bowel Cancer Screening Programme

October 2010

- Department of Health announced £60m over the next four years to introduce a flexible sigmoidoscopy screen at around age 55,
- subject to approval by UK National Screening Committee

April 2011

- UK National Screening Committee granted approval
- Department of Health announced that FS screening will be available for people aged 55-59 and then FOBT from age 60-74
- Roll out will start in 2012, with complete coverage of the English population by 2016

Challenges in implementing a national FS screening programme

- Acceptability
- Workforce to do the screening
- Quality/performance of screening

Acceptability of FS Screening

- Quick exam, average 4 minutes (4exams/hour)
- Enema more acceptable than oral laxative
- High attendance rates in men
- None or only mild discomfort: 98%
- Very safe: removed 19,000 polyps

Population pilot of nurse-led FS screening



- At least as effective as specialist doctors
- More acceptable, particularly to women
 - 43% women prefer female endoscopist*
 - 80% gastroenterologists male
- Provide holistic approach
 - health education
 - counselling and patient support
- High uptake rates, particularly in women

* Menees: Gastro Endosc 2005, Schoenfeld: Gastrointest endosc, 1999 **49**:158-62; Bresalier: Gastroenterology, 2002. **122**:A479 Moayyedi:Can J Gastroenterol, 2007

Flexible sigmoidoscopy screening for colorectal cancer: uptake in a population-based pilot programme

Kathryn Robb, Emily Power, Ines Kralj-Hans, Robert Edwards, Maggie Vance, Wendy Atkin and Jane Wardle

J Med Screen 2010;**17**:75–78
DOI: 10.1258/jms.2010.010055

Invited 2260 men and women, aged 58 and 59 years, from 34 GP practices, for nurse-delivered FS screening at St Mark's, Nov 2006-Apr 2008

	Invited	FS screening uptake	gFOBT uptake
Harrow	991	53%	47%
Brent	1269	39%	40%

Nurses' experiences of a colorectal cancer screening pilot.
Robb et al., Br J Nurs. 2011 Feb 24-Mar 9;20(4):210, 212, 214

Measures of endoscopist performance

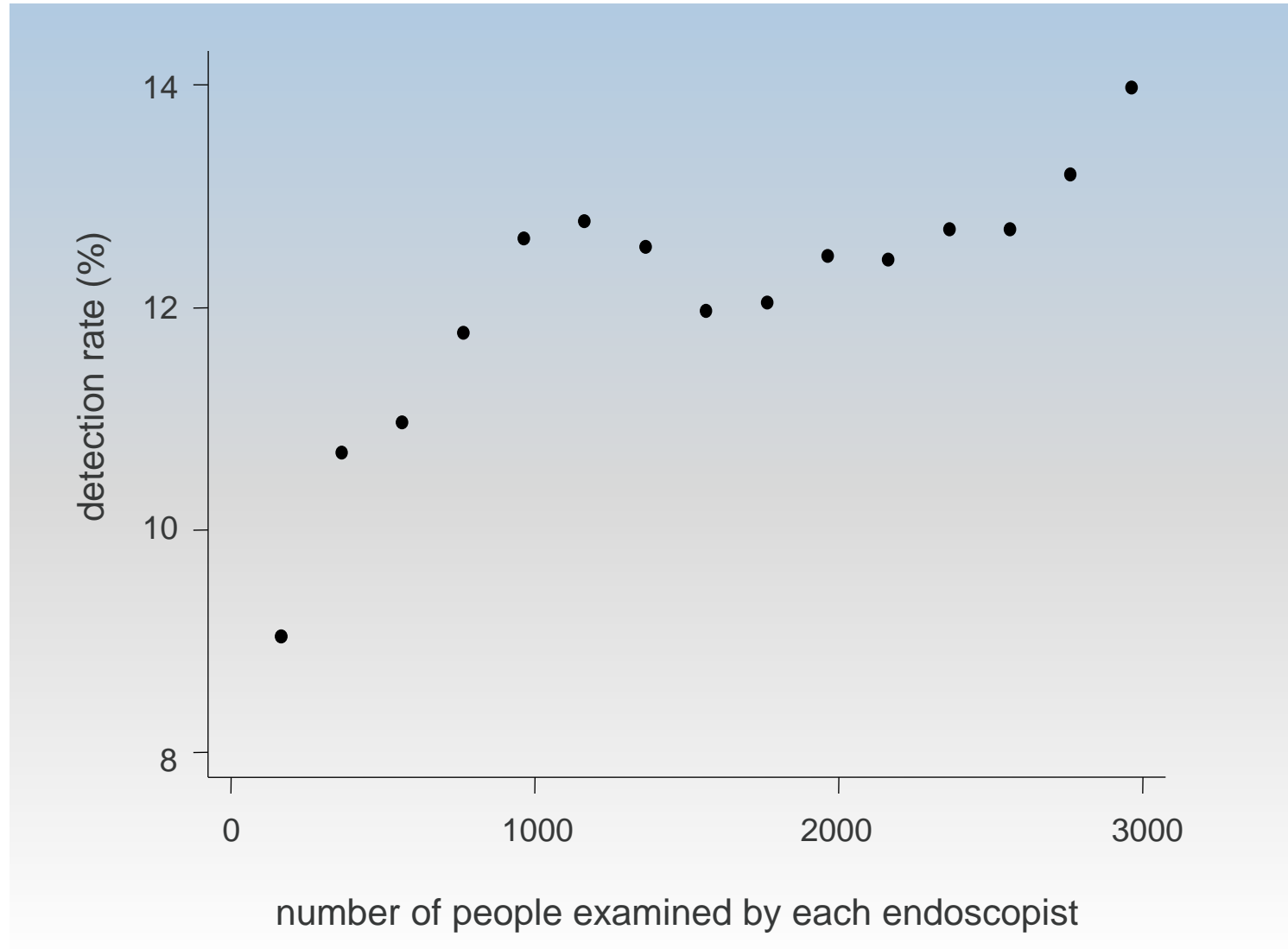
- Poor bowel prep
- Withdrawal time
- Incomplete exam
- Pain experienced
- Polyp detection rates

Adenoma detection rates

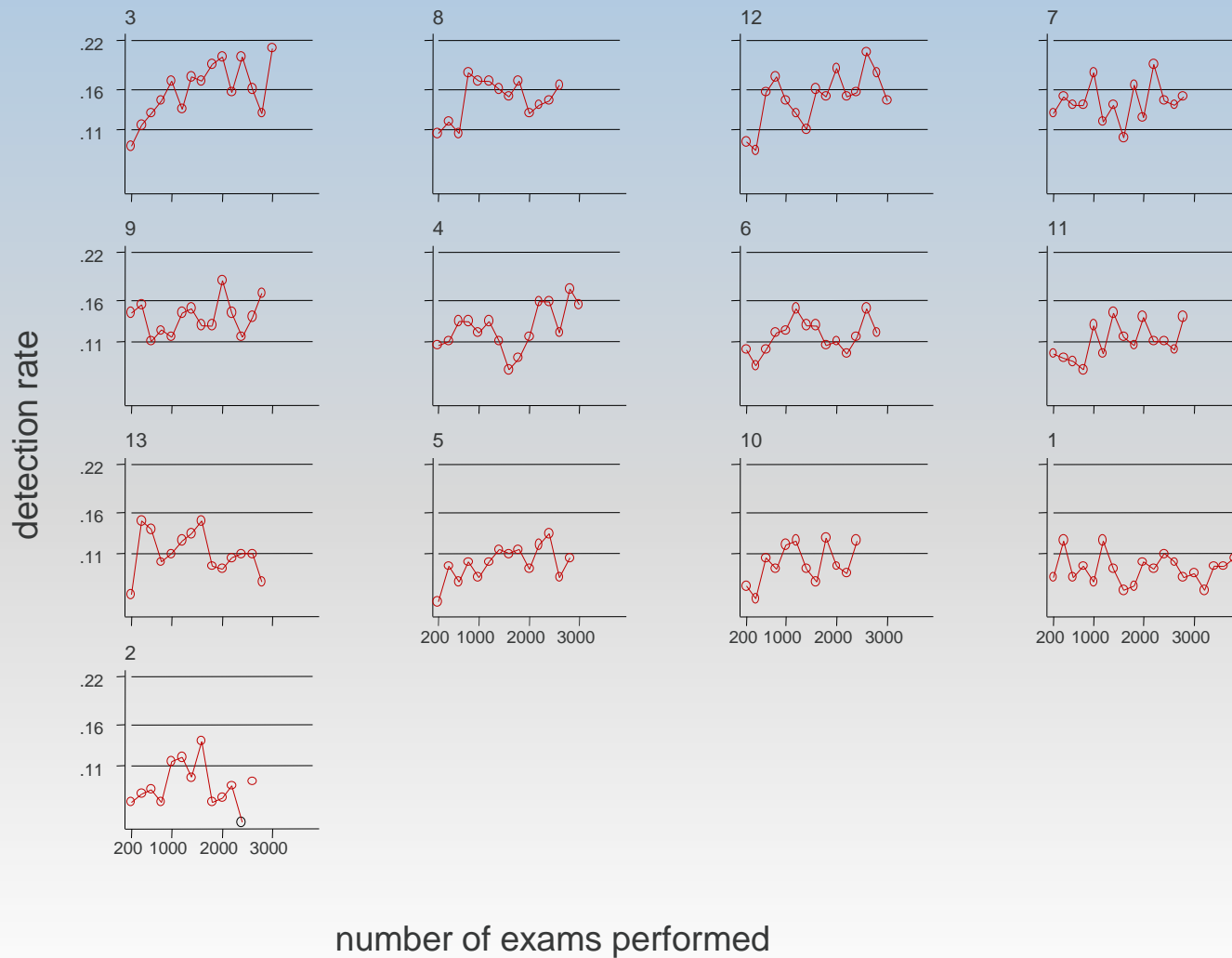
Variation in adenoma detection rates at FS

Trial endoscopist's ADR rank	People screened (n)	≥1 adenoma (ADR)	≥ 2 adenomas In people with ≥ 1adenoma detected (%)	Average no. of adenomas per 100 cases examined
1	3015	15.9	24.5	21.7
2	2646	14.7	21.5	19.3
3	3178	14.7	19.9	19.3
4	2907	14.5	24.0	19.2
5	2905	14.0	19.6	17.8
6	3085	12.6	22.8	16.2
7	2987	11.8	20.7	15.7
8	2902	11.3	18.4	14.0
9	2970	10.9	19.1	13.4
10	2948	9.8	13.2	11.5
11	2482	9.6	15.9	11.8
12	3902	9.1	15.8	10.9
13	2674	8.6	15.2	10.4
Total	38,601	12.1	19.3	15.4

Learning curve among FS trial endoscopists



Endoscopists' monthly ADRs



Delivering high quality FS screening exams

Endoscopist

- JAG accreditation (www.thejag.org.uk/), including polypectomy
- Minimum number of procedures per year to maintain proficiency
- Continuous monitoring of performance (ADR) with feedback
- Management of poor performance

Equipment: optional

- paediatric scopes
- imager to improve orientation, comfort & completeness
- CO₂ to improve safety and comfort

Colonoscopy and CRC prevention

Case-control studies	Distal (OR)	Proximal (OR)
Baxter (death) ¹	0.33	0.99
Brenner ²	0.33	1.05
Cotterchio ³	0.41	1.02
Lakoff ⁴	0.21	0.57
Kavanagh ⁵	0.41	0.91
Singh ⁶	Men: 0.44 Women: 0.44	Men: 0.88 Women: 0.99

1 Baxter et al. *Ann Intern Med.* 2009 Jan 6;150(1):1-8

2 Brenner *JNCI* 2010;102:89-95

3 Cotterchio et al. *Cancer Causes Control.* 2005 Sep;16(7):865-75

4 Lakoff et al. *Clin Gastroenterol Hepatol.* 2008 Oct;6(10):1117-21

5 Kavanagh et al. *Cancer Cause Control.* 1998; 9: 455-462

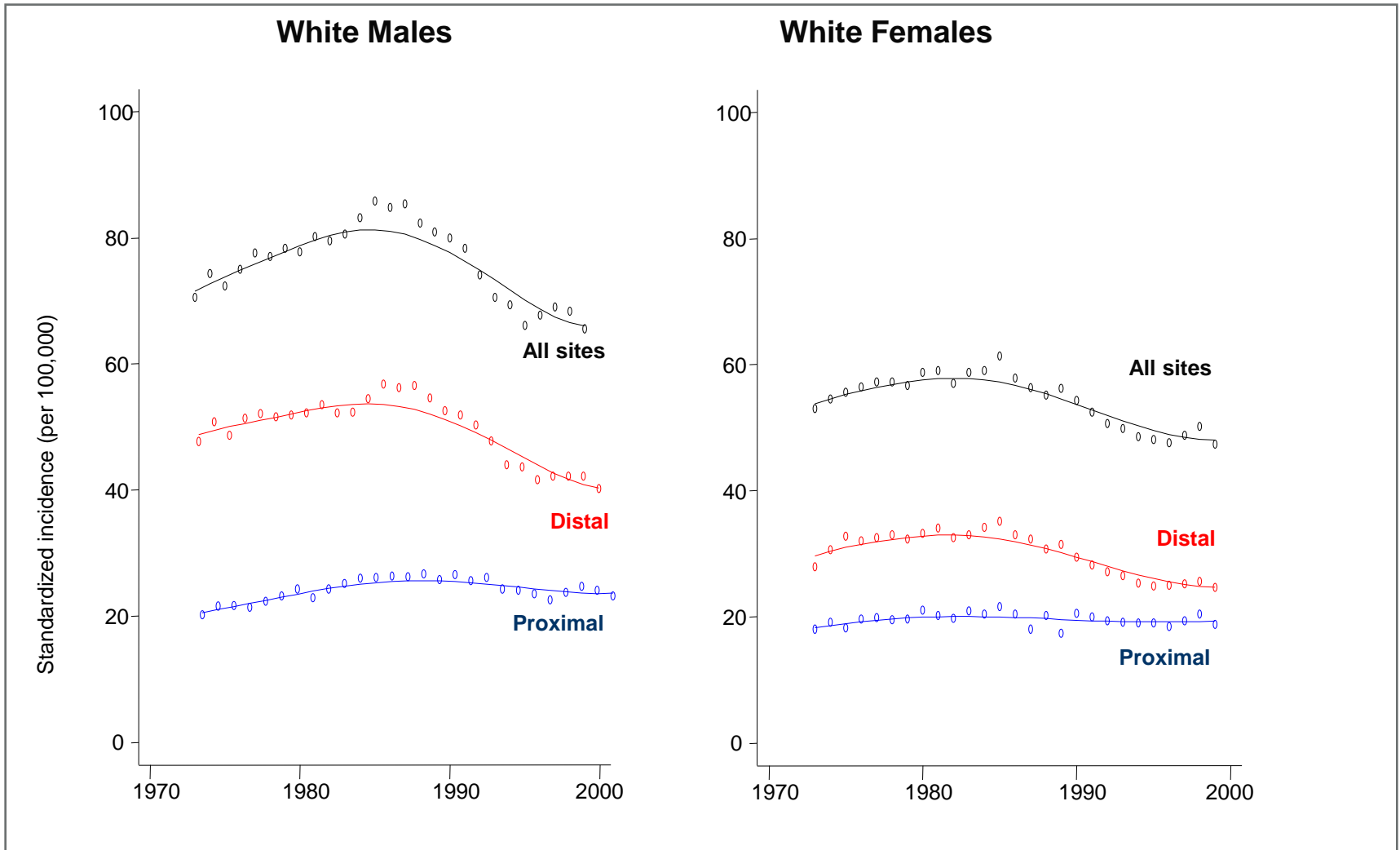
6 Singh et al. 2010. *Am J Gastroenterol.* 2010;105(3):663-673.

Colonoscopy RCTs in progress

	Age	Colo vs...	Sample size	Follow-up	
NORDICC*	55-64	Usual care	66,000 (1:2)	15 yrs	2025
COLOPREV Spain	50-69	FIT 2yrly 75ng/ml	55,000 (1:1)	10 yrs	2019
CONFIRM USA	50-75	FIT yrly 100ng/ml	50,000 (1:1)	10 yrs	2025

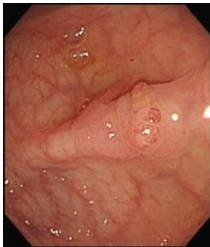
* Poland, Norway, Sweden, Netherlands, Iceland

USA – Trends in incidence colorectal cancer

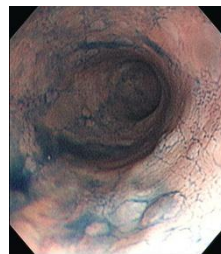


Why is colonoscopy ineffective in preventing proximal cancer?

- Performance of colonoscopy sub-optimal?
- The precursors flat lesions rather than easily detected polyps?
- The precursor not an adenoma and not considered to be important?
- The development of cancer is much faster in the proximal than the distal colon, so that more frequent colon exams are necessary?



Serrated polyp



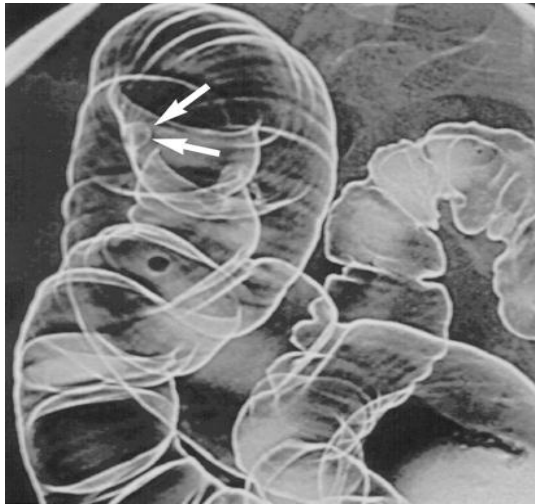
Multiple hyperplastic polyps



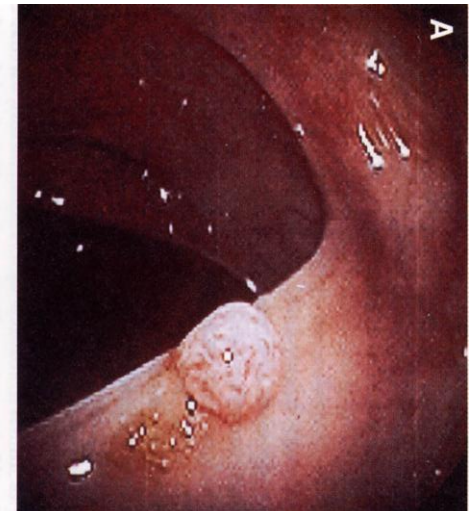
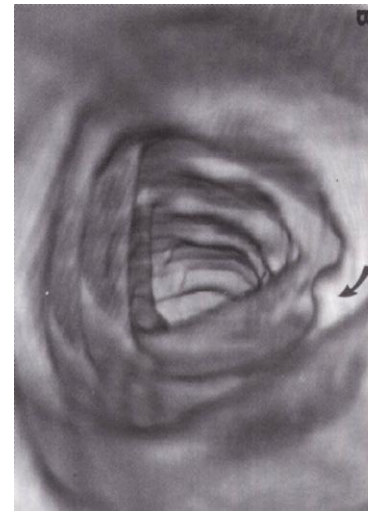
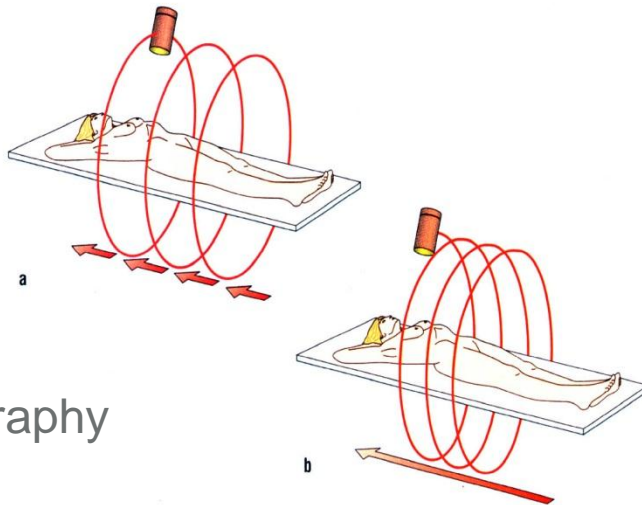
Large hyperplastic polyps

Radiological imaging of the colon

Barium enema



CT colonography



Studies of CTC followed by colonoscopy for **screening**: Accuracy for detecting polyps of different sizes

Threshold for referral	≥ 6 mm	≥ 10 mm
Sensitivity	89%	94%
Specificity	80%	96%
False positive	20%	4%
Positivity rate	30%	7%

Pickhardt et al., NEJM 2003

SIGGAR1 trial

(Special Interest Group in Gastrointestinal Radiology)

CT colonography vs.
barium enema or colonoscopy
for diagnosis of colorectal cancer
in *symptomatic* patients

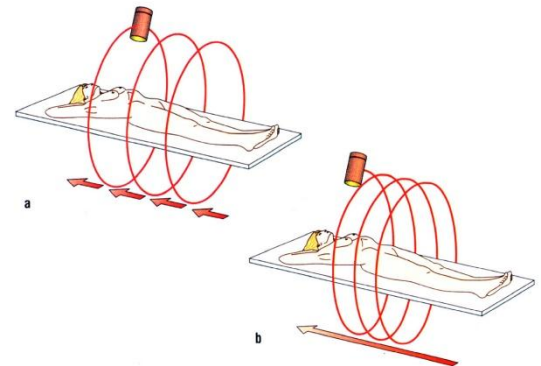
Wendy Atkin & Steve Halligan

Aims of the SIGGAR1 trial

To compare

CT colonography vs. barium enema or colonoscopy for investigating patients with *symptoms of colorectal cancer*

- Efficacy in detecting colorectal cancer or large polyps (≥ 1 cm)
- Predictive value of positive examination
- Efficiency in diagnosing or excluding cancer
- Patient preference
- Extra-colonic lesions detected by CTC:
 - *Frequency, clinical relevance, costs*



Barium Enema

Advantages

Safe

Little discomfort

No sedation required

More capacity, so shorter delay

Possibly better location of cancers than at colonoscopy

Disadvantages

Messy

Less accurate for detection of cancers

Need endoscopy to remove any polyps detected

Variation in radiologist performance (sensitivity, specificity)

08/01/2013

Colonoscopy

Advantages

Possibly more accurate for detection of cancers

Definitely more accurate for detection of smaller polyps

Can remove polyps at time of examination

Disadvantages

Need sedation, can be uncomfortable

Inadequate capacity so sometimes long delay

Only sees the large bowel, other procedures may be required to exclude other causes of symptoms

08/01/2013

CT colonography (CTC)

Advantage

- Less invasive than colonoscopy

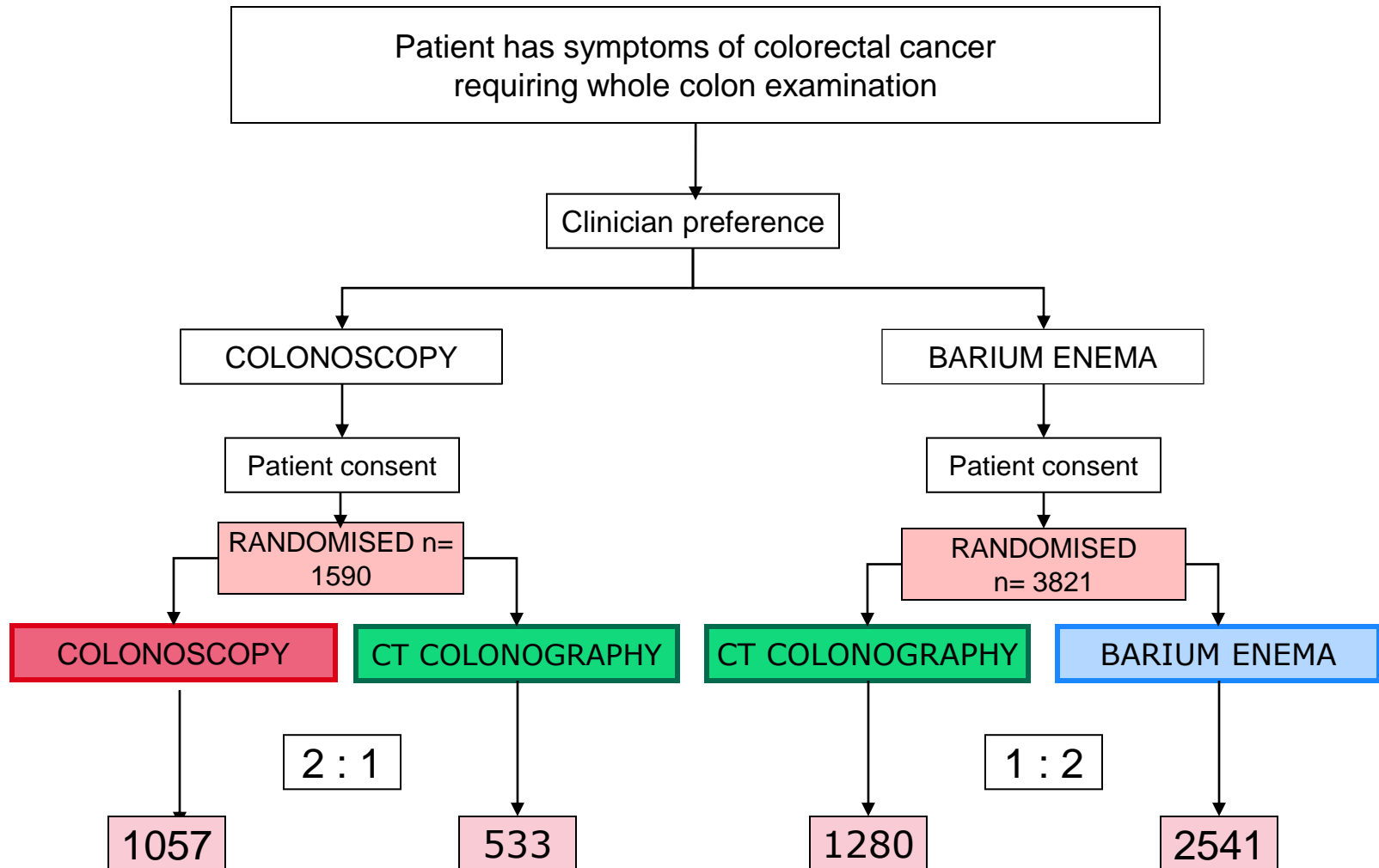
Challenges

- Optimum bowel prep
- Radiation exposure
- Sensitivity, specificity for colonic lesions
- Threshold for positivity (i.e. for referral for colonoscopy)
- Quality/training/QA
- Extra-colonic lesions

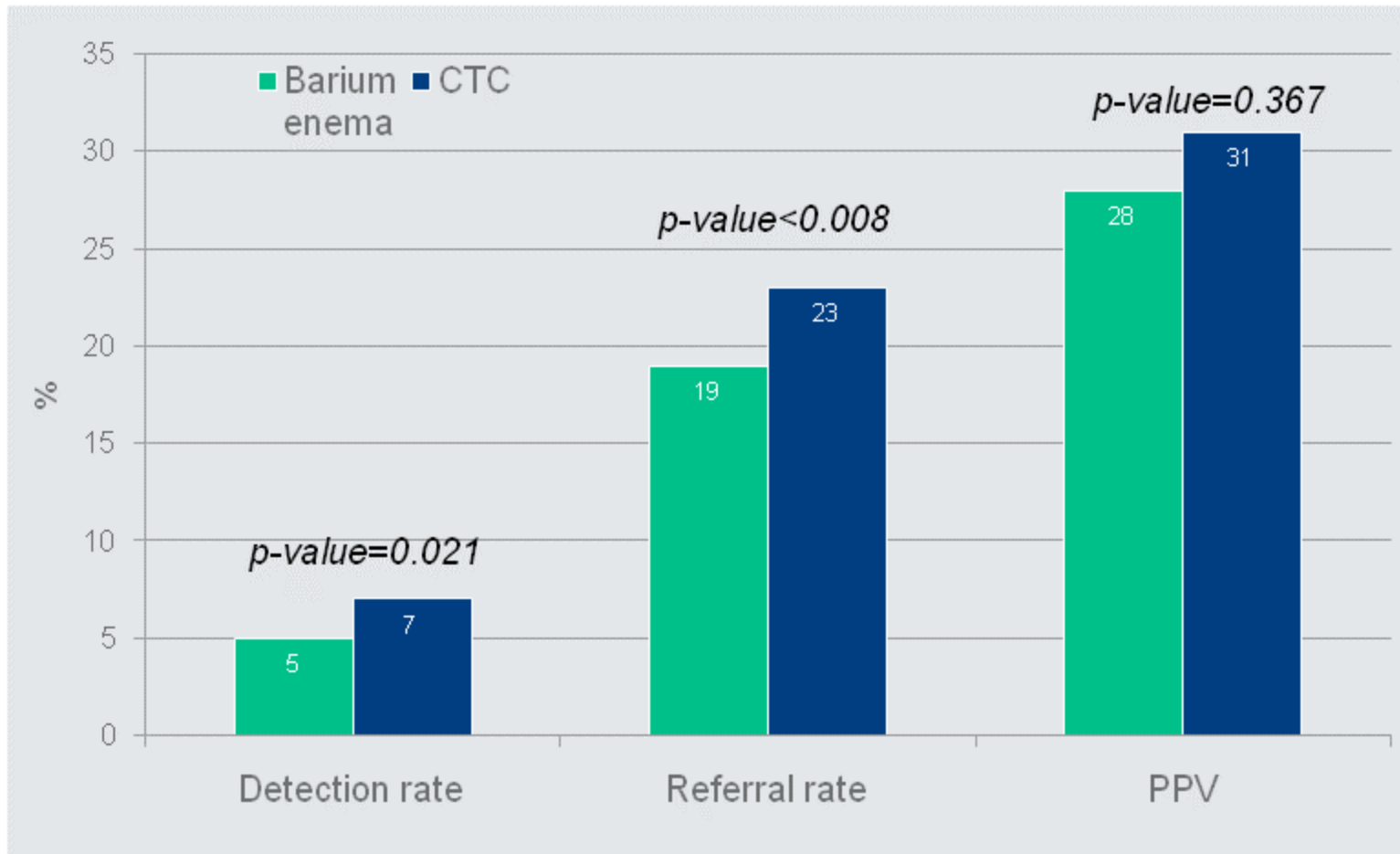
SIGGAR centres



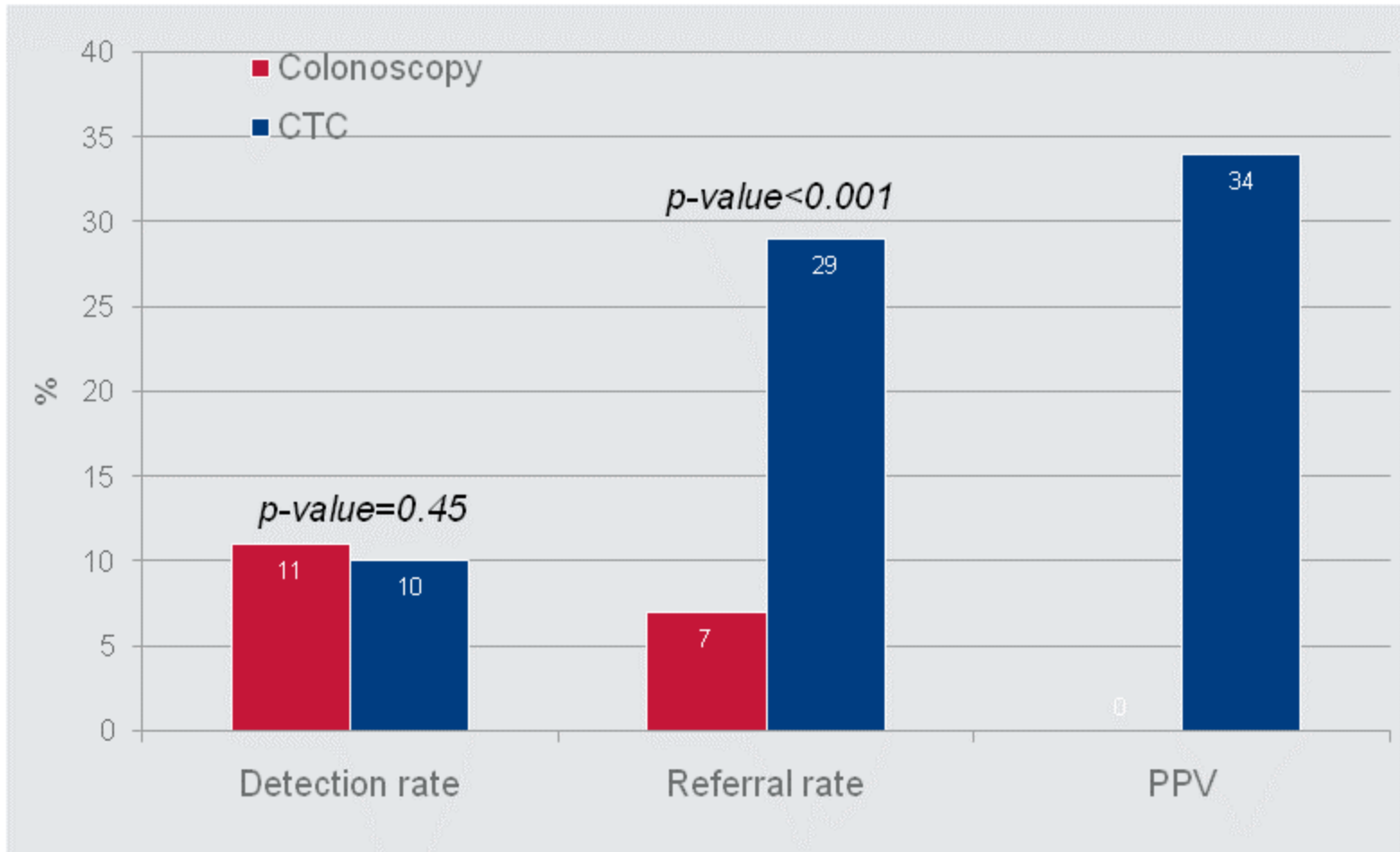
Two parallel trials



Barium enema trial



Colonoscopy Trial



Summary of results

Barium Enema (BE) trial

- CTC has higher detection rates of cancers and large polyps
- BE missed 8 cancers (miss-rate: 9.6%). CTC missed no cancers
- Barium enema has slightly lower referral rates than CTC but the same PPV, so barium enema is more specific than CTC

Colonoscopy trial

- The detection rates of CTC and colonoscopy are the same
- CTC has much higher referral rates than colonoscopy

Clinical imaging in colorectal cancer screening

Has potential to render colorectal cancer
a rare disease in England

